NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C – part review of exisiting guidance no. 75[1]

Final scope

Appraisal objective

To review, and update as necessary, the guidance to the NHS in England and Wales on the clinical and cost effectiveness of interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C (CHC), which was issued in January 2004.

This review will examine the use of interferon alfa (pegylated and non-pegylated) and ribavirin in people with mild chronic hepatitis C. The date for the revision of this technology for mild CHC (and any consequent changes that this may have on this Guidance No 75, particularly with respect to biopsy) was set to take place after the publication of two relevant clinical trials. Reports on these trials have now been accepted for publication. The guidance will only pertain to people with moderate or severe CHC insofar as it may have implications for biopsy for at least some groups of these people. The full guidance No 75 will be reviewed in November 2006.

Background

Hepatitis C is a viral disease of the liver. It frequently causes few or no symptoms at first infection, but has a high probability of becoming a chronic disease. About 20%-40% of those infected manage to clear the virus. Around 5-20% of those with chronic infection will develop cirrhosis of the liver over the next 20-30 years, and a small proportion will go on to develop cancer of the liver. Hepatitis C is one of the main reasons for liver transplantation.

Estimates indicate that around 200,000 people in England are chronically infected with hepatitis C, yet only 38,000 diagnosed have been reported. [2] Most people with diagnosed hepatitis C infection are men aged between 25 and 45 years, reflecting the age and sex bias of injecting drug users and the sex bias of people with haemophilia.

Patients with hepatitis C are classified into mild, moderate or severe disease categories. One way of doing this depends on the histological appearance of liver biopsy: mild if (on examination by a histopathologist) the fibrosis score is less than or equal to 2/6, and if the necroinflammatory score is less than or equal to 3/18 (the

[1] The remit for this part review was set in para 9.1 of the guidance for Technology Appraisal 75: "The use of this technology for mild CHC (and any consequent changes that this may have on this guidance) will be considered after the publication of the results of the two relevant clinical trials, and at the earliest in August 2004. The full guidance will be reviewed in November 2006.

[2] Hepatitis C Action Plan for England. Department of Health July 2004

Ishak classification).[3] Other classification schemes exist, such as the Metavir fibrosis score.

The technology

There are two forms of pegylated interferon alfa available in the UK; peginterferon alfa 2a (Pegasys, Roche) and peginterferon alfa 2b (Viraferonpeg, Schering-Plough). Peginterferon alfa 2a is licensed for adults with CHC, with normal or elevated transaminases who are positive for serum HCV-RNA, including patients with compensated cirrhosis. Peginterferon alfa 2b is indicated for the treatment of adult patients with CHC who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

The precise antiviral mode of action of pegylated and non-pegylated interferon alfa is unknown. However, it appears to alter host cell metabolism. The pegylated form of interferon alfa slows down the rate at which the body eliminates the molecule, enabling dosing to be less frequent.

Intervention(s)	1. Dual therapy (pegylated interferon alfa and ribavirin) 2. Monotherapy (pegylated interferon alfa) (for those who cannot tolerate ribavirin) 3. Non-pegylated interferon alfa[4] and ribavirin.
Population(s)	Adults with mild CHC.
Standard	Best standard care, including either treatment without any form of interferon therapy, or (for the pegylated interferon intervention) treatment with non-pegylated interferon, if the evidence allows.
Outcomes	• sustained virological response to treatment • virological response to treatment • virological response at 12 weeks of treatment • ALT levels • adverse effects of treatment • health-related quality of life • mortality (if evidence allows).

[3] Clinical guidelines on the management of hepatitis C, Royal College of Physicians of London and the British Society of Gastroenterology, J C L Booth, J O'Grady, J Neuberger, 2001

[4] The reason for including non-pegylated interferon alfa as an intervention is to allow one of the two major trials of an interferon product in mild CHC to be considered.

Economic analysis	Modelling will be required for economic analysis. The following points should be included: • The comparisons to be modelled should include pegylated interferon alfa plus ribavirin versus interferon alfa plus ribavirin versus best supportive care (without interferon alfa therapy of any kind) • The possibility of stopping treatment after 12 weeks for people who do not respond • Whether it is cost-effective to avoid biopsy for some genotypes of the hepatitis C virus, and possible consequences for the treatment of moderate to severe CHC. • The possibility of inferring the cost effectiveness of treatment with peginterferon alfa 2b in combination with ribavirin from that of interferon alfa 2b with ribavirin. Ideally, the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Costs should be considered from an NHS and Personal Social Services perspective.

Other considerations	The following points should be covered: • The extent to which clinical effectiveness and cost effectiveness varies according to presence of factors associated with a sustained virological response (eg genotypes 2 and 3, baseline viral load, no or only portal fibrosis). Clinical effectiveness and cost effectiveness will be estimated for subgroups of patients in whom these factors are present, where data are available. • Adjustments of dose according to body weight, if evidence permits • The possibility of using virological response at 12 weeks to determine whether to continue treatment • Particular subgroups of interest (if the evidence permits): current intravenous drug users, current heavy users of alcohol, people with haemophilia, people co-infected with the HIV virus. • The possibility of using subgroup analysis on data from previous trials, to isolate and analyse "mild" groups. In particular, the Zeuzem (2004) trial of people with CHC and normal ALT levels should be used to inform the appraisal of the subgroup of those with mild CHC. • The relevant evidence base for the use of interferon alfa in people with mild hep C may include both Peg and non-Peg formulations
Related NICE recommendations	Related Technology Appraisals: Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C (review and extension of technology appraisal guidance No 14 issued in October 2000) Technology Appraisal guidance No 75. January 2004 Guidance on the use of ribavirin and interferon alpha for hepatitis C. Technology appraisal guidance No 14. October 2000

Related NICE recommendations (contd)	1.1 Combination therapy with peginterferon alfa and ribavirin is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. 1.2 People with moderate to severe CHC are suitable for treatment if they have: • Not previously been treated with interferon alfa or peginterferon alfa, or • Been treated previously with interferon alfa or peginterferon alfa, or • Been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or • Previously received peginterferon alfa monotherapy only and responded at the end of treatment but subsequently relapsed, or did not respond at the end of treatment 1.3 People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with peginterferon alfa. 1.4 Treatment for the groups identified in Sections 1.1 and 1.2 should be as follows: • People infected with hepatitis C virus (HCV) of genotype 2 and/or 3 should be treated for 24 weeks. • For people infected with HCV of genotype 1,4,5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of it's level at the start of treatment (at least a 2-log reduction, see section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued. • People infected with more than one genotype that includes one or more genotypes 1, 4, 5, or 6 should be treated as for genotype 1. 1.5 People satisfying the conditions in Sections 1.1 and 1.2 but for whom ribavirin is contraindicated or is not tolerated should be treated with peginterferon alfa monotherapy.

Related NICE recommendations (contd)	1.6 People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an adverse event after undergoing a previous liver biopsy and people with symptoms of extra-hepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification. 1.7 There is insufficient evidence to recommend combination therapy using peginterferon alfa or interferon alfa in people who: • Have previously been treated with combination therapy using peginterferon alfa, and/or • Are younger than 18 years or age, and/or • Have had a liver transplantation. Treatment of CHC recurrence after liver transplantation (whether or not the person had been treated with interferon alfa or peginterferon alfa therapy at any time before transplantation) should be considered as experimental and carried out in the context of a clinical trial.