Interferon alfa and ribavirin for the treatment of mild chronic hepatitis C

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation

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Executive summary

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Executive summary

Objective

The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of pegylated interferon alfa (PEG) and non-pegylated interferon alfa (IFN) and ribavirin (RBV) for the treatment of adults with histologically mild chronic hepatitis C infection.

Epidemiology and background

Hepatitis C virus (HCV) is a blood-borne virus that can be transmitted by infected blood or blood products, via blood transfusion or clotting factors (as used in haemophilia) and contaminated hypodermic needles. It is estimated that between 200,000 and 400,000 people may be chronically infected in the UK, the majority of whom are male. Estimates of the proportion of infections that could be considered mild vary, but could be as high as 85%. Because of shared routes of transmission, a proportion of those infected with HCV are also co-infected with HIV and hepatitis B virus (HBV). It is estimated that around 1800 people with haemophilia are living with chronic HCV infection.

After exposure, up to 80% of people develop chronic infection. Disease progression is variable, occurring over a 20–50-year period. Although some people may never progress, around 30% will develop liver cirrhosis over a 20–30-year period. The severity of disease is established via liver biopsy, with fibrosis scores of 0–2 generally indicating milder disease (depending on which classification system is used).

Currently, patients who present with histologically mild HCV are monitored with repeat biopsies every few years. Antiviral treatment is only initiated when fibrosis and inflammation levels are indicative of moderate to severe disease. The National Institute for Health and Clinical Excellence (NICE) has previously issued guidance on the use of antiviral treatment in moderate to severe HCV; however, antiviral treatment in patients with histologically mild HCV has not been assessed at a policy level before. This assessment therefore compares treatment of patients early on, when liver disease is mild, with a policy of 'watchful waiting' whereby treatment is offered when the infection has advanced.

Methods

A systematic review and an economic evaluation were conducted. A sensitive search strategy was designed and applied to a number of electronic bibliographic databases up to July 2005. Manufacturer and sponsor submissions to NICE were also searched. The trials were reviewed in a narrative synthesis, but meta-analysis was not undertaken due to heterogeneity in the interventions and comparators evaluated.

A Markov state transition model was developed to estimate the cost-effectiveness of treatment strategies for adults with mild chronic HCV, from the perspective of the NHS and personal social services. The model includes eight health states through which a cohort of patients pass at different rates. A lifetime horizon was employed, with a cycle length of 1 year. Published quality of life weights were taken from a UK randomised control trial (RCT) in order to derive quality-adjusted life-years (QALYs). Transition rates through the health states were estimated from published literature, including the UK RCT. Costs and resources were estimated from published literature and clinical opinion.The cost year was 2003–4. Costs were discounted at 6% and benefits at 1.5%.

Uncertainty in assumptions and parameters was investigated through probabilistic and deterministic sensitivity analyses.

Results

Clinical effectiveness results

Virological response

In two PEG RCTs, treatment for 48 weeks with PEG 2a + RBV was significantly more effective than the same treatment for 24 weeks [sustained virological response (SVR) at 48 weeks, range 52–63%]. In the third PEG trial, treatment with PEG + RBV resulted in a significantly ▶

higher SVR than treatment with IFN + RBV. All five IFN trials reported significantly higher SVR rates with IFN + RBV (range 33–69%) compared with either IFN monotherapy (range 18–23%) or no treatment (zero response).

All eight trials reported SVRs for subgroups of patients according to different prognostic and demographic factors. Logistic regression analysis was also performed to examine the independent effect of these factors on virological response.

In the three PEG 2a + RBV trials, higher SVRs were seen in genotype non-1 patients compared with genotype 1 patients, regardless of length of therapy. Genotype 1 patients treated with PEG + RBV for 48 weeks had significantly higher response rates than patients on the same therapy for only 24 weeks. Treatment duration did not have a significant effect on virological response for patients with genotype 2 or 3.

Patients with genotype 1 and low baseline viral load treated for 48 weeks had significantly higher SVRs than genotype 1 patients with high baseline viral load. In patients with genotypes 2 or 3, there was little additional benefit in extending treatment to 48 weeks, regardless of viral load.
Patients with genotype non-1 aged 40 years or younger had a 26% higher probability of achieving an SVR compared with patients who were older than 40 years (relative risk 1.26; 95% confidence interval 1.02 to 1.55). One trial reported results for subgroups of patients with varying stages of fibrosis. In general, SVRs were higher in patients with mild HCV (fibrosis score F0 or F1, scored using the Knodell system) compared with those with bridging fibrosis/cirrhosis (F3 or F4) (it was not reported whether this difference was statistically significant). In mild HCV patients with genotypes 2 or 3, there was a small net loss of benefit when treatment was extended to 48 weeks.

