NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (Part-review of TA75 and TA106)

Final scope

Appraisal objective

To review, and update as necessary, the Institute's current guidance on the clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.

Background

Hepatitis C is a disease of the liver caused by infection with the hepatitis C virus (HCV). Generally the virus is transmitted parenterally, but the natural history of the disease is not completely understood. The virus is primarily acquired through percutaneous exposure to contaminated blood. Since the viral inactivation programme was implemented in the mid-1980s and blood donor screening started in 1991, the transmission of HCV in the UK, via transfusion of blood, blood products or organ transplantation, has all but ceased. However, injecting drug use, cosmetic and other practices involving percutaneous exposure remain common routes of transmission. HCV prevalence is correlated with markers of sexual activity, but HCV incidence in monogamous heterosexual partners of infected people is extremely low. There is a transmission rate of about 6% from mother to child if the mother is an HCV carrier. Concomitant HIV infection increases the risk of transmission.

Estimates from the Health Protection Agency suggest that approximately 142,000 people between the ages of 15-59 years were infected with chronic HCV in England and Wales in 2003; a prevalence rate of 0.44% in this age group. More than 90% of all newly diagnosed infections in the UK occur in injecting drug users.

People infected with HCV are often asymptomatic, but about 20% will develop acute hepatitis and will experience non-specific symptoms including malaise, weakness and anorexia. About 80% of those exposed go on to develop chronic hepatitis. The rate of progression of the disease is slow but variable, usually taking about 20–50 years from the time of infection. About 30% of those who are infected develop cirrhosis within 20–30 years, and a small percentage of these people are at a high risk of developing hepatocellular carcinoma. A third may never progress to cirrhosis or will not progress for at least 50 years. Some people with end-stage liver disease or hepatocellular carcinoma may require liver transplantation.

There are 6 major genotypes and several sub-types of HCV, the prevalence of which varies geographically. Genotype 1 is the most common in the UK, accounting for about 40–50% of cases. Genotypes 2 and 3 contribute another

40–50%; and genotypes 4, 5 and 6 constitute the remainder, about 5%. Genotype is a key predictor of the effectiveness of anti-viral treatment and patients with genotypes 2 and 3 generally respond better to treatment than those with genotypes 1, 4, 5 and 6.

A person is classified as having mild, moderate or severe chronic hepatitis C based on the extent of liver damage. The main indicator of liver damage is the degree of fibrosis, although the degree of necroinflammation also contributes to the diagnosis.

For the majority of people with hepatitis C (regardless of disease severity), the standard treatment is combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b. Monotherapy with peginterferon alfa is used only for people unable to tolerate ribavirin (in line with NICE guidance TA75 and TA106).

The technologies

Interferons (interferon alfa-2a and -2b / peginterferon alfa-2a and -2b)

Two forms of interferon alfa (interferon alfa-2a [Roferon-A, Roche Products] and interferon alfa-2b [IntronA, Schering-Plough]) and two forms of pegylated interferon alfa (peginterferon alfa-2a [Pegasys, Roche Products] and peginterferon alfa-2b [Viraferonpeg, Schering-Plough]) have marketing authorisations in the UK for adult patients with chronic hepatitis C. In all cases it is recommended that interferon or peginterferon is used in combination with ribavirin. Monotherapy with an interferon is only recommended for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.

Since TA075 and TA106 were published there have been changes to the Summary of Product Characteristics for the peginterferons, including extensions to the licences as follows:

- Peginterferon alfa-2a
  - Extension of the therapeutic indication to include treatment in patients who previously did not respond to interferon (pegylated or non-pegylated) in combination therapy with ribavirin. This includes patients that achieved an early virological response but then did not achieve an end of treatment sustained virological response (relapsers) and patients that were treated but did not achieve a virological response (non-responders).
  - Option to shorten the treatment duration in patients with genotype 2 or 3 with low viral load at the start of the treatment and a rapid viral response (defined as HCV RNA undetectable by week 4) from 24 weeks to 16 weeks.
  - Option to shorten the treatment duration in patients with genotype 1 with a low viral load and rapid viral response (defined as HCV RNA

undetectable at week 4 and at week 24) and patients with genotype 4 and a rapid viral response from 48 weeks to 24 weeks

The posology section has also been updated to include recommendations for people co-infected with HIV.

- Peginterferon alfa-2b

  – Extension of the therapeutic indication of peginterferon alfa-2b in combination with ribavirin to include treatment in patients who previously did not respond to interferon (pegylated or non-pegylated) in combination therapy with ribavirin or interferon monotherapy.

  – Extension of the therapeutic indication in combination with ribavirin to include treatment in patients co-infected with HIV

The posology section has also been updated regarding the lack of data to support the re-treatment of non-responding patients with genotype 1 HCV for more than 48 weeks.

For full details of the therapeutic indications, posology and method of administration see the relevant summary of product characteristics.

Ribavirin

Ribavirin (Copegus, Roche Products; Rebetol, Schering-Plough) is indicated for the treatment of chronic hepatitis C and must only be used as part of a combination regimen with peginterferon alfa or interferon alfa. Monotherapy must not be used.

There are differences in the licensed indications for the two products in that each is only licensed for use with the interferon products made by the same manufacturer.

Intervention(s)	• Combination therapy (peginterferon alfa and ribavirin) • Peginterferon alfa monotherapy (for those who cannot tolerate ribavirin)
Population(s)	Adults with chronic hepatitis C infection. The following groups will be considered: • people who have been previously treated with peginterferon alfa and ribavirin in combination • people who meet the criteria within the marketing authorisation for receiving shortened courses of peginterferon alfa and ribavirin in combination (for example, patients with specific genotypes) • people with HCV/HIV co-infection

Comparators	For people who have been previously treated with peginterferon alfa and ribavirin in combination: • supportive care, in line with current clinical practice For people who meet the criteria for receiving shortened courses of peginterferon alfa and ribavirin in combination: • standard-duration courses of peginterferon/ribavirin (up to 24 or 48 weeks as appropriate): For people with HCV/HIV co-infection: • supportive care, including treatment without any form of interferon therapy.
Outcomes	The outcome measures to be considered include: • virological response to treatment • sustained virological response • biochemical response (e.g. ALT) • histological improvement (inflammation and fibrosis) • survival • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. The extent to which clinical effectiveness and cost effectiveness varies according to presence of factors associated with a sustained virological response (for example, genotype and baseline viral load) will be estimated for subgroups of patients in whom these factors are present, where data are available.

Related NICE recommendations	Related Technology Appraisals: Technology Appraisal 75 (Jan 2004), 'Interferon alfa and ribavirin for the treatment of chronic hepatitis C - part review of existing guidance no.14'. Technology Appraisal 106 (Aug 2006), 'Peginterferon alfa and ribavirin for the treatment of mild hepatitis C'.