The clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people: a systematic review and economic evaluation

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Scientific summary

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Background

The hepatitis C virus (HCV) in children and young people is most commonly acquired via vertical transmission where the virus is passed down from a HCV-infected mother to her child in the perinatal period. The prevalence of HCV in children of all ages is unclear and difficult to establish but estimates are in the region of 0.1–0.4%. Progressive liver disease, as a result of chronic HCV infection, usually develops slowly over a number of years, often decades. Spontaneous viral clearance may occur early in the history of infection in young children, but once established chronic HCV tends to persist into adult life. Many children and young people will have mild disease with few obvious signs and symptoms of infection, although a small proportion of children with chronic HCV will develop significant liver disease during childhood. Quality of life (QoL) may be affected and some may experience the burden of social stigma. The National Institute for Health and Care Excellence (NICE) has previously recommended the use of peginterferon alfa and ribavirin (RBV) combination therapy in adults with chronic HCV in the UK. Optimal therapy for children is less clear but it has been suggested that they should be treated using the same principles applied to the treatment of adults. Successful treatment is considered to be attainment of a sustained virological response (SVR), defined as undetectable serum HCV ribonucleic acid levels 6 months after treatment cessation. The marketing authorisations for the two available brands of peginterferon (peginterferon alfa-2a [Pegasys®, Roche] and peginterferon alfa-2b [ViraferonPeg®, Merck Sharp & Dohme (MSD)]) have been extended to allow children and young people to also receive treatment. This review focuses specifically on these new indications.

Objectives

To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b in combination with RBV, within the licensed indications, for the treatment of chronic HCV in children and young people aged 3–17 years.

Methods

Clinical effectiveness

A search strategy was developed and applied to 12 electronic bibliographic databases (including The Cochrane Library, MEDLINE and EMBASE) from database inception to November 2012. Bibliographies of retrieved papers were screened, general and key hepatitis C websites and symposia were searched, and experts were also contacted to identify any additional published and unpublished references. Manufacturers’ submissions (MSs) to NICE were also searched.

Titles and abstracts (where available) were screened for potential eligibility by two reviewers independently, using inclusion criteria that were defined a priori. Screening of the full text of retrieved papers was performed by one reviewer and checked by a second. Studies were eligible for inclusion if the participants were children and young people aged 3–17 years with compensated chronic HCV of any severity, including those with HIV co-infection and those who were treatment naive or had been previously treated. Randomised controlled trials (RCTs) and non-RCTs were eligible for inclusion; uncontrolled studies were considered in the absence of any controlled studies. Data extraction and assessment of methodological quality were undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion at each stage or consultation with a third reviewer if necessary. Data were synthesised through a narrative review with
tabulation of the results of included studies. It was not considered appropriate to combine the studies in a meta-analysis primarily because of study design and poor study quality.

Cost-effectiveness
A systematic review of economic evaluations of peginterferon alfa for children was conducted using standard methods for evidence synthesis. MSs to NICE were also reviewed. We adapted our previously published economic models of chronic HCV in adults to estimate the cost-effectiveness of peginterferon alfa-2a and -2b (in combination with RBV) compared with best supportive care (BSC), and one another, in children. The Markov cost-effectiveness model included health states for progression between chronic HCV health states and the more severe disease states of decompensated cirrhosis, hepatocellular carcinoma and liver transplant. Patients who responded to treatment achieved a SVR. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs. A systematic review of health-related quality of life (HRQoL) for patients with hepatitis C was conducted, and utility values extracted from the identified studies were used to derive the quality-adjusted life years (QALYs) associated with each treatment strategy. Resource use assumptions were adopted from our previously published models for adults with hepatitis C. Drug costs were taken from the British National Formulary. To estimate costs associated with the management of chronic HCV, values from a UK trial in adult patients with chronic HCV and other published sources were used. Costs and benefits were discounted at 3.5% per annum. The perspective of the cost-effectiveness analysis was that of the NHS and personal social services. Uncertainty was explored through deterministic and probabilistic sensitivity analysis.

Results
Clinical effectiveness
A total of 811 references were identified after deduplication. Seven studies (reported in 15 publications) were included in the review of clinical effectiveness, of which two evaluated peginterferon alfa-2a and RBV (Copegus®, Roche) and five evaluated peginterferon alfa-2b and RBV (Rebetol®, MSD). Six of the included studies were single-arm, uncontrolled cohort studies and one was a RCT for which only data for a single arm met the inclusion criteria. No studies were identified that compared peginterferon alfa and RBV with BSC, or peginterferon alfa-2a with peginterferon alfa-2b. On the whole, the cohort studies were relatively small and of generally poor quality.

Sustained virological response rates ranged from 53% to 66% in children treated with peginterferon alfa-2a and 29% to 75% in those treated with peginterferon alfa-2b. The two peginterferon alfa-2b studies at the extremes of this range had very small participant numbers ($n = 7$, $n = 12$) which may raise a question over the reliability of the data. If these two studies are excluded, the SVR for peginterferon alfa-2b ranged from 49% to 65%.

Secondary outcomes were not always reported by all the studies. In five studies (two peginterferon alfa-2a and three peginterferon alfa-2b), children with genotype 2 or 3 appeared to have higher SVR rates than those with genotype 1, and three studies (two peginterferon alfa-2a and one peginterferon alfa-2b) found that children with low viral load at baseline achieved higher SVR rates than those with high viral load. In two peginterferon alfa-2b studies, children who were treatment naive were more likely to achieve an SVR than those who had been previously treated. It should be noted that numbers of children in some of these subgroups were very small and none of the studies was statistically powered for subgroup analysis; therefore, results should be interpreted with caution.

