Health Technology Assessment 2004; Vol. 8: No. 39

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October 2004

Health Technology Assessment
NHS R&D HTA Programme

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Declared competing interests of authors: John Gabbay is Director of the NCCHTA, but is not directly involved in setting research agendas. He is also a member of the editorial board for *Health Technology Assessment*, although was not involved in the editorial process for this report. JG is a member of the consumer involvement steering group at the NCCHTA and also is a member of INVOLVE, which promotes public involvement in the NHS, public health and social care research.

Published October 2004

This report should be referenced as follows:

Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004;**8**(39).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 02/20/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

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Abstract

Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation

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Objectives: To assess the clinical-effectiveness and cost-effectiveness of pegylated interferon-α combined with ribavirin in the treatment of chronic hepatitis C.

Data sources: Electronic databases, reference lists of retrieved reports, and the industry submissions to the National Institute for Clinical Excellence.

Review methods: Sources were rigorously searched and studies were selected that met the inclusion criteria of being randomised controlled trials (RCTs) involving comparisons between pegylated interferon-α plus ribavirin and non-pegylated interferon plus ribavirin (two trials) or pegylated interferon alone and non-pegylated interferon alone (four trials). The primary outcome in all trials was sustained virological response (SVR) at follow-up. The trials were generally of good quality, although reporting of methodological details could have been more thorough in places. A cost-effectiveness model followed a hypothetical cohort of 1000 individuals with chronic hepatitis C over a 30-year period.

Results: In the two trials that tested pegylated interferon plus ribavirin against non-pegylated interferon plus ribavirin the combined percentage of sustained virological response was 55%. The relative risk (RR) for remaining infected was reduced by 17% for pegylated interferon plus ribavirin compared with non-pegylated interferon plus ribavirin. Response to therapy varied according to viral genotype. Patients with genotype 1 had the lowest levels of sustained virological response and patients with genotype 2 or 3 had the highest. In the four trials that evaluated pegylated interferon monotherapy against non-pegylated interferon the combined sustained virological response rates were 31% for pegylated interferon and 14% for non-pegylated interferon. The RR for remaining infected with hepatitis C was reduced by 20% with the use of pegylated interferon. Patients with genotype 1 had the lowest levels of sustained virological response. There were also variations in sustained virological response according to other prognostic variables such as baseline viral load. Regimens involving pegylated interferon appear to be fairly well tolerated. Adverse events were been reported, but they did not differ substantially from levels of adverse events in regimens involving non-pegylated interferon. The incremental discounted cost per QALY for comparing no active treatment to 48 weeks of dual therapy with pegylated interferon and ribavirin (PEG + RBV) was £6045. When moving from 48 weeks of dual therapy with non-pegylated interferon and ribavirin (IFN + RBV) to 48 weeks of dual therapy with PEG + RBV the figure was £12,123. Subgroup analyses for dual PEG + RBV therapy demonstrated that the most favourable incremental discounted cost per QALY estimates were for patients infected with genotypes 2 and 3, and with low baseline viral load (£3921) compared with no active treatment. Results of one-way sensitivity analyses showed that the estimates varied according to differences in SVRs, drug costs and discount rates. In general estimates remained under £30,000 per QALY. The incremental discounted cost per QALY when moving from no active treatment to 48 weeks of monotherapy with pegylated interferon was £6484. When moving from 48 weeks of monotherapy with IFN to 48 weeks of monotherapy with PEG the figure was £8404. As with dual therapy, the lowest incremental cost per QALY was for patients with genotypes 2 and 3 and low baseline viral load, in the range £2641–4194. The highest estimates were for patients with genotype 1 and high baseline viral load, around £30,000.

Conclusions: Well-designed RCTs show that patients treated with pegylated interferon, both as dual therapy and as monotherapy, experience higher sustained viral

response rates than those treated with non-pegylated interferon. Patients with genotypes 2 and 3 experience the highest response, with rates in excess of 80%. Patients with the harder to treat genotype 1 nevertheless benefit, with up to 46% of patients experiencing an SVR in one of the trials. Pegylated interferon also appears to be relatively cost-effective in both monotherapy and dual therapy, with cost per QALY estimates remaining generally under £30,000. The most favourable estimates were for patients with genotypes 2 and 3. Pegylated interferon is a relatively new intervention in the treatment of hepatitis C and therefore there are areas where further research is needed. These include: efficacies of therapy with PEG-α-2a vs PEG-α-2b; retreatment of previous non-responders using pegylated interferon; efficacy of treatments and long-term outcomes in patients who have other co-morbidities; prospective tests of rules governing stopping treatment; treating patients with acute hepatitis C; problems that may occur in a minority of patients with hepatitis C, such as cryoglobulinaemia and vasculitis; additional psychological effects on quality of life due to hepatitis C and also on the treatment of children and adolescents with hepatitis C.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Alanine aminotransferase An enzyme that indicates liver inflammation.

Alpha-fetoprotein A protein substance normally produced by the liver. Measurement of AFP in the bloodstream can be used as an early detection test for hepatocellular carcinoma.

Ascites Large accumulation of fluid in the abdominal cavity.

Biochemical response Normalisation of alanine aminotransferase levels, often defined as <40 UI l^{-1}.

Cirrhosis A condition in which the liver responds to injury or death of some of its cells by producing interlacing stands of fibrous tissue between which are nodules or regenerating cells.

Compensated liver disease Compensation is the act of making up for a functional or structural deficiency. For example, compensation for the loss of a diseased kidney is brought about by an increase in size of the remaining kidney, so restoring the urine-producing capacity.

Controlled clinical trial Trial without random allocation to study groups.

Decompensated liver disease Ascites, variceal haemorrhage and hepatic encephalopathy are complications that can follow decompensated liver disease.

Early virological response Fall in hepatitis C virus RNA by at least 2 log10 units or to an undetectable level at week 12 of treatment.

EuroQol Also known as the EQ-5D instrument, used to estimate a patient's quality of life.

Fibrosis Thickening and scarring of connective tissue, most often a consequence of inflammation or injury.

HALT-C (Hepatitis C Antiviral Long-term Treatment Against Cirrhosis) A trial sponsored by the US National Institute of Diabetes and Digestive and Kidney Diseases on the long-term use of pegylated interferon in patients who failed to respond to prior interferon treatment.

Hepatitis C virus RNA Genetic material that indicates the replication of the virus and therefore persistence of infection.

Histological response A decrease of at least 2 points in the total score on the histological activity index, where a score of 0 indicates no inflammatory changes and no fibrosis, and a score of 22 indicates multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation and cirrhosis.

IFN + RBV Non-pegylated interferon and ribavirin given in combination during the same period.

Interferon There are several forms of interferon. Unless otherwise stated it is used in this report to refer to interferon-α.

International normalised ratio A measure of the clottability of the blood.

METAVIR A scoring system for hepatic inflammation and fibrosis (from 0 to 4).

Non-response Patients who do not show evidence of clearing the hepatitis C virus either during treatment or after the cessation of treatment.

continued

Glossary *continued*

Polymerase chain reaction A sensitive technique of molecular genetics in which the DNA of a single cell, by treatment with polymerase enzymes, is induced to replicate many times. This enables the DNA to be amplified in sufficient quantities to enable generic analysis. A negative PCR indicates absence of virus in the blood and is one indication of treatment response.

Relapse Patients who have shown evidence of having cleared the hepatitis C virus during treatment, but who did not maintain a sustained virological response, i.e. the virus became detectable again within the follow-up period.

Sustained complete response Both a biochemical and virological response to treatment, sustained after treatment generally measured 24 weeks after treatment ends.

Sustained virological response Often defined as hepatitis C virus RNA <100 copies ml^{-1} that is maintained after treatment cessation, usually measured 24 weeks after treatment stops.

Transcription-mediated amplification Can detect residual levels of virus less than 50 hepatitis C virus RNA copies.

Viraemia Presence of virus in the blood.

Viral load Amount of hepatitis C virus RNA present in the body.

Virological response Absence of hepatitis C virus RNA on polymerase chain reaction.

A note about terminology

Different terms have been used for pegylated interferon, interferon and ribavirin in the text of this report. This has been done in an attempt to maximise clarity for the reader. In the narrative sections of the report (e.g. Chapter 2, 'Background') the drugs have generally been referred to by their full names (e.g. pegylated interferon). In the methods and results sections, data extraction tables and cost-effectiveness sections, where these terms are used very frequently, abbreviations are used (e.g. PEG, IFN, RBV). The use of abbreviations in these sections saves space and potentially avoids ambiguity in the use of the word 'interferon', which could refer to either the pegylated or non-pegylated form. (Note: we have refrained from using the term 'standard' interferon to denote the previous version of this drug. Instead, the term 'non-pegylated' interferon is used.)

PEG: pegylated interferon; IFN: non-pegylated interferon (what some people refer to as 'standard' interferon); RBV: ribavirin.

List of abbreviations

AFP	alpha-fetoprotein
AHRQ	Agency for Healthcare Research and Quality
ALT	alanine aminotransferase
AMA	amantadine hydrochloride
BNF	British National Formulary
BSG	British Society of Gastroenterology
CCT	controlled clinical trial
CCTR	Cochrane Controlled Trials Register
CDSC	Communicable Disease Surveillance Centre
CDSR	Cochrane Database of Systematic Reviews

continued

List of abbreviations *continued*

Chem path	chemical pathology
CI	confidence interval
CIFN	consensus interferon
CRD	NHS Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effectiveness
EMEA	European Agency for the Evaluation of Medicinal Products
EOTR	end of treatment response
EVR	early virological response
FBC	full blood count
FSS	Fatigue Severity Scale
GGT	γ-glutamyl-transferase
GSL	α-glutathione-*S*-transferase
GUM	genitourinary medicine
HA	hyaluronic acid
HAART	highly active antiretroviral therapy
HAI	histological activity index
HALT-C	Hepatitis C Antiviral Long-term Treatment Against Cirrhosis
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HE	hepatic encephalopathy
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
IFN	non-pegylated interferon (α-2a or α-2b)
INR	international normalised ratio
ITT	intention to treat
LFT	liver function test
MIU	million international units
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
NNT	number needed to treat
NRR	National Research Register
OR	odds ratio
PCR	polymerase chain reaction
PEG	pegylated interferon (α-2a or α-2b)
PHLS	Public Health Laboratory Service
QALY	quality-adjusted life-year
RBV	ribavirin
RCT	randomised controlled trial
RR	relative risk
SCI	Science Citation Index
SF-36	Short Form 36 instrument
SHPIC	Scottish Health Purchasing Information Centre
SR	sustained response
STD	non-pegylated interferon (used when applying inclusion criteria)
SUHT	Southampton University Hospitals Trust
SVR	sustained virological response
TAR	technology assessment report
TFT	thyroid function tests
U&E	urea and electrolytes

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objective

The aim of this systematic review and economic evaluation was to assess the clinical-effectiveness and cost-effectiveness of pegylated interferon-α combined with ribavirin in the treatment of chronic hepatitis C. The comparator was the current standard of treatment, non-pegylated interferon-α combined with ribavirin. Because some patients cannot tolerate ribavirin, treatment with pegylated interferon-α alone was also compared with treatment with non-pegylated interferon-α alone. Additional secondary questions were also addressed, including the effectiveness of retreating non-responders to interferon-α monotherapy, the use of non-invasive tests for gauging the severity of disease (e.g. fibrosis), and the effectiveness of antiviral treatment of patients with mild hepatitis C.

Epidemiology and background

Hepatitis C is a slowly progressive disease of the liver that is caused by infection with the hepatitis C virus (HCV). The virus can be transmitted in a number of ways, but the most common sources of infection are through injected drug use and infected blood products. Although some people infected with hepatitis C spontaneously clear the virus, up to 85% of those exposed develop chronic hepatitis. The rate of progression is slow and variable over 20–50 years. About 20–30% of those initially infected develop cirrhosis within 20 years and a small percentage of these are at high risk of hepatocellular carcinoma. Patients with chronic hepatitis C report diminished health-related quality of life, which can be improved by eradication of the virus. The prevalence of chronic hepatitis C in the UK is uncertain, but is estimated to be between 0.1 and 1%. Prevalence varies across different areas according to risk factors such as injecting drug use. Accurate prevalence rates are difficult to estimate because infection can remain asymptomatic for very long periods. There are several genotypes of the virus, the most common in England and Wales being 1a, 1b and 3a. Genotype 1 is harder to treat than genotypes 2 and 3.

Methods

Several electronic databases were searched including Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, MEDLINE and EMBASE. Other sources searched included the reference lists of retrieved reports, and the industry submissions to the National Institute for Clinical Excellence (NICE). These searches revealed six studies that met the inclusion criteria of being randomised controlled trials (RCTs) involving comparisons between pegylated interferon-α plus ribavirin and non-pegylated interferon plus ribavirin (two trials) or pegylated interferon alone and non-pegylated interferon alone (four trials). The primary outcome in all trials was sustained virological response (SVR) at follow-up. The trials were generally of good quality, although reporting of methodological details could have been more thorough in places.

Results

Dual therapy

In the two trials that tested pegylated interferon plus ribavirin against non-pegylated interferon plus ribavirin the combined percentage of sustained virological response was 55% [95% (confidence interval (CI) 52–58%] when using pegylated interferon and 46% (95% CI 43–49%) for non-pegylated interferon.

When the two trials were meta-analysed the relative risk (RR) for remaining infected was reduced by 17% for pegylated interferon plus ribavirin compared with non-pegylated interferon plus ribavirin (RR 0.83, 95% CI 0.76 to 0.91).

Response to therapy varied according to viral genotype. Patients with genotype 1 had the lowest levels of sustained virological response (42% and 46% for pegylated interferon plus ribavirin in the two trials) and patients with genotype 2 or 3 had the highest levels of sustained virological response (82% and 76% for pegylated interferon plus ribavirin in the two trials).

There were also variations in sustained virological response according to other prognostic variables such as baseline viral load.

Monotherapy

In the four trials that evaluated pegylated interferon monotherapy against non-pegylated interferon the combined sustained virological response rates were 31% (95% CI 27 to 34%) for pegylated interferon and 14% (95% CI 12 to 17%) for non-pegylated interferon.

The RR for remaining infected with hepatitis C was reduced by 20% with the use of pegylated interferon (RR 0.80, 95% CI 0.76 to 0.85).

As reported in three of the trials, response to therapy varied according to viral genotype. Patients with genotype 1 had the lowest levels of sustained virological response (12%, 14% and 31% for treatment with pegylated interferon in the three trials reporting response by genotype). Only one trial differentiated patients with non-1 genotypes and reported higher response rates in patients with genotype 4, 5, or 6 (60%) than in patients with genotype 2 or 3 (49%) when treated with pegylated interferon.

In the two trials that considered prognostic variables, there were also variations in sustained virological response according to other prognostic variables such as baseline viral load.

Regimens involving pegylated interferon appear to be fairly well tolerated. Adverse events were reported, but they did not differ substantially from levels of adverse events in regimens involving non-pegylated interferon.

Economic analysis

A cost-effectiveness model originally developed by the Scottish Health Purchasing Information Centre and used in the previous NICE assessment report of treatment for hepatitis C was updated for the calculation of costs and benefits. The model followed a hypothetical cohort of 1000 individuals with chronic hepatitis C over a 30-year period. Options that were considered included: no treatment (except symptomatically), interferon-α plus ribavirin for 48 weeks, pegylated interferon-α plus ribavirin for 48 weeks, interferon monotherapy for 48 weeks, and pegylated interferon-α monotherapy for 48 weeks. SVRs from the key trials were pooled and entered into the model. The results were presented in terms of costs per quality-adjusted life-years (QALYs) gained.

Dual therapy

The incremental discounted cost per QALY for comparing no active treatment to 48 weeks of dual therapy with pegylated interferon and ribavirin (PEG + RBV) is £6045. When moving from 48 weeks of dual therapy with non-pegylated interferon and ribavirin (IFN + RBV) to 48 weeks of dual therapy with PEG + RBV the figure is £12,123.

Subgroup analyses for dual PEG + RBV therapy demonstrated that the most favourable incremental discounted cost per QALY estimates were for patients infected with genotypes 2 and 3, and with low baseline viral load (£3921) compared with no active treatment.

Patients infected with genotype 1 and high baseline viral load had much higher estimates (£8305, no active treatment compared with dual therapy; £13,701, dual therapy with IFN compared with dual therapy with PEG).

Results of one-way sensitivity analyses showed that the estimates varied according to differences in SVRs, drug costs and discount rates. For example, when SVRs were increased or decreased in line with the highest and lowest limits of the confidence interval around the pooled SVR estimate, the highest discounted incremental cost per QALY was £37,611 (lowest PEG SVR and highest IFN SVR), compared with £7060 (highest PEG SVR and lowest IFN SVR).

In general estimates remained under £30,000 per QALY.

Monotherapy

The incremental discounted cost per QALY when moving from no active treatment to 48 weeks of monotherapy with pegylated interferon was £6484. When moving from 48 weeks of monotherapy with IFN to 48 weeks of monotherapy with PEG the figure was £8404.

As with dual therapy, the lowest incremental cost per QALY was for patients with genotypes 2 and 3 and low baseline viral load, in the range £2641–4194. The highest estimates were for patients with genotype 1 and high baseline viral load, around £30,000.

A separate published meta-analysis of the two pivotal pegylated dual-therapy RCTs (not conducted by the authors of this report) found that excluding the 19% of patients who do not achieve early viral response at 12 weeks only

misses 0.6% of potential responders. On the basis of these data it was recommended that only genotype 1 patients be assessed at week 12, with those not having an early viral response ceasing treatment, and those classed as having an early response completing the full 48 weeks of treatment, unless remaining HCV RNA positive at week 24, in which case they should stop treatment.

The following secondary questions were addressed.

Because treatment of hepatitis C is far from universally successful in eradicating the HCV, many patients remain infected after receiving treatment. Completed trials using pegylated interferon have not yet been reported in these patients, but published data on the efficacy of retreatment with non-pegylated interferon plus ribavirin compared with interferon alone are available. Meta-analysis of 20 of these trials found that SVR in retreatment was greater in patients given dual therapy than for those given monotherapy with interferon alone. The risk of remaining infected was reduced by 11% (RR 0.89, 95% CI 0.84 to 0.95) after 6 months of treatment (16 trials). The risk of remaining infected was reduced by 20% in two trials in which treatment was longer than 24 weeks (RR 0.80, 95% CI 0.66 to 0.96).

Because of the possibility that treating patients with acute hepatitis C infection might prevent chronic infection, treatment of patients with acute infection was briefly considered. Again, complete trials using pegylated interferon were not available. Trials in acute groups were of poorer methodological quality, but were suggestive that eradication rates much higher than spontaneous eradication are achievable with treatment.

Since many patients with hepatitis C have other co-morbidities such as co-infection with HIV or haemophilia, it was of interest to consider the efficacy of treatments within these patient groups. No fully published reports of trials using pegylated interferon were found. The existing evidence suggests that treatment efficacy in subpopulations with co-morbidities is generally similar to that in patient groups without significant co-morbidities. However, this does not necessarily mean that cost-effectiveness will be comparable, as this is based on estimating future disbenefits that would have occurred in the absence of treatment, which is sensitive to duration of survival, which in turn is influenced by the presence of co-morbidity.

Non-invasive tests have been proposed as an alternative to biopsy as a means of assessing fibrosis. The best indicators appear to be combinations or panels of tests, preferably those that are routinely available in clinics. They may be most useful at the ends of the spectrum; that is for identifying those with serious liver damage who would be treated, and those with mild disease who currently would not. For patients around the current treat/do not treat margin, the consensus is that liver biopsy is still often necessary, although the balance of risks is different in those with haemophilia.

Evidence on the effectiveness of treating patients with mild disease is awaited. If it can be demonstrated that treatment significantly improves quality of life for these patients then this could be an argument for treating all those with mild disease, without necessarily the need for liver biopsy. A reduction in quality of life has been reported in chronic infection, and if treatment with combined therapy restores quality of life to normal, it may be cost-effective on those grounds alone.

Conclusions

Well-designed RCTs show that patients treated with pegylated interferon, both as dual therapy and as monotherapy, experience higher sustained viral response rates than those treated with non-pegylated interferon. Patients with genotypes 2 and 3 experience the highest response, with rates in excess of 80%. Patients with the harder to treat genotype 1 nevertheless benefit, with up to 46% of patients experiencing an SVR in one of the trials. Pegylated interferon also appears to be relatively cost-effective in both monotherapy and dual therapy, with cost per QALY estimates remaining generally under £30,000. The most favourable estimates were for patients with genotypes 2 and 3.

Recommendations for further research

Pegylated interferon is a relatively new intervention in the treatment of hepatitis C and therefore there are areas where further research is needed. These are listed below:

- There are no trials in which the efficacies of therapy with PEG-α-2a and PEG-α-2b are compared directly.

- There are no full reports of retreatment of previous non-responders using pegylated interferon (either with or without ribavirin).
- There is very little information on the efficacy of treatments for hepatitis C (particularly using PEG) in patients who have other co-morbidities.
- Other treatment regimens that may prove to be overall more effective than dual therapy with PEG should be evaluated.
- More evidence about the long-term outcomes for such patients would be useful. In addition it would be useful to test prospectively which treatment regimens achieve the best improvements in liver histology and which are most cost-effective.
- Prospective tests of rules governing stopping treatment would be useful, particularly with concurrent collection of cost data.
- Further investigation of treating patients with acute hepatitis C may be merited potentially to avoid the long-term morbidity involved for some patients when they reach the stage of chronic infection.
- Problems that may occur in a minority of patients with hepatitis C, such as cryoglobulinaemia and vasculitis, are not likely to be the subject of clinical trials because of the relatively small number of patients affected. However, clinicians point out that in some patients with vasculitis due to viral/antibody complexes the vasculitis can resolve after long-term treatment. Appropriate treatment of such patients needs to be addressed.
- Additional psychological effects on quality of life due to hepatitis C need to be evaluated.
- Further research is needed on the treatment of children and adolescents with hepatitis C. Previous studies of interferon monotherapy in children have been generally small, uncontrolled trials involving highly selected patients. New therapies, including PEG, should be studied in children. The long-term safety of these medications also needs to be studied in children.

Chapter 1

Aim of the review

Pegylated interferon has recently been introduced for the treatment of hepatitis C and has the advantage of a longer-lasting effect with once-weekly dosing compared with three times a week for 'standard' non-pegylated interferon. Higher rates of sustained virological response (SVR) with pegylated interferon have been observed both as monotherapy and in combination with ribavirin, although it is also more expensive.

The aim of this technology assessment report (TAR) is therefore to assess the clinical-effectiveness and cost-effectiveness of pegylated interferon-α in combination with ribavirin in the treatment of chronic hepatitis C. The comparator is the current standard treatment, dual therapy with non-pegylated interferon-α and ribavirin. For patients who cannot tolerate ribavirin the comparison is between monotherapy with pegylated and non-pegylated interferon-α.

Chapter 2
Background

Description of underlying health problem

Chronic hepatitis C is a slowly progressive disease of the liver caused by the hepatitis C virus (HCV). In general, the virus is transmitted parenterally, but the natural history of the disease is not completely understood. It is acquired through injecting drug use and through sharing of needles. The virus was spread through the use of contaminated blood products before the introduction of a heat-inactivation step in 1986, and before the introduction of blood screening in 1991.[1,2] HCV was spread through blood transfusions. There is also a small risk associated with tattooing, electrolysis, ear-piercing and acupuncture. Sexual infection and transmission from mother to child can also occur. Concomitant HIV infection is thought to increase the risk of transmission. The risk of transmission from an infected patient by needle-stick injury to a healthcare worker is about 1 in 30 (1 in 3 for hepatitis B and 1 in 300 for HIV).

After exposure, patients are often asymptomatic, but about 20% will develop an acute hepatitis, some of whom will experience malaise, weakness and anorexia. Up to 85% of those exposed fail to clear the virus and go on to develop chronic hepatitis,[3] although it has been suggested that this may be an overestimate (see Appendix 1 for a review of natural history studies). This is attributed to its genetic diversity, which prevents the immune system mounting an effective response. Chronic disease can be distinguished by mild necroinflammatory activity in the liver, with no or minimal fibrosis, or more severe disease with fibrosis, and in patients with very advanced disease cirrhosis, liver failure and hepatocellular carcinoma (HCC).

The rate of progression of the disease is slow and variable, over 20–50 years. About 20–30% of those initially infected develop cirrhosis within 20 years[4] and 1–4% of these are at high risk of HCC.[5] One-third may never progress to cirrhosis or will not progress for at least 50 years.[4] Patients often do not become symptomatic until liver disease is advanced. Some patients with end-stage liver disease or HCC may require liver transplantation.

Seef[6] reviewed the risk factors associated with disease progression. There is some evidence to suggest a lower rate of progression among women, and also a lower progression to cirrhosis among African–Americans in comparison to Caucasians. Co-infection with HIV is also associated with more rapid progression of hepatitis C. Genotype, however, is not thought to be associated with progression. Obesity also appears to increase the risk of progression.[7]

External factors associated with progression include excessive alcohol consumption, and it is suspected that smoking may play a role, although there is little evidence to confirm this yet. A likely confounder is the fact that many people who smoke also consume alcohol, sometimes excessively, making it difficult to assess the independent effect of tobacco. Data also suggest that the younger the age at infection, the slower the rate of progression. Infection at a 'younger' age (i.e. <40 years) progresses so that 20 years after acute infection cirrhosis will have developed in 2–8% of individuals. In contrast, 20% of patients infected at an 'older' age (i.e. >40 years) will be cirrhotic within 20 years. Poynard and colleagues[8] found that fibrosis progression was greatest after the age of 50 years, and is related to age at infection. For example, major acceleration could occur 10 years after infection at the age of 50, or 40 years after infection at the age of 10 years. This underscores the importance of treating patients with antiviral therapy as early as possible.

Incidence and prevalence

It is believed that 100–170 million people worldwide are infected with hepatitis C. In a population survey conducted in the USA the prevalence was much higher, at 1.8% (approximately 4 million people),[9] and the Centers for Disease Control estimated that the disease causes 8000–10,000 deaths each year in the USA.[5]

The prevalence in the UK is uncertain, but estimated to be between 0.1 and 1%. In Scotland prevalence is estimated to be 0.6%, the majority of whom are injecting drug users (IDUs). Between

1992 and 1996 a total of 5232 reports of HCV infection was received from laboratories in England and Wales.[10] The majority, 38%, were in the 25–34-year age group, with 27% in the 35–44-year age group, and males were more than twice as likely to be infected than females. Data from the Trent HCV Study Group show that the total number of anti-HCV-positive patients recorded in the region (assumed total population of 5.12 million) between 1991 and 1998 was 2546, representing a population-based prevalence of 0.05%.[11] These figures should be treated with caution, since they come from population-based reporting of positive tests, and there will be other patients who are asymptomatic and who have not been tested. Public Health Laboratory Service (PHLS) data show that prevalence in specific groups is higher: 0.2% (Northern and Yorkshire) to 0.4% (London) in antenatal clinic attenders, and 1.07% in genitourinary medicine (GUM) clinic attenders, but with a higher rate in London (2.75%) than elsewhere (<1%), which can be explained by the prevalence of drug use. The prevalence was 37% among IDUs and 0.07% after excluding them. Prevalence is estimated as 0.06% in new blood donors, 0.2–0.4% in antenatal clinic attenders (varying among regions), 0.72% in organ donors[12] and among IDUs it is reported to be 60–85%. The number of notifications to the Communicable Disease Surveillance Centre (CDSC) rose from a few hundred a year in the early 1990s to over 5000 a year in 2002. However, the number of new cases detected through the testing of residual samples in microbiological laboratories has varied from 1.07% in 1986 to 0.55% in 1991 and 0.70% in 1996, suggesting that there may have been a peak of infection before the mid-1980s. Viral inactivation of blood products such as clotting factors started in 1985, but drug abuse may be the most likely cause, with a mid-1980s peak of hepatitis B infection among IDUs, which may be a marker for hepatitis C spread as well.

There are up to 11 different genotypes of HCV, the prevalence of which varies geographically. Genotype 1a is common in North and South America, and Australia, while 1b is mostly found in Europe and Asia. Genotype 2a is common in Japan and China, 2b is prevalent in the USA and northern Europe, 3a is most common in Australia and South Asia, while 4 is commonly found in Egypt and central Africa. In England and Wales the most prevalent genotypes are 3a (37%), 1a (32%) and 1b (15%).[13] In general, genotypes 1a, 1b and 4 respond less favourably to interferon treatment in comparison to other genotypes.

There are variations by the source of infection, with type 1 being more common (60%) in haemophiliacs than type 3, which is the most common type in IDUs (47% type 1 and 43% type 3). This means that those infected with blood products may respond less well to treatment than those who acquired the virus through drug abuse.

Treatment is regarded as successful if blood tests indicating inflammatory liver damage [alanine aminotransferase (ALT)] return to normal and if the HCV disappears from the blood. A complete response is defined as acceptable ALT levels and no detectable HCV RNA at the end of treatment, and a sustained response constitutes maintenance of these levels for at least 6 months after the treatment has stopped. Early studies used ALT levels and liver histology as outcome measures; later trials added disappearance of the virus, once it could be measured. It is assumed that such measurements indicate response to treatment and if patients respond this will prevent progression of liver disease and development of cirrhosis, portal hypertension, liver failure and possible HCC.[14] Those patients with long-term remission and loss of the virus are thought to be unlikely to develop cirrhosis or liver cancer.[15] It is recognised that the outcomes used are surrogate markers, but it is still unclear whether a sustained response improves the long-term prognosis for these patients or whether this represents a cure. A recent cohort of 80 patients who had sustained a response to interferon-α have been followed for up to 6 years. Response to treatment was maintained and liver histology improved in more than 90% of patients.[16]

Health-related quality of life in hepatitis C patients

As many patients do not display symptoms, the burden of ill-health for patients with chronic hepatitis C is not thought to be great. However, non-specific symptoms including fatigue, irritability, depression, nausea, headache, muscle ache, anorexia, abdominal discomfort and right upper quadrant pain have been reported.[17–19] There is also some preliminary evidence to suggest cognitive impairment in patients with mild disease, a so-called 'brain fog'.[20,21]

The general perception that chronic HCV infection is an asymptomatic disease having a marginal impact on a patient's health-related quality of life (HRQoL) has been challenged by a number of studies in recent years. Studies

evaluating the HRQoL in HCV patients have relied on the 36-item Short Form health survey (SF-36). Derived from the Medical Outcomes Survey, the survey instrument comprises eight subscales, which evaluate the degree of impairment from a patient's ideal state of health.[22] The SF-36 is generally supplemented with several disease-specific scales to characterise particular problems experienced by patients (e.g. health distress and limitations caused by HCV infection).[17]

Reductions in HRQoL for HCV patients are suggested to be clinically and socially relevant.[23] A study that examined the HRQoL of patients with chronic hepatitis C found that these patients scored significantly lower on all subscales of the SF-36 in comparison to population norms. The disease that was analogous to the HRQoL of the HCV group was type 2 diabetes, although chronic HCV patients scored significantly lower than diabetes patients on the vitality, social functioning and bodily pain SF-36 subscales.[24] These results have been confirmed in two recent studies where chronic HCV patients again scored significantly lower on all SF-36 subscales than both a UK healthy control population and healthy controls in the USA.[23] Furthermore, significant reductions in HRQoL have been shown to occur in patients with mild HCV[20] and for chronic HCV patients who do not have cirrhosis or a history of injecting drug use.[25]

The causes of impaired HRQoL and the aetiology of extrahepatic symptoms in patients with HCV are poorly understood.[21] Patients with psychiatric disorders are reported to have a higher prevalence of hepatitis C, and psychiatric symptoms and emotional distress appear to be more common among hepatitis C patients than in the general population.[26] In a recent study of 220 patients not selected for antiviral therapy which aimed to determine the prevalence, type and severity of psychological symptoms, clinically significant emotional distress was detected in 35% of the study population. (NB. A history of alcoholism and intravenous drug use was not associated with emotional distress.)[26] This figure is much larger than that found in population controls (10%) and compares to that seen in asymptomatic people with HIV infection and rheumatoid arthritis. Significantly elevated scores for depression, anxiety, somatisation, psychoticism and obsessive–compulsive disorders were found in 28–40% of patients. Psychiatric and medical co-morbidities (defined as active problems requiring treatment and/or monitoring) were identified in 71% of patients. There was also a significant correlation between elevated emotional distress (Global Severity Index scores) and lower HRQoL (SF-36) scores. It was also found that patients who expected not to survive because of their illness had the highest psychiatric distress scores. This study therefore underscores the significant relationship between hepatitis C, HRQoL and poor mental health, and the need for further investigation into the mechanisms between them.

Clinicians point out that patients' awareness that they carry a transmissible disease and the perceived risk of passing the disease to others can also significantly affect their quality of life. Although this psychological effect has not been specifically quantified, it may help to motivate patients to seek treatment.

Successful eradication of hepatitis C has been demonstrated to improve HRQoL. Patients who respond to interferon-α monotherapy (biological and virological sustained responders) have significantly greater improvement in HRQoL than patients who do not respond to treatment[23,27,28] (although it is suggested that HRQoL scores of sustained responders remain slightly lower than population controls[26]). Improvements are primarily related to the SF-36 subscales of perception of general health, vitality and social functioning, and to disease-specific scales concerning feelings of health distress and limitations caused by HCV infection.[23,28] Treatment with interferon monotherapy causes an overall decrease in HRQoL scores from baseline during therapy, returning to pretreatment levels at the cessation of therapy.[28,29] Although the HRQoL of patients while receiving dual therapy with interferon and ribavirin decreased slightly more than monotherapy patients during treatment, patients receiving dual therapy exhibited greater improvements in vitality, social functioning, health distress and general health than monotherapy patients at the end of treatment.[29] This raises the question of whether pegylated interferon is likely to result in greater HRQoL benefits at the end of treatment in comparison to non-pegylated interferon.

Increases in HRQoL due to successful treatment have been suggested to equate to meaningful improvements in the performance of daily activities and lower rates of tiredness and concern regarding hepatitis infection.[28] This may be predictive of a reduced demand for healthcare services and an increase in productivity in the workplace for these individuals.[29] Hence, although

the usual purpose of treatment is to prevent progression to more serious liver disease, in some patients it is worthwhile in terms of symptom relief and quality of life alone. This raises another issue, the extent to which patients with mild chronic hepatitis C experience better HRQoL as the result of antiviral therapy. If this can be demonstrated it would provide a stronger argument for treating all patients with mild disease. This issue is being investigated by the UK HTA programme-funded randomised controlled trial (RCT) of antiviral therapy (IFN + RBV versus IFN) in patients with mild hepatitis C (see section 'Treatment of patients with mild hepatitis C', p. 42). The trial is using the SF-36 instrument (including a validated hepatitis C disease-specific module) to measure changes in HRQoL before, during and after treatment. Patients will also complete a socioeconomic questionnaire before and after treatment.

Current service provision

Until several years ago, patients with moderate to severe chronic hepatitis C were treated with interferon-α (Intron A®, Schering-Plough; Roferon A®, Roche) via subcutaneous injection around three times a week, but only around 17% of patients achieved a sustained virological response.[30] Dual therapy consisting of interferon-α 2 with the oral antiviral drug ribavirin (Rebetol®, Schering-Plough; Virazole®, ICN) led to response rates of 41% in patients not previously treated with interferon[31] and 49% in those who had relapsed following previous interferon treatment,[32] and gained a licence in 1999.

On the basis of these landmark trials dual therapy replaced monotherapy as the treatment of choice in patients with hepatitis C. However, Foster and Chapman,[33] writing in the *British Medical Journal* just before the publication of guidance from the National Institute for Clinical Excellence (NICE) on this issue noted that, on the basis of a postal survey of 447 clinicians of whom 80 (18%) replied, adequate funding for dual therapy was only available in a minority of health districts, suggesting 'postcode prescribing'. For example, only around one-third of respondents indicated that their health authority had a budget for dual therapy.

In October 2000 NICE issued guidance on treatment for chronic hepatitis C, based on an assessment report,[34] recommending dual therapy with interferon-α and ribavirin for the treatment of moderate to severe hepatitis C [defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation], at standard doses for patients over the age of 18 years.[35] For patients not previously treated with interferon ('treatment-naive' patients) and those who have relapsed following previous therapy, 6 months of treatment was recommended. A further 6 months of therapy was recommended only for patients infected with genotype 1 who have had an initial response by 6 months.

Clinical guidelines for the management of hepatitis C have also been published by the Royal College of Physicians of London and the British Society of Gastroenterology (BSG).[36] These were published in 2001 and include evidence-based information on the background of the disease, diagnosis and treatment. At the time of publication, little information was available on the efficacy of pegylated interferon (PEG). Since then guidelines have been updated to include PEG, with the recommendation that it be the first choice of treatment for patients with chronic hepatitis C who fulfil treatment criteria as defined by previous NICE guidance and previous BSG guidelines.[37]

These clinical guidelines are consistent with the existing NICE guidance on treatment for hepatitis C. Using the evidence available, both sets of recommendations suggest that interferon (IFN) and ribavirin (RBV) dual therapy is the treatment of choice for patients who had not previously been treated or for those who had been treated with IFN monotherapy and relapsed. The recommendations differ slightly in the durations of treatment recommended for patients with genotype 1 infection. The NICE guidance recommends that these patients should be treated for 6 months and for an additional 6 months only in those who become clear of HCV RNA within the first 6 months. The Royal College guidelines recommend 6 months of treatment for patients with genotype 1 and low levels of infection (<2 million copies ml^{-1}) and 12 months of treatment in patients with genotype 1 and high levels of infection (>2 million copies ml^{-1}) or cases in which HCV quantitation is not available.

The Royal College guidelines recommend liver biopsy for patients found to be viraemic, whether or not liver function tests (LFTs) are abnormal. Liver biopsy is valuable for assessing the status of liver inflammation, potential progression of fibrosis and the presence or absence of cirrhosis. Biopsy is recommended for these assessments and to assess suitability for treatment.

The guidelines also acknowledge that there is disagreement about the treatment of patients with mild disease. On the basis of relatively low-quality evidence they conclude that treatment can reasonably be withheld in patients with mild disease, but they should be followed to determine whether there is progressive liver disease by the use of repeated biopsy after every 2–3 years, or whether there is a significant change in LFTs, that is two to three times normal levels.

Description of new intervention

Pegylated interferon for previously untreated patients

Since the NICE guidance was issued pegylated interferon has been licensed and has received increasing attention.[38] 'Pegylation' involves the addition of polyethylene glycol molecules to the interferon-α active molecule via either linear or branched chains. It is a method for ensuring delayed renal clearance of the drug, thus prolonging action, necessitating fewer doses and resulting in greater efficacy. Pegylated interferon can therefore be given (by subcutaneous injection) once a week rather than three times a week as for interferon-α, thus being more convenient for the patient and potentially lessening the likelihood of non-compliance. Products have been developed by Roche (40 kDa pegylated interferon-2a, Pegasus®) and by Schering-Plough (12 kDa pegylated interferon-2b, ViraferonPeg®/PegIntron®). Although they are in the same class of drug there are differences between them, such as the size and structure of their polyethylene glycol molecule, and the bond between the PEG molecule and the interferon.

The indication is for the treatment of adult patients (both those who are interferon naive and those who have relapsed following previous treatment) with histologically proven chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV RNA or anti-HCV. Pegylated interferon can be combined with ribavirin or as monotherapy if ribavirin is contraindicated.[39] PEG 2a is indicated for use with Copegus® (Roche's proprietary brand of ribavirin) and PEG 2b is indicated for use with Rebetol (Schering-Plough's brand of ribavirin). A licence variation was submitted to the European Agency for the Evaluation of Medicinal Products (EMEA) during 2003 to remove the phrase "histologically proven" from the indication for PEG 2a for patients with genotypes 2 and 3. This was based on data from an as yet unpublished trial demonstrating the efficacy of dual therapy in patients treated for 24 weeks in comparison to 48 weeks [see section 'Assessment of effectiveness in untreated patients: dual therapy (PEG + RBV)', p. 15]. Thus, the licence for PEG 2a is in the process of being revised.

Dose-ranging studies have established 180 μg weekly as the optimum dose for pegylated interferon-2a[40] and 1.5 μg kg^{-1} per week as the recommended dose for pegylated interferon-2b. It has been shown that adjusting the dose of 2b according to body weight optimises SVR rates.[41]

Attention has turned to the combination of pegylated interferon and ribavirin as a potential replacement for dual therapy with interferon-α and ribavirin. However, pegylated interferon is more expensive. There may be some offsetting savings both in the shorter term (from the reduced frequency of injections) and in the longer term.

Although dual therapy with non-pegylated interferon is the current treatment of choice, anecdotal evidence suggests that pegylated interferon is routinely used in some areas. In 2002, the Scottish Medicines Consortium advised that pegylated interferon-α (2a and 2b) was an appropriate treatment for adults with chronic hepatitis C.[42]

In 2000 the US National Institutes of Health (NIH) recommended pegylated interferon for the initial treatment of previously untreated patients with chronic hepatitis C.[43] In 2002 an NIH consensus conference recommended that genotype 1 patients be treated with pegylated interferon (2b) dual therapy for 48 weeks, and patients with genotypes 2 and 3 be treated for only 24 weeks, but with a lower dose of ribavirin (800 mg per day).[44] It is also recommended that assessment of viral response should be routine in patients with genotype 1, and those who do not achieve a viral response after 12 weeks should discontinue treatment.

Retreatment of non-responders to interferon-alpha monotherapy

Another important issue is the clinical-effectiveness and cost-effectiveness of retreating patients who fail to respond (i.e. do not become HCV RNA negative) to interferon monotherapy, the one-time standard treatment. It is not clear how many patients in England and Wales fit into this category, although Cammà and colleagues[45] suggest that worldwide "a large cohort of IFN

monotherapy non-responders still exists within the of subjects with chronic hepatitis C" (p. 864). A Cochrane systematic review of retreatment with another course of IFN monotherapy found that only around 17% patients achieved an SVR, with 48 weeks of treatment being more effective than 24 weeks.[46] Given that dual therapy with interferon and ribavirin has succeeded interferon monotherapy as the standard treatment in recent years, it seems unlikely that many patients would now be given monotherapy unless they were intolerant to ribavirin. However, there is no guidance from NICE for such patients. With the introduction of pegylated interferon it is also likely that these patients may be retreated with dual therapy with PEG instead of dual therapy with IFN. However, it is unlikely that at this stage there will be much evidence relating to retreatment using PEG dual therapy.

One of the aims of this review is therefore to assess the clinical effectiveness and cost-effectiveness of retreating patients who have failed to respond to a previous course of IFN monotherapy. Retreatment strategies include dual therapy with pegylated interferon and ribavirin (where evidence is available), and retreatment with non-pegylated interferon and ribavirin.

Mild chronic hepatitis C and the need for biopsy

Standard practice at present is to perform liver biopsy before starting treatment, to assess severity of disease. The consensus is that patients with only mild liver disease should not be treated. Verbaan and colleagues,[47] in their RCT of antiviral therapy, define mild disease in terms of a Knodell activity score of between 1 and 6 inclusive, with additional conditions as follows: periportal piecemeal necrosis with or without bridging, necrosis interlobular degeneration and focal necrosis and portal inflammation. Only patients with a fibrosis stage of 1 or lower could be included.

There are, however, several scenarios in which liver biopsy would not be required. The first would be if blood tests such as hyaluronic acid (HA) were a sufficiently good correlate of histology. There is some evidence to suggest that this may be the case. Serum HA was compared with conventional LFT including alanine aminotransferase (ALT), α-glutathione-S-transferase (GST) and serum HCV RNA in a study of 130 patients with chronic hepatitis C to determine which identified the stage of liver fibrosis most accurately as assessed by liver biopsy.[48] Serum HA had a higher sensitivity and specificity than ALT and GST, suggesting it as a useful marker of liver fibrosis. However, the use of such tests assumes that treatment is dependent on the severity of liver changes, and there would be less justification for biopsy in patients in whom treatment was being considered because of systemic symptoms: the biopsy need not be done if a decision was made to treat the symptoms. The clinical effectiveness and cost-effectiveness of non-invasive tests compared with liver biopsy will be examined, where evidence is available.

The second scenario would be if it were demonstrated that treating patients with mild disease was cost-effective. As mentioned earlier, an HTA-funded RCT of dual therapy (interferon-α and ribavirin) in patients has been conducted and is due to report in 2005 (see section 'Treatment of patients with mild hepatitis C', p. 42). If this trial showed that it was of benefit in those patients (either in terms of preventing long-term complications or in improving immediate quality of life), the need for biopsy would again be reduced.

There are occasional deaths after biopsy, but an audit in England and Wales found a death rate of between 0.13 and 0.33%.[49] The complication rate, as indicated by bleeding after biopsy, was lower (by about two-thirds) in those whose biopsies were done by more experienced operators, and this was more common in gastroenterological patients than in general medical ones. Patients with hepatitis C are more likely to be cared for in specialist centres and to have a complication rate lower than the average in the audit. There has, however, been uncertainty about treating patients with mild disease because of a lack of knowledge on the natural history in this patient group, and hence precisely what is being prevented with treatment. Expert opinion suggests that some clinicians may be reluctant to treat those with minimal symptoms owing to uncertainty regarding whether they derive substantial benefit. However, it may be cost-effective to treat this group, even if only a proportion go on to develop more aggressive disease, because others may have symptoms due to hepatic or extrahepatic disease that would improve after treatment.

The third scenario is the treatment of patients with genotypes 2 and 3 regardless of histology. SVR rates for these patients treated with pegylated interferon dual therapy reached between 76 and 82%[41,50] [see section 'Assessment of effectiveness in untreated patients: dual therapy (PEG + RBV)',

p. 15]. Consequently, support for treating these patients without biopsy is gaining ground among clinicians. Furthermore, French guidelines also suggest that these patients do not need a biopsy.

The fourth scenario would be if it were shown that treatment was indicated early after infection, in which case patients would be treated before the severity of future liver disease could be known. A recent study of 24 weeks of treatment with interferon-α monotherapy in 44 patients known or suspected to have been exposed to HCV in the previous 4 months showed encouraging results[51] (see section 'Treatments of acute hepatitis C', p. 45).

Chapter 3

Effectiveness

Methods for reviewing effectiveness

Inclusion criteria

The following inclusion criteria, as specified in the study protocol, were set (see Appendix 3 for the inclusion worksheet used).

Interventions:
- Dual therapy (pegylated interferon-α and ribavirin) versus dual therapy (interferon-α and ribavirin).
- Monotherapy (pegylated interferon-α) versus monotherapy (interferon-α).

Patients:
- For the primary research question on the effectiveness of pegylated interferon treatment the patient group was those with moderate to severe chronic hepatitis C infection not previously treated with interferon-α.
- The protocol for the review also mentions the possible extension of the scope to include patients with chronic mild disease. However, results of a key trial of antiviral therapy in mild disease will not be available until 2005. Consequently, the focus is primarily on patients with more advanced disease. However, a brief summary of the current evidence in this area is provided later in this chapter ('Treatment of patients with mild hepatitis C', p. 42).
- For the secondary research question on retreatment, the patients of interest were those who had previously failed interferon-α monotherapy (i.e. failed to achieve an SVR) and were being retreated with dual therapy (interferon-α and ribavirin).
- Patients with acute hepatitis C were not included in the current report; however, a brief summary of evidence for the effectiveness of antiviral treatment in this area is provided in the final section of this chapter.

Outcome measures (for clinical-effectiveness studies):
- Sustained viral response as shown by absence of viral RNA for 6 months or longer after the end of treatment.
- Adverse effects of treatment.

Study types:
- Clinical effectiveness of treatment: systematic reviews (including meta-analyses) of RCTs and Phase III RCTs.
- Cost-effectiveness: cost-effectiveness/cost–utility studies and quality of life studies.

Publication status:
- Fully published peer-reviewed reports and articles were used for primary analysis.
- Unpublished material (including conference abstracts) was used primarily for background information and context. Where relevant, studies reported in conference abstract form are summarised in the current report, but their results are not used in economic modelling (although they potentially could be used in sensitivity analysis), or to support conclusions or recommendations. Caveats are included to urge caution in the interpretation of such material. See Appendix 4 for a table of conference abstracts of pegylated interferon treatment.

