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Rapid review

Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review

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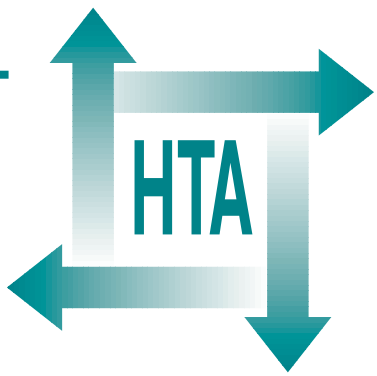
Health Technology Assessment
NHS R&D HTA Programme



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Contents

List of abbreviations and glossary

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.

List of abbreviations

CCT	controlled clinical trial (without random allocation to study groups)*
CI	confidence interval
EASL	European Association for the Study of the Liver
HAI	Hepatitis Activity Index*
HBV	hepatitis B virus
HCC	hepatocellular carcinoma*
HCV	hepatitis C virus
HRQOL	health-related quality of life
IFN	interferon*
IHITG	International Hepatitis Interventional Therapy Group
ITT	intention to treat*
LYG	life-years gained
mU	millions of units
NS	not statistically significant*
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SF-36	36-item short-form health survey
SHPIC	Scottish Health Purchasing Information Centre
SNAP	Scottish Needs Assessment Programme

* Used only in tables and figures

Glossary

Alanine aminotransferase (ALT) An enzyme that indicates ongoing liver inflammation.

Biochemical response Defined as serum ALT levels within the normal range (< 40 UI/l).

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

Complete response Normalisation of ALT and clearance of serum HCV-RNA.

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

Hepatitis C viral RNA (HCV-RNA) Genetic material from the virus, indicating persistence of infection.

Haemolysis The destruction of red blood cells, and one of the main adverse effects of ribavirin.

Interferon There are several forms of interferon; unless otherwise stated it is used in this report to refer to interferon alfa.

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

Non-response Patients who do not show both biochemical and virological response (serum ALT levels at least twice the upper limit of the normal range) on two separate occasions (at least 1 month apart) and detectable HCV-RNA.

Polymerase chain reaction (PCR) A sensitive technique of molecular genetics in which the DNA of a single cell treated with polymerase enzymes, is induced to replicate many times.

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Continued

This enables the DNA to be amplified in sufficient quantities to enable genetic analysis. A negative PCR indicates absence of virus in the blood, and is one indication of treatment response.

Relapse In the context of hepatitis C this signifies an elevation in serum ALT concentrations and detectable HCV-RNA.

Rebetol™ Brand name for ribavirin.

Sustained biochemical response ALT levels are normal during 24 weeks of follow-up; an unsustained response would be noted if ALT levels become elevated during the follow-up period.

Sustained virological response Clearance of HCV-RNA, which is maintained for at least 24 weeks after treatment stops (< 100 copies/ml).

Viral load The amount of HCV-RNA present in the body.

Viraemia The presence of virus particles in the blood.

Virological response Absence of detectable HCV-RNA on PCR.

Executive summary

Background

Hepatitis C is a viral disease of the liver, which frequently causes few or no symptoms at first infection but has a high probability of becoming an insidious chronic disease. Treatment has traditionally been with interferon alfa but only a small proportion of patients have been cured by this method. The recent introduction of ribavirin, given in combination, has led to a re-appraisal of the management of chronic hepatitis C.

The current report considers the additional benefit of combination therapy (interferon alfa and ribavirin) compared with monotherapy (interferon alfa alone) for the treatment of patients with chronic hepatitis C. It supersedes two reports of combination therapy conducted by the Scottish Health Purchasing Information Centre and the Wessex Institute for Health Research and Development.

Objective

To review the clinical effectiveness and cost-effectiveness of combination therapy with interferon alfa and ribavirin in patients with chronic hepatitis C.

Methods

Effectiveness

Electronic databases were searched from 1993 to the end of 1999, to identify randomised controlled trials (RCTs) or systematic reviews of RCTs that evaluated interferon alfa in combination with ribavirin compared with interferon alfa alone (or placebo) in patients with chronic hepatitis C. Bibliographies from previous studies were also examined.

Economic analysis

The economic evaluation is based on the three largest RCTs of combination therapy, and a pooled analysis of two of these trials. Sustained virological response rates were entered into a spreadsheet model incorporating a hypothetical cohort of 1000 patients who were followed over a 30-year period.

Results

Effectiveness

Nineteen RCTs and two meta-analyses were identified. The methodological quality of the included studies was variable, though the larger RCTs and meta-analyses were considered to be of high quality. Results of these trials indicate that combination therapy produces larger sustained response rates than monotherapy. For patients naïve to interferon treatment, sustained virological response rates were: 33% (95% confidence interval (CI), 29 to 37) for combination therapy compared with 6% (95% CI, 3 to 10) for monotherapy, based on 24 weeks of treatment; and 41% (95% CI, 36 to 45) compared with 16% (95% CI, 13 to 19), respectively, for 48 weeks of treatment. For patients who had relapsed following a previous course of interferon, sustained virological response rates were 49% (95% CI, 42 to 57) compared with 5% (95% CI, 2 to 9), respectively, based on 24 weeks of treatment.

Two groups of chronic hepatitis C patients are expected to benefit from combination therapy: interferon-naïve patients and relapse patients.

Economic analysis

A 4-week cycle of interferon alfa at 3 mU three times a week costs £194; ribavirin costs £543. Thus, ribavirin substantially increases drug costs compared with interferon monotherapy. Six months of combination therapy will cost £4422 (excluding monitoring costs).

For interferon alfa-naïve patients, the **additional** discounted cost per quality-adjusted life-year (QALY) gained from treatment with combination therapy for 6 months compared with no active treatment is £7578. For patients who have relapsed after a previous course of interferon alfa, the **additional** discounted cost per QALY gained from treatment with combination therapy for 6 months compared with monotherapy for 6 months is £3503.

A subgroup analysis was conducted to examine the sensitivity of the cost per QALY based on the response rates of different patient subgroups (chronic hepatitis C patients with between none

and five favourable response factors). This shows it is worth treating all patients with combination therapy as first-line treatment for 6 months, but only worth treating those with one or two response factors for a further 6 months. Those with three or four factors do well by 6 months, but gain very little from further treatment (cost per QALY is approximately £150,000). Those with no favourable response factors do badly with 6 months of treatment – only 8% responded by 6 months, and further treatment is not cost-effective (cost per QALY of approximately £300,000).

Conclusions

There is benefit associated with combination therapy and treatment can be cost-effective. It is appropriate to offer 6 months of combination therapy as first-line treatment to patients not previously treated with interferon and also to patients who have relapsed following a previous course of interferon. At 6 months, continuation of treatment should depend on factors that may predict a good sustained response.

Uncertainties

Variations in the prevalence of hepatitis C virus mean that the cost of combination therapy would vary considerably among health authorities; for example, areas with significant drug abuse problems might sustain higher total costs than areas where drug abuse is not a big problem, though compliance among users to attend for treatment and to stop injecting is known to be poor.

The rate of progression of hepatitis C is very slow and, at present, knowledge of the natural history of the disease is incomplete. There is uncertainty about the benefits of treating patients with mild disease and few or no symptoms. Trials are underway.

Chapter 1

Aim and background

Aim of the review

Hepatitis C is a viral disease of the liver, which frequently causes few or no symptoms at first infection but has a high probability of becoming an insidious chronic disease. Treatment has traditionally been with interferon alfa but only a small proportion of patients have been cured by this method. The recent introduction of ribavirin, given in combination, has led to a re-appraisal of the management of chronic hepatitis C. The aim of this report is to undertake a review of the clinical and cost-effectiveness of combination therapy with interferon alfa and ribavirin in patients with hepatitis C.

The report builds upon two recent reviews, one produced by the Scottish Health Purchasing Information Centre (SHPIC) originally published in 1998,[1] and updated in 1999,[2] and one produced for the South-West and South-East Development and Evaluation Committee in June 1999.[3] The economic model developed for the SHPIC report was reviewed and tested by the Scottish Needs Assessment Programme (SNAP) Hepatitis C Working Group in 2000, and its validity confirmed.

Background

Description of underlying health problem

Chronic hepatitis C is a slowly progressive disease of the liver caused by the hepatitis C virus (HCV). Generally, HCV is transmitted parenterally but the natural history of the disease is not completely understood. It is acquired through intravenous drug use and the sharing of needles, and prior to the introduction of screening in 1991,[4,5] it was spread through blood transfusions. There is also a small risk associated with tattooing, electrolysis, ear-piercing and acupuncture.[5] Sexual infection and transmission from mother to child can also occur.[5] Concomitant HIV infection is thought to increase the risk of transmission.[4] The risk of transmission from a patient with HCV by needle-stick injury to a healthcare worker is about 1 in 30 (1 in 3 for hepatitits B virus and 1 in 300 for HIV).

After exposure to HCV, patients are often asymptomatic but about 20% will develop an acute hepatitis, some of whom will experience malaise, weakness and anorexia. In up to 85% of those exposed, the virus fails to clear naturally and patients go on to develop chronic hepatitis.[6,7] This is attributed to the genetic diversity of HCV, which prevents the immune system mounting an effective response. 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,[8] and a small percentage of these are at high risk of hepatocellular carcinoma.[4,7] A third may never progress to cirrhosis or will not progress for at least 50 years.[8] Often, patients do not become symptomatic until liver disease is advanced.[6] Some patients with end-stage liver disease or hepatocellular carcinoma may require liver transplantation.

Incidence and prevalence

It is believed that 100 million people worldwide are infected with HCV.[9] In a population survey conducted in the USA, prevalence was much higher at 1.8% (approximately 4 million people), and the Centers for Disease Control estimated that the disease causes 8000–10,000 deaths each year.[10] Prevalence is estimated as 0.06% in new blood donors, 0.2–0.4% in antenatal clinic attendees (varying among regions), 0.72% in organ donors,[11] and among injecting drug users it is reported to be 60–85%.[12] The numbers of notifications to the Communicable Disease Surveillance Centre has risen from a few hundred a year in the early 1990s to over 5000 a year at its current rate.

In Scotland prevalence is estimated to be 0.6%, the majority of infections being in injecting drug users. Data from long-term studies of the natural history of the disease suggest that there is only a small excess of morbidity and mortality in the first 20 years after infection but that this increases with time, particularly in those with cirrhosis.[13] The outcome among those patients with chronic hepatitis but no cirrhosis is unclear.[13] In men, over 40 years old, or with high alcohol consumption, the disease develops faster.[8] In England and Wales the most prevalent viral genotypes are 3a (37%), 1a (32%) and 1b (15%).[14] Genotypes 1a, 1b and 4 respond less favourably to interferon treatment compared with other genotypes.

There are variations with the source of infection, with type 1 being more common (60% of cases) in haemophiliacs than type 3, which is seen more often in intravenous drug users (47% type 1 and 43% type 3). This means that those infected with blood products will 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 were able to measure HCV-RNA as well, so were able to include disappearance of the virus altogether as an outcome measure. 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 hepatocellular carcinoma.[13,15] Those patients with long-term remission and loss of the virus are thought to be unlikely to develop cirrhosis or liver cancer.[16] 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 if this represents a cure. Patients in a recent cohort study of 80 patients who had sustained a response to interferon alfa have been followed for up to 6 years. Response to treatment was maintained and liver histology improved in more than 90% of patients.[17]

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, nausea, headache, muscle aches, anorexia, abdominal discomfort, and right upper quadrant pain have been reported.[18,19]

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 is comprised of eight subscales, which evaluate the degree of impairment from a patient's ideal state of health.[20] The SF-36 is generally supplemented with several disease-specific scales to characterise particular problems experienced by HCV patients (e.g. health distress, limitations caused by HCV infection).[19]

Reductions in HRQOL for HCV patients are considered to be clinically and socially relevant.[21] 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 compared with population norms. The disease group that was analogous to the HRQOL of HCV group was type II diabetes patients, though chronic HCV patients scored significantly lower than diabetes patients on the vitality, social functioning and bodily pain SF-36 subscales.[22] These results have been confirmed in two recent studies in which chronic HCV patients again scored significantly lower on all SF-36 subscales compared with both a UK healthy control population[23] and healthy controls in the USA.[21] Furthermore, significant reductions in HRQOL have been shown to occur in patients with mild HCV[24] and for chronic HCV patients who do not have cirrhosis or a history of intravenous drug use.[23]

Successful eradication of HCV has been demonstrated to improve patient HRQOL. HCV patients who respond to interferon alfa therapy (biological and virological sustained responders) have shown significantly greater improvement in HRQOL than for patients who do not respond to treatment.[21,25,26] 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.[21,25] Treatment with interferon alfa generally causes an overall decrease in HRQOL scores from baseline during therapy, returning to pre-treatment levels at the cessation of therapy.[25,27] Although the HRQOL of combination therapy patients decreased slightly more than monotherapy patients during treatment, patients receiving combination therapy exhibited greater improvements in vitality, social functioning, health distress and general health than monotherapy patients at the end of treatment.[27]

In conjunction with higher rates of sustained response for patients receiving interferon alfa and ribavirin, combination therapy would seem to also result in greater HRQOL improvements compared

with patients receiving interferon alone.[27] 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.[25] This may be predictive of a reduced demand for healthcare services and an increase in productivity in the workplace for these patients.[27] Hence, although the usual purpose of treatment is to prevent progression to more serious liver disease, in some patients treatment is worthwhile simply in terms of symptom relief and quality of life.

Current service provision

Until recently interferon alfa was the only licensed treatment for chronic hepatitis C. However, expert opinion suggests that there may be marked geographical variations in provision. Several meta-analyses that review the effectiveness of interferon alfa in chronic hepatitis C have been performed.[12,28,29] Approximately 47% of patients initially respond when treated with interferon. Half of these will relapse within 6 months of stopping treatment.

Interferons are naturally occurring proteins with complex effects on immunity and cell function, and there are at least 15 different molecular species. Interferon alfa was the first pure human protein found to be effective in the treatment of cancer and has been used to treat chronic myelogenous leukaemia and other myeloproliferative disorders, renal carcinoma and infections such as chronic hepatitis B. It has also been indicated for use with AIDS patients with progressive, asymptomatic Kaposi's sarcoma. It is thought that once bound to a cell membrane, interferon initiates a complex sequence of intracellular events including the induction of certain enzymes. The precise antiviral mode of action of interferon is unknown; however it appears to alter host cell metabolism.[30]

Dose

Treatment is usually at the dose of 3 million units (mU) three times a week by either subcutaneous or intravenous injection. Injections may be administered by clinical staff or by the patient after adequate training. Patients who respond usually do so within 3–4 months, and it is recommended that they continue with this dose for 12 months. Treatment for longer and at higher doses increases the number of patients with a sustained response to treatment. Forty-nine per cent of those treated with 6 mU three times a week for 12 months had a sustained response compared with 29% in those treated for only 6 months.

Interferon causes a wide range of adverse events, which are dose-dependent. These include flu-like symptoms (41%), alopecia (16%) and depression (7%)[12] plus severe or life-threatening adverse events in 0.1–1% of patients.[31] These adverse events have to be offset against the improved response with higher doses.

Safety

The safety profile of interferon alfa is well documented, and gastroenterologists/hepatologists and infectious disease physicians have extensive experience in managing patients receiving interferon alfa therapy.[32] Standard haematological tests and blood chemistries (e.g. full blood count and differential, platelet count, electrolytes, liver enzymes, serum protein, serum bilirubin and serum creatinine) are recommended at pre-treatment and at weeks 1, 2, 4, 8, 12, 16 and every other month during therapy for hepatitis C. If ALT levels flare to at least twice the baseline level during treatment, liver function tests (e.g. ALT, prothrombin time, alkaline phosphatase, albumin and bilirubin) should be monitored at 2-week intervals. If symptoms of liver failure are observed during an ALT flare, interferon alfa therapy must be discontinued.

