TECHNOLOGY ASSESSMENT REPORTS FOR THE HTA PROGRAMME

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C

Southampton Health Technology Assessments Centre (SHTAC)

Final version (21/3/05). Note: this protocol is provisional and subject to change.

A. Details of review team

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B. Full title of research question

- What is the clinical-effectiveness and cost-effectiveness of Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C?

C. Clarification of research question and scope

- The aim of this systematic review and economic evaluation is to assess the clinical-effectiveness and cost-effectiveness of interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C.

- This review builds on two previously published Technology Assessment Reports (TARs) produced by SHTAC underpinning guidance from the National Institute for Clinical Excellence (NICE) on moderate-to-severe chronic hepatitis C (Guidance No. 14 on interferon alfa and ribavirin, published in 2000[1]; and Guidance No. 75 on pegylated interferon alfa and ribavirin, published in 2004[2]).

- Comparators include best standard care, including either treatment without any form of interferon therapy (e.g. supportive care), or (for the pegylated interferon intervention) treatment with non-pegylated interferon, if the evidence allows.

- Relevant study designs for clinical-effectiveness include systematic reviews of randomised controlled trials (RCTs), and Phase II/III RCTs.

- Cost-effectiveness will be from an NHS and personal social services perspective (costs and benefits). Estimates of cost-effectiveness will be presented as incremental cost per quality adjusted life-year gained.

D. **Report methods**

- The review will be undertaken as systematically as time allows following the general principles outlined in NHS CRD Report 4[3].

- The protocol will be updated where necessary as the research programme progresses. NCCHTA and NICE will be notified of any changes in the protocol.

D.1 Search strategy

- Literature searching will build upon the searches conducted for two previous Technology Assessment Reports on interferon alfa and ribavirin for chronic hepatitis C (2000)[1], and pegylated interferon alfa and ribavirin for chronic hepatitis C (2004)[2].

- A search strategy will be devised to identify potentially relevant studies. Specific searches will be conducted to identify studies of clinical-effectiveness; cost-effectiveness; quality of life; resource use/costs; and epidemiology/natural history (see Appendix 1 for draft clinical effectiveness search strategy).

- Electronic databases to be searched include: Cochrane Systematic Reviews Database; Cochrane Central Register of Controlled Trials; NHS CRD (University of York) databases: DARE (Database of Abstracts of Reviews of Effects), Health Technology Assessment (HTA) database, NHS EED (Economic Evaluations Database); Medline (Ovid); PreMedline; PubMed; Embase (Ovid); EconLit; National Research Register; ISI Web of Science - Science Citation Index; ISI Web of Knowledge Proceedings; BIOSIS; Clinical trials.gov; Current Controlled Trials.

- The websites of the following organisations will be searched: The Department of Health; Health Protection Agency; European Agency for the Evaluation of Medicinal Products; British Association for the Study of the Liver (BASL), European Association for the Study of the Liver (EASL), American Association for the Study of the Liver (AASL); British Society of Gastroenterology; Foundation for Liver Research; The British Liver Trust, The British Association for Sexual Health and HIV; The British HIV Association; The Food and Drug Administration (FDA).

- Searches for clinical-effectiveness and cost-effectiveness studies of pegylated interferon alfa will cover the period 2003 to the present (the assessment report on pegylated interferon for hepatitis C searched up to the end of 2002). Searches for clinical-effectiveness and cost-effectiveness studies of non-pegylated interferon alfa will cover the period 2000 to the present (the assessment report on interferon alfa for hepatitis C searched up to the end of 1999/early 2000). A search for general cost-effectiveness studies in hepatitis C will cover the period 2000 to the present. Searches for quality of life and epidemiological/natural history studies will cover the period 2003 to the present.

- Bibliographies of related papers will be assessed for relevant studies.

- Experts will be contacted for advice and peer review, and to identify additional published and unpublished references.

- Manufacturer and sponsor submissions to the National Institute for Clinical Excellence (NICE) will be searched for studies that meet the inclusion criteria.

D.2 Inclusion and exclusion criteria

- Inclusion criteria will be applied by one reviewer and a random 10% sample checked by a second, with any disagreements resolved through discussion and recourse to a third reviewer if necessary.