Language:
- Only English language articles were included.

Literature searching

A sensitive search strategy was developed, tested and refined by an information scientist to capture the range of relevant study types (see Appendix 2 for search strategy). The strategy was applied to the following electronic bibliographic databases:

- MEDLINE (Silverplatter)
- Pre-MEDLINE (PubMed)
- EMBASE (Silverplatter)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Controlled Trials Register (CCTR)
- BIOSIS
- Web of Science Proceedings
- Science Citation Index (SCI)
- Database of Abstracts of Reviews (DARE)
- NHS Centre for Reviews and Dissemination (CRD) HTA database (University of York)
- NHS Economic Evaluation Database (NHS EED)
- National Research Register (NRR).

Searches were run for the period 2000 to August/September 2002. The period before 2000 was covered by the previous assessment report.[34] In March 2003 searches were repeated to identify any studies published since September 2002. Searching for studies of retreatment to interferon monotherapy followed a slightly different method and full details are provided later in this chapter ('Evidence from related systematic reviews', p, 31).

Contact was made with experts in the field to identify relevant trials, and Internet sites listing details of current controlled trials and those dealing with hepatitis and liver disease were also searched. The submissions to NICE from the drug companies were also used as a method of identifying relevant studies.

References to studies identified through literature searching were downloaded into Reference Manager software (version 10). Inclusion criteria were applied to titles and abstracts and, where necessary, full reports were retrieved for further inspection. A keywording classification system for the database was devised, tested and refined. The purpose was to facilitate efficient retrieval from the database of relevant studies. A keyword was applied to each record in the database to indicate whether it was to be included or excluded. Further keywords were applied to included studies to indicate study type (e.g. clinical effectiveness, cost-effectiveness, epidemiology). Clinical-effectiveness studies were further classified according to the nature of the intervention (e.g. PEG dual therapy), the study type (e.g. RCT) and whether or not any additional relevant information was provided (e.g. an integral cost-effectiveness analysis).

Data extraction and critical appraisal

Included clinical-effectiveness studies of pegylated interferon treatment underwent detailed data extraction to a standardised template. Studies were also critically appraised using criteria devised by the NHS CRD (see Appendix 5). Extraction and appraisal were performed by one reviewer and checked by a second, with disagreements resolved through discussion.

Methods of analysis and synthesis

Both qualitative and quantitative approaches were used to synthesise the results of the RCTs. Data extraction tables were used to compile a narrative summary of the main characteristics and results of the trials. In addition, a meta-analysis was performed with Cochrane Review Manager Software (version 4.1) using a random effects model. Confidence Interval Analysis software (version 0.2, © Gardner, 1989) was used to compute confidence intervals where not provided by the study authors.

Results: clinical-effectiveness of antiviral therapy

Quantity and quality of research available

Initial literature searching generated a total of 637 hits (i.e. references to studies). As the review progressed 198 references were added to the database, most of which had been identified through searching reference lists of papers already retrieved. At the end of March 2003 the original literature search was repeated to identify studies published since the original search. A further 159 references were added to the database, bringing the grand total of articles identified to 996.

Six fully published RCTs of the effectiveness of pegylated interferon treatment met the inclusion criteria for this review. (See the section 'Results: retreatment of non-responders to interferon monotherapy', p. 34, for full details of the number of retreatment studies identified.)

Design

The number of participants in the six RCTs varied considerably in size, ranging from 159 to 1530. Five were parallel group designs, while the sixth[40] randomised three separate cohorts either to IFN or to successively higher doses of PEG. This design was used to examine the safety of each PEG dose before using higher doses.

Two trials evaluated the effectiveness of dual therapy (PEG + RBV[41,50] *Table 1*). One of these trials used PEG-α-2b and IFN-α-2b,[41] whereas the other used PEG-α-2a and IFN-α-2b.[50] The trial by Manns, and colleagues[41] used a design in which the manipulation of the dosing of PEG-α-2b and RBV was confounded. The two arms combining PEG and RBV were compared with an arm combining IFN and RBV. The trial by Fried and colleagues[50] compared the same dose of PEG-α-2a with and without RBV against IFN plus RBV.

Four trials tested monotherapy with PEG against monotherapy using IFN (*Table 2*). One of these trials tested PEG-α-2b against IFN-α-2b (Lindsay and colleagues),[52] whereas the three others tested PEG-α-2a against IFN-α-2a. One of these (Reddy and colleagues[40] tested small groups of participants on four different doses of PEG-α-2a versus IFN-α-2a. This was a Phase II dose-finding

TABLE 1 *Characteristics of included RCTs of combination therapy*

Author	Study ID/ (sponsor)	No. of participants	Arm 1	Arm 2	Arm 3
Manns *et al.*, 2002[41]	C/98-580 (Schering-Plough)	1530	PEG IFN-α-2b, 1.5 μg kg^{-1} per week + RBV 800 mg per day (n = 511)	PEG IFN-α-2b, 1.5 μg kg^{-1} per week for 4 weeks, then 0.5 μg kg^{-1} per week for 44 weeks + RBV 1000–1200 mg per day (n = 514)	IFN-α-2b, 3 MIU three times per week + RBV 1000–1200 mg per day (n = 505)
Fried *et al.*, 2002[50]	NV15801 (Hoffman-La Roche)	1121	PEG IFN-α-2a, 180 μg per week + RBV 1000–1200 mg per day (n = 453)	PEG IFN-α-2a, 180 μg per week + placebo (n = 224)	IFN-α-2b, 3 MIU three times per week + RBV 1000–1200 mg per day (n = 444)

MIU, million international units.

study which led to the Phase III trial by Zeuzem and colleagues[53] which tested one dose of PEG-α-2a against IFN-α-2a. This was accompanied by another Phase II/III trial testing two doses of PEG-α-2a against IFN-α-2a specifically in cirrhotic patients (Heathcote and colleagues)[54].

The two trials that tested PEG-α-2b both applied doses of PEG and the comparator IFN according to body weight. The four trials that used PEG administered fixed doses of PEG and IFN.

Both of the dual-therapy trials included arms in which the dose of RBV was administered according to body weight with patients who weighed ≤ 75 kg receiving 1000 mg per day and those weighing > 75 kg receiving 1200 mg per day. The Manns trial[41] included one arm in which the RBV dose combined with PEG-α-2b was fixed at 800 mg per day and one arm in which the RBV dose was administered according to weight as above.

All six trials administered the study interventions for 48 weeks with a follow-up interval of 24 weeks (final evaluation at 72 weeks from inception). There was general uniformity in the choice of outcome measures across the trials. The primary outcome in every trial was SVR at follow-up (72 weeks). In all trials the SVR was defined as undetectable levels of HCV RNA at follow-up. In four trials plasma HCV RNA levels were evaluated using the Cobas Amplicor HCV test (version 2.0) with a lower limit of detection of 100 copies ml^{-1}. In one trial[52] a different polymerase chain reaction (PCR) assay (National Genetics Institute) with the same lower detection limit was used. In the remaining trial[40] an earlier version of the HCV RNA test was used with a detection limit of 2000 copies ml^{-1}, but samples at follow-up that had undetectable levels of HCV RNA were retested with the more sensitive test. All trials also reported virological response at end of treatment (48 weeks). Some trials reported virological responses at earlier time-points (e.g. after 12 weeks of treatment, see the following subsections on Assessment of effectiveness in untreated patients, pp. 15 and 22) as well as correlations between baseline characteristics and/or early viral response and SVR.

Other outcomes included biochemical response (ALT levels), histological response (e.g. liver biopsy), and adverse effects and laboratory abnormalities. Each of the trials reporting histological responses used the same system for grading histological response. The Knodell histological activity index (HAI) was used. This index produces scores ranging from 0 to 22, with 18 points for inflammation (0 = none, 18 = severe) and 4 points for fibrosis (0 = none, 4 = cirrhosis). In each case, a histological response was defined as a decrease in HAI score of at least 2 units. In two trials[41,52] changes in inflammation and fibrosis were reported separately, with fibrosis score changes of at least 1 unit defined as improvement or worsening.

Methodological quality

The trials were similar in methodological characteristics (see Appendix 6). In general, trials were of good quality, although reporting of

TABLE 2 *Characteristics of included RCTs of monotherapy*

Author	Study ID (sponsor)	No. of participants	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Heathcote *et al.*, 2000[54]	NV 15495 (Hoffman-La Roche)	271	PEG IFN-α-2a, 90 μg per week (n = 96)	PEG IFN-α-2a, 180 μg per week (n = 87)	IFN-α-2a, 3 MIU three times per week (n = 88)		
Zeuzem *et al.*, 2000[53]	NV 15497 (Hoffman-La Roche)	531	PEG IFN-α-2a, 180 μg per week (n = 267)	IFN-α-2a, 6 MIU three times per week for 12 weeks, then 3 MIU three times per week for 36 weeks (n = 264)			
Lindsay *et al.*, 2001[52]	C/197-010 (Schering-Plough)	1219	PEG IFN-α-2b, 0.5 μg kg^{-1} per week (n = 315)	PEG IFN-α-2b, 1.0 μg kg^{-1} per week (n = 297)	PEG IFN-α-2b, 1.5 μg kg^{-1} per week (n = 304)	IFN-α-2b, 3 MIU three times per week (n = 303)	
Reddy *et al.*, 2001[40]	Hoffman-La Roche	159	PEG IFN-α-2a, 45 μg per week (n = 20)	PEG IFN-α-2a, 90 μg per week (n = 20)	PEG IFN-α-2a, 180 μg per week (n = 45)	PEG IFN-α-2a, 270 μg per week (n = 41)	IFN-α-2a, 3 MIU three times per week (n = 33)

methodological details could have been more thorough. For example, only one trial[54] explicitly reported a randomisation procedure that assured true random assignment and only one trial[41] explicitly reported allocation concealment. In most cases, groups appeared similar at baseline on important demographic and prognostic characteristics, although in some cases supporting statistical comparisons were not provided. In two trials[40,52] there were baseline differences that may have affected results (*Table 3*). Given the different timing of administration of PEG and IFN (once per week versus three times per week, respectively), most of the trials were open label. In one trial that manipulated the addition of RBV or placebo to PEG there was double blinding as to whether participants were receiving RBV or placebo. Pathologists who evaluated liver histology were always blinded as to treatment status and assays were generally said to be conducted at central laboratories although there was often not specific mention of blinding of these assessors. All trials performed an intention-to-treat (ITT) analysis for the primary outcome of SVR. In the Fried trial,[50] the last observed HCV RNA level was used in assessment of efficacy for patients with at least 20 weeks of follow-up. All patients with follow-up of less than 20 weeks were considered to have had no response to treatment. In the Zeuzem trial[53] patients not present at the 72-week assessment were classed as non-responders at that point. For safety analyses, it was generally the case that all patients who had received at least one dose of study medication were included in the analysis.

Relatively high numbers of patients withdrew from trials (approximately 20–30%) because of adverse effects or other reasons (e.g. after failing to achieve a 12- or 24-week response). There was variation in the detailed reporting of numbers of patients withdrawing and losses to follow-up and reasons for losses. Only two trials[41,53] reported conducting a power analysis to determine the optimum sample size necessary.

Participant inclusion/exclusion criteria

The inclusion and exclusion criteria for all six trials were broadly similar. All included adult patients with chronic hepatitis C who had not received previous treatment with IFN. Four[41,50,52,54] of the six required a liver biopsy consistent with chronic hepatitis C (most within the previous year). The same four trials specified that HCV RNA must be detectable in serum. Five[41,50,52–54] specified that serum ALT levels

should be elevated. Most of these required at least two elevated serum ALT readings within 6 months before entry into the trial.

Most trials reported excluding participants who had various co-morbidities. Two trials reported excluding patients with "substantial co-existing conditions"[50] or conditions that would "interfere with participation".[52] Other conditions were specific exclusion criteria. Five trials specifically excluded patients with HIV infection and the sixth[40] excluded patients on immunomodulatory, antiviral or investigational compounds, which would seem effectively to exclude patients with HIV among others. Other causes of liver disease excluded participants in four trials.[40,41,52,54] Patients with decompensated cirrhosis[41,54] or decompensated liver disease[50,53] were also generally excluded. Most trials excluded participants with co-morbidities such as psychiatric disorders,[40,41,50,53,54] seizure disorder,[40,41,53,54] cardiovascular disease,[40,41,53,54] retinopathy[40,53,54] or cancer/neoplastic disease.[40,53,54] Two trials[41,52] excluded patients with haemophilia or haemoglobinopathies. Two trials excluded patients with autoimmune disorders.[41,53]

All trials had certain laboratory readings that were required. All excluded patients with thrombocytopenia, requiring platelet counts ranging from above 75,000 mm^{-3} to above 130,000 $mm.^{-3}$ Five[41,50,52–54] excluded patients with low neutrophil counts, with the minimum required ranging from 1500 to 1800 mm^3. Three[41,50,52] excluded patients with anaemia who had haemoglobin below 12 g dl^{-1} for females and below 13 g/dl^{-1} for males. Three[40,41,52] excluded patients with low white blood call counts ranging from 1500 to 4000 $mm.^3$ Four[41,52–54] excluded patients with abnormal α-fetoprotein (AFP) levels, with exclusion thresholds ranging from above 25 to 100 ng ml^{-1}. Four[40,41,50,53] required serum creatinine within normal limits or excluded patients with levels over 1.5 times the upper limit of normal.

Other exclusion criteria included substance abuse,[40,50,52] pregnancy or breast-feeding,[40,52] or inability or unwillingness to use contraception.[41,53]

Participant characteristics

The trials were broadly similar in their participant samples with two exceptions (*Table 3*). The Heathcote trial[54] specifically recruited patients with biopsy-proven cirrhosis (78%) or bridging fibrosis (21%), whereas the other trials, when reported, specifically excluded patients with bridging fibrosis or cirrhosis, or recruited relatively few patients with bridging fibrosis or cirrhosis (approximately 10–15% of participants). The other important difference among trials was the baseline viral load. In three trials the average baseline viral load was over 6 million copies ml^{-1},[50,53,54] whereas in the remaining three trials the baseline viral load was less than 3.5 million copies ml^{-1}.[40,41,52]

Generalisability to UK populations

The patient samples in the trials seem similar to patients with hepatitis C in England and Wales in some respects. The average age of participants, in their forties, is consistent with a cohort of patients in the Trent region, the bulk of whom were born between 1950 and 1969.[11] This cohort was also found to have a male:female ratio of 2:1, which is similar to that in the trials. The trial participants were predominantly of genotype 1, which may not necessarily be similar to the distribution in the UK. Two reports suggest that genotype 3a may be the most common in England and Wales.[13,55] However, one of these reports[13] offers no data as to the representativeness of the sample from which these genotypes were assessed, and the other[55] used only an antenatal sample. Another report[11] suggested that genotype 1 was most common, but excluded patients with haemophilia, HIV infection or chronic renal failure.

This report found that 47% of hepatitis C patients were infected with genotype 1 and 39% with genotype 3. Regardless of the precise distribution, there is the suggestion that genotype 1 may be less prevalent in the UK population than in the trial samples. This may be important because past therapies have been least effective in patients with genotype 1 infection (see the following subsections on Assessment of effectiveness in untreated patients for response rates of PEG according to genotype).

In summary, the patients included in the trials comprised a generally homogeneous group of previously untreated patients, the majority male, white, in their forties with genotype 1 and without significant co-morbidities.

Assessment of effectiveness in untreated patients: dual therapy (PEG + RBV)

Virological response

Table 4 shows the end of treatment response and (EOTR) SVR rates for the two RCTs. In both trials dual therapy with PEG was significantly more effective, with a pooled EOTR rate of 67% [95%

TABLE 3 *Baseline characteristics of participants in included trials*

Characteristic	Dual therapy		Monotherapy			
	Manns et *al.*, 2001[41]	Fried et *al.*, 2002[50]	Heathcote et *al.*, 2000[54]	Zeuzem et *al.*, 2000[53]	Lindsay et *al.*, 2001[52]	Reddy et *al.*, 2001[40]
Age	43.3	42.5	47.1	40	43	42
% Male	66	71	72	69	63	79
% Genotypes						
1	68	64.9	56.5	62[a]	69.8[a]	73.6
1a	–	32.5	32.5	31	–	–
1b	–	30.8	24	31	–	–
1 other	–	1.6	–	–	–	–
2	29[d]	13.6	12.2	11	10.2	–
3	[d]	18	26.9	25	16.4	–
4	3	3	1.1	2	–	–
Other	–	0.5	3.3	1	3.5[b]	23.9[ac]
Baseline viral load	2.7	6	6.1	7.8	3.35	2.4
Ethnic groups:						
White	–	84.1	88.2	85	91	87
Asian/Oriental	–	5.7	2.6	9	–	1.3
Black	–	4.7	4.1	2	–	9
Other	–	5.4	5.2	3	–	2.5

[a] Because of rounding percentages do not add up to 100%.
[b] All genotypes other than 1–3 (thus may include patients with genotype 4).
[c] All non-1 genotypes (for 2.5% of patients the genotype was missing).
[d] Genotypes 2 and 3.
–, not reported.

TABLE 4 *Virological response rates for 48 weeks of dual therapy*

Study	End of treatment response		End of follow-up response	
	PEG IFN-α + RBV	IFN-α + RBV	PEG IFN-α + RBV	IFN-α + RBV
Manns et *al.*, 2001[41]	65%*	54%	54%	47%
Fried et *al.*, 2002[50]	69%†	52%	56%	44%

* Statistically significant difference between groups ($p < 0.05$).
† Statistically significant difference between groups ($p \leq 0.01$).

confidence internal (CI) 64 to 69%], compared with 53% (95% CI 49 to 56%) for dual therapy with IFN + RBV. The pooled relative risk (RR) was 0.70 (95% CI 0.63 to 0.78) (*Figure 1*).

The pooled SVR rate was 55% (95% CI 52 to 58%) for dual therapy with PEG + RBV, compared with 46% (95% CI 43 to 49%) for dual therapy with IFN + RBV, with a pooled relative risk of 0.83 (95% CI 0.76 to 0.91) (*Figure 2*).

Predictors of virological response: early response

Fried and colleagues[50] reported 12-week data for the dual therapy arm of their trial, with a virological response rate of 86% (95% CI 83 to 89%). More common, however, was reporting of the proportion of patients who had achieved a response at week 12 who subsequently achieved a sustained response. In Fried's trial[50] this proportion was 65%, while in Manns' trial[41] the proportion of those who became HCV RNA negative for first time at 12 weeks and achieved SVR was 75% (with 32% HCV RNA negative for first time at week 24 achieving an SVR). Therefore up to three-quarters of patients who had experienced a virological response after 12 weeks of therapy maintained their response at week 72. In Fried's trial[50] 97% of patients who did not have an early virological response (EVR) to dual therapy with PEG did not achieve an SVR.

The poor long-term outcome for non-responders at 12 weeks has prompted the suggestion that therapy could potentially be stopped at this time

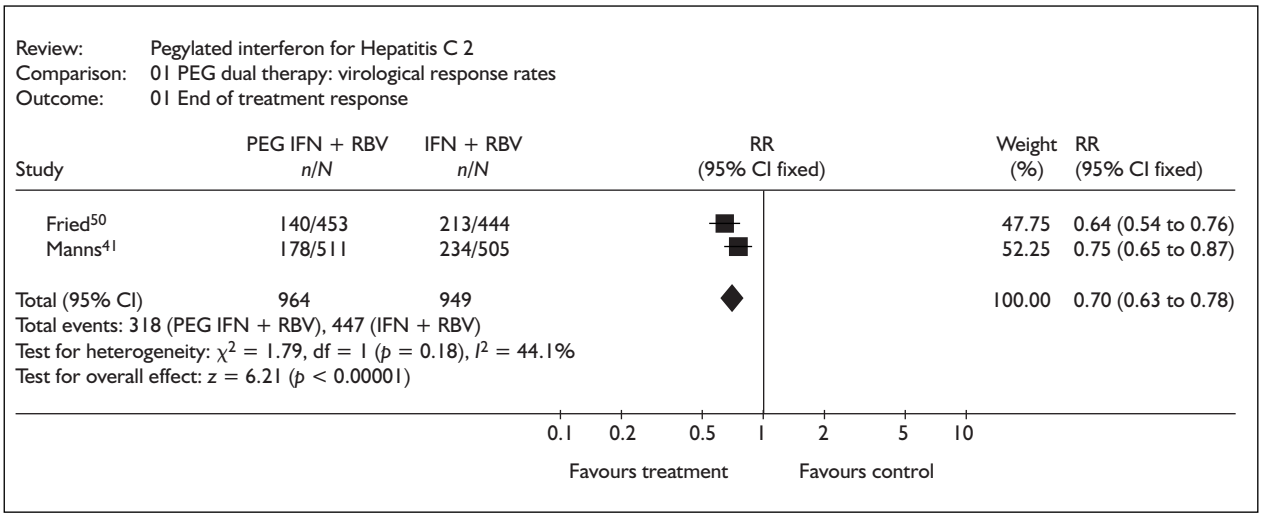

FIGURE 1 *Pooled relative risk (end of dual therapy)*

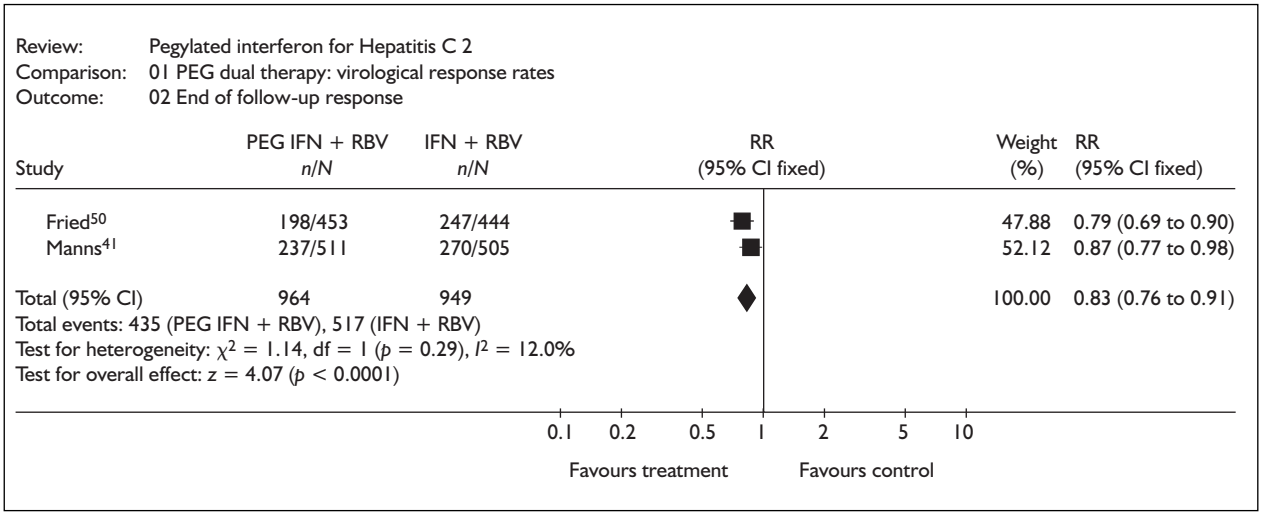

FIGURE 2 *Pooled relative risk (end of follow-up dual therapy)*

for these patients. However, historically there has been no optimal definition of an 'early response' threshold. To this end Davis 2002[56] pooled and analysed unpublished virological response data supplied by the sponsors of the trials by Manns and Fried and colleagues to determine the optimal time for an early response.

- Patients included in the analysis comprised 453 who received pegylated interferon-2a 180 μg combined with 1000–1200 mg of ribavirin, and 512 who were given pegylated interferon-2b 1.5 μg kg^{-1} weekly and 800 mg ribavirin daily. (Note that the analysis did not include patients who received non-pegylated interferon.)
- The definition of early response used was a fall in HCV RNA from baseline at week 12 of therapy (in the range of ≥ 3 to ≥ 1 log_{10} units) or to an undetectable level by qualitative PCR.
- Of the 965 patients analysed 446 were genotype 1 and 277 were genotype 2 or 3.
- Of the 965 patients, 778 (81%) achieved a 12-week viral response (276 of whom were genotype 2 or 3 patients; the remaining 502 comprised mostly genotype 1 patients, although exact figures are not specified – it is likely that some of these were genotype 4 patients).
- In total, 529 patients (55%) achieved an SVR (283 genotype 1, 227 genotype 2 or 3 and 19 other genotype).
- Of the 187 (19%) patients who failed to respond at 12 weeks only three (2%) had an SVR. If a 12-week stopping rule had been initiated only three of the 529 patients who had an SVR

would have had treatment stopped prematurely (thus a negative predictive value of 98.4%).

It was concluded that EVR is best defined as "a fall in HCV RNA by at least 2 $\log_{10}$ units or to an undetectable level by a sensitive PCR after the first 12 weeks of treatment" (p. s150). The following recommendations were made:

- Patients with genotype 1 who achieve EVR at week 12 should complete the full 48 weeks of treatment. Those who do not achieve EVR should discontinue the treatment.
- Patients with genotype 1 who achieve EVR but who are still HCV RNA positive at week 12 should be retested at week 24 using sensitive qualitative PCR. If they are still HCV RNA positive at week 24 then treatment should stop.
- Patients with genotype 2 or 3 should be treated for 24 weeks and need not have a 12-week assessment of EVR (given that all except for one patient with these genotypes achieved an EVR).

What this study adds, therefore, is evidence that nearly all genotype 2 or 3 patients achieve an early viral response. While a large proportion of genotype 1 patients also achieve an early response, the pool of patients not responding is comprised almost entirely of patients with genotype 1, who are very unlikely to respond with continued treatment. Davis[56] suggested that withdrawing the 19% of patients at 12 weeks who have not responded (and who are unlikely to respond) will reduce treatment costs by 16% (although no data are provided to illustrate how this figure was calculated).

Virological response according to prognostic factors

Both trials performed logistic regression analysis to examine the independent effect of a range of prognostic factors on sustained response, with broadly similar results. Factors such as age (≤ 40 years), body weight (≤ 75 kg) and genotype (non-1) were significantly associated with SVR in both trials. Gender, low baseline viral load (≤ 2 million copies ml^{-1}), and absence of bridging fibrosis and cirrhosis were also significantly associated with SVR in Manns and colleagues trial.[41]

Table 5 shows the extent to which SVRs varied according to genotype. Across the genotypes patients treated with PEG + RBV dual therapy had higher response rates than those treated with dual therapy with IFN + RBV. However, there were some key differences between the two trials.

TABLE 5 *Sustained virological response rates by genotype (dual therapy)*

Study	End of follow-up response	
	PEG IFN-α + RBV	**IFN-α + RBV**
Manns *et al.*, 2001[41]		
1	42%**	33%
2 or 3	82%	79%
4, 5 or 6	50%	38%
Fried *et al.*, 2002[50]		
1	46%*	36%
2 or 3	76%**	61%
4	77%	44%
5 or 6	–	–

* $p \leq 0.01$ for comparison between groups.
** $p < 0.05$ for comparison between groups.

Whereas patients with genotypes 2 and 3 did better on PEG dual therapy in the trial by Fried and colleagues[50] there was only a marginal difference for such patients in the trial by Manns and colleagues[41] where SVRs were around 80% for both treatments (although the difference between groups was not statistically significant). This is at odds with the results of trials of non-pegylated dual therapy in previously untreated patients included in the previous assessment report,[34] where only 64% of patients with genotypes 2 and 3 achieved an SVR after 48 weeks of dual therapy.[57] Nevertheless, despite the marginal difference between study groups in the Manns trial,[41] the results of these two trials demonstrate that interferon treatment can result in SVRs in excess of 80%, albeit in one subgroup of one trial. It is likely that the 79% response to IFN and RBV in the Manns study is by chance better than expected. Were it not by chance, there would be a case for not using PEG in genotypes 2 and 3.

Both trials presented SVRs according to baseline viral load, stratified into low or high load (≤ 2 million copies ml^{-1} versus >2 million copies ml^{-1} respectively) (*Table 6*). For the present report, it was assumed that baseline viral loads were determined from tests used to screen patients for inclusion. In the Fried trial the Cobas Amplicor HCV test (version 2.0) with a lower detection limit of 100 copies ml^{-1} was used for inclusion. In the Manns trial the test used was not specified. Patients with detectable HCV RNA in serum by PCR assay were included.

In both trials patients with low baseline viral load had higher SVRs than those with higher load, irrespective of the treatment they received.

TABLE 6 *Sustained virological response rates by baseline viral load; baseline viral load and genotype (dual therapy)*

Study	End of follow-up response	
	PEG IFN-α + RBV	**IFN-α + RBV**
Manns *et al.*, 2001[41]		
Low viral load	78%*	56%
High viral load	42%	42%
Fried *et al.*, 2002[50]		
Low viral load	62%**	52%
Genotype 1	56%	43%
Genotype 2/3	81%	65%
High viral load	53%***	41%
Genotype 1	41%	33%
Genotype 2/3	74%	58%

* $p \leq 0.01$ for comparison between groups.
** $p = 0.04$ for comparison between groups.
*** $p = 0.003$ for comparison between groups.

Patients in the Fried trial[50] with a high baseline viral load were significantly more likely to have an SVR if treated with PEG than with IFN (53% versus 41%, respectively, $p = 0.003$). However, in the Manns trial[41] there was no difference in SVRs for these patients between study groups (42%). Patients infected with genotype 1 in the trial by Fried and colleagues who had a high baseline viral load (i.e. those who are harder to treat successfully) were more likely to have a SVR with PEG treatment than with IFN (41% versus 33%, respectively). Baseline viral load data were not stratified by genotype by Manns and colleagues. It is worth noting that the two trials differed in terms of average baseline viral loads, with a much lower average in Manns (2.7 million copies ml^{-1}) than in Fried (6 million copies ml^{-1}).

Given that it was previously shown that lighter patients treated with IFN-α-2b have higher SVR rates than heavier patients, PEG-α-2b is administered according to patients' body weight. A logistic regression analysis in the Manns study[41] showed that baseline weight was an important predictor of SVR. This may be due to the nature of the study design, in which a fixed dose of RBV (800 mg per day) was administered together with the higher dose of PEG (1.5 $\mu g\ kg^{-1}$), but a variable dose of RBV (1000/1200 mg per day) was administered with the lower dose of PEG (0.5 $mg\ kg^{-1}$ for 44 of the 48 weeks). Logistic regression analyses were used to explore further the relation between SVR and different doses of both PEG and RBV. The two doses of PEG were treated as categorical variables and dose of RBV was treated as a continuous variable expressed in $mg\ kg^{-1}$. The analysis found that doses of both drugs significantly predict SVR [odds ratio (OR) 1.7, $p = 0.002$, for higher dose versus lower dose PEG, and slope 0.07, $p = 0.015$, for RBV]. The likelihood of SVR increases as the dose of RBV increases and when the dose of RBV is controlled on a weight ($mg\ kg^{-1}$) basis, the effect of a higher dose of PEG is greater compared with the lower dose. A regression model that included a term for the product of the two drug doses indicated that the optimal dose of RBV (for both safety and efficacy) was between 11 and 15 $mg\ kg^{-1}$ (for a person weighing 75 kg this would correspond to daily doses of 800–1200 mg). When SVR was considered according to weight-based RBV dose, the SVR was higher in all groups when the dose of RBV was greater than 10.6 $mg\ kg^{-1}$ of body weight (i.e. above 800 mg per day) (*Table 7*). These SVRs are higher than those given in *Tables 4* and *5* for this trial (which represent the primary ITT analysis). For example, the SVR for all PEG-treated patients (irrespective of genotype) is 61%, compared with only 54% in *Table 4*. Furthermore, the SVR for PEG-treated genotype 2 or 3 patients is 88%, compared with only 82% in *Table 5*. These figures are based on what is now the licensed dose of RBV with PEG-α-2b.

TABLE 7 *SVR rates by ribavirin dose adjustments (stratified by genotype)*

Study	End of follow-up response	
	PEG IFN-α + RBV	**IFN-α + RBV**
Manns *et al.*, 2001[41]		
RBV dose $\leq$ 10.6 $mg\ kg^{-1}$ (i.e. $\leq$ 800 mg)	50%	27%
RBV dose > 10.6 $mg\ kg^{-1}$ (i.e. >800 mg)	61%	47%
RBV dose $\leq$ 10.6 $mg\ kg^{-1}$ (i.e. $\leq$ 800 mg) genotype 1	38%	20%
RBV dose > 10.6 $mg\ kg^{-1}$ (i.e. >800 mg) genotype 1	48%	34%
RBV dose $\leq$ 10.6 $mg\ kg^{-1}$ (i.e. $\leq$ 800 mg) genotype 2/3	79%	50%
RBV dose > 10.6 $mg\ kg^{-1}$ (i.e. >800 mg) genotype 2/3	88%	80%

Histological response

Of the two dual-therapy trials, only Manns and colleagues[41] reported histological results. Paired biopsy samples were available in 1034 (68%) of patients randomised. Around two-thirds of patients in each treatment group experienced reduced inflammation (defined as decrease of ≥ 2 units in the Knodell score for inflammation), with a reduction of 3.4 points in each case. A high proportion of patients with SVR experienced a reduction in inflammation, around 90% in each study group. For patients without SVR the proportion was in the range 38–49%, with lower dose PEG-treated patients experiencing the greatest reduction in inflammation. There was a reduction in fibrosis in around 20% of patients, irrespective of the treatment received. Of those patients with an SVR, around 21–26% experienced a reduction in fibrosis, with the greatest reduction in the higher dose PEG group. Percentage reductions were marginally lower in patients without SVR, in the range 14–19%.

Compliance

McHutchison and colleagues 2001[58] retrospectively considered the effects of adherence to therapy in one arm of each of three trials that evaluated IFN + RBV or PEG + RBV. Two of these were trials of IFN-α-2b (n = 1010) (McHutchison and colleagues[59] and Poynard and colleagues[57]) and one trial evaluated PEG-α-2b (n = 511) (Manns and colleagues[41]). The analysis also included patients from the PEG-α-2b monotherapy trial by Lindsay and colleagues[52] (n = 607). The treatment arms selected were those in which the virological response had been greatest. The data were analysed two ways. One approach assigned patients who received combination therapy into subgroups according to their adherence. The other approach incorporated adherence as a covariate in a statistical model.

In the subgroup analysis, patients were divided according to adherence on the basis of drug dispensing/return records and patient dosing diaries. One group was 80% adherent (i.e. received ≥ 80% of their total interferon dose and ≥ 80% of the RBV dose and were treated for ≥ 80% of the expected duration of therapy). The other group underwent dose reduction (<80% of one or both drugs for ≥ 80% of expected duration). Patients who withdrew from the study prematurely were excluded from the analysis (these patients had lower SVRs than groups who received ≥ 80% of the assigned duration of therapy). Across the four trials 407 patients were excluded because they remained in the trial for less than 80% of the expected duration. Across the four trials 1414 patients remained in the trial for at least 80% of the duration and received at least 80% of their medications. The primary reason for not achieving adherence to drug doses was adverse events to therapy (in >75% of patients).

When comparing adherent and less adherent patients, they were similar in most baseline characteristics, but a larger proportion of the adherent patients were male and weighed more. Of particular interest for the current report are the findings for patients on the PEG regimens. SVR was greater for patients who were adherent to the therapy regimen than for those who received less than 80% of one or both drugs (*Table 8*).

Because of the possibility of adherence being affected by selection bias, a statistical method was also used to estimate the effects of treatment adherence. These estimates are shown in *Table 8*.

These results indicate that adherence to therapy is important and enhances SVR. In particular, SVR was greater in patients receiving PEG + RBV in a fixed dose who were adherent to therapy than in the overall analysis or in patients who were not at least 80% adherent. In general, the pattern of greater SVR with adherence to therapy was only seen in patients with genotype 1 infection. In the analysed trials, the majority of patients were adherent to therapy, but this might not be the case outside the context of a trial.

Unpublished data: Hadziyannis and colleagues

[NB. Some of the data from this trial have been presented at a conference, and other commercial in confidence data have been provided by the manufacturer. The confidential data have been removed from this publication.]

The trial by Hadziyannis and colleagues, at the time this report was written, was only available as a conference abstract. It has now been fully published.[60] It is described only briefly here and not considered an 'included' trial because of the lack of opportunity at the time of writing to evaluate its methods fully.

The trial randomly allocated 1284 previously untreated patients into four groups:

1. PEG-α-2a 180 μg per week plus RBV 800 mg per day (24 weeks) (n = 207)
2. PEG-α-2a 180 μg per week plus RBV 1000–1200 mg per day (24 weeks) (n = 280)
3. PEG-α-2a 180 μg per week plus RBV 800 mg per day (48 weeks) (n = 361)

TABLE 8 *SVR according to adherence*

Trial	Primary ITT analysis	80% adherent patients	< 80% adherent patients	Estimated sustained response with full adherence
Manns *et al.*, 2002[41] (PEG + RBV)				
All patients	54%	63%*†	52%	62%
Genotype 1	42%	51%*†	34%	50%
Genotype 2/3	82%	90%	89%	
Manns *et al.*, 2002[41] (PEG + RBV >10.6 mg kg^{-1})				
All patients	61%	72%	57%	71%
Genotype 1	48%	63%†	34%	61%
Genotype 2/3	88%	94%	95%	
Lindsay *et al.*, 2001[52] (PEG monotherapy)				
All patients	23%	27%	26%	
Genotype 1	14%	17%	7%	
Genotype 2/3	49%	54%	57%	

* $p < 0.05$ for comparison between ITT analysis and 80% adherence.
† $p < 0.05$ for comparison between 80% adherence and <80% adherence.

4. PEG-α-2a 180 μg per week plus RBV 1000–1200 mg per day (48 weeks) ($n = 436$).

Because of concern that 24 weeks of treatment may not be sufficient in genotype 1, randomisation was weighted so that genotypes non-1 high and low viral loads or genotype 1 with low viral load were allocated evenly across all treatment groups. Patients with genotype 1 and high viral loads were weighted 1:1:4:4 towards the longer treatment durations. Inclusion of a non-pegylated comparison group was considered unethical given that the superiority of PEG over IFN had been already been demonstrated in large RCTs. However, it is partially relevant to this report because it appears to be the first large RCT of PEG to compare shorter with a longer treatment duration (i.e. 24 weeks versus 48 weeks).

All patients were followed up to assess SVR 24 weeks after the end of treatment. The participants were predominantly Caucasian (85%), male (65%) and genotype 1 (58%), and averaged about 5.9 million copies ml^{-1} of virus at baseline. The majority of patients with genotype non-1 were those with genotypes 2 and 3. Only a minority of genotype 4 patients were included ($n = 36$, 3%). A larger proportion of patients had bridging fibrosis or cirrhosis than in previous studies of dual therapy.

Unpublished data: genotype 4 patients

Two trials of treatment using PEG specifically in patients with genotype 4 have been published only in abstract form. These will be briefly reviewed here because of the differential response of patients with different genotypes of infection and the dearth of information available from fully published RCTs. However, it should be noted that the methodological quality of trials cannot be fully assessed from abstracts, thus caution is advised when interpreting the results.

One trial evaluated the effectiveness of PEG-α-2a[61] in 120 genotype 4 patients who were randomly assigned to PEG 180 μg 0.5 ml^{-1} per week plus RBV 800 mg per day, or to PEG 180 μg per week alone for 48 weeks. SVR data were not reported, but at the end of treatment 67% of patients treated with PEG + RBV had a virological response, whereas 59% of those on PEG monotherapy had a virological response. In another abstract,[62] a third group from apparently the same trial was reported. These patients were randomised to receive IFN 4.5 MIU plus RBV 800 mg per day. The EVR (based on 2-log drop of HCV RNA negatively at week 12) was 77% in the PEG + RBV group, 60% in the PEG group and 22% in the IFN group.

A second trial[63] evaluated the effectiveness of PEG-α-2b and randomised 172 patients, 80% of whom had genotype 4 infection. The patients received either PEG 100 μg per week plus RBV 800–1000 mg per day based on weight, or IFN 3 MIU three times per week plus RBV (same dose). At the time of reporting the trial was ongoing. Of those who had completed 12 weeks HCV RNA was undetectable in 71% of the PEG group and 65% of the IFN group. Of those who

TABLE 9 *Virological response rates for 48 weeks of monotherapy*

Study	End of treatment response		End of follow-up response	
	PEG IFN-α	IFN-α	PEG IFN-α	IFN-α
Heathcote *et al.*, 2000[54]	44%	14%	30%	8%
Zeuzem *et al.*, 2000[53]	69%	28%	39%	19%
Lindsay *et al.*, 2001[52]	49%	24%	23%	12%
Reddy *et al.*, 2001[40]	60%	12%	36%	3%
All comparisons were statistically significant ($p < 0.05$).				

had completed 24 weeks of therapy, HCV RNA was undetectable in 66% of the PEG group and 59% of the IFN group.

These two trials seem somewhat inconsistent in that the first trial seemed to show much higher responses to PEG than to IFN, whereas there was little difference in the second trial. This might be due to differences in efficacy between PEG-α-2a and PEG-α-2b in genotype 4. However, caution should be applied in interpreting very preliminary results.

Summary

- In the two RCTs comparing treatment with PEG + RBV with IFN + RBV, the PEG + RBV treatment resulted in significantly higher rates of sustained response. The pooled SVR for PEG + RBV treatment was 55% (95% CI 52 to 58%) and was 46% (95% CI 43 to 49%) for IFN + RBV. The pooled relative risk was 0.83 (95% CI 0.76 to 0.91).
- A published analysis of early response data from the PEG + RBV arms of these two RCTs recommended that patients with genotype 1 and EVR complete 48 weeks of treatment. Patients with genotype 1 without EVR at 12 weeks should discontinue treatment and those with EVR but who are HCV RNA positive at 24 weeks should discontinue treatment. EVR does not need assessment in patients with genotype 2 or 3, who should be treated for 24 weeks.
- Both trials found that lower age, lower body weight and non-1 genotype were associated with higher SVR. In one trial gender, lower baseline viral load and absence of bridging fibrosis or cirrhosis were also significantly associated with SVR.
- In one trial, both treatments resulted in reduced liver inflammation. Those with SVR had a greater histological response, but there were also histological responses in some patients without SVR.

Assessment of effectiveness in untreated patients: monotherapy (PEG)

Virological response

Table 9 shows the end of treatment and sustained virological response rates in the four RCTs which compared pegylated interferon monotherapy with non-pegylated monotherapy. The dose for non-pegylated interferon was the same in each trial (3 MIU three times per week, except in the trial by Zeuzem and colleagues[53] where for the first 12 weeks patients received 6 MIU three times per week, followed by 3 MIU three times per week for the remaining 36 weeks); however, as reported in *Table 2*, dosages for pegylated interferon varied between different arms of the trials (*Table 9*); consequently, the table reports the response rates for the arm in which the 'standard' dose was given (e.g. 180 μg per week, except for Lindsay,[52] where the dose was 1.5 μg kg^{-1} per week). (See *Table 10* for response rates for various doses of PEG.) Caution is advised when comparing rates across the trials given differences in average baseline viral load between them, and the fact that the majority of patients in the trial by Heathcote and colleagues[54] were cirrhotic.

The pooled EOTR rates for PEG monotherapy were 57% (95% CI 53 to 60%) in comparison to 24% (95% CI 20 to 26%) for IFN monotherapy, with a pooled relative risk of 0.57 (95% CI 0.18 to 0.29) (*Figure 3*).

In all trials PEG monotherapy was significantly superior to IFN monotherapy, with SVRs in the range of 23–39% and 3–19%, respectively.

Pooled SVRs were 31% (95% CI 27 to 34%) and 14% (95% CI 12 to 17%) for PEG and IFN monotherapy, respectively. The pooled odds ratio was 0.36 (95% CI 0.27 to 0.47) and the pooled relative risk was 0.80 (95% CI 0.76 to 0.85), respectively (*Figure 4*). In summary, monotherapy with PEG is around twice as effective, in terms of sustained response, as monotherapy with IFN.

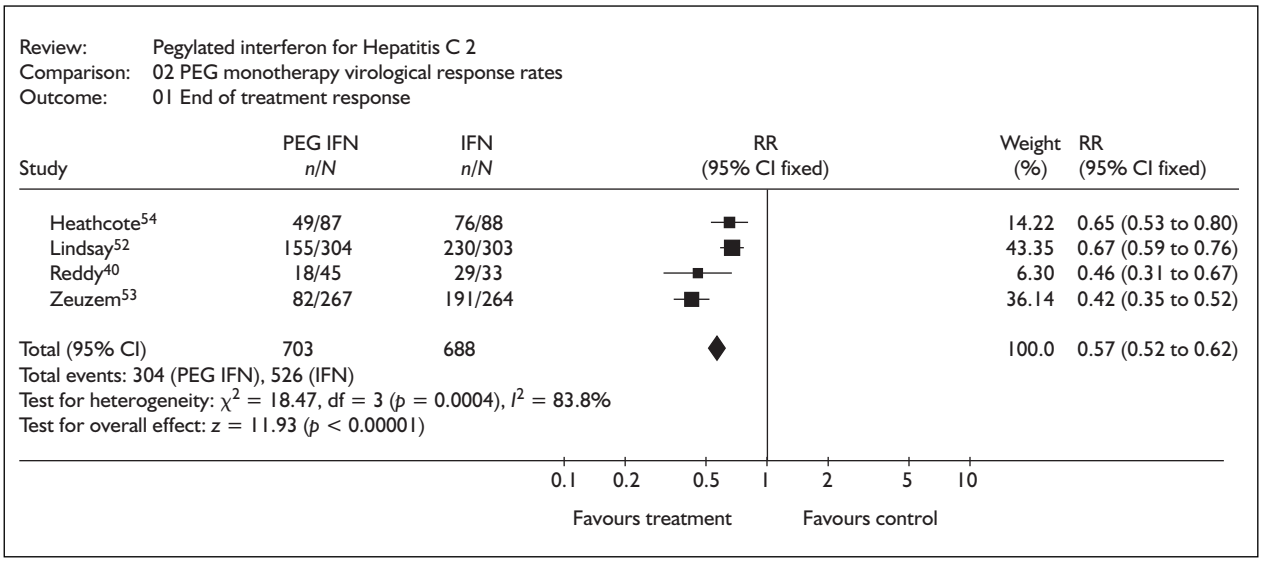

FIGURE 3 *Pooled relative risk (end of monotherapy)*

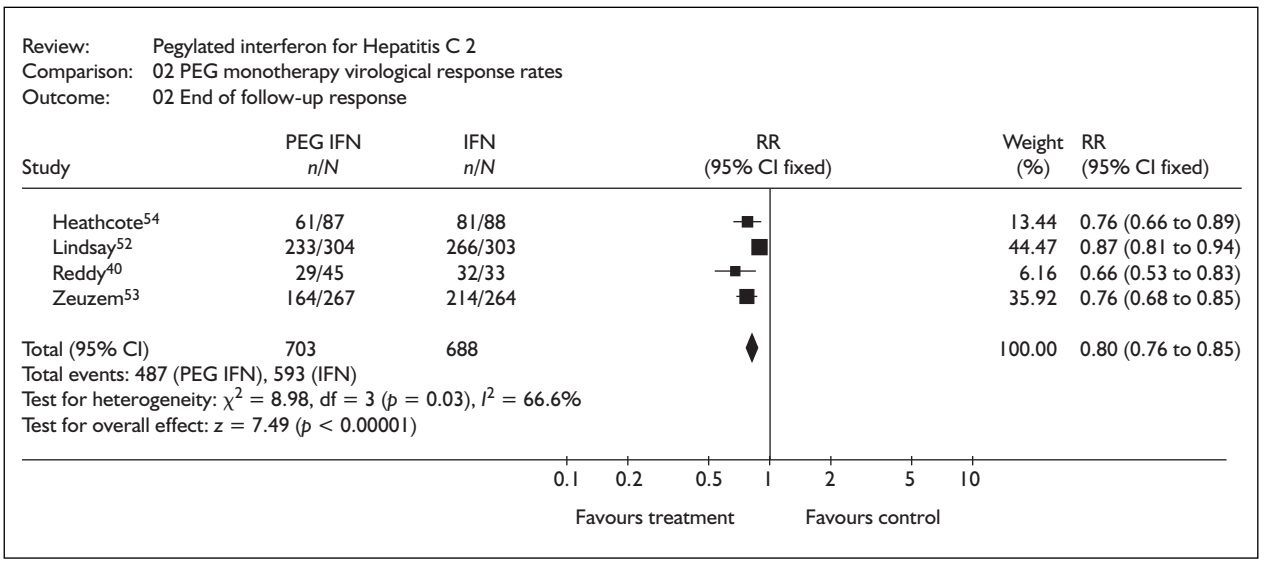

FIGURE 4 *Pooled relative risk (end of follow-up monotherapy)*

In the studies that measured the effectiveness of different doses of pegylated interferon the response rates generally increased in line with ascending doses (*Table 10*). The exception was the trial by Reddy and colleagues 2001[40] where the optimum dose appeared to be 180 μg per week rather than 270 μg. Moreover, sustained response rates were slightly higher for 1.0 μg kg^{-1} than 1.5 μg kg^{-1} in the trial by Lindsay and colleagues.[52]

Predictors of treatment response: early response

Data were provided in the reports of the monotherapy trials on the proportion of patients who responded early who sustained their response. Reddy and colleagues[40] reported that most patients who had an SVR had responded within the first 16 weeks of treatment. They also found that 65% of the sustained responders in the 180 μg PEG group had undetectable HCV RNA by week 4. Similarly, Lindsay and colleagues[52] reported the proportion of sustained responders who had responded at week 4. For each treatment group the likelihood of an SVR occurring was highest in patients whose first negative HCV RNA had occurred at treatment week 4, compared with those in whom HCV RNA was first negative at week 12. In the trial by Heathcote and colleagues[54] all patients who received 180 μg of PEG who had an SVR had responded by 12 weeks. In Zeuzem and colleagues' trial[53] 98% of the 103 patients in the PEG group who had an SVR had

TABLE 10 *Virological response rates for 48 weeks of monotherapy (dose variations, pegylated interferon only)*

	PEG IFN-α-2a 45 μg	**PEG IFN-α-2a 90 μg**	**PEG IFN-α-2a 180 μg**	**PEG IFN-α-2a 270 μg**
Reddy *et al.*, 2001[40]				
End of treatment	30%	45%	60%	56%
End of follow-up	10%	30%	36%	29%
Heathcote *et al.*, 2000[54]				
End of treatment		42%	44%	
End of follow-up		15%	30%	
Zeuzem *et al.*, 2000[53]				
End of treatment			69%	
End of follow-up			39%	
	PEG IFN-α-2b 0.5 μg kg^{-1}	**PEG IFN-α-2b 1.0 μg kg^{-1}**	**PEG IFN-α-2b 1.5 μg kg^{-1}**	
Lindsay *et al.*, 2001[52]				
End of treatment	33%	41%	49%	
End of follow-up	18%	25%	23%	

no detectable HCV RNA or the viral load decreased by a factor of 100 by week 12. In the IFN group 98% of those who had an SVR had a decrease in viral titre of at least 2 log at week 12. Hence in non-responders, treatment can be stopped at 12 weeks.