Description of new intervention

The proposed service is combination therapy (interferon alfa plus ribavirin) for patients with chronic hepatitis C. Interferon alfa in combination with ribavirin received a licence for use in patients with chronic hepatitis C from the European Union in May 1999. As yet unpublished data from a retrospective analysis of treatment centres by the UK Hepatitis C Study Group show that, prior to its licensing, 1214 patients in the UK had received combination therapy, on a named-patient basis. This suggests that combination therapy is already an established treatment. Expert opinion suggests that in some districts it is now considered unethical to use monotherapy and thus patients may receive no active treatment until combination therapy is available/approved.

Dose

Ribavirin (brand name Rebetol™, Schering-Plough, Welwyn) is a nucleoside analogue with a broad spectrum of antiviral activity against RNA viruses. It is administered orally at a dose of between 1000 mg/day (for patients who weigh < 75 kg) to 1200 mg/day (for patients weighing > 75 kg), usually in divided doses (200 mg per capsule). Ribavirin given as monotherapy reduces ALT levels but not HCV-RNA and has not been found to be effective.[33,34] The combination of interferon alfa with ribavirin is thought to produce a synergistic antiviral effect.[35]

Combination therapy is unlikely to produce significant increases in drug **administration** costs due to the fact that ribavirin is taken orally rather than by injection. However, regular monitoring of full blood counts to detect haemolysis anaemia is required in order to reduce or cease ribavirin treatment.

A consensus statement, published in 1999 by the European Association for the Study of the Liver (EASL),[36] recommends that interferon-naïve patients should be offered combination therapy for 6–12 months according to genotype and viral load. Patients who have relapsed should receive combination therapy for 6 months or high-dose interferon alfa for 12 months (> 3 mU three times a week).

Monitoring and safety

The monitoring recommendations for patients receiving combination therapy are that standard haematological tests and blood chemistries (e.g. full blood count and differential, platelet count, electrolytes, liver function tests, uric acid, serum bilirubin and serum creatinine) be performed for all patients prior to initiating therapy. Furthermore, if anaemia occurs with ribavirin treatment, it may exacerbate cardiac disease, and cardiac function should be considered before initiating treatment. Ribavirin should also be used with great caution (or not at all) in patients with pre-existing anaemia or haemolytic disorders, a history of severe depression, severe cardiac disease or hypoxia.[30,37] Other contraindications include pregnancy, a history of autoimmune disease, patients with haemoglobinopathies, severe hepatic dysfunction and pre-uncontrolled thyroid disease (unless controlled with conventional treatment). Haematological tests and blood chemistry evaluations should be performed at weeks 2 and 4 during therapy, and periodically thereafter as clinically appropriate.[38] However, as haematological alterations (e.g. anaemia) can be clinically important immediately after initiating therapy, it has been suggested that weekly monitoring of blood counts should be performed in the first 4 weeks of therapy and monthly thereafter.[37] Discontinuation and dose modification guidelines for physiological events are shown in *Table 1*.

Slightly increased rates of depression have been reported in patients taking combination therapy compared with patients receiving monotherapy. Therefore, all patients receiving combination therapy should be monitored for signs of psychiatric symptoms.[32]

TABLE 1 *Dosage modification guidelines for combination therapy*

Laboratory values	Reduce ribavirin only (to 600 mg/day)	Reduce interferon alfa-2b only (to 1.5 mU/dose)	Discontinue both ribavirin and interferon alfa-2b
Haemoglobin	< 10 g/dl	–	< 8.5 g/dl
Haemoglobin (in patients with stable cardiac disease)	≥ 2 g/dl decrease in haemoglobin during any 4-week period during treatment (permanent dose reduction)		< 12 g/dl after 4 weeks of dose reduction
White blood cells	–	< 1500 cells/mm^3	< 1000 cells/mm^3
Neutrophils	–	< 750 cells/mm^3	< 500 cells/mm^3
Platelets	–	< 50,000 cells/mm^3	< 30,000 cells/mm^3
Bilirubin (direct)	–	–	2.5 x upper limit of normal
Bilirubin (indirect)	> 5 mg/dl	–	> 4 mg/dl (for > 4 weeks)
Creatinine	–	–	≥ 2.0 mg/dl
ALT	–	–	≥ 2 x baseline and ≥ 10 x upper limit of normal

Chapter 2

Effectiveness

Methods for reviewing effectiveness

A search strategy was designed using appropriate key words and controlled vocabulary terms (e.g. MeSH terms). Randomised controlled trials (RCTs) or systematic reviews of RCTs evaluating interferon alfa and ribavirin compared with interferon alfa alone (or with placebo) were sought.

The following search strategies were used:

- **electronic databases**, including the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, MEDLINE (and Pre-MEDLINE), and EMBASE. MEDLINE and EMBASE were searched for the period between 1996 and the end of 1999, and the Cochrane Controlled Trials Register was searched from 1993
- **bibliography of studies** identified for the previous SHPIC review on combination therapy[1,2]
- **company submissions made to the National Institute for Clinical Excellence (NICE)** by Schering-Plough and Roche.

Studies were included if they met the following criteria:

- **intervention**: interferon alfa (monotherapy) compared with interferon alfa plus ribavirin (combination therapy)
- **study design**: for primary studies (and systematic reviews of primary studies) allocation to study groups should have been randomised (in the absence of any randomised studies, quasi-randomised or non-randomised studies would have been considered)
- **patient group**: chronic hepatitis C
- **publication status**: only full papers, published or unpublished would be used for efficacy and cost-effectiveness analysis, though other material such as conference abstracts and personal communications could be used with caution for purposes such as sensitivity analysis.

Relevant articles were read and data on study design and results were extracted to a standard template (see appendix 2 for template). Each RCT was subjected to quality assessment by one reviewer according to the UK Critical Appraisal Skills Programme guidelines,[39] and the Jadad scoring checklist.[40] A second reviewer checked the results of this process and disagreements were resolved through discussion.

Results

Number of studies identified

Literature searching of electronic databases yielded 565 citations. The titles and abstracts were scanned for relevance by one person. The abstracts of 50 were examined in greater detail and of these, 20 met the inclusion criteria for the review. The bibliography of the previous SHPIC review provided one extra reference to an RCT not already identified through electronic searching. Sixteen conference abstracts were also identified (see appendix 3).

In total, nineteen published RCTs and two meta-analyses were identified. These can be classified as:

- trials published prior to, or around, 1998.[41–46] Some of these were reviewed in the first edition of the SHPIC review, and some were also included in the meta-analysis by Schalm and co-workers[47]
- the three large RCTs[48–50] included in the SHPIC update review of 1999, two of which were meta-analysed by Poynard and co-workers[51]
- trials published since then.[52–61]

There were no studies included in the industry submissions that had not already been identified in the searches for this review.

Assessment of effectiveness

Schalm and co-workers[47] conducted a meta-analysis of individual patient data from six RCTs, published between 1991 and 1998, which evaluated the efficacy of combination therapy (n = 344 patients). Multivariate analysis was conducted in which patients were characterised according to previous interferon therapy, presence of cirrhosis, and genotype 1. Patients were those who were naïve to treatment as well as those who had relapsed after, or not responded to, a previous course of interferon alfa. Sustained response rates (all patients) were 28% for combination patients compared with 9% for monotherapy patients. For patients with

cirrhosis (n =75 (22%)) sustained rates were 17% for combination patients and 0% for those receiving monotherapy. Patients with genotypes 2 and 3 responded more frequently than patients with genotype 1. Previous interferon non-responders had a lower chance of sustained response than previously untreated patients or relapsers.

Three large RCTs were published in 1998 by **Poynard and co-workers**,[50] (n = 832), **McHutchison and co-workers**[49] (n = 912) and **Davis and co-workers**[48] (n = 345). The first two RCTs compare combination therapy against interferon alfa plus placebo in patients not previously treated with interferon alfa (interferon-naïve). They are very similar in design and are probably the same trial conducted in centres in the USA, Europe and Canada. The third RCT evaluates combination therapy in patients who have been treated with interferon alfa previously and who have subsequently relapsed. In this study the results from the USA, Europe, Canada and Australia have been combined. All three studies were Phase III trials conducted by the International Hepatitis Interventional Therapy Group or the Hepatitis Interventional Therapy Group and were supported in part by research grants from Schering Plough. All three studies included patients who were transfusion recipients and intravenous drug users but excluded haemophiliacs.

Clearance of detectable HCV in the blood was the main outcome measure whereas earlier studies used reduction of the liver enzyme, serum ALT, to normal levels. Changes in the extent of liver disease (histology) and improvement in liver enzyme levels are used as additional outcome measures. A sustained virological response is defined as clearance of the virus, which is maintained for at least 24 weeks after treatment stops. These trials were of generally good methodological quality (see appendix 4, *Table 14*) and confirmed the results of the earlier studies with statistically significant sustained response rates for patients treated with combination therapy compared with those treated with monotherapy (*Table 2*).

McHutchison and Poynard pooled the individual data from their respective trials[49,50] into a meta-analysis of 1744 interferon-naïve patients (**Poynard *et al.*, 2000**[51]) (see appendix 2, *Table 12*). The aim was to ascertain the degree of benefit for various patient subgroups. Five independent factors were associated with sustained virological response:

- genotypes 2 or 3
- baseline viral load less than 3.5 million copies/ml
- no or only portal fibrosis
- female gender
- age younger than 40 years.

TABLE 2 *Summary of sustained virological response*

Duration of treatment	Combination therapy	Monotherapy
Virological sustained response % (95% CI)		
Poynard *et al.*, 1998[50] (n = 832)*		
24 weeks	35 (29 to 41)	
48 weeks	43 (37 to 49)	19 (15 to 24)
McHutchison *et al.*, 1998[49] (n = 912)*		
24 weeks	31 (25 to 37)	6 (3 to 9)
48 weeks	38 (32 to 45)	13 (9 to 17)
Davis *et al.*, 1998[48] (n = 345)†		
24 weeks	49 (42 to 57)‡	5 (2 to 9)*

CI, confidence interval
* *Patients naïve to treatment*
† *Patients who relapsed following previous treatment*
‡ *CIs calculated by the authors of this report (where not reported by the authors of the trials)*

TABLE 3 *Summary of virological response of treatment-naïve patients from meta-analysis by Poynard and co-workers*[51]

Length of treatment	Combination therapy	Monotherapy
End of treatment response % (95% CI)*		
24 weeks	55 (51 to 59)	29 (23 to 35)
48 weeks	51 (46 to 55)	29 (25 to 33)
End of follow-up response % (95% CI)*		
24 weeks	33 (29 to 37)	6 (3 to 10)
48 weeks	41 (36 to 45)	16 (13 to 19)

* *CIs calculated by the authors of this report (not reported by the authors of the trials)*

There were statistically significant differences between groups in virological response rates (*Table 3*) with the combination group outperforming the monotherapy group (level of significance not provided).

It was recommended that all patients should be treated for 24 weeks, with those who do not respond and who have fewer than four favourable factors being treated for an additional 24 weeks. It was suggested that the most appropriate time to decide whether a patient should be treated further is at the end of the initial 24-week period. The need to take into account all five factors was also stressed when deciding whether treatment can be stopped. This recommendation contradicts the recent EASL international consensus statement,[36] which suggests that patients with genotype 2 or 3 need only be treated for 24 weeks regardless of other factors. Stopping treatment at 12 weeks in subgroups for whom there is a high probability of non-response was not recommended, as 10% of patients (treated for 48 weeks) with a positive

polymerase chain reaction (PCR) at 12 weeks went on to achieve a sustained response. Interferon monotherapy at 3 mU three times a week was not recommended for any patients unless combination therapy is contraindicated.

The more recently published trials vary in size with the largest containing 400 patients,[54] and the smallest with 50[52] (average, $n = 133$). Two contained interferon-naïve patients,[56,59] five included both relapsers and non-responders,[54–57,60] and four contained non-responders only.[52,53,58,61] Five trials used higher doses of interferon (4.5 mU three times a week;[55] 6 mU three times a week[53,54,57,58]) and two used lower doses of ribavirin (600 mg/day;[60] 800 mg/day[52]). In two studies different sequences of interferon and ribavirin were evaluated.[58,61] The type of interferon alfa used varied, with IFN-2b the most common (six studies[53,54,56,58–60]), followed by natural human leukocyte (IFN-n3) (three studies[52,57,61]), and IFN-2a (one study[55]). Treatment lasted for 24 weeks in all but one trial, where it lasted for 12–14 months.[58] Follow-up was measured for 24 weeks post-treatment in all but three trials, where it took place 1 year after the end of treatment.[57,59,60] Methodological quality was variable, with most trials using intention-to-treat analysis, and computer-generated randomisation. However, identical placebos were generally not used and thus patients were aware of their treatment assignment. Details can be found in appendix 4, *Table 14*.

The newer trials show similar results to the three major RCTs, with higher percentages of combination patients sustaining a virological response than monotherapy patients (*Table 4*). End of treatment and sustained (24-week) response rates were in the range of 4–60% and 0–44%, respectively, for combination patients. For those receiving monotherapy ranges were 5–52% and 0–22%, respectively. In some cases differences between treatment groups were not statistically significant. At 1-year follow-up virological response rates were maintained in monotherapy patients and were improved in combination patients

TABLE 4 *End of treatment and sustained virological response rates in ten RCTs (published since 1998)*

	Length of treatment	End of treatment			End of follow-up		
		Combination	Monotherapy	Significance between groups	Combination	Monotherapy	Significance between groups
Barbaro *et al.*, 1998[53] ($n = 303$)*	24 weeks	25%	5%	$p < 0.001$	21%	1%	$p < 0.001$
Bell *et al.*, 1999[55] ($n = 53$)*†	24 weeks	44%	38%	NS ($p > 0.10$)	23%	22%	NS
Pol *et al.*, 1999[58] ($n = 126$)*	12–14 months	25%	8%	$p < 0.02$	10%	8%	NS
Sostengi *et al.*,1998[61] ($n = 96$)*	24 weeks	27%	7%	NS	15%	0%	$p = 0.02$
Reichard *et al.*, 1998[59] ($n = 100$)‡	24 weeks	52%	52%	NS ($p = 1.00$)	36% (42%)	18% (20%)	$p = 0.047$ ($p = 0.03$)
Andreone *et al.*, 1999[52] ($n = 50$)*	24 weeks	4%	13%	Not stated	0%	0%	Not stated
Salmeron *et al.*, 1999[60] ($n = 62$)*†	24 weeks	Not stated	Not stated		23% (6.4%)	13% (3.2%)	NS
Barbaro *et al.*,1999[54] ($n = 400$)*†§	24 weeks	60%	14%	Not stated	44%	6%	Not stated
Millela *et al.*, 1999[57] ($n = 88$)*†	24 weeks	27%	13%	Not stated	15%	0%	Not stated
El-Zayadi *et al.*, 1999[56] ($n = 52$)‡	24 weeks	38%	16%	$p = 0.038$	21%	8%	$p = 0.1916$

Note: dosages vary between trials; figures in brackets signify response rates at 1-year follow-up
NS, not significant
* *Patients who failed to respond to previous treatment*
† *Patients who relapsed following previous treatment*
‡ *Patients naïve to treatment*
§ *Combined virological and biochemical response rates*

in one trial,[59] while in another response rates declined to less than 10% for both groups (non-significant difference between groups).[60]

Although genotype 3a was associated with a favourable response,[54,55,59] in some cases no association between genotype and outcome could be identified.[53,58] Treatment of patients with genotype 1 was more effective with combination therapy than with monotherapy.[53] Sequential administration of ribavirin followed by interferon was not as effective as concomitant administration of the two,[61] and combination therapy with lower doses of ribavirin (600–800 mg/day) was not associated with sustained response.[52,60] Response rates were generally higher among previous relapsers than previous non-responders.[53,55,57]

Adverse events

Adverse events related to interferon alfa therapy include flu-like symptoms (fatigue, headache, fever), decreases in haematological parameters (neutrophil and platelet counts), gastrointestinal complaints (anorexia, nausea), dermatological symptoms (alopecia) and psychiatric disturbances (depression, anxiety, insomnia).[32,48–50] The most frequently reported adverse psychiatric events were depression, insomnia and irritability, which are more frequently associated with dose modifications in combination therapy than with monotherapy.[32,48–50] Although patients reporting depression or suicide ideation generally had a history of psychiatric disorder or substance abuse, completed suicides have occurred in patients without a previous psychiatric history.[32] Other adverse events associated with combination therapy are similar in type and frequency to the known safety profile of treatment with interferon alfa, though nausea, dyspnoea, rash and pruritus have been reported more frequently for patients receiving combination therapy.[48–50] The percentage of patients experiencing adverse events reported in two large scale trials[48,49] are shown in *Table 5*.