D.2.1 Interventions

- Pegylated interferon
  - Dual therapy (pegylated interferon alfa-2a / pegylated interferon alfa-2b and ribavirin).
  - Monotherapy* (pegylated interferon alfa-2a / pegylated interferon alfa-2b)

- Non-pegylated interferon
  - Dual therapy (interferon alfa-2a / interferon alfa-2b and ribavirin)

* for patients who are unable to tolerate ribavirin

- Comparisons
  - Best standard care, including either treatment without any form of interferon therapy (e.g. best supportive care), or (for pegylated interferon) treatment with non-pegylated interferon (i.e. interferon alfa-2a / interferon alfa-2b) where evidence allows.

D.2.2 Patients

- Adult patients with mild chronic hepatitis C. Mild hepatitis C can be defined according to histological scoring / grading systems such as Knodell[4]; Ishak[5]; or Metavir[6]. For example, using the Ishak system histological appearances are classified as 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.

D.2.3 Types of studies

- Systematic reviews of randomised controlled trials (RCTs) and Phase II/III RCTs comparing the different drugs with placebo or each other or best supportive care will be included in the review of clinical-effectiveness.

- Studies published as abstracts or conference presentations will not be included in the primary analysis of clinical and cost-effectiveness. However, their key characteristics will be recorded to provide context around the discussion of effectiveness.

- Full economic evaluations of the specified interventions in patients with chronic mild HCV will be included.

- A range of designs for studies on quality of life, and epidemiology/natural history will be considered.

D.2.4 Outcomes

- The following outcome measures will be included (where data allow):
  - virological response (12 weeks treatment, end of treatment; and end of follow-up)
  - histological improvement (e.g. inflammation/fibrosis – on biopsy)

- biochemical response (e.g. liver function – alanine aminotransferase)
- adverse effects of treatment
- survival
- health related quality of life

D.3 Data extraction strategy

- Data will be extracted from the included clinical-effectiveness studies using a standardised template (see Appendix 2).

- Data extraction will be undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion, and recourse to a third reviewer if necessary.

D.4 Quality assessment strategy

- The quality of included systematic reviews and RCTs will be assessed using NHS CRD (University of York) criteria[3] (see Appendix 3).

- Economic evaluations will be assessed according to a checklist adapted from that used by Drummond *et al*. 1997 (Appendix 4).

- Quality criteria will be applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

D. 5 Methods of analysis/synthesis

- A narrative synthesis will be undertaken with the main results of the included clinical-effectiveness and cost-effectiveness studies described qualitatively, and in tabular form. Where possible a meta-analysis of the clinical-effectiveness studies will be performed, using software such as Cochrane Review Manager.

- Where data allow clinical and cost-effectiveness will be assessed according to sub-groups including the following: patients with different genotypes (e.g. genotypes 2 and 3); patients with low baseline viral load; patients with co-infections including Human Immunodeficiency Virus (HIV) and Hepatitis B virus (HBV).

- Implications for the following sub-groups will be discussed where possible: current heavy users of alcohol; current (and previous) intravenous drug users; people with haemophilia; ethnic minorities, male/female patients; younger/older patients; people with depression and other psychiatric disorders; pregnant and breast feeding women; healthcare workers; prisoners and asylum seekers.

- The effectiveness of applying different treatment stopping rules in sub-groups of patients (e.g. those who have not demonstrated a virological response at 12 weeks treatment) will be considered where data allow.

- The role of biopsy in guiding treatment decisions will also be taken into consideration, where data allow.

D.6 Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY

- Where appropriate a suitable cost-effectiveness model will be constructed using the best available evidence in a UK setting. Previous assessments for NICE of the treatment of moderate-to-severe chronic hepatitis C have been based on a Markov model originally developed by the Scottish Health Purchasing Information Centre (SHPIC) and revised by SHTAC[1;2]. The structure of this model will be reviewed to assess its applicability to modelling disease states and health care costs for mild chronic hepatitis C. If considered appropriate it will be updated with data on disease progression in mild chronic hepatitis C from the best available published literature and with appropriate cost data, which may be drawn from published literature, NHS sources (including Finance Department at Southampton University Hospitals Trust) and industry submissions, where applicable.