Response according to prognostic factors

Only two of the monotherapy trials[52,53] performed logistic regression analysis to examine the independent effect of baseline prognostic factors on SVR. Two factors shown to be significantly related to response were common to both trials: baseline viral load (≤ 2 million copies ml^{-1}) and genotype non-1. The remaining variables were all from the Zeuzem trial,[53] including age, body surface area, baseline ALT quotient greater than 3, no cirrhosis or bridging fibrosis, and treatment with PEG.

Table 11 shows the extent to which sustained virological response rates varied according to genotype. All of the trials, except for the Zeuzem trial[53] reported such information. In two trials results were aggregated to groups of genotypes (e.g. genotype 1 versus all non-1 genotypes), whereas in the other trial they were presented according to individual or smaller aggregations (e.g. 1, 2 or 3), making it difficult to make comparisons between trials.

Patients with the harder to treat genotype 1 who received pegylated interferon did better than those who received non-pegylated interferon. In one trial response rates for patients with this genotype were up to eight times greater with pegylated interferon[40] (although the relatively small number of participants in this trial should be noted). Response rates for patients with subtypes 1a and 1b in the pegylated interferon group of the trial by Heathcote and colleagues[54] were also higher than for the non-pegylated group.

Table 12 reports the SVRs according to baseline viral load, and stratified according to genotype. Only Heathcote and colleagues[54] and Lindsay and colleagues[52] provided these data. In both trials patients had higher SVRs with PEG than IFN

TABLE 11 *Sustained virological response rates by genotype (monotherapy)*

Study	**End of follow-up response**	
	PEG IFN-α	**IFN-α**
Heathcote *et al.*, 2000[54]		
1	12%	2%
1a	9%	0%
1b	20%	5%
Other than 1/unknown	51%	15%
Lindsay *et al.*, 2001[52]		
1	14%	6%
2 or 3	49%	28%
4, 5 or 6	60%	0%
Reddy *et al.*, 2001[40]		
1	31%	4%
Non-1	50%	0%

Significance values for the comparison between PEG and IFN are not presented in the trials.

TABLE 12 *Sustained virological response rates by baseline viral load; baseline viral load and genotype (monotherapy)*

Study	End of follow-up response	
	PEG IFN-$\alpha^{a,b}$	**IFN-α**
Heathcote *et al.*, 2000[54]		
Low viral load	37%	5%
Genotype 1	16%	0%
Genotype non-1	55%	10%
High viral load	23%	9%
Genotype 1	10%	4%
Genotype non-1	50%	20%
Lindsay *et al.*, 2001[52]		
Low viral load	–	–
Genotype 1	34%	21%
Genotype 2/3	68%	36%
High viral load	–	–
Genotype 1	7%	2%
Genotype 2/3	41%	25%

[a] Data presented for Heathcote *et al.* are for the higher dose PEG group (180 μg).
[b] Data presented for Lindsay *et al.* are for the higher dose PEG group (1.5 μg kg^{-1}).

treatment irrespective of whether they had a high or low viral load at baseline. SVRs for patients with low baseline viral load and genotype non-1 (i.e. the easier to treat patients) were in the range 55–68% when treated with PEG in comparison to only 10–36% when receiving IFN. Patients with high baseline viral load and genotype 1 (i.e. the harder to treat patients) again did better with PEG than IFN treatment, but SVRs were much lower, in the range 7–10% and 2–4%, respectively. [For the present report, it was assumed that baseline viral loads were determined from tests used to screen patients for inclusion. In the Heathcote trial no information was given about the assessment of HCV RNA levels for inclusion. In the Lindsay trial the test used was not specified. Patients with detectable HCV RNA in serum by PCR assay were included.]

Histological response

Paired biopsy results (i.e. from baseline to follow-up) were available in around 61–72% of patients across the four monotherapy trials. Between 31 and 66% of patients achieved a histological response (generally defined as a decrease of ≥ 2 units on the Knodell HAI) across the trials, with greatest response generally among PEG-treated patients. Histological response was highly correlated with SVR in all trials, with the proportion of patients experiencing both within the range 77–100%, whereas among patients without SVR the proportions were much lower, in the range 4–60% (see the subsection on the study by Poynard and colleagues, p. 32, for results of a meta-analysis of PEG IFN-α-2b as dual and monotherapy on fibrosis).

The trial by Lindsay and colleagues[52] was the only one of the monotherapy trials to report histology results separately for fibrosis and inflammation. All treatment groups experienced a decrease in hepatic inflammation, with percentage reductions in the range 47–50% (similar across treatment groups). Sustained virological responders experienced the greatest reduction in inflammation, the proportion of patients in the range 77–90% compared with 33–46% of those who relapsed after EOTR, or those who did not respond at all (33–41%). Percentage improvements in fibrosis were in the range 20–13%, with the greatest improvement in the lower dose PEG group (0.5 μg kg^{-1}) and the lowest in the IFN group. Changes in fibrosis scores followed a similar pattern to inflammation scores, with sustained virological responders experiencing a greater improvement (21–37%) than those who relapsed or did not respond (4–17%). Again, the proportion of patients with improvement was greatest in the higher dose PEG group and lower in the IFN group.

In the Zeuzem trial[53] 63% of PEG-treated patients experienced a histological response in comparison to only 55% in the IFN group. The largest mean change was also experienced by PEG patients (–2.4 units versus –2.0). The proportion of patients with both SVR and histological response was marginally higher in the IFN group than the

PEG group (86% versus 82%, respectively). For patients without an SVR the proportion experiencing a histological response was much lower, with 47% in the PEG group and 44% in the IFN group.

The percentage of histological responders in the trial by Reddy and colleagues[40] was in the range 47–66%, with the biggest and smallest improvement in the higher dose (270 μg) PEG group and lower dose PEG group (45 μg), respectively. The biggest mean change in HAI score was in the 180 μg PEG group, with a reduction of 2.8 units. All but two patients who achieved an SVR also achieved a histological response. The proportion of patients without an SVR who achieved a histological response was much lower, varying between 42 and 60% in the PEG groups, and 55% in the IFN group.

In the Heathcote study[54] the proportion of patients experiencing a histological response was in the range 31–54%, with the greatest improvement in the higher dose (180 μg) PEG group. Again, SVR was highly correlated with histological response, with 80% of patients receiving IFN, 100% of patients receiving 90 μg PEG and 88% of patients receiving 180 μg PEG experiencing a reduction in HAI scores. For patients without SVR the proportions experiencing a histological response were 26%, 33% and 35%, respectively.

Unpublished data

One trial, by Pockros and colleagues, is published thus far only in abstract form.[64] It is described only briefly here and not considered an 'included' trial because of the lack of opportunity to evaluate its methods fully. The trial tested PEG-α-2a monotherapy against IFN monotherapy and was an open-label RCT in which 215 participants were treated with PEG-α-2a 135 μg per week, 210 participants were treated with PEG-α-2a 180 μg per week, and 214 participants were treated with IFN-α-2a 3 MIU three times per week. The participants were predominantly Caucasian (86%), male (60–70%) and genotype 1 (65–70%), and averaged about 7 million copies ml^{-1} of virus at baseline. As in other trials, patients were treated for 48 weeks with an untreated follow-up of 24 weeks. SVR in both PEG groups was 28% compared with 11% in the IFN group.

Summary

- In the four RCTs comparing PEG monotherapy with IFN monotherapy, the pooled SVR for PEG was 31% (95% CI 27 to 34%) and for IFN was 14% (95% CI 12 to 17%). The pooled relative risk was 0.80 (95% CI 0.76 to 0.85).
- In general, the results of early viral responses in these trials indicated that the majority of patients who would have a sustained response to treatment had responded by 12 weeks of treatment.
- In the two trials that evaluated the effects of prognostic factors on SVR, lower baseline viral load and non-1 genotype were associated with higher SVR.
- When responses were considered by genotype, patients with the harder to treat genotype 1 seemed particularly to benefit from PEG treatment.
- Among patients with paired before and after treatment biopsies, histological response was highly correlated with SVR and histological responses were generally greater among patients treated with PEG.

Adverse events associated with pegylated interferon therapy

Dual therapy

Trials are generally not powered to enable statistically significant differences in adverse events between study groups to be detected, making it difficult to draw firm conclusions about relative safety. However, in both trials there was a large number of possible adverse events, many of which occurred in a large proportion of patients (*Table 13*). For example, adverse events included effects on haematological parameters as well as influenza-like symptoms, psychiatric symptoms and gastrointestinal symptoms. However, the levels of adverse events were generally similar between regimens involving PEG and those involving IFN. As there is not a within-trial randomised comparison between the two PEG formulations, no conclusions about relative safety can be drawn.

PEG-α-2a plus RBV (Fried and colleagues[50])

Most adverse events in all groups were those commonly associated with non-pegylated IFN-based treatment. There were similar levels of discontinuations of treatment across PEG and IFN groups. There were some adverse events that were significantly less frequent in the PEG groups: depression, pyrexia, rigors and myalgia. If depression is consistently less frequent when using PEG than IFN, then this would be an important advance as the psychiatric adverse events associated with treatment are often among the most serious.

The addition of RBV to PEG-α-2a did not lead to significantly more treatment discontinuations, but

TABLE 13 *Adverse events (dual therapy)*

Reported adverse events (% of patients affected)[a]	Manns *et al.*, 2001[41]			Fried *et al.*, 2002[50]					
	PEG IFN-α-2b 1.5 μg kg^{-1} + RBV (800 mg) (n = 511)	**PEG IFN-α-2b 1.5 μg kg^{-1} then 0.5 μg kg^{-1} + RBV (1000–1200 mg) (n = 514)**	**IFN 3 MIU three times per week + RBV (1000–1200 mg) (n = 505)**	**PEG IFN-α-2a 180 μg per week + RBV (1000–1200 mg) (n = 453)**		**PEG IFN-α-2a 180 μg per week + placebo (n = 224)**		**IFN 3 MIU three times per week + RBV (1000–1200 mg) (n = 444)**	
Discontinuation of treatment									
Adverse event[b]	14	13	13	7.1		5.8		9.7	
Laboratory abnormality				2.6		0.9		0.9	
Dose reduction[c]				PEG	RBV	PEG	Placebo	IFN	RBV
Adverse event[b]	42	36	34	11	21	6	17	11	22
Laboratory abnormality				25	24	24	4	8	19
Due to anaemia	9	12	13	1	22	0	4	3	19
Neutropenia	18	10	8	20	1	17	0	5	<1
Thrombocytopenia				4	<1	6	<1	<1	0
Influenza-like symptoms									
Asthenia	18	16	18						
Fatigue	64	62	60	54		44		55	
Fever/pyrexia	46	44	33	43		38		56*	
Headache	62	58	58	47		51		52	
Rigors	48	45	41	24		23		35*	
Weight decrease	29	17	20						
Dizziness	21	21	17						
Arthralgia	34	34	28	27		29		25	
Musculoskeletal pain	21	17	19						
Myalgia	56	48	50	42		42		50*	
Insomnia				37		23		39	
Gastrointestinal symptoms									
Anorexia	32	29	27						
Diarrhoea	22	16	17						
Nausea	43	36	33	29		26		33	
Vomiting	14	14	12						
Decreased appetite				21		11		22	
Psychiatric symptoms									
Concentration impairment	17	16	21						
Depression	31	29	34	22		20		30*	
Insomnia	40	40	41						
Irritability	35	34	34	24		25		28	
Respiratory tract symptoms									
Cough	17	15	13						
Dyspnoea	26	23	24						
Dermatological symptoms									
Alopecia	36	29	32	28		21		34	
Pruritus	29	26	28	22		18		20	
Rash	24	22	23						
Dry skin	24	18	23						
Dermatitis				21		13		18	
Injection-site inflammation	25	27	18						
Injection-site reaction	58	59	36						

[a] Events that occurred in at least 10% of patients in the Manns trial.[41]

[b] Adverse events apparently included laboratory abnormalities in the Manns trial,[41] but adverse events and laboratory abnormalities (including neutropenia, thrombocytopenia, abnormal ALT levels) were reported separately in the Fried trial.[50]

[c] Some patients in the Fried trial who required dose modifications had both adverse events and laboratory abnormalities.

* $p < 0.05$ for the comparison with the PEG IFN + RBV group.

the RBV dose was modified in more patients than placebo.

PEG-α-2b plus RBV (Manns and colleagues[41])
As in the Fried trial, the side-effect profiles for regimens involving PEG were similar to the regimen using IFN. No new or unique adverse effects were associated with the use of PEG. The levels of discontinuation for the three regimens were virtually identical. A few adverse events were more frequent in the PEG regimens, including some influenza-like symptoms in the high PEG dose. There were more injection-site reactions in the PEG groups than the IFN group, but these reactions were generally mild and not treatment limiting.

Monotherapy

As with dual therapy, there was a large number of possible adverse events, many of which affected substantial numbers of patients (*Table 14*). Adverse events included effects on haematological parameters, as well as influenza-like, psychiatric and gastrointestinal symptoms. Most of these were not considered serious and were not treatment limiting. There were no new or unexpected adverse events associated with PEG. The most common adverse events were influenza-like symptoms that are commonly associated with IFN-based therapies. In general, the adverse events were typical of those produced by unmodified IFN. There is some suggestion of slightly higher levels of discontinuation of treatment in the PEG groups than in the IFN groups (although this was not the case in the Zeuzem trial,[53] see *Table 14*). There is also a slight suggestion that treatment with PEG-α-2b might result in a higher incidence of myalgia and injection-site inflammation than treatment with PEG-α-2a.

The incidence of fatigue may be slightly lower with PEG-α-2b than with PEG-α-2a treatment. As mentioned previously, any potential differences between PEG-α-2a and PEG-α-2b would need to be evaluated in the context of an RCT in which the two formulations were directly compared.

The incidence of adverse events may be somewhat higher in the dual regimens than in monotherapy, which would imply that some adverse events are due to RBV. This would not be unexpected. However, to draw firm conclusions, trials in which dual therapy and monotherapy were directly compared would need to be considered. If such trials did not include a non-PEG arm they did not meet the inclusion criteria for this review as the primary question was the efficacy of PEG. (The Fried trial[50] did include a comparison between PEG-α-2a plus RBV and PEG-α-2a plus placebo. These two arms did not appear to differ consistently in adverse events.) A previous review[34] compared IFN plus placebo with IFN plus RBV, and reported findings that haematological events such as anaemia were greater when RBV was part of the regimen.

PEG-α-2a
In the three trials using PEG-α-2a there were few differences in adverse effects between the PEG and IFN groups. In the Heathcote trial[54] there were more instances of myalgia and inflammation of the injection site in the high-dose PEG group than in the low-dose PEG or IFN groups (note that the majority of patients in this trial were cirrhotic and potentially more susceptible to adverse events). In the Reddy trial[40] depression, pruritus and irritability were more common in the PEG groups than in the IFN group. (Recall that depression was less frequent in the PEG group in the Fried dual-therapy trial.[50] Therefore, conclusions about depression should be tentative at best.) Dizziness and myalgia were higher in the IFN group than in the PEG groups. This trial reported more dose modifications in the groups receiving 270 μg PEG than in the other groups and more discontinuations in the PEG groups than in the IFN group. Differences between arms in this trial in particular should be viewed with caution as the numbers of patients in the groups in this trial were relatively small and could result in spurious differences. In the Zeuzem trial[53] it appears there were slightly fewer adverse events in the PEG group than in the IFN group. In general, however, all differences in self-reported adverse events should be viewed with caution in open-label trials.

In the Heathcote trial[54] there were significantly fewer patients with low platelet counts ($<50{,}000$ mm^{-3}) in the IFN group than in the two PEG groups. Zeuzem and colleagues[53] reported than thrombocytopenia was rare in both groups, and Reddy and colleagues[40] reported dose-dependent drops in platelets in the PEG groups that corrected by week 52. There is little additional indication of dose-related increases in adverse events, although this possibility was not strongly tested in the included studies.

PEG-α-2b
Only one trial[52] compared PEG-α-2b with IFN-α-2b. In this trial PEG was considered to be comparable to IFN in safety and tolerability, with no new or unexpected adverse events specific to PEG. The higher doses of PEG produced

TABLE 14 *Adverse events (monotherapy)*

Reported adverse events (% of patients affected)[a]	Heathcote *et al.*, 2000[54]			Zeuzem *et al.*, 2000[53]		Lindsay *et al.*, 2001[52]				Reddy *et al.*, 2001[40]				
	PEG IFN-α-2a 90 μg per week (n = 96)	PEG IFN-α-2a 180 μg per week (n = 86)	IFN-α-2a 3 MIU three times per week (n = 86)	PEG IFN-α-2a 180 μg per week (n = 265)	IFN-α-2a 6 MIU then 3 MIU[b] (n = 261)	PEG IFN-α-2b 0.5 μg kg^{-1} per week (n = 315)	PEG IFN-α-2b 1.0 μg kg^{-1} per week (n = 297)	PEG IFN-α-2b 1.5 μg kg^{-1} per week (n = 304)	IFN-α-2b 3 MIU three times per week (n = 303)	PEG IFN-α-2a 45 μg per week (n = 20)	PEG IFN-α-2a 90 μg per week (n = 20)	PEG IFN-α-2a 180 μg per week (n = 45)	PEG IFN-α-2a 270 μg per week (n = 40)	IFN-α-2a 3 MIU three times per week (n = 30)
Discontinuation of treatment														
Adverse event	7	13	8	7	10	9	11	9	6	10	0	22	20	9
Laboratory abnormality	4	1	2											
Dose reduction[c]														
Adverse event	2	14	14	8	11	9	14	19	6				49	
Laboratory abnormality[d]				14	9									
Neutropenia	9	10	14											
Thrombocytopenia	18	18	6											
Influenza-like symptoms														
Fatigue	53	62	60	60	65	43	51	45	50	70	85	67	70	70
Fever/pyrexia	29	38	36	37	52	31	45	44	30	15	10	24	28	30
Headache	54	50	53	60	66	61	64	64	58	40	35	58	48	60
Rigors/chills	38	43	45	27	43	34	40	44	33	5	20	47	50	47
Dizziness	20	15	16	23	16					10	20	13	18	23
Arthralgia										20	40	18	30	23
Musculoskeletal pain						19	28	20	22					
Myalgia	36	51	38	42	43	48	54	61	53	40	65	31	48	63
Gastrointestinal symptoms														
Anorexia/decreased appetite	15	14	7	20	21	10	20	25	17	15	20	16	13	7
Diarrhoea	21	24	19	19	20					25	25	31	33	20
Nausea	30	34	34	21	35	21	26	25	20	45	15	44	30	47
Vomiting	12	13	15	6	12					20	0	16	3	17
Upper abdominal pain	19	26	24	13	14					30	10	18	28	17
Psychiatric symptoms														
Concentration impairment	6	7	12	5	11					10	20	7	30	7
Depression	21	26	21	16	23					30	35	27	38	10
Insomnia	19	19	22	18	24	17	23	20	23	25	5	33	30	23
Irritability						19	18	17	24	35	20	29	33	13
Anxiety	11	3	7											
Respiratory tract symptoms														
Cough	10	17	5	9	10									
Sinusitis	12	8	7											
Nasopharyngitis				11	8									

continued

TABLE 14 *Adverse events (monotherapy) (cont'd)*

Reported adverse events (% of patients affected)[a]	Heathcote et *al.*, 2000[54]			Zeuzem et *al.*, 2000[53]		Lindsay et *al.*, 2001[52]				Reddy et *al.*, 2001[40]				
	PEG IFN-α-2a 90 μg per week (n = 96)	PEG IFN-α-2a 180 μg per week (n = 86)	IFN-α-2a 3 MIU three times per week (n = 86)	PEG IFN-α-2a 180 μg per week (n = 265)	IFN-α-2a 6 MIU then 3 MIU[b] (n = 261)	PEG IFN-α-2b 0.5 μg kg^{-1} per week (n = 315)	PEG IFN-α-2b 1.0 μg kg^{-1} per week (n = 297)	PEG IFN-α-2b 1.5 μg kg^{-1} per week (n = 304)	IFN-α-2b 3 MIU three times per week (n = 303)	PEG IFN-α-2a 45 μg per week (n = 20)	PEG IFN-α-2a 90 μg per week (n = 20)	PEG IFN-α-2a 180 μg per week (n = 45)	PEG IFN-α-2a 270 μg per week (n = 40)	IFN-α-2a 3 MIU three times per week (n = 30)
Dermatological symptoms														
Alopecia	15	17	22	27	37	20	22	34	22	5	30	22	25	20
Pruritus	16	16	8	18	12					10	15	11	13	3
Dermatitis	8	17	7							15	0	13	28	7
Injection-site inflammation	15	31	14	10	7	44	42	40	16	35	30	24	25	20
Other														
Pain	10	10	12							20	0	20	13	13
Pain in limb	11	8	5							15	25	9	8	13
Back pain											15	16	15	17
Epistaxis	11	7	14											

[a] Adverse events during treatment or first 8 weeks of follow-up occurring in at least 10% of patients in the Heathcote trial.[54] Adverse events reported in Reddy[40] were those observed in at least 10% of patients. Discontinuation in the Zeuzem,[53] Lindsay[52] and Reddy[40] trials was not reported separately for adverse event and laboratory abnormalities. Therefore, the value reported for adverse events reflects the total proportion of treatment discontinuations. Some patients in the Zeuzem trial had more than one adverse event.

[b] Regimen was IFN-α-2a at 6 MIU three times per week for 12 weeks, than 3 MIU three times per week for 36 weeks.

[c] Dose reductions in the Lindsay trial[52] were not reported separately for adverse events and laboratory abnormalities. Dose reductions in the Reddy trial[40] were not reported for all treatment arms and were not reported separately for adverse events and laboratory abnormalities in the reported arm.

[d] Laboratory abnormalities that could result in dose modifications in the Zeuzem trial[53] consisted of neutropenia, thrombocytopenia, abnormal ALT values, hypothyroidism and hyperthyroidism. Some patients in this trial who required dose modifications had both an adverse event and a laboratory abnormality.

somewhat higher frequency of fever and chills. Injection-site reactions were approximately twice as frequent in the PEG groups, but were generally mild and not treatment limiting. Dose reductions for thromobocytopenia were more common in the PEG groups and dose reduction for neutropenia was more frequent in the 1.5 μg kg^{-1} PEG group. Dose reductions increased with higher doses of PEG, but treatment discontinuations were comparable across the PEG groups and slightly higher than in the IFN group.

Summary

In summary, regimens involving PEG appear to be fairly well tolerated and do not differ substantially in levels of adverse events from regimens involving unmodified IFN. Dose modifications may be needed in more patients with higher doses of PEG (particularly monotherapy). There is some suggestion that dual therapy including RBV may result in more adverse events than PEG monotherapy.

All of the tested treatment regimens have effects on levels of haemoglobin, platelets and neutrophils. In general, discontinuations due to anaemia, thrombocytopenia or neutropenia were rare. Most trials reported patterns of decreased haemoglobin, platelets and neutrophils associated with treatment, which generally stabilised during treatment and returned to baseline levels after the end of treatment. These effects require careful monitoring during treatment, in case dose modification or discontinuation should become necessary. The effects on haematological parameters may be somewhat greater in PEG regimens than in IFN regimens.

Two trials reported deaths after the end of treatment.[50,54] In the Fried trial[50] none of the three deaths was considered treatment related. In the Heathcote trial,[54] any potential relationship between treatment and the four deaths was unclear. Two patients died of hepatic failure, 420 and 179 days after the end of treatment, one patient died of hepatic neoplasm 219 days after the end of treatment, and one patient (180 μg PEG) died of a cerebral haemorrhage after a suspected methadone overdose, 24 days after the end of treatment.

Evidence from related systematic reviews

Two systematic reviews identified during literature searching also shed light on the clinical effectiveness of pegylated interferon. A third review is planned by the Cochrane Hepato-Biliary Group.

Agency for Healthcare Research and Quality

The Agency for Healthcare Research and Quality (AHRQ) recently published a report for the US Department of Health and Human Services on Management of Chronic Hepatitis C.[65] This report was also summarised in a journal publication by Chander and colleagues.[66]

Methods such as searching and implementation of inclusion/exclusion criteria were very similar to those of the current review. The method of quality assessment of included studies was somewhat different, using a scale to rate studies as opposed to assessment of the individual components of study methodology. Narrative approaches to synthesis were followed, as opposed to the mixture of narrative and quantitative approaches used in the current report.

Questions covering a broader area were posed:

1. "How well do the results of initial liver biopsy predict measures of disease progression and outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?
2. How well do biochemical blood tests and serological measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?
3. What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including pegylated interferon plus ribavirin, pegylated interferon alone, interferon plus ribavirin, and interferon plus amantadine?
4. What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected sub-groups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, race/ethnicity, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, non-response to initial interferon-based therapy, and relapse after initial interferon-based therapy?
5. What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?
6. What is the efficacy of using screening tests for

hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?
7. What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially respectable carcinoma) in patients with chronic hepatitis C?" (p. 6).

The most directly relevant question to the current review is question 3 (although question 2 is considered later in this chapter – Results: effectiveness of non-invasive tests for fibrosis on biopsy). With regard to the efficacy of PEG, the AHRQ review did not report on any trial data that is not included in the current review and concluded that:

> "studies of treatment-naïve patients with chronic hepatitis C showed greater efficacy of pegylated interferon plus ribavirin when compared to standard interferon plus ribavirin or peginterferon alone, greater efficacy of peginterferon when compared to standard interferon, and no significant increase in efficacy with standard interferon plus amantadine when compared to interferon monotherapy; for non-responders and relapsers, standard interferon plus ribavirin was more efficacious than interferon alone; little evidence existed on treatment efficacy in HIV-infected patients, renal patients, haemophiliacs, or injecting drug users" (p. 4).

Additional results from the AHRQ report were:

1. "studies were relatively consistent in suggesting that advanced fibrosis or cirrhosis on initial liver biopsy may independently predict a slightly decreased likelihood of SVR to treatment ...
2. studies were mildly consistent in suggesting that interferon-based therapies decrease the risk of HCC and cirrhosis in complete responders ...
3. one study suggested that HCC was detected earlier and was more often resectable in patients who had quarterly screening with serum alpha-fetoprotein (AFP) and ultrasound than in those who had usual care …
4. studies were relatively consistent in suggesting that a serum AFP greater than 10 ng/ml has a sensitivity of 75 to 80 percent and a specificity of about 95 percent in screening for HCC, and a serum AFP greater than 400 ng/mL has a specificity of nearly 100 percent for detection of HCC" (p. 4).

Poynard and colleagues

Poynard and colleagues[67] conducted a meta-analysis to estimate the impact of pegylated interferon-α-2b on liver fibrosis (see Appendix 7). Data from four trials that tested either IFN-α-2b or PEG IFN-α-2b regimens in chronic hepatitis C were combined. These regimens could be either monotherapies or could include dual therapy combining RBV with IFN or PEG. (The two trials that used PEG dual therapy were included in the current review.[41,52]) The control regimen was considered to be IFN-α-2b at a dose of 3 MIU three times per week for 24 weeks. The results from the ten included regimens were considered primarily for changes in liver fibrosis.

Data from 3010 treatment-naive patients with pretreatment and post-treatment biopsies were pooled. The inclusion and exclusion criteria were generally the same as those outlined for the trials included in the current review: patients with chronic hepatitis C, but without significant co-morbidities. The particular treatment regimens included are listed in Appendix 7. Liver biopsies were scored using the METAVIR scoring system (one grade in METAVIR is equivalent to four grades in the Knodell index, which is twice the usual definition of histological improvement). Fibrosis was scored on a scale of 0 to 4. Activity (i.e. necroinflammatory activity) was also scored on a scale of 0 to 3. Different treatment regimens were compared for the percentage of patients who improved by at least one fibrosis stage, remained stable or worsened by at least one stage. Regimens were also compared according to the fibrosis progression rates per year before and after treatment. The impact of different regimens on the percentage of patients with significant fibrosis at the second biopsy was also assessed, adjusted by other risk factors in multivariate analyses. Finally, the hypothesis that the non-control regimens could reverse cirrhosis was tested.

A range of detailed results was presented. The primary results in terms of liver fibrosis were:

- necrosis and inflammation improvement ranged from 39 to 73% (PEG 1.5 $\mu g\ kg^{-1}$ + RBV)
- fibrosis worsening ranged from 23 to 8% (PEG 1.5 $\mu g\ kg^{-1}$ + RBV)
- all regimens significantly reduced fibrosis progression rates relative to pretreatment
- reversal of cirrhosis (change in fibrosis score from pretreatment) was observed in 49% of patients who had baseline cirrhosis
- six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage, SVR, age <40 years, body mass index <27 $kg\ m^{-2}$, no or mild baseline necroinflammatory activity (based

primarily on necrosis) and viral load <3.5 million copies ml^{-1}.

There was significantly less worsening of fibrosis among patients who achieved SVR (7%) than among relapsers (17%) or non-responders (21%). There was also significantly more necroinflammatory activity improvement in those with SVR than in relapsers or non-responders. Rates of fibrosis progression were lower after treatment in both virological responders and non-responders, with no significant differences between different treatment regimens (but there was a significant difference between responders and non-responders). Histological response was related both to viral response and several baseline factors. The results suggest that even without an SVR treatment may slow the progression of liver fibrosis and would therefore argue against early cessation of treatment in patients without a virological response. Histological response should also be evaluated in these patients. The question of which regimen would be best for such patients should be evaluated prospectively.

Some caution should be used in interpreting this report because only some of the comparisons are randomised, within-trial comparisons. In addition, most of the included regimens (particularly those using PEG) were tested in only one or two trials. Finally, this analysis only considered trials using PEG or IFN-α-2b; therefore, the findings cannot necessarily be generalised to PEG or IFN-α-2a.

Cochrane Hepato-Biliary Group

"Pegylated interferon alpha for chronic hepatitis C"[68] is the title of a protocol for a systematic review currently on the Cochrane Library. The review will assess the clinical effectiveness of RCTs of pegylated interferon in previously untreated patients, relapsers and non-responders to previous treatment. The review will assess the effectiveness of monotherapy (PEG versus no intervention; PEG versus placebo; PEG versus IFN) and dual therapy (PEG + RBV versus IFN + RBV). Primary outcomes will include SVR, liver-related morbidity and survival, while secondary outcomes include end of treatment virological response, end of treatment and sustained biochemical response, histological response, adverse events, treatment discontinuation, dose reduction, quality of life and cost-effectiveness. Subgroup analyses will be performed to assess the effect of factors including gender, genotype, baseline viral load, presence of bridging fibrosis and cirrhosis on SVR. Analyses will also examine the effect of PEG dose (<180 versus 180 μg per week, <1.5 versus ≥ 1.5 kg per week), duration of therapy (<24 weeks versus >24 weeks) and formulation of PEG on SVR (2a versus 2b).

Treatment for patients with co-morbidities

The question of treatment of hepatitis C in patients who have other illnesses such as HIV or haemophilia is important, but has received relatively little attention. The major trials testing the efficacy of PEG and other hepatitis C treatments have excluded patients with significant co-morbidities.

The recent systematic review by the AHRQ (discussed above) specifically addressed the question of treatment of hepatitis C with co-morbidities.[65] This review reported on three trials that tested treatment in patients undergoing haemodialysis, in patients with haemophilia, or in patients co-infected with hepatitis C and hepatitis B. However, none of these trials tested the efficacy of PEG in these groups. Likewise, the search performed in the current review revealed no full reports of controlled trials of PEG in patients with co-morbidities. However, many patients with HCV do have other co-morbidities and some evidence, albeit not using PEG, is available.

Many patients with HIV also are infected with hepatitis C and therefore the question of efficacy of HCV treatment in patients co-infected with HIV is germane. HIV and HCV share common routes of transmission. With recent improvements in the treatment of HIV leading to increased life expectancy, the treatment of co-infections such as hepatitis C in this population has received more attention. Between 7 and 57% of patients with HIV are also infected with hepatitis C.[69] The variation in co-infection rates is related to the varying hepatitis C risk factor distributions of the study populations. Among co-infected patients, hepatitis C is the leading non-AIDS cause of death, and end-stage liver disease due to hepatitis C accounts for up to 50% of deaths.[69] Although the mechanisms are not fully understood, it appears that HIV is associated with accelerated liver disease and reduced survival in hepatitis C-infected patients. Likewise, hepatitis C is an independent factor associated with HIV progression to AIDS and AIDS-related death.[69] Treating co-infected patients is complicated by the possibility of adverse drug interactions.

A recent systematic review of the management of co-infection with HIV and HCV[69] revealed no placebo-controlled trials of HCV treatment conducted in co-infected patients. Twelve studies using either IFN monotherapy or IFN + RBV reported equivalent SVR rates in co-infected and HCV infected patients. However, none of these studies used PEG and none was an RCT.

There are several ongoing trials of treatment in patients with co-infections (see Appendix 10). Preliminary reports from some trials are available in abstract form. Only three trials that included a comparison between PEG and non-pegylated interferon are mentioned here. It should be noted that the methodological quality of studies reported only in abstracts cannot currently be fully evaluated.

Two abstracts[70,71] report preliminary data from a trial that involved 416 patients co-infected with HIV. Patients were randomised to receive either PEG-α-2b (1.5 mg kg^{-1} per week) plus RBV (800 mg per day) or IFN-α-2b (3 MIU three times per week) plus RBV (800 mg per day) for 48 weeks. Although a 24-week follow-up for the trial was scheduled the abstract only reported results from the end of treatment.[70] An EOTR was seen in 44% of the PEG group and 27% of the IFN group (p = 0.009). The response rate for patients with genotype 1 or 4 was 19%, whereas the response rate for patients with genotype 2 or 3 was 57%. (The abstract did not specify whether these response rates by genotype were in the IFN or the PEG group.) Treatment was discontinued in 30% of patients and severe adverse events occurred in 24% (42 in the IFN group and 57 in the PEG group, p = 0.08). The second abstract[71] considered the effects of HCV treatment on HIV viraemia, concluding that the treatment did not significantly increase or decrease plasma HIV viraemia during the first 6 months of treatment. At week 48, a mean decrease of 115 CD4 cells mm^{-3} was observed. The results did not support a benefit of PEG in treating HIV infection in HCV co-infected patients.

Another study[72] included 47 IDUs who were co-infected with HIV and HCV. The patients were treated with IFN-α-2b (5 MIU daily for 3 months, then 5 MIU three times per week) plus RBV (1000–1200 mg per day) or PEG-α-2b (1.5 μg kg^{-1} per week) plus RBV (800 mg per day). Treatment was for 24 weeks for genotypes 2 and 3 and for 48 weeks for genotypes 1 and 4. It is not clear when results were obtained. Among those receiving IFN + RBV, 23% had a sustained response, 21% had an early response, 29% were non-responders and 27% discontinued therapy. Among those receiving PEG + RBV, 20% had a sustained response, 36% had an early response, 12% were non-responders and 32% discontinued therapy. These results indicate lower rates of sustained response than in patients who are not co-infected. This may be due to high levels of discontinuation owing to side-effects such as psychiatric co-morbidity and drug interactions with concomitant highly active antiretroviral therapy (HAART).

Another abstract[73] offered a preliminary report of 36 patients randomised to receive IFN-2b (Intron A 3 MIU three times per week) plus RBV (800 mg per day) or PEG-2b (Peg-Intron 1.5 μg kg^{-1} per week) + RBV (800 mg per day) for 6–12 months according to genotype. No viral response data were presented, but the PEG treatment was associated with significantly greater neutropenia than IFN. Even low-dose RBV may lead to life-threatening lactic acidosis in patients taking nucleoside reverse transcriptase inhibitors containing HAART. These findings suggest that co-infected patients should be very carefully monitored during HCV treatment.

No trials were located in which patients with other co-morbidities were treated in a design involving a control condition.

Results: retreatment of non-responders to interferon monotherapy

This section is split into two subsections, the first looking at the evidence for the effectiveness of retreatment with PEG dual therapy, and the second looking at retreatment with non-PEG dual therapy.

Assessment of effectiveness of retreatment: dual therapy (PEG + RBV)

No fully published trials of the retreatment of non-responders to IFN monotherapy with PEG were identified in this review. The paucity of literature is probably due to the relatively recent introduction of pegylated interferon. However, conference abstracts were located relating to two ongoing studies. As these have yet to undergo peer review their results should be interpreted with caution. Furthermore, neither of these studies includes an arm in which patients receive IFN monotherapy as a comparator. This is likely to be

because advances in therapy over recent years would probably now make it unethical to retreat patients with IFN monotherapy. Therefore, one can only make indirect comparisons between retreatment with PEG dual therapy and IFN monotherapy.

Shiffman[74] presents the results to date of the lead-in phase of the HALT-C (Hepatitis C Anti-viral Long Term Treatment against Cirrhosis) trial in which patients with advanced fibrosis or cirrhosis who remain HCV positive despite dual therapy with PEG receive long-term maintenance PEG interferon monotherapy over 4 years in an attempt to prevent histological progression, reduce the development of hepatocellular carcinoma and lessen the need for hepatic transplantation. The trial is supported by the US National Institute of Diabetes and Digestive and Kidney Diseases, and Hoffman-LaRoche (USA). Non-responders to IFN monotherapy and dual therapy with IFN+RBV were retreated with PEG-2a (180 mg per week) plus RBV (1000 mg per day) for 24 weeks. Patients who were HCV RNA positive at week 20 were classed as non-responders and entered the long-term HALT-C trial, while those who were RNA negative were treated until week 48, and then followed up until week 72. Results are currently presented for 212 of the 863 patients enrolled in the trial for whom SVRs are available. The majority of patients had advanced fibrosis or cirrhosis, were infected with genotype 1 and were predominantly male. EOTRs were achieved in 53%, with SVR achieved in only 20%. SVRs were significantly greater in patients who had previously failed IFN monotherapy than in those who had failed dual therapy with IFN + RBV (34% versus 11%, $p < 0.005$). Patients with genotype non-1 and who were less than 50 years of age also achieved higher SVRs. Factors not related to SVR included gender, body weight and baseline viral load. Again, caution must be exercised in interpreting these results of this study, given its status as a conference abstract and the absence of any control of comparison group.

Jacobson and colleagues[75] present the results to date of a Schering-Plough-supported RCT in which patients who had failed to respond to either IFN monotherapy or IFN dual therapy, or who had relapsed following IFN dual therapy, were randomised to receive a lower dose of PEG-2b (1.0 $\mu g\ kg^{-1}$) with a higher dose of RBV (1000–1200 mg per day), or conversely a higher dose of PEG (1.5 $\mu g\ kg^{-1}$) and a lower dose of RBV (800 mg per day). Treatment is planned for 48 weeks with cessation after 24 weeks if HCV RNA remains positive. Results are presented for the 231 of the 330 patients enrolled who have completed 24 weeks of treatment. Response rates at 24 weeks of treatment were highest for relapsers to previous IFN + RBV therapy followed by non-responders to IFN monotherapy and were lowest in non-responders to dual therapy with IFN + RBV, irrespective of the dose of PEG.

As might be expected, both of these studies suggest that retreatment with PEG dual therapy is more effective for patients who have failed IFN monotherapy than for those who failed previous dual therapy with IFN + RBV. Shiffman[76] suggests that the likelihood that retreatment will be effective is directly related to the differences in efficacy between the initial and the retreatment regimens. The expected range for SVR during retreatment can be estimated by calculating the difference in end of treatment virological response rates between the two therapies and the relapse rate of the newer treatment. It is estimated that non-responders to IFN monotherapy would have a higher chance of an end of treatment response when retreated with PEG dual therapy than with dual therapy with IFN.

In summary, the evidence for the clinical effectiveness of retreatment with PEG dual therapy is currently only available in conference abstract form and is based on two studies, one of which is an uncontrolled evaluation of dual therapy as a lead-in phase to an RCT of long-term maintenance therapy, and the other an RCT comparing two different dose regimens of dual PEG. Preliminary evidence suggests higher EOTR and SVRs for patients retreated after failing IFN monotherapy than those retreated after failing IFN + RBV dual therapy. Further RCTs are required, comparing PEG dual therapy with IFN dual therapy.

Assessment of effectiveness of retreatment: dual therapy (IFN + RBV)

Given the lack of fully published evidence for the clinical effectiveness of retreatment of patients with pegylated interferon, the evidence base for retreatment with non-pegylated interferon was examined. To be included in this section of the review studies had to assign patients who had failed a previous course of monotherapy (IFN) randomly to dual therapy (IFN+RBV) or to monotherapy (IFN). Trials with more than one comparator were also eligible as long as there was an arm that received IFN monotherapy (e.g. IFN+RBV versus IFN ± placebo versus IFN + amantadine). Trials that included a mixture of

TABLE 15 *Quality assessment of included systematic reviews*

Review	Good relation between study question and inclusion/ exclusion criteria	Evidence of thorough search for all relevant research	Validity of included studies adequately assessed	Sufficient detail of individual studies presented	Primary studies summarised appropriately
Cheng *et al.*, 2001[77]	✓	Primarily MEDLINE	✓	✓	✓
Cummings *et al.*, 2001[78]	✓	✓	✓	✓	✓
Kjaergard *et al.*, 2002[79]	✓	✓	Randomisation and blinding	In ancillary table	✓
AHRQ, 2002[65,66]	✓	✓	✓	✓	Narrative only
San Miguel *et al.*, 2002[80]	✓	✓	✓	✓	✓

non-responders and relapsers to previous interferon monotherapy were also eligible. The minimum period of previous treatment had to be 3 months.

The clinical effectiveness of retreatment with non-pegylated dual therapy is presented below, first in terms of the results of previous systematic reviews identified; second, through the results of a meta-analysis of individual patient data; and third, through the results of a meta-analysis of all published studies identified to date.

Results of previous systematic reviews of retreatment

The previous assessment report by this group included 12 trials assessing the effectiveness of dual therapy (IFN+RBV) as retreatment for patients who either failed to respond or relapsed following a previous course of interferon monotherapy. Since publication of the report in late 2000 several systematic reviews have emerged that have also addressed the question of retreatment of interferon monotherapy non-responders. These reviews included some of the 12 trials in the assessment report, in addition to a number of other relevant trials, most of which were published since the original assessment report. Rather than performing data extraction and critical appraisal of these additional trials (and thus duplicating the effort of others), the systematic reviews were used as a basis for estimating the clinical effectiveness of retreatment. The reviews were critically appraised, and it was shown that they had systematically searched for relevant trials, assessed their quality and synthesised their results appropriately (*Table 15*).

The inclusion criteria used in these reviews were broadly similar to those used in the current review. Each of these reviews included only RCTs in their primary analyses. Two reviews (Cheng[77] and San Miguel[80]) used more stringent inclusion criteria with regard to doses of IFN and RBV, dose frequency and treatment duration. The other three reviews did not restrict inclusion based on these criteria. In general, trials have tended to be very similar in these characteristics, such that the use of these inclusion criteria is not likely to have had much effect on study selection. Three reviews (Cheng,[77] Kjaergard[79] and San Miguel[80]) explicitly excluded studies in patients with other diseases such as HIV infection or haemophilia. One review (Kjaergard[79]) included trials published as conference abstracts. SVR in all reviews was based on results from 24 weeks or longer after the end of treatment.

All reviews assessed the quality of included studies. The Cheng and Kjaergard reviews[77,79] reported for each included study whether there was appropriate generation of the allocation sequence and appropriate allocation concealment, and whether the trial was double blind. This approach is very similar to that used in the current review. The remaining three reviews assessed study quality using scales, with each using a different scale. The total quality scale scores were presented in the Cummings and San Miguel reviews,[78,80] whereas quality subscale scores (including a bias subscale) as well as a total quality score were presented in the AHRQ review.

Table 16 presents a summary of results from the four reviews that performed statistical meta-analyses pertaining specifically to the comparison of IFN + RBV versus IFN retreatment in previous non-responders to IFN monotherapy.

In terms of results there was general concordance between the reviews with pooled SVRs for retreatment with dual therapy in the range

TABLE 16 *Results from previous systematic reviews of IFN + RBV versus IFN in non-responders to previous IFN monotherapy*

Study	No. of included studies (total *n*)	Pooled SVR result
Cheng *et al.*, 2001[77]	8 trials (n = 726)	SVR IFN + RBV = 13.2% (95% CI 10.0 to 17.3%) OR 4.9 (95% CI 2.1 to 11.2) in favour of IFN + RBV
Cummings *et al.*, 2001[78]	11 studies (n = 899)	SVR IFN + RBV = 14% (95% CI 11 to 17%) SVR IFN = 2% (95% CI 1 to 4%) Risk difference = 7.0% (95% CI 2 to 13%)
Kjaergard *et al.*, 2002[79]	10 trials	RR of not having SVR = 0.89 (95% CI 0.83 to 0.96) in favour of IFN + RBV
San Miguel *et al.*, 2002[80]	5 trials (n = 786)	SVR IFN + RBV = 12.6% (95% CI 9.5 to 16.3%) SVR IFN = 2% (95% CI 0.9 to 4.0%) OR 5.49 (95% CI 1.9 to 15.89)
The AHRQ review did not perform quantitative synthesis.		