Previous studies have reported that discontinuation of treatment is more frequent in patients receiving combination therapy than in those receiving interferon alone.[32] More recent trials have confirmed this trend, though the differences between the two groups are modest.[52–60] The most common reason for either study withdrawal or dose reduction for combination therapy patients is related to haematological events. Ribavirin is known to accumulate in red blood cells, resulting in haemolysis, causing a mean maximum decrease in haemoglobin of approximately 2.9–3.1 g/dl within the first 1–4 weeks of combination therapy.[32] This decrease in haemoglobin is reported to revert to baseline levels within 1–8 weeks after the cessation of ribavirin treatment.[48–50,54,58]

The frequency and severity of adverse events reported in the most recent trials are similar to those reported in previous studies.[48–50] For example, combination therapy patients experienced a significant decrease in haemoglobin compared with patients receiving interferon alfa monotherapy.[52–61] FIu-like symptoms were reported in 58–65% of monotherapy patients and in 61–78% of combination therapy patients.[53,54,60] In the more recent larger trials (≥ 50 patients per treatment group), withdrawal of patients due to serious adverse events or intolerance to treatment ranged from 3% to 9% for interferon alfa monotherapy patients and 6% to 13% for combination therapy patients.[53,54,58,59] A greater range of withdrawals were reported in the smaller (< 50 patients per treatment group) newer trials; between 0% and 19% for interferon alfa only patients and between 0% and 18% for combination therapy patients.[52,55–57,60,61] Adverse events requiring a dose reduction in combination therapy patients were primarily related to ribavirin administration (haematological disturbances, dermatological symptoms, nausea), and to a lesser degree, interferon alfa-related adverse events (depression, flu-like symptoms).[52–61]

Summary of efficacy

Three large RCTs, published in 1998, have shown that ribavirin given in combination with interferon alfa monotherapy produces larger sustained response rates than monotherapy alone. For treatment-naïve patients, sustained virological response rates after 24 weeks of therapy were 33% for combination patients and 6% for monotherapy patients. After 48 weeks of treatment, rates were 41% and 16%, respectively. For patients who have relapsed after initial interferon therapy, sustained virological response rates were 49% and 5%, respectively. Other more recent, smaller trials have shown similar rates. It is recommended that all treatment-naïve patients receive 6 months of combination therapy as first-line treatment, with those who have fewer than four factors predictive of a good response receiving a further 6 months.

Following submission of the report, NICE requested a meta-analysis of hepatitis C combination therapy studies, details of which are shown in appendix 5.

TABLE 5 *Percentage of adverse events for monotherapy and combination therapy for naïve and relapse patients*

Adverse events	Relapse patients*			Naïve patients†		
	IFN (n = 172)‡	IFN plus ribavirin (n = 173)‡	IFN (n = 231)‡	IFN plus ribavirin (n = 228)‡	IFN (n = 225)§	IFN plus ribavirin (n = 228)§
Discontinuation of treatment						
Any severe event	3	6	9	14	8	21
Dose reduction						
Due to anaemia	–	7	0	7	0	9
Due to other adverse event	3	5	12	13	9	17
Flu-like symptoms						
Headache	54	55	63	63	67	66
Fatigue	39	46	62	68	72	70
Myalgia	39	44	57	61	63	64
Arthralgia	23	21	27	30	36	33
Fever	33	32	35	37	40	41
Musculoskeletal pain	21	26	26	20	32	28
Gastrointestinal symptoms						
Anorexia	13	20	16	27	19	25
Nausea	20	35#	35	38	33	46
Diarrhoea	18	12	22	18	26	22
Psychiatric symptoms						
Depression	11	16	25	32	37	36
Insomnia	23	20	27	39	30	39
Respiratory tract symptoms						
Cough	9	10	5	15	9	14
Dyspnoea	6	14¶	9	19	10	18
Pharyngitis	9	11	9	11	10	20
Dermatological symptoms						
Alopecia	18	21	27	28	28	32
Rash	5	13¶	9	20	8	28
Pruritus	6	13	9	21	8	19

IFN, interferon

**Adverse event rates from McHutchison, et al., 1998[49]*

†Adverse event rates from Davis et al., 1998[48]

‡24 weeks of treatment

§48 weeks of treatment

#p = 0.002 compared with interferon alone

¶p = 0.02 compared with interferon alone

Chapter 3

Economic analysis

Methods for economic analysis

A cost-effectiveness spreadsheet model developed by SHPIC for their previous hepatitis C reports was updated and used for the calculation of benefits (details available from authors). The model incorporates a hypothetical cohort of 1000 individuals with chronic hepatitis C infection who are followed-up over a 30-year period. It aims to predict the natural history of the disease, the health states through which the cohort passes (e.g. percentage developing cirrhosis, ascites, variceal bleeds, requiring transplantation), how long they spend in each state, and the NHS costs of treating a patient in each state. The original options were:

- no treatment (except symptomatically)
- interferon monotherapy for 3 months, then a further 9 months for responders
- combination therapy for 6 months.

The no-treatment option is based on natural history events over a 30-year period as derived from the published literature and clinical consensus (see appendix 6, *Table 15*). The efficacy trials of combination therapy did not include an arm in which patients were randomised to a no-treatment placebo control group. Disease progression in this comparator is based upon published literature and clinical consensus.
A fourth option, combination therapy for 12 months was added to the update in 1999. However, ribavirin costs were based on an estimate of its predicted market price made in 1995, thus the costs per life-year gained (LYG) were underestimated.

Cost–utility analysis

The model has also been run by the SNAP Hepatitis C Working Group using quality-of-life data (derived from published literature) with up-to-date ribavirin costs to produce a cost–utility analysis. The assumptions used in the model have been reviewed by the SNAP Working Group in the context of recently published data and have been found to be robust. (The SNAP report has now been published.)

The model has been re-run for the current report in a way similar to that used by SNAP, with slightly revised costs (see appendix 7) to provide a cost–utility as well as a cost-effectiveness analysis. The aim of the current report is to define the added benefit derived from ribavirin taken in combination with interferon alfa, the standard treatment for hepatitis C. However, some health authority districts have not yet even funded interferon alfa monotherapy and some are choosing to withdraw it altogether in favour of combination therapy. Therefore the economic analysis presented here considers options to reflect current practice:

- no treatment (except symptomatically)
- interferon monotherapy for 12 months
- combination therapy for 6 months
- combination therapy for 12 months.

The cost–utility analysis is based on the pooled sustained virological response rates from the synthesis of the trials by Poynard[50] and McHutchison[49] (Poynard *et al.*, 2000).[51] These data were chosen as they represent the biggest single interferon-naïve population upon which combination therapy has been evaluated, and are based upon a methodologically sound study design. The subgroup analysis is based upon the results of Poynard and co-workers[50] (rather than the pooled analysis used in the base-case analysis). This is because sustained virological response rates for all patient subgroups are presented (e.g. those with four of five favourable response factors, those with three, and so on). For patients who have previously relapsed, response rates are based on the trial by Davis and co-workers.[48] Likewise, this trial was chosen as it is the biggest known study of interferon relapsers to be published.

The quality-of-life utilities are taken from the published literature (see page 2), which were estimated indirectly by a panel of US hepatologists using time trade-off and linear scaling techniques. Benefits and costs are discounted at 6%, the standard Treasury rate. It is assumed that patients received full treatment (i.e. that those non-responding after 3 months) continue for the full length. For a list of the main clinical assumptions in the model see appendix 6.

Results

There have been a number of studies on the cost-effectiveness of interferon therapy for hepatitis C, particularly with use of the Markov modelling technique.[62–64] The only published cost-effectiveness evaluation of combination therapy found was the study by Younossi and co-workers.[65] Six treatment strategies for chronic hepatitis C were compared in a Markov model. Quality of life was valued directly by a patient survey using the Health Utility Index (mark III), as well as from published utilities.[62,63] The main results are summarised in *Table 6*.

Testing for genotype to determine appropriate treatment was the most cost-effective strategy with an incremental cost per QALY of $7500 (£4751) when moving from strategy 3 to 6.

Figure 1 schematically describes the progression of hepatitis C from exposure to treatment with combination therapy.

Estimation of net costs

Patients referred for confirmation and assessment of hepatitis C will incur some costs regardless of whether they proceed to treatment. Evaluation of a new patient costs approximately £200. Further investigation of a patient with HCV considered for treatment is approximately £400. Total monitoring costs of a patient receiving treatment with monotherapy or combination therapy are £1900 per patient, plus costs of continued surveillance after completing treatment.

A 4-week cycle of interferon alfa at 3 mU three times a week costs £194, and for ribavirin the cost is £543 (an average of the dose range recommended for ribavirin (1000–1200 mg/day)). Thus, ribavirin substantially increases drug costs. Six months of combination therapy will cost £4422 (excluding monitoring costs).

The cost assumptions made in the model are detailed in appendix 6, and details of investigation and monitoring costs can be found in appendix 7.

Estimation of cost–utility

The additional cost per QALY gained when moving from one treatment option to another was estimated for the base-case scenario (sustained virological response rates for all naïve and relapsed patients) and for a subgroup analysis (sustained virological response rates for different patient subgroups).

Base-case scenario

For interferon-naïve patients the **additional** discounted cost per QALY gained from treatment with combination therapy for 6 months compared with interferon monotherapy for 12 months was £6839 (*Table 7*). If providing 6 months of combination therapy as first-line treatment the marginal cost per QALY is £7578. A move from 6 to 12 months combination therapy incurs a marginal discounted cost per QALY of £36,971.

For patients who have **relapsed** following a previous course of interferon alfa, the **additional** discounted cost per QALY gained from treatment with combination therapy for 6 months compared with monotherapy for 6 months is £3503 (*Table 8*).

Subgroup analysis

A subgroup analysis was conducted to examine the sensitivity of the cost per QALY according to the response rates for different patient subgroups (based on the trial by Poynard *et al.,* (1998)[50]). Virological response rates for the subgroups are determined by factors such as age, gender, fibrosis, genotype and baseline viral load. These factors were chosen for this sensitivity analysis as they represent the most significant independent variables in predicting treatment outcome. Knowledge of which patients are most likely to benefit will facilitate effective resource targeting. However, the model was not originally designed to incorporate patient subgroups and the clinical variables in the model may not apply equally to these groups. Furthermore, the numbers in the subgroups are relatively small, therefore caution is required when interpreting these results.

TABLE 6 *Costs of treatment strategies*

Strategy	Cost US $	Cost UK £*	QALYs
1. No treatment	38,747	24,583	13.10
2. Monotherapy 48 weeks	35,642	22,611	14.05
3. Monotherapy followed by combination therapy for relapsers and non-responders	34,561	21,903	15.53
4. Monotherapy followed by combination therapy for relapsers only	34,758	22,024	14.40
5. Combination therapy as initial treatment	34,792	22,046	15.31
6. Pre-treatment genotyping and adjusting duration of combination accordingly	37,263	23,609	15.89

* *Converted by the authors of this report based on an exchange rate of £1 = $1.57, not a healthcare equivalence rate*

FIGURE 1 *Flow diagram representing a patient's progression from exposure to HCV to treatment with combination therapy*

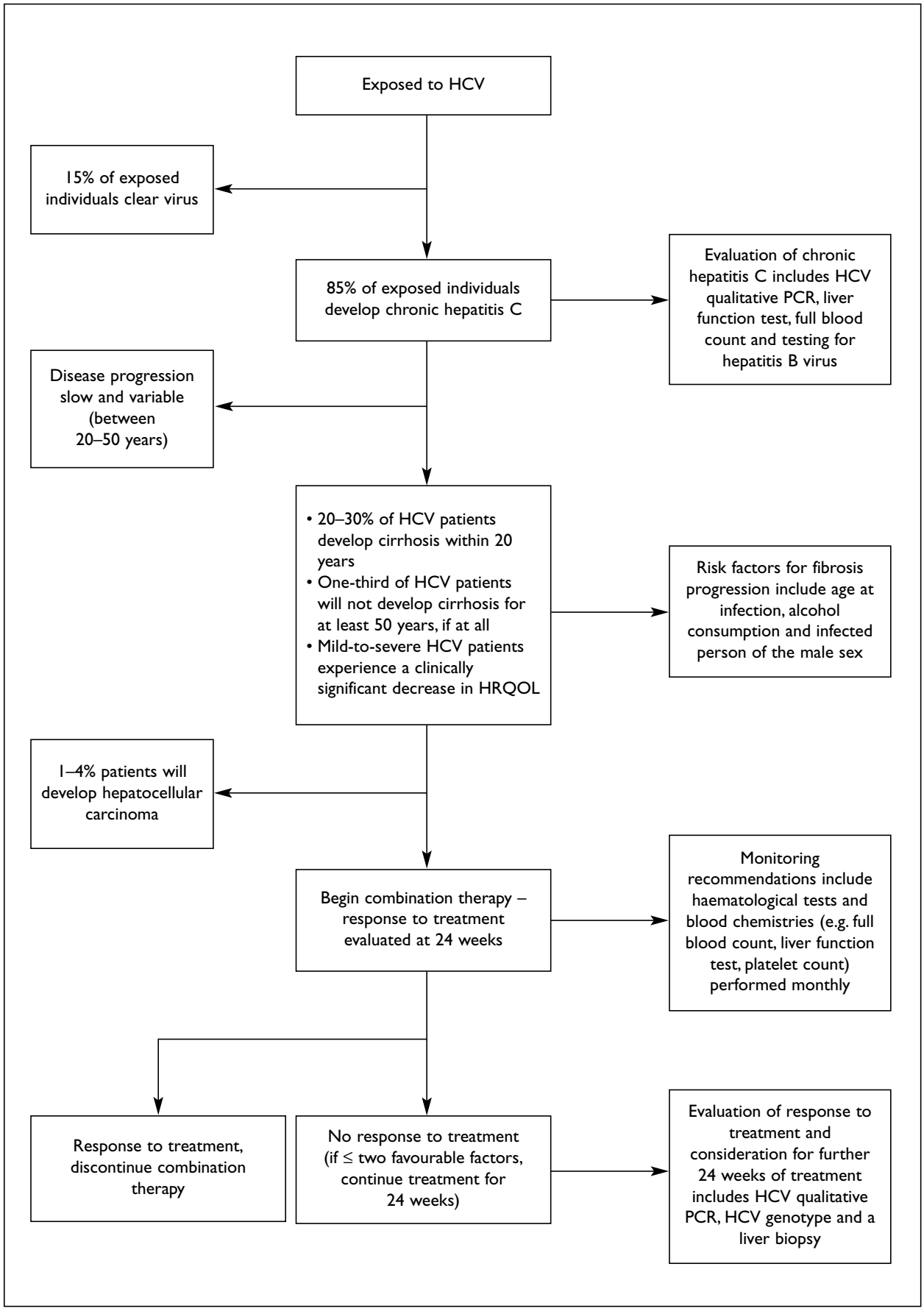

TABLE 7 *Marginal cost–utility analysis for different treatment options. Interferon-naïve patients (modelled on 1000 patients followed-up over a 30-year period)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
Moving from monotherapy for 48 weeks to combination therapy for 24 weeks					
Monotherapy 48 weeks	£4,220,030	13,528			
Combination 24 weeks	£5,929,690	13,778	£1,709,660	250	£6839
Moving from monotherapy for 48 weeks to combination therapy for 48 weeks					
Monotherapy 48 weeks	£4,220,030	13,528			
Combination 48 weeks	£10,174,354	13,896	£5,954,324	368	£16,180
Moving from combination therapy for 24 weeks to combination therapy for 48 weeks					
Combination 24 weeks	£5,929,690	13,778			
Combination 48 weeks	£10,174,354	13,896	£4,244,664	118	£35,971
Moving from no active treatment to combination therapy for 24 weeks					
No active treatment	£2,246,702	13,292			
Combination 24 weeks	£5,929,690	13,778	£3,682,988	486	£7578

Based on sustained virological response rates from Poynard et al., *2000*[51]
- *33% (24 weeks of combination therapy)*
- *41% (48 weeks of combination therapy)*
- *16% (48 weeks of monotherapy)*

TABLE 8 *Marginal cost–utility analysis for different treatment options. Interferon relapsers (modelled on 1000 patients followed-up over a 30-year period)*

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost/ QALY saved
Moving from monotherapy for 24 weeks to combination therapy for 24 weeks					
Monotherapy 48 weeks	£3,300,767	13,366			
Combination 24 weeks	£5,570,218	14,014	£2,269,451	648	£3502

Based on sustained virological response rates from Davis et al., *1998*[48]
- *49% (24 weeks of combination therapy)*
- *5% (24 weeks of combination therapy)*

Poynard and co-workers[51] recommends that all patients receive combination therapy as first-line treatment for 6 months and that those with fewer than four favourable factors predictive of a virological response should be treated for an additional 6 months. *Table 9* shows the marginal costs per QALY for subgroups of patients if moving from 6 to 12 months' therapy. The fewer the response factors the more acceptable the cost per QALY becomes. The sustained response rate for patients with one to two favourable factors treated with combination therapy for 12 months is double that for those only treated for 6 months. These are the patients with most to gain from a longer course of treatment. Our results show that the most cost-effective option is to treat those with one to two factors for a further 6 months, producing a cost per QALY of £17,252.

