Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation

D Hartwell,* J Jones, L Baxter and J Shepherd

Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, Southampton, UK

*Corresponding author

Executive summary

Health Technology Assessment 2011; Vol. 15: No. 17
DOI: 10.3310/hta15170

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Background

Chronic infection with the hepatitis C virus (HCV) is a significant public health problem in England and Wales. It is thought that around 0.5% of people aged 15–59 years are chronically infected, although prevalence estimates vary both geographically and in different population groups. Progressive liver disease, as a result of chronic HCV infection, usually develops slowly over 20–50 years and may lead to cirrhosis, hepatocellular carcinoma, liver failure and eventual death. Symptoms are typically mild and non-specific but nevertheless can cause a decrease in quality of life (QoL). Peginterferon alfa and ribavirin combination therapy is currently used in the UK for treatment of chronic HCV, having been recommended by the National Institute for Health and Clinical Excellence (NICE). Successful treatment is considered to be attainment of a sustained virological response (SVR), defined as undetectable serum HCV ribonucleic acid (RNA) 6 months after cessation of treatment. Since these recommendations, there have been extensions to the licences for both peginterferons to allow patients who have a low viral load (LVL) and achieve a rapid virological response (RVR) at 4 weeks' treatment to receive shortened treatment courses; patients who relapsed or did not respond to a previous course of peginterferon alfa combination therapy to undergo a second course; and patients with HCV/human immunodeficiency virus (HIV) co-infection to receive treatment. This review focuses specifically on these new indications.

Objectives

To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa plus ribavirin for the treatment of chronic HCV in three specific patient subgroups: those eligible for shortened treatment courses, those eligible for re-treatment following previous non-response or relapse; and those who are co-infected with HIV.

Methods

Clinical effectiveness

A sensitive search strategy was designed and applied to 14 electronic bibliographic databases (including the Cochrane Library, MEDLINE and EMBASE) from the year 2000 to October 2009. Bibliographies of retrieved papers were screened, key hepatitis C resources and symposia were searched, and experts were also contacted to identify any additional published and unpublished references. Manufacturers' submissions to NICE were also searched.

Titles and abstracts were screened for eligibility by one reviewer. Inclusion criteria were defined a priori and applied independently by two reviewers to the full text of retrieved papers using a standard form. Studies were eligible for inclusion if the participants were adults with chronic HCV, restricted to the patient groups described above. The relevant intervention was peginterferon alfa and ribavirin combination therapy (or monotherapy for those who were unable to tolerate ribavirin) compared with shortened-duration courses of combination therapy (24 weeks for genotype 1, 16 weeks for genotypes 2 and 3) or best supportive care (BSC). The outcomes included measures of virological response during and after treatment, and adverse effects. Only randomised controlled trials (RCTs) were eligible for inclusion.

Data extraction and assessment of methodological quality was undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion at each stage. The trials were reviewed in a narrative synthesis with tabulation of the results of all included studies. A meta-analysis was not undertaken owing to differences in the drug regimens, and because outcome data were based on relatively small subgroups of the randomised patients.

Cost-effectiveness

A systematic review of economic evaluations of peginterferon alfa in the specified patient groups was undertaken using standard methods for evidence synthesis. We adapted our previously published economic model of antiviral treatment for chronic HCV to estimate the cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b in subgroups of adults who were eligible for a shortened duration of treatment with peginterferon alfa; had failed to respond to or had relapsed on previous treatment with peginterferon alfa; or were co-infected with HCV/HIV. The perspective of the cost-effectiveness analysis was that of the UK NHS and Personal Social Services. The short-term outcome of treatment was SVR. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs for each subgroup of patients with HCV. Published QoL weights estimated for a UK trial in patients with chronic HCV were used to derive the quality-adjusted life-years (QALYs) associated with each treatment strategy. Resource use associated with antiviral treatment was estimated from clinical guidelines and advice from clinical practitioners. Drug costs were taken from the *British National Formulary* (No. 58). To estimate costs associated with the management of chronic HCV, values from a UK trial in patients with chronic HCV were used. Costs and benefits were discounted at 3.5%. Uncertainty was explored through probabilistic and deterministic sensitivity analysis.

Results

Clinical effectiveness

A total of 2400 references were identified. Six RCTs (reported in eight publications) were included in the review of clinical effectiveness, all reporting peginterferon alfa and ribavirin combination therapy in patients who were eligible for shortened treatment duration. No RCTs comparing peginterferon alfa with or without ribavirin with BSC were identified for the re-treatment or co-infection populations. Shortened treatment in patients with genotype 1 was evaluated in four trials, genotype 2 in one trial, and genotypes 2 and 3 in one trial. In five of the trials, patients had LVL at baseline (based on mean viral load). Assessment of methodological reporting and quality varied between the included studies but was judged as good overall.

In the subgroup of patients who achieved an RVR and had LVL [< 400,000 international units (IU)/ml or ≤ 800,000 IU/ml] at baseline, SVR rates were comparable between groups who received standard treatment (range 83%–100%) and shortened treatment (range 84%–96%), with no statistically significant differences between groups. Rates were broadly similar regardless of genotype. However, none of the studies was statistically powered for these relatively small subgroups and results should therefore be interpreted with caution.

For both genotype 1 and genotype 2 and 3 patients, there were no statistically significant differences in rates of RVR between treatment groups that received the standard duration of treatment compared with those that received shortened courses. The proportion of patients achieving an RVR was observed to be higher in those with genotypes 2 and 3 than in those with genotype 1.