12–14% compared with 2% for retreatment with monotherapy only, indicating that dual therapy is far more effective as a retreatment strategy. However, given the response rates of 49% for patients retreated with IFN + RBV following relapse from previous monotherapy,[32] these results appear disappointing.

Only one review considered the effects of prognostic variables on response by meta-regression.[79] The Kjaergard review found a significant positive association between the effect of IFN + RBV and the proportion of patients with genotype 1 after adjusting for previous treatment, intervention regimen and patient characteristics, suggesting the patients with genotype 1 benefit more from IFN + RBV as opposed to IFN alone than do patients with other genotypes. There was a significant negative association between the benefit of dual therapy and the proportion of patients with cirrhosis, suggesting that patients with cirrhosis benefit less from combination therapy. The Cummings review[78] considered only the effects of treatment variables in metaregressions.

Two reviews considered effects of prognostic variables by means of sensitivity analyses.[77,80] In the Cheng review[77] SVRs were determined after excluding studies containing the highest or lowest proportion of patients with the covariate. The overall SVR for trials that included more than 50% of patients with genotype 1 was decreased compared with the primary analysis. Minimal differences from the primary analysis were detected when sensitivity analyses were performed on trials varying in baseline levels of HCV RNA. The San Miguel review[80] considered trials with more than or less than 50% of patients with genotypes 1 and 4. The confidence intervals for these analyses overlapped, but a greater response was seen in trials with a lower proportion of patients with genotypes 1 and 4.

Results from an individual patient data meta-analysis

Cammà and colleagues[45] questioned the usefulness of retreating all patients indiscriminately given the disappointing results from the systematic reviews discussed above. To that end they performed an independent patient data meta-analysis to reassess efficacy and safety of retreatment with IFN and RBV, to assess the best retreatment schedule, and to identify predictors of sustained response to enable better targeting of therapy to patients most likely to respond. Data on 581 non-responders to previous IFN monotherapy were obtained from ten European (mostly Italian) treatment centres, published as RCTs (n = 3), controlled clinical trials (CCTs) (n = 1) and prospective cohort studies (n = 6). Five of the studies had been fully published, three were conference abstracts and two remained unpublished, representing 312 (54%), 189 (32%) and 80 (14%) of the patients, respectively. The sample comprised mostly males (66%), mean age 46 years, and infected with genotype 1 (54%), with only 11% having cirrhosis. Retreatment regimens varied from 3 MIU IFN three times per week plus RBV over 6 months to 12 MIU three times per week plus RBV over 12 months. Around two-thirds of patients were retreated for a total of 12 months (61.3%). The type of IFN used included 2b (91%) and leucocytic N-3 (5.7%), but 2a does not appear to have been used.

A 'complete' sustained response (SR; defined as both a biochemical and a virological response) was achieved by 15.7% (95% CI 15.6 to 22%) of

patients (n = 88/559), while 9.2% of patients (n = 54/581) withdrew owing to side-effects associated with retreatment. There was no statistically significant difference in the probability of achieving a complete SR according to prognostic factors such as genotype, baseline liver histology and baseline viral load. Univariate analysis identified three factors significantly associated with a complete SR:

- younger age
- γ-glutamyltransferase (GGT) levels
- retreatment with a total IFN dose of ≥ 432 MIU.

Absence of cirrhosis was marginally significant (p = 0.061). A subgroup analysis was performed on the 396 patients retreated with the higher total dose of IFN (≥ 432 MIU) to assess whether there was a significant effect of duration of treatment. A complete SR was achieved in 74 (18.6%; 95% CI 14.9 to 22.6%) of these patients. Among these patients the likelihood of a complete SR was significantly lower when the higher dose was administered over a shorter period (≤ 26 weeks) (n = 7/73, 9.5%; 95% CI 3.5 to 19.5%) versus a longer period (>26 weeks) (n = 67/323, 20.7%; 95% CI 16.4 to 25.3%) (p = 0.027).

Multivariate analysis identified the following factors as independent predictors of complete SR (in decreasing order of significance):

- retreatment with a total IFN dose of ≥ 432 MIU (OR 2.25)
- normal pretreatment GGT levels (OR 0.54)
- age (<45 years old) (OR 0.62).

These factors were grouped together in combinations to be applied to subgroups of patients with best and worst case scenarios (i.e. those in whom all three factors apply; for those whom only one applies). Predictably, the SRs were higher for patients with all three factors than those with only one (n = 36/118, 30.5%, versus n = 3/55, 5.4%, respectively). The number needed to treat (NNT) to obtain one complete SR in patients with all three factors was 3.3, while for those with only one factor the NNT was 15.8.

The results of this meta-analysis are of limited value to this report as no IFN monotherapy comparator arm is included, precluding an assessment of the marginal clinical and cost-effectiveness. Nevertheless, the results provide some indication of predictors of SR and thus how retreatment may be targeted to specific subgroups of patients.

Results from the meta-analysis

The systematic reviews described above included literature published only up to November 2001. Therefore, an additional literature search was performed to identify studies published between then and February 2003 (see Appendix 8). This search yielded an additional three RCTs. The search also identified studies in which patients were retreated with IFN + RBV but without an IFN-only/IFN + placebo comparator (e.g. comparing different doses/durations of IFN +RBV).[76,81–89] These studies were excluded as they prohibited analysis of the marginal clinical effectiveness and cost-effectiveness of moving from IFN to IFN + RBV.

The grand total of retreatment studies meeting the inclusion criteria was therefore 20:

- 12 from the previous assessment report[90–101]
- an additional five from other systematic reviews[102–106]
- three from the updated February 2003 search.[107–109]

Although the reviews had relied on the previous systematic reviews as a means of identifying quality assessed relevant trials, the February 2003 search yielded newer studies that have not been subjected to formal systematic review. Therefore, a meta-analysis was performed to synthesise all of the available evidence. This represents the most up-to-date meta-analysis in this area, with the largest number of RCTs, containing the biggest total number of patients retreated (n = 2144).

The proportion of patients remaining infected with HCV after retreatment was entered into Cochrane Review Manager 4.1 software. Two separate analyses were performed. The primary analysis included trials in which therapy was administered for 24 weeks (n = 1515). (This analysis also consisted of subgroups of trials that included only patients who had never responded to previous IFN treatment and trials that included both non-responders and patients who had relapsed after initial response to previous IFN treatment. Two included trials[98,105] randomised and reported separately results from non-responders and relapsers. Only the non-responder data are included from these trials.)

A second analysis was performed on trials with treatment durations greater than 24 weeks (n = 274). When trials reported the results from ITT analyses, these results were entered into the meta-analyses. Four trials reported on-treatment

analyses only and an additional four trials were unclear as to whether their SVR results were based on an ITT analysis. When ITT analyses were used, patients whose data were not available at follow-up were considered non-responders to treatment. Owing to significant statistical heterogeneity, a random effects model was used in each of the analyses.

- The primary analysis included 16 trials in which either non-responders (ten trials) or a mix of non-responders and relapsers (six trials) were retreated with either IFN + RBV or IFN monotherapy for 24 weeks.
- In the ten trials that included only non-responders (which included two trials that recruited both non-responders and relapsers, but that randomised and reported upon the two groups separately), the meta-analysis showed that the combined relative risk was 0.92 (95% CI 0.86 to 0.98), favouring treatment with IFN + RBV.
- Combining these ten trials together, the SVR for retreatment with IFN + RBV was 12% (95% CI 8.8 to 14.8%) and for retreatment with IFN was 2% (95% CI 0.7 to 3.5%).
- For the six trials that included both non-responders and relapsers the combined relative risk was 0.82 (95% CI 0.75 to 0.91), favouring treatment with IFN + RBV.
- Combining the six trials together, the SVR for retreatment with IFN + RBV was 23% (95% CI 18.2 to 27.2%) and for retreatment with IFN was 5% (95% CI 2.8 to 7.9%).
- For all 16 trials taken together, the combined relative risk was 0.89 (95% CI 0.84 to 0.95), favouring treatment with IFN + RBV.
- Combining all 16 trials together, the SVR was 16% (95% CI 13.8 to 19%) for retreatment with IFN + RBV and 3% (95% CI 2.0 to 4.6%) for retreatment with IFN (*Figure 5*).

The effect of combined IFN and RBV treatment was greater in the trials that included both relapsers and non-responders. Among the trials reporting SVR separately for previous non-responders and relapsers, the relapsers were far more likely to achieve a sustained response in the retreatment trial.

There was significant heterogeneity, which may be due to several differences among the trials. The trials differed in the doses of IFN given and the trials with the lower doses are displayed first within each subgroup in the figure. There do not appear to be reliably differing effects according to IFN doses. There were also small variations in RBV doses. Trials also differed in which type of IFN was used. Trials using either recombinant IFN or natural IFN were included. The nature of the previous unsuccessful treatment may also have differed among trials (e.g. IFN dose or duration).

An additional analysis was performed on two trials that continued treatment for longer than 24 weeks. The meta-analysis results for these two trials are shown in *Figure 6*. This analysis again demonstrated an advantage of retreatment using the combination of IFN and RBV.

- The combined relative risk was 0.80 (95% CI 0.66 to 0.96), favouring IFN + RBV.
- The SVR for these two trials combined was 22% (95% CI 15.4 to 29.0%) for retreatment with IFN + RBV and 5% (95% CI 2.2 to 10.8%) for retreatment with IFN. These longer trials included only patients who had not responded to previous IFN monotherapy (i.e. there were no relapsers).
- In comparison with the shorter trials with non-responders, these longer trials suggest the possibility that for non-responders dual therapy of a longer duration may be more effective than a 6-month course of treatment.

Two trials that met the inclusion criteria were nonetheless not included in either meta-analysis because they differed significantly from other trials. One trial, by Andreone and colleagues,[106] included two conditions testing IFN + RBV and IFN retreatment in previous non-responders. However, the treatment was only given for 4 months. The SVR of 14% in the IFN + RBV group was similar to that seen in trials lasting for 6 months, but there were no patients with SVR in the IFN group. A trial by Pol and colleagues[92] retreated non-responders for 12–14 months, but the combined treatment with IFN and RBV lasted for only 2 months and occurred between phases of RBV alone and IFN alone. Perhaps not surprisingly, the SVR in the group receiving IFN + RBV for part of the treatment was only 10%. These results suggest that dual therapy may need to be administered for some minimum period in combination rather than sequentially for the best effect.

Retreatment with alternative interventions: amantadine

Although not within the scope of this assessment report, several RCTs of retreatment with various combinations of IFN, RBV and amantadine hydrochloride (AMA) were identified. For example, there has been evaluation of dual

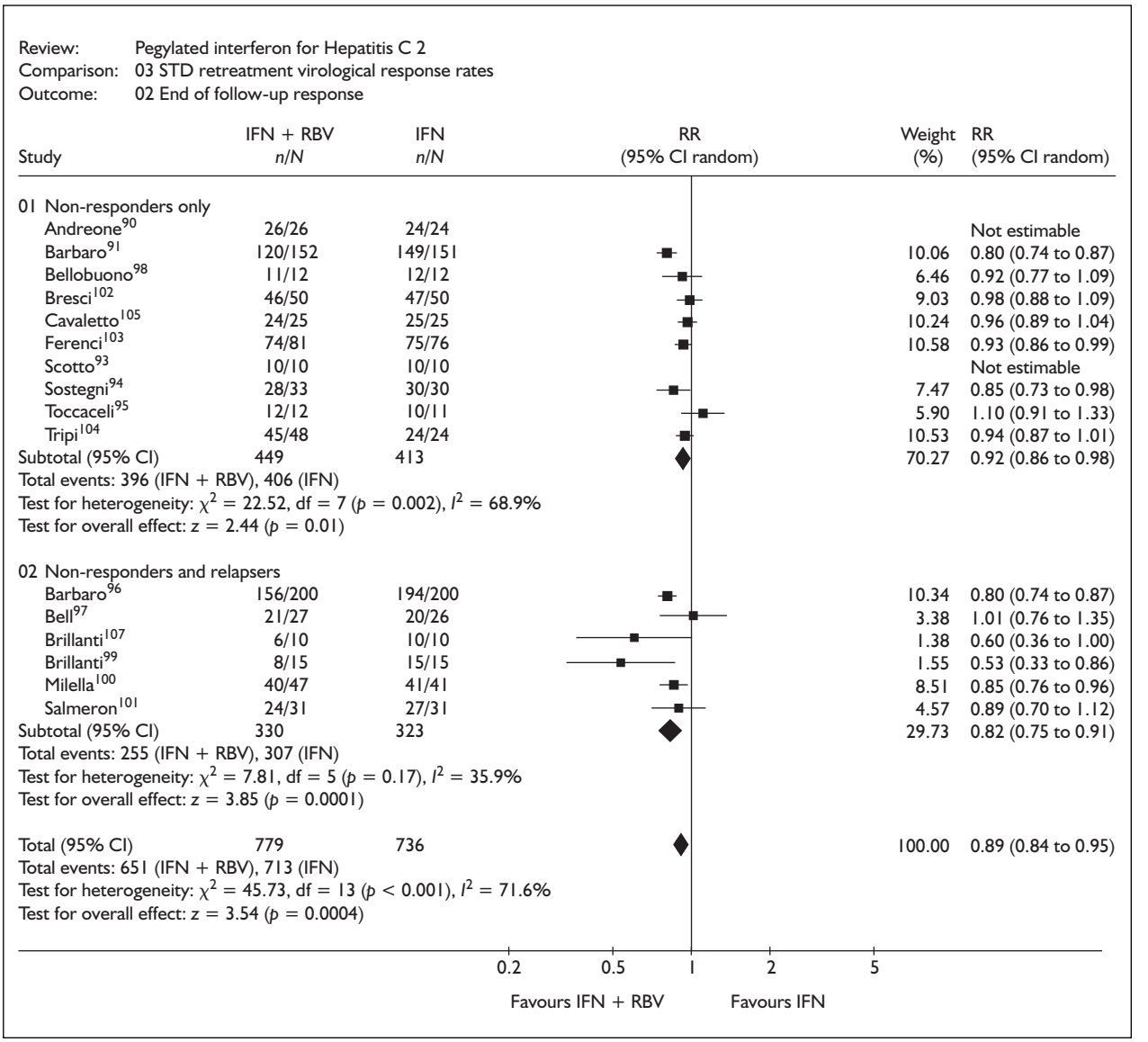

FIGURE 5 *Relative risk for retreatment (24 weeks). STD, non-pegylated interferon.*

therapy with IFN + AMA versus IFN monotherapy,[110] or AMA monotherapy,[111] or IFN + placebo.[112] There has also been a head-to-head comparison of dual therapy with IFN + RBV against dual therapy with IFN + AMA,[112] as well as retreatment with triple therapy (IFN + RBV + AMA) versus dual therapy (IFN + RBV).[113] Triple therapy in one RCT of 94 patients was associated with an SVR of 48% in comparison to an SVR of 5% dual therapy (IFN + RBV).[114] A systematic review of 'Amantadine with or without interferon for chronic hepatitis C' may potentially be conducted by the Cochrane Hepato-Biliary Group in the near future, although it is not yet clear whether this will include studies of patients who are non-responsive to prior IFN monotherapy.

Retreatment: summary and discussion

- The evidence for the clinical effectiveness of retreatment with PEG is at present limited to conference abstracts. Preliminary results suggest EOTRs in 53% of patients, and SVRs only in around 20%. SVRs were significantly greater in patients who had previously failed IFN monotherapy than in those who had failed dual therapy with IFN + RBV.
- At least one RCT is likely to publish fully the results of retreatment with PEG dual therapy in the near future.
- There is a much larger evidence base for retreatment with dual IFN + RBV, comprising a number of systematic reviews, an individual patient data meta-analysis, and the authors'

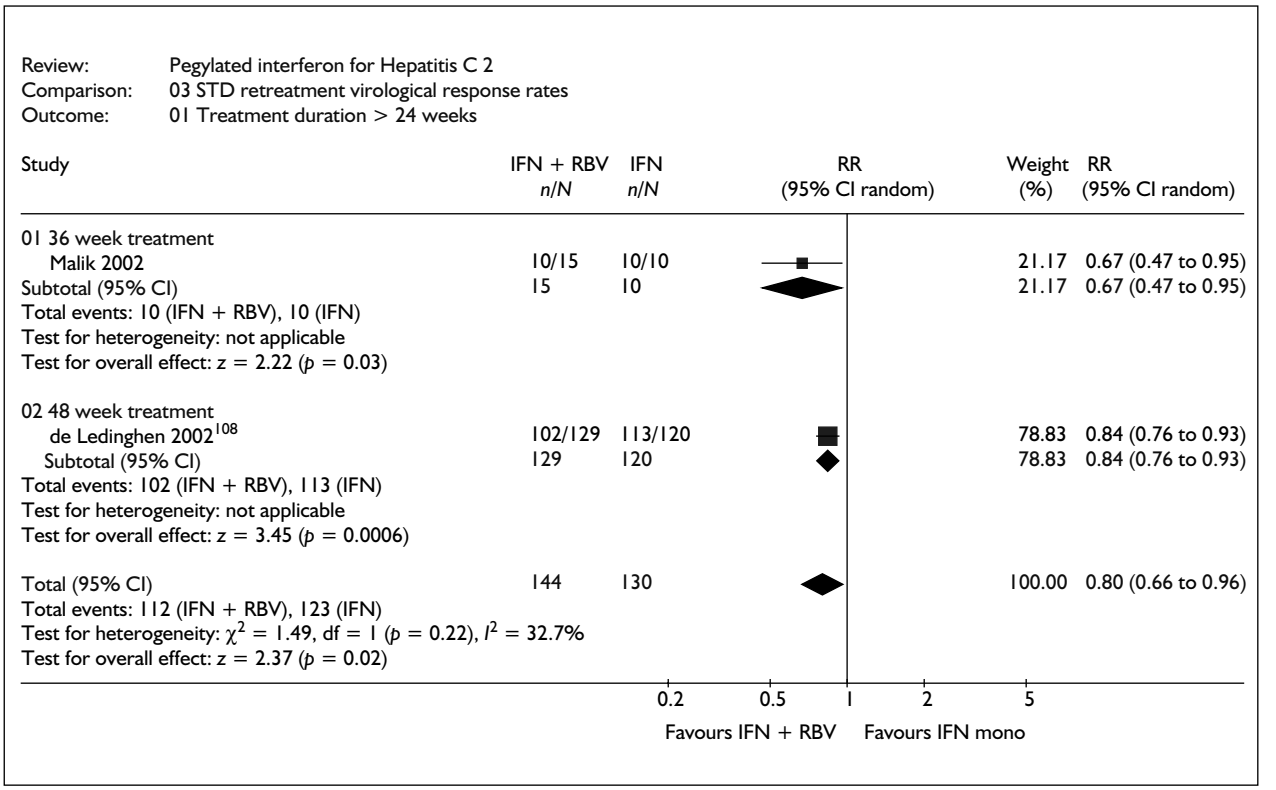

FIGURE 6 *Relative risk for retreatment (>24 weeks)*

meta-analysis encapsulating all of the available evidence.

- Results from other systematic reviews reporting SVRs for retreatment with dual IFN + RBV are in the range 12–14%, compared with only 2% for retreatment with IFN monotherapy. The SVR for retreatment with IFN + RBV is only slightly lower than the 20% SVR observed for retreatment with PEG + RBV, although this is an indirect comparison based on a conference abstract so caution is urged in this interpretation.
- The current review meta-analysed all located RCTs that compared combination IFN + RBV therapy and IFN monotherapy in the retreatment of non-responders and relapsers to previous IFN monotherapy. These analyses demonstrate that the risk of remaining infected with HCV is reduced by approximately 11% after 6 months of treatment. The risk reduction is slightly greater (18%) in trials that included patients who had relapsed after response to previous IFN monotherapy as well as those who had never responded to previous IFN monotherapy, suggesting that retreatment with combination therapy is slightly more effective in relapsers than in non-responders. These results are very similar to those from the other systematic reviews; however, it is useful to see the differences between trials that included non-responders to previous IFN treatment versus trials with a mix of non-responders and relapsers.
- The two trials that retreated non-responders for longer than 24 weeks are new and only one of these had been included in one previous systematic review. The analysis of these trials suggests that retreatment of non-responders with 36 or 48 weeks of IFN + RBV may be more effective than shorter durations of retreatment, resulting in a 20% reduced risk of remaining infected with HCV for IFN + RBV treatment versus IFN alone. However, as this is an indirect comparison, it should be treated with caution.
- Multivariate analysis performed on the individual patient meta-analysis found that younger patients with normal baseline GTT levels retreated with a total dose of ≥ 432 MIU of IFN over a duration of longer than 26 weeks are likely to derive the most benefit. A complete sustained response (i.e. both biochemical and virological) was achieved in 30.5% of patients who met these criteria, compared with only 5.4% who only met one criterion.

The relatively low proportion of patients who respond after retreatment with both IFN + RBV and PEG + RBV raises the issue of what course of action should be taken for patients who have yet to respond. Shiffman[76] classified these patients according to those with advanced fibrosis or cirrhosis and those with either no or only mild degrees of fibrosis, the latter of whom are at low risk of developing cirrhosis within the next 5–10 years or potentially longer. For these patients long-term monitoring is recommended and retreatment only if a potentially more effective therapy emerges. For patients at higher risk of cirrhosis and hepatic decompensation long-term maintenance therapy is recommended to improve hepatic inflammation and fibrosis. This suggestion is based on the results of trials of IFN monotherapy in which patients experienced a 40% histological response during treatment. Shiffman and colleagues later conducted an RCT that formally tested this hypothesis, whereby non-responders to IFN monotherapy were randomly assigned to remain on IFN long term or to cease treatment.[115] After 2.5 years, patients on maintenance therapy experienced reduced HCV RNA levels and improvements in hepatic inflammation and fibrosis, in contrast to those who ceased treatment, who experienced no such benefits. The effectiveness of long-term maintenance therapy with PEG IFN is the subject of the HALT-C trial as mentioned above, which is due to complete in 2006.

Treatment of patients with mild hepatitis C

Although the focus of the current report is primarily the effect of treating severe chronic hepatitis C, many patients have mild histological changes on liver biopsy and are at lower risk of developing liver-related morbidity or mortality. It has been assumed that this lower risk is outweighed by the potential risks of treating the infection. These patients, however, may be at risk of disease progression. There has been some research on responses to treatment in patients with mild disease. There are no reports of trials using pegylated interferon, but the use of non-pegylated interferon has been tested in these patients.

One Swedish trial[47] randomised 116 patients with histologically mild disease (Knodell activity score ≥ 1 and ≤ 6, periportal piecemeal necrosis $\pm$ bridging necrosis ≤ 3, interlobular degeneration and focal necrosis ≤ 3 and portal inflammation ≤ 4, fibrosis stage ≤ 1) to treatment using IFN-α-2b (3 MIU three times per week) with or without RBV (1000–1200 mg per day depending on weight) for 52 weeks. Treatment was stopped according to the protocol after 6 months in 42 patients (18 in the combination group) who were still HCV RNA positive. At follow-up (week 78) there was a 54% SVR for patients on IFN + RBV and a 20% SVR for patients on IFN and placebo ($p = 0.001$). The SVR was significantly higher for combination therapy both in patients with non-1 genotypes (81% versus 36%) and for genotype 1 (28% versus 4%). Viral loads were significantly lower in those patients who cleared the virus than in those who were not responders in both treatment groups. Among those patients with evaluable liver biopsies, there was a significant improvement in mean histology grade score in all sustained responders independent of treatment arm. No improvement in histology was seen in those patients without SVR. All but 12 patients reported at least one adverse event, the majority being classified as mild to moderate. Treatment was discontinued in nine patients because of side-effects, three of which were classified as serious adverse events. These results suggest that combination IFN + RBV therapy is safe and effective in patients with mild disease. It is noteworthy that the SVRs achieved in this trial are higher than for some of the larger trials evaluating this therapy in patients with more severe disease. On this basis it could be argued that pegylated interferon treatment in these patients is also likely to be effective.

Further evidence for the effectiveness of treating patients with mild disease will soon be published from the UK NHS HTA programme-funded Mild HCV trial (due to report in 2005). This multicentre RCT recruited 205 patients and compared the effects of combined IFN-2b (Viraferon, 3 MIU three times per week) plus RBV (1000–1200 mg per day) with no treatment. The patients were adults with mild chronic hepatitis C (Ishak necroinflammatory score <4, fibrosis score <3) who had not been previously treated with IFN and did not have significant co-morbidities. Patients were treated for 48 weeks and monitored throughout the trial. Patients were also seen for follow-up 12, 24 and 48 weeks after the end of treatment.

The trial will report on virological, histological and biochemical response to treatment 12 months after discontinuation of therapy. The trial will also consider the effects of genotype on response, whether early viral kinetics or host factors can predict a long-term response in combination

therapy, the effect of treatment on quality of life, the cost of the treatment regimen, the potential cost savings of early treatment, and the potential cost savings of targeting therapy and avoiding ineffective therapy.

HRQoL will be assessed using the SF-36 modules 12 and 13 and a validated hepatitis C disease-specific module 14. Health economic issues will be evaluated using a socioeconomic questionnaire. (These are both self-report measures.) The health-economic component is being conducted at three of the 12 centres (St Mary's Hospital, London; Newcastle; and Southampton).

Results: effectiveness of non-invasive tests for fibrosis on biopsy

If treatment for chronic hepatitis C were inexpensive and had no side-effects, it would be given to everyone infected. However, there are life-diminishing treatment side-effects and risks, which have to be offset against clinical benefit, especially as not all patients respond (so that treating all patients means causing side-effects in some who will not benefit). The cost also has to be borne in mind, because treatment is not cheap, and there are the usual opportunity cost considerations, usually reflected in a cost per quality-adjusted life-year (QALY) threshold.

The present consensus is that those with only mild liver disease, or less, should not be treated, because their rate of progression to serious disease is thought to be low and slow. Hence, even leaving monetary considerations aside, the benefits of treatment are thought insufficient to justify the side-effects of treatment. This belief is partly due to a lack of evidence of the costs and benefits of treatment in mild disease, and as mentioned an RCT commissioned by the UK HTA programme is due to report in 2005 (see previous section).

The consensus is based mainly on expectations of progression to more serious liver disease. One of the evidence gaps is in the effect on quality of life of HCV infection in those with only mild liver disease. If their quality of life were reduced to the extent that treatment would achieve a cost-effective improvement in quality of life, then these patients would receive treatment and there would be no need for liver biopsy. The evidence needed is of quality of life at three points:

- before treatment: the effect of chronic viral infection, systemic not just hepatic
- during treatment: a temporary diminution due to side-effects, for 24 or 48 weeks
- after treatment: in those who achieve sustained viral clearance, does quality of life return to normal?

One point worth noting is that in diseases of insidious onset, low-grade symptoms may not be fully appreciated; the patient may not realise how unwell they felt until restored to normal health.

Hence, in most places, the current consensus is that liver biopsy should be done to identify those in whom treatment is appropriate. This applies less to those with haemophilia, because of the risk of bleeding.[116]

Liver biopsy is not without serious though fairly rare side-effects, such as hepatic bleeding. However, it requires hospital care and associated resource use. Other options, less invasive than biopsy, have therefore been sought. These fall into five groups:

- markers of inflammation such as transaminases (e.g. ALT)
- markers of fibrosis such as extracellular matrix tests (e.g. HA laminin)
- cytokines and receptors such as tumour necrosis factors (most of these are associated with fibrosis; however, tumour necrosis factor-α is associated with inflammation but not fibrosis)
- a wide range of other tests
- combinations (sometimes called panels) of tests: these have been used in the hope that the combination would give greater predictive value than single tests.

These were the subject of a recent high-quality systematic review by Gebo and colleagues,[65] on behalf of the US AHRQ (see section 'Evidence from related systematic reviews', p. 31). This review included studies published up to March 2002, and thus a full systematic review of such studies need not be repeated here. The main findings were as follows.

- The transaminases have only modest ability to predict fibrosis on liver biopsy.
- The extracellular matrix tests were of more value, with HA giving the best correlation, though with a wide range of sensitivity and specificity among studies.
- The cytokines are of less value than the extracellular matrix tests.

- Panels of tests gave best results, although they may be of most use at the ends of the disease spectrum, for predicting no or only minimal fibrosis, or at the other end, the presence of cirrhosis.

However, at the borderline that currently matters in clinical care, between mild and moderate liver disease, none of the above tests appeared to be adequate for decisions on treatment.

The reliability of liver biopsy was examined in an earlier (non-systematic) review by Fontana and Lok 2002.[117] They note that a 2-cm core of liver tissue represents 1/50,000 of the whole organ. This may explain therapeutic studies that appear to show regression of changes; the post-treatment biopsy may by chance have been from a less affected section of the liver. Fontana and Lok report reasonably good interobserver agreement among pathologists on fibrosis (70–90%), but less with inflammation.

Herve and colleagues[118] (a study that does not seem to have been included in the Gebo review[65]) examined a group of patients who had persistently normal ALTs. Compared with patients who had chronically elevated ALTs, their group had less fibrosis (mean Knodell score 3.2 versus 7.2). However, only 9% had normal liver histology, and 75% had some histological evidence of progression to chronic liver damage, ranging from mild disease to cirrhosis. Thus, a persistently normal ALT may be associated with less severe liver damage, but may not be a strong enough predictor for treatment decisions.

Albloushi and colleagues[119] found that in the cohort of Irish women infected through contaminated anti-D immunoglobulin, there was little progression seen in biopsies done 2 years apart. They also found that the majority of women had only mild disease 19 years after infection. The average age was 46 years. This study also found that ALT was a poor predictor of fibrosis. [Note that the Trent Hepatitis C Study Group provided unpublished data on disease progression from paired biopsies in patients with initially mild disease; however, their data are academic in confidence and are not reported here (Ryder S, on behalf of the Trent Hepatitis C Study Group: unpublished manuscript, 2003).]

Forns and colleagues[120] (another study not included in the Gebo review[65]) used a panel of tests. Unlike some of the panels proposed, their panel consisted of simple and routinely collected data and tests: age, GGT, platelet count and cholesterol. Their cohort of patients included only 25% with significant fibrosis, and hence is a group more representative of typical patients. They used a score based on Scheuer's classification, and found that only 4% of those with a cut-off of 4.2 or less had fibrosis. About one-third of patients had scores below this level. Furthermore, the small number of positive cases below the cut-off did not have serious liver disease such as cirrhosis. Hence it appears that this group could be spared biopsy since at present they are unlikely to have severe enough disease to be treated. However, they would need to be followed up.

Dienstag[121] in another recent non-systematic review, also concluded that biopsy remained necessary for most patients; again, this was based on the belief that those with mild disease need not be treated. Like some other commentators, he makes the point that better treatments may become available, and that those with only mild disease may do better to wait.

One problem with assessing the value of non-invasive tests is that different studies have been based on different groups of patients, sometimes with more advanced disease. For the present purposes, studies using population-based groups (hence with large numbers of patients with only mild disease) are most useful.

Treatment is currently given mainly with a view to preventing long-term liver disease. However a few studies have now reported on the extent of reduction in quality of life from chronic HCV: about 5% in the study by Siebert and colleagues.[122]

In summary, the main purpose of biopsy is to distinguish those with mild disease from those with more serious liver changes. If it is shown that it is cost-effective to treat those with mild disease, then liver biopsy may become unnecessary.

Meanwhile, it looks as though the best indicators are panels of tests, preferably those that are routinely available in clinics, such as those used by Forns and colleagues.[120] They may be most useful at the ends of the spectrum; that is, for identifying those with serious liver damage who would be treated, and those with mild disease who would not be treated, at present. For patients around the current treat/do not treat margin, the consensus is that liver biopsy is still often necessary, although the balance of risks is different in those with haemophilia.

As discussed elsewhere in this review, pegylated interferon is more effective and has fewer side-effects compared to non-pegylated interferon. Assuming that it is also effective in patients with mild disease will tilt the balance of risk somewhat, and may reduce the need for biopsy. As mentioned earlier (see section 'Pegylated interferon for previously untreated patients', p. 7), the licence for PEG-2a in combination with RBV for patients with genotypes 2 and 3 is changing to remove the phrase "histologically proven" chronic hepatitis C. This suggests that biopsy is not always required in these patients.

Treatment of acute hepatitis C

Although the focus of the current report is on treatments for chronic hepatitis C infection, it is of interest to consider whether treatment of acute infection might be effective and therefore prevent chronic infection. The current literature search strategies were not designed to uncover systematically all studies on this question, but a recent review by Alberti and colleagues[123] considered the studies published in this area. Unfortunately, there have been no published studies identified using PEG in patients with acute HCV. Therefore, the evidence on the use of IFN will be briefly summarised.

Seventeen studies of IFN in patients with acute HCV were included in the Alberti review.[123] Six of these were RCTs that included treated and untreated groups, and four were conducted in similar patient groups with post-transfusion hepatitis. In a meta-analysis of the four trials, IFN therapy was associated with a statistically significant 29% increase in the rate of SVR relative to no treatment. These trials used an IFN dose of 3 MIU three times per week for 12 weeks. More recently, more aggressive treatments have been tested, but unfortunately these studies did not include control groups. Three studies ranged in size from seven to 44 participants and used doses of IFN ranging from 5 to 10 MIU. Each study had an initial phase (or a single phase) that involved daily doses of IFN. These studies reported SVRs of 83%, 98% and 100%. Expected rates of spontaneous resolution of infection would be 30–50%.[123] Tolerability of IFN treatment in patients with acute infection was similar to that usually observed in chronic hepatitis C.

The largest of these more aggressive treatment studies, by Jaeckel and colleagues,[51] recruited 44 patients with acute hepatitis C infection in Germany. They received 5 MIU of IFN-α-2b daily for 4 weeks and then three times per week for an additional 20 weeks. In this study 43 of 44 (98%) of the participants demonstrated undetectable levels of HCV RNA at the end of treatment and at the end of a 24-week follow-up. Response to treatment was not affected by viral genotype, patients' gender or the mode of transmission (although the study may have been too underpowered to detect such effects). One patient stopped therapy after 12 weeks because of side-effects. These results suggest the possibility that chronic disease may be prevented by controlling viral replication early after infection.

These more aggressive treatment studies have been criticised on the grounds that they are prospective case series without a control group, the only comparator in the largest study being a small study of historical control patients.[124] Although progression from acute to chronic HCV infection does occur in a majority of cases, a proportion of patients (perhaps 30% or more) would have had self-limited disease without treatment. The German study has also been criticised for the patient selection.[125] These patients were symptomatic and there is some evidence that symptomatic patients may be more likely to resolve the infection spontaneously than patients who have silent acute disease. Despite these difficulties, the possibility of preventing chronic infection may merit more attention and the use of PEG in such treatment may enhance the early viral replication suppression achieved by daily doses of IFN in studies showing the greatest effects of treatment. Because a relatively large number of patients with acute infection will recover spontaneously, the timing of when to treat acute patients would require careful consideration to minimise treating patients who would have recovered spontaneously.

Chapter 4
Economic analysis

Review of economic studies

Cost-effectiveness studies of dual therapy (PEG)

Several cost-effectiveness analyses of hepatitis C treatment have been published over recent years.[126–129] Some of these studies are based on health economic models that have been developed and revised over time to incorporate changes in health technology. For example, models were recently revised to incorporate the introduction of ribavirin to interferon-α. Likewise, models are now being revised to incorporate the introduction of pegylated interferon, and some of these are described below.

Published data

Siebert and colleagues[122] published a cost-effectiveness analysis of the RCT of dual therapy (PEG-2b + RBV) by Manns and colleagues[41] based on a previously published Markov model.[126,128] The model was adapted to estimate the incremental cost–utility of dual therapy with PEG in comparison to dual therapy with IFN + RBV. The model projects the SVRs from each arm of the trial into 20-year risks for liver-related complications in a hypothetical cohort of patients. Transition probabilities for histological progression, clinical decompensation, mode of decompensation, HCC, liver transplantation and mortality were taken from the published literature. Quality of life was estimated from a cross-sectional interview survey of 348 German HCV patients using a visual analogue scale. Multivariate regression analysis was used to derive utility weights. The patient survey was used for the base-case analysis; however, the EuroQol instrument and physician-based estimates were used in sensitivity analysis. Cost data were obtained from the German healthcare system with non-drug costs inflated to 2000 costs and converted from the German mark to Euros. Cost-effectiveness was estimated using the incremental cost-effectiveness ratio (ICER), and the analysis adopted a societal perspective. Results were presented separately for fixed dose and weight-based dosing of ribavirin, given that the trial identified a statistically significant relationship between SVR and ribavirin dosed according to body weight. Although it is rarely possible to transfer studies from other countries uncritically to UK data, the cost per QALY figures presented in this current assessment report have been converted from Euros into Sterling (at an exchange rate of £1 = €1.46). Costs were discounted at 3%.

Incremental discounted cost per QALYs are presented below (base case highlighted in bold):

- dual therapy with PEG (+ weight-based RBV) in comparison to dual therapy with IFN + RBV = **£4520**
- dual therapy with PEG (+ fixed dose RBV) in comparison to dual therapy with IFN + RBV = **£8082**
- dual therapy with PEG (+ weight-based RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: utility estimate based on EuroQol) = £5479
- dual therapy with PEG (+ fixed dose RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: utility estimate based on EuroQol) = £9931
- dual therapy with PEG (+ weight-based RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: physician utility estimate) = £3356
- dual therapy with PEG (+ fixed dose RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: physician utility estimate) = £5753.

These results show that in general weight-based dosing of ribavirin is more cost-effective than fixed dosing. The cost per QALY estimates for weight-based dosing remained under €50,000 (around £34,000) for a number of clinical subgroups for which assumptions were varied in the sensitivity analysis. For example, the incremental cost per QALY for patients with genotypes other than 2 or 3 was around £3400, while for those with genotype 2 or 3 the figure was around £10,200. Likewise, for patients with low baseline viral load the incremental discounted cost per QALY was approximately £2400 in comparison with £14,300 for patients with high viral load. Sensitivity analysis estimates for fixed dosing of RBV showed that treatment was cost-effective for clinical subgroups, except for patients with high baseline viral load and those with genotypes 2 and 3.

Again, this may reflect the high SVRs experienced by patients in this trial with these genotypes irrespective of treatment. Life expectancy increased by 3.8 years (when treated with IFN + RBV), 4.3 years (PEG with fixed RBV) and 4.9 (PEG with weight-based RBV). One of the limitations of the study, as acknowledged by the authors, is the assumption that the results of weight-based dosing, which was only received by a subgroup of patients in the trial, can be applied to all patients treated.

In a cost-effectiveness analysis by Buti and colleagues[130] of PEG-α-2b + RBV, a Markov decision analysis model was used. The model appears to be similar to that used by Siebert and colleagues,[122] described above, and adopted the Spanish health system perspective. The demographics and virological characteristics of the patients were obtained from the Manns study.[41] Additional patient characteristics were considered to be the same as in previous multicentre trials of PEG or IFN.

Four treatment strategies were considered:

- IFN-α-2b 3 MIU three times per week + RBV 1000–1200 mg per day depending on body weight for 48 weeks
- PEG-α-2b 1.5 $\mu g\ kg^{-1}$ per week + RBV 800 mg per day for 48 weeks
- PEG-α-2b 1.5 $\mu g\ kg^{-1}$ per week + RBV adjusted for body weight (800–1200 mg) for 48 weeks
- PEG-α-2b 1.5 $\mu g\ kg^{-1}$ per week + RBV adjusted for body weight (800–1200 mg) for 48 weeks with patients compliant with therapy (received at least 80% of both drugs for at least 80% of treatment duration).

This analysis focused on patients with different genotypes (particularly genotype 1), the effect of different dosing methods (adjustment by body weight) and on the effects of compliance with therapy. Quality of life estimates were determined by a panel of hepatologists. The model incorporated only direct costs from the perspective of the Spanish national health system. Costs were adjusted for inflation to year 2000 values. A discount rate of 3% was applied to costs and health benefits. Cost per QALY figures from the report have been converted in the current report from Euros into Sterling at an exchange rate of £1 = €1.46.

The incremental discounted costs per QALY for PEG therapies compared with IFN + RBV therapy are presented below:

- all patients:
  - PEG + RBV 800 mg per day (fixed dose) versus IFN + RBV = £2559
  - PEG + RBV (adjusted for body weight) versus IFN + RBV = £1732
  - PEG + RBV (by body weight) + compliant with therapy versus IFN + RBV = £494
- patients with genotype 1:
  - PEG + RBV 800 mg per day (fixed dose) versus IFN + RBV = £1750
  - PEG + RBV (adjusted for body weight) versus IFN + RBV = £1732
  - PEG + RBV (by body weight) + compliant with therapy versus IFN + RBV = £277.

The incremental discounted costs per QALY for other therapy comparisons are presented below:

- All base-case patients:
  - PEG + RBV (adjusted for body weight) versus PEG + RBV 800 mg per day (fixed dose) = £911
  - PEG + RBV (by body weight) + compliant with therapy versus PEG + RBV (adjusted for body weight) = cost saving

These results demonstrate that the optimal strategy is a combination of PEG-α-2b (PEG-α-2a was not considered in this study) and RBV adjusted to the patients' body weight for 48 weeks with good compliance to therapy. This strategy is even more cost-effective for patients with genotype 1 than for patients in general. This study did not include the possibility of stopping therapy for patients with genotype 1 who were still HCV RNA positive at week 24 or who had a less than 2 log decrease in HCV RNA at week 12.

Because of the generally slow progression of hepatitis C, the age at the time of initial of therapy affects the cost-effectiveness ratio of treatment. The ICER increases as the age at start of treatment increases. Although a determination of what is 'cost-effective' is a subjective judgement, the age threshold for treatment remaining cost-effective increases for each therapy, with a higher age threshold for treatment with PEG + RBV with good compliance.

The base-case results assumed that all patients completed 48 weeks of treatment. Sensitivity analyses considered effects of earlier treatment discontinuation in some patients as well as body weight distributions, as in the clinical trials. Key probabilities of disease progression were halved or

doubled and different discount rates for costs and health benefits (0% and 5%) were used. SVR rates were also modified. In all sensitivity analyses PEG + RBV with good compliance remained the most cost-effective therapy.

Unpublished data

Several conference abstracts reporting the cost-effectiveness of dual therapy with PEG-2b + RBV based on the RCT by Manns and colleagues[41] were identified. Again, as these have not been subjected to peer review for full publication the results must be interpreted with caution.

Wong and Nevens [131] performed a cost–utility analysis, again based on the Manns trial,[41] using an adapted version of the Markov model used by Siebert and colleagues.[122] This short publication carries the status of an 'extended abstract' and thus it is not clear whether it has been fully peer-reviewed. The predicted estimates in the model had previously been shown to match closely the results of natural history studies.[126] Belgian costs were estimated in the model and the cost per QALY figures presented in this current assessment report have been converted from Euros into Sterling (at an exchange rate of £1 = €1.46). The discount rate for costs and survival was 3%. Marginal discounted cost per QALYs are presented below (base case highlighted in bold):

- dual therapy with PEG in comparison to no treatment = **£1618**
- dual therapy with PEG in comparison to dual therapy with IFN + RBV = **£4362**
- dual therapy with PEG in comparison to dual therapy with IFN + RBV (genotypes 2 and 3) = £8446
- dual therapy with PEG in comparison to dual therapy with IFN + RBV (genotype 1, 4 or 5) = £2864.

The higher cost per QALY for patients with genotypes 2 and 3 in relation to that for patients with genotype 1, 4 or 5 probably reflects the similar SVRs for patients treated with PEG dual therapy (82%) and patients treated with IFN + RBV dual therapy (79%) in this trial.

Wong and colleagues[132] performed a cost–utility analysis examining the incremental cost per discounted QALY (3% discount rate) associated with the following treatment options:

(i) no treatment
(ii) dual therapy (IFN + RBV)
(iii) dual therapy (PEG + 800 mg RBV)
(iv) dual therapy (PEG + >10.6 mg kg^{-1} RBV).

The cost-effectiveness of three different 'optimised' treatment algorithms was explored:

(a) discontinuing therapy in viral positive patients after 24 weeks of treatment (Stop 24);
(b) same criteria in Stop 24 but also limiting therapy in those with genotype 2/3 to 24 weeks (Stop 2/3);
(c) same criteria in Stop 2/3 but also discontinuing therapy in those viral positive or <2 log drop in viral load in non-genotype 2/3 patients after 12 weeks.

Costs were presented as US dollar and converted in this report to Sterling (£1 = $1.58).

Compared with no treatment (option i):

- The marginal discounted costs per QALY for option (ii) were £2088 (Stop 24) and £1202 (Stop 12). For options (iii) and (iv) the marginal discounted costs per QALY were £2721 (Stop 24) and £1708 (Stop 12), and £2784 (Stop 24) and £1772 (Stop 12), respectively.
- The marginal discounted costs per QALY for the three treatment options ranged from £632 to £1708 (Stop 24, genotype 2/3 patients). All three treatment options became cost saving even with discounting.
- For genotype 1 patients moving the Stop 24 to the Stop 12 rule improved the cost-effectiveness of treatment from £3481–3924 to £2974–3481.

Compared with dual therapy (IFN + RBV) (option ii):

- the marginal discounted cost per QALY for option (iii) was £4746 (Stop 24) and £3291 (Stop 12), and for option (iv) it was £7215 (Stop 24) and £5253 (Stop 12).
- For genotypes 2/3 the cost-effectiveness of option (iii) improved from £28,860 with Stop 24 to £12,151 with Stop 12, and for option (iv) cost-effectiveness improved from £3227 with Stop 24 to £474 with Stop 2/3.

The results show that applying treatment stopping rules in patients who have not responded can improve the cost-effectiveness of antiviral therapy, with the 12-week stopping rule generating the lowest marginal cost per QALY.

A similar cost–utility analysis was performed by the same team but with drug costs based on doses

used and vial sizes in the UK.[133] Again, the treatment options considered were:

(i) no treatment
(ii) dual therapy (IFN + RBV)
(iii) dual therapy (PEG + RBV 800 mg)
(iv) dual therapy (PEG + >10.6 mg kg^{-1} RBV).

Compared with no treatment (option i) cost-effectiveness ratios were:

- £920 (option ii), £2100 (option iii) and £1900 (option iv).
- For genotype 1 patients the cost-effectiveness ratios were: £2300 (option ii), £3500 (option iii) and £3100 (option iv).
- For patients with genotypes 2 and 3 cost savings were incurred for the comparison between options (i) and (ii). The cost-effectiveness ratio when moving from option (i) to option (iii) was £450 and to option (iv) was £440.

Compared with option (ii):

- The ratios were £9100 for option (iii) and £5200 for option (iv). The cost-effectiveness of option (iii) versus option (iv) was £960.
- For genotype 1 patients, ratios were £7600 (option iii) and £4700 (option iv).
- For genotype 2/3 patients, cost-effectiveness ratios were £24,700 (option iii) and £7300 (option iv). Therefore, in patients with these genotypes, moving from dual therapy (IFN + RBV) to dual therapy (PEG + RBV) was less cost-effective than moving from no treatment to dual therapy (with either PEG or non-PEG). This probably reflects the similar SVRs for patients with these genotypes in this trial irrespective of whether they were treated with PEG or non-PEG dual therapy.

Review of HRQoL studies

Several studies assessing the HRQoL of patients receiving treatment with PEG, as both dual and monotherapy, were identified. These were all based on patients treated in the RCTs of pegylated interferon described in Chapter 3 (Subsections on assessment of effectiveness in untreated patients, pp. 15 and 22). The majority are conference abstracts and thus caution is advised in their interpretation.

Dual therapy (unpublished data)

Gish and colleagues[134] in a conference abstract, report HRQoL data from the trial of dual therapy by Manns and colleagues,[41] where patients received dual therapy with either PEG-2b + RBV or IFN-2b + RBV. Patients completed the SF-36 before, during and after treatment. Scores were higher for patients receiving PEG dual therapy at both 12 and 48 weeks of treatment, indicating better on-treatment quality of life for pegylated compared with non-pegylated interferon. The difference between the groups reached statistical significance for the prespecified domain of 'vitality' at 12 weeks of treatment. Improvements in scores were higher for sustained responders than for non-responders, whose scores did not improve.