Rates of non-response were variable, ranging from 12% to 25% (two peginterferon alfa-2a studies) and 17% to 51% (three peginterferon alfa-2b studies). A relapse rate of 17% was reported by one peginterferon alfa-2a study and a range of 3–17% across four peginterferon alfa-2b studies. Adverse events were not consistently reported across all the studies but generally appeared typical of those associated with peginterferon and RBV, and included flu-like symptoms, headache, gastrointestinal
symptoms and anaemia. The incidence of dose discontinuation due to adverse events was relatively low and ranged from 3% to 7% (two peginterferon alfa-2a studies) and 1% to 10% (two peginterferon alfa-2b studies). The rate of dose modifications was variable and inconsistently reported. Adverse events leading to dose modification were usually anaemia and neutropenia. There was very limited data on QoL and growth. In one peginterferon alfa-2a study, most children showed no clinical changes in any of the measures of QoL. The impact on growth was often presented only in a brief narrative so no firm conclusions can be drawn.

Cost-effectiveness

The systematic review of published economic evaluations identified two cost-effectiveness studies for the treatment of children with antiviral therapy, but neither of these met the inclusion criteria. The systematic review of HRQoL in children with hepatitis C did not identify any relevant studies. An update of HRQoL in adults found one new study and one previously unidentified study that provided European Quality of Life-5 Dimensions (EQ-5D) utility values for patients with chronic HCV.

Two manufacturers submitted evidence to be considered:

- MSD, the manufacturer of peginterferon alfa-2b, constructed a lifetime Markov model with a model structure based upon that developed for previous NICE appraisals for adults. The model used the effectiveness of the treatments from a meta-analysis of the clinical trials. The base-case results from the submission found that both combinations of peginterferon alfa dominated BSC in all age and genotype subgroups. There were small differences in costs and health outcomes between peginterferon alfa-2a and -2b. Peginterferon alfa-2b dominated peginterferon alfa-2a for most age and genotype subgroups.
- Roche, the manufacturer of peginterferon alfa-2a, also constructed a Markov model based upon that developed for previous NICE appraisals for adults, with a time horizon of 30 years. The model used the effectiveness of peginterferon alfa-2a from a weighted average of four clinical trials. The base case results from the submission found that peginterferon alfa-2a is a cost-effective option for the treatment of paediatric HCV compared with BSC. Roche did not assess peginterferon alfa-2a compared with peginterferon alfa-2b.

In the independent Markov model, a time horizon of 70 years was used. The treatment effect was calculated using weighted averages taken from the studies included in the clinical effectiveness review. From this model, peginterferon alfa (alfa-2a or -2b) in combination with RBV was more effective and had lower lifetime costs than BSC. Peginterferon alfa-2a had slightly lower lifetime costs and higher QALYs than peginterferon alfa-2b; therefore, peginterferon alfa-2b was dominated by peginterferon alfa-2a. Sensitivity analyses suggest that the results were generally robust to all changes to the structural assumptions and input parameters. The model results were most sensitive to changes to the discount rate, time horizon, SVR and baseline fibrosis of the cohort.

Discussion

The treatment of children and young people with peginterferon (alfa-2a or -2b) and RBV may be an effective treatment, with SVR rates around 50–60%. However, the reliability of the available evidence is questionable given the single-cohort study designs, small sample sizes and poor methodological quality.

The data available to populate the cost-effectiveness models were poor, and in many cases lacking altogether. For this reason, the models were largely based upon those previously developed for adults, assuming that these data would be appropriate and relevant for this population. Caution is therefore required in interpretation of the results.

The cost-effectiveness analyses submitted by the manufacturers were similar to that developed by the Southampton Health Technology Assessments Centre (SHTAC) independent model, with regard to model
structure and data inputs, with all models largely based upon the previously developed model for adults. There were variations between the models in the time horizon chosen and the transition probabilities for progression between chronic HCV health states. The results from the cost-effectiveness analyses submitted were consistent between the MSs and the SHTAC independent model.

This assessment was carried out following recognised guidelines and addresses a specific knowledge gap concerning the clinical effectiveness and cost-effectiveness of peginterferon alfa and RBV treatment in children and young people with chronic HCV. In terms of limitations, there were a lack of good quality effectiveness data, and parameter values for the model had to be taken from the adult population as no suitable data for children and young people were identified.

Conclusions

Treatment of children and young people with peginterferon (alfa-2a or -2b) and RBV may be an effective treatment. Results from the independent Markov model suggest that peginterferon (alfa-2a or -2b) in combination with RBV is more effective and has lower lifetime costs than BSC. However, the available evidence is of poor quality.

Implications for service provision

There are currently three specialised paediatric hepatology centres in the UK with well-established shared-care pathways. However, a recommendation for treatment with peginterferon alfa and RBV in children and young people with chronic HCV could potentially have implications for delivery of the service in terms of accessibility. The challenge of treating children and young people in more centres would be in making treatment accessible to all patients but with each centre treating enough patients to maintain expertise. Other implications include the need for more clinical nurse specialists and the additional burden on general practitioners, haematologists and child psychology services as a result of managing adverse effects.

Suggested research priorities

Well-conducted, head-to-head RCTs of peginterferon alfa-2a and RBV versus peginterferon alfa-2b and RBV are required, although these are unlikely given the emergence of newer treatments. If larger cohort studies are carried out, they should be statistically powered for the various subgroups in whom treatment response varies and should be conducted in participants who reflect the chronic HCV paediatric population in the UK. Longer-term, more robust data are required to ascertain the long-term impact of peginterferon alfa treatment on the growth and QoL of children and young people with chronic HCV. Research in this area would perhaps be the most valuable.

Study registration

This study is registered as PROSPERO CRD42012002743.

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