TABLE 9 *The cost–utility of moving from 6 to 12 months of combination therapy according to patient subgroups (number of factors predicting a good response)*

Response factors	Sustained response rate*		cost/QALY
	Combination therapy for 6 months (*n*/*N*)	Combination therapy for 12 months (*n*/*N*)	
3–4	54% (69/127)	56% (74/132)	£148,703
3	47% (37/79)	51% (41/80)	£73,589
1–2	14% (19/135)	30% (37/123)	£17,252

**Based on Poynard et al., 1998*[50]

Sustained virological response rates for 'extreme populations' (e.g. patients with either all five or none of the favourable response factors) are

presented in the pooled analysis[51] of the Poynard[50] and McHutchison[49] trials. These were put into our model and results are presented in *Table 10*. The extended treatment period does not seem worthwhile in the group with no factors. Again, caution is advised due to the small numbers in each group.

TABLE 10 *The cost–utility of moving from 6 to 12 months of combination therapy according to extreme population scenarios*

Response factors	Sustained response rate*		cost/QALY
	Combination therapy for 6 months (*n*/*N*)	Combination therapy for 12 months (*n*/*N*)	
All five	69% (11/16)	79% (15/19)	£28,520
None	8% (2/26)	9% (2/23)	£298,933

**Based on pooled anaysis[51] of Poynard and McHutchison trials*

Paradoxically, these cost per QALY figures are in contrast to those presented in *Table 9*. This is due to differences in response rates for patient subgroups between the pooled analysis and the Poynard and co-workers (1998)[50] trial on its own, where the fewer the response factors the lower the cost per QALY.

Estimation of cost-effectiveness

The SHPIC spreadsheet model was also used to estimate the cost-effectiveness of combination therapy in terms of LYG.

For treatment-naïve patients, virological response rates were based on results from the synthesis of the Poynard and McHutchison trials (Poynard *et al.*, 2000[51]). Additional figures are presented in brackets based on virological response rates from the Poynard and co-workers (1998) trial **only**.[50] These rates are slightly higher than the pooled rates and illustrate the sensitivity of the cost per LYG to slight changes in response. For patients who have relapsed after a previous course of monotherapy, response rates are taken from the trial by Davis and co-workers.[48]

In interferon-**naïve** patients:

- the **additional** discounted cost per LYG from treatment with interferon monotherapy for 12 months compared with no active treatment is £12,369 (£10,060)
- the **additional** discounted cost per LYG from treatment with combination therapy for 6 months compared with interferon monotherapy for 12 months is £10,086 (£5638)
- the **additional** discounted cost per LYG from treatment with interferon plus ribavirin (combination therapy) for 6 months compared with combination therapy for 12 months is £53,213 (£26,307)
- the **additional** discounted cost per LYG from treatment with combination therapy for 6 months compared with no active treatment is £19,392 (£18,385).

For patients who have **relapsed** after monotherapy:

- the **additional** discounted cost per LYG gained from treatment with combination therapy for 6 months compared with monotherapy for 12 months is £5173.

Chapter 4

Discussion and conclusions

Main results

The evidence for the efficacy of combination therapy comes from three large methodologically sound RCTs, as well as a number of smaller trials. Our cost-effectiveness and cost–utility analyses show that combination therapy, offered to the most suitable patient groups and for the most appropriate duration, is of reasonable value for money.

The marginal cost per QALY gained from using combination therapy for 6 months as first-line treatment (i.e. moving from no active treatment) is £7578. The move from 6 to 12 months of combination therapy generates a marginal cost per QALY of £35,971. This figure is based upon virological response rates for **all** interferon-naïve patients in two large international RCTs. Although Poynard and co-workers[51] recommends that patients with fewer than four favourable factors should be treated for a further 6 months, our subgroup analysis suggests that it may only be cost-effective to treat those with only one or two favourable response factors for the additional period. This will incur a marginal cost per QALY of approximately £17,252. This is in contrast to the £148,703 incurred for treating patients with three to four factors for a further 6 months, which will be unacceptable to healthcare purchasers.

However, an alternative calculation, based upon extreme population scenarios, shows a different picture. The move from 6 to 12 months of treatment for patients for whom all five favourable factors are present has a marginal cost per QALY of £28,520, whereas for those with no favourable factors the marginal cost is £298,933. However, the latter figures are based upon very small patient numbers and should thus be interpreted with caution. Furthermore, the assumptions in the model may not apply equally to each subgroup.

Implications

One implication of the variations in prevalence of HCV is that the cost of combination therapy would vary enormously among health authorities. Some health authorities, particularly those that include cities or districts with large numbers of intravenous drug users, might have a much higher total cost than others, though economies of scale may be achieved through treating sufficient quantities of patients. However, this assumes high compliance with treatment. We have good data on acceptance rates of initial assessment (Mohsen A and the Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. Sheffield: Department of Infection and Tropical Medicine; unpublished report, 2000), which has to include liver biopsy, as clinical and biochemical assessment is not a good guide to severity of liver damage in the early stages.[23] However, advice from clinical colleagues is that compliance by intravenous drug users is poor, particularly as treatment is appropriate only for those who cease injection because of the high risk of re-infection if they do not. This may counter the point made above, as non-compliance would make provision of treatment more affordable. The specific needs of this patient group need to be assessed, with services adapted accordingly.

Implications for others

One possible effect of provision of an assessment and treatment package for hepatitis C is that it might reduce the spread of infection by persuading injecting drug users to stop injecting. This is speculative and at present is unproven.

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.

Budget impacts

The total cost will depend on a number of factors:

- prevalence
- proportion diagnosed
- proportion of those diagnosed who attend for assessment

- proportion considered suitable for treatment – those who continue to abuse drugs will be excluded (but have poor attendance and compliance anyway); those with mild disease are not routinely treated at present; the most elderly will have little to gain from treatment unless troubled by symptoms; a proportion will decide not to seek further investigation and treatment.

The most useful data come from the Trent group (see unpublished report above), and can be used for estimating cost to an average health authority as follows:

- prevalence of diagnosed disease is 0.05%
- only half are under specialist care – 0.025% of population
- half of these have had biopsies – 0.0125% of population
- only 26% of these are treated, mainly because those with minimal or mild liver changes are not usually treated at present – 0.00325%
- hence, number to be treated in population of 500,000 is 1625
- drug costs alone are approximately £4422, which would lead to a bill of approximately £7.2 million if all potential patients could tolerate the drugs. If 10% stop because of adverse events, the cost falls to about £6.5 million, for treating the prevalent patients. After the first couple of years (it would take time to process all the patients through clinics, so the cost might be spread over 1–2 years), the numbers to be treated would drop, perhaps to a tenth (assuming some prevalent cases progressing to grades of liver disease, which would be treated, and some new cases arise from new infection, or new presentation of old infections).

These figures should be regarded as rough estimates only, and would only apply to an area with relatively low prevalence. Health authorities in cities with large drug abuse problems, such as London, might incur much higher costs per 500,000 population, though one of the key variables would be compliance among the drug abusers.

Assumptions, limitations and uncertainties

There are a number of uncertainties regarding natural history and treatment of mild disease. A brief review of some relevant studies is included in appendix 8. The main uncertainty is whether the group who have mild hepatitis will remain at that level, or whether all patients would progress to cirrhosis if given enough time.

A related issue is whether to treat mild disease, as defined by findings on liver biopsy. The trials did include some patients with mild disease, and it is reasonable to assume anti-viral efficacy of combination therapy. The uncertainty arises because we do not fully know the natural history in this patient group, and therefore precisely what we are preventing with treatment. Hence, the cost per QALY might be extremely high. Expert opinion suggests that some clinicians may be reluctant to treat those with minimal symptoms due to uncertainty regarding whether they derive substantial benefit. However, it might 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 extra-hepatic disease, which would improve after treatment. A trial of combination therapy with mild hepatitis C patients has been funded by the UK NHS Health Technology Assessment (HTA) programme and is due to report in early 2003.

The need for liver biopsy as a guide to treatment has been questioned, with the arrival of new non-invasive guides to liver disease, such as hyaluronic acid estimation. The consensus is that biopsy should still be done to obtain histological evidence of severity of liver disease. Although the diagnosis of chronic hepatitis C does not need liver biopsy, there is evidence that clinical assessment is not as good at diagnosing cirrhosis, and that biopsies are still indicated.[66] However, this assumes that treatment is dependent on 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 it was decided to treat the symptoms. If the UK trial of combination therapy in mild disease showed that it was of benefit in those patients, the need for biopsy would again be reduced. There are occasional deaths after biopsy, but the audit in England and Wales found a death rate of only 1 per 1000 biopsies.[67] 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 gastroenterology patients (compared with general medicine patients). 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.

Other interventions and further research

In terms of other options for the treatment of hepatitis C, a longer acting version of interferon alfa, pegylated interferon, is currently being evaluated in dose-ranging studies in combination with ribavirin. Preliminary results indicate that it has a similar tolerance profile to current combination therapy. A marketing application has been submitted to the European Agency for the Evaluation of Medicinal Products by Schering-Plough for PEG-INTRON™ to be injected subcutaneously once a week for a year in patients with chronic hepatitis C. A review of pegylated interferon in chronic hepatitis C patients is planned by the Cochrane Hepato-billary Group. There has been some interest in the role of amantadine, formerly used to treat herpes zoster, Parkinson's disease, and influenza, in treatment of hepatitis C. There have been some trials of combination treatment with amantadine versus combination treatment with ribavirin, but as yet these are not fully published.[68,69]

The role of interferon beta in hepatitis C has also been investigated.[70] In a recently published RCT, 200 patients were randomised to receive a 12-week course of interferon beta or combination therapy with ribavirin and interferon alfa. A sustained response rate was observed in 21% of the patients treated with interferon beta and 13% of those treated with combination therapy. It was noted that long-term administration of interferon beta may be impractical.

Conclusion

The results of this review show that there is benefit associated with combination therapy and that it can be a cost-effective treatment option. It is appropriate to offer 6 months of combination therapy as first-line treatment to patients not previously treated with interferon and also to patients who have relapsed after a previous course of interferon.

At 6 months, continuation of treatment for patients should depend on factors that may predict a good sustained response. For treatment-naïve patients these are:

- genotype 2 or 3
- baseline viral load less than 3.5 million copies/ml
- no or portal fibrosis
- female gender
- age younger than 40 years.

A further 6 months of treatment is recommended in the literature for those who have fewer than four favourable factors.[51] However, for those with three to four factors, further treatment is unlikely to derive any additional benefit and should thus cease. The most cost-effective option is to treat those with one to two favourable factors for a further 6 months.

Re-treatment with combination therapy for non-responders to interferon monotherapy is unlikely to be cost-effective.[37] As combination therapy is becoming increasingly accepted as first-line therapy it is unlikely that in the future there will be many monotherapy non-responders/relapsers seeking re-treatment. Interferon monotherapy should only be prescribed to patients in whom combination therapy is contraindicated.

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Appendix 1

Literature search

The most recent issue or date searched is as follows:

- Cochrane Library 14/02/00
- MEDLINE (SilverPlatter) 20/01/00
- 'Pre-MEDLINE' InterNet Grateful Med 26/01/00
- EMBASE (SilverPlatter) 20/01/99
- Health Technology Assessment database 6/04/00

Text words and MeSH headings (not all applicable to every search)

Disease-specific terms freetext terms:
interferon alfa in ti, ab
interferon alpha in ti, ab
ribavirin in ti, ab

MeSH terms:
"Interferon-Alfa-Recombinant"/ therapeutic-use
"Antiviral-Agents"/ therapeutic-use
"Interferon-Alfa-2b"/ therapeutic-use
"Interferon-alpha"/ therapeutic-use
"Hepatitis-C-Chronic"/ drug-therapy
"Ribavirin"/ therapeutic-use

EMTREE terms:
alpha 2b-interferon
alpha 2-interferon
recombinant-alpha2b-interferon
ribavirin
hepatitis-C
chronic-hepatitis

Appendix 2

Data extraction tables

TABLE 11 *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Poynard *et al.*, 1998[50] 43 centres International trial	(i) 3 mU IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 48 weeks (*n* = 277) (ii) 3 mU IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 24 weeks (*n* = 277) (iii) 3 mU IFN alfa 3x a week and placebo for 48 weeks (*n* = 278)	*N* = 832 adults Chronic hepatitis C Interferon-naïve Exclusions: Decompensated cirrhosis; HIV; HBV; previous organ transplantation; pre-existing psychiatric disease; cardiovascular disease; haemoglobinopathies; haemophilia; poorly controlled diabetes; autoimmune type disease	• HCV-RNA • Serum ALT • Histology • Adverse events
Results HCV-RNA • Complete response / sustained response (i) IFN + ribavirin (48 weeks) = 145 (52%) / 118 (43%) (ii) IFN + ribavirin (24 weeks) = 157 (57%) / 96 (35%) (iii) IFN + placebo (48 weeks) = 93 (33%) / 53 (19%) IFN + ribavirin vs IFN + placebo $p < 0.001$ at both 24 and 48 weeks Biochemical response • Complete response / sustained response (i) IFN + ribavirin (48 weeks) 196 (71%) / 138 (50%) (ii) IFN + ribavirin (24 weeks) 196 (71%) / 109 (39%) (iii) IFN + placebo (48 weeks) 123 (44%) / 67 (24%) IFN + ribavirin vs IFN + placebo $p < 0.001$ at both 24 and 48 weeks Histology • Improvement was observed in all regimens compared with baseline scores • Significantly more improvement in inflammation scores in combination groups vs IFN			
Comments • Allocation to treatment groups: central randomisation, balanced and stratified for cirrhosis, viral load and genotype (ratio 1/1/1) • Comparability of treatment groups at pre-treatment: equivalent • Blinding: pathologist- and patient-blinded • Method of data analysis: patients who did not have a week 24 follow-up assessment for serum HCV-RNA were classified as non-responders in the analysis. Data presented on all patients who had at least one dose, ITT analysis in sensitivity analysis included an additional eight patients • Statistical power calculation: power and sample size calculation on primary endpoint • Attrition/drop-out: 840 were randomised with eight (0.9%) dropping out before treatment. Adverse events led to the departure of 52 patients (19%) in the IFN + ribavirin (48 weeks) group; 22 (8%) in the IFN + ribavirin (24 weeks) group and 36 (13%) in the monotherapy (48 weeks) group • Knodell score histologic activity • METAVIR used for inflammation and fibrosis • Supported by research grant and advice from Schering Plough			