In the one trial reporting virological relapse rates in the subgroup of patients with an RVR and LVL, rates were low and not significantly different between those treated for 24 versus 48 weeks

(3.6% vs 0% respectively, $p = 1.000$). Adverse events were reported for treatment groups as a whole and the reporting of statistical tests varied. The most frequently occurring adverse events were similar across all of the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia. There was a trend for a lower incidence of adverse events and fewer dose discontinuations in patients receiving a shortened treatment regimen, although on the whole there were no statistically significant differences between treatment arms (where reported). None of the trials measured QoL as an outcome measure.

Cost-effectiveness

The systematic review of cost-effectiveness studies identified two published economic evaluations that met the inclusion criteria, both of which focused on patients co-infected with HCV/HIV. The included economic evaluations used Markov models to extrapolate from SVRs reported in clinical trials to life expectancy and (in one case) quality-adjusted life expectancy gains associated with antiviral treatment strategies for patients who were co-infected with HCV/HIV. Both evaluations indicated that HCV antiviral treatment was associated with gains in life expectancy for HCV/HIV co-infected patients. A systematic search for published studies of QoL found no relevant studies.

Roche submitted a dossier in support of peginterferon alfa-2a combined with ribavirin in three subgroups of patients: shortened duration of treatment for patients with LVL who exhibited an RVR; re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon alfa; and treatment of patients with HCV/HIV co-infection. Roche's base-case results comparing shortened treatment with standard treatment duration indicated positive ICERs of £15,472 per QALY gained for genotype 1 and 4 patients and £2719 for genotypes 2 and 3 with LVL and RVR. For non-responders, comparing re-treatment with BSC, the ICERs were £3334 and £809 per QALY gained for genotypes 1 and 4, and 2 and 3, respectively. Re-treatment with peginterferon alfa dominated BSC in patients who relapsed after previous treatment. Roche reported that, overall in patients co-infected with HCV/HIV, peginterferon dominated non-peginterferon and ribavirin combination therapy.

Schering-Plough submitted a dossier in support of peginterferon alfa-2b combined with ribavirin in two of the three subgroups of patients within the scope of the NICE appraisal: re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon alfa, and treatment of patients with HCV/HIV co-infection. For re-treatment with peginterferon alfa-2b compared with BSC, the overall ICER in non-responders/relapsers was £4387 per QALY gained. In genotypes 1 and 4 the ICER was £7177, and in genotypes 2 and 3 it was £783 per QALY gained. The ICER for peginterferon alfa-2b in HCV/HIV patients compared with BSC was £1637 in genotypes 1 and 4, and £403 in patients with genotypes 2 and 3. The ICER for all patients was £1077.

In our base-case analysis, SVRs for peginterferon alfa-2a from two trials included in our systematic review of clinical effectiveness were used to model cost-effectiveness in genotype 1 patients who were eligible for shortened treatment. The ICERs ranged from £35,000 to £65,000. A further two trials from our systematic review were used to model cost-effectiveness in genotype 2 and 3 patients in this group. In this case, shortened treatment dominated standard treatment duration. For genotype 1 patients with LVL and RVR, shortened treatment duration with peginterferon alfa-2b dominated standard treatment.

In genotype 1 and genotype non-1 patients who were re-treated with peginterferon alfa-2a, the ICERs were £9169 and £2294, respectively. In genotype 1 and 4 patients who were re-treated with peginterferon alfa-2b, the ICER was £7681, whereas re-treatment dominated BSC for genotype 2 and 3 patients. In HCV/HIV co-infected patients receiving peginterferon alfa-2a the ICER was

£7941 per QALY gained in genotype 1 and 4 patients, whereas peginterferon alfa-2a dominated BSC in genotypes 2 and 3. In co-infected patients receiving peginterferon alfa-2b the ICER was £11,806 in genotypes 1 and 4, and £2161 in genotypes 2 and 3.

Discussion

The evidence suggests that patients can receive shorter courses of peginterferon combination therapy without compromising the likelihood of achieving an SVR. However, SVRs according to baseline LVL and RVR were based on subgroups of varying sizes of the randomised patients, and these are likely to be underpowered. The results of the trials in these subgroups should therefore be regarded as speculative.

There is substantial uncertainty over the data used to populate the economic model, with little evidence available to update the model for the subgroups of patients covered by the review.

Conclusions

In summary, the clinical trial evidence indicates that patients may be successfully treated with a shorter course of peginterferon alfa and ribavirin combination therapy for 16 weeks (genotypes 2 and 3), or 24 weeks (genotype 1), without compromising SVR rates. However, the cost-effectiveness analyses indicate that a judgement is required on the value of the QALY loss that may result from adopting shorter treatment duration, if shorter treatment duration is associated with a lower SVR than standard duration. The cost-effectiveness results submitted by the manufacturers and those reported in our independent analysis suggest that treatment with peginterferon alfa in the specified subgroups of patients will yield QALY gains, without excessive increase in costs, and may be cost saving in some situations.

There is a need for further RCT evidence, particularly in people who have not responded to, or who have relapsed following, treatment. Phase II and Phase III trials are currently in progress, evaluating the safety and efficacy of protease inhibitors and nucleoside analogues for treatment-naive and treatment-experienced people with chronic HCV infection.

Funding

The National Institute for Health Research Health Technology Assessment programme.

Publication

Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(17).

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 08/98/01. The protocol was agreed in July 2009. The assessment report began editorial review in December 2009 and was accepted for publication in July 2010. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.