- Effectiveness data, in terms of the outcomes described in Section D.2.4, will be extracted from published trials and systematic reviews and used in association with cost data to populate the model to obtain measures of cost-effectiveness. Trials identified thus far report short term outcomes (e.g. virological response, histology, and biochemical). Consideration of modelling methods to consider the long term consequences will therefore be necessary.

- Estimates of cost-effectiveness will be presented as incremental cost per quality adjusted life-year gained (cost/QALY). In deriving quality of life adjustments from the published literature, preference will be given to patient-based measures over those derived purely from clinician ratings. Clinical trials identified thus far have documented significant adverse effects associated with treatments for hepatitis C. While most economic evaluations have acknowledged the likely impact of these adverse effects on compliance with treatment they have not always included quantitative estimates of the impact of treatment side-effects on patients' quality of life in terms of health state utilities. This assessment will aim to identify adverse effects of treatment that are likely to have a substantial impact on patients' quality of life and to include these effects in estimates of health state utility while on treatment. The robustness of the results to the assumptions made in the cost analysis and the cost-effectiveness model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

- The perspective of the economic analysis will be that of the NHS and Personal Social Services. Where costs and resource use related to treatment fall outside of this perspective we will report these separately where data are available.

E. Handling the company submission(s)

- Industry submissions will be checked for additional studies that meet the inclusion criteria, for data on costs and for data on the current use of interferon (both pegylated and non-pegylated) and ribavirin.

- Results of cost-effectiveness analyses from industry submissions will be compared with our own analysis, but this will not be a line by line critique of sponsor models.

- Any ‘commercial in confidence’ data taken from the industry submissions will be clearly marked (underlined) in the report submitted to the HTA programme and to NICE. In addition, any information provided by others that is deemed in confidence will be marked as academic in confidence. A separate version with any such data removed will also be submitted.

- **Project management**

  a. **Timetable/milestones** - submission of:

Draft protocol: 7/2/05
Progress report: 22/6/05
'Complete and near final' draft of Assessment Report sent to external reviewers and NICE: 25/7/05
Final Assessment Report submitted: 16/9/05

b. **Competing interests**

None

c. **External review**:

The Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking which we will hold on file. Comments from referees and the Technical lead, together with our responses will be made available to NCCHTA in strict confidence for editorial review and approval.

F. Appendices

1) Draft search strategies
2) Draft data extraction templates
3) Quality Assessment Instruments
4) Drummond ten-point check-list for assessing economic evaluations
5) Background

Appendix 1) Draft search strategies (Medline only)

Draft Medline clinical effectiveness search strategy

1 (hepatitis c or HCV).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Hepatitis C/
3 Hepatitis C, Chronic/
4 Hepacivirus/
5 1 or 2 or 3 or 4
6 (peginterferon$ or peg-ifn or peg-interferon$ or (pegylat$ adj3 interferon$) or peg$ or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or Pegasys).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 limit 7 to (english language and yr=2003-2005)
9 exp interferon type i, recombinant/ or exp interferon-alpha/ or exp interferon alfa-2a/ or exp interferon alfa-2b/ or exp interferon alfa-2c/
10 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab.
11 9 or 10
12 11 and 5
13 limit 12 to (english language and yr=2000-2005)
14 13 not 8
15 meta-analysis/
16 (meta analysis or metaanalysis).ab,pt,ti.
17 (systematic$ adj2 (review$ or overview$)).ti,ab,pt.
18 or/15-17
19 (letter or editorial or comment).pt.
20 18 not 19
21 randomized controlled trial.pt.
22 controlled clinical trial.pt. (
23 randomized controlled trials/
24 random allocation/
25 double-blind method/
26 single-blind method/
27 exp evaluation studies/
28 exp clinical trials/
29 clinical trial.pt.
30 (clin$ adj5 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
33 exp placebos/
34 placebo$.tw.
35 random$.tw.
36 exp research design/
37 32 or 33 or 34 or 35 or 36
38 31 or 37
39 8 and 20
40 8 and 38
41 14 and 20
42 14 and 38

