Complete Summary

GUIDELINE TITLE

Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 31 p. (Technology appraisal guidance; no. 106).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Mild chronic hepatitis C

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases

Internal Medicine
Pharmacology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the clinical effectiveness and cost-effectiveness of pegylated and non-pegylated interferon alfa and ribavirin for the treatment of adults with histologically mild chronic hepatitis C infection

TARGET POPULATION

Patients 18 years and older with mild chronic hepatitis C

INTERVENTIONS AND PRACTICES CONSIDERED

1. Peginterferon alfa and ribavirin combination therapy
2. Peginterferon alfa monotherapy

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - 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
- Costs per quality adjusted life year (QALY)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent

academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessment Centre (see the "Availability of Companion Documents" field.)

Clinical Effectiveness

Search Strategy

A sensitive search strategy was developed, tested, and refined by an experienced information scientist. Separate searches were conducted to identify studies of clinical effectiveness; cost-effectiveness; quality of life; resource use/costs; and epidemiology/natural history (see Appendices 3 to 6 in the Assessment Report for search strategies [refer to the "Availability of Companion Documents" field]). Search filters were run where possible to locate randomised controlled trials and systematic reviews. The strategies were applied to the following electronic databases:

- Cochrane Systematic Reviews Database
- Cochrane Central Register of Controlled Trials
- National Health Service (NHS) Centre for Reviews and Dissemination (CRD) (University of York) databases: Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, NHS Economic Evaluations Database (EED)
- Medline (Ovid)
- PreMedline
- PubMed
- Embase (Ovid)
- EconLit
- National Research Register
- ISI Web of Science - Science Citation Index
- ISI Web of Knowledge Proceedings
- BIOSIS
- www.clinicaltrials.gov
- Current Controlled Trials

Searches were designed to build on the searching employed by the Assessment Group's previous assessment reports on (non-pegylated) interferon alfa in 2000 and pegylated interferon alfa in 2004, as follows:

- Searches for clinical-effectiveness and cost-effectiveness studies of pegylated interferon alfa were run from 2003 to July 2005 (the previous assessment report on pegylated interferon for hepatitis C virus [HCV] searched up to the end of 2002).
- Searches for clinical-effectiveness and cost-effectiveness studies of non-pegylated interferon alfa were run from the period 2000 to July 2005. The previous assessment report on non-pegylated interferon alfa for hepatitis C searched up to the end of 1999/early 2000. To identify studies published prior to 2000, the Assessment Group rescreened the original database, looking specifically for randomized controlled trials (RCTs) which included patients with mild HCV.

- A search for general cost and cost-effectiveness studies in HCV (i.e., not limited to just interferon alfa) was run from 2000 to July 2005.
- Searches for health related quality of life and epidemiological/natural history studies were run from 2003 to July 2005.

Bibliographies of retrieved papers were screened, where possible, for relevant studies. Manufacturer and sponsor submissions to the NICE were also searched for studies. All search results were downloaded into a Reference Manager database.

The Assessment Group also searched the following websites for completed or on-going studies, and background material:

- British Association for the Study of the Liver (BASL)
- European Association for the Study of the Liver (EASL)
- American Association for Study of Liver Diseases
- British Society of Gastroenterology
- Foundation for Liver Research
- British Liver Trust
- British Association for Sexual Health and HIV
- HIV and hepatitis.about.com/
- Food and Drug Administration
- Health Protection Agency
- Department of Health (England)

Inclusion and Exclusion Criteria

Each study was screened on the basis of title and/or abstract for inclusion by one reviewer. A random 10% sample of these was screened independently by a second reviewer. Publications for those marked as relevant were then ordered for further screening. An inclusion worksheet was used (see Appendix 7 of the Assessment Report [refer to the "Availability of Companion Documents" field]). Further details on the criteria are set out below.

Interventions

Studies reporting the following interventions were included:

- 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.

Patients

With a few exceptions, it is not always apparent from the title or abstract of a clinical trial whether or not the patients included have mild, moderate, or severe HCV. It is therefore necessary to examine the baseline characteristics of included patients (where reported) to assess the proportion who can be classed as having histologically mild liver disease. For a detailed discussion, see section 3.2.2 in the Assessment Report (refer to "Availability of Companion Documents" field.

Types of Studies

Systematic reviews of randomised controlled trials (RCTs) and Phase II/III RCTs comparing the different drugs with placebo, each other, or best supportive care, were included in the review of clinical-effectiveness. Also included were full economic evaluations of the specified interventions in patients with chronic mild HCV. For studies reporting health related quality of life and epidemiology/natural history the Assessment Group included a range of study designs (e.g., cohort studies, cross-sectional surveys). Studies published as abstracts or conference presentations were included in the primary analysis of clinical and cost-effectiveness.

Outcomes

See the "Major Outcomes Considered" field above.