No RCTs of the other pegylated interferon alfa, PEG 2b, in patients with mild HCV met the inclusion criteria. However, a large multi-centre international RCT of PEG 2b + RBV in patients with moderate to severe HCV reported subgroup analyses based on fibrosis stage. For patients with no or minimal fibrosis treated with the standard dose of PEG 2b + RBV for 48 weeks, SVRs were in the range 54–61%, depending on RBV dose. For patients with bridging fibrosis/cirrhosis, SVRs were in the range 39–55%.

In the five IFN + RBV trials, SVRs were higher for patients with non-1 genotypes compared with genotype 1 in all trials. In two RCTs, within-group differences were statistically significant ($p \leq 0.05$). In one RCT, SVRs were significantly higher for patients with low baseline viraemia in both the dual therapy treatment group (92 vs 46%, $p < 0.05$) and monotherapy treatment group (50 vs 0%, $p < 0.005$). The baseline histological staging (scored using the Scheuer criteria) significantly affected the SVR within the combination therapy group of one trial. SVRs for patients with a lower fibrosis stage (F0 or F1) were more than twice that of patients with a higher fibrosis stage (F >1) (63 vs 28%, respectively, $p = 0.004$). Differences in SVR according to age >40 years or <40 years (measured in two trials), or normal or raised baseline alanine aminotransferase levels (one trial), were not significant.

Health-related quality of life (HRQoL)

Published data on HRQoL were available for only one of the RCTs (comparing IFN + RBV versus no treatment) using the Short Form with 36 Items (SF-36). At 24 weeks after the end of treatment, there was a mean improvement from baseline in seven out of eight of the SF-36 subscales in patients with an SVR. Significant improvement was reported for bodily pain, general health and vitality ($p = 0.01$ compared with controls). Mean improvements were also observed in five of eight subscales in treatment failures (non-responders and relapsed patients).

The impact of PEG 2a + RBV on HRQoL is currently available only in a conference abstract. SF-36 and Fatigue Severity Scale scores were better for patients achieving an SVR than non-responders or untreated controls.

Adverse events

The trials varied substantially in the detail of their reporting of adverse events. However, the most frequently occurring adverse events were the same in all eight RCTs, and included influenza-like symptoms such as headache, fatigue, fever and myalgia. Depression also occurred fairly commonly. Overall, the incidence of adverse events did not differ greatly between treatment groups for all the trials, although in two trials the incidence was higher in the treatment groups compared to no treatment, as would be expected. Two trials reported statistical tests for comparisons between groups.

The incidence of any dose discontinuations due to adverse events was reported by all eight trials and was similar across treatment groups (range 8–17%) for the five IFN trials and one PEG ▶

trial. For the other two PEG trials, there was larger variation between treatment groups (range 7–57%). In both studies, the highest proportion of patients who had to stop treatment due to adverse events occurred in those receiving PEG + RBV for the longer duration of 48 weeks (range 18–57%), and was two to four times the incidence in patients receiving the same treatment for 24 weeks (range 7–12%).

Monotherapy

The two PEG monotherapy trials containing predominantly mild HCV patients reported SVRs of up to 30%, depending on PEG formulation and dose.

Subgroups of mild and moderate to severe patients

In general, higher SVRs were observed for patients classified as having mild fibrosis at baseline, compared with those classified as advanced fibrosis/cirrhosis (n= 7 studies). However, this was statistically significant in only one study, with the remaining studies not reporting any significance values. In five studies, no or minimal fibrosis was significantly and independently associated with SVR, as assessed in multivariate logistic regression analyses.

Cost-effectiveness results

Systematic review of cost-effectiveness studies

All six selected studies indicate that antiviral treatment is effective in terms of improved life expectancy and quality-adjusted life expectancy compared with no antiviral treatment. Those studies which compared the effects of immediate versus delayed treatment (i.e. watchful waiting) generally showed that early intervention is cost-effective for genotype non-1 patients, but less so for genotype 1 patients.