Appendix 2) Draft data extraction templates

Template for RCTs

Reference and Design	Intervention	Participants	Outcome measures
Surname ,Year, ref citation: Trial design: Country:	<u>Intervention 1:</u> n = Drug 1 Dose: Duration: Dose: Duration: Drug 2 Dose: Duration: <u>Intervention 2:</u> n = Drug 1 Dose: Duration: Dose: k Duration: Drug 2 Dose: Duration: <u>Intervention 3:</u> n = Drug 1 Dose: Duration: Drug 2 Dose: Duration:	Total numbers involved: Eligibility: Recruitment: Genotypes (proportions) 1: 2 or 3: 4, 5 or 6: Exclusion criteria: Baseline characteristics: • Sex: • Age (mean & range): • Ethnic groups: • Viral Load: • ALT level • Fibrosis score • Necro-inflammatory score Losses to follow up: Compliance:	Primary outcomes used: Secondary outcomes used: Length of follow up:

Outcome	Intervention 1	Intervention 2	Intervention 3
Viral Response 4 wk 12 wk end of treatment follow-up (SVR) SVR by genotype 1 2 or 3 4, 5, or 6 Other Viral Response outcomes			
Histology (proportion with improvement) Inflammation mean change Fibrosis mean change			

Adverse Events dose discontinuation for any adverse event dose reduction for any adverse event anaemia neutropenia			
Additional Results (e.g., early response factors adverse events comparisons): Methodological comments: *Allocation to treatment groups:* *Allocation concealment:* *Blinding of outcome assessors:* *Analysis by intention to treat:* *Comparability of treatment groups at pre-treatment:* *Method of data analysis:* *Power analysis:* *Attrition/drop-out:* General comments: *Generalisability:* *Conflict of interests:* *Other:* *Definitions:*			

Appendix 2 (cont) Template for systematic reviews

<table>
<tr><td colspan="2">Extracted by: Date:</td></tr>
<tr><td>Reference and Design</td><td>Methods</td></tr>
<tr><td>Author

Year

Country:

Funding:</td><td>Aim (Question):

Search strategy: databases and other sources searched; years searched

Inclusion criteria used:
Interventions:
Participants:
Outcome measures:
Study design:

Quality assessment:

Method of analysis:

Application of methods:</td></tr>
<tr><td colspan="2">Results (including):
• Quantity and quality of included studies.
• What was the combined treatment effect? (including point estimates and confidence intervals/standard deviations, P values etc for each outcome assessed):
• Assessment of heterogeneity:</td></tr>
<tr><td colspan="2">Comments:
• e.g. funding, conflicts of interest, any other methodological elements that may affect the rigour of the systematic review</td></tr>
</table>

Appendix 3) Quality Assessment Instruments

a. Quality assessment for RCTs (Quality Criteria - CRD Report 4)[3]

Quality criteria for assessment of experimental studies

Criterion	*Judgement**
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

* e.g. adequate; inadequate; not reported; unclear

b. Quality assessment for Systematic Reviews

Quality assessment for systematic reviews using the DARE criteria

Quality Item	**Yes/No/Uncertain**	**Methodological Comments**
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?		
2. Is there evidence of a substantial effort to search for all relevant research?		
3. Is the validity of included studies adequately assessed?		
4. Is sufficient detail of the individual studies presented?		
5. Are the primary studies summarised appropriately?		

Appendix 4) Drummond ten-point check-list for assessing economic evaluations

(**Drummond M et al. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford. Oxford University Press. 1997**)

1. Was a well-defined question posed in answerable form?

1.1. Did the study examine both costs and effects of the service(s) or programme(s)?
1.2. Did the study involve a comparison of alternatives?
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?

2.1. Were there any important alternatives omitted?
2.2. Was (should) a do-nothing alternative be considered?

3. Was the effectiveness of the programme or services established?

3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?
3.2. Was effectiveness established through an overview of clinical studies?
3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. Were all the important and relevant costs and consequences for each alternative identified?

4.1. Was the range wide enough for the research question at hand?
4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)
4.3. Were the capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?

5.1. Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?
5.2. Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were the cost and consequences valued credibly?

6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)
6.2. Were market values employed for changes involving resources gained or depleted?
6.3. Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
6.4. Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?

7. Were costs and consequences adjusted for differential timing?

7.1. Were costs and consequences that occur in the future 'discounted' to their present values?
7.2. Was there any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?

8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?

9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?
9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?
9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?