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
McHutchison *et al.*, 1998[49] 44 centres USA	(i) 3 mU IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 24 weeks (*n* = 228) (ii) 3 mU IFN alfa 3x a week plus placebo 24 weeks (*n* = 231) (iii) 3 mU IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 48 weeks (*n* = 228) (iv) 3 mU IFN alfa 3x a week plus placebo for 48 weeks (*n* = 225)	*N* = 912 adults Chronic hepatitis C Interferon-naïve Exclusions: Decompensated cirrhosis; raised serum alfa feto protein; anaemia; HIV; psychiatric disorders; seizure disorders; cardiovascular disease; haemophilia; poorly controlled diabetes; autoimmune disease; organ transplantation	• HCV-RNA • Histology • Serum ALT

Results

HCV-RNA

• Complete response / sustained response

(i) IFN + ribavirin (24 weeks) = 121 (53%; 95% CI, 47 to 60) / 70 (31%; 95% CI, 25 to 37); $p < 0.001$

(ii) IFN + placebo (24 weeks) = 66 (29%; 95% CI, 23 to 34) / 13 (6%; 95% CI, 3 to 9)

(iii) IFN + ribavirin (48 weeks) = 115 (50%; 95% CI, 44 to 57) / 87 (38%; 95% CI, 32 to 45); $p < 0.001$

(iv) IFN + placebo (48 weeks) = 54 (24%; 95% CI, 18 to 30) / 29 (13%; 95% CI, 9 to 13)

Biochemical response

• Complete response / sustained response

(i) IFN + ribavirin (24 weeks) = 133 (58%) / 72 (32%)

(ii) IFN + placebo (24 weeks) = 56 (24%) / 25 (11%)

(iii) IFN + ribavirin (48 weeks) = 149 (65%) / 83 (36%)

(iv) IFN + placebo (48 weeks) = 62 (28%) / 35 (16%)

IFN + ribavirin 48 weeks = $p < 0.001$ vs either IFN

Histology

• Improvement was observed in all regimens compared with baseline scores. Significantly more improvement in inflammation scores in combination groups

Adverse events

• Haemoglobin decreased (one patient stopped)

• Reduction and discontinuation more common in IFN + ribavirin

Comments

• Allocation to treatment groups: method of randomisation not described but presumed to be central

• Comparability of treatment groups at pre-treatment: equivalent

• Blinding: pathologist-blinded

• Method of data analysis: not ITT analysis in that 933 randomised but analysis based on 912 who received at least one dose

• Statistical power calculation: stated

• Attrition/drop-out: 933 were randomised but 21 dropped out before treatment. During treatment 119 patients (13%) discontinued due to adverse events: 21 (9%) in the IFN 24-week group; 32 (14%) in the IFN 48-week group; 18 (8%) in the IFN–ribavirin 24-week group; 48 (21%) in the IFN–ribavirin 48-week group

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Davis *et al.*, 1998[48] Multicentre placebo-controlled trial	(i) 3 mU IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 24 weeks (*n* = 173) (ii) 3 mU IFN alfa 3x a week plus placebo for 24 weeks (*n* = 172)	*N* = 345 adults Chronic hepatitis C Treatment relapsers Relapsers with previously normalised serum ALT at end of treatment Exclusions: Decompensated cirrhosis; low haemoglobin and other parameters; HIV; prior organ transplantation; severe psychiatric disease; seizure disorder; cardiovascular disease; renal disease; haemoglobinopathy; haemophilia; poorly controlled diabetes; autoimmune disease	• HCV-RNA • Serum ALT • Adverse events

Results

HCV-RNA
• End of treatment / sustained response
(i) IFN + ribavirin = 141 (82%) / 84 (49%)
(ii) IFN + placebo = 80 (47%) / 8 (5%)
$p < 0.001$

Biochemical
• End of treatment / sustained response
(i) IFN + ribavirin = 154 (89%) / 81 (47%)
(ii) IFN + placebo = 98 (57%) / 8 (5%)
$p < 0.001$

Histology
• Improvement in both groups but more common in combination group
• Sustained response was more common in the combination group with low viral loads or genotype other than type 1

Adverse events
• Drop in haemoglobin
• Other adverse events similar to IFN monotherapy

Comments

• Allocation to treatment groups: centralised randomisation stratified by cirrhosis, HCV genotype and HCV viral load
• Comparability of treatment groups at pre-treatment: generally equivalent
• Blinding: pathologist- and patient-blinded
• Method of data analysis: comparison of US and non-US patients allowed combination of results, four withdrew before receiving treatment and were excluded from analysis; therefore not ITT
• Statistical power calculation: no details of sample size calculation
• Attrition/drop-out: four withdrew before receiving treatment. Five patients (3%) in the monotherapy group and ten (6%) in the combination group discontinued treatment. One patient committed suicide 3 months after treatment finished. It is not clear whether data from these patients were included in the analysis
• Assessments were made at 1, 2, 4, 6 and 8 weeks of treatment and then monthly thereafter and 4, 8, 12 and 24 weeks after treatment was discontinued
• Fewer patients with cirrhosis or genotype 1 as these are less likely to have responded and then relapsed
• All patients who had a sustained response HCV-RNA became undetectable in the first 12 weeks

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Pol *et al.*, 1999[58]	(i) 6 mU IFN alfa 3x a week for 6 months followed by 3 mU 3x a week for 6 months (total 12 months' treatment) (*n* = 64) (ii) 2-month course of ribavirin followed by combination with the same IFN alfa dose for 2 months then IFN alfa (at same dose) alone for 10 months (total 14 months) (*n* = 62)	*N* = 126 Non-responders Adults	• Virological: HCV-RNA (by PCR) • Biochemical: ALT rates • Histological: HAI • Adverse events

Results

HCV-RNA

- Disappearance of serum HCV-RNA (by PCR) was significantly more frequent at the end of treatment in the combination group than the monotherapy group (24.5 vs 7.7%; $p = 0.02$), but did not differ 6 months after the end of therapy (9.8 and 8.3, respectively; NS)

ALT normalisation rates

- Monotherapy: 22.7% (at 12 months' treatment); 12.2% (at 6 month follow-up)
- Combination: 30.6% (at 12 months' treatment); 25.0% (at 6 month follow-up)
- No significant difference between groups
- Normalisation was significantly more frequent after 4 months of ribavirin plus 2 months of IFN, than after 2 months of IFN alone (52.8 vs 26.2%; $p < 0.01$) but this difference was not maintained after ribavirin withdrawal

HAI scores

- Monotherapy: 9.23 (pre-treatment), 9.37 (post-treatment); NS
- Combination: 9.29 (pre-treatment), 8.54 (post-treatment); NS

Adverse events

- More common in the combination group than the monotherapy group. Six patients withdrew in the monotherapy group (due to IFN-related effects: fatigue, suicide attempt, gastric carcinoma, haematological disturbances) and ten in the combination group (due to ribavirin-related toxicity)
- Haemoglobin concentration was significantly lower in the combination than the monotherapy group ($p < 0.001$), but decrease resolved after ribavirin was withdrawn
- Long-term response was not associated with a given genotype

Comments

- Allocation to treatment groups: random no information given on procedure
- Comparability of treatment groups at pre-treatment: generally equivalent
- Blinding: pathologist-blinded
- Method of data analysis: not clear whether data from withdrawals were included in the follow-up analysis. HAI data were only available for 81 patients at post-treatment (from 120 at pre-treatment)
- Statistical power calculation: not stated
- Attrition/drop-out: total withdrawal from treatment = 16 patients (12%): six patients (9%) from the monotherapy group; ten patients (16%) from the combination group
- Jadad checklist score: 2/5
- Follow-up assessment: 6 months after treatment finished (18 months after treatment began)

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Barbaro *et al.*, 1998[53] Multicentre RCT No funding information provided	(i) 3 mU IFN 3x a week plus 1000–1200 mg/day ribavirin for 24 weeks (*n* = 152) (ii) 6 mU IFN 3x a week for 24 weeks (*n* = 151)	*N* = 303 adults Non-responders	• Virological: HCV-RNA • Biochemical: ALT levels • Histological: HAI scores • Adverse events

Results

Virological response at 24 weeks
- Monotherapy = 8 (5.3%); combination = 38 (25%)

Biochemical response at 24 weeks
- Monotherapy = 33 (21.8%); combination = 93 (61.2%)

Sustained virological response at 48 weeks
- Monotherapy = 2 (1.3%); combination = 32 (21%)

Sustained biochemical response at 48 weeks
Monotherapy = 15 (10%); combination = 61 (40.1%)

$p < 0.001$

- In combination-treated patients, HCV-RNA was not detectable in 38 of 93 (41%) patients with biochemical response at week 24, and remained undetectable in 23 patients with sustained biochemical response at week 48. In monotherapy-treated patients, HCV-RNA was not detectable in eight of 33 patients (24.2%) with biochemical response at week 24, and remained undetectable in two patients with sustained biochemical response at week 48
- Biochemical response, improvement in HAI, changes in HCV titres, and age of patient responders were not correlated with HCV genotype
- Compliance to therapy (as monitored by patient diaries) was 94.7% in the combination group and 96.6% in the monotherapy group (95% CI for the difference: –6.5 to 2.7%; $p = 0.597$)
- Flu-like symptoms were the most common adverse event (combination group = 77.7%; monotherapy group = 65%). Other adverse events included fever, bone pain and malaise. Modest anaemia was present in a large number of the combination group (91.6%). In these patients the mean haemoglobin level decreased by 9.5% at the end of treatment and red blood cell count by 12.7%

Comments
- Allocation to treatment groups: random by computer-generated sequential list of block randomised assignments maintained by the coordinating centre of the study
- Comparability of treatment groups at pre-treatment: no statistically significant differences between groups at baseline except for genotype 3a, which was more common in the monotherapy group ($p = 0.051$)
- Blinding: open label, data investigator-blind
- Method of data analysis: ITT
- Statistical power calculation: stated
- Attrition/drop-out: in the combination group eight patients (5%) withdrew due to adverse events/intolerance to pharmacological therapy, and nine patients (6%) were lost to follow-up. In the monotherapy group five patients (3%) withdrew due to intolerance to pharmacological therapy. Total treatment withdrawal = 13 patients (4.2%); total loss to follow-up = 3%
- Jadad checklist score: 3/5
- Assessments (safety) were made at baseline, and at week 1, 4, 8, 12, 16, 20 and 24 during treatment and at week 28, 36 and 48 after cessation of treatment (i.e. up to 6 months after end of treatment). Biochemical and virological response assessed at baseline and weeks 12, 20, 24, 36 and 48. Liver biopsy performed at baseline and weeks 24 and 48

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Bell *et al.*, 1999[55] The CONSTRUCT group RCT No funding information provided	(i) 4.5 mU IFN alfa 3x a week for 6 months (*n* = 26) (13 relapsers; 13 non-responders) (ii) 4.5 mU IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 6 months (*n* = 27) (14 relapsers; 13 non-responders)	*N* = 53 Non-responders (*n* = 26) Relapsers (*n* = 27) Adults	• Virological: HCV-RNA • Biochemical: ALT levels • Hb concentration • Adverse events

Results

Virological response at 24 weeks
• Monotherapy = 10 (38%); combination = 12 (44%)
NS

Biochemical response at 24 weeks
Monotherapy = 14 (54%); combination = 16 (59%)
NS

Sustained virological response at 48 weeks
• Monotherapy = 6 (23%); combination = 6 (22%)
NS

Sustained biochemical response at 48 weeks
• Monotherapy = 7 (27%); combination = 7 (26%)
(no level of significance provided)

- The authors posit that the similarity in sustained response rates between the two groups might be due to type II error with a small number of patients in each group. Previous relapsers were sustained HCV-RNA responders more often than in previous non-responders ($p = 0.0054$). A sustained virologic response was not related to an increased IFN dose on re-treatment
- There was no significant association between genotype and outcome
- Dose of ribavirin was lowered in eight (30%) combination patients due to a fall in haemoglobin concentrations. Ribavirin was stopped or reduced for 1–12 weeks
- Eight patients (15%) withdrew from the study. In the monotherapy group, three refused to start treatment, one withdrew due to depression, one withdrew due to unknown reasons after 2 months. In the combination group one withdrew due to rhinoconjunctivitis and urticaria, one due to depression and one due to extreme fatigue. One man developed hyperthyroidism and one man in the combination group developed diabetes mellitus type I

Comments

- Allocation to treatment groups: random, stratification was performed in accordance with treatment response to previous IFN therapy
- Comparability of treatment groups at pre-treatment: no significant differences between groups. However, the authors state that the distribution of genotypes was even among the groups (p. 195), yet they also say that the distribution of genotype 3 was uneven between the monotherapy group (16 of 26 patients) and the combination group (ten of 27 patients) and use this as a possible explanation for the similarity in sustained response rates between the two groups (p. 197).
- Blinding: not stated
- Method of data analysis: ITT
- Statistical power calculation: not stated
- Attrition/drop-out: eight patients (15%) did not complete the study, five (19%) in the monotherapy group and three (11%) in the combination group. The authors state that one patient from the monotherapy group developed hyperthyroidism after 2 months (uncertain if patient was withdrawn) and one patient from the combination group developed diabetes mellitus after 4 months, with therapy being withdrawn (though this is not reported in the total withdrawals from the study)
- Jadad checklist score: 3/5

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Milella *et al.*, 1999[57] RCT	(i) 6 mU natural IFN 3x a week plus 1000 mg/day ribavirin for 6 months (*n* = 47) (ii) 6 mU natural IFN 3x a week for 6 months (*n* = 41)	*N* = 88 49 previous non-responders (28 combination group; 21 monotherapy group) 39 previous relapsers (19 combination group; 20 monotherapy group)	Biochemical and virological response rates

Results

Virological response rates
- Monotherapy = 6 (13%); combination therapy = 13 (27%)

Sustained virological response rates
- Monotherapy = 0 (0%); combination therapy = 7 (15%)
- Response rates were higher among patients who had relapsed to a previous course of interferon than those who failed to respond

Adverse events
- Pruritus more common among patients treated with ribavirin (8.5%)
- Haemolysis developed shortly after initiating ribavirin in all patients treated with the combination therapy; at the end of therapy these patients demonstrated a mean haemoglobin concentration that decreased from 15.3 ± 1.08 to 12.8 ± 1.76 (no significance level provided)
- 54 patients (61%) had genotype 1b; 40 patients (45%) had cirrhosis

Comments
- Allocation to treatment groups: random, no information provided on procedure
- Comparability of treatment groups at pre-treatment: there were no statistically significant differences between groups
- Blinding: not stated
- Method of data analysis: not stated whether ITT, but no attrition is reported, thus all patients randomised are assumed to be included in the analysis
- Statistical power calculation: not stated
- Attrition/drop-out: no patients withdrew due to adverse events (not stated whether there was any loss to follow-up, however with follow-up taking place 1 year after treatment it is likely that there may be some)
- Jadad score: 2/5
- Patients were followed-up for 1 year

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Andreone *et al.*, 1999[52] Randomised, multicentre trial No funding information provided	(i) 3 mU IFN (leukocyte) 3x a week plus 800 mg/day ribavirin for 6 months (*n* = 26) (ii) 3 mU IFN (leukocyte) 3x a week for 6 months (*n* = 24) 6 months of treatment and 6 months of follow-up	*N* = 50 adults (non-responders to previous treatment with IFN recombinant or lymphoblastoid) 24 of combination group (one patient on reduced dose of ribavirin) and 21 patients in monotherapy group completed the trial (ITT used)	• Sustained response: normal ALT and no detectable HCV-RNA by PCR • Complete response: normal ALT and no detectable HCV-RNA by PCR at the end of treatment • Biochemical response: ALT normal at end of treatment • Histological: classified by HAI • Safety: adverse effects, biochemical and haematological

Results

- Serum ALT levels significantly decreased for patients in the combination group ($p = 0.0001$), NS for monotherapy group. No patients achieved a sustained or complete response. No patients achieved ALT normalisation or negative serum HCV-RNA at the end of follow-up
- ALT normalisation at end of treatment (% of patients): combination group = 9 (35%), monotherapy group = 2 (8%); $p = 0.027$
- HCV-RNA negative at end of treatment (% of patients): combination group = 1 (4%), monotherapy group = 3 (13%); NS

Histological

- 34 patients (18 combination, 16 monotherapy) underwent second biopsy. No significant changes in HAI for either group