Hassanein and colleagues[135] reported the HRQoL data from the trial of dual therapy by Fried and colleagues.[50] Patients received PEG-α-2a + RBV, IFN-α-2b + RBV or PEG-α-2a + placebo and completed the SF-36 and the Fatigue Severity Scale (FSS) before, during and after treatment. During treatment those on PEG + RBV reported higher HRQoL and less fatigue than those taking IFN + RBV on all domains of the SF-36 and the FSS, with statistically significant differences in vitality, body pain, social functioning and burden of fatigue. Patients receiving PEG + placebo also had better HRQoL than those receiving IFN + RBV for all SF-36 domains and the FSS. At the end of follow-up (72 weeks) patients who had attained a virological response reported significant HRQoL improvements from baseline in all domains of the SF-36 and FSS scores with the greatest improvements in role–physical, general health, vitality and role–emotional scales.

A second conference abstract by Hassanein and colleagues[136] reports HRQoL benefits from patients treated with PEG-α-2a + RBV versus IFN + RBV. HRQoL was assessed using the SF-36 and the FSS. This study evaluated quality of life changes over a finer time-scale. HRQoL scores declined from baseline to week 2 in both groups, declined further by week 12, and then remained stable until week 48. HRQoL was better for the PEG + RBV group than for the IFN + RBV group at week 2 on all scales, at week 12 on six SF-36 domains and the FSS, and at weeks 24 and 48 on all scores. These results suggest that advantages in HRQoL for PEG + RBV emerge early and that more favourable HRQoL may reduce premature discontinuation of treatment.

Monotherapy (published data)

Bernstein and colleagues[137] pooled HRQoL data from three open-label trials of PEG-α-2a versus IFN-α-2a (Zeuzem,[53] Heathcote[54] and the currently unpublished trial by Pockros and colleagues[64]). In these trials the patients completed the SF-36 Health Survey and the FSS at

baseline and weeks 2, 12, 24, 48 and 72. The primary objective of the pooled analysis was to examine the relationship between SVR and HRQoL. SVR was significantly associated with changes in fatigue scores and all domains of the SF-36. The effect was primarily due to improvement in HRQoL from baseline to week 72 follow-up in responders, and secondarily to HRQoL declines from baseline to week 72 among non-responders. During treatment (first 24 weeks) the patients receiving PEG reported significantly better HRQoL and less fatigue than those taking IFN in seven of eight SF-36 domains, both SF-36 summary scores, and the FSS total and visual analogue scale scores. During the initial 24 weeks of therapy worsening fatigue scores and declines in SF-36 were significant predictors of treatment discontinuation. This analysis suggests that PEG therapy may involve less diminution of HRQoL during therapy and impact on adherence to therapy.

Monotherapy (unpublished data)

A report by Rasenack and colleagues[138] considered HRQoL within the Zeuzem trial.[53] In this trial 531 patients were randomised to PEG-α-2a or IFN-α-2a. Again, HRQoL was assessed using the SF-36 and the FSS. At weeks 2 and 12 HRQoL was significantly better in the PEG group in seven of eight domains and both summary scores of the SF-36. At weeks 2, 12 and 24, patients receiving PEG had significantly less disabling fatigue than those receiving IFN.

Another conference abstract (Feagan and colleagues[139]) reported changes in HRQoL of PEG-2b, based on the trial by Lindsay and colleagues.[52] The primary outcome was the SF-36 vitality scale. During treatment patients receiving 0.5 $\mu g\ kg^{-1}$ reported significantly better HRQoL than patients receiving IFN (this was consistent with the lower incidence of adverse events in this group). The difference between these groups in the change from baseline vitality score remained at the end of treatment. However, there was no difference in HRQoL between patients receiving 1.0 $\mu g\ kg^{-1}$ of PEG and those receiving IFN. HRQoL scores were slightly worse for patients receiving 1.5 $\mu g\ kg^{-1}$ of PEG, and during follow-up all SF-36 scales for all treatment groups returned to pretreatment values.

In summary, the main findings from these studies are:

- Reported HRQoL, as measured using the SF-36 and FSS, during treatment is generally higher for patients receiving PEG than for those receiving IFN, as both dual therapy and monotherapy. This may facilitate improved patient compliance with therapy.
- There is a significant association between sustained response and improved HRQoL, consistent with previous studies.

Methods for economic analysis

This economic evaluation follows the principles of a cost–utility analysis, whereby the outcomes of treatment are measured in terms of HRQoL. The perspective taken is that of the NHS, assessing not only clinical effects but also gains in length of life and quality of life. Thus, costs for treatment are seen not only in a budget perspective, but also in relation to the improved or maintained quality of life that the treatment can achieve. The analysis follows the framework set out by NICE[140] in the guidelines for manufacturers and sponsors. Other principal sources include Drummond and colleagues,[141] as well as earlier literature in the area.

A state transition Markov cost–utility model originally developed by the Scottish Health Purchasing Information Centre (SHPIC; http://www.nhsconfed.org/Scotland/shpic/) and used in the previous assessment report was updated and used for the calculation of annual costs and benefits (available on request). The model follows a hypothetical cohort of 1000 individuals with chronic hepatitis C infection over a 30-year period. The average age at diagnosis was 36 years. It aims to predict the natural history of the disease, the health states through which the cohort passes, how long they spend in each state and the NHS costs of treating a patient in each state. The health states, or stages, of the model are:

- chronic hepatitis C
- progression to cirrhosis
- development of ascites
- development of variceal bleeds
- development of hepatic encephalopathy
- progression to hepatocellular cancer (HCC)
- liver transplantation
- death.

The options in the original SHPIC report were:

- interferon monotherapy for 3 months, then a further 9 months for responders
- dual therapy with IFN + RBV for 6 months
- no treatment (except symptomatically).

TABLE 17 *Utilities used in the cost-effectiveness analysis*

Health state	Utility	Evidence
Successful antiviral treatment	1.00	Assumption
Chronic hepatitis	0.92	Wong and Koff (2000)[146]
Cirrhosis	0.82	Wong and Koff (2000)[146]
Ascites	0.52[a]	Wong and Koff (2000)[146]
Hepatic encephalopathy	0.55	Wong and Koff (2000)[146]
Variceal bleeds	0.50	Assumption
Liver transplant	0.86	Wong and Koff (2000)[146]
HCC	0.55	Wong and Koff (2000)[146]

[a] Diuretic refractory ascites.

The no-treatment option was based on projected natural history events over a 30-year period as derived from the published literature and clinical consensus (for further details see Appendix 1). Disease progression in this comparator was based on published literature and clinical consensus.

The options and assumptions were then revised in the previous assessment report with the addition of a fourth option, dual therapy for 12 months, to reflect current practice:

- interferon monotherapy for 12 months
- dual therapy with IFN + RBV for 6 months
- dual therapy with IFN + RBV for 12 months
- no treatment (except symptomatically).

For the current report the options have been further revised to reflect the treatment comparators in the published RCTs of pegylated interferon:

- dual therapy (interferon-α and ribavirin) for 48 weeks
- dual therapy (pegylated interferon and ribavirin) for 48 weeks
- monotherapy (interferon-α) for 48 weeks, or for shorter periods if published data are available
- monotherapy (pegylated interferon) for 48 weeks, or for shorter periods if published data are available.
- no treatment (except symptomatically).

Note that even though none of these trials includes a no-treatment arm, this comparator has been retained as a baseline, to estimate the incremental cost-effectiveness of moving from no active treatment to pegylated interferon, which would be likely to reflect practice for newly diagnosed untreated patients.

Estimation of net benefits

In theory, the benefits of hepatitis C treatment can be estimated using life-years gained or intermediary clinical manifestations such as cirrhosis of the liver. However, quality of life, as discussed earlier, is an important consideration for patients with hepatitis C. For this reason the cost–utility technique was used. The concept of HRQoL is often estimated using precalibrated questionnaires. For instance, several of the studies described above (Review of HRQol studies) report results from the SF-36 questionnaire. Another method is to compare quality of life to monetary values or length of life. This is done in the willingness-to-pay approach, or the time-trade-off technique. Standard gamble is another method. It uses the respondents' direct perceptions about probabilities to form values. Although it is considered to be high quality it may be difficult to comprehend by the respondents. (For further reading see Gold,[142] Chapters 4 and 7.)

A second problem is that it is often impractical, expensive and sometimes impossible to ask patients about their true quality of life values. Examples of such patient groups are young children or those with severe mental health problems. In the current report most of the HRQoL values used are taken from the literature (*Table 17*). They were estimated using consensus-based exercises such as the Delphi technique using a time trade-off procedure, in which an expert panel of senior hepatologists was asked to estimate the HRQoL values of patients in certain hypothetical conditions (e.g. chronic hepatitis C and cirrhosis).[126,128,143–145] Although obtaining values directly from patients is obviously preferable, given the lack of published data available it is pragmatic to use indirect estimations from hepatologists as a suitable alternative.

TABLE 18 *Clinical assumptions*

Health state	Transition probability	Source
Proportion progressing to chronic HCV[a]	85%	Thomas *et al.* (1996)[3]
Progression to cirrhosis from HCV p.a.	1%	Di Bisceglie (1998)[5]
Percentage developing ascites from cirrhosis	1.6%	Clinical opinion
Percentage developing variceal bleeds from cirrhosis	1.6%	Clinical opinion
Percentage developing HE from cirrhosis	1.6%	Clinical opinion
Annual death rate from HE, ascites and variceal bleeds	75%	Clinical opinion
Percentage requiring transplant from complex cirrhosis states	1%	Clinical opinion
Remain in cirrhotic state without complications	94%	Clinical opinion
Progression to HCC from cirrhosis p.a.	1.4%	Di Bisceglie (1998)[5]
Deaths following HCC diagnosis p.a.	80%	Cancer registry data
Successful transplant	90%	Clinical opinion
Require second transplant	10%	Clinical opinion

[a] Based on 20% progression over midpoint of 15 years converted to annual rate.
HE, hepatic encephalopathy; p.a., per annum.

All HRQoL values were converted to QALYs and the long-term consequences of reduced quality of life due to hepatitis were discounted to present value as outlined below.

As long-term results of clinical trials and natural history studies are not available, several assumptions about disease progression over time were made in the form of annual transition probabilities (*Table 18*, see also *Figure 7*). Recent studies suggest an increasing, non-linear progression for those infected at an older age (see Appendix 1). However, there are no data that could be entered into the present model to support this. The effect of a moderate progressive element would have little effect on the overall results owing to the discounting of costs and effects. The costs over 30 years are reduced to about 17% of their value when discounting of 6% is applied. Benefits are discounted at 1.5% and over the 30 years they are reduced to a present value of about 60%.

SVRs following antiviral treatment have been entered into the model from the meta-analysis of the key RCTs for the primary base-case analysis (see section 'Assessment of effectiveness in untreated patients: dual therapy', p. 15). The RCTs identified a number of prognostic factors (e.g. genotype, baseline viral load) that are predictors of SVR. Therefore, subgroup analyses were performed, whereby SVRs from the RCTs were entered into the model, to examine how the incremental cost per QALY varies according to these factors (see *Tables 5, 6, 10* and *11*). Caution is advised when interpreting these results as some of the subgroups contained relatively low numbers of patients.

Estimation of net costs

Cost data from the international literature reviewed above are of uncertain relevance to the UK healthcare system. For example, literature reporting on insurance-based healthcare systems often considers the treatment cost to be identical to the charges claimed from insurance companies. However, if such data need to be used it should be noticed that charges also include all kinds of administration costs and profits from the hospital to cover the 'full cost'. Such cost data do not reflect the true resource use (opportunity cost) needed in an HTA study.

Two concepts are especially important in the costing of health technologies: the marginal cost and the incremental cost. First, to find the true resource use the marginal cost of treatment has to be calculated for each treatment arm (e.g. the extra cost for one patient or extra cost per hospital day when the hospital is in full operation) without fixed cost elements, administration or other organisation costs. Neither should transferred costs from supporting functions be included (e.g. laboratory costs for practical reasons not possible to assign to a specific patient). In this evaluation cost data from the NHS have been used, especially arranged very close to the marginal cost fashion.

Different hospitals have different ways of organising care. Some hospitals use special treatment units, and there are also different ways of distributing costs for supporting care and administration onto the accounts of the treating wards. The marginal cost principle will ensure that costs from different treating units as well as units with small or large volumes of patients are reasonably comparable.

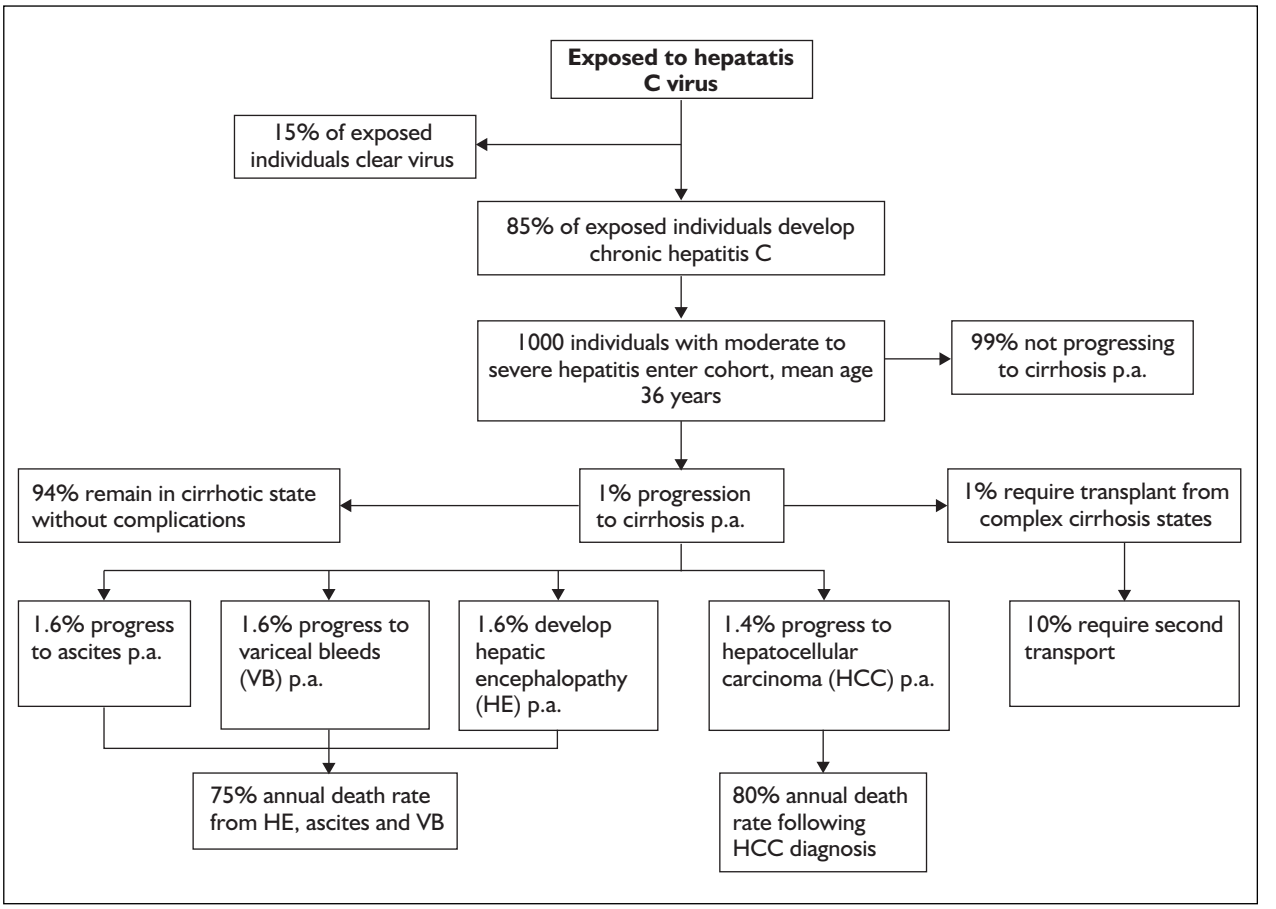

FIGURE 7 *Diagrammatic representation of transition probabilities used in the economic model*

Second, the choice of treatment method should be based on comparable costs between treatment arms. The incremental cost, that is, the difference in costs between one treatment method and another (i.e. the change in cost if treatment B is used instead of treatment A), therefore should not be confounded by cost elements of the types described above, which would differ between treatment units and also between treatments.

Information on investigation, monitoring and treatment costs was provided by the Finance Department of Southampton University Hospitals Trust (SUHT) in 2002 values (*Table 19*, see also Appendix 9). The opportunity, marginal and incremental cost principles will concentrate on the differences between direct operative costs of the activities concerned. Capital costs are not included in the analysis as in most cases they will stay unchanged when moving from non-pegylated to pegylated interferon, but they are also in many cases funded from sources other than the NHS operative costs. Overhead costs pose a similar problem. If the capital budget is annuitised and transferred to the operating budget, the costs of, for instance, buildings and expensive equipment would have turned up as a part of the overhead cost, fixed over time and also unchanged with the number of patient consultations. Other such fixed costs are those of general administration, and transferred costs from departments serving other departments rather than patients directly (often named 'indirect costs' in the accounts).

Drug costs were taken from the British National Formulary (BNF) (Issue 44). Costs for PEG were based on the dose of 1.5 μg kg^{-1} per week (PEG-2b). If one assumes that the average weight of a patient is 79 kg the total weekly dose will be 79 kg × 1.5 μg = 118.5 μg. A 120 μg vial of PEG-2b costs £162.00, representing the total weekly cost. PEG-2a at the recommended dose of 180 μg per week is slightly cheaper at £142 per week (180 μg prefilled syringe = £142.00). If one assumes that the latter was the only available drug in the market the cost-effectiveness ratio would be 10.4% cheaper for monotherapy and 5.8% for dual therapy. However, PEG-2b was used in this economic analysis as it represents a more conservative estimate of cost-effectiveness.

TABLE 19 *Unit and resource costs*

Economic assumption	Figure	Evidence
Unit costs		
Cost of attendance at general practice	£18	SUHT (see Appendix 9)
Average cost per outpatient visit to general medicine	£66	SUHT (see Appendix 9)
Average cost per inpatient day in general medical ward	£133	SUHT (see Appendix 9)
Weekly cost for PEG IFN-2b (PegIntron) (1.5 μg per kg^{-1} per week, assuming average patient weight of 79 kg)	£162	BNF 44
Weekly cost per 10 MIU vial of interferon-α 2b (Intron A) (dose = 3 MIU three times per week)	£53	BNF 44
Weekly cost for 6 × 200 mg capsules of ribavirin (Rebetol) per day (dose = 1200 mg per day)	£148.20	BNF 44
Weekly cost for 4 × 200 mg capsules of ribavirin (Rebetol) per day (dose = 800 mg)	£118	BNF 44
Resource costs		
Annual average cost with HCC (based on 60 inpatient days in general medicine)	£7,980	Duration of stay based on clinical opinion
Annual average cost with cirrhosis (based on three outpatient attendances and three general practice visits)	£252	Frequency of visits based on clinical opinion
Annual average cost associated with chronic HCV infection (based on one visit to outpatients in general medicine and two GP-associated visits)	£102	Based on one outpatient attendance and two general practice visits (clinical opinion)
Annual average cost associated with ascites (based on 49 inpatient days in general medicine)	£6,517	Duration of stay based on clinical opinion
Annual average cost associated with hepatic encephalopathy (based on 49 inpatient days in general medicine)	£6,517	Duration of stay based on clinical opinion
Annual average cost associated with variceal bleeds (based on 14 inpatient days in general medicine)	£1,862	Duration of stay based on clinical opinion
Cost of liver transplant and follow-up care	£46,551	National contract cost

Costs for IFN (Intron A) were based on a dose of 3 MIU three times per week, and costs for RBV (Rebetol) were based on 1200 mg per day. Doses adjustments were made in subgroup analyses whereby patients received a high (>10.6 mg kg^{-1}; >800 mg) or a lower dose (≤ 10.6 mg kg^{-1}; ≤ 800 mg).

In November 2002 Roche received approval for its proprietary ribavirin 'Copegus' to be used in conjunction with PEG-2a (or IFN-2a 'Roferon A'). There appears to be a difference in cost between Rebetol and Copegus. The BNF (Version 45) net price for 168-cap pack of Rebetol is £592.80 compared with £497.28 for a 168-tab pack of Copegus. By using Copegus in place of Rebetol the weekly drug cost would decrease by 9.4% and the cost-effectiveness would improve very slightly (0.001%). Costs for Rebetol in conjunction with PEG-2b are used in this report, representing a more conservative estimate of cost-effectiveness.

The literature does not explicitly discuss costs and effects for patients with haemophilia. It may very well be that they are more expensive to treat (e.g. more inpatient stays for liver biopsy), but there is no basis for specific assumptions on such costs or effects, positive or negative.

All costs were discounted at the rate of 6%.

Sensitivity analysis

As the results of all economic models are subject to uncertainty it is essential to test the extent to which the results differ according to variations in inputs and assumptions. However, there is little guidance in the literature about which parameters should be subject to a sensitivity analysis. While it would be informative to conduct a multidimensional or probabilistic sensitivity analysis, the assumptions about the statistical distributions of the relevant variables could only be speculative.

Three parameters were chosen for inclusion in the sensitivity analysis. First, cost–utility estimates were generated according to variations in SVRs. This is the primary treatment outcome, and one of the key variables that drives the model. Cost–utility was estimated according to SVRs at the lower and higher end of the confidence interval around the

TABLE 20 *Incremental discounted cost-utility for dual therapy (base case)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG dual therapy (48 weeks)					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,862,982	23,417	£11,808,692	1,953	£6,045
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks)					
Dual treatment (IFN + RBV)	£9,987,505	23,098	–	–	–
Dual treatment (PEG + RBV)	£13,862,982	23,417	£3,875,478	320	£12,123

Based on SVRs from meta-analysis.

pooled estimate in the meta-analysis. It is particularly useful to gauge a worst case scenario as it has been suggested that, for interferon monotherapy at least, response rates in practice can be lower than found in clinical trials. Second, estimates were made according to variations in the discount rate. It is well known that the results of cost-effectiveness analyses are sensitive to variations in discount rates, particularly in the long-term perspective. Third, estimates were produced according to variations in drug costs. It is believed that some hospital pharmacies are able to negotiate large discounts in such costs, particularly for bulk purchases. However, there was no basis for a specific choice of variation, but it was assumed that variations of more than 50% percent in either direction would be unlikely.

Estimation of cost-effectiveness

Dual therapy

Table 20 presents incremental discounted cost–utility estimates for the base case (i.e. all patients) for PEG dual therapy, based on the cohort of 1000 patients in the model. SVRs are from the pooled analyses of the Manns and Fried trials[41,50] (see Chapter 3). The incremental cost per QALY for no active treatment compared with 48 weeks of PEG dual therapy is £6045. IFN dual therapy for 48 weeks compared with PEG dual therapy for 48 weeks generated a cost per QALY of £12,123.

Results of the subgroup analyses for dual therapy are presented below. In general, cost per QALY estimates for no active treatment compared with PEG dual therapy were lower than for IFN dual therapy compared with PEG dual therapy.

Table 21 presents the incremental discounted cost–utility subgroup estimates for patients treated with dual therapy stratified by genotype (the RCTs from which efficacy data are taken are indicated in parenthesis). The most favourable estimates are for genotype 2 and 3 patients treated with dual therapy in comparison to no active treatment, where the incremental discounted cost per QALY ratios were £3866 (based on the Manns trial[41]) and £4216 (based on the Fried trial[50]). When comparing IFN dual therapy with PEG dual therapy in these patients, estimates were £37,578 and £7051 for the two trials, respectively. In Manns there was only a marginal difference in SVRs for PEG and IFN-treated genotype 2 and 3 patients (82% versus 79%), which may explain the high cost per QALY.

Tables 22 and *23* present the incremental discounted cost–utility subgroup estimates for patients treated with dual therapy according to baseline viral load, and baseline viral load stratified according to genotype, respectively. The lowest estimate, £3921, was for no active treatment compared with dual therapy with PEG in patients with low baseline viral load and genotype 2 or 3. Predictably, the highest estimate, £13,701, was for IFN dual therapy compared with PEG dual therapy in patients with high baseline viral load and genotype 1.

Table 24 presents incremental cost–utility estimates for low or high doses of ribavirin, while *Table 25* presents incremental cost–utility estimates for low or high doses of ribavirin, stratified according to genotype. To recap, Manns and colleagues[41] reported that the SVR was higher in all groups when the dose of RBV was greater than 10.6 mg kg^{-1} of body weight (i.e. above 800 mg per day). The most favourable estimate, £1987, was for patients with genotypes 2 and 3 treated with the lower dose of RBV, in comparison to dual therapy with IFN. The least favourable estimate, £13,734, was for genotypes 2 and 3 treated with the higher dose of RBV, in comparison to dual therapy with IFN. The difference in estimates for patients with this genotype might be explained by the fact that for the lower RBV dose subgroup the

TABLE 21 *Incremental discounted cost–utility for dual therapy (subgroup analysis: genotype)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG dual therapy (48 weeks) genotype 1 (Fried *et al.*[50])					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£14,046,070	23,098	£11,991,780	1,634	£7,340
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks) in genotype 1 (Fried *et al.*[50])					
Dual treatment (IFN + RBV)	£10,192,934	£22,743	–	–	–
Dual treatment (PEG + RBV)	£14,046,070	£23,098	£3,853,136	355	£10,848
No active treatment compared with PEG dual therapy (48 weeks) in genotype 2/3 (Fried *et al.*[50])					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,435,778	24,163	£11,381,488	2,699	£4,216
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks) in genotype 2/3 (Fried *et al.*[50])					
Dual treatment (IFN + RBV)	£9,679,361	23,631	–	–	–
Dual treatment (PEG + RBV)	£13,435,778	24,163	£3,756,417	533	£7,051
No active treatment compared with PEG dual therapy (48 weeks) in genotype 2/3 (Manns *et al.*[41])					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,313,719	24,377	£11,259,429	2,913	£3,866
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks) in genotype 2/3 (Manns *et al.*[41])					
Dual treatment (IFN + RBV)	£9,309,589	24,270	–	–	–
Dual treatment (PEG + RBV)	£13,313,719	24,377	£4,004,130	107	£37,578
No active treatment compared with PEG dual therapy (48 weeks) in genotype 4, 5 or 6 (Manns *et al.*[41])					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,964,698	23,240	£11,910,408	1,776	£6,707
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks) in genotype 4, 5 or 6 (Manns *et al.*[41])					
Dual treatment (IFN + RBV)	£10,151,848	22,814	–	–	–
Dual treatment (PEG + RBV)	£13,964,698	23,240	£3,812,850	426	£8,946

difference in SVR between PEG dual therapy and IFN dual therapy was much greater (29%) than for the higher RBV dose subgroup (8%), thus generating more QALYs.

Table 26 shows estimates generated by varying the SVR according to the 95% confidence interval around the pooled estimate in the meta-analysis. The highest incremental discounted cost per QALY, £37,611, was for the lower PEG SVR and higher IFN SVR (i.e. the smallest difference between groups). In contrast, the lowest estimate was for the higher PEG SVR and lower IFN SVR, at £7060 (i.e. the largest difference between the two treatments).

Table 27 shows differences in cost–utility estimates according to variations in the discount rate for costs and benefits. Predictably, estimates are lower at the 0% rate. *Table 28* illustrates how the estimates vary according to variations in drug costs. Again, the lowest estimates correspond to the lower drug cost variation. The costs for the pharmaceuticals are the most important part of the direct treatment costs. Different hospitals and trusts have been able to negotiate different discounts from pharmaceutical companies and the list prices in the BNF do probably not reflect the true costs. No firm data were available, however, about the deviations from the true cost. Drug costs were varied by plus and minus 50% to see how the variation reflects in the final results.

Early stopping rules

The cost–utility of stopping treatment in patients who had not responded after 12 weeks was investigated. Early studies of patients treated with non-pegylated interferon monotherapy showed that patients who remained HCV RNA positive at 12 weeks were unlikely to achieve an SVR. In contrast, later trials of dual therapy with IFN and RBV found that many patients who achieved an SVR had been viral positive at 12 weeks. Thus, 24 weeks became the standard threshold for deciding whether or not a patient should cease or continue treatment. Nevertheless, kinetic studies suggested that viral response could be assessed at earlier time-points using quantitative assays for HCV RNA. As described in Chapter 3, Davis[56] pooled data from the dual PEG trials by Fried and Manns and colleagues[41,50] to identify how many patients achieved a viral response at 12 weeks, and of

TABLE 22 *Incremental discounted cost–utility for dual therapy (sub-group analysis: baseline viral load)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG dual therapy (48 weeks), high baseline viral load (Fried *et al.*[50])					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,903,669	£23,346	£11,849,378	1,882	£6,295
IFN dual therapy (48 weeks) compared with PEG dual therapy, high baseline viral load (48 weeks) (Fried *et al.*[50])					
Dual treatment (IFN + RBV)	£10,090,219	22,920	–	–	–
Dual treatment (PEG + RBV)	£13,903,669	23,346	£3,813,449	426	£8,947
No active treatment compared with PEG dual therapy (48 weeks), low baseline viral load (Manns *et al.*[41])					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,395,092	£24,234	£11,340,802	2,770	£4,094
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), low baseline viral load (Manns *et al.*[41])					
Dual treatment (IFN + RBV)	£9,782,076	23,453	–	–	–
Dual treatment (PEG + RBV)	£13,395,092	24,234	£3,613,016	781	£4,624

TABLE 23 *Incremental discounted cost–utility for dual therapy (subgroup analysis: baseline viral load and genotype)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG dual therapy (48 weeks), high baseline viral load + genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£14,147,785	22,920	£12,093,495	1,456	£8,305
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), high baseline viral load + genotype 1					
Dual treatment (IFN + RBV)	£10,254,562	22,636	–	–	–
Dual treatment (PEG + RBV)	£14,147,785	22,920	£3,893,223	284	£13,701
No active treatment compared with PEG dual therapy (48 weeks), high baseline viral load + genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,476,464	24,092	£11,422,174	2,628	£4,346
IFN Dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), high baseline viral load + genotype 2/3					
Dual treatment (IFN + RBV)	£9,740,990	23,524	–	–	–
Dual treatment (PEG + RBV)	£13,476,464	24,092	£3,735,474	568	£6,573
No active treatment compared with PEG dual therapy (48 weeks), low baseline viral load + genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,842,639	23,453	£11,788,349	1,989	£5,927
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), low baseline viral load + genotype 1					
Dual treatment (IFN + RBV)	£10,049,133	22,991	–	–	–
Dual treatment (PEG + RBV)	£13,842,639	23,453	£3,793,506	462	£8,216
No active treatment compared with PEG dual therapy (48 weeks), low baseline viral load + genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,334,062	24,341	£11,279,772	2,877	£3,921
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), low baseline viral load + genotype 2/3					
Dual treatment (IFN + RBV)	£9,597,190	23,773	–	–	–
Dual treatment (PEG + RBV)	£13,334,062	24,341	£3,736,873	568	£6,576

Based on SVRs from Fried *et al.*[50]

TABLE 24 *Incremental discounted cost–utility for dual therapy (subgroup analysis: ribavirin dose adjustments)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG dual therapy (48 weeks), RBV dose ≤ 10.6 mg kg^{-1} (i.e. ≤ 800 mg)					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£12,541,978	23,240	£10,487,688	1,776	£5,906
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), RBV dose ≤ 10.6 mg kg^{-1} (i.e. ≤ 800 mg)					
Dual treatment (IFN + RBV)	£10,377,820	22,423	–	–	–
Dual treatment (PEG + RBV)	£12,541,978	23,240	£2,164,158	817	£2,649
No active treatment compared with PEG dual therapy (48 weeks), RBV dose >10.6 mg kg^{-1} (i.e. >800 mg)					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,740,924	23,631	£11,686,634	2,167	£5,394
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), RBV dose >10.6 mg kg^{-1} (i.e. >800 mg)					
Dual treatment (IFN + RBV)	£9,966,962	23,133	–	–	–
Dual treatment (PEG + RBV)	£13,740,924	23,631	£3,773,962	497	£7,589

TABLE 25 *Incremental discounted cost–utility for dual therapy (subgroup analysis: ribavirin dose adjustments stratified by genotype)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG dual therapy (48 weeks), RBV dose ≤ 10.6 mg kg^{-1} (i.e. ≤ 800 mg) in genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£12,786,095	22,814	£10,731,805	1,350	£7,951
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), RBV dose ≤ 10.6 mg kg^{-1} (i.e. ≤ 800 mg) in genotype 1					
Dual treatment (IFN + RBV)	£10,521,620	22,174	–	–	–
Dual treatment (PEG + RBV)	£12,786,095	22,814	£2,264,475	639	£3,542
No active treatment compared with PEG dual therapy (48 weeks), RBV dose >10.6 mg kg^{-1} (i.e. >800 mg) in genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£14,005,384	23,169	£11,951,094	1,705	£7,010
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), RBV dose >10.6 mg kg^{-1} (i.e. >800 mg) in genotype 1					
Dual treatment (IFN + RBV)	£10,234,019	22,672	–	–	–
Dual treatment (PEG + RBV)	£14,005,384	23,169	£3,771,364	497	£7,584
No active treatment compared with PEG dual therapy (48 weeks), RBV dose ≤ 10.6 mg kg^{-1} (i.e. ≤ 800 mg) in genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£11,952,029	24,270	£9,897,738	2,806	£3,527
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), RBV dose ≤ 10.6 mg kg^{-1} (i.e. ≤ 800 mg) in genotype 2/3					
Dual treatment (IFN + RBV)	£9,905,333	23,240	–	–	–
Dual treatment (PEG + RBV)	£11,952,029	24,270	£2,046,696	1,030	£1,987
No active treatment compared with PEG dual therapy (48 weeks), RBV dose >10.6 mg kg^{-1} (i.e. >800 mg) in genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Dual treatment (PEG + RBV)	£13,191,661	24,590	£11,137,371	3,126	£3,563
IFN dual therapy (48 weeks) compared with PEG dual therapy (48 weeks), RBV dose >10.6 mg kg^{-1} (i.e. >800 mg) in genotype 2/3					
Dual treatment (IFN + RBV)	£9,289,046	24,305	–	–	–
Dual treatment (PEG + RBV)	£13,191,661	24,590	£3,902,615	284	£13,734

Based on SVRs from Manns *et al.*[41]

TABLE 26 *Sensitivity analysis: variations in SVR (dual therapy)*

Cost–utility estimates according to varying SVR, IFN dual therapy compared with PEG dual therapy			
		IFN+RBV SVR	
		43%	49%
PEG+RBV SVR	52%	£12,152	£37,611
	58%	£7,060	£12,152

TABLE 28 *Sensitivity analysis: variations in drug costs (dual therapy)*

Range of incremental cost–utility ratio, varying drug costs ± 50%		
Drug cost	**–50%**	**+50%**
No treatment to dual PEG	£2,736	£9,363
Dual IFN to dual PEG	£5,787	£18,517

these, how many went on to achieve an SVR. (Note that only patients treated with PEG dual therapy were analysed, as opposed to patients treated with the comparator, IFN dual therapy, thus prohibiting assessment of the incremental cost–utility between these two treatments in the context of stopping rules.)

The SVR figures derived by Davis were applied to the cost–utility model of 1000 hypothetical patients in the current report.

- If one assumes that the 19% of patients (most of whom are genotype 1) without an early viral response leave treatment after 12 weeks, and nothing else changes except for savings in treatment costs, the total discounted costs will be £11,683,203, with a cost saving of £2,188,772 (15.7%).
- Treating the 19% of patients who failed to respond by week 12 for the remaining 36 weeks (bearing in mind that 2% of them achieve a SVR) will result in total discounted costs of £14,968,965 and a total of 21,521 QALYs. When comparing this to no active treatment (total discounted costs of £2,054,290 and total QALYs 21,464) the incremental discounted cost per QALY will be £226,573.

These data therefore illustrate that excluding non-responding genotype 1 patients from dual therapy after 12 weeks can lead to savings of around 16%, a similar figure to that quoted by Davis.[56] It is important to note, however, that although the pool of non-responders is mostly comprised of genotype 1 patients, some patients with this genotype do achieve an early viral response.

Monotherapy

To recap, the cost–utility of monotherapy was estimated given that not all patients can tolerate ribavirin. *Table 29* presents incremental discounted cost–utility estimates for the base case (i.e. all patients) for PEG monotherapy based on the cohort of 1000 patients in the model. SVRs are from the meta-analyses of the monotherapy trials (see section 'Assessment of effectiveness in untreated patients: monotherapy', p. 22). The incremental cost per QALY for no active treatment compared with 48 weeks of PEG monotherapy is £6484. Comparing 48 weeks of IFN monotherapy with 48 weeks of PEG monotherapy generates a cost per QALY of £8404.

As with the dual therapy analyses presented above, subgroup analyses were conducted for monotherapy, the results of which are presented below. *Table 30* presents the incremental discounted cost–utility estimates for patients treated with monotherapy, stratified by genotype. As would be expected, the costs per QALY are lower for patients with genotypes 2 and 3 than for patients with genotype 1. However, in this instance the costs per QALY for patients with genotypes 4, 5 and 6 were lower than those for patients with genotypes 2 and 3 (who generally respond better to treatment). This is probably because the SVR for genotype 4, 5 and 6 patients treated with PEG

TABLE 27 *Sensitivity analysis: variations in discount rate (dual therapy)*

Cost–utility estimates according to varying discount rate from 0 to 6% (costs/benefits)				
	0/0%	**3.5/3.5%**	**6/1.5%**	**6/6%**
No treatment to dual PEG	£4,132	£7,996	£6,049	£11,628
Dual IFN to dual PEG	£8,846	£16,335	£12,152	£23,357

TABLE 29 *Incremental discounted cost–utility for monotherapy (base case)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG monotherapy (48 weeks)					
No treatment	£2,054,290	21,464	–	–	–
Monotherapy PEG	£9,193,460	22,565	£7,139,170	1,101	£6,484
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks)					
Monotherapy IFN	£4,118,689	21,961	–	–	–
Monotherapy PEG	£9,193,460	22,565	£5,074,771	604	£8,404

Based on SVRs from meta-analysis.

TABLE 30 *Incremental discounted cost–utility for monotherapy (subgroup analysis: genotype)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG monotherapy (48 weeks) in genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£9,542,689	21,961	£7,488,399	497	£15,060
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks) in genotype 1					
Mono treatment IFN	£4,283,033	21,677	–	–	–
Mono treatment PEG	£9,542,689	21,961	£5,259,657	284	£18,510
No active treatment compared with PEG monotherapy (48 weeks) in genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£8,823,688	£23,204	£6,769,398	1,740	£3,890
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks) in genotypes 2/3					
Mono treatment IFN	£3,831,089	22,458	–	–	–
Mono treatment PEG	£8,823,688	23,204	£4,992,599	746	£6,693
No active treatment compared with PEG monotherapy (48 weeks) in genotype 4, 5 or 6					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£8,597,716	23,595	£6,543,426	2,131	£3,070
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks) in genotype 4, 5 or 6					
Mono treatment IFN	£4,406,290	21,464	–	–	–
Mono treatment PEG	£8,597,716	23,595	£4,191,426	2,131	£1,967

All SVRs from Lindsay *et al.*[52] (data for PEG monotherapy are from the 1.5 μg kg^{-1} dose arm).

monotherapy in the Lindsay trial[52] were relatively high (60% compared with 49% for genotypes 2 and 3), and because none of the patients in the trial treated with IFN monotherapy achieved an SVR. However, caution is advised in the interpretation of these figures as the number of genotype 4, 5 and 6 patients in the trial treated with PEG monotherapy (at a dose of 1.5 μg kg^{-1}) or IFN monotherapy was less than ten, compared with 77 for genotypes 2 and 3.

Tables 31 and *32* present the incremental discounted cost–utility estimates for patients treated with monotherapy according to baseline viral load, and baseline viral load stratified according to genotype, respectively. Costs per QALY were lower for patients with a lower baseline viral load. It is of note that a high proportion of patients in the Heathcote trial[54] were cirrhotic (n = 212, 78.2%), and the average baseline viral load was over 6 million copies ml^{-1}, compared with the trial by Lindsay and colleagues,[52] where less than 4% were cirrhotic and the average baseline viral load was around 3.5 million copies ml^{-1}. As was the case with dual therapy the highest estimates were for patients with genotype 1 and high baseline viral load, in the range £29,963–30,701. The lowest incremental cost per QALY was for patients with genotypes 2 and 3 and low baseline viral load, in the range £2641–4194. These estimates appear to correspond with what one would expect for harder

TABLE 31 *Incremental discounted cost–utility for monotherapy (subgroup analysis: baseline viral load)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG monotherapy (48 weeks), high viral load					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£9,357,803	22,281	£7,303,513	817	£8,941
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks), high viral load					
Mono treatment IFN	£4,221,404	21,784	–	–	
Mono treatment PEG	£9,357,803	22,281	£5,136,399	497	£10,329
No active treatment compared with PEG monotherapy (48 weeks), low viral load					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£9,070,203	22,778	£7,015,913	1,314	£5,339
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks), low viral load					
Mono treatment IFN	£4,303,576	21,642	–	–	–
Mono treatment PEG	£9,070,203	22,778	£4,766,627	1,137	£4,194

All SVRs from Heathcote *et al.*[54]

TABLE 32 *Incremental discounted cost–utility for monotherapy (subgroup analysis: baseline viral load and genotype)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
No active treatment compared with PEG monotherapy (48 weeks), high viral load + genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£9,686,490	21,713	£7,632,200	249	£30,701
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks), high viral load + genotype 1					
Mono treatment IFN	£4,365,204	21,535	–	–	–
Mono treatment PEG	£9,686,490	21,713	£5,321,285	178	£29,963
No active treatment compared with PEG monotherapy (48 weeks), high viral load + genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£8,988,031	22,920	£6,933,741	1,456	£4,761
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks), high viral load + genotype 2/3					
Mono treatment IFN	£3,892,718	22,352	–	–	–
Mono treatment PEG	£8,988,031	22,920	£5,095,314	568	£8,966
No active treatment compared with PEG monotherapy (48 weeks), low viral load + genotype 1					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£9,131,831	22,672	£7,077,541	1,208	£5,861
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks), low viral load + genotype 1					
Mono treatment IFN	£3,974,889	22,210	–	–	–
Mono treatment PEG	£9,131,831	22,672	£5,156,942	462	£11,168
No active treatment compared with PEG monotherapy (48 weeks), low viral load + genotype 2/3					
No treatment	£2,054,290	21,464	–	–	–
Mono treatment PEG	£8,433,373	23,879	£6,379,083	2,415	£2,641
IFN monotherapy (48 weeks) compared with PEG monotherapy (48 weeks), low viral load + genotype 2/3					
Mono IFN	£3,666,746	22,743	–	–	–
Mono PEG	£8,433,373	23,879	£4,766,627	1,137	£4,194

All SVRs from Lindsay *et al.*[52]

TABLE 33 *Sensitivity analysis: variations in SVR (monotherapy)*

Cost–utility estimates according to varying SVR, IFN monotherapy compared with PEG monotherapy			
		IFN SVR	
		12%	17%
PEG SVR	27%	£9,602	£14,692
	34%	£6,363	£8,404

TABLE 35 *Sensitivity analysis: variations in drug costs (dual therapy)*

Range of incremental cost–utility ratio, varying drug costs ±50%		
Drug cost	–50%	+50%
No treatment to mono PEG	£2,953	£10,015
Mono IFN to mono PEG	£1,965	£14,843

to treat patients (i.e. genotype 1 and high baseline viral load) and patients with a better prognosis (i.e. genotypes 2 and 3 and low baseline viral load).

Again, a sensitivity analysis was performed to examine the extent to which the cost–utility estimates for monotherapy differ according to variations in costs and assumptions. *Table 33* shows estimates generated by varying the SVR according to the 95% confidence interval around the pooled estimate in the meta-analysis. The highest incremental cost per QALY, £14,692, was for the lower PEG SVR and higher IFN SVR (i.e. the smallest difference between groups). In contrast, the lowest estimate, £6363, was for the higher PEG SVR and lower IFN SVR (i.e. the largest difference between the two treatments). This was the same pattern observed for dual therapy.

Table 34 shows differences in cost–utility estimates according to variations in the discount rate. Predictably, estimates are lower at the 0% rate.

Table 35 illustrates how the estimates vary according to variations in drug costs. Again, the lowest estimates correspond to the lower drug cost variation.

The economics of treating mild disease

As discussed in Chapter 3 ('Treatment of patients with mild hepatitis C', p. 42), there is currently uncertainty about whether to treat patients with mild disease. The results of the UK trial have not yet been published. However, some data from other studies are available at present, and one may speculate as follows.

The benefits of treating those with mild disease would be:

1. Improvement in quality of life: the average quality of life of people with chronic HCV infection is reported to be 0.95 (although note that 0.92 was used in the economic model; see Appendix 9). If it was assumed that an SVR was sustained for 20 years (i.e. a conservative estimate based on the lifetime of the patients), then successful treatment would give 1.0 QALY (0.5×20). This ignores any short-term diminution in quality of life due to side-effects while on treatment.
2. Reductions in future serious liver disease: this would be less in those with mild disease since progression is slower, but the disease does progress over a few years, and some patients will go on to develop serious disease.
3. Reductions in transmission of virus.

In the absence of hard data on items 2 and 3, one may consider what the cost-effectiveness of treatment would be if the only gain was improved quality of life in responders. If 100 patients were treated and 55% had an SVR, the QALY gain over 20 years would be 55 QALYs (note that this would need to be discounted). The cost of treating 100 patients for 24 weeks would be around £900,000 and for 48 weeks would be around £1,700,000,

TABLE 34 *Sensitivity analysis: variations in discount rate (monotherapy)*

Range of incremental cost–utility ratio, varying discount rate from 0 to 6% (costs/benefits)				
	0/0%	3.5/3.5%	6/1.5%	6/6%
No treatment to mono PEG	£4,468	£8,590	£6,484	£12,463
Mono IFN to mono PEG	£5,952	£11,215	£8,404	£16,155

which may give (undiscounted) costs per QALY of around £16,000 and £31,000, respectively. Since there would undoubtedly be some future serious liver pathology prevented in those who would have progressed, hence offsetting treatment costs by future savings (even after discounting), the true cost per QALY will be less.

However, there are various uncertainties around all of these costs. The response rate in patients with mild disease in the Swedish trial[47] was 54% on combination therapy, but that was with non-pegylated interferon. Results would be expected to be better with pegylated interferon. That trial gave treatment for 53 weeks in responders, and it may be that 24 weeks would suffice. Various stopping rules could be applied to reduce costs, by earlier discontinuation in non-responders.

The relatively low costs per QALY obtained when taking the improvement in quality of life as the only benefit arise because the cost of treatment is short term (24 weeks or 48 weeks), but the benefit in those who respond is for life.

The financial implication for the NHS would be large, because there are many people with mild disease and it is assumed that they are currently not treated.

Further consideration of the economics of treating this group will need to await the results of the UK trial, funded by the HTA programme.

Economic analysis: summary

- Several economic evaluations of pegylated interferon are available, some fully published, others only available as abstracts. Most use Markov models to estimate the cost–utility of dual therapy over time, according to optimal treatment strategies (e.g. dosing according to body weight; applying early stopping rules).
- A cost–utility analysis was undertaken in the current report, using a Markov model which follows a hypothetical cohort of 1000 people with chronic hepatitis C infection who progress through a number of disease states over a 30-year period. Data on natural history and health utilities were taken from the available literature. Clinical consensus was also used where necessary. Cost data were supplied from an NHS trust.
- The results showed that pegylated interferon is relatively cost-effective, with estimates generally below £30,000 per QALY. The incremental discounted cost per QALY for 48 weeks of PEG + RBV dual therapy compared with 48 weeks of IFN + RBV dual therapy was approximately £12,100.
- Subgroup analyses demonstrated that the most favourable cost per QALY estimates were for patients infected with genotypes 2 and 3 (£7000, PEG + RBV compared with IFN + RBV dual therapy). Patients infected with genotype 1 had higher estimates (cost per QALY around £11,000, PEG + RBV dual therapy compared with IFN + RBV dual therapy).
- Results of sensitivity analyses showed that the estimates varied according to differences in SVRs, drug costs and discount rates. For example, estimates reached as high as £37,611 when varying SVR according to the confidence intervals around the pooled analysis of the key RCTs.
- Estimates were also generally favourable for pegylated interferon monotherapy. The incremental discounted cost per QALY for 48 weeks of PEG monotherapy compared with IFN monotherapy was around £8400. Again, patients with genotypes 2 and 3 had lower cost per QALY estimates than patients with genotype 1 (around £6700 versus £18,500 respectively, for PEG compared with IFN monotherapy).
- Stopping treatment in the 19% of patients without an EVR results in an estimated cost saving of 15.7%. Continuing treatment in these patients (only around 2% of whom achieve an SVR) leads to an estimated cost per QALY of approximately £227,000.