10. Did the presentation and discussion of study results include all issues of concern to users?

10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?
10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?
10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?
10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

Appendix 5) Background

Description of underlying problem

Chronic hepatitis C (HCV) is a slowly progressive disease of the liver caused by the hepatitis C virus. It is believed that 100 - 170 million people worldwide are infected, whilst in the UK the prevalence is estimated at between 0.1% and 1%. Around two-thirds of those infected are men. The number of people presenting with liver complications is expected to rise considerably over the coming decades.

The natural history of the disease is not completely understood but after exposure around 20% will develop acute hepatitis, some of whom will experience malaise, weakness and anorexia. Up to 80% of those exposed fail to clear the virus and go on to develop chronic hepatitis. Disease progression is slow and variable, occurring over 20 - 50 years. Between 5-20% of those infected develop cirrhosis within 20 years and 1 - 4% of these are at high risk of hepatocellular carcinoma[7]. A third may never progress to cirrhosis or will not progress for at least 50 years[8], and patients often do not become symptomatic until liver disease is advanced. Some patients with end stage liver disease or hepatocellular carcinoma may require liver transplantation, with HCV being the major cause of transplantation in Europe and the USA. Estimates indicate that around 200,000 people in England have chronic hepatitis C, with approximately only 38, 000 diagnoses.

HCV genotype, of which there are up to 11, is the most important factor predicting treatment outcome. In general, genotypes 1a, 1b and 4 respond less favorably to treatment in comparison to other genotypes. Prevalence varies geographically with genotype 1a common in North and South America, and Australia, and 1b mostly found in Europe and Asia. Genotype 2a is common in Japan and China, 2b is prevalent in the US and Northern Europe, 3a is most common in Australia and South Asia, whilst 4 is commonly found in Egypt and central Africa. Baseline viral load also predicts treatment outcome.

Disease severity is usually classed as being mild, moderate or severe. Mild HCV is distinguished from moderate-to-severe disease using a classification system applied to liver biopsy samples. Using the Ishak system histological appearances are classified as 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.

As well as liver histology, bio-chemical markers are also used to stage the severity of liver damage. (e.g. Alanine amino-transferase (ALT) levels). Patients with persistently normal ALT levels are considered as having mild HCV, although this does not necessarily preclude liver damage[9]. The results of routine liver tests correlate poorly with both necroinflammatory and fibrosis scores found on liver biopsy[10].

Anti-viral treatment in patients with mild disease (thought to comprise up to 30% of those chronically infected, based on persistently normal ALT levels[11]) has generally not been indicated since it is unclear, in the absence of treatment, how many would progress to advanced disease (and at what rate) and how many would remain in their current disease state (although recently the Trent HCV Study group reported that, based on their cohort of 219 patients with predominantly mild HCV, 33% showed significant fibrosis progression on biopsy over a median period of 30 months[12]). Furthermore, the adverse effects associated with anti-viral treatment can be difficult for some patients to tolerate and given the uncertainty around what would be prevented by treatment a policy of 'watchful waiting' has been employed. However, it has recently been suggested that treatment may be beneficial if an improvement in health related quality of life can be demonstrated. Several studies have shown that patients with HCV exhibit low quality of life scores independent of disease severity[13;14]. Symptoms include fatigue, nausea, depression, headache and cognitive impairment (so-called 'brain fog'). If treatment can be demonstrated to improve quality of life this would add weight to the decision to treat this patient group.

Another issue is the role of biopsy in guiding treatment decisions. Liver biopsy is generally performed to stage the severity of disease and to enable clinicians to decide whether to treat or not. However, biopsy can be a painful procedure, and carries the risk of complications (e.g. hepatic bleeding) including, in a minority of cases, mortality. The Royal College of Physicians and the British Society of Gastroenterology state in their clinical guidelines (2001)[10] that the decision to offer treatment should be influenced by histological findings. They recommend that treatment can be reasonably withheld in patients with mild disease on liver biopsy but that these patients should be reviewed every 6 months, with repeat liver biopsy every 2-3 years or if there is a significant change in liver function tests (i.e. 2-3 times normal levels). If the biopsy shows evidence of progressive liver disease, treatment should then be considered. The guidelines also recommend that liver biopsy should be performed in all patients found to be viraemic, whether or not liver function tests are abnormal (e.g. ALT).