Safety

- There were no withdrawals due to serious adverse events. Adverse events included: flu-like symptoms, myalgia, weakness, dyspepsia, insomnia, pruritus, irritability, diarrhoea, weight loss, depression, anaemia (haemoglobin < 12 g/dl)
- Decrease in mean haemoglobin levels ($p = 0.0000$) for combination group compared with monotherapy group

Comments

- Allocation to treatment groups: patients randomised using a computer program
- Comparability of treatment groups at pre-treatment: baseline characteristics between two groups similar (no significant differences)
- Blinding: independent observer for analysis of liver biopsy
- Method of data analysis: ITT used
- Statistical power calculation: stated that sample group needed to be 120 for detection of statistical significance. Study was discontinued 15 months after start due to poor recruitment of patients
- Attrition/drop-out: two patients withdrew from treatment in combination group due to poor compliance and three patients in the monotherapy group were lost to follow-up
- Jadad checklist score: 2/5
- Monitored for adverse events, haematological and biochemical parameters monthly during treatment (6 months) and during follow-up (6 months); serum HCV-RNA extracted at baseline, end-of-treatment and 6 months after cessation of treatment

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Barbaro *et al.*, 1999[54] Multicentre, randomised trial No funding support stated	(i) 3 mU IFN 3x a week plus 1000–1200 mg 3x a day ribavarin for 24 weeks (n = 200) (100 non-responders; 100 relapsers) (ii) 6 mU IFN 3x a week for 24 weeks (n = 200) (100 non-responders; 100 relapsers) 24 weeks of treatment with 24 weeks of follow-up	N = 400 adults (non-responders and relapsers) 179 of combination group and 189 patients in monotherapy group completed the trial (ITT used)	Primary • Sustained response at end-of-treatment response and end of follow-up (no detectable HCV-RNA; normal serum ALT concentrations) Secondary • Improvement of histological activity in patients responding to treatment (HAI) • Safety: biochemical and haematological

Results

Sustained response at end of follow-up (non-responders)
- Combination = 14% monotherapy = 1% ($p < 0.001$)

Sustained response at end of follow-up (relapsers)
- Combination = 30% monotherapy = 5% ($p < 0.001$),

Response at end of treatment (non-responders)
- Combination = 21% monotherapy = 5% ($p = 0.001$)

Response at end of treatment (relapsers)
- Combination = 39% monotherapy = 9% ($p = 0.001$)

Histological
- Among responders (at end of treatment), 18 (86%) of 21 non-responders in the combination and two of five non-responders in the monotherapy group had improved HAI scores. 28 (72%) of 39 relapsers in the combination group and four of nine relapsers in the monotherapy group had improved HAI scores. No significant changes in HAI were observed between end-of-treatment and follow-up

Safety
- Flu-like symptoms in 68% of combination group (57 non-responders and 79 relapsers) and 61% (57 non-responders and 68 relapsers). Anaemia reported in 84% of the combination group (no breakdown reported)

Comments
- Allocation to treatment groups: computer-generated block-randomised assignment to treatment groups from university coordinating centre
- Comparability of treatment groups at pre-treatment: baseline characteristics between two groups similar, with the exception of ALT levels for non-responders/monotherapy group lower than for other treatment groups (no significance calculation performed)
- Blinding: results analysed in a blinded fashion by independent investigator (steps taken to ensure blinding of patient results)
- Method of data analysis: ITT (if no follow-up information the patient was considered to have no change from previous assessment)
- Statistical power calculation: stated (needed 100 patients per group for 80% power at 5% significance level).
- Attrition/drop-out: 21% patients receiving combination therapy (seven non-responders, six relapsers and eight during follow-up; no information provided on whether non-responders or relapsers) withdrew from the study due to adverse events or intolerance to treatment; 11% patients receiving monotherapy (five non-responders, six relapsers) withdrew due to refusal to continue treatment
- Jadad checklist score: 3/5 (2/5? withdrawals)
- HCV-RNA and ALT levels monitored at baseline, weeks 12, 24 and 48. Liver biopsy performed at baseline and weeks 24 and 48
- Concern for the lack of information regarding treatment adverse effects (number of patients reporting events)

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Salmeron *et al.*, 1999[60] Randomised trial No funding information provided	(i) 3 mU IFN 3x a week plus 600 mg/day ribavirin for 6 months (*n* = 31) (ii) 3 mU IFN 3x a week for 6 months (*n* = 31) 6 months of treatment with 12 months of follow-up	*N* = 62 adults (relapsers and non-responders) 27 of combination group and 28 patients in monotherapy group completed treatment (no ITT analysis; efficacy results based on reduced sample size)	• Sustained response: ALT normalisation during treatment and follow-up • Relapse: ALT normalised during treatment, increased during follow-up • No response: ALT values remain elevated • Serum HCV-RNA analysed at 12 months, and if negative, PBMC HCV-RNA also analysed • Histological: classified by HAI • Safety: adverse events, biochemical and haematological

Results

Sustained response
- Combination = 2 (7%); monotherapy = 2 (7%)

NS (no value given)

Relapse
- Combination = 16 (59%); monotherapy = 11 (39%)

NS (no value given)

No response
- Combination = 9 (34%); monotherapy = 15 (54%)

NS (no value given)

Histological
- Post-treatment liver biopsy evaluation revealed minimal lesions for two patients with negative serum HCV-RNA and PBMC HCV-RNA.

Safety
- Adverse events included: pseudo-influenza symptoms (combination = 19 patients, 61%; monotherapy = 18 patients, 58%), somnolence (combination = 2; monotherapy = 1); weight loss (combination = 3; monotherapy = 1); diarrhoea (combination = 1); alopecia (combination = 2); anxiety/depression (combination = 2; monotherapy = 1); tachycardia (combination = 2)
- Slight decrease in mean haemoglobin levels ($p < 0.005$) for combination patients compared with monotherapy patients in first month of treatment

Comments
- Allocation to treatment groups: patients randomly divided into two groups
- Comparability of treatment groups at pre-treatment: baseline characteristics between two groups similar (no significant differences)
- Blinding: no information provided
- Method of data analysis: ITT not used
- Statistical power calculation: not stated
- Attrition/drop-out: three patients withdrawn from therapy due to adverse events; one from combination (fever/severe asthenia) and two from monotherapy group (tachycardia and elevated free T3 values). Two patients from each group withdrew from trial voluntarily
- Jadad checklist score: 2/5
- Monitored for adverse events, haematological and biochemical parameters monthly during treatment (6 months) and months 7, 9, 12 and 18 after therapy. Serum and peripheral HCV-RNA extracted at baseline and at 12 months
- Concern that the study did not include an ITT analysis

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Reichard *et al.*, 1998[59] Randomised, double-blind, placebo-controlled trial Supported by Schering-Plough	(i) 3 mU IFN 3x a week plus 1000–1200 mg ribavirin 3x a day for 24 weeks (*n* = 50) (ii) 3 mU IFN 3x a week plus placebo for 24 weeks (*n* = 50) 24 weeks of treatment with follow-up at 24 weeks and 1 year	*N* = 100 adults (no previous treatment) 43 of combination group (nine reduced dose) and 47 patients in placebo group (three reduced dose) completed treatment (ITT used)	Primary • Virological: no detectable HCV-RNA by PCR Secondary • Biochemical: serum ALT concentrations • Histological: grade (inflammation) and stage (fibrosis) ranked on a scale • Safety: biochemical, haematological, patient history and physical examination (compliance by history and pill count)

Results

Virological sustained response
- Combination = 18 (36%); placebo = 9 (18%)

$p = 0.047$

Biochemical sustained response
- Combination = 22 (44%); placebo = 12 (24%)

NS ($p = 0.057$)

Virological end-of-treatment response
- Combination = 26 (52%); placebo = 26 (52%)

NS

Biochemical end-of-treatment response
- Combination = 33 (66%); placebo = 28 (56%)

NS

- Four patients (three combination and one placebo) were HCV-RNA-negative at week 48 (not classified as sustained response as not HCV-RNA-negative at end of treatment). At 1 year after treatment all of these patients were HCV-RNA-negative/ALT normal (therefore could be classified as sustained response).

Histological
- No difference in histological improvement between the two groups. Mean grade score decreased significantly for both groups ($p < 0.001$); mean stage score did not change in either group
- Low baseline viral load predictive of sustained response in placebo group ($p = 0.008$); no baseline factor predictive for combination group. Patients with genotype 3a were more likely to have sustained virological response than other genotypes, particularly among combination-treated patients

Safety
- Fatigue most common adverse event (combination = 90%; placebo = 78%). Nausea significantly ($p = 0.02$) more common in combination group (34%) than placebo group (12%). Other adverse events included: headache, myalgia, arthralgia, fever, vertigo, abdominal pain, anorexia, depression, irritability, insomnia, alopecia, pruritus, coughing, hypothyroidism and hyperthyroidism and did not differ between the two groups (data not provided)

Comments
- Allocation to treatment groups: randomly generated numbers distributed in blocks of ten (in sealed envelopes) to study centres (five university hospitals in Sweden) from a central pharmacy
- Comparability of treatment groups at pre-treatment: baseline characteristics between two groups similar (no significant differences)
- Blinding: randomisation code not broken until the end of follow-up (liver biopsy investigator blinded to treatment response or allocation or to timing of the biopsy)
- Method of data analysis: ITT (patients who discontinued treatment or were lost to follow-up were classified as non-responders to allow for a 20% drop-out rate)
- Statistical power calculation: stated (needed 100 patients for 80% power at 5% significance level)
- Attrition/drop-out: 10% patients withdrew from the trial. Seven from the combination group (three depression, one anaemia, three lost to follow-up) and three from the placebo group (two depression and one intravenous drug user). 12 patients continued treatment at a reduced dose: nine in the combination group (seven depression, one low neutrophil count, one low Hb level); three in the placebo group (low neutrophil count)
- Jadad checklist score: 5/5
- Clinical and laboratory assessments every 4 weeks during treatment and follow-up. Liver biopsy taken within 12 months of enrolment in the study and at week 24
- Concern for the lack of information regarding treatment adverse effects (number of patients reporting events)

continued

TABLE 11 contd *Details of RCTs*

Study	Intervention	Subjects	Outcome measures
Sostegni *et al.*, 1998[61] Randomised trial No funding support stated	Three groups: (i) Group 1: 1000 mg ribavirin 3x a day for 6 months, then 3 mU IFN 3x a week for 6 months (n = 33) (ii) Group 2: 3 mU IFN 3x a week plus 1000 mg ribavirin 3x a day for 6 months (n = 33) (ii) Group 3: 3 mU IFN 3x a week for 6 months (n = 30) Groups 2 and 3, 6 months of treatment with 6 months of follow-up. Group 1, 12 months of treatment with 6 months of follow-up	N = 96 adults (non-responders previously received minimum dose of 9 mU/week IFN for minimum of 12 weeks) Two patients in Group 1 did not receive therapy (not included in ITT analysis). 83 patients completed the trial (Group 1 = 29; Group 2 = 29; Group 3 = 28). Six patients in Group 1 and eight patients in Group 2 received reduced doses of ribavirin (due to hemolytic anaemia)	• Efficacy: plasma HCV-RNA and serum ALT levels • Safety: recording adverse events and periodic biochemical and haematological tests • Histology: HAI grading and staging scores

Results

HCV-RNA-negative (end of treatment)
- Group 1 = 4 (12%); Group 2 = 9 (27%); Group 3 = 2 (7%)

NS between groups; NS in mean viraemic levels between the groups at end of treatment or follow-up

HCV-RNA-negative (end of follow-up)
- Groups 1 and 3 = 0; Group 2 = 5 (15%; p = 0.02)

Normal ALT levels at end of follow-up
- Group 1 = 3 (10%), Group 2 = 13 (41%), Group 3 = 5 (17%)

p = 0.008 for difference between Group 2 and Groups 1 and 3

Normal ALT levels at end of follow-up
- Group 2 = 4 (12.5%)

p = 0.03 for difference between Group 2 and Groups 1 and 3

Mean ALT levels at end of treatment
- Significantly reduced in Group 2 compared with Groups 1 and 3 at end of treatment

p = 0.01; and at follow-up, p = 0.007

Histological
- 28 included in analysis (second biopsy; Group 1 = 8, Group 2 = 12, Group 3 = 8). Significant reduction in necroinflammatory scores for Group 2 compared with Groups 1 and 3 (p = 0.03). No significant differences between groups for staging scores
- Low viral load at baseline and a history of blood transfusions correlated with sustained response for patients in Group 2

Safety
- Anaemia only significant difference between groups with regards to adverse events (no significance level provided)

Comments
- Allocation to treatment groups: randomly assigned by computer coding
- Comparability of treatment groups at pre-treatment: no significant differences in baseline characteristics between groups (significance levels not provided)
- Blinding: results analysed in a blinded fashion by independent investigator (steps taken to ensure blinding of patient results)
- Method of data analysis: ITT (concern that two patients were randomised but were not included in ITT as they received no treatment)
- Statistical power calculation: not stated
- Attrition/drop-out: five (16%) patients in Group 1, three [4 – p.345] (9%) patients in Group 2, and two (7%) patients in Group 3 withdrew due to adverse events. Reasons for withdrawal were: Group 1 = two severe depression (IFN treatment) and one haemolytic anaemia, one abdominal pain, one pruritus (ribavirin treatment); Group 2 = two headache, one severe depression, one ischaemic cardiac episode due to low haemoglobin; Group 3 = one headache, one myalgias
- Jadad checklist score: 3/5
- ALT levels monitored at baseline and monthly thereafter (during both treatment and follow-up). HCV-RNA measured at baseline, end of treatment and end of follow-up. Liver biopsy was taken within 6 months of study entry and at the end of follow-up (if patient consented)
- Concern for the lack of information provided regarding type of adverse events and frequency (only anaemia reported and reasons for withdrawals)
- Difference in reporting of withdrawals due to adverse events. p.344 states ten patients withdrew, p.345 states 11 patients withdrew (this does not include the two patients who were randomised but not included in the analysis as they did not receive treatment)

ITT, intention to treat; HAI, hepatitis activity index

TABLE 12 *Details of systematic reviews and meta-analysis*

Study	Intervention	Subjects	Outcome measures
Poynard *et al.*, 2000[51] Pooled data from: Poynard *et al.*, 1998[50] and McHutchison *et al.*, 1998[49]	(i) IFN alfa plus ribavirin 48 weeks (*n* = 505) (ii) IFN alfa plus ribavirin 24 weeks (*n* = 505) (iii) IFN alfa plus placebo for 48 weeks (*n* = 503) (iv) IFN alfa plus placebo 24 weeks (*n* = 231)	*N* = 1744 treatment-naïve patients	HCV-RNA by PCR

Results

End of treatment virological response
- Combination (24 weeks) = 278 (55%)
- Combination (48 weeks) = 260 (51%)
- Monotherapy (24 weeks) = 66 (29%)
- Monotherapy (48 weeks) = 147 (29%)

Sustained virological response
- Combination (24 weeks) = 166 (33%)
- Combination (48 weeks) = 205 (41%)
- Monotherapy (24 weeks) = 13 (6%)
- Monotherapy (48 weeks) = 82 (16%)

Five factors are associated with reduction of HCV-RNA (< 100 copies/ml)
- genotypes 2 or 3
- baseline viral load < 3.5 million copies/ml;
- no or portal fibrosis
- female gender
- age younger than 40 years

- For combination patients, 41% were PCR-positive at 24 weeks, while 59% were PCR-negative
- Among patients receiving combination therapy, and for whom there was a negative PCR at 24 weeks treatment there was a sustained response for 59% (24 weeks), and for 74% (48 weeks)
- Patients who test PCV-negative at 24 weeks and have less than four favourable factors should **continue** for another 24 weeks. Those with four or five factors can **stop** treatment
- Patients who test PCV-**positive** at 24 weeks should **stop** treatment
- Reliance upon just the genotype as a factor in whether to continue or stop treatment is not satisfactory. All five independent predictive factors must be taken into account
- For patients who fail to respond at 24 weeks there may be an argument for treatment continuation on the grounds that interferon and ribavirin have antifibrotic and immunomodulatory effects as well as antiviral properties, and thus may reduce histological damage
- For those subgroups for whom there is a high probability of non-response, stopping treatment at 12 weeks is not recommended. There was a sustained response in 10% of patients who had a positive PCR at 12 weeks (in the 48-week regimen)
- Interferon monotherapy should only be offered to patients to whom combination therapy is contraindicated