Chapter 5

Implications for other parties

Acceptance of assessment and treatment

One implication of the variations in prevalence is that the cost of therapy may vary enormously between health authorities. Some, particularly in the cities or districts with large numbers of IDUs, may have a much higher total cost than others, although economies of scale may be achieved through treating sufficient quantities of patients. (To be eligible for treatment they usually would have to have ceased using injected drugs, although in some areas currently IDUs are treated.) However, this assumes high compliance with treatment. Advice from clinical colleagues is that although fewer IDUs enrol in treatment, those who do are not necessarily as non-compliant with treatment as previously thought. The specific needs of this client group should be assessed, with services adapted accordingly. Good data are available on acceptance rates of initial assessment (which currently has to include liver biopsy, since clinical and biochemical assessment is not a good guide to the severity of liver damage in the early stages).[11,25] Data from the clinical trials of pegylated interferon indicate that adverse events were certainly no worse with this treatment than with non-pegylated interferon. Patients also report higher quality of life with pegylated interferon during treatment than with non-pegylated interferon, suggesting better rates of compliance.

Implications for others

One possible effect of provision of an assessment and treatment package for hepatitis C is that it may reduce the spread of infection by persuading IDUs to stop sharing needles and injecting altogether. This is speculative and at present is unproven. However, an HTA report on the effectiveness of screening among IDUs found no compelling evidence to support the idea that behavioural change will occur as a result of learning hepatitis status.[147]

Provision of care

There would probably be merit in providing care through a limited number of specialist clinics, partly because of the nature of assessment and treatment, and partly to facilitate systematic data collection, including long-term follow-up. This would also foster further research into response rates and prediction factors which, by allowing better targeting of treatment, would improve cost-effectiveness and reduce costs.

Chapter 6

Factors relevant to the NHS

The prevalence of hepatitis C is uncertain, 200,000–400,000 in the UK, and it is likely that many infected people are unaware of their disease. As many as 15–35% will clear the virus spontaneously within 2–6 months. The availability of effective treatment will influence the active search and screening for infected patients in the population, as will the increased costs of treatment. Against this background the budgetary impact of pegylated interferon compared with non-pegylated interferon treatment can only be speculative. In the long term some costs would be offset by fever secondary complications.

As mentioned previously, the cost of therapy for HCV will not fall evenly on all areas of the country, because of differences in the prevalence of IDUs, although the key group in this case is former drug users. Another factor to take into account is that there will be a large group of people infected with hepatitis C over many years; once they have all been treated (if diagnosed), costs would fall.

It is not possible to predict whether other and perhaps more effective drug combinations will appear (see Chapter 7 for future research needs). Some have argued that those with only mild disease could wait in the hope of better treatments in the future.

The fact that pegylated interferon treatment appears clinically effective and cost-effective will augment the Hepatitis C Strategy for England,[148] which places emphasis upon effective antiviral treatment as described in the existing NICE guidance, which will be updated by the forthcoming guidance. Treatment forms part of a wider strategy to ensure effective monitoring, prevention, diagnosis and care for those infected, in terms of managed clinical networks and coordinated pathways of patient care. The strategy includes an awareness campaign for the public (particularly those at highest risk) and health professionals (including GPs, nurses and people working with IDUs) which will increase the number of people screened, and subsequently increase rates of treatment.

Chapter 7
Discussion

Assumptions, limitations and uncertainties

The nature of the model makes the results sensitive to the assumptions used. The costs gathered from NHS registers or from other verifiable sources stem from a relatively short period during which pegylated interferon has been available. However, treating or not treating hepatitis C will, in many cases, have consequences for 30 years or more. Small changes in elements of the model will therefore have large, long-term consequences, as the sensitivity analyses clearly show.

It should be noted that the clinical-effectiveness data used in the cost–utility model come from relatively few trials. Therefore, some effectiveness estimates may be based on relatively small numbers of patients. This is particularly true when considering subgroups of patients with different combinations of viral genotype and baseline viral load, for instance. In addition, although some trials stratified their randomisation on the basis of these baseline characteristics, other results are based on post-hoc subgroups.

It is also worth noting that the cost per QALY estimates for genotype 2 and 3 patients receiving non-pegylated IFN dual therapy are based on 48 weeks of treatment, when in practice they would usually receive only 24 weeks. A more appropriate comparison would be 24 weeks of IFN dual therapy versus 24 weeks of PEG dual therapy. However, such comparisons have not been made in the currently published RCTs of PEG treatment, although unpublished data are available (see the Hadziyannis trial,[60] as described in Chapter 3, p. 20). As outlined earlier, unpublished data were not used in the model.

Apart from uncertainties in the data used, the model also has to work in a simplified manner in relation to both specification errors of the included parameters and the nature of the algorithms. Real-life changes in treatment costs and effects are rarely linear over time, but are treated as such in the model. Even a slightly more realistic model with the usual assumption that costs follow a log-linear distribution would have increased the complexity of the model without necessarily yielding much extra information. Further, data are currently lacking on the natural history of hepatitis C, thus limiting the ability to model more complex relations such as disease progression over a long-term period. For instance, there is very little information on how to model compliance rates in a non-experimental routine treatment, or on how information campaigns about available pegylated treatment would affect the willingness to undergo treatment.

As noted in Chapter 3 (section 'Quantity and quality of research available', p. 12), there is a relatively high withdrawal rate from treatment even in the context of a trial. These withdrawals occur for several reasons, but include patients who simply failed to comply with the fairly rigorous treatment regimen. It has been shown that patients with higher rates of compliance are associated with higher SVRs within the context of clinical trials, particularly for genotype 1 patients. The rate of compliance and treatment withdrawals in practice may be even higher than seen in the trials. Ways to maximise compliance and adherence in this population, many of whom are IDUs and have psychosocial difficulties, need to be considered. This is a particularly important issue for those former IDUs who are at risk of resuming their drug use, thus dropping out of treatment. Specialist centres may achieve better compliance through the use of specific reminder systems and other management methods.

Further, the limited data on the HRQoL of patients in different phases of treatment make assumptions highly speculative. In particular, it is not known whether quality of life returns to a level comparable to normal population after successful treatment. Finally, the model is also sensitive to assumptions about reinfection rates, but again, very few data are available to support advanced modelling.

In summary, the model was kept as simple as possible owing to the paucity of available evidence and considerable uncertainties surrounding natural history, quality of life, and issues such as compliance and reinfection. To some extent the sensitivity analysis may help to explore some of

the uncertainties; however, the ability to conduct more advanced techniques such as multidimensional or probabalistic sensitivity analysis is limited by the lack of definitive evidence.

Further research needs

Pegylated interferon is a relatively new intervention in the treatment of hepatitis C and therefore there are gaps in the evidence where further research is needed (see Appendix 10 for details of research in progress):

- There are no trials in which the efficacies of therapy with PEG-α-2a and PEG-α-2b are directly compared. It would be useful to compare the efficacy of these two pegylated interferons with and without ribavirin to determine whether there are any differences either in efficacy or in adverse events. One area where the two drugs differed in the current report was the difference in SVRs for patients infected with genotypes 2 and 3. In the dual-therapy trial of PEG-2b (Manns and colleagues,[41]) there was little difference between PEG and IFN-treated patients, whereas in the other dual-therapy trial (PEG-2a, Fried and colleagues[50]) the difference was greater, leading to widely different cost–utility estimates.
- As there are many patients who have been treated with previous therapies (non-pegylated interferon with or without ribavirin) without achieving a sustained response, there are patients who still need treatment that may clear their virus. There are no full reports of retreatment of previous non-responders using pegylated interferon (either with or without ribavirin).
- There is very little information on the efficacy of treatments for hepatitis C (particularly using PEG) in patients who have other co-morbidities. With increased life expectancy in patients with HIV, the effects of hepatitis C on morbidity and mortality in this population have become more salient. Trials testing regimens including PEG should be conducted in this population (and some are ongoing, see Appendix 10). Many patients with haemophilia or renal disease are infected with hepatitis C and little information is available about the efficacy of hepatitis treatments in these populations. In general, patients with co-morbidities have been explicitly excluded from the primary efficacy trials for PEG. Careful evaluation of adverse events may be particularly important in these patient groups with co-morbidities because of the possibility of adverse interactions of hepatitis C treatment with other drugs that these patients may be taking. Others (e.g. IDUs) may be at higher risk of certain adverse events such as psychiatric events (e.g. severe depression).
- Despite increases in efficacy with the use of PEG over IFN, many patients remain infected with hepatitis C. Other treatment regimens that may prove to be overall more effective than dual therapy with PEG should be evaluated. For instance, treatment regimens that include amantadine may merit further evaluation. At least one conference abstract was identified in this review wherein patients were treated with triple therapy (PEG + RBV + AMA).
- There is some evidence that treatments for the eradication of hepatitis C may improve liver histology even in patients who do not clear the virus. More evidence about the long-term outcomes for such patients would be useful. In addition it would be useful to test prospectively which treatment regimens achieve the best improvements in liver histology and which are most cost-effective.
- In the context of existing trials of PEG that generally treated patients for 48 weeks, secondary analyses have suggested that stopping treatment relatively early (e.g. 12 weeks for patients with non-1 genotypes or 24 weeks for patients with genotype 1) may be a cost-effective approach to treatment that would also reduce the exposure to adverse events of patients who are unlikely to benefit. Prospective tests of these stopping rules would be useful, particularly with concurrent collection of cost data.
- Further investigation of treating patients with acute hepatitis C may be merited potentially to avoid the long-term morbidity involved for some patients when they reach the stage of chronic infection. However, careful attention to treatment of patients who are acutely symptomatic versus those who are infected but remain asymptomatic may be important in terms of treatment efficacy, the overall populations to be treated and the potential cost-effectiveness of treating patients with acute infection.
- Problems that may occur in a minority of patients with hepatitis C, such as cryoglobulinaemia and vasculitis, are not likely to be the subject of clinical trials because of the relatively small number of patients affected. However, clinicians point out that in some patients with vasculitis due to viral/antibody complexes the vasculitis can resolve after long-

term treatment. Appropriate treatment of such patients needs to be addressed.
- Additional psychological effects on quality of life due to hepatitis C need to be evaluated. For instance, the simple fact of being infected with a transmissible disease is a significant motivator for treatment for many patients.
- Further research is needed on the treatment of children and adolescents with hepatitis C. Previous studies of interferon monotherapy in children have been generally small, uncontrolled trials involving highly selected patients. New therapies, including PEG, should be studied in children. The long-term safety of these medications also needs to be studied in children.

Should patients with mild disease be treated?

An interim position is needed while awaiting the results of the UK Mild HCV study. The case for treatment depends at present on the unpublished Trent data on progression, and the reduction in quality of life in untreated patients with hepatitis C. If the average reduction is 0.05 QALY, and if an SVR indicates permanent clearance, then given the fairly young age of many people with hepatitis C, successful treatment will achieve at least 20 years of gain, equating to 1.0 QALY. Hence, it could be argued that there is a case for treating mild disease on quality of life gains alone.

Chapter 8
Conclusions

Pegylated interferon is more clinically effective than non-pegylated interferon, both as dual therapy and as monotherapy for those unable to tolerate ribavirin. It is also relatively cost-effective, particularly for patients with genotypes 2 and 3, with cost per QALY estimates falling within the range considered by NHS decision-makers to represent good value for money. There is some evidence to suggest that a proportion of patients with genotype 1 who do not respond by week 12 can cease treatment, as it is unlikely that they will experience a later, sustained response. This will lead to some cost savings (mainly in terms of drug costs), and will spare patients the adverse effects that are associated with treatment (which appear to be no worse than those experienced with non-pegylated interferon). Evidence for the clinical and cost-effectiveness of antiviral treatment in patients with mild disease (i.e. non-pegylated and ribavirin dual therapy) is imminent. If it can be assumed that treatment is effective and has benefits for patients' HRQoL, this would be an argument for extending treatment to a much larger group of patients than are currently eligible.

Acknowledgements

We approached advisors who were selected for their expert knowledge in this area. They saw a complete, nearly final version of the report and provided helpful comments about its comprehensiveness and whether we had correctly interpreted the evidence. The advisory panel comprised: Professor Howard Thomas (St Mary's Hospital, London), Mr Nigel Hughes (British Liver Trust, Ispwich), Dr John Morris (The Haemophilia Society, London), Dr Helen Howie (Grampian Health Board), Dr Henry Watson (Aberdeen Royal Infirmary), Professor Will Irving (Queens Medical Centre, Nottingham), Professor Roger Finch (Nottingham City NHS Trust), Dr Mary Ramsay (PHLS Communicable Disease Surveillance Centre, London) and Dr Nick Sheron (Southampton University Hospitals Trust).

This report builds upon the earlier work of Andrew Walker, Kirsten Major, Helen Howie and Paul Hewitson.

We are grateful to Cathy Benyon (Finance Department, Southampton University Hospitals Trust) for supplying cost information and to Joanna Kirby (Southampton Health Technology Assessment Centre, SHTAC) for checking the accuracy of the data extracted.

This report was commissioned by the NHS R&D HTA programme.

Contributions of authors

Jonathan Shepherd (Senior Research Fellow in Health Technology Assessment) was responsible for overall coordination of the review, writing the protocol, screening studies for inclusion, data extraction and critical appraisal of included studies, refining the economic model, writing up the report (including the introductory sections, methods, results and synthesis of results), and analysis and summary of the industry submissions.

Håkan Brodin (Senior Research Fellow in Health Economics) was responsible for coordination of the cost-effectiveness of the review (including obtaining and analysing cost data, refining the economic model and performing cost–utility analysis) and analysis of the industry submissions.

Carolyn Cave (Research Fellow in Health Technology Assessment) was responsible for screening studies for inclusion, processing retrieved reports, data extraction and critical appraisal, writing up the report (including synthesis of results and tabulation of data in the appendices), and analysis and summary of the industry submissions.

Norman Waugh (Professor of Public Health) was responsible for writing up the report (including writing the section on the effectiveness of non-invasive tests and the section on the natural history of hepatitis C) and the internal review of the draft report.

Alison Price (Information Officer) was responsible for designing, testing, refining and running the literature searches.

John Gabbay (Professor of Public Health) is guarantor for the report, and was responsible for the internal review of the draft report.

References

1. Royal College of Physicians of Edinburgh. *Hepatitis C: a report produced by a working party of the Royal College of Physicians of Edinburgh.* Edinburgh: Royal College of Physicians of Edinburgh; 1995.
2. Chief Medical Officer. *Hepatitis C (HCV) and blood transfusion.* Edinburgh: Scottish Home Office and Health Department; 1995.
3. Thomas HC, Weatherall DT, Ledingham J, Warrell DA. Clinical features of viral hepatitis. *Oxford textbook of medicine.* 3rd ed. Oxford: Oxford University Press; 1996. pp. 2061–9.
4. Poynard T, Bedossa P, Opolon, P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997;**349**;825–32.
5. Di Bisceglie AM. Hepatitis C. *Lancet* 1998; **351**:351–5.
6. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;**36**:S35–46.
7. Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol* 2002;**97**:2408–14.
8. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol* 2001;**34**:730–9.
9. McQuillan GM, Alter MJ, Moyer LA, Lambert SB, Margolis HS. A population based serologic study of hepatitis C virus infection in the United States. In: Rizzetto M, Purcell R, Gerin J, Verne G, editors. *Viral hepatitis and liver disease*. Turin: Edizioni Minerva Medica; 1997. pp. 267–70.
10. Ramsay ME, Balogun MA, Collins M, Balraj V. Laboratory surveillance of hepatitis C virus infection in England and Wales: 1992 to 1996. *Commun Dis Public Health* 1998;**1**:89–94.
11. Mohsen AH, Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 2001; **48**:707–13.
12. Public Health Laboratory Service. *Unlinked Anonymous HIV Prevalence Monitoring Programme – England and Wales.* London: Department of Health; 1996.
13. Harris KA, Gilham C, Mortimer PP, Teo CG. The most prevalent hepatitis C virus genotypes in England and Wales are 3a and 1a. *J Med Virol* 1999;**58**:127–31.
14. Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. *Hepatology* 1995;**22**:1863–73.
15. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, *et al.* Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; **346**:1051–5.
16. Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, *et al.* Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. *Ann Intern Med* 1997;**127**:875–81.
17. Bayliss MS. Methods in outcomes research in hepatology: definitions and domains of quality of life. *Hepatology* 1999;**29**:3–6S.
18. Conry CC, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L, *et al.* Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996;**334**:1691–6.
19. Poynard T, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, *et al.* Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 2002;**9**:295–303.
20. Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J, *et al.* Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology* 2002;**35**:433–9.
21. Forton DM, Taylor-Robinson SD, Thomas HC. Reduced quality of life in hepatitis C – is it all in the head? *J Hepatol* 2002;**36**:435–8.
22. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 health survey: manual and interpretation guide*. Boston, MA: Health Institute, New England Medical Center; 1993.
23. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy.The Consensus Interferon Study Group. *Hepatology* 1999;**29**:264–70.
24. Carithers RL, Sugano D, Bayliss M. Health assessment for chronic HCV infection: results of quality of life. *Dig Dis Sci* 1996;**41**:75–80S.
25. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology* 1998;**27**:209–12.

26. Fontana RJ, Hussain KB, Schwartz SM, Moyer CA, Su GL, Lok AS. Emotional distress in chronic hepatitis C patients not receiving antiviral therapy. *J Hepatol* 2002;**36**:401–7.

27. Hunt CM, Dominitz JA, Bute BP, Waters B, Blasi U, Williams DM. Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. *Dig Dis Sci* 1997;**42**:2482–6.

28. Ware JE, Bayliss MS, Mannocchia M, Davis GL, Bassaris H, Batey R, *et al.* Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. *Hepatology* 1999;**30**:550–5.

29. Neary MP, Cort S, Bayliss MS, Ware JE. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. *Semin Liver Dis* 1999; **19**:77–86.

30. Myers RP, Regimbeau C, Thevenot T, Leroy V, Mathurin P, Opolon P, *et al.* Interferon for interferon naive patients with chronic hepatitis C (Cochrane Review). *Cochrane Database Syst Rev* 2002;CD000370.

31. Poynard T, McHutchison J, Goodman Z, Ling MH, Albrecht J. Is an 'à la carte' combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. *Hepatology* 2000;**31**:211–18.

32. Davis GL, Esteban MR, Rustgi V, Hoefs J, Gordon SC, Trepo C, *et al.* Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;**339**:1493–9.

33. Foster GR, Chapman R. Combination treatment for hepatitis C is not being given. *BMJ* 2000; **321**:899.

34. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technol Assess* 2000;**4**(33).

35. National Institute for Clinical Excellence. *Guidance on the use of ribavirin and interferon alpha for hepatitis C*. London: National Institute for Clinical Excellence; 2000.

36. Booth J, O'Grady J, Neuberger J, on behalf of the Royal College of Physicians of London and the British Society of Gastroenterology. Clinical guidelines on the management of hepatitis C. *Gut* 2001;**49**:1–21.

37. Cramp M, Rosenburg W. *Guidance on the treatment of hepatitis C incorporating the use of pegylated interferons*. London: British Society for Gastroenterology; 2003.

38. Davis GL. Treatment of chronic hepatitis C. *BMJ* 2001;**323**:1141–2.

39. British Medical Association. *British National Formulary*. London: Royal Pharmaceutical Society of Great Britain; 2002.

40. Reddy KR, Wright TL, Pockros PJ, Shiffman M, Everson G, Reindollar R, *et al.* Efficacy and safety of pegylated (40-kd) interferon α-2a compared with interferon α-2a in noncirrhotic patients with chronic hepatitis C. *Hepatology* 2001;**33**:433–8.

41. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;**358**:958–65.

42. Scottish Medicines Consortium. The Scottish Medicines Consortium advises on pegylated interferon alpha-2b (ViraferonPeg). http://www.htbs.co.uk/smc/press/index.asp?did=697 (Accessed 6 May 2003.)

43. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C. 10–12 June 2002. *Hepatology* 2003;**36**:S3–20.

44. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement Management of Hepatitis C. 10–12 June 2002. http://consensus.nih.gov/cons/116/091202116cdc_statement.htm (Accessed 18 November 2002).

45. Cammà C, Bruno S, Schepis F, Lo IO, Andreone P, Gramenzi AG, *et al.* Retreatment with interferon plus ribavirin of chronic hepatitis C non-responders to interferon monotherapy: a meta-analysis of individual patient data. *Gut* 2002;**51**:864–9.

46. Myers R P, Poynard T. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C (Cochrane Review). *Cochrane Database Syst Rev* 2002(4).

47. Verbaan HP, Widell HE, Bondeson TL, Lindgren SC. High sustained response rate in patients with histologically mild (low grade and stage) chronic hepatitis C infection. A randomized, double blind, placebo controlled trial of interferon alpha-2b with and without ribavirin. *Eur J Gastroenterol Hepatol* 2002;**14**:627–33.

48. Wong VS, Hughes V, Trull A, Wight DG, Petrik J, Alexander GJ. Serum hyaluronic acid is a useful marker of liver fibrosis in chronic hepatitis C virus infection. *J Viral Hepat* 1998;**5**:187–92.

49. Gilmore I T, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, and Hopkins A. Indications, methods, and outcomes of precutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and Royal College of Physicians London. *Gut* 1995;**36**:437–41.

50. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;**347**:975–82.

51. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, *et al.* Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001;**345**:1452–7.

52. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, *et al.* A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001;**34**:395–403.

53. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;**343**:1666–72.

54. Heathcote EJ, Shiffman ML, Cooksley WGE, Dusheiko GM, Lee SS, Balart L, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;**343**:1673–80.

55. Balogun MA, Ramsay ME, Parry JV, Donovan L, Andrews NJ, Newham JA, *et al.* The prevalence and genetic diversity of hepatitis C infection in antenatal clinic attenders in two regions of England. *Epidemiol Infect* 2000;**125**:705–12.

56. Davis GL. Monitoring of viral levels during therapy of hepatitis C. *Hepatology* 2002; **36**:S145–51.

57. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, *et al.* Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998;**352**:1426–32.

58. McHutchison J, Manns M, Harvey J, Albrecht JK. Adherence to therapy enhances sustained response in chronic hepatitis C patients receiving peg-interferon alfa-2b plus ribavirin [abstract]. *J Hepatol* 2001;**34**:2–3.

59. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;**339**:1485–92.

60. Hadziyannis SJ, Cheinquer H, Morgan T, Diago M, Jensen DM, Sette H, *et al.* Peginterferon alfa-2a (40 Kd) (Pegasys) in combination with ribavirin (RBV): efficacy and safety results from a phase III, randomized, double-blind, multicentre study examining effect of duration of treatment and RBV dose. *J Hepatol* 2002;**36**(1):3.

61. Shobokshi O, Skakni L. Peg-IFN alfa-2a (40kDa) as a monotherapy or in combination with ribavirin significantly improve end of treatment response rate in HCV genotype 4 chronic active hepatitis (CAH) patients [abstract]. 53rd Annual Meeting on the Liver, 1–5 November 2002, Boston, MA, USA. *Hepatology* 2002;**36**:362A.

62. Shobokshi O, Serebour F, Skakni L, Tantawi A, Dinish T, Al-Quaiz M. Efficacy of pegylated (40 kDa) IFN alfa-2a (Pegasys) plus ribavirin in the treatment of hepatitis C genotype 4 chronic active patients in Saudi Arabia [abstract]. *J Hepatol* 2002;**36**:129.

63. Esmat GM, Abdel-Aziz FK, Abdel-Hamid MS, Ismail SA, Zalata KR, Mikhail NN.Treatment with PEG-interferon alfa-2b (PEG-IFN) plus ribavirin compared to interferon alfa-2b (IFN alfa-2b) plus ribavirin on subjects with chronic hepatitis C infected with HCV genotype 4 [abstract]. 53rd Annual Meeting on the Liver, 1–5 November 2002, Boston, MA, USA. *Hepatology* 2002;**36**:364A.

64. Pockros P, Carithers R, Desmond P, Dhumeaux D, Fried M, Marcellin P. Evaluation of two doses of peginterferon alfa-2a for the treatment of chronic hepatitis C (CHC) [abstract]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2001) 16–19 December 2001, Chicago, IL, USA.

65. Gebo, KA, Jenckes MW, Chander G, Torbenson MS, Ghanem KG, Herlong HF, *et al.* Management of chronic hepatitis C. Evidence Report/Technology Assessment No.60. Agency for Healthcare Research and Quality; 2002. www.ahrq.gov

66. Chander G, Sulkowski MS, Jenckes MW, Torbenson MS, Herlong HF, Bass EB, *et al.* Treatment of chronic hepatitis C: a systematic review. *Hepatology* 2002;**36**:S135–44.

67. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, *et al.* Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002;**122**:1303–13.

68. Myers RP, Abdo A, Poynard T. Pegylated interferon alfa for chronic hepatitis C (Protocol for a Cochrane Review). In *The Cochrane Library* (Issue 1). Oxford: Update Software; 2003.

69. Mohsen A, Easterbrook P, Taylor C, Norris S. Hepatitis C and HIV-1 coinfection. *Gut* 2002; **51**:601–8.

70. Perronne C, Carrat F, Banisadr F, Morand P, Lunel F, Rosenthal E, *et al.* ANRS HC02-Ribavic: a randomized controlled trial of pegylated interferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin as primary treatment of chronic hepatitis C in HIV co-infected patient [abstract]. *Hepatology* 2002;**36**:283A.

71. Banisadr F, Carrat F, Pol S, Rosenthal E, Morand P, Lunel F, *et al.* Effects of HCV treatment on HIV course. Preliminary results of the ANRS HC 02-Ribavic study: a randomized, controlled trial of pegylated interferon alpha-2B with ribavirin vs interferon alpha-2b with ribavirin for the tratment of chronic HCV in HIV co-infection [abstract]. *Hepatology* 2002;**36**:585A.

72. Goelz J, Klausen G, Moll A, Schleehauf D, Przwara D, Cordes C, Nzimegne, GA. Efficacy and tolerance of therapy in IFN-alpha/RBV and pegIFN-alpha/RBV in HIV-/HCV-coinfected IVDUs [abstract]. XIV International AIDS Barcelona, Conference, 7 July 2002.

73. Juarez A, Esteban JI, Sauleda S, Ribera E, Ocana I, Ruiz I, *et al.* Randomized trial of Intron A and ribavirin versus Peg-Intron and ribavirin in HIV HCV coinfected patients. Interim report on safety data [abstract]. *Hepatology* 2001;**34**:418A.

74. Shiffman M. Retreatment of HCV non-responders with peginterferon and ribavirin: results from the lead in phase of the Hepatitis C Antiviral Long Term Treatment against Cirrhosis (HALT-C) trial [abstract]. *Hepatology* 2002;**36**:295A.

75. Jacobson IM, Russo MW, Brown RS, Lebovics E, Min A, Esposito S, *et al.* Pegylated interferon alfa-2b plus ribavirin in patients with chronic hepatitis C: a trial in prior nonresponders to interferon monotherapy or combination therapy and in combination therapy relapsers. *Gastroenterology* 2002;**122**:79.

76. Shiffman ML. Retreatment of patients with chronic hepatitis C. *Hepatology* 2002;**36**:S128–34.

77. Cheng SJ, Bonis PA, Lau J, Pham NQ, Wong JB. Interferon and ribavirin for patients with chronic hepatitis C who did not respond to previous interferon therapy: a meta-analysis of controlled and uncontrolled trials. *Hepatology* 2001;**33**:231–40.

78. Cummings KJ, Lee SM, West ES, Cid-Ruzafa J, Fein SG, Aoki Y, *et al.* Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C previously nonresponsive to interferon: a meta-analysis of randomized trials. *JAMA* 2001; **285**:193–9.

79. Kjaergard LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. *Cochrane Database Syst Rev* 2002; CD002234.

80. San Miguel R, Guillen F, Cabases JM, Buti M. Meta-analysis: combination therapy with interferon-alpha 2a/2b and ribavirin for patients with chronic hepatitis C previously non-responsive to interferon. *Aliment Pharmacol Ther* 2002; **16**:1611–21.

81. Bonkovsky HL, Stefancyk D, McNeal K, Banner BF, Liu Q, Zucker GM, *et al.* Comparative effects of different doses of ribavirin plus interferon-alpha 2b for therapy of chronic hepatitis C: results of a controlled, randomized trial. *Dig Dis Sci* 2001;**46**:2051–9.

82. Brillanti S, Foli M, Di Tomaso M, Gramantieri L, Masci C, Bolondi L. Pilot study of triple antiviral therapy for chronic hepatitis C in interferon alpha non-responders. *Ital J Gastroenterol Hepatol* 1999; **31**:130–4.

83. Di Bisceglie AM, Thompson J, Smith-Wilkaitis N, Brunt EM, Bacon BR.Combination of interferon and ribavirin in chronic hepatitis C: retreatment of nonresponders to interferon. *Hepatology* 2001;**33**:704–7.

84. Enriquez J, Gallego A, Torras X, Perez-Olmeda T, Diago M, Soriano V, *et al.* Retreatment for 24 vs 48 weeks with interferon-alpha2b plus ribavirin of chronic hepatitis C patients who relapsed or did not respond to interferon alone. *J Viral Hepat* 2000;**7**:403–8.

85. Min AD, Jones JL, Esposito S, Lebovics E, Jacobson IM, Klion FM, *et al.* Efficacy of high-dose interferon in combination with ribavirin in patients with chronic hepatitis C resistant to interferon alone. *Am J Gastroenterol* 2001; **96**:1143–9.

86. Puoti M, Cadeo GP, Putzolu V, Forleo MA, Barni MC, Cristini G, *et al.* Pilot dose-finding trial on interferon alpha in combination with ribavirin for the treatment of chronic hepatitis C in patients not responding to interferon alone. *Dig Liver Dis* 2001;**33**:163–72.

87. Saracco G, Ciancio A, Olivero A, Smedile A, Roffi L, Croce G, *et al.* A randomized 4-arm multicenter study of interferon alfa-2b plus ribavirin in the treatment of patients with chronic hepatitis C not responding to interferon alone. *Hepatology* 2001;**34**:133–8.

88. Younossi ZM, Mullen KD, Zakko W, Hodnick S, Brand E, Barnes DS, *et al.* A randomized, double-blind controlled trial of interferon alpha-2b and ribavirin vs. interferon alpha-2b and amantadine for treatment of chronic hepatitis C non-responder to interferon monotherapy. *J Hepatol* 2001;**34**:128–33.

89. Fontana RJ, Walsh J, Moyer CA, Lok ASF, Webster S, Klein S. High-dose interferon alfa-2b and ribavirin in patients previously treated with interferon – results of a prospective, randomized, controlled trial. *J Clin Gastroenterol* 2002; **34**:177–82.

90. Andreone P, Gramenzi A, Cursaro C, Sbolli G, Fiorino S, di Giammarino L, *et al.* Interferon-alpha plus ribavirin in chronic hepatitis C resistant to previous interferon-alpha course: results of a randomized multicenter trial. *J Hepatol* 1999; **30**:788–93.

91. Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Bellomo G, Belloni G, *et al.* Interferon-alpha-2B and ribavirin in combination for chronic hepatitis C patients not responding to interferon-alpha alone: an Italian multicenter, randomized, controlled, clinical study. *Am J Gastroenterol* 1998; **93**:2445–51.

92. Pol S, Couzigou P, Bourliere M, Abergel A, Combis J, Larrey D, *et al.* A randomized trial of ribavirin and interferon-alpha vs. interferon-alpha alone in patients with chronic hepatitis C who were non-responders to a previous treatment. *J Hepatol* 1999;**31**:1–7.

93. Scotto G, Fazio V, Tantimonaco G. Pilot study of a short course of ribavirin and alpha-interferon in the treatment of chronic active hepatitis C not responding to alpha-interferon alone. *Ital J Gastroenterol* 1996;**28**:505–11.

94. Sostegni R, Ghisetti V, Pittaluga F, Marchiaro G, Rocca G, Borghesio E, *et al.* Sequential versus concomitant administration of ribavirin and interferon alfa-n3 in patients with chronic hepatitis C not responding to interferon alone: results of a randomized, controlled trial. *Hepatology* 1998; **28**:341–6.

95. Toccaceli F, Grimaldi M, Rosati S, Palazzini E, Laghi V. Ribavirin plus human leucocyte interferon alpha for the treatment of interferon resistant chronic hepatitis C: a controlled trial. *Hepatol Res* 1997;**8**:106–12.

96. Barbaro G, Di Lorenzo G, Belloni G, Ferrari L, Paiano A, Del Poggio P, *et al.* Interferon alpha-2B and ribavirin in combination for patients with chronic hepatitis C who failed to respond to, or relapsed after, interferon alpha therapy: a randomized trial. *Am J Med* 1999;**107**:112–18.

97. Bell H, Hellum K, Harthug S, Myrvang B, Ritland S, Maeland A, *et al.* Treatment with interferon-alpha2a alone or interferon-alpha2a plus ribavirin in patients with chronic hepatitis C previously treated with interferon-alpha2a. *Scand J Gastroenterol* 1999;**34**:194–8.

98. Bellobuono A, Mondazzi L, Tempini S, Silini E, Vicari F, Ideo G. Ribavirin and interferon-alpha combination therapy vs interferon-alpha alone in the retreatment of chronic hepatitis C: a randomized clinical trial. *J Viral Hepat* 1997; **4**:185–91.

99. Brillanti S, Miglioli M, Barbara L. Combination antiviral therapy with ribavirin and interferon alfa in interferon alfa relapsers and non-responders: Italian experience. *J Hepatol* 1995;**23**:13–15.

100. Milella M, Santantonio T, Pietromateria G, Maselli R, Casalino C, Mariano N, *et al.* Retreatment of non-responder or relapser chronic hepatitis C patients with interferon plus ribavirin vs interferon alone. *Ital J Gastroenterol Hepatol* 1999;**31**:211–15.

101. Salmeron J, Ruiz E, Torres C, Rodriguez R, Lavin I, Quintero D, *et al.* Interferon versus ribavirin plus interferon in chronic hepatitis C previously resistant to interferon: a randomized trial. *Liver* 1999;**19**:275–80.

102. Bresci G, Parisi G, Bertoni M, Capria A. High-dose interferon plus ribavirin in chronic hepatitis C not responding to recombinant alpha-interferon. *Dig Liver Dis* 2000;**32**:703–7.

103. Ferenci P, Stauber R, Steindl-Munda P, Gschwantler M, Fickert P, Datz C, *et al.* Treatment of patients with chronic hepatitis C not responding to interferon with high-dose interferon alpha with or without ribavirin: final results of a prospective randomized trial. *Eur J Gastroenterol Hepatol* 2001;**13**:699–705.

104. Tripi S, DiGaetano G, Soresi M, Cartabellotta F, Vassallo R, Carroccio A. Interferon-alpha alone versus interferon-alpha plus ribavirin in patients with chronic hepatitis C not responding to previous interferon-alpha treatment. *Biodrugs* 2000;**13**:299–304.

105. Cavalletto L, Chemello L, Donada C, Casarin P, Belussi F, Bernardinello E, *et al.* The pattern of response to interferon alpha (alpha-IFN) predicts sustained response to a 6-month alpha-IFN and ribavirin retreatment for chronic hepatitis C. TVVH Study Group. *J Hepatol* 2000; **33**:128–34.

106. Andreone P, Cursaro C, Gramenzi A, Fiorino S, di Giammarino L, Miniero R, *et al.* Interferon alpha plus ketoprofen or interferon alpha plus ribavirin in chronic hepatitis C non-responder to interferon alpha alone: results of a pilot study. *Ital J Gastroenterol Hepatol* 1999;**31**:688–94.

107. Brillanti S, Garson J, Foli M, Whitby K, Deaville R, Masci C, *et al.* A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa-resistant chronic hepatitis C. *Gastroenterology* 1994;**107**:812–17.

108. De Ledinghen V, Trimoulet P, Winnock M, Bernard PH, Bourliere M, Portal I, *et al.* Daily or three times per week interferon alpha-2b in combination with ribavirin or interferon alone for the treatment of patients with chronic hepatitis C not responding to previous interferon alone. *J Hepatol* 2002;**36**:819–26.

109. Malik AH, Kumar KS, Malet PF, Ostapowicz G, Adams G, Wood M, *et al.* A randomized trial of high-dose interferon alpha-2b, with or without ribavirin, in chronic hepatitis C patients who have not responded to standard dose interferon. *Aliment Pharmacol Ther* 2002;**16**:381–8.

110. Gaeta GB, Stornaiuolo G, Stanzione M, Ascione T, Pasquazzi C, Taliani G, *et al.* Interferon-alpha plus amantadine in chronic hepatitis C resistant to interferon alone: a pilot randomized study. *J Viral Hepat* 2001;**8**:284–6.

111. Bacosi M, Russo F, D'innocenzo S, Santolamazza M, Miglioresi L, Ursitti A, *et al.* Amantadine and interferon in the combined treatment of hepatitis C virus in elderly patients. *Hepatol Res* 2002; **22**:231–9.

112. Teuber G, Berg T, Naumann U, Raedle J, Brinkmann S, Hopf U, *et al.* Randomized, placebo-controlled, double-blind trial with interferon-alpha with and without amantadine sulphate in primary interferon-alpha nonresponders with chronic hepatitis C. *J Viral Hepat* 2001;**8**:276–83.

113. Teuber G, Berg T, Lafrenz M, Weidenbach H, Schoelmerich J, Wietzke-Braun P, *et al.* Randomized, controlled trial with interferon-alpha (IFN-alpha) combined with ribavirin with and without amantadine sulfate in primary IFN-alpha nonresponsive patients with chronic hepatitis C. *J Hepatol* 2001;**34**:23.

114. Brillanti S, Levantesi F, Masi L, Foli M, Bolondi L. Triple antiviral therapy as a new option for patients with interferon nonresponsive chronic hepatitis C. *Hepatology* 2000;**32**:630–4.

115. Shiffman ML, Hofmann CM, Gabbay J, Luketic VA, Sterling RK, Sanyal AJ, *et al.* Treatment of chronic hepatitis C in patients who failed interferon monotherapy: effects of higher doses of interferon and ribavirin combination therapy. *Am J Gastroenterol* 2000;**95**:2928–35.

116. Makris M, Baglin T, Dusheiko G, Giangrande PL, Lee CA, Ludlam CA, *et al.* Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia. *Haemophilia* 2001; **7**:339–45.

117. Fontana RJ, Lok ASF. Noninvasive monitoring of patients with chronic hepatitis C. *Hepatology* 2002;**36**:S57–64.

118. Herve S, Savoye G, Riachi G, Hellot MF, Goria O, Lerebours E, *et al.* Chronic hepatitis C with normal or abnormal aminotransferase levels: is it the same entity? *Eur J Gastroenterol Hepatol* 2001;**13**:495–500.

119. Albloushi SS, Murray FE, Callagy G, Courtney MG, O'Keane JC, Kay E. Changes in liver histopathology in women infected with hepatitis C through contaminated anti-D immunoglobulin injections in Ireland. *Eur J Gastroenterol Hepatol* 1998;**10**:69–73.

120. Forns X, Ampurdanes S, Llovet JM, Aponte J, Quinto L, Martinez-Bauer E, *et al.* Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology* 2002;**36**:986–92.

121. Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2002;**36**:S152–60.

122. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM, *et al*. Cost-effectiveness of peginterferon 2 b plus ribavirin versus interferon 2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut* 2003;**52**:425–32.

123. Alberti A, Boccato S, Vario A, Benvegnu L. Therapy of acute hepatitis C. *Hepatology* 2002; **36**:S195–200.

124. Patel R, Germer JJ, Tocci G, Visco-Comandini U, Antonucci G, Muir AJ, *et al.* Treatment of acute hepatitis C with interferon alfa-2b [1](multiple letters). *N Engl J Med* 2002;**346**:1091–2.

125. Patel R, Germer JJ, Tocci G, Visco-Comandini U, Antonucci G, Muir AJ, *et al.* Treatment of acute hepatitis C with interferon alfa-2b [1](multiple letters). *N Engl J Med* 2002;**346**:1091–2.

126. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**:855–65.

127. Stein K, Rosenberg W, Wong J. Cost effectiveness of combination therapy for hepatitis C: a decision analytic model. *Gut* 2002;**50**:253–8.

128. Wong JB, Bennett WG, Koff RS, Pauker SG. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. *JAMA* 1998;**280**:2088–93.

129. Younossi ZM, Singer ME, McHutchison JG, Shermock KM. Cost effectiveness of interferon alpha 2b combined with ribavirin for the treatment of chronic hepatitis C. *Hepatology* 1999;**30**:1318–24.

130. Buti M, Medina M, Casado MA, Wong JB, Fosbrook L, Esteban R. A cost-effectiveness analysis of peginterferon alfa-2b plus ribavirin for the treatment of naive patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2003;**17**:687–94.

131. Wong JB, Nevens F. Cost-effectiveness of peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin as initial treatment of chronic hepatitis C in Belgium. *Acta Gastroenterol Belg* 2002;**65**:110–11.

132. Wong JB, McHutchison JG, Manns MP, Albrecht JK. Economic and clinical implications of the loss of adherence to weight-based dosing of ribavirin and peginterferon alfa-2b for chronic hepatitis C. Boston, MA: American Association for the Study of Liver Diseases; 2002.

133. Wong JB, Rosenber WM, Manns MP, McHutchison JG, Davis GL, Albrecht JK. Is peginterfon alfa-2b plus ribavirin cost-effective for treating chronic hepatitis C in the United Kingdom? Geneva: European Association for the Study of the Liver; 2003.

134. Gish R, Bzowej N, Brooks L. Treatment with pegylated interferon alfa-2b in combination with ribavirin improved health-related quality of life compared with interferon alfa-2b plus ribavirin in chronic hepatitis C. Alexandra, VA: American Association for the Study of Liver Diseases; 2002.

135. Hassanein TI, Cooksley G, Sulkowski M, Smith C, Marinos G, Lai MY, *et al.* Treatment with 40 kDa peginterferon alfa-2a (Pegasys®) in combination with ribavirin significantly enhances quality of life compared with interferon alfa-2b plus ribavirin [abstract]. *Hepatology* 2001;**34**:243A.

136. Hassanein TI, Cooksley GE, Sulkowski M, Smith C, Marinos G, Lai M-Y, *et al.* QoL benefits observed as early as week 2 with peginterferon alfa-2a (40kD) (Pegasys) in combination with ribavirin (RBV) versus interferon alfa-2b plus RBV. European Association for the Study of the Liver, 37th Annual Meeting, Madrid, 15–21 April 2002.

137. Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology* 2002; **35**:704–8.

138. Rasenack J, Zeuzem S, Feinman S, Heathcote E, Manns M, Yoshida E, *et al.* Peginterferon alpha-2a (40kD) [Pegasys®] Improves HR-QoL outcomes compared with unmodified interferon alpha-2a [Roferon®-A] In patients with chronic hepatitis C. *Pharmacoeconomics* 2003;**21**:341–9.

139. Feagan BG, Trepo C, Lindsay KL, Niederau C, Wong CJ, Weng CSW, *et al.* The impact of pegylated interferon alfa-2b on health-related quality of life in chronic hepatitis C patients. *Hepatology* 2000;**32**:590.

140. National Centre for Clinical Excellence. *Guidance for manufacturers and sponsors*. Technology Appraisals Process Series No. 5. London: NICE; 2002.

141. Drummond MF, O'Brien BJ, Stoddart G, Torrance GW. *Methods for the economic evaluation of health care programmes*, 2nd ed. New York: Oxford University Press; 1997.

142. Gold M. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press; 1996.

143. Kim WR, Poterucha JJ, Hermans JE, Therneau TM, Dickson ER, Evans RW, *et al.* Cost-effectiveness of 6 and 12 months of interferon-alpha therapy for chronic hepatitis C. *Ann Intern Med* 1997;**127**:866–74.

144. Wong JB. Interferon treatment for chronic hepatitis B or C infection: costs and effectiveness. *Acta Gastroenterol Belg* 1998;**61**:238–42.

145. Wong JB. Estimating the cost-effectiveness of ribavirin and pegylated interferon alfa-2B for chronic hepatitis C. *Hepatology* 2000;**32**:1062.

146. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med* 2000;**133**:665–75.

147. Stein K, Jenkins B, Dalziel K, Horne J, Walker A, Royle P, *et al.* Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* 2002;**6**(31).

148. Department of Health. *Hepatitis C strategy for England*. London: Department of Health; 2002.

149. Seeff, L. Natural history of hepatitis C. *Hepatology* 1997;**26**(3), 21–8S.

150. Crowe J, Doyle C, Fielding JF. Presentation of hepatitis C in a unique uniform cohort 17 years from inoculation [abstract]. *Gastroenterology* 1995;**108**:1054A.

151. Power JP, Lawlor E, Davidson F, Yap PL, Kenny WE, Whelton MJ, *et al.* Hepatitis C viraemia in recipients of Irish intravenous anti-D immunoglobulin. *Lancet* 1994;**344**:1166–7.

152. Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR, Dusheiko GM, *et al.* Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet* 1997;**350**:1425–31.

153. Regan F, Hewitt P, Contreras BJ, on behalf of the TTI Study Group. Prospective investigation of transfusion transmitted infection in recipients of over 20,000 units of blood. *BMJ* 2000;**320**:403–7.

154. Harris HE, Ramsay ME, Heptonstall J, Soldan K, Eldridge KP. The HCV National Register: towards informing the natural history of hepatitis C infection in the UK. *J Viral Hepat* 2000;**7**:420–7.

155. Alter HJ, Conry CC, Melpolder J, Tan D, Van Raden M, Herion D, *et al.* Hepatitis C in asymptomatic blood donors. *Hepatology* 1997; **26**:29–33S.

156. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, *et al*. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;**34**:809–16.

157. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;**112**:463–72.

158. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology* 1997;**26**:34–8S.

159. Dienstag JL. The natural history of chronic hepatitis C and what we should do about it. *Gastroenterology* 1997;**112**:651–5.

160. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;**26**:15–20S.

161. Afdhal N, Flamm S, Imperial J, Malet PF, Tong M, Campagna J, *et al.* Pegylated (40 kDa) interferon alfa-2a (Pegasys®) in combination with ribavirin, mycophenolate mofetil (CellCept®), amantadine, or amantadine plus ribavirin in patients that did not respond to Rebetron® therapy: a preliminary

report of a randomized, multicenter study [abstract]. *Gastroenterology* 2001;**120**:1963.

162. Herrine SK, Brown R, Jr, Esposito S, Lok A, Galati JS, Bernstein DE, *et al.* Pegylated (40 kDa) interferon alfa-2a (Pegasys®) in combination with ribavirin, mycophenolate mofetil (CellCept®), amantadine, or amantadine plus ribavirin in patients that relapsed on Rebetron™ therapy: a preliminary report of a randomized, multicenter efficacy and safety study [abstract]. *Gastroenterology* 2001;**120**:A-384.

163. Di Bisceglie A-M, Bernstein, DE, Rustgi V.-R, Gitlin N, Jeffers LJ, Simon D. Pegylated (40 kDa) interferon alfa-2A (Pegasys®) in new combination therapies: a report of a randomized, multicenter efficacy and safety study [abstract]. *J Hepatol* 2001;**34**:143.