Cost Effectiveness

A systematic literature search was undertaken to identify economic evaluation comparing interferon-based treatment for adults with mild chronic hepatitis C compared to delaying treatment until the disease has progressed to moderate or severe chronic hepatitis C or compared to best supportive care. The details of databases searched and search strategy are documented in Appendix 4 of the Assessment Report (refer to the "Availability of Companion Documents" field). The manufacturers' submissions to NICE were reviewed for additional studies.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by a health economist. Economic evaluations were eligible for inclusion if they were full economic evaluations reporting on the cost-effectiveness of (pegylated or non-pegylated) interferon treatment for adults with mild chronic hepatitis C compared to treatment once the disease has progressed to moderate or severe chronic hepatitis C or compared to best supportive care.

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

Three trials of peginterferon alfa-2a and five trials of interferon alfa-2b that included people with chronic hepatitis C, at least 70% of whom had mild disease, were included in the assessment report.

Cost Effectiveness

A total of 316 cost-effectiveness publications were identified. Sixty-five of these were full economic evaluations. Six of these were included.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the Southampton Health Technology Assessment Centre (See the "Availability of Companion Documents" field.)

Data Extraction Strategy

Data were extracted from the included clinical-effectiveness studies using a standardised template. Data extraction was undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion. Full data extraction forms of all the included studies can be found in Appendices 8 to 17 of the Assessment Report (see the "Availability of Companion Documents" field).

Quality Assessment Strategy

The quality of included systematic reviews and randomized controlled trials (RCTs) was assessed using National Health Service (NHS) Centre for Reviews and Dissemination (CRD) (University of York) criteria. Quality criteria were applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

Methods of Analysis/Synthesis

A narrative synthesis was undertaken with the main results of the included clinical effectiveness and cost-effectiveness studies described qualitatively, and in tabular form. A meta-analysis was not possible due to heterogeneity in the interventions and comparators evaluated. Where data allowed, clinical and cost-effectiveness was assessed according to patient sub-groups (e.g., by genotype, baseline viral load, etc).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The assessment report found six studies examining the cost effectiveness of treatment for people with mild disease. Three of these studies compared interferon combination therapy with no treatment rather than with delayed treatment. These three studies showed that interferon combination therapy was cost effective when compared with standard care (all estimated mean incremental cost-effectiveness ratios [ICERs] were less than £10,000 per quality-adjusted life year [QALY]). Two studies compared early treatment with peginterferon alfa combination therapy with delayed treatment. They showed that, for genotypes 2 and 3, early treatment is apparently cost effective when compared with delayed treatment, but the case for early treatment for genotype 1 is less clear.

See section 4.2 in the original guideline document for a detailed discussion of the cost-effectiveness evidence and interpretation, including information about non-1 genotype hepatitis C virus (HCV), genotype 1 HCV, monotherapy: all genotypes, and sensitivity analyses.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The National Institute for Health and Clinical Excellence (NICE) issued guidance on the use of interferon alfa, pegylated interferon alfa (peginterferon alfa) and ribavirin in the treatment of people with moderate to severe chronic hepatitis C in January 2004 (*NICE technology appraisal guidance* 75; TA 75). The evidence in this appraisal relates to the extension of this treatment to people with mild chronic hepatitis C. For people with moderate or severe disease, the guidance in TA 75 still stands.

- Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C.
- Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.
- The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ("watchful waiting") should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen.
- The duration of treatment should vary according to the licensed indications of the chosen drug, the genotype of the virus, the initial viral load, the response to treatment, and the treatment regimen chosen.
- Second or subsequent courses of treatment are not recommended for people who have been treated with a first course of either combination therapy or monotherapy with peginterferon alfa if they have not had an early response (as indicated by reduction in viral load at 12 weeks).
- There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who are under the age of 18 years, or those who have had a liver transplant.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C

POTENTIAL HARMS

- Both pegylated interferon and interferon give rise to flu-like symptoms in many people.
- Ribavirin leads, in a proportion of cases, to anaemia, pruritus, rash, insomnia, and dyspnoea.

For full details of side effects and contraindications, see the Summary of Product Characteristics for each drug, available at http://emc.medicines.org.uk/.

CONTRAINDICATIONS

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QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organisations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by The National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

- "Healthcare Standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (www.nice.org.uk/TA106 [see also the "Availability of Companion Documents" field]).
    - Costing report and costing template to estimate the savings and costs associated with implementation.
    - Audit criteria (see appendix C of the original guideline document).

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 31 p. (Technology appraisal guidance; no. 106).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Aug

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 2 p. (Technology appraisal 106). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Costing template and costing report. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. Various p. (Technology appraisal 106). Available in Portable Document Format (PDF) from the NICE Web site.
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C—a systematic review and economic evaluation. Assessment report. Southampton Health Technology Assessments Centre. 2005 Oct 17. Electronic copies: Available from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1099. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the original guideline document.

PATIENT RESOURCES

The following is available:

- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Aug. 4 p. (Technology appraisal 106).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site. Also available in Welsh from the NICE Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1100. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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