Comments
- The review addressed four focused questions: (i) What factors are associated with favourable viral response? (ii) When is it useful to test HCV-RNA? (iii) Is there a subgroup of patients with several favourable response factors who still could be treated by interferon monotherapy? (iv) Do the therapeutic recommendations of the recent international consensus need to be revisited after using this database?
- Individual patient data obtained from two RCTs were used for this analysis and was entered into a database
- The two trials are of similar design, length and outcomes

continued

TABLE 12 contd *Details of systematic reviews and meta-analysis*

Study	Intervention	Subjects	Outcome measures
Schlam *et al.*, 1999[47] Meta analysis of individual patient data from six RCTs of combination therapy conducted between 1991 and March 1998[41,43,44,57,59,71,72]	(i) 3 mU of IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 6 months (*n* = 197) (ii) 3 mU of IFN alfa 3x a week plus 1000–1200 mg/day ribavirin for 6 months (*n* = 147) 6 months' follow-up	*N* = 344 adults naïve/relapsers/non-responders Mean age = 45 years	• HCV-RNA • ALT levels 'Sustained response' is defined as normal ALT level and undetectable HCV-RNA by reverse transcriptase-PCR at end of therapy and at 6 months after therapy, respectively

Results

Sustained response rates (all patients)
- Combination: 56/197 (28%); monotherapy: 14/147 (9%)

Sustained response rates (cirrhosis patients only)
- Combination: 9/51 (18%); monotherapy: 0/24 (0%)

- In **non-cirrhosis patients** sustained response rates were significantly higher among those treated with combination therapy than those treated with monotherapy: three-fold for previously untreated patients (combination therapy: genotype 1, 33%, genotype 2/3, 65%; monotherapy: genotype 1, 8%, genotype 2/3, 24%)
- In **cirrhosis patients** sustained response rates with combination therapy (previously untreated: genotype 1, 33%, genotype 2/3, 24%) were also significantly higher than those with monotherapy (previously untreated: genotype 1, 1%, genotype 2/3; 5%)
- Multivariate analysis found that previous interferon non-responders had a lower chance of a sustained response than previously untreated patients or relapsers
- 58% of patients had genotype 1; 37% had genotype 2 or 3; 4 % had other
- 22% of patients had cirrhosis
- 81% completed the course; 12% needed reductions of doses

Comments
- Comparability of treatment groups at pre-treatment: generally equivalent except for presence of cirrhosis, which was higher among combination patients ($p = 0.03$) and there were more non-responders to previous IFN treatment in the combination group
- Method of data analysis: ITT and per-protocol basis
- Attrition/drop-out: data were not available for 27 (8%) patients (this constitutes the per protocol analysis)
- The trials were performed in different parts of the world. No effect of study centre on sustained response rate could be detected
- Trials were identified by screening the abstracts of major liver meetings in Europe up to 1997. No other sources (e.g. electronic databases) are mentioned
- Data were submitted by investigators from participating centres on a one-page case record form per patient. These were checked and where necessary returned to the local investigators for correction

Appendix 3

Conference abstracts of trials of combination therapy

TABLE 13

Study	Intervention	Design	Patients
Clarkston *et al.*, 1998[73]	(i) 5 mU IFN alfa 3 x a week plus 1000 mg/day ribavirin (ii) 3 mU IFN alfa 3 x a week plus daily placebo	RCT	*n* = 15 Non-responders/relapsers
Gish *et al.*, 1998[74]	(i) IFN alfa daily for 1 month then 3 x a week for 1 year plus ribavirin (ii) IFN alfa daily 3 x a week for 1 year plus ribavirin	RCT	*n* = 348 Non-responders/relapsers
Sarabanchong *et al.*, 1998[75]	(i) 3 mU IFN alfa 3 x a week plus 1000–1200 mg ribavirin (ii) 3 mU IFN alfa 3 x a week plus placebo 1000–1200 mg/day	RCT	*n* = 111 Non-responders/relapsers
Waters *et al.*, 1998[76]	(i) IFN alfa plus ribavirin (ii) IFN alfa plus placebo	RCT	*n* = 329 Non-responders/relapsers
Berg *et al.*, 1998[77]	(i) 6 mU IFN alfa 3 x a week plus 14 mg/kg/day ribavirin (ii) 6 mU IFN for 12 weeks then 3 mU IFN alfa for 40 weeks (responders only)	RCT	*n* = 185 Treatment-naïve
Wood *et al.*, 1998[78]	(i) 10 mU IFN alfa daily for 10 days then 5 mU daily for 74 days then 5 mU 3 x a week for 24 weeks (ii) As above with addition of 1000 mg ribavirin at day 11	RCT	*n* = 26 Non-responders
Min *et al.*, 1998[79]	(i) 3 mU IFN alfa plus 1000–1200 mg ribavirin (ii) 5 mU IFN alfa plus 1000–1200 mg ribavirin	RCT	*n* = 155 Non-responders/relapsers
Herrine *et al.*, 1998[80]	(i) 3 mU IFN alfa plus 1000–1200 mg ribavirin (ii) 5 mU IFN alfa plus 1000–1200 mg ribavirin	RCT	*n* = 79 Non-responders/relapsers
Bacon *et al.*, 1998[81]	(i) 3 mU IFN alfa plus 10000–1200 mg ribavirin, for 24 weeks (ii) 3 mU IFN alfa plus 1000–1200 mg ribavirin, for 48 weeks	RCT	*n* = 132 Non-responders
Bernstein *et al.*, 1998[82]	(i) 5 mU IFN alfa 3 x a week plus 600 mg/day ribavirin for 6 months followed by IFN alfa for 6 months (ii) 5 mU IFN alfa 3 x a week plus 1000 mg/day ribavirin for 6 months followed by IFN alfa for 6 months	RCT	*n* = 58 Non-responders/relapsers
Cheinquer *et al.*, 1998[83]	(i) 3 mU IFN alfa 3 x a week (ii) 3 mU IFN alfa 3 x a week plus 1000 mg/day ribavirin	possibly CCT	*n* = 34
Tripi *et al.*, 1998[84]	(i) Ribavirin alone 1000–1200 mg/day for 6 months (ii) 6 mU IFN alfa 3 x a week plus 1000–1200 mg/day ribavirin (6 months)	possibly CCT	*n* = 43 Non-responders
Ascione *et al.*, 1998[85]	(i) 6 mU IFN alfa 3 x a week for 6 months (ii) 6 mU IFN alfa 3 x a week plus 1000 mg/day ribavirin for 6 months	RCT	*n* = 20 Non-responders
Chemello *et al.*, 1998[43]	(i) 6 mU IFN alfa 3 x a week for 6 months (ii) 6 mU IFN alfa 3 x a week plus 800–1200 mg/day ribavirin for 6 months	RCT	*n* = 100 Relapsers/non-responders
de Bac *et al.*, 1998[86]	(i) 3 mU IFN alfa 3 x a week for 12 months (ii) 6 mU IFN alfa 3 x a week plus 1000–1200 mg/day ribavirin for 12 months	possibly CCT	*n* = 62 Non-responders
de Ledinghen *et al.*, 1998[87]	(i) 6 mU IFN alfa 3 x a week for 24 weeks then 3 mU 3 x a week for 24 weeks (ii) 6 mU IFN alfa 3 x a week for 24 weeks then 3 mU 3 x week for 24 weeks plus 1000 mg/day ribavirin for 48 weeks (iii) 3 mU IFN alfa daily for 24 weeks then 3 mU 3 x a week for 24 weeks plus 1000 mg/day ribavirin for 48 weeks	RCT	*n* = 390 Non-responders

CCT, controlled clinical trial

Appendix 4

Methodological quality of RCTs of combination therapy (from 1998 onwards)

TABLE 14

	Blinding of outcome assessors	Equivalent groups at baseline	Method of randomisation/ concealment	Data analysis method	Power calculation	Drop-out from treatment *n* (%)	Loss to follow-up *n* (%)	Jadad score (out of 5)
Davis *et al.*, 1998[48]	Yes	Yes	Central computerised stratified randomisation	Not ITT	Not stated	19 (5)	Not stated	4
Poynard *et al.*, 1998[50]	Yes	Yes	Central randomisation, balanced and stratified	ITT only in sensitivity analysis	Stated	60 (7)	Pateients with no follow-up HCV-RNA data classified as non-responders	4
McHutchison *et al.*, 1998[49]	Yes	Yes	Not Stated	Not ITT	Stated	140 (15)	Not stated	3
Andreone *et al.*, 1999[52]	Yes	Yes	Computer-generated randomisation	ITT	Stated	2 (4)	3 (6)	2
Milella *et al.*, 1999[57]	Not stated	Yes	Not stated	ITT*	Not stated	Not stated	Not stated	2
Barbaro *et al.*, 1999[54]	Yes	Yes (apart from one measure)	Block randomisation by computer	ITT	Stated	24 (6)	8 (2)	3
Salmeron *et al.*, 1999[60]	Not stated	Yes	Not stated	Not ITT	Not Stated	5 (8)	Not stated	2
Pol *et al.*, 1999[58]	Yes	Yes	Not stated	Not clear	Not stated	16 (12)	Not stated	2
Bell *et al.*, 1999[55]	Not stated	Yes (apart from one measure)	Statification	ITT	Not stated	8 (15)	Not stated	3
Reichard *et al.*, 1998[59]	Yes	Yes	Block random-isation (sealed envelopes) from central pharmacy	ITT	Stated	7 (7)	3 (3)	5
Barbaro, 1998[53]	Yes	Yes (apart from one measure)	Block randomisation by computer	ITT	Stated	13 (4.2)	9 (3)	3
Sostegni *et al.*, 1998[61]	Yes	Yes	Computer-generated randomisation	ITT	Not stated	10 (10.4)	Not stated	3

* *Not stated whether ITT analysis was conducted, but no attrition is reported, thus all randomised patients are assumed to be included in the analysis*
Note:The study by El-Zayadi et al., *1999[56] was not tabulated as the full paper was not available to the review team during the production of the report*

Appendix 5

Subsequent meta-analysis

Following the submission of this report, NICE requested a meta-analysis of randomised trials of combination therapy for hepatitis C. The main outcome measure used was sustained complete response indicated by the disappearance of HCV-RNA from the bloodstream, maintained for at least 6 months after cessation of 24 weeks/6 months of treatment. Nineteen RCTs were identified for possible inclusion in the meta-analysis. Four studies were excluded due to failure to report sustained virological response after 24 weeks/6 months of combination therapy.[50,58,60,71] Fifteen studies were included in the meta-analyses.[41,42,44–46,48,49,52–57,59,61]

The Cochrane Review Manager software (RevMan 3.1) was used for the meta-analysis of RCTs. Studies were pooled using a random-effects model, and were subgrouped according to patient group (interferon-naïve, relapsers and non-responders to previous interferon treatment). Data on sustained virological responses after 24 weeks of treatment were computed.

The funnel plot (*Figure 2*) suggests that there is no publication bias.

The results of the meta-analysis suggested that for both previously untreated patients and for those who have relapsed after interferon monotherapy, combination therapy is much more effective than monotherapy for chronic hepatitis C (*Figure 3*). The proportions achieving a sustained response after 24 weeks of treatment were 32% (95% CI, 27 to 37%) for combination therapy and 8% (95% CI, 5 to 11%) for interferon monotherapy in interferon-naïve patients, and 40% (95% CI, 35 to 45%) and 6% (95% CI, 3 to 9%), respectively, in those who had relapsed after previous monotherapy. In those who did not respond to a first course of interferon (non-responders), combination therapy was less effective with rates of 15% (95% CI, 12 to 19%) and 0.8% (95% CI, 0.3 to 2%), respectively.

FIGURE 2 *Funnel plot of trials*

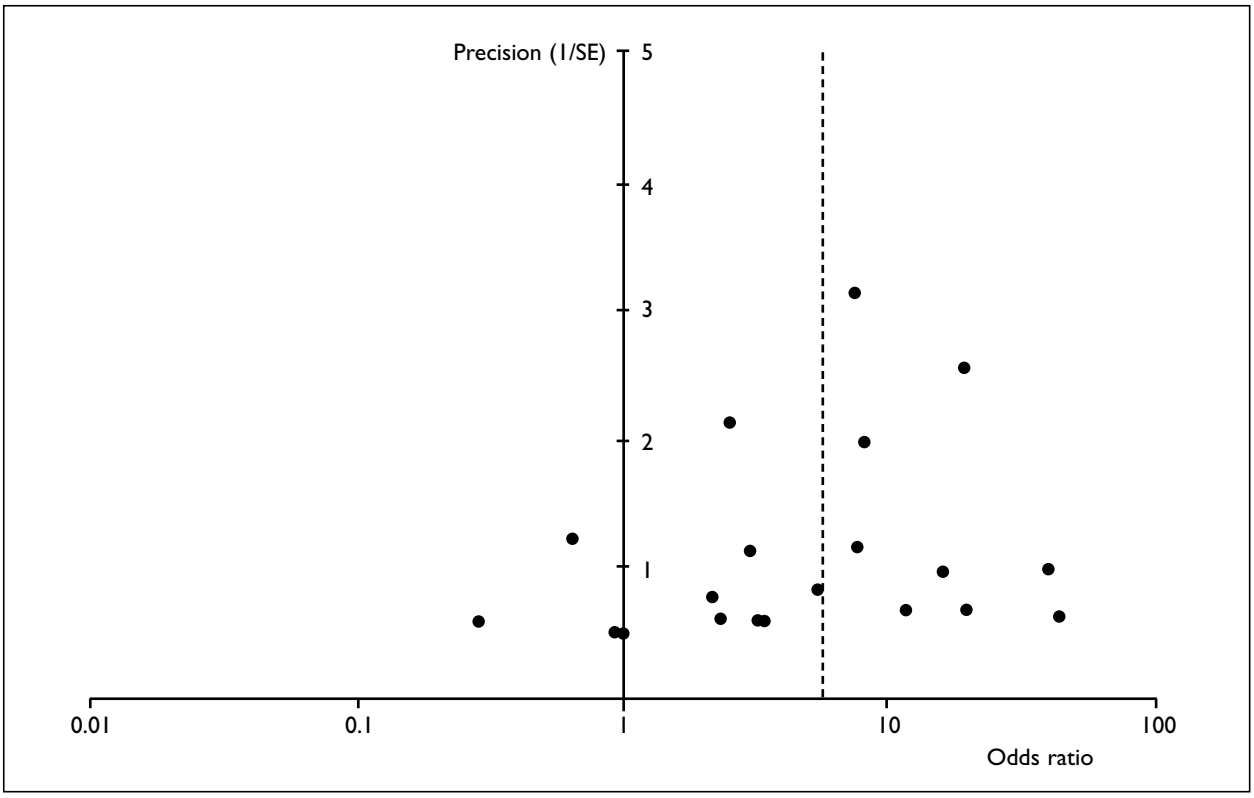
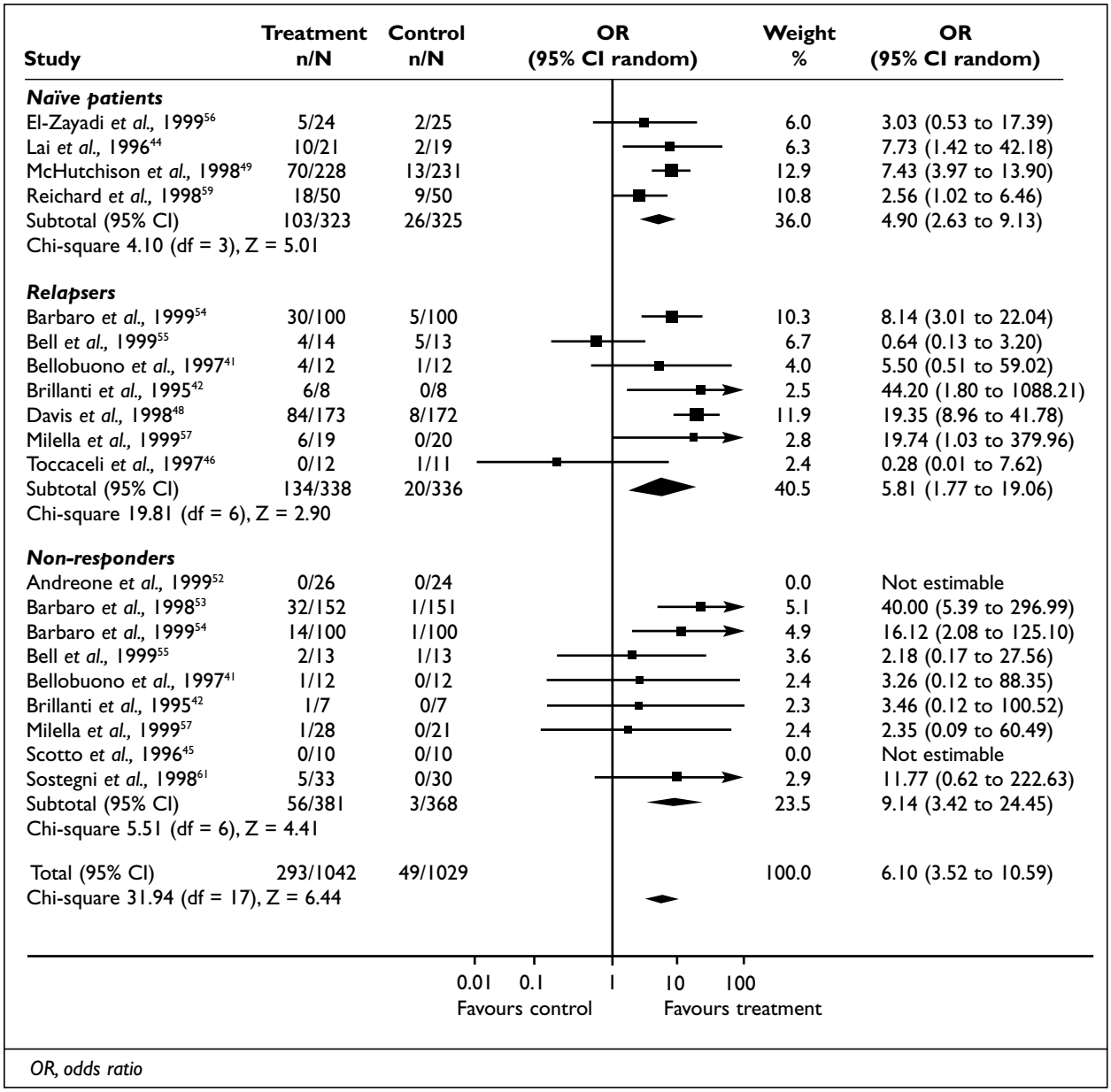