However, it has been suggested that in some sub-groups a biopsy may not be necessary as most patients will attain a sustained viral response to anti-viral treatment. In the pivotal trials of pegylated interferon and ribavirin in patients with moderate-to-severe disease reported in our previous assessment report, SVRs reached as high as 80% in patients with genotypes 2 and 3 (the genotypes which tend to correlate most strongly with treatment response). Consensus is now that these patients would automatically be eligible for treatment and consequently a biopsy would no longer be required to guide treatment decisions. In 2003 a licence variation for pegylated interferon alfa-2a was issued in Europe with the removal of the words 'histologically proven' hepatitis C from the indication. If corresponding response rates in patients with mild HCV are comparable to those with moderate-to-severe disease it could be argued that biopsy should also be withheld in this patient group.

A final issue to consider is the value of stopping treatment early in patients who have not attained a viral response after 12 weeks, thus sparing them adverse effects, and leading to potential cost savings to health services. A pooled analysis of the pivotal RCTs of pegylated interferon and ribavirin in moderate-to-severe disease found that 19% of patients failed to respond by 12 weeks, and only a minority of them later achieved an SVR[15]. It will be important to assess the proportion of patients with mild disease who fail to achieve an early response when treated with pegylated and non-pegylated interferon, and to gauge cost-effectiveness of discontinuing treatment early.

Technologies to be appraised

Interferon alfa-2a / 2b

Interferon alfa has been used in the treatment of chronic hepatitis C for a number of years, primarily as a single agent, until the introduction of combination therapy with ribavirin in 1999. Interferons are naturally occurring proteins with complex effects on immunity and cell function, and there are at least 15 different molecular species. Interferon alfa was the first pure human protein found to be effective in the treatment of cancer and has been used to treat chronic myelogenous leukaemia and other myeloproliferative disorders, renal carcinoma and infections such as chronic hepatitis B.

Three preparations are available:

- interferon alfa-2a ("Roferon A", Roche)
- interferon alfa-2b ("Intron A", Schering-Plough)
- interferon alfa-2b ("Viraferon, Schering-Plough)

NICE issued guidance to the health service in England and Wales in 2000 recommending the use of interferon alfa and ribavirin for the treatment of chronic hepatitis C based on a Technology Assessment Report by SHTAC[1].

Pegylated interferon alfa-2a / 2b

A newer 'pegylated' derivative of interferon alfa has become available recently, superseding the use of 'conventional' non-pegylated interferon. Pegylation involves the attachment of an inert polyethylene glycol polymer to the interferon molecule to produce a larger molecule with a prolonged half life. Pegylation prolongs the biological effect necessitating fewer injections and therefore is more convenient for patients. There are differences between the two pegylated interferons, such as the size and structure of their polyethylene glycol molecule, and the bond between the PEG molecule and the interferon.

The pegylated interferons are licensed in Europe for the treatment of chronic hepatitis C in combination with ribavirin (or as monotherapy in those for whom ribavirin is contra-indicated). Treatment is indicated in both previously untreated patients, and for those who have previously been treated with, and responded to, interferon alfa but who have subsequently relapsed.

Three preparations are available:

- 40 kD Pegylated interferon alfa-2a ("Pegasys"; Roche). Currently indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV-RNA, including patients with compensated cirrhosis. A licence variation was announced in 2003 to remove the phrase "histologically proven" for patients with genotypes 2 and 3. Further, the European Medicines Agency (EMEA) announced in November 2004 that it had approved Pegasys for the treatment of chronic hepatitis C patients with persistently normal liver enzymes (it had previously been indicated in patients with elevated ALT levels).
  - Dose: 180 µg/week via subcutaneous injection.
- 12 kD Pegylated interferon alfa-2b ("PegIntron", Schering-Plough). Currently indicated for the treatment of adult patients who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.
  - Dose: 1.5 µg/kg/week via subcutaneous injection.
- 12 kD Pegylated interferon alfa-2b ("ViraferonPeg"; Schering-Plough). (licensed indication – as for PegIntron).

Pegylated interferon alfa in combination with ribavirin is the current 'gold standard' treatment for chronic moderate-to-severe hepatitis C. In 2004 NICE issued guidance to the health service recommending this combination, based on a Technology Assessment Report by SHTAC[2].

Ribavirin

Ribavirin is a synthetic nucleoside analogue with a broad spectrum of antiviral activity against DNA and RNA viruses. It is indicated in combination with pegylated interferon alfa or interferon alfa for patients with chronic hepatitis C not previously treated, without liver decompensation and who have fibrosis or high inflammatory activity or for relapse following previous response to interferon alfa.