164. Lawitz EJ, Cantu NS, Adams F, Davis M, Sperling R, Fein S, *et al.* Triple therapy compared to standard pegylated interferon alfa 2b plus weight based ribavirin for treatment naive patients with chronic hepatitis C: 24 week viral clearance [TRI-STAR trial] [abstract]. *Gastroenterology* 2002;**123**:74.

165. Zeuzem S, Herrmann E, Lee JH, Marinos G, Modi M, Roth WK. Effect of ribavirin on viral kinetics in hepatitis C virus genotype 1 infected patients treated with pegylated interferon alpha 2a [abstract]. *Hepatology* 2001;**34**:1544.

166. Lindsay KL, McHutchison JG, Ling MH, Albrecht JK. Response to PEG-IFN alpha2b (PEG-Intron) in Blacks and Hispanics with HCV is higher than with standard IFN alpha2b (IFN) [abstract]. *Hepatology* 2000;**32**:347A.

167. Wong JB, Siebert U, Manns MP, McHutchison JG, Sroczynski G, Wasem J, *et al.* Cost-effectiveness of ribavirin and pegylated interferon alfa-2b for initial treatment of chronic hepatitis C [abstract]. *Hepatology* 2001;**34**:2075.

168. Buti M, Casado MA, Medina M, Fosbrook L, Esteban R. Is Peg-interferon plus Ribavirin a cost-effective therapy, and if so, what is the most efficient way to use this therapy in naive patients with chronic hepatitis C? [abstract]. *J Hepatol* 2002;**36**:357.

169. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM, *et al.* Cost-effectiveness of peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C [abstract]. *J Hepatol* 2002;**36**:463.

170. Shiffman M, Pockros PJ, Reddy RK, Wright TL, Reindollar R, Fried MW, *et al.* A controlled, randomized, multicenter, descending dose phase II trial of pegylated interferon alfa-2a (PEG) vs standard interferon alfa-2a (IFN) for treatment of chronic hepatitis C [abstract]. *Gastroenterology* 1999;116:A1275.

171. Neumann AU, Zeuzem S, Brunda MJ, Hoffman JH. Rapid viral response to treatment with pegylated (40kDa) interferon ALFA-2A (Pegasys™) is strongly predictive of a sustained virologic response in patients with chronic hepatitis C (CHC) [abstract]. *Hepatology* 2000; **32**:633.

172. Pockros PJ, Heathcote EJ, Shiffman ML, Bain VG, Zeuzem S, Rustgi VR, *et al.* Efficacy of pegylated (40kDa) interferon alfa-2A (Pegasys™) in randomized trials of patients with chronic hepatitis C with and without cirrhosis: correlation of virologic responses with baseline liver histology and genotype [abstract]. *Hepatology* 2000;**32**:1131.

173. Sherman M, Dusheiko GM, Haeussinger D, Marinos G, Munoz-Espinoza L, Salmeron J, *et al.* Superior virologic response in genotype 4 chronic hepatitis C patients treated with pegylated (40kDa) interferon alfa-2A (Pegasys™) compared with standard interferon [abstract]. *Hepatology* 2000; **32**:754.

174. Shiffman ML, Fromm H, Mills P, Moonka DK, Fried MW, Berg C, *et al.* Enhanced efficacy of pegylated (40kDa) interferon alfa-2A (Pegasys™) compared with interferon alfa-2A (Roferon-A™) for chronic hepatitis C in Blacks [abstract]. *Hepatology* 2000;**32**:753.

175. Zeuzem S, Heathcote EJ, Shiffman ML, Wright TL, Bain VG, Sherman M, *et al.* Twelve weeks of follow-up is sufficient for the determination of sustained virologic response in patients with chronic hepatitis C treated with pegylated (40 kDa) interferon alfa-2a (Pegasys™) and interferon alfa-2a (Roferon-A®). *Hepatology* 2000;**32**:785.

176. Cooksley G, Foster G, Green J, Kleinman L, Hakim Z, Revicki D. The effect of successful anti-viral therapy on health-related quality of life for patients with chronic hepatitis C and cirrhosis. *Gastroenterology* 2000;**118**. Dallas, TX: American Association for the Study of Liver Diseases.

177. Kamal SM, Peter T, Rasenack JW. PEG (40kDa) interferon alpha-2a therapy enhances HCV specific CD4+ T helper 1 responses during and after treatment [abstract]. *Gastroenterology* 2001; **120**:A-55.

178. Heathcote EJ, Balart LA, Shiffman ML, Pockros PJ, Lee SS, Reddy KR, *et al.* Pegylated (40kDa) interferon alfa-2a (Pegasys™) is superior to interferon alfa-2a (Roferon-A®) in improving posttreatment histologic outcome in chronic hepatitis C patients 1584 [abstract]. *Hepatology* 2000;**32**:246.

Appendix 1

Natural history of chronic hepatitis C

Introduction

The natural history of hepatitis C is still poorly understood. Information on the long-term outcomes for untreated patients is required for a number of reasons, including to provide a baseline for estimating the relative cost-effectiveness of the various treatment options. There are several problems associated with assessing natural history.

- The first is that it is a relatively new disease, in the sense that the virus was identified only in 1989. However, since it seems to have been responsible for about 95% of cases of what was called 'non-A, non-B' hepatitis, that can be used as a reasonably accurate proxy.
- The second is that because most people have no acute illness at onset, the date of onset and hence the duration of disease are often uncertain. However, there have been a number of unfortunate events involving contamination of blood or blood products that have led to several outbreaks with a point source, allowing accurate analysis by duration.
- This leads to a third issue: is it safe to extrapolate from the populations involved in these outbreaks, to the different patient mix of those who have been infected more recently?

For the purposes of this review, a number of assumptions for economic modelling need to be made, to do with progression from one disease stage to another, in terms of both numbers who progress and time taken to progress. The group of most concern comprises those who develop the more serious consequences such as decompensated cirrhosis and hepatocellular cancer, many of whom will die, partly because of the seriousness of these conditions to patients, and partly because of the potential savings to the NHS if some of these conditions can be avoided. However, the much lesser effect on quality of life in those with mild chronic hepatitis should also be borne in mind, since although the effect is much smaller, numbers are greater.

Review of studies

The natural history has been reviewed by Seeff.[6,149] He notes that the problems of assessing natural history include:

- the time of initial infection is often not known (in about 60–80% of patients)
- representative cohorts are needed, to avoid the bias towards severity if only those referred with problems were used
- the very long follow-up time needed, because some consequences take decades to appear
- the difficulty in obtaining natural history for recent patients, because of treatment with antiviral therapy (although a proportion do not respond, the responders may be a group who would have had a better natural history)
- the need for population control groups (particularly if assessing symptoms such as tiredness).

Infection from contaminated blood

Antirhesus immunisation

In Ireland in 1977, a batch of anti-D immunoglobulin was contaminated with HCV. Crowe and colleagues[150] and Power and colleagues[151] followed up 232 women 17 years after inoculation. Of these, 70% had no symptoms, and the main symptom in the rest was fatigue. Liver biopsy showed mild or mild/moderate inflammation in 70%, moderate inflammation in 24% and severe inflammation in 7%. Only 2.4% had cirrhosis, mostly early (i.e. nodules with bridging fibrosis). This would be considered a low-risk group because of their age.

Clotting factors for haemophilia

Darby and colleagues[152] studied mortality in men who received clotting factor after the introduction of large pool methods (which replaced treatment by blood transfusion, starting in 1969, and which greatly increased the risk of infection). The risk of infection with hepatitis C is close to 100% in this group, dropping to 60% in those who received cryoprecipitate. Darby and colleagues used the National Haemophilia Register to create a cohort of men who were treated from 1969 to 1985, and then obtained data on deaths from liver disease or liver cancer, to estimate the interval between

infection and death. There was a 17-fold risk of death from liver disease, after excluding those with HIV infection. The risk was not apparent for the first 10–15 years of follow-up, but became noticeable after 20 years. There was a strong relationship with age, with cumulative risks of liver-related disease including cancer at 25 years being 14% in those with severe haemophilia who were over 45 years of age at first known exposure, compared with 2% in those aged 25–44 years at infection.

Blood transfusion

Seeff[149] summarises the findings of five studies of transfusion-associated HCV infection. There was a range of follow-up intervals of 8–14 years. Cirrhosis had developed in 8–24%, liver cancer was rare and liver-related deaths ranged from 2 to 6%. Most patients had no symptoms. In another two studies where subsets of patients believed to have been infected by transfusion could be identified, the mean durations between transfusion and development of cirrhosis and HCC were 10 and 14 years, and 29 and 28 years.

In a paper on current practice, Regan and colleagues[153] followed up 5579 recipients of 21,923 units of blood, and found that screening now ensures prevention of hepatitis C by blood transfusion. There was not a single instance of transmission.

In the UK, the National HCV Register provides a valuable resource for natural history and other studies.[154] It is based on the national 'lookback' exercise carried out in 1995, of all patients who received blood transfusions from donors found to be HCV positive when testing started in 1991. The study reports on 924 patients with known date of infection traced during the HCV lookback programme and 475 transfusion recipients who tested negative for antibodies to HCV (controls). This study reports on the results for the first 10 years since infection. As of 1999, 117 of 924 eligible patients had died. All-cause mortality was not significantly different between patients and controls (Cox's hazard ratio 1.41, 95% CI 0.95 to 2.08). Patients were almost six times more likely than controls to die directly from liver disease, but this difference was not significant. (The excess of liver-related deaths among the patients may be partially explained by the fact that knowledge of HCV status may influence the content of the death certificate.) Forty per cent of those who died from liver disease were known to have consumed excess alcohol. The majority of infected patients had no signs or symptoms of liver disease, but nearly 40% had abnormal liver function and 91% of patients biopsied had abnormal liver histology. Patients who had developed symptoms were more likely to have been infected for longer, to be positive for HCV-RNA and to have acquired the infection at an older age. Those with features of severe liver disease were also more likely to be male. This study suggests that HCV infection does not have a great impact on all-cause mortality in the first decade of infection, but infected patients have an increased risk of dying from a liver-related cause, particularly if they consume excess alcohol. Continued evaluation of this cohort will provide more information about the outcome of HCV infection over a longer time-course.

Studies in blood donors

Since the start of testing for HCV in blood donors, many asymptomatic cases of hepatitis C have been found. Alter and colleagues[155] studied a group of 481 blood donors who had anti-HCV antibodies. 86% had HCV RNA indicating chronic infection: the other 14% had presumably recovered spontaneously. Most of those with chronic hepatitis C had only mild liver disease. In 74 subjects, a reasonable estimate of time of onset of infection could be made, either because transfusion was the only apparent risk factor, or because intravenous drug use had been carried out for a limited period. Data from these patients suggest an interval to severe hepatitis of 14 years, and to cirrhosis of 27 years. Those with severe outcomes (15% in the NIH study) tended to be older (most over 60 years at onset of infection) and a high proportion had a history of alcohol abuse. In this study, the likely sources of infection were blood transfusion, intranasal cocaine use, intravenous drug use, ear-piercing in males and tattooing.

Progression to cirrhosis

Seeff,[6] in his review of natural history studies, notes the discordance in mean frequency in evolution to cirrhosis according to study design. The mean frequency was 42% for retrospective studies, 11% for prospective studies and 2.1% for retrospective–prospective cohort studies. Lowest rates of progression were among young people, particularly young women. The higher estimation from retrospective studies was probably because they included patients with established disease sampled from the referral base and prospective studies from people infected via blood

transfusions, with the retrospective–prospective studies benefiting from including a wide variety of ages and genders, from acute infection to long-term follow-up.

Freeman and colleagues[156] (as cited in Seeff[6]) conducted a systematic review of studies specifically to investigate progression to cirrhosis. Four categories of studies were identified, and rates of cirrhosis after 20 years were estimated for each:

- cross-sectional studies of patients referred to tertiary care centres (n = 33 studies), rate = 22% (95% CI 18 to 26%), with a mean age of 29 years at acquisition of infection
- longitudinal post-transfusion hepatitis studies (n = 5 studies), rate = 24% (95% CI 11 to 37%), with a mean age of 42 years at acquisition of infection
- cross-sectional surveys of people newly diagnosed at blood donor screening (n = 10 studies), rate = 4% (95% CI 1 to 7%), with a mean age of 22 years at acquisition of infection
- longitudinal community-based studies (n = 9 studies), rate = 7% (95% CI 4 to 10%), with a mean age of 26 years at acquisition of infection.

The authors of this study suggested that the community-based cohort studies with a mean frequency of 7% for the development of cirrhosis were the most representative for the estimation of progression in the general population. They identified older age at infection, gender and heavy alcohol intake as the major factors associated with rapid disease progression.

Cohorts of patients with chronic hepatitis C

Poynard and colleagues[4] studied a French cohort of 2235 patients with liver biopsies, although not all had known the date of onset. Estimated duration of infection to cirrhosis was 30 years, ranging from 13 years in men infected over the age of 40, to 42 years in women who were infected under the age of 40 and who did not drink alcohol. The main risk factors for more rapid progression were age, alcohol consumption and male gender. This study is useful for the mix of sources of infection: transfusion 39% and intravenous drug use 25%. There seemed to be no relationship between source of infection and risk of progression, which implies that less concern is needed about the generalisability of findings from those groups with known date of infection.

More recently, Poynard and colleagues[8] reported results of another cross-sectional cohort study of 2313 untreated patients infected either through intravenous drug use or blood transfusion, who underwent a single biopsy. The aim was to assess disease progression in terms of the linearity or other configuration of fibrosis progression. Progression was modelled using the hazard function (the probability that an individual experiences the event of interest, such as fibrosis progression, during a small time interval, given that the individual has survived up to the beginning of the interval). There were approximately four periods with a linear progression:

- during the first 10 years of infection there was little progression (except for patients infected after the age of 50)
- for the next period of 15 years progression was slow and regular
- progression was intermediate during the next 10 years
- finally, during the final 5 years progression was at its fastest.

Regression analysis was performed to identify risk factors associated with fibrosis progression:

- Whatever the fibrosis stage there were higher probabilities of progression according to age at infection, with most rapid progression in patients infected after the age of 50.
- Alcohol consumption only affected progression for fibrosis stages F2, F3 and F4, after 10 years of infection.
- Male gender was associated with fibrosis independent of age at infection and of alcohol consumption, primarily for latter stages of progression.
- There was no significant relationship between genotype or viral load and progression.

Fattovich and colleagues[157] from the EUROHEP study (in which St Mary's in London was one of the seven centres) followed 384 patients who already had compensated cirrhosis for a mean of 5 years. The 5-year risk of decompensation was 18% and that of hepatocellular cancer was 7%. The 5-year survival was 91% in all patients, but 50% in those who developed decompensated cirrhosis.

Di Bisceglie[158] reviewed the evidence on the development of hepatocellular cancer, and concluded that there was an incubation period of two to three decades between infection and HCC, and that it usually followed cirrhosis rather than developing *de novo*. Since about 20% of patients with chronic hepatitis C develop cirrhosis over the first 10 years, this suggests that between 2 and 7% will develop cancer by 20 years after infection. The risk is increased by alcohol and by concomitant infection with hepatitis B.

Are all patients at risk?

One issue that has yet to be resolved is whether all patients would develop cirrhosis if given sufficient time; that is, that all progress but at different rates, or whether some would not progress beyond mild disease. Dienstag[159] believes that progression is inevitable, but that in some patients it may take up to five decades, with 20% developing end-stage liver disease at some time. Hoofnagle[160] notes that 20–30% of patients develop cirrhosis after a slow and insidious process, but comments that it is unclear whether the remaining patients would develop cirrhosis eventually, or not at all.

What is clear is that current methods of assessing risk are not good enough to identify subgroups of patients who are not at risk, and the implication of this is that all patients need to be treated.

Conclusions

There are still uncertainties about the natural history, but it appears that:

- Most (85%) patients who are infected develop chronic hepatitis C.
- Most are asymptomatic; progression is usually very slow and insidious.
- Some groups (older patients, men and alcohol users) are at higher risk of progression.
- The source of infection does not affect the risk of progression once factors such as age are taken into account, and so the natural history observed from the groups infected via blood transfusion and products can be applied to newer cohorts such as IDUs.
- Twenty per cent will develop cirrhosis by 20 years' duration.
- About 2.5% of those with cirrhosis will develop HCC per annum.
- Once decompensated cirrhosis or cancer develops, most patients die within a year (if not given a liver transplant).

Appendix 2

Search strategy: pegylated interferon-alpha in chronic hepatitis C

Searched from 2000 to March 2003

Databases	Search strategy
Cochrane Library	Peg* OR polyethylene Glycol and interferon* Hepatitis-C or HCV and #1
MEDLINE	Search hist: hepc_medsrch ((((‘Interferon-Alfa-2b’ / all subheadings in MIME,MJME) or (‘Interferon-Type-I’ / all subheadings in MIME,MJME) or (‘Interferon-Alfa-2a’ / all subheadings in MIME,MJME) or (‘Interferon-Alfa-2c’ / all subheadings in MIME,MJME) or (‘Interferon-Type-I-Recombinant’ / all subheadings in MIME,MJME) or (‘Interferon-alpha’ / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) and ((peginterferon) or (pegylat* near interferon) or (peg* or polyethylene glycol) or (ViraferonPeg or Pegasys))) and ((hepatitis-c or HCV) or ((‘Hepatitis-C’ / all subheadings in MIME,MJME) or (‘Hepatitis-C-Chronic’ / all subheadings in MIME,MJME)) or (‘Hepacivirus-’ / all subheadings in MIME,MJME))) or (((((‘Interferon-Alfa-2b’ / all subheadings in MIME,MJME) or (‘Interferon-Type-I’ / all subheadings in MIME,MJME) or (‘Interferon-Alfa-2a’ / all subheadings in MIME,MJME) or (‘Interferon-Alfa-2c’ / all subheadings in MIME,MJME) or (‘Interferon-Type-I-Recombinant’ / all subheadings in MIME,MJME) or (‘Interferon-alpha’ / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) and ((peginterferon) or (pegylat* near interferon) or (peg* or polyethylene glycol) or (ViraferonPeg or Pegasys))) and ((ribav?rin) or (‘Ribavirin-’ / all subheadings in MIME,MJME) or (rebetol))) and ((hepatitis-c or HCV) or ((‘Hepatitis-C’ / all subheadings in MIME,MJME) or (‘Hepatitis-C-Chronic’ / all subheadings in MIME,MJME)) or (‘Hepacivirus-’ / all subheadings in MIME,MJME))) or ((((((‘Interferon-Alfa-2b’ / all subheadings in MIME,MJME) or (‘Interferon-Type-I’ / all subheadings in MIME,MJME) or (‘Interferon-Alfa-2a’ / all subheadings in MIME,MJME) or (‘Interferon-Alfa-2c’ / all subheadings in MIME,MJME) or (‘Interferon-Type-I-Recombinant’ / all subheadings in MIME,MJME) or (‘Interferon-alpha’ / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) and ((peginterferon) or (pegylat* near interferon) or (peg* or polyethylene glycol) or (ViraferonPeg or Pegasys))) and ((ribav?rin) or (‘Ribavirin-’ / all subheadings in MIME,MJME) or (rebetol))) and ((amantadine or amantadine hydrochloride or Lysovia) or (‘Amantadine-’ / all subheadings in MIME,MJME))) and ((hepatitis-c or HCV) or ((‘Hepatitis-C’ / all subheadings in MIME,MJME) or (‘Hepatitis-C-Chronic’ / all subheadings in MIME,MJME)) or (‘Hepacivirus-’ / all subheadings in MIME,MJME))) IFNa + Amantadine + HepC
EMBASE	Search strategy: emb_hepc_RCTs (((explode ‘interferon-’ / all subheadings) or (interferon*)) and ((peg* or polyethylene glycol) or (pegylat* near interferon) or (peginterferon) or (ViraferonPeg or Pegasys or Pegintron))) and ((hepatitis-c or HCV) or ((‘chronic-hepatitis’ / all subheadings) or (‘hepatitis-C’ / all subheadings) or (‘Hepatitis-C-virus’ / all subheadings))) Interferon + amantadine + hepC (for comparatives)
PubMed (for recent studies)	Peg* and interferon*
Web of Science Proceedings	hepatitis-c and (peg* and interferon)
SCI	hepatitis-c and (peg* and interferon) hepatitis-c and amantadine
NRR	Peg* OR polyethylene Glycol and interferon* and hepatitis-c
Edina BIOSIS	Peg* and interferon*
CRD HTA	Peg* and interferon*
NHS EED	Hepatitis-c and interferon* (no pegylated interferon costs)

Appendix 3

Inclusion worksheet for primary clinical-effectiveness trials

Trial name or number:				
Patients with **chronic hepatitis C**? (treatment naive, relapsed, or not responded to previous treatment regardless of source of infection or severity)	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Type
Pegylated interferon treatment programme? *NB. Exclude interventions without pegylated interferon (unless in retreatment of previous non-responders)*	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Design: RCT or sys review	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Appropriate **comparator?** 1) dual PEG vs dual STD 2) mono PEG vs mono STD 3) triple PEG vs dual PEG	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Note here if dual or triple STD vs mono STD in retreated:
In retreatment: 1) dual PEG v mono STD 2) triple PEG v mono STD *NB. Exclude screening for hepatitis C*				
Report one or more of **primary outcomes**: sustained clearance of infection (absence of viral RNA 6 months or longer after end of treatment); adverse effects; quality of life; long-term complications avoided	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Final decision	**INCLUDE**	**UNCLEAR (Discuss)**	**EXCLUDE**	**Results of Discussion:**

Appendix 4

Conference abstracts of trials involving pegylated interferon in hepatitis C

Study	Interventions	Design and reported primary outcome	Participants
Triple therapies versus dual therapies			
Afdhal *et al.*, 2001[161]	1. PEG-α-2a + RBV 2. PEG-α-2a + mycophenylate mofetil 3. PEG-α-2a + amantadine 4. PEG-α-2a + amantadine + RBV	RCT Virological response 24 weeks	n = 93 Not responded to ≥ 12 week of IFN + RBV
Herrine *et al.*, 2001[162]	1. PEG-α-2a + RBV 2. PEG-α-2a + mycophenylate mofetil 3. PEG-α-2a + amantadine 4. PEG-α-2a + amantadine + RBV	RCT Virological response 12 weeks	n = 90 Broke through or relapsed on IFN-α-2b + RBV
Di Bisceglie *et al.*, 2001[163]	1. PEG-α-2a + mycophenylate 2. PEG-α-2a + amantadine 3. PEG-α-2a + mycophenylate + amantadine 4. IFN-α-2b + RBV	RCT Virological response 24 weeks	n = 153 Previously untreated with CHC
Lawitz *et al.*, 2002[164]	1. PEG-α-2b (1.5 μg kg^{-1} per week) + RBV (13 μg kg^{-1} per week ± 2) + amantadine (100 mg b.d.) 2. PEG-α-2b (1.5 μg kg^{-1} per week) + RBV (13 mg kg^{-1} per week ± 2)	RCT Virological response	n = 1000 Treatment naive
Dual PEG therapy versus dual IFN therapy or monotherapies			
Hassanein *et al.*, 2001[135]	1. PEG-α-2a + RBV 2. PEG-α-2a + placebo 3. IFN-α-2b + RBV	RCT Quality of life (SF-36 and FSS)	n = not reported Chronic Hepatitis C
Zeuzem *et al.*, 2001[165]	1. PEG-α-2a (180 μg per week) 2. PEG-α-2a (180 μg per week) + RBV (1000–1200 per week) 3. IFN-α-2a (3 MIU three times per week) + RBV (1000–1200 per day)	RCT Viral kinetics	n = 36
McHutchison *et al.*, 2001[58]	1. PEG-α-2b (0.5 μg kg^{-1} per week) + RBV 2. PEG-α-2b (1.5 μg kg^{-1} per week) +RBV 3. IFN-α-2b + RBV	Analysis of included RCT not reported in primary report[41] Effect of adherence on SVR	n = 1530 Treatment naive
Lindsay *et al.*, 2000[166]	1. PEG-α-2b (0.5 μg kg^{-1} or 1.0 μg kg^{-1} or 1.5 μg kg^{-1} 2. IFN-α-2b (3 MIU three times per week) + RBV (1000–1200 mg per day) 3. IFN-α-2b (3 MIU three times per week)	Pooled data from three RCTs SVR in Caucasians, blacks and Hispanics	n = 2173 CHC, elevated ALT, compensated liver disease
Wong *et al.*, 2001[167]	1. PEG-α-2b (0.5 μg kg^{-1} per week) + RBV 2. PEG-α-2b (1.5 μg kg^{-1} per week) +RBV 3. IFN-α-2b + RBV	Economic analysis of included RCT not reported in primary report[41]	n = 1530 Treatment naive

continued

Study	Interventions	Design and reported primary outcome	Participants
Buti *et al.*, 2002[168]	1. PEG-α-2b (1.5 μg kg^{-1} per week) +RBV (800 mg per day) 2. PEG-α-2b + RBV (adjusted for body weight) 3. IFN-α-2b + RBV	Economic analysis (Spain) of effectiveness data from an included RCT[41]	n = 1530 Treatment naive
Siebert *et al.*, 2002[169]	PEG-α-2b + RBV compared with IFN-α-2b + RBV	Cost-effectiveness analysis (Markov model) of effectiveness data from an included RCT[41] Analyses in Euros/QALY	n = not stated (assume 1530) Treatment naive
Monotherapies			
Shiffman *et al.*, 1999[170]	1. PEG-α-2a (45, 90, 180 or 270 μg per week) 2. IFN-α-2a (3 MIU three times per week)	RCT SVR	n = 155
Neumann *et al.*, 2000[171]	1. PEG-α-2a (180 μg per week) 2. IFN-α-2a (6 MIU then 3 MIU)	Analysis of included RCT not reported in primary report[53] Relation between rapid viral response and SVR	n = 513 IFN naive
Pockros *et al.*, 2000[172]	1. PEG-α-2a (180 μg per week) 2. IFN-α-2a (3 MIU or 6 MIU, then 3 MIU)	Pooled data from three RCTs Relation of genotype and baseline histology with SVR	n = 1130 IFN naive
Sherman *et al.*, 2000[173]	1. PEG-α-2a (180 μg per week) 2. IFN-α-2a (3 MIU or 6 MIU, then 3 MIU three times per week)	Database from RCTs SVR	n = 1205 in database CHC, genotype 4 (n =16)
Shiffman *et al.*, 2000[174]	1. PEG-α-2a (180 μg per week) 2. IFN-α-2a (3 MIU or 6 MIU, then 3 MIU three times per week)	Database from RCTs SVR	n = 1205 in database CHC, black (n = 55)
Zeuzem *et al.*, 2000[175]	1. PEG-α-2a (90, 135 or 180 μg per week) 2. IFN-α-2a (3 MIU or 6 MIU, then 3 MIU three times per week)	Pooled data from RCTs Follow-up time for relapse following EOTR	n = 1441 IFN naive
Cooksley *et al.*, 2000[176]	1. PEG-α-2a 2. IFN-α-2a	RCT HRQoL	n = 250 With cirrhosis
Kamal *et al.*, 2001[177]	1. PEG-α-2a 2. IFN-α-2a (6 MIU for 12 weeks, then 3MIU for 36 weeks)	HCV-specific CD4$^+$ and cytokine responses	n = 28 Previously untreated
Heathcote *et al.*, 2000[178]	1. PEG-α-2a 2. IFN-α-2a	Pooled data from two RCTs Relation between SVR and histological response	n = 430 IFN naive

Appendix 5

Quality assessment scale: experimental studies

Adapted from NHS CRD Report 4

1. Was the assignment to the treatment groups really random?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were the point estimates and measure of variability presented for the primary outcome measure?
6. Did the analysis include an intention-to-treat analysis?
7. Were withdrawals and dropouts completely described?

Some instructions for using a checklist for RCTs

Quality item	Coding	Explanation
1. Was the assignment to the treatment groups really random?		
Random sequence generation	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate:** random numbers table or computer and central office or coded packages **Partial:** (sealed) envelopes without further description or serially numbered opaque, sealed envelopes **Inadequate:** alternation, case record number, birth date or similar procedures **Unknown:** just the term 'randomised' or 'randomly allocated', etc.
2. Was the treatment allocation concealed?		
Concealment of randomisation The person(s) who decide on eligibility should not be able to know or be able to predict with reasonable accuracy to which treatment group a patient will be allocated. In trials that use good placebos this should normally be the case; however, different modes or timing of drug administration in combination with the use of small block sizes of known size may present opportunities for clinicians who are also involved in the inclusion procedure to make accurate guesses and selectively exclude eligible patients in the light of their most likely treatment allocation; in centres with very low inclusion frequencies combined with very brief follow-up times this may also present a potential problem because the outcome of the previous patient may serve as a predictor of the next likely allocation	**Adequate** **Inadequate** **Unknown**	**Adequate:** when a paper convinces you that allocation cannot be predicted [separate persons, placebo really indistinguishable, clever use of block sizes (large or variable)]. Adequate approaches might include centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer-based system with a randomisation sequence that is not readable until allocation, and other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients **Inadequate:** this option is often difficult. You have to visualise the procedure and think how people might be able to circumvent it. Inadequate approaches might include use of alternation, case record numbers, birth dates or week days, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation) and any other measures that cannot prevent foreknowledge of group allocation **Unknown:** no details in text. Disagreements or lack of clarity should be discussed in the review team

continued

Quality item	Coding	Explanation
3. Were the groups similar at baseline in terms of prognostic factors?		
Baseline characteristics Main aim is to enable the reviewer to see which patients were actually recruited. It enables one to get a rough idea on prognostic comparability. A real check on comparability requires multivariable stratification (seldom shown)	**Reported** **Unknown**	Consult the list of prognostic factors or baseline characteristics (not included in this appendix). Reviewer decides
4. Were the eligibility criteria specified?		
	Adequate **Partial** **Inadequate** **Unknown**	
5. Were the point estimates and measure of variability presented for the primary outcome measure?		
Results for the primary outcome measure	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate:** mean outcome in each group together with mean difference and its standard error (SE) or standard deviation (SD) or any CI around it or the possibility to calculate those from the paper. Survival curve with log rank test and patient numbers at later time-points **Partial:** partially reported **Inadequate:** no SE or SD, or SD without *N* (SE = SD/*N*) **Unknown:** very unlikely
6. Did the analysis include an intention-to-treat analysis?		
Intention-to-treat analysis (ITT) Early dropout can make this very difficult. Strictest requirement is sensitivity analysis including early dropouts.	**Adequate** **Inadequate**	Reviewers should not just look for the term ITT, but assure themselves that the calculations were according to the ITT principle
7. Were withdrawals and dropouts completely described?		
Loss to follow-up This item examines both numbers and reasons; typically an item that needs checking in the methods section and the marginal totals in the tables. Note that it may differ for different outcome phenomena or time-points. Some reasons may be reasons given by the patient when asked and may not be the true reason. There is no satisfactory solution for this	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate:** number randomised must be stated. Number(s) lost to follow-up (dropped out) stated or deducible (from tables) for each group and reasons summarised for each group **Partial:** numbers, but not the reasons (or vice versa) **Inadequate:** numbers randomised not stated or not specified for each group **Unknown:** no details in text

Appendix 6

Clinical-effectiveness studies: data extraction tables

Reference and design	Intervention	Participants	Outcome measures
Manns *et al.*, 2001[41] **Trial design**: RCT (open label) **Country**: International	**Intervention 1**: $n = 511$ PEG IFN-α-2b (s.c.) Dose: 1.5 μg kg^{-1} per week Duration: 48 weeks RBV (oral) Dose: 800 mg per day Duration: 48 weeks **Intervention 2**: $n = 514$ PEG IFN-α-2b (s.c.) Dose: 1.5 μg kg^{-1} per week Duration: 4 weeks Dose: 0.5 μg kg^{-1} per week Duration: 44 weeks RBV (oral) Dose: 1000 mg per day for patients <75 kg, 1200 mg per day for patients ≥ 75 kg Duration: 48 weeks **Intervention 3**: $n = 505$ IFN-α-2b (s.c.) Dose: 3 MIU three times per week Duration: 48 weeks RBV (oral) Dose: 1000 mg per day for patients <75 kg, 1200 mg per day for patients ≥ 75 kg Duration: 48 weeks RBV for all groups administered in two divided doses per day PEG IFN-α-2b administered once per week according to weight	**Total numbers involved:** 2316 screened, 1530 randomised **Eligibility and exclusion criteria:** see Chapter 3[a] for general criteria, plus: exclude previous organ transplant, poorly controlled diabetes, autoimmune-type disease **Recruitment**: 62 centres, worldwide **Genotypes (proportions)**: 1: 68% 2 or 3: 30% 4, 5 or 6: 2% **Baseline measurements**: Viral load: geometric mean HCV RNA in serum (copies ml$^{-1} \times 10^6$): 2.7; number with $> 2 \times 10^6$ copies: 1044 (68%) **Gender**: 1003 male (66%), 527 female (34%) **Age** (mean and range): 43.3 (21–68) years **Ethnic groups**: not reported **Losses to follow-up**: not reported **Compliance**: not reported	**Primary outcome used:** SVR (HCV RNA) **Secondary outcomes used:** histological response (Knodell HAI), adverse events **Length of follow-up:** 24 weeks post-treatment (72 weeks from treatment initiation)

continued

Outcome	PEG IFN-α-2b 1.5 μg kg^{-1} + RBV (800 mg)	PEG IFN-α-2b 1.5 then 0.5 μg kg^{-1} + RBV (1000–1200 mg)	IFN + RBV (1000–1200 mg)
Viral response			
4 weeks	–	–	–
12 weeks	–	–	–
End of treatment	65% (333/511)*	56% (289/514)	54% (271/505)
SVR	54% (274/511)†	47% (244/514)	47% (235/505)
SVR by genotype			
1	42% (145/348)*	34% (118/349)	33% (114/343)
2 or 3	82% (121/147)	80% (122/153)	79% (115/146)
4, 5 or 6	50% (8/16)	33% (4/12)	38% (6/16)
SVR by ribavirin dose			
$\leq$ 10.6 mg kg^{-1}	50% (160/323)	41% (13/32)	27% (6/22)
$>$10.6 mg kg^{-1}	61% (114/188)	48% (231/482)	47% (229/483)
Biochemical response (ALT)			
End of treatment	65%	63%	69%
Sustained response	54%	48%	47%
Histology (proportion with improvement)			
Inflammation	68% (232/339)	70% (254/361)	69% (232/334)
mean change	–3.4	–3.4	–3.4
Fibrosis	21% (71/333)	19% (69/361)	20% (66/328)
mean change	–0.1	–0.2	–0.2
Adverse events			
Dose discontinuation for			
any adverse event	14%	13%	13%
Dose reduction for			
any adverse event	42%	36%	34%
anaemia	9%	12%	13%
neutropenia	18%	10%	8%

[a] Chapter 3, Quantity and quality of research available.
* $p < 0.05$ compared with IFN + RBV by Fisher's exact test.
† $p < 0.05$ compared with IFN + RBV by logistic regression.

Additional results:

- For the higher dose of PEG IFN, 75% of patients who were HCV RNA negative for the first time at 12 weeks achieved an SVR; 32% of those who were HCV RNA negative for that first time at week 24 achieved an SVR.
- Factors associated with SVR: ($p < 0.0001$): HCV genotype (other than 1), baseline viral load (lower load), gender, baseline weight (lighter), age (younger); ($p = 0.01$): gender (was not a significant factor in a backward elimination procedure); ($p = 0.07$): absence of cirrhosis.
- The likelihood of SVR increases as the ribavirin dose increases.

Methodological comments:

Allocation to treatment groups: random assignment to groups stratified within groups by HCV genotype (1 vs others) and presence or absence of cirrhosis. In blocks of three. Schedule generated by Schering-Plough and performed by an independent central randomisation centre.
Allocation concealment: centralised randomisation by fax.
Blinding of outcome assessors: open-label trial. Biochemical and haematological testing done by a central laboratory (blinding not specifically mentioned); liver histology analysed by a single blinded pathologist.
Analysis by ITT: yes, for all participants who received at least one dose of study medication.
Comparability of treatment groups at pretreatment: groups appear comparable, but statistical equivalence not presented.
Method of data analysis: pairwise treatment comparisons by logistic regression; analyses of changes from baseline by paired Student's *t*-tests; evaluations of relation of baseline characteristics with treatment response by logistic regression. Power analyses to achieve 90% power to detect a 10% difference in SVR rates at the 5% level of significance required 525 participants per group. Logistic regression to consider relation between baseline disease characteristics and treatment response.

continued

Attrition/dropout: analyses included all participants who had at least one dose of study medication. Patients with missing HCV RNA values were classified as non-responders.

General comments
Generalisability: participants would appear to be representative of patients with chronic hepatitis C who have not had liver transplant or significant co-morbidities. The Authors report that the proportion of patients with genotype 1, high viral load, cirrhosis and distributions by age, gender and other characteristics are similar to populations in previous studies.
Conflict of interests: Study sponsor was Schering-Plough Research Institute.
Definitions: SVR: undetectable HCV RNA in serum. Histological response assessed by Knodell HAI, with improvement in fibrosis = decrease of ≥ 1 from pretreatment to post-treatment score and worsening = increase of ≥ 1 from pretreatment to post-treatment score.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the patient blinded?	Inadequate
6. Did the analysis include an intention-to-treat analysis?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Fried *et al.*, 2002[50] **Trial design**: RCT **Country**: International, Pegasys International Study Group	**Intervention 1**: *n* = 453 PEG IFN-α-2a (s.c.) Dose: 180 μg per week Duration: 48 weeks RBV (oral) Dose: 1000 mg per day for patients ≤ 75 kg, 1200 mg per day for patients >75 kg Duration: 48 weeks **Intervention 2**: *n* = 224 PEG IFN-α-2a Dose: 180 μg per week Duration: 48 weeks Placebo (oral) Dose: daily Duration: 48 weeks **Intervention 3**: *n* = 444 IFN-α-2b Dose: 3 MIU three times per week Duration: 48 weeks RBV Dose: 1000 mg per day for patients ≤ 75 kg, 1200 mg per day for patients >75 kg Duration: 48 weeks	**Total numbers involved**: 1459 screened, 1149 randomised, 1121 received at least one dose of study medication **Eligibility and exclusion criteria**: see Chapter 3 for general criteria **Recruitment**: 81 centres, worldwide, conducted between February 1999 and April 2001 **Genotypes (proportions)**: 1a: 365 (32.5%) 1b: 345 (30.8%) 1 other: 18 (1.6%) 2: 152 (13.6%) 3: 202 (18.0%) 4: 33 (3%) Other: 6 (0.5%) **Baseline measurements**: Viral load: mean HCV RNA level (copies ml^{-1} 10^6): 6.0 **Gender**: 800 male (71%), 321 female (29%) **Age** (mean): 42.5 years **Ethnic groups**: White: 943 (84.1%) Black: 53 (4.7%) Asian: 64 (5.7%) Other: 61 (5.4%) **Cirrhosis**: *n* = 144 (13%) **Losses to follow-up**: 28 patients randomised, but did not receive any study medication. Patients who withdrew during weeks 1–48: 312 (27.8%); patients who withdrew during weeks 49–72: 39 (3.5%) **Compliance**: not reported	**Primary outcome used**: SVR (HCV RNA at end of follow-up by PCR assay) **Secondary outcomes used**: adverse events, factors associated with SVR **Length of follow-up**: 24 weeks

continued

Outcome	PEG IFN-α-2a + RBV	PEG IFN-α-2a + placebo	IFN-α-2b + RBV
Viral response			
4 weeks	–	–	–
12 weeks[a]	86% (390/453)	–	–
End of treatment	69% (313/453)*	59% (132/224)+	52% (231/444)
SVR at follow-up	56% (255/453)*	29% (66/224)†	44% (197/ 444)
SVR by genotype			
1	46% (138/298)*	21% (30/145)	36% (103/285)
2 or 3	76% (106/140)††	45% (31/69)	61% (88/145)
4	77% (10/13)	36% (4/11)	44% (4/9)
5 or 6	–	–	–
SVR by baseline HCV RNA (copies ml^{-1})			
$\leq 2 \times 10^6$	62% (99/159)††	46% (32/69)	52% (78/150)
$>2 \times 10^6$	53% (156/293)††	22% (34/155)	41% (119/292)
SVR by genotype and baseline HCV RNA (copies ml^{-1})			
Genotype 1			
$\leq 2 \times 10^6$	56% (64/115)	39% (17/44)	43% (40/94)
$>2 \times 10^6$	41% (76/103)	13% (13/101)	33% (63/189)
Genotype 2 or 3			
$\leq 2 \times 10^6$	81% (30/37)	58% (11/19)	65% (34/52)
>2 x 10^6	74% (76/103)	40% (20/50)	58% (54/93)
SVR by histological diagnosis			
Cirrhosis	43% (24/56)	21% (7/34)	33% (18/54)
Adverse events			
Dose discontinuation for			
adverse event	7% (32/453)	5.8% (13/224)	9.7% (43/444)
laboratory abnormality	2.6% (12/453)	0.9% (2/224)	0.9% (4/444)

Dose reduction for	PEG IFN	RBV	PEG IFN	Placebo	IFN	RBV
any adverse event	48 (11%)	95 (21%)	14 (6)	39 (17%)	47 (11%)	97 (22%)
anaemia	4 (1%)	99 (22%)	0	8 (4%)	13 (3%)	83 (19%)
neutropenia	91 (20%)	6 (1%)	38 (17%)	0	24 (5%)	1 (<1%)
thrombocytopenia	18 (4%)	2 (< 1%)	14 (6%)	1 (<1%)	1 (< 1%)	0

[a] 12-week virological response = 2-log decrease from baseline HCV RNA levels or no detectable serum HCV RNA.
* $p \leq 0.01$ for comparisons between PEG + RBV and PEG + placebo and PEG + RBV and IFN + RBV.
+ $p = 0.06$ for comparison between PEG + placebo and IFN + RBV.
† $p < 0.001$ for comparison between PEG + placebo and IFN + RBV.
†† $p < 0.05$ for comparison between PEG + RBV and IFN + RBV.

Additional results

- Three factors independently and significantly increased the odds of achieving an SVR: an HCV genotype other than 1 (OR 3.25; 95% CI 2.09 to 5.12, $p < 0.001$), an age of <40 years (OR 2.60, 95% CI 1.72 to 3.95, $p < 0.001$) and a body weight of ≤ 75 kg (OR 1.91, 95% CI 1.27 to 2.89, $p = 0.002$).
- Of those with early virological responses, 65% subsequently had an SVR.
- Those with non-detectable HCV RNA by week 12 were more likely to have an SVR than those who had only a 2 log decrease in HCV RNA.
- Among the 63 patients who did not have an EVR in the PEG + RBV group, 61 (97%) did not have an SVR.
- The proportions of patients withdrawn from treatment because of laboratory abnormalities or other adverse events were similar in all three groups.
- Among patients who had an early virological response on PEG + RBV, the proportion with an SVR was similar among those who had a substantial dose reduction and those who maintained the full dosing schedule.
- Patients treated with PEG had a lower incidence of influenza-like symptoms than those treated with IFN (statistically significant for pyrexia, myalgia and rigors).
- Patients treated with PEG had a lower incidence of depression than those treated with IFN ($p = 0.01$).

continued

Methodological comments:
Allocation to treatment groups: randomly assigned in a 2:1:2 ratio with a block size of five. Randomisation stratified according to country and HCV genotype (HCV genotype 1 vs other genotypes).
Allocation concealment: not reported.
Blinding of outcome assessors: investigators were unaware of who received ribavirin or placebo among patients receiving PEG. No other information about blinding.
Analysis by ITT: all patients who received at least one dose of study medication were included in efficacy analyses, and if they had undergone at least one safety assessment after baseline, they were included in the safety analysis. For patients with at least 20 weeks of follow-up, the last observed HCV RNA level was used in the assessment of efficacy. All patients with follow-up of less than 20 weeks were considered to have had no response to treatment.
Comparability of treatment groups at pretreatment: baseline characteristics appear similar among groups, but statistical comparisons are not reported.
Method of data analysis: the Cochran–Mantel–Haenszel test was used for all possible pairwise comparisons and global comparisons of the three groups. The test was stratified according to the combination of country and HCV genotype (type 1 vs other genotypes). Stepwise, backward and multiple logistic regression models were used to explore baseline factors predicting an SVR.
Power analysis: not reported.
Attrition/dropout: 28 participants were lost between randomisation and beginning of treatment without explanation, other discontinuations with reasons where fully reported. Patients who discontinued therapy prematurely because of intolerance were encouraged to remain in the study.
Safety: patients were withdrawn from treatment if they continued to have viraemia at week 24, if they missed four consecutive doses, or at the discretion of the investigator.

General comments
Generalisability: patients would appear to be representative of patients with chronic HCV without other co-morbidities.
Conflict of interests: trial sponsor was Hoffmann-LaRoche. Data analysis was performed by the sponsor and the authors of this report; the authors had full access to the data, and the decision to publish was not limited by the sponsor.
Definitions: 12-week virological response: 2-log drop or undetectable HCV RNA.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate for RBV; inadequate for PEG vs IFN
5. Was the patient blinded?	Adequate for RBV; inadequate for PEG vs IFN
6. Did the analysis include an intention-to-treat analysis?	Adequate
7. Were losses to follow-up completely described?	Adequate

continued

Reference and design	Intervention	Participants	Outcome measures
Heathcote *et al.*, 2000[54] **Trial design**: RCT, open label **Country**: International, Pegasys International Study Group	**Intervention 1** $n = 88$ IFN-α-2a Dose: 3 MIU three times per week, s.c. Duration: 48 weeks **Intervention 2** $n = 96$ PEG IFN-α-2a Dose: 90 μg once per week, s.c. Duration: 48 weeks **Intervention 3** $n = 87$ PEG IFN-α-2a Dose: 180 μg once per week, s.c. Duration: 48 weeks	**Total numbers involved**: 397 screened, 271 met eligibility criteria and were randomised **Eligibility and exclusion criteria**: see Chapter 3 for general criteria, plus: biopsy-proved liver cirrhosis or bridging fibrosis **Recruitment**: 30 centres in USA, Canada, Australia and UK between September 1997 and October 1999 **Genotypes (proportions)**: 1:153 (56.5%) 1a: 88 (32.5%) 1b: 65 (24.0%) 2: 33 (12.2%) 3: 73 (26.9%) 4: 3 (1.1%) Other/unknown: 9 (3.3%) **Baseline measurements**: Viral load (copies $ml^{-1} \times 10^6$): 6.1 HAI: 12.96 **Cirrhosis**: 212 (78.2%) **Bridging fibrosis**: 58 (21.4%) **Gender**: 196 male (72.3%), 75 female (27.7%) **Age** (mean): 47.1 years **Ethnic groups**: White : 239 (88.2%) Black: 11 (4.1%) Asian: 7 (2.6%) Other: 14 (5.2%) **Losses to follow-up**: treatment completed by 64, 78 and 67 patients, respectively; follow-up completed by 68, 79 and 74 patients. Total loss to follow-up = 50 patients	**Primary outcomes used**: sustained virological and biochemical responses **Secondary outcome used**: histological response **Length of follow-up**: 24 weeks

continued

Outcome	IFN-α-2a	PEG IFN-α-2a 90 μg	PEG IFN-α-2a 180 μg
Viral response			
4 weeks	–	–	–
12 weeks	–	–	–
End of treatment (48 weeks)	14% (12/88)	42% (40/96)*	44% (38/87)*
SVR (72 weeks)	8% (7/88)	15% (14/96)	30% (26/87)*
Combined virological and biochemical response			
48 weeks	10% (9/88)	8% (1/13)	40% (2/5)
72 weeks	8% (7/88)	16% (13/83)	29% (24/82)
SVR by genotype			
1	2% (1/47)	5% (3/58)	12% (6/48)
1a	0 (0/28)	4% (1/27)	9% (3/33)
1b	5% (1/19)	6% (2/31)	20% (3/15)
Other than 1 or unknown	15% (6/41)	29% (11/38)	51% (20/39)
SVR by HCV RNA level (copies ml^{-1})			
$\leq 2 \times 10^6$	5% (2/41)	22% (10/45)	37% (16/31)
$>2 \times 10^6$	9% (4/45)	8% (4/51)	23% (10/44)
SVR by total HAI score			
$\leq$ 10	0% (0/5)	8% (1/13)	40% (2/5)
$>$ 10	8% (7/83)	16% (13/83)	29% (24/82)
SVR by histological diagnosis			
Cirrhosis	7% (5/67)	14% (11/76)	32% (22/69)
Bridging fibrosis	10% (2/21)	16% (3/19)	22% (4/18)
SVR by genotype and HCV RNA level			
1 and $\leq 2 \times 10^6$	0% (0/21)	12% (3/26)	16% (3/19)
1 and $>2 \times 10^6$	4% (1/25)	0% (0/32)	10% (3/29)
Other than 1 and $\leq 2 \times 10^6$	10% (2/20)	33% (6/18)	55% (12/22)
Other than 1 and $>2 \times 10^6$	20% (4/20)	22% (4/18)	50% (7/14)
Unknown and $\leq 2 \times 10^6$	–	100% (1/1)	50% (1/2)
Unknown and $>2 \times 10^6$	–	0% (0/1)	0% (0/1)
Histological response week 72 (proportion with improvement)	31% (17/55)	44% (27/61)	54% (37/68)*
Adverse events			
Dose discontinuation for			
adverse event	8% (7/88)	7% (7/96)	13% (11/87)
laboratory abnormality	2% (2/88)	4% (4/96)	1% (1/87)
Dose reduction for			
adverse event	14% (12/88)	2% (2/96)	14% (12/87)
thrombocytopenia	6% (5/88)	18% (17/96)	18% (16/87)
neutropenia	14% (12/88)	9% (9/96)	10% (9/87)

* $p < 0.05$ for comparison with IFN-α-2a.

continued

Additional results:

- A response to therapy at week 12 predicted an SVR: at week 12 all of the 26 patients who had an SVR to 180 μg of PEG had had a decrease in viral load by a factor of at least 100 compared with baseline, and 23 of them had had undetectable HCV RNA.
- A histological response correlated with an SVR: among patients with a virological response at week 72, 80% of those assigned to receive IFN also had a historical response, as did 100% of those assigned to 90 μg of PEG and 88% of those assigned to the 180 μg dose of PEG.
- A histological response was seen in 26%, 33% and 35%, respectively, of patients who did not have an SVR.
- Among patients with a combination of poor prognostic factors (genotype 1 and $>2 \times 10^6$ copies ml^{-1}), 10% of those assigned to 180 μg of PEG and none of those assigned to 90 μg had an SVR.
- More than half of the patients assigned to receive 180 μg of PEG who had paired biopsy specimens had a histological response at week 72, regardless of the virological or biochemical response.
- Among patients who did not have a virological response, more than one-third had histological improvement.
- The proportion of patients with a platelet count below 50,000 mm^{-3} at any time during treatment was significantly lower among those assigned to IFN (7%) than among those assigned to 90 μg PEG (26%) or 180 μg PEG (19%) ($p = 0.04$).
- A higher proportion of the patients assigned to receive 180 μg PEG had myalgia and inflammation at the injection site than of patients in the other two groups.
- Four deaths were reported, but their potential relation to treatment was unclear (one patient assigned to 90 μg PEG IFN and three were assigned to 180 μg PEG IFN).

