NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people aged 3-17 years

Manufacturer submission of evidence:

Peginterferon alfa-2b and ribavirin

MSD

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Executive Summary

Background

Chronic hepatitis C (CHC) is a slowly progressing disease caused by infection with the hepatitis C virus (HCV), which can cause severe liver damage in the form of fibrosis and cirrhosis, and can eventually lead to death. The exact numbers of children and young people infected with HCV in England and Wales are not known, however an estimated 47 children aged under 15 years were diagnosed with HCV in England and Wales in 2010, and a small proportion of the estimated 463 people aged between 15 and 24 diagnosed in the same year would also fall under the remit of this appraisal[1]. Although the disease progresses slowly and is commonly asymptomatic in children, effective treatments for this age group are available and guidance for their use is needed.

In developed countries, the HCV infection is most commonly transmitted to children from their mothers by vertical transmission[2-4]. Parenteral transmission of HCV, for example through blood transfusion or hospital procedures, can occur but is now very rare in developed countries[2;3]. Six genetic types of HCV, known as genotypes, have been identified. In adults in England and Wales, genotype 1 is the most common, accounting for about 40% to 50% of those infected with HCV. Genotypes 2 and 3 together contribute another 40% to 50%, while genotypes 4, 5 and 6 account for the remaining infections. Data regarding HCV genotypes in children are limited, however the distribution is believed to be similar to that in adults.

Spontaneous clearance of the HCV in children infected by vertical transmission is lower than in those infected parenterally, therefore a high proportion of HCV infected children go on to develop chronic disease. Spontaneous viral clearance has been reported to range from 2.4% to 25% in vertically infected children, whereas clearance occurs in up to 35% to 45% of parenterally infected children and adolescents[2]. The majority of vertically infected children who clear the virus spontaneously will do so by their second or third year of life, with spontaneous clearance becoming unlikely by age 4 years[2;4].

CHC is commonly asymptomatic in children, however progressive liver disease appears to be inevitable[5]. Progression of liver disease is slow during the first two decades of life and advanced disease is rare during childhood and adolescence[2;5-7], however approximately 4% to 6% of children will develop advanced fibrosis or cirrhosis during this time[2;5;8;9]. In adults with CHC, about 30% develop cirrhosis within 20 to 30 years, and some of these will develop hepatocellular carcinoma. Some people with end-stage liver disease or hepatocellular carcinoma will require liver transplantation.

Current Treatment

In England and Wales children with CHC are managed by either a ‘watchful waiting’ approach, during which their condition is monitored and they may receive supportive care but no active treatment, or by treatment with either peginterferon (PEG INF) alfa-2a or alfa-2b, in combination with ribavirin. At

present, only PEG INF alfa-2b is licensed for treatment of children with CHC, however clinical studies have been conducted with both combination therapies and both are used in clinical practice.

The decision of when to treat a child or adolescent with CHC is made by the treating clinician. Treatment is rarely given to children under the age of three years, as they may still clear the HCV spontaneously until this age. The primary aim of treating children with CHC is to eradicate the HCV and to prevent the progression of liver disease and development of cirrhosis and hepatocellular carcinoma. In addition, treating and clearing the HCV infection prevents transmission of the virus to others, reducing the pool of infected individuals. Although some clinicians may decide that a watchful waiting approach is most appropriate for their patients, the benefits of treating at a younger age have been reported to include improved response rates and tolerability of treatment in younger patients, prevention or minimisation of stigmatisation and social disintegration, and the facilitation of compliance by parents[2;8].

Successful treatment is usually indicated by achievement of a sustained virologic response (SVR), which is defined as undetectable serum HCV-RNA 6 months after the end of treatment. SVR is commonly considered in clinical practice as being equivalent to cure, with relapse following SVR being rare in both children and adults[10;11].

The exact mechanism of action of PEG INF alfa-2b is unknown, but it is thought to inhibit viral replication by altering the host cell metabolism[12]. PEG INF alfa-2b is dosed once weekly based on patient body surface area. ViraferonPeg (PEG INF alfa-2b) is available in pens of different strengths and the dose administered by each pen can be altered, allowing flexibility, in particular if a patient's dose needs altering. Ribavirin, a synthetic nucleoside analogue, is administered in combination with PEG INF alfa-2b and the mechanism by which it exerts its effects against HCV is also unknown. Rebetol (ribavirin) is administered orally, and is available as a solution and capsules[13;14].