FIGURE 3 *Meta-analysis of RCTs*



OR, odds ratio

Appendix 6

Assumptions of economic analysis model

TABLE 15 *Assumptions used in the base case cost-effectiveness/cost–utility analysis*

Assumptions	Figure	Evidence
Clinical assumptions		
Progression to cirrhosis per annum from HCV	1%	Based on 20% progression over midpoint of 15 years converted to annual rate (Di Bisceglie, 1998[10])
Percentage developing ascites, variceal bleeds, and hepatic encephalopathy from cirrhosis	1.6%	Clinical consensus
Annual death rate from hepatic encephalopathy, ascites and variceal bleeds	75.0%	Clinical consensus
Percentage requiring transplant from complex cirrhosis states	1%	Clinical consensus
Remain in cirrhotic state without complications	93.8%	Clinical consensus
Progression to hepatic carcinoma per annum from cirrhosis	1.4%	Based on Di Bisceglie, 1998[10]
Death rate per annum following HCC diagnosis	80%	Cancer registry
Age at diagnosis	36 years	Based on median age data from the Scottish Centre for Infection and Environmental Health
Life expectancy in absence of HCV at diagnosis	30 years	Best guess based on acknowledgement of lower life expectancy in groups at risk
Successful transplant (it is assumed that patients do not re-enter the model after transplant)	90%	Clinical consensus
Require second transplant	10%	Clinical consensus
Compliance	100%	Based on approximately 95% compliance rate in Barbaro *et al.,* 1998.[53] This represents the population that actually commence treatment. Expert opinion suggests that in Glasgow, an area with a high prevalence of injecting drug users, only approximately 50% of patients will attend initial clinic assessment, and only 25% of those initially found positive at screening will begin treatment
Economic assumptions		
Unit costs		
Cost of attendance at general practice	£16	Unit cost for 1998/99, from Netten *et al.,* 1999[88]
Average cost outpatient visit to general medicine	£63	Unit cost for 1996/97 inflated using the Hospital and Community Health Services pay and prices index, from Netten *et al.,* 1999[88]
Average cost per inpatient day in general medical ward	£222	Unit cost for 1996/97 inflated using the Hospital and Community Health Services pay and prices index, from Netten *et al.,* 1999[88]
Cost per 200 mg capsule of ribavirin (Rebetol™)	£3.52	BNF 39 March 2000
Cost per 3 mU vial IFN alfa 2b (Intron A™)	£16.20	BNF 39 March 2000*

continued

TABLE 15 contd *Assumptions used in the base case cost-effectiveness/cost–utility analysis*

Assumptions	Figure	Evidence
Resource costs		
Annual average cost with HCC based on 60 inpatient days in general medicine	£13,320	Duration of stay based on clinical opinion
Annual average cost with cirrhosis based on three outpatient visits and three general practice visits	£237	Frequency of visits based on clinical opinion
Annual average cost associated with chronic HCV infection	£95	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	£10,878	Duration of stay based on clinical opinion
Annual average cost associated with hepatic encephalopathy based on 49 inpatient days in general medicine	£10,878	Duration of stay based on clinical opinion
Annual average cost associated with variceal bleeds based on 14 inpatient days in general medicine	£3108	Duration of stay based on clinical opinion
Cost of liver transplant and follow-up care	£46,551	National contract cost
Four weekly drug costs IFN alfa (3 mU 3x a week)	£194.40	BNF (39) March 2000
Four weekly drug costs ribavirin	£543.40	BNF (39) March 2000
Discount rate for costs and benefits	6%	Treasury discount rates

HCC, hepatocellular carcinoma
**The BNF price for interferon alfa has not changed since 1997*

TABLE 16 *Utilities used in the cost–utility analysis (from published literature)*[62–64,89]

	Utilities
Drug treatment	1.00
Chronic hepatitis	0.95
Cirrhosis	0.80
Ascites	0.50
Hepatic encephalopathy	0.50
Variceal bleeds	0.50
Liver transplant	0.80
HCC	0.25

Appendix 7

Costs of investigation and monitoring of patient with chronic hepatitis C

These costs come from the Aberdeen Royal Hospital Trust HCV working group, the SHPIC Costing Unit, and the Scottish Health Service Costs.[90] They mostly relate to Aberdeen and, where available Dundee. Unit costs pertaining to the UK as a whole are also provided.[88] There will be some variation in timing and nature of investigations requested. These are presented to allow an estimate of approximate costs and facilitate comparison with individual Health Authority data.

TABLE 17 *Evaluation of a new patient with confirmed HCV*

Item	Aberdeen costs (£)	Dundee costs (£)
Outpatient appointment (Generic)*	63.00	
HCV qualitative PCR†	6.85	
HBV (HBsAg and anti-core, if both negative)	15.90	9.00
Liver function tests, ALT	6.85	3.00
Alpha-fetoprotein	7.20	4.30
TSH, free T4	8.30	5.50
Full blood count	4.00	3.80
Prothrombin time, APITT (coagulation screen)	6.00	
Autoantibodies	10.00	
Immunoglobulins	8.83	7.00
Ferritin	6.00	7.00
Ultrasound scan of the liver	44.00	52.75
Total	186.93	

**Cost of hospital generic outpatient appointment (from Netten* et al., *1999[88])*
†Qualitative PCR in Glasgow is £25 and Edinburgh £35, transport cost negligible

TABLE 18 *Further investigations of a patient with HCV considered for treatment*

Item	Aberdeen costs (£)	Dundee costs (£)
Overnight hospital admission*	249.00	
HCV quantitative PCR†	86.05	
HCV genotype	15.00	
HIV (if screen negative)	8.70	6.00
Liver biopsy (except haematology patients)	40.00	
Total	398.75	

**Average costs per day for major Scottish teaching hospitals £249, range £214–313. Scottish Health Service Costs (1998)[90]*
†The cost of quantitative PCR in Edinburgh reference laboratory is £60. These require transport with dry ice by courier. Aberdeen costs include cost of dry ice and transport. This is relevant to any health authority/board without easy access to reference laboratory

TABLE 19 *Monitoring during active treatment with alpha-interferon (3 months)*

Item	Aberdeen costs (£)	Dundee costs (£)
Three outpatient appointments*	189.00	
HCV qualitative PCR	6.85	
Eight full blood counts	32.00	30.40
Three ALT	19.50	9.00
Three urea and electrolytes	18.30	11.25
TSH	8.30	5.50
Total	273.95	

**Cost of hospital generic outpatient appointment (from Netten* et al., *1999[88])*

TABLE 20 *Monitoring during alpha-interferon treatment (1 year)*

Item	Aberdeen costs (£)	Dundee costs (£)
Overnight hospital admission*	249.00	
12 outpatient appointments† (@63.00 each)	756.00	
Full blood count x 17	68.00	64.60
ALT x 12	78.00	36.00
TSH x 2	16.60	11.00
Qualitative PCR x 2	13.70	
Alpha-fetoprotein x 2	14.40	8.60
Liver biopsy	40.00	
Ultrasound of liver	44.00	52.75
Total	1279.70	

**Average costs per day for major Scottish teaching hospitals £249, range £214–313. Scottish Health Service Costs (1998)[90]*
†Cost of hospital generic outpatient appointment (from Netten et al., *1999[88])*

TABLE 21 *Surveillance of patients failing, refusing or unsuitable for treatment*

Item	Aberdeen costs (£)	Dundee costs (£)
Three outpatient appointments*	189.00	
Three ALT per year	19.50	9.00
Three Alpha-fetoprotein per year	21.60	12.90
Prothrombin time once a year	6.00	
Ultrasound of liver	44.00	52.75
Total	£287.09	

* *Cost of hospital generic outpatient appointment (from Netten* et al., *1999[88])*

Note: the costs of investigations pre-treatment and monitoring during and after treatment would be unchanged if combination interferon alfa and ribavirin were used.

TABLE 22 *Surveillance of patients following response after1 year of treatment completed (per year)*

Item	Aberdeen costs (£)	Dundee costs (£)
One outpatient appointment*	65.33	
Two ALT	13.00	6.00
Qualitative HCV-PCR†	6.85	
Prothrombin time	6.00	
Ultrasound of liver	44.00	
Total	£135.18	

* *Cost of hospital generic outpatient appointment (from Netten* et al., *1999[88])*
† *Qualitative PCR in Glasgow is £25 and Edinburgh £35, transport cost negligible*

Appendix 8

Chronic hepatitis C – natural history

We need data on the natural history of untreated hepatitis C to provide a baseline for estimating the relative cost-effectiveness of the various treatment options. There are several problems.

The first problem is that it is a relatively new disease, in the sense that the virus was not identified until 1989.[91] However, as HCV seems to have been responsible for about 95% of cases of so-called "non-A, non-B" hepatitis, it can be used as a reasonably accurate proxy.

The second problem is that because most people have no acute illness at onset, the date of onset and hence the duration of disease is often uncertain. However, there have been a number of unfortunate events involving contamination of blood or blood products, which have led to several outbreaks with a point source, allowing accurate analysis by duration.

This leads to the third problem – 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, we need to make a number of assumptions in the economic model, to do with progression from one disease stage to another, both in terms of numbers who progress, and time taken to progress. *Figure 1* (page 13) showed an outline of progression pathways. The group that most concerns us is patients who develop the more serious consequences of HCV such as decompensated cirrhosis and hepatocellular cancer, many of whom will die. The concern lies partly with the seriousness of these conditions to patients, and partly because of the potential savings to the NHS if some of these conditions could be avoided. However, the much lesser effect on quality of life in those with mild chronic hepatitis should also be borne in mind, as, although the effect is much smaller, numbers are greater.

Studies used

The natural history has been well reviewed recently by **Seeff**.[13] He notes that the problems of assessing natural history include the following.

- The time of initial infection is often not known – about 60–80% of patients.
- Representative cohorts are needed in order to avoid the bias towards severity that would occur if only patients referred with problems were studied.
- A very long follow-up time is needed because some consequences take decades to manifest.
- There is difficulty in obtaining natural history for recent patients, because of treatment with interferon. (Although most do not respond, the responders may be a group who would have had a better natural history).
- Population control groups are needed, particularly for the assessment of symptoms such as tiredness.

Infection from contaminated blood

Anti-rhesus immunisation

In Ireland in 1977, a batch of anti-D immunoglobulin was contaminated with HCV. **Crowe and co-workers**[92] and **Power and co-workers**[93] followed-up 232 women 17 years' after inoculation. Seventy per cent of the women had no symptoms, and the main symptom in the rest was fatigue. Liver biopsy showed mild or mild/moderate inflammation in 70%, moderate in 24% and severe 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 co-workers[94] studied mortality in men who received clotting factor after the introduction of large pool methods, which replaced treatment by blood transfusion (started in 1969), and which greatly increased the risk of infection. The risk of infection with HCV is close to 100% in this group, dropping to 60% in those who received cryoprecipitate. Darby and co-workers 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, in order to estimate 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[13] summarises the findings of five studies of transfusion-associated HCV infection (Hopf *et al.*,[95] Di Bisceglie,[96] Tremolada *et al.*,[97] Koretz *et al.*,[98] Mattson *et al.*,[99]). There was a range of follow-up intervals of 8–14 years. Cirrhosis had developed in 8–24%; liver cancer was rare; 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 hepatocellular carcinoma were 10 years and 14 years, and 29 years and 28 years, in the studies by Kiyosawa and co-workers[100] and Tong and co-workers,[101,102] respectively.

(In a recent paper on current practice, **Regan *et al.*,**[103] 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.)

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 co-workers**[104] studied a group of 481 blood donors who had anti-HCV antibodies. Eighty-six per cent 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 onset of infection could be made, either because transfusion was the only apparent risk factor, or because intravenous drug abuse 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 this 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.

Cohorts of patients with chronic hepatitis C

Poynard and co-workers[8] studied a French cohort of 2235 patients with liver biopsies, though not all had known date of onset. Estimated duration of infection to cirrhosis was 30 years, ranging from 13 years in men infected over the age of 40 years, to 42 years in women who were infected under the age of 40 years and who did not drink alcohol. The main risk factors for more rapid progression were age, alcohol consumption and male sex. This study is useful for the mix of sources of infection – transfusion 39%, intravenous drug use 25%. There seemed to be no relationship between source of infection and risk of progression.

Fattovich and co-workers[105] from the EUROHEP study (in which St Mary's in London was one of the seven centres) followed 384 patients who had been suffering from compensated cirrhosis for a mean of 5 years. The 5-year risk of decompensation was 18%, and of hepatocellular cancer 7%. The 5-year survival was 91% in all patients, but 50% in those who developed decompensated cirrhosis.

Di Bisceglie[96] reviewed the evidence on the development of hepatocellular cancer, and concluded that there was an incubation period of 2–3 decades between infection and hepatocellular carcinoma, and that it usually followed cirrhosis rather than developing *de novo*. As 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 (i.e. that all progress but at different rates), or whether some would not progress beyond mild disease. **Dienstag**[106] believes that progression is inevitable, but that in some patients it might take up to five decades, with 20% developing end-stage liver disease at some time. **Hoofnagle**[107] 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 need to be treated.

Conclusion

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, alcohol users – are at high risk of progression
- source of infection does not affect 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 intravenous drug users
- 20% will develop cirrhosis by 20 years' duration
- about 2.5% of those with cirrhosis will develop hepatocellular cancer per annum once decompensated cirrhosis or cancer develop, most die within a year (if not given a liver transplant).

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