Authors' cost-effectiveness analysis

The base case incremental costs per QALY for 48 weeks of treatment are as follows:

- watchful waiting with IFN + RBV versus best supportive care = £3097–6585
- early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £5043–8092
- watchful waiting with PEG 2a + RBV versus best supportive care = £3052
- early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £5900
- watchful waiting with PEG 2b + RBV versus best supportive care = £2534
- early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £5774.

Early treatment compared with watchful waiting is associated with QALY gains and increased treatment costs. Cost per QALY estimates are therefore higher than watchful waiting compared with best supportive care. Early treatment involves providing interferon dual therapy to all patients with mild disease, some of whom will never progress to the moderate to severe stage. In contrast, the watchful waiting strategy involves providing antiviral treatment only to those patients where disease progresses. Moreover, early treatment means that drug costs and excess costs for monitoring patients are all incurred in the first year of the strategy, rather than at a future date determined by the rate of disease progression.

For genotype 1 patients the incremental costs per QALY for 48 weeks of treatment are as follows:

- watchful waiting with IFN + RBV versus best supportive care = £7766–19,022
- early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £9021–15,954
- watchful waiting with PEG 2a + RBV versus best supportive care = £6867
- early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £10,270
- watchful waiting with PEG 2b + RBV versus best supportive care = £4670
- early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £8324.

For genotype non-1 patients the incremental costs per QALY for 48 weeks of treatment are as follows:

- watchful waiting with IFN + RBV versus best supportive care = £1558–3105
- early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £3528–5050
- watchful waiting with PEG 2a + RBV versus best supportive care = £1326
- early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £3725
- watchful waiting with PEG 2b + RBV versus best supportive care = £1387
- early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £4320.

Comparisons are also made between PEG and IFN, in terms of early versus early treatment, and delayed versus delayed treatment. Results vary according to which PEG is used (2a or 2b), and the SVR.

When applying early stopping rules for patients not demonstrating a viral response after 12 weeks, costs for the watchful waiting strategies typically

reduce by around £700 and for early treatment fall by around £3000. There is less of an impact in terms of QALYs. Early stopping strategies are also modelled according to genotype. The order of reduction in lifetime costs is slightly lower for genotype 1 patients than for the mixed cohort of genotype 1 and genotype non-1. The greatest reductions in cost are realised by applying a 24-week duration of treatment to genotype non-1 patients. Costs for watchful waiting reduce by approximately £1000 and for early treatment by approximately £4000.

A number of scenarios to explore differences in SVR for IFN compared with PEG were conducted. The SVRs for PEG used in the model were replaced by lower values. These were based on the SVR reported for IFN in the UK Mild HCV trial and odds ratios for SVR with PEG 2b and IFN taken from a large multi-centre RCT. The incremental cost-effectiveness ratios (ICERs) for watchful waiting and early treatment with PEG are much greater than under the base case. The ICER for early treatment with PEG 2a compared with IFN is £23,252. This contrasts with a value of approximately £2000 for the base case with the low SVR for IFN.

The second scenario used a similar approach, but increased the difference between the SVR for PEG and IFN, based on outcomes for patients receiving higher doses of RBV. The ICERs were lower than for the previous analysis but were still greater than for the base case.

Changing the discount rates (from 6 to 3.5%) has a greater effect on the watchful waiting strategy than on early treatment. This has the effect of increasing the impact of costs borne in the future. Increasing the disease progression rates increases the cost-effectiveness of all strategies. Varying the health state utilities used in the model has a different impact between the early and delayed treatment strategies. There is little impact on the ICERs for the delayed treatment strategies, but an increase for the early treatment strategies.

The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis. Early treatment with PEG appears to be the optimal intervention over a wide range of values for willingness to pay (which reflects the difference in SVR with PEG 2a against IFN in the data used in the evaluation), although there is a non-negligible probability that early treatment with IFN may be optimal. Results are similar for PEG 2b.

Conclusions

The results of this systematic review and economic evaluation show that patients with histologically mild HCV can be successfully treated with both PEG and IFN. Early treatment and watchful waiting strategies are associated with acceptable cost per QALY estimates.

Recommendations for future research

Research and development need to be directed towards newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects.

Further research is required into the natural history of HCV to estimate better the rate of liver disease progression, and also into the effectiveness of non-invasive biochemical markers of liver disease, as an alternative to liver biopsy.

Publication

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