Clinical Effectiveness

A meta-analysis including clinical trials of PEG INF alfa-2a or alfa-2b, in combination with ribavirin, showed that 58% of children with CHC achieved SVR following treatment with either combination therapy[15]. No significant difference in efficacy was found between PEG INF alfa-2a and alfa-2b, when administered in combination with ribavirin. The SVR rates observed in children (58%) are higher than those seen in studies of adult patients treated with PEG INF alfa-2a or alfa-2b and ribavirin (41%)[16].

The most common adverse events (AEs) experienced by children and young people receiving PEG INF alfa-2b and ribavirin, were flu-like symptoms, including fever, headache and fatigue. Haematological AEs including neutropenia, leukopenia and anaemia were also commonly reported and were managed by dose reduction of either PEG INF alfa-2b or ribavirin[15;17-21]. Despite most patients reporting at least one AE, few patients discontinued treatment due to adverse events (4%; 95% CI 1,10%)[15], suggesting the side effect profile of PEG INF alfa-2b and ribavirin is manageable. A similar pattern of adverse events was seen in clinical trials of children treated with both PEG INF alfa-

2a and alfa-2b, and there was no difference in treatment discontinuation due to AEs between PEG INF alfa-2a and alfa-2b[15].

An effect on height and growth velocity has been reported in some trials of children treated with PEG INF alfa-2b and ribavirin. These data suggest that growth velocity was reduced during the treatment period but returned to normal or faster than normal for most patients during the follow-up phase[18;19]. In the largest of these studies, the mean height percentile at the end of follow-up (44.25) was -6.62 percentiles lower than at baseline, and slightly lower than the median for the US population[18].

Cost-effectiveness

A Markov model was developed based on a previous economic evaluation for treatment with PEG INF alfa and ribavirin in adults with CHC[22]. The model evaluated the cost-effectiveness of combination therapy with PEG INF alfa-2a or alfa-2b and ribavirin, and supportive care, for the treatment of children and young people aged 5-17 years. An additional analysis was conducted on 3-4 year olds comparing supportive care to PEG INF alfa-2b and ribavirin as this was the only PEG INF alfa with a licence for treating this age group. The cost-effectiveness was evaluated using the incremental cost-effectiveness ratio (ICER) from the perspective of the NHS over a lifetime horizon.

The results reported that both combinations of PEG INF alfa and ribavirin dominated supportive care for all patients. This result was also shown in all age and genotype subgroups, and for the scenario comparing PEG INF alfa-2b to supportive care in 3-4 year olds. Driven by small differences in the comparative efficacy and costs, the comparison between PEG INF alfa-2a and alfa-2b, in combination with ribavirin, showed that PEG INF alfa-2b dominated PEG INF alfa-2a overall and in the following subgroups: 5-8 years, 14-17 years and genotypes 2/3. The ICER for the 9-13 years subgroup was £4,697. PEG INF alfa-2a dominated PEG INF alfa-2b for the other genotype subgroup. The results demonstrate that treatment of 3-17 year olds with PEG INF alfa and ribavirin is a cost-effective treatment option.

Conclusion

Treating children and young people with either PEG INF alfa-2a or PEG INF alfa-2b, in combination with ribavirin, is clinically efficacious, with 58% of those treated achieving SVR. No differences have been found between the efficacy and tolerability of PEG INF alfa-2a and alfa-2b, when administered in combination with ribavirin, for children with CHC. The results of the economic evaluation demonstrated that treatment with both combinations of PEG INF alfa and ribavirin are cost-effective options. Successful treatment and eradication of the HCV in young people prevents the progression of liver disease and reduces the development of complications such as cirrhosis and hepatocellular carcinoma. Treating CHC at a younger age allows for improved efficiency, tolerability and compliance with treatment, as well as minimising potential stigmatisation from peers and reducing the incidence of onwards transmission of the virus.