Methodological comments

Allocation to treatment groups: allocation to group according to centre in blocks of six patients with random assignments made according to a computer-generated scheme. Patients allocated to groups in a 1:1:1 ratio.
Allocation concealment: not reported.
Blinding of outcome assessors: laboratory tests at central laboratories. Pretreatment biopsies were examined without blinding before randomisation, and subsequently coded and evaluated in parallel with those obtained at week 72 by pathologists unaware of treatment assignments.
Analysis by ITT: end-points (except for histological response) were evaluated by ITT. Two patients assigned to IFN did not receive therapy and one assigned to 180 μg PEG elected alternative therapy, but all were included in ITT analysis. The analysis of histological response included only patients who underwent both pretreatment and post-treatment biopsies. The analysis of safety included all patients who received at least one dose of study medication and who underwent at least one assessment of safety during the study.
Comparability of treatment groups at pretreatment: no statistical comparisons were reported, but groups appear comparable.
Method of data analysis: categorical comparisons of PEG with IFN were made with the Cochran–Mantzel–Haenszel test with stratification according to centre.
Power analysis: not reported.
Attrition/dropout: patients were withdrawn from the study if they missed 4 consecutive weeks of treatment or if an investigator was concerned about their safety. Overall, an 18% loss to follow-up was relatively high. Treatment was discontinued in slightly more patients in the IFN group than in the two PEG groups, 27% vs 19% and 23%, respectively.

General comments:

Generalisability: patients seem representative of those with HCV and cirrhosis or bridging fibrosis.
Conflict of interests: trial partially designed by Hoffman-LaRoche, which was responsible for monitoring adherence to the International Conference on Harmonization guidelines and for monitoring the analysis of data collected by the investigators.
Definitions: SVR: undetectable levels of HCV RNA (<100 copies ml^{-1}) at the end of the follow-up period. Histological response: decrease of ≥ 2 points in the total score on the HAI (fibrosis and inflammation combined). The HAI is a 22-points index in which inflammation is graded from 0 (none) to 18 (severe) and fibrosis is graded from 0 (none) to 4 (cirrhosis: 3 indicates bridging fibrosis). If a patient received more than three consecutive reduced doses or more than a total of six reduced doses, the dose could not subsequently be increased.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the patient blinded?	inadequate
6. Did the analysis include an intention-to-treat analysis?	Adequate
7. Were losses to follow-up completely described?	Adequate

continued

Reference and design	Intervention	Participants	Outcome measures
Zeuzem *et al.*, 2000[53] **Trial design:** RCT, open label **Country:** International, Pegasys International Study Group	**Intervention 1** *n* = 267 PEG IFN-α-2a Dose: 180 μg per week Duration: 48 weeks **Intervention 2** *n* = 264 IFN-α-2a Dose: 6 MIU three times per week Duration: 12 weeks Dose: 3 MIU three times per week Duration: 36 weeks	**Total numbers involved**: 613 screened, 531 met inclusion criteria and were randomised **Eligibility and exclusion criteria**: see Chapter 3 for general criteria, plus: positive test for anti-HCV antibody; exclude co-infection: hepatitis A, B, organ transplant, chronic pulmonary disease **Recruitment**: 36 centres, internationally, recruited between December 1997 and November 1999 **Genotypes (proportions)**: 1a: 163 (30.6%) 1b: 166 (32.4%) 2: 59 (11.1%) 3: 131 (24.6%) 4: 8 (1.5%) Other/unknown: 4 (0.75%) (because of rounding percentages do not add up to 100%) **Baseline measurements**: Viral load: mean HCV RNA level copies $ml^{-1} \times 10^6$: 7.8 Total HAI score: 8.6–9.0 **Cirrhosis**: 38 (7.1%) **Bridging fibrosis**: 32 (6%) **No cirrhosis or bridging fibrosis**: 460 (87%) **Gender**: 354 male (69%) **Age** (mean): 40 years **Ethnic groups**: White: 454 (85%) Black: 11 (2%) Asian: 50 (9.4%) Other: 16 (3%) **Losses to follow-up**: patients who withdrew during weeks 1–48: 147 (27%); PEG IFN-α-2a: 44 (16%), IFN-α-2a: 103 (39%); patients not available at week 72: 171 (32.2%); PEG IFN-α-2a: 61 (23%), IFN-α-2a: 110 (42%) **Compliance**: not reported	**Primary outcomes**: SVR (HCV RNA at end of follow-up by PCR assay), biochemical response (normalisation of serum ALT levels) **Secondary outcomes**: histological response (fibrosis, cirrhosis) **Length of follow-up**: 24 weeks post-treatment (72 weeks from treatment initiation)

continued

Outcome	PEG IFN-α-2a	IFN-α-2a
Viral response		
End of treatment	69% (95% CI 63 to 75%) (185/267)*	28% (95% CI 22 to 33%) (73/264)
SVR	39% (95% CI 33 to 45%) (103/267)*	19% (95% CI 14 to 24%) (50/264)
Histology		
All patients with paired specimens, $n = 351$		
% with histological response	63% (116)	55% (92)
Mean change in HAI score from baseline	–2.4	–2.0
Patients with a SVR		
% with histological response	82% (95)	86 (79%)
Mean change in HAI score from baseline	–4.1	–4.9
Adverse events		
Dose discontinuation	7% (19/265)	10% (27/261)
Dose reduction[a]		
adverse event	8% (21/265)	11% (30/261)
laboratory abnormality	14% (37/265)	9% (24/261)

[a] Some patients who required dose modification had both an adverse event and a laboratory abnormality.
*$p < 0.5$ for comparison with IFA-α-2a.

Additional results

- Almost all ($n = 101$) of the 103 patients in the PEG group who had an SVR had no detectable HCV RNA or the viral load decreased by a factor of 100 at week 12. In the IFN-α-2a group 98% of those who had an SVR had a decrease in viral titre of ≥ 2 log at week 12.
- Multiple logistic regression analysis identified the following as independently and significantly increasing the odds of an SVR: younger age (<40 years), smaller body surface area (≤ 2 m^2), lower level of HCV RNA, higher ALT quotient, absence of cirrhosis or bridging fibrosis, and HCV genotype other than type 1.
- Frequency and severity of adverse events were similar in the two treatment groups.
- There was a high degree of correlation between SVR and biochemical response.

Methodological comments:

Allocation to treatment groups: random, no further information given.
Allocation concealment: no information given.
Blinding of outcome assessors: slides of liver biopsy specimens obtained before the study and 24 weeks after discontinuation of treatment were coded and read by the study pathologist, who was unaware of the patients' identity and treatment and date of biopsy. Open label; patient and investigators were given 24-week viral results.
Analysis by ITT: used for all measures of efficacy except for changes from baseline in histological findings. Patients not present at the 72-week assessment were classed as non-responders at that point. Patients who received at least one dose of study medication were included in the analysis of safety.
Comparability of treatment groups at pretreatment: the authors assert that the baseline characteristics of the patients in the two treatment groups were similar (p. 1667). From the data provided in Table 1 (p. 1668) the groups appear equivalent, although no *p*-values are given.
Method of data analysis: Cochran–Mantel–Haenszel test for primary efficacy analysis (categorical variables).
Objectives/hypotheses (i) PEG IFN-α-2a is equivalent to IFN-α-2a; (ii) PEG IFN-α-2a is superior to IFN-α-2a. Multiple and stepwise logistic regression analysis was used to examine the relationship between baseline variables and SVR.
Power analysis: 456 patients were required, allowing for a dropout rate of 15%, assuming a sustained response rate of 25% in the IFN-α-2a group and 35% in the PEG IFN-α-2a group.
Attrition/dropout: even though an ITT analysis was performed, the loss to follow-up rate is relatively high (32%). Note that withdrawal and loss to follow-up rates are higher in the IFN-α-2a group, which suggests that PEG IFN-α-2a may be more acceptable to patients.

General comments

Generalisability: the authors comment that the baseline characteristics of the groups in this study are similar to patients in the two large trials evaluating the effectiveness of dual therapy with IFN-α-2.
Conflict of interests: data analysis was performed by Hoffmann-LaRoche in conjunction with the authors.

continued

Quality criteria (CRD Report 4)	
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the patient blinded?	Partial
6. Did the analysis include an intention-to-treat analysis?	Adequate
7. Were losses to follow-up completely described?	Partial

Reference and design	**Intervention**	**Participants**	**Outcome measures**
Lindsay *et al.*, 2001[52] **Trial design**: RCT **Country**: international	**Intervention 1** *n* = 315 PEG IFN-α-2b Dose: 0.5 μg kg^{-1}, once per week, s.c. Duration: 48 weeks **Intervention 2** *n* = 297 PEG IFN-α-2b Dose: 1.0 μg kg^{-1}, once per week, s.c. Duration: 48 weeks **Intervention 3** *n* = 304 PEG IFN-α-2b Dose: 1.5 μg kg^{-1}, once per week, s.c. Duration: 48 weeks **Intervention 4** *n* = 303 IFN-α-2b Dose: 3 MIU, three times per week, s.c. Duration: 48 weeks	**Total numbers involved**: 1224 initially randomised, 1219 received at least one dose of study medication and were included in analyses; five were not treated for reasons unrelated to the study **Eligibility and exclusion criteria**: see Chapter 3 for general criteria, plus any other cause for liver disease; HIV infection; haemophilia; haemoglobinopathies; active substance abuse; any known pre-existing medical condition that could interfere with participation; pregnant or breast-feeding **Recruitment**: 53 study sites worldwide, conducted from August 1997 to August 1999 **Genotypes (proportions)**: 1: 851 (69.8%) 2: 125 (10.2% 3: 200 (16.4%) Other: 43 (3.5%) (because of rounding percentages do not add up to 100%) **Baseline measurements**: Viral load: geometric mean (copies $\times$ 10^6 ml^{-1}: 3.35; >2 million copies ml^{-1} serum: 903 (74.1%) Mean HAI (Knodell) score: inflammation: 6.9; fibrosis: 1.4 **Cirrhosis**: 43 (3.5%) **Bridging fibrosis**: 164 (13.4%) **Gender**: 770 male (63.2%), 449 female (36.8%) **Age** (mean): 43.0 years **Ethnic group**: Caucasian: 1109 (91%) **Losses to follow-up**: of 1219 treated patients, 943 (77%) competed the 72-week study. Pretreatment and post-treatment liver biopsies were analysed in 744/1219 (61%) patients	**Primary outcome used:** SVR **Secondary outcomes used**: normalisation of ALT and improvement in liver histology **Length of follow-up**: 24 weeks

continued

Outcome	PEG IFN-α-2b 0.5 μg kg^{-1}	PEG IFN-α-2b 1.0 μg kg^{-1}	PEG IFN-α-2b 1.5 μg kg^{-1}	IFN-α-2b 3 MIU
Viral response				
4 weeks	–	–	–	–
12 weeks	–	–	–	–
End of treatment (48 weeks)	33% (105/315)*	41% (121/297)*	49% (149/304)*	24% (73/303)
SVR (72 weeks)	18% (57/315)*	25% (73/297)*	23% (71/304)*	12% (37/303)
Combined virological and biochemical response				
48 weeks	25% (79/315)	31% (92/297)*	33% (100/304)*	20% (61/303)
72 weeks	17% (52/315)	24% (70/297)*	23% (69/304)*	12% (37/303)
SVR by genotype and baseline viral load (copies ml^{-1}) (week 72)				
1 (all)	10% (12/211)	14% (28/199)	14% (31/223)	6% (14/217)
$\leq 2 \times 10^6$	27% (14/52)	38% (16/42)	34% (19/56)	21% (10/48)
$>2 \times 10^6$	5% (8/159)	8% (12/157)	7% (12/167)	2% (4/169)
2 or 3 (all)	35% (31/88)	47% (39/83)	49% (36/73)	28% (23/81)
$\leq 2 \times 10^6$	58% (14/24)	62% (13/21)	68% (15/22)	36% (9/25)
$>2 \times 10^6$	27% (17/64)	42% (26/62)	41% (21/51)	25% (14/56)
4, 5 or 6 (all)	20% (2/10)	31% (4/13)	60% (3/5)	0/4
$\leq 2 \times 10^6$	33% (2/6)	50% (4/8)	75% (3/4)	0/2
$>2 \times 10^6$	0/4	0/5	0/1	0/2
Histology (proportion with improvement)				
Inflammation	49% (97/098)	50% (89/178)	48% (85/177)	47% (90/191)
mean change	–1.5	–1.8	–1.5	–1.2
Fibrosis	20% (40/198)	19% (34/178)	15% (27/177)	13% (25/191)
mean change	–0.1	0	0.1	0.1
Relapse rate by genotype and baseline viral load (copies ml^{-1})				
1 (all)	Not reported	46% (23/50)‡	66% (57/87)‡	Not reported
$\leq 2 \times 10^6$		17% (3/18)	36% (10/28)	
$>2 \times 10^6$		63% (20/32)	80% (47/59)	
2 or 3 (all)		38% (24/63)	36% (20/56)	
$\leq 2 \times 10^6$		19% (3/16)	12% (2/17)	
$>2 \times 10^6$		45% (21/47)	46% (18/39)	
Adverse events				
Dose discontinuation	9%	11%	9%	6%
Dose reduction for	9%	14%	19%	6%
thrombocytopenia	2–3%	2–3%	2–3%	0.3%
neutropenia	2–3%	2–3%	5%	2–3%

‡ $p = 0.26$ for comparison between 1.0 and 1.5 μg kg^{-1} doses.
* $p < 0.05$ for comparison with IFN.

continued

Additional results

- Logistic regression analysis identified only two covariates associated with SVR: HCV genotype other than 1 and baseline HCV RNA levels of $\leq 2 \times 10^6$ copies ml^{-1} serum, ($p < 0.001$).
- In each treatment group, the likelihood of an SVR occurring was highest in patients whose first negative HCV RNA occurred at treatment week 4 (77–86%), compared with those in whom HCV RNA was first negative at treatment week 12 (32–52%) and those whose HCV RNA was first negative at treatment week 24 (13–20%).
- Nearly all patients who eventually became sustained responders had developed undetectable serum HCV RNA by treatment week 24 (93–100%).
- Negative predictive values (the likelihood that an SVR would occur if HCV RNA was not detected) for treatment week 4 were 85% and 77%, respectively for patients treated with 1.0 and 1.5 $\mu g\ kg^{-1}$ PEG IFN.
- Positive predictive value (the likelihood that an SVR would not occur if HCV RNA was detected) at treatment week 4 was 84% and 90%, respectively, for 1.0 and 1.5 $\mu g\ kg^{-1}$ PEG.
- The incidence of injection-site reactions was approximately twice the level in patients treated with PEG as in those treated with IFN.

Methodological comments

Allocation to treatment groups: randomised into groups, but no further information.
Allocation concealment: not reported.
Blinding of outcome assessors: study double-blinded for all PEG doses. Assays performed by a central laboratory. Liver biopsies scored by single blinded pathologist.
Analysis by ITT: efficacy assessments were obtained in all patients who were randomised and received at least one dose of study drug ($n = 1219$).
Comparability of treatment groups at pretreatment: there was a higher proportion of patients with genotype 1 in the 1.5 $\mu g\ kg^{-1}$ group (73%) than in the 1.0 and 0.5 $\mu g\ kg^{-1}$ groups (67% in each, $p = 0.09$).
Method of data analysis: SVR for PEG vs IFN by χ^2. Baseline characteristics compared using the Kruskal–Wallis test. Relation of baseline characteristics and treatment response evaluated by logistic regression.
Power analysis: not reported.
Attrition/dropout: efficacy results based on all patients receiving at least one dose. Number discontinuing treatment reported, but reasons not reported. Overall, 23% of patients not completing the study was relatively high, but the report states that discontinuation rates were comparable across all treatment groups.

General comments

Generalisability: patients seem representative of European patient populations, with a high percentage of genotype 1 and high baseline HCV RNA levels.
Conflict of interests: supported in part by Schering–Plough.
Definitions: virological response = loss of detectable serum HCV RNA (<100 copies ml^{-1}) at any time during the study. SVR: undetectable levels of HCV RNA 24 weeks after treatment. Relapse: undetectable serum levels of HCV RNA at the end of treatment and detectable levels at 24 weeks follow-up. Improved inflammatory score: decrease of ≥ 2 units. Improved fibrosis score = decrease of ≥ 1 unit.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the patient blinded?	Adequate for PEG doses
6. Did the analysis include an intention-to-treat analysis?	Adequate
7. Were losses to follow-up completely described?	Partial

continued

Reference and design	Intervention	Participants	Outcome measures
Reddy *et al.*, 2001[40] **Trial design:** RCT (three cohorts), open-label **Country:** USA	**Intervention 1** *n* = 33 IFN-α-2a Dose: 3 MIU three times per week Duration: 48 weeks **Intervention 2** *n* = 20, 20, 45, 41 PEG -IFN-α-2a Dose: 45, 90, 180 or 270 μg Duration: 48 weeks	**Total numbers involved: 159** **Eligibility and exclusion criteria:** see Chapter 3 for general criteria, plus: chronic hepatitis C without bridging fibrosis or cirrhosis (15 patients with bridging fibrosis inadvertently included); exclude fibrosis score 3 and 4, exclude history of pre-existing medical conditions such as unstable thyroid dysfunction or renal disease; exclude therapy with systemic antineoplastic or immunomodulatory agents within the past 6 months or administration of antiviral or investigational compounds within the past 3 months **Recruitment**: multicentre, three successive cohorts with ascending doses of PEG-2a were recruited (45 or 90 μg of PEG vs IFN, then 180 μg of PEG vs IFN, then 270 μg of PEG vs IFN). Randomisation to PEG vs IFN in 4:1 ratio. Conducted from February 1997 to March 1999 **Genotypes (proportions)**: 1: 73.6% Non-1: 23.9% Missing: 2.5% **Baseline measurements**: Viral load (copies ml^{-1} x 10^6): 2.4 Total HAI score (for patients with paired pretreatment and post-treatment biopsies): mean = 10.4, median = 10.0–12.0 across treatment groups **Bridging fibrosis**: 15 (9.4%) (patients with bridging fibrosis were to be excluded, but these were inadvertently enrolled) **Gender**: 125 male (79%), 34 female (21%) **Age** (mean): 42.0 years **Ethnic groups**: White: 139 (87%) Black: 14 (9%) Oriental: 2 (1.3%) Other: 4 (2.5%) **Losses to follow-up**: 122 completed 48 weeks of treatment; 23 were withdrawn owing to adverse events	**Primary outcome used:** SVR (proportion of patients with < 100 copies ml^{-1} HCV RNA at week 72) **Secondary outcomes used**: sustained biochemical response at week 72, virological and biochemical responses at week 48, histological response **Length of follow-up**: 24 weeks

continued

Outcome	IFN-α-2a 3 MIU	PEG IFN-α-2a 45 μg	PEG IFN-α-2a 90 μg	PEG IFN-α-2a 180 μg	PEG IFN-α-2a 270 μg
Viral response					
4 weeks	–				
12 weeks	–				
End of treatment (48 weeks)	12% (4/33)	30% (6/20)	45% (9/20)*	60% (27/45)*	56% (23/41)*
SVR	3% (1/33)	10% (2/20)	30% (6/20)*	36% (16/45)*	29% (12/41)*
SVR by genotype					
1	4% (1/25)	7% (1/15)	14% (2/14)	31% (11/35)	12% (3/26)
Non-1	0 (0/4)	20% (1/5)	67% (4/6)	50% (5/10)	67% (8/12)
Other viral response outcomes					
Histology (in patients with paired pretreatment and post-treatment biopsies)					
Change from baseline mean total HAI score	–2.0 ± 0.6	–0.9 ± 0.8	–2.6 ± 1.0	–2.8 ± 0.6	–2.5 ± 0.7
Change from baseline median total HAI score	–2.0	–1.0	–2.0	–3.0	–2.0
Proportion of histological responders	57% (13/23)	47% (7/15)	59% (10/17)	63% (19/30)	66% (19/29)
Adverse events					
% reported as severe	10%	7%	2%	10%	7%
Withdrawn for adverse events or laboratory abnormalities	9%	10%	0%	22%	20%
Dose reduction for					
any adverse event					49% (20/41)
anaemia					
neutropenia					

Additional results

- SVR increased in a dose-dependent manner between 45 and 180 μg PEG, with no further increase in response at the 270-μg dose.
- Most patients (94/159) who achieved a virological response did so within the first 16 weeks of treatment, particularly those in the 180 and 270-μg dose groups (78% and 73%, respectively).
- Of the patients with paired biopsies who achieved SVR, all but two (in the 270-μg group) also achieved histological responses.
- Among the 88 patients with paired biopsies who did not have an SVR, between 42 and 60% in the PEG groups and 55% in the IFN group achieved a histological response.
- Depression, pruritus and irritability were reported in a higher percentage of patients in the PEG groups than in the IFN group.
- Treatment with PEG was associated with mild, dose-dependent decreases in haemoglobin (<12 g dl^{-1}), but median haemoglobin concentrations remained within the normal range throughout the treatment period, and no patients discontinued because of anaemia.

Methodological comments:

Allocation to treatment groups: randomised within three cohorts in which patients were assigned to 45 or 90 μg PEG or IFN (cohort 1), 180 μg PEG or IFN (cohort 2), or 270 μg PEG or IFN (cohort 3). Initial safety data (8 weeks) were reviewed by an independent safety review board for each cohort before successive cohorts were randomised to higher doses of PEG. Open-label.

Allocation concealment: not reported.

Blinding of outcome assessors: open-label. Virological and biochemical assays were performed at a central laboratory. Histological response was evaluated by a central pathologist in a coded, blinded fashion.

Analysis by ITT: efficacy analyses included all randomised patients, including four patients who were not treated. Safety analyses included all patients who received at least one dose of study medication and had at least one postbaseline safety assessment.

Comparability of treatment groups at pretreatment: statistical comparisons were not reported. The IFN group had the highest proportion of patients with genotype 1, a higher mean HCV RNA concentration, and more patients with cirrhosis and bridging fibrosis. This group also had more non-white patients.

continued

Method of data analysis: Fisher's exact test was used to compare biochemical, virological and histological responses between PEG and IFN groups.
Power analysis: not reported.
Attrition/dropout: 23% of randomised patients did not complete 48 weeks of treatment. There was no information as to whether these were equally distributed between treatment groups. Twenty-three patients (14.4%) were prematurely withdrawn from the trial due to adverse events. Withdrawals due to adverse events were higher in the 180 and 270 μg PEG groups than in the other treatment groups.

General comments
Generalisability: patients seem representative of patients with chronic hepatitis C without severe liver disease (no cirrhosis or bridging fibrosis) or other co-morbidities.
Conflict of interests: one author was employed by Hoffmann-LaRoche.
Definitions: chronic hepatitis C required documentation of persistently abnormal serum ALT activity (two occasions ≥ 14 days apart), a positive anti-HCV antibody (anti-HCV-EIA version 2), pretreatment liver biopsy obtained within 12 months before study treatment consistent with chronic hepatitis and detectable pretreatment HCV RNA by a PCR within 35 days before the first dose of study medication. Histological response: ≥ 2-point decrease in the total HAI between biopsies obtained at baseline and week 72.

*$p < 0.05$ in comparison with IFN-α-2a group.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the patient blinded?	Inadequate
6. Did the analysis include an intention-to-treat analysis?	Adequate
7. Were losses to follow-up completely described?	Partial

Appendix 7

Data extraction for meta-analysis of trials assessing histological improvement

Reference and design	Intervention	Participants	Outcome measures
Poynard *et al.*, 2002[67] **Trial design**: pooled data from Lindsay *et al.*, 2001[52]; Manns *et al.*, 2001[41]; Poynard *et al.*, 1998[57] ; and McHutchison, *et al.*, 1998[59]	*Ten regimens compared*: *'Control' regimen*: IFN-α-2b, 3 MIU three times per week (24 week) *'Reinforced' regimens*: IFN-α-2b, 3MIU three times per week (48 weeks) PEG-α-2b 0.5 μg kg^{-1} (48 weeks) PEG-α-2b 1.0 μg kg^{-1} (48 weeks) PEG-α-2b 1.5 μg kg^{-1} (48 weeks) IFN + RBV(1000 mg if weight <75 kg, 1200 mg if weight ≥ 75 kg) (24 weeks) IFN + RBV (48 weeks) PEG-α-2b 1.5 for 1 month, then 0.5 PEG + RBV (1000 mg if weight <75 kg, 1200 mg if weight ≥ 75 kg) PEG-α-2b 1.5 μg kg^{-1} + low dose RBV (≤ 10.6 mg kg^{-1}) PEG-α-2b 1.5 μg kg^{-1} + high-dose RBV >10.6 mg kg^{-1})	Total numbers involved: individual data from 3010 treatment-naive patients Eligibility: patients with serological confirmation of chronic hepatitis C with both pretreatment and post-treatment liver biopsies Exclusion criteria: HBV, HIV, daily alcohol consumption > 50 g or other forms of liver disease	Primary outcomes used: changes in METAVIR necrosis and inflammation score

continued

Results

- The SVR varied from 5% (IFN, 24 weeks) to 63% (PEG 1.5 $\mu g\ kg^{-1}$ + high-dose RBV).
- Fibrosis stage improved in 20% of patients, was stable in 65% and worsened in 15%.
- Among patients who achieved an SVR, there was less frequently worsening of fibrosis (7%) in comparison with relapsers (17%) or non-responders (21%) ($p < 0.001$ for both comparisons). There was also more activity improvement in those with SVR (86%) vs 43% and 36%, respectively ($p < 0.001$). Relapsers also differed significantly from non-responders.
- In histological response, there were highly significant differences between regimens. Fibrosis worsening ranged from 8% in patients receiving the PEG 1.5 $\mu g\ kg^{-1}$ + RBV high-dose combination to 23% in patients treated with IFN for 24 weeks. Activity improvement ranged from 73% in patients receiving PEG 1.5 $\mu g\ kg^{-1}$ and high-dose RBV to 39% in patients treated with IFN for 24 weeks.
- All rates of fibrosis progression were lower after treatment than before in both responders and non-responders ($p < 0.001$). There were no significant differences between different treatments. There was a significant difference between responders and non-responders.
- Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (OR = 0.12, $p < 0.0001$), SVR (OR = 0.36, $p < 0.0001$), age younger than 40 years (OR = 0.51, $p < 0.001$), body mass index $<27\ kg\ m^{-2}$ (OR = 0.65, $p < 0.001$), no or mild baseline activity (OR = 0.70, $p = 0.02$), and viral load <3.5 million copies ml^{-1} (OR = 0.79, $p = 0.03$).
- In patients without SVR (relapsers and non-responders), in comparison with the other regimens, PEG 0.5 $mg\ kg^{-1}$ + RBV had a better impact on fibrosis and on activity, with 21% having demonstrable fibrosis improvement vs 12% for 24-week IFN ($p = 0.04$) and vs 15% for 48-week IFN. Activity improvement was also best in the PEG 0.5 $\mu g\ kg^{-1}$ + RBV group, with 50% improvement activity, with other regimens ranging from 33 to 44% improved activity.
- The 'reversal' of cirrhosis was observed in 75 patients of the 153 who had cirrhosis at the time of their first biopsy. None of these was in the 24 week IFN regimen.

General comments

Four comparisons were addressed:

- comparison of the impact of the different treatment regimens on the percentage of patients who improved by at least one fibrosis stage, remained stable or worsened by at least one stage
- comparison of the different treatment regimens according to the fibrosis progression rates per year before and after treatment
- Assessment of the impact of the different treatment regimens adjusted by other risk factors in multivariate analyses with the end-point being the percentage of patients with significant fibrosis at the second biopsy
- Testing the hypothesis that 'reinforced' regimens can reverse cirrhosis in comparison with the 'control' regimen.

Definitions: liver biopsies were evaluated for stage of fibrosis according to METAVIR scoring system with fibrosis staged on a scale of 0–4 and the grading of necroinflammatory activity scored on a three-point scale. Fibrosis progression rate after treatment was the ratio between the difference in fibrosis stage expressed in METAVIR units between the two biopsies and the interval between the two biopsies in years. The progression rate before treatment was the ratio between the fibrosis stage in METAVIR units before the biopsy before treatment and the estimated duration of infection in years. One grade in METAVIR is equivalent to four grades in the Knodell index and is twice the usual definition of histological improvement.

Appendix 8

Search strategy: Hepatitis C – Retreatment of non-responders to interferon alpha monotherapy with dual therapy (interferon-alpha and ribavirin)

Databases	Date and years searched	Search strategy	No. retrieved	No. downloaded
MEDLINE	2001 to January 2003; 5 February 2003	((hepatitis-c or HCV) or (explode 'Hepatitis-C' / all subheadings in MIME,MJME) or ('Hepacivirus-' / all subheadings in MIME,MJME)) and (((explode 'Interferons-' / all subheadings in MIME,MJME) or (explode 'Interferon-Type-I' / all subheadings in MIME,MJME) or (explode 'Interferon-Type-II' / all subheadings in MIME,MJME) or (explode 'Interferon-alpha' / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) or (mono?therapy)) and ((('Ribavirin-' / all subheadings in MIME,MJME) or (ribav?rin) or (rebetol)) or ('Combined-Modality-Therapy' / all subheadings in MIME,MJME) or (dual therapy or combination therapy) or (explode 'Drug-Therapy-Combination' / all subheadings in MIME,MJME)) and ((non adj respon*) or (non?respon*))	89	35 RCTs or SRs
EMBASE	July 2001 to January 2003	((('ribavirin-' / all subheadings) or ('rebetron-' / all subheadings) or (ribav?rin) or (rebetol)) or (dual adj therapy) or (combination adj therapy) or (explode 'drug-combination' / all subheadings)) and (((explode 'interferon-' / all subheadings) or (interferon*) or (roferon-A or viraferon)) or (mono adj therapy)) and (('hepatitis-C' / all subheadings) or (hepatitis-c or hcv)) and ((non adj respon*) or non?respon*)	80	18 SRs, 59 RCTs
SCI	2001–2003	Title=hepatitis-c and interferon* and (nonrespon* or non respon*); DocType=All document types; Language=All languages;	88	87
Cochrane	Issue 2003/1, search limited from 2001	hepatitis-c or hcv and interferon* and (non-respon* or nonrespon*)	33 Central, 3 CDSR, 1 Protocol, 2 DARE, 2 NHS EED	26 Central

Appendix 9

Costs of investigation and monitoring of patients with chronic hepatitis C

These costs have been provided in 2002 values by the Finance Department of SUHT and are provided to allow an estimate of approximate costs and facilitate comparison with individual Trust/Authority data. The cost of initial evaluation of a patient, further investigation, and monitoring during and after treatment are likely to be the same whether pegylated or non-pegylated interferon is given. However, there may be some variation in the timing and nature of investigations. There is likely to be some regional variation in the costs for some of the tests.

Costs are measured according to the opportunity cost principle. To make costs comparable between different treatment alternatives fixed costs, which cannot be saved if the treatment is not carried out, should then be excluded from the analysis. Included costs, therefore, are mainly direct operating costs plus costs for possible expensive equipment paid by the operating budget.

Evaluation of a new patient with confirmed HCV

Item		Costs (£)
Outpatient appointment		
Time with nurse: 1 h (grade H assumed)	£16.56	£16.56
Time with doctor: 20 minutes (consultant assumed)	£46.35	£15.45
Total staff time		£32.01
Overheads for clinic administration (pulling notes, etc.)	10%	£3.20
Staff cost for outpatient appointment		£35.21
Tests and investigations		
Hepatitis C screen (HCV RNA)	Virology	£11.33
HBV (for 50% of patients)	Virology	£5.18
LFTs	Chem path	£3.60
AFP (cirrhotic patients: 15%)	Chem path	£1.31
α-Antitrypsin	Chem path	£5.50
Thyroid-stimulating hormone	Chem path	£3.60
Free thyroxine	Chem path	£3.60
FBC	Haematology	£2.20
Autoantibodies	Immunology	£22.30
Immunoglobulins	Immunochemistry	£2.20
Ferritin	Haematology	£10.00
Caeruloplasmin	Chem path	£6.60
Iron	Chem path	£4.30
U&E (including renal profile and urea)	Chem path	£5.60
INR	Haematology	£2.40
Glucose	Chem path	£2.50
Ultrasound scan of liver	Radiology	£48.00
Chest X-ray	Radiology	£15.00
Electrocardiogram		£31.00
Cryoglobulin	Immunochemistry	£11.90
Pulmonary function tests (estimated 5% of patients)		£1.00
Total		**£236.53**

Chem path, chemical pathology; FBC, full blood count; HBV, hepatitis B virus; INR, international normalise ratio; U&E, urea and electrolytes.

Further investigations of a patient with HCV considered for treatment

Item			Costs (£)
Outpatient visit			
To review results from above tests and brief on treatment options			
Time with nurse: 20 minutes (grade H assumed)		£16.56	£5.52
Time with doctor: 20 minutes (consultant assumed)		£46.35	£15.45
Overheads for clinic administration (pulling notes, etc.)		10%	£2.10
Staff cost for outpatient appointment			£23.07
HCV Quantitative PCR	Molecular pathology		£152.27
HCV Genotype	Not done at SUHT		£148.00
Pregnancy test (estimated 5% of patients)	Chem path		£0.25
Day case for liver biopsy			
Additional tests undertaken before biopsy:			
FBC	Haematology		£2.20
INR	Haematology		£2.40
Blood group	Haematology		£2.20
Ultrasound-guided biopsy (by radiologists)	Radiology		£173.00
Liver biopsy costs in pathology	Histopathology		£126.00
Clerking in patient: 30 minutes (grade D nurse assumed)	£10.18		£5.09
Ward time for recovery postbiopsy: 6 h			£18.66
Additional costs for time on ward estimated at 10%			£1.87
Total			**£655.00**

Monitoring during 24 weeks of treatment

Item			Costs (£)
First appointment			
Time with nurse: 120 minutes (grade H assumed)		£16.56	£33.13
Time with doctor: 10 minutes (consultant assumed)		£46.35	£7.72
Overheads for clinic administration (pulling notes, etc.)			£4.09
Staff cost for outpatient appointment			£44.94
FBC	Haematology		£2.20
INR	Haematology		£2.40
U&E	Chem path		£5.60
LFTs	Chem path		£3.60
HCV Quantitative viral load	Molecular pathology		£152.27
Pregnancy test (5% of patients)	Chem path		£0.25
Total for first treatment appointment			**£211.25**
Subsequent appointments			
Basic checks (at weeks 1, 2, 6, 16 and 20)			
Time with nurse: 30 minutes (grade H assumed)		£16.56	£8.28
Time with doctor: 5 minutes (consultant assumed)		£46.35	£3.86
Overheads for clinic administration			£1.21
Staff cost for appointment			£13.36
FBC	Haematology		£2.20
U&E	Chem path		£5.60
LFTs	Chem path		£3.60
Pregnancy test (week 16 + 20)			£0.25
Total for each basic assessment			**£25.00**
Hence total cost for basic assessments			£125.02

continued

Item			Costs (£)
More detailed assessment (at weeks 4 and 8)			
Time with nurse: 30 minutes (grade H assumed)		£16.56	£8.28
Time with doctor: 5 minutes (consultant assumed)		£46.35	£3.86
Overheads for clinic administration			£1.21
Staff cost for appointment			£13.36
FBC	Haematology		£2.20
U&E	Chem path		£5.60
LFTs	Chem path		£3.60
INR	Haematology		£2.40
Pregnancy test (5% of patients)	Chem path		£0.25
Total for 4- and 8-week assessments			**£27.40**
Hence total cost for 4- and 8-week assessments			£54.81
Detailed assessment (week 12)			
Time with nurse: 30 minutes (grade H assumed)		£16.56	£8.28
Time with doctor: 10 minutes (consultant assumed)		£46.35	£7.72
Overheads for clinic administration			£1.60
Staff cost for appointment			£17.61
FBC	Haematology		£2.20
U&E	Chem path		£5.60
LFTs	Chem path		£3.60
INR	Haematology		£2.40
TFT	Chem path		£13.30
AFP (cirrhotic patients: 15%)	Chem path		£1.31
HCV viral load	Molecular pathology		£152.27
Pregnancy test (5% of patients)	Chem path		£0.25
Total cost for 12-week assessment			**£198.53**
Detailed assessment (week 24)			
Time with nurse: 30 minutes (grade H assumed)		£16.56	£8.28
Time with doctor: 15 minutes (consultant assumed)		£46.35	£11.59
Overheads for clinic administration (10%)			£1.99
Staff cost for appointment			£21.86
FBC	Haematology		£2.20
U&E	Chem path		£5.60
LFTs	Chem path		£3.60
INR	Haematology		£2.40
TFT	Chem path		£13.30
AFP	Chem path		£1.31
HCV RNA (qualitative)	Virology		£11.33
Ultrasound of liver (cirrhotic patients only)	Radiology		£7.20
Pregnancy test (5% of patients)	Chem path		£0.25
Total cost for 24-week assessment			**£69.03**

TFT, thyroid function tests.

Monitoring during 48 weeks of treatment

Item	Costs (£)
All patients would receive the treatments as per the 24-week patients	
First appointment	£211.25
Basic assessments (weeks 1, 2, 6, 16 and 20)	£125.02
Week 4 and week 8 assessments	£54.81
Week 12 assessment	£198.53
Week 24 assessment	£69.03
Total	**£658.63**
Subsequent assessments	
Weeks 28, 32, 40 and 44 (as basic assessments, plus pregnancy test)	
Per assessment	£25.25
Total assessments	£100.99
Week 36 (as week 12, excluding viral load)	£46.26
Week 48 (as week 24)	£69.03
Total monitoring cost for 48-week patient	**£874.92**

Surveillance of patients failing, refusing or unsuitable for treatment (per year)

Item		Costs (£)
Three outpatient appointments		
Staff costs: assumes 20 minutes per appointment with	£16.56	£31.45
doctor or nurse (alternates: average cost is taken)	£46.35	
ALT three times per year		£10.80
LFTs		£10.80
AFP (three times per year)		£3.92
INR (twice per year)		£4.80
Tests for cirrhotic patients only (estimated 15%)		
Liver ultrasound (twice per year)		£14.40
Additional out patient appointment (four per year)		£8.55
Total for year		**£84.72**
NB. Commitment to caring for these patients will be long term.		

Surveillance of patients 24 weeks after treatment

Item		Costs (£)
4 weeks post-treatment		
Staff costs: assumes 20 minutes per appointment with doctor or nurse (alternates: average cost is taken)		£10.48
Overheads for clinic administration (10%)		£1.05
Total staff costs		£11.53
FBC	Haematology	£2.20
INR	Haematology	£2.40
U&E	Chem path	£5.60
LFTs	Chem path	£3.60
Pregnancy test (5%)	Chem path	£0.25
Total		**£25.58**
12 weeks post-treatment		
Staff costs: assumes 20 minutes per appointment with doctor or nurse (alternates: average cost is taken)		£10.48
Overheads for clinic administration (10%)		£1.05
Total staff costs		£11.53
FBC	Haematology	£2.20
U&Es	Chem path	£5.60
LFTs	Chem path	£3.60
AFP	Chem path	£1.31
Pregnancy test (5%)	Chem path	£0.25
Total		**£24.48**
24 weeks post-treatment		
Staff costs: assumes 20 minutes per appointment with doctor or nurse (alternates: average cost is taken)		£10.48
Overheads for clinic administration (10%)		£1.05
Total staff costs		£11.53
U&E	Chem path	£5.60
LFTs	Chem path	£3.60
HCV RNA	Virology	£11.33
Ultrasound on liver	Radiology	£48.00
AFP (cirrhotic patients)	Chem path	£1.31
Pregnancy test (5%)	Chem path	£0.25
Total		**£81.61**
Total monitoring costs per year		**£131.67**

Appendix 10

Research in progress involving pegylated interferon

Study name and sponsor	Interventions	Design	Participants (expected enrolments)	Status as of 4 February 2003
Triple therapies				
South East Regional Office (UK)	1. PEG-α-2a + RBV 2. PEG-α-2a + RBV + mycophenylate	RCT	n = not reported HCV patients who had failed to respond to previous conventional therapy	Ongoing; end date: 27 April 2004
Dual Therapies				
US National Institute of Diabetes and Digestive and Kidney Diseases, Hoffman-LaRoche, HALT-C (USA)	All patients treated for 6 months with PEG-α-2a + RBV then responders treated for an additional 6 months. Non-responders randomised: 1. PEG-α-2a for 3.5 years 2. Discontinue treatment for 3.5 years	RCT	Failed to respond to prior IFN or IFN + RBV treatment	Currently recruiting, study completion date May 2006
SciClone Pharmaceuticals (USA)	1. PEG-α-2a 180 μg per week + thymosin-α_1 1, 1.6 mg twice per week 2. PEG-α-2a + placebo	RCT	n = 500 HCV without cirrhosis who have not responded to previous treatment with IFN or IFN + RBV	Currently recruiting
SciClone Pharmaceuticals (USA)	1. PEG-α-2a 180 μg per week + thymosin-α_1, 1.6 mg twice per week 2. PEG-α-2a + placebo	RCT	n = 500 HCV with cirrhosis who have not responded to previous treatment with IFN or IFN + RBV	Currently recruiting
Liver Research Trust (UK)	PEG-α-2b + RBV "Does a longer course of combination treatment reduce liver fibrosis and prevent further progression of liver disease in patients with chronic hepatitis C cirrhosis?"	RCT	n = 20	End date: 4 January 2003
Columbia Presbyterian Medical Center, New York (USA)	1. PEG-α-2a + RBV 2. IFN-α-2a + RBV	RCT	n = not reported Treatment naive	Unknown
Monotherapies				
Schering-Plough (USA)	1. PEG-α-2a 2. No treatment	RCT (prevention of fibrosis progression)	n = 700 Patients with moderate to severe fibrosis who failed previous PEG-α-2a + RBV treatment	Currently recruiting
Schering-Plough (USA)	1. PEG-α-2a 2. No treatment	RCT (prevention of disease progression)	n = 1000 Patients with compensated cirrhosis who failed previous IFN-α-2a + RBV treatment	Currently recruiting

continued

Study name and sponsor	Interventions	Design	Participants (expected enrolments)	Status as of 4 February 2003
Trials in co-infected populations				
APRICOT (USA)	1. PEG-α-2a 180 μg per week + placebo 2. PEG-α-2a 180 μg per week + RBV 800 mg per day 3. IFN-α-2a 3 MIU three times per week + RBV 800 mg per day	RCT	n = 740 HIV/HCV co-infected, all patients taking stable HAART at entry	Unknown
US National Institute of Allergy and Infectious Diseases, ACTG 5071 (USA)	1. PEG-α-2a + RBV 2. IFN-α-2a + RBV	RCT	n = 132 HIV/HCV co-infected	No longer recruiting patients
US National Institute of Allergy and Infectious Diseases, 020139 (USA)	1. PEG + RBV 2. HAART for 6 months then PEG + RBV	RCT	n = 128 HIV/HCV co-infected	Currently recruiting patients
Canadian HIV Trials Network, CTN 141 (Canada)	1. PEG 180 μg per week + RBV 800 mg per day + dideoxyinosine 400 mg per day + 3 lamivudine C 300 mg/day	Phase II, open-label pilot, single group	n = 20 HIV/HCV co-infected	Open
US National Institute of Allergy and Infectious Diseases, ACTG A5149 (USA)	1. PEG + RBV + adefovir dipivoxil 2. PEG + RBV + placebo	RCT	n = 110 Triple infected with HBV/HCV/HIV	Not yet open for patient recruitment
Other				
Schering-Plough Research Institute (UK)	Assess duration of virological response in those with SVR Assess disease progression in all who completed 24 weeks of follow-up	5-year follow-up of patients	n = 177 Paediatric patients who completed 24-week follow-up in hepatitis C treatment trial	Ongoing

Sources searched: Current Controlled Trials: all registers (http://controlled/-trials.com), National Research Register, CenterWatch (http://www.centerwatch.com) and AIDSinfo (http://www.aidsinfo.nih.gov/clinical_trials/). Searches were conducted on 21 January 2003 and 4 February 2003.

A range of research involving PEG is ongoing. The studies were designed to address a number of different questions. PEG is being combined with drugs other than RBV, including mycophenylate and thymosin in three trials. These are trials evaluating possible virological response in patients who had failed to respond to previous conventional hepatitis C treatment. Other studies using dual therapy or monotherapy are evaluating whether the progression of liver disease might be affected by treatment with PEG or combination therapy. The HALT-C trial will treat some patients who fail to respond to PEG + RBV with PEG for 3.5 years. With improved success in treating HIV more attention has turned to treating co-infections such as hepatitis C in patients who have HIV. Five identified trials are evaluating combination therapies including PEG (and sometimes manipulating HIV treatment) in patients with HIV and HCV (and in one case HIV, HCV and HBV). Finally, one study is conducting 5-year follow-up of paediatric patients who were treated for hepatitis C to evaluate the long-term virological response in those who responded and disease progression in others who completed the trial.

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We look forward to hearing from you.

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ISSN 1366-5278