

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

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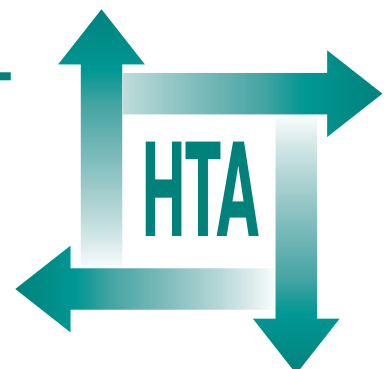
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Executive summary

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Executive summary

Objective

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

Epidemiology and background

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

Methods

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

Results

Dual therapy

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

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

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

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

Monotherapy

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

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

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

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

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

Economic analysis

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

Dual therapy

The incremental discounted cost per QALY for comparing no active treatment to 48 weeks of dual

therapy with pegylated interferon and ribavirin (PEG + RBV) is £6045. When moving from 48 weeks of dual therapy with non-pegylated interferon and ribavirin (IFN + RBV) to 48 weeks of dual therapy with PEG + RBV the figure is £12,123.

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

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

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

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

Monotherapy

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

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

A separate published meta-analysis of the two pivotal pegylated dual-therapy RCTs (not conducted by the authors of this report) found that excluding the 19% of patients who do not achieve early viral response at 12 weeks only misses 0.6% of potential responders. On the basis of these data it was recommended that only genotype 1 patients be assessed at week 12, ►

with those not having an early viral response ceasing treatment, and those classed as having an early response completing the full 48 weeks of treatment, unless remaining HCV RNA positive at week 24, in which case they should stop treatment.

The following secondary questions were addressed.

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

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

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

Non-invasive tests have been proposed as an alternative to biopsy as a means of assessing fibrosis. The best indicators appear to be

combinations or panels of tests, preferably those that are routinely available in clinics. They may be most useful at the ends of the spectrum; that is for identifying those with serious liver damage who would be treated, and those with mild disease who currently would not. For patients around the current treat/do not treat margin, the consensus is that liver biopsy is still often necessary, although the balance of risks is different in those with haemophilia.

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

Conclusions

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

Recommendations for further research

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

- There are no trials in which the efficacies of therapy with PEG- α -2a and PEG- α -2b are compared directly.
- There are no full reports of retreatment of previous non-responders using pegylated interferon (either with or without ribavirin). ►

- There is very little information on the efficacy of treatments for hepatitis C (particularly using PEG) in patients who have other co-morbidities.
- Other treatment regimens that may prove to be overall more effective than dual therapy with PEG should be evaluated.
- More evidence about the long-term outcomes for such patients would be useful. In addition it would be useful to test prospectively which treatment regimens achieve the best improvements in liver histology and which are most cost-effective.
- Prospective tests of rules governing stopping treatment would be useful, particularly with concurrent collection of cost data.
- Further investigation of treating patients with acute hepatitis C may be merited potentially to avoid the long-term morbidity involved for some patients when they reach the stage of chronic infection.
- Problems that may occur in a minority of patients with hepatitis C, such as cryoglobulinaemia and vasculitis, are not likely to be the subject of clinical trials because of the relatively small number of patients affected. However, clinicians point out that in some

patients with vasculitis due to viral/antibody complexes the vasculitis can resolve after long-term treatment. Appropriate treatment of such patients needs to be addressed.

- Additional psychological effects on quality of life due to hepatitis C need to be evaluated.
- Further research is needed on the treatment of children and adolescents with hepatitis C. Previous studies of interferon monotherapy in children have been generally small, uncontrolled trials involving highly selected patients. New therapies, including PEG, should be studied in children. The long-term safety of these medications also needs to be studied in children.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

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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.

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