Two preparations are available for use in chronic hepatitis C:

- "Rebetol", Schering-Plough.
  - Dose: body-weight < 65 kg, 400 mg twice daily; body-weight 65–85 kg, 400 mg in the morning and 600 mg in the evening; body-weight over 85 kg, 600 mg twice daily.
- "Copegus", Roche.
  - Dose: body-weight < 75 kg, 400 mg in the morning and 600 mg in the evening; body-weight 75 kg and over, 600 mg twice daily. For patients with genotypes 2 or 3 the dose of Copegus is lower (800mg), usually administered as 400mg twice daily.

Costs

Economic evaluations of interventions for Hepatitis C report substantial costs for patients due progression to high morbidity/ mortality health states (such as hepatocellular carcinoma) for a proportion of cases. Steinke's assessment of the costs of viral hepatitis reported that patients with Hepatitis C had three times the number of hospital admissions and a cost per admission 8% greater age/sex matched controls in the general population[16].

- A 24 week course of conventional interferon alfa costs £1166 (3 x 3 million units per week). This compares to costs for pegylated interferon monotherapy of £3408 (Pegasys 180 µg once weekly) and £3888 (PegIntron, 1.5 µg /kg once weekly).
- For patients with genotype 1 the cost of 48 weeks IFN combination therapy with ribavarin is £8366.
- For patients with genotypes 2/3 the cost of 24 weeks IFN combination therapy with ribavirin is £4183.
- For patients with genotype 1 the costs of 48 weeks PEG combination therapy with ribavarin are £12,783 (Pegasys 180 µg once weekly and Copegus 600 mg twice a day) and £13,704 (PegIntron, 1.5 µg/kg once weekly and Rebetol 400 mg in the morning and 600 mg in the evening).
- For patients with genotypes 2/3 the cost of 24 weeks PEG combination therapy with ribavarin are £5397 (Pegasys 180 µg once weekly and Copegus 400 mg twice a day) and £6852 (PegIntron, 1.5 µg/kg once weekly and Rebetol 400 mg in the morning and 600 mg in the evening).
- All these calculations assume an average patient weight of 75 kg.

Reference List

(1) Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. Health Technology Assessment 2000; 4(33):1-67.

(2) Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon alpha 2a and 2b in combination with ribavirin in the treatment of chronic hepatitis C : a systematic review. Health Technology Assessment 2004; 8(39).

(3) NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for those Carrying Out or Commissioning Reviews (2nd Edition). CRD Report Number 4 (2nd Edition). 2001. York, York Publishing Services Ltd.
Ref Type: Report

(4) Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981; 1(5):431-435.

(5) Ishak K, Baptista A, Bianchi L, Callea F, De GJ, Gudat F et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995; 22(6):696-699.

(6) Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996; 24(2):289-293.

(7) Di Bisceglie AM. Hepatitis C. LANCET 1998; 351(9099):351-355.

(8) Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. LANCET 349, 825-832. 1997.
Ref Type: Journal (Full)

(9) Puoti C, Magrini A, Stati T, Rigato P, Montagnese F, Rossi P et al. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels.[see comment]. Hepatology 26(6):1393-8, 1997.

(10) Booth J, O'Grady J, Neuberger J, on behalf of the Royal College of Physicians of London and the British Soceity of Gastroenterology. Clinical guidelines on the management of hepatitis C. Gut 2001; 49(Suppl I):i1-i21.

(11) Puoti C, Bellis L, Castellacci R, Montagnese F, Bergami N, Petrone De LP. HCV carriers with persistently normal aminotransferase levels.[comment]. Hepatology 40(1):266-7; author reply 267-8, 2004.

(12) Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Gut 2004; 53(3):451-455.

(13) Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. HEPATOLOGY 2002; 35(2):433-439.

(14) Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis [see comments]. HEPATOLOGY 1998; 27(1):209-212.

(15) Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C.[see comment]. Hepatology 2003; 38(3):645-652.

(16) Steinke DT, Weston TL, Morris AD, MacDonald TM, Dillon JF. Epidemiology and economic burden of viral hepatitis: an observational population based study. Gut 2002; 50(1):100-105.