Productivity improvements in hepatitis C treatment: impact on efficacy, cost, cost-effectiveness and quality of life

Lidgren M, Hollander A, Weiland O, Jonsson B

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined several current and proposed treatment strategies for hepatitis C virus (HCV). Five key steps in the development of HCV treatment were considered. These were the introduction of interferon (IFN); the introduction of ribavirin (RIB) as an add-on to IFN; the introduction of treatment according to genotype; the replacement of IFN with peginterferon (PEG); and newly proposed treatments according to genotype, viral response and viral load.

Overall, 9 strategies were evaluated, 5 currently or previously used strategies and 4 proposed strategies:

Strategy 1 was no treatment.

Strategy 2 was IFN monotherapy for 48 weeks.

Strategy 3 was IFN and RIB therapy for 48 weeks.

Strategy 4 was IFN and RIB therapy for 24 weeks for genotypes 2 and 3, and for 48 weeks for genotype 1.

Strategy 5 was PEG and RIB therapy for 24 weeks for genotypes 2 and 3, and for 48 weeks for genotype 1.

Strategy 6 was PEG and low-dose RIB therapy for 24 weeks for genotypes 2 and 3, and PEG and RIB therapy for 48 weeks for genotype 1.

Strategy 7 was low-dose PEG and RIB therapy for 24 weeks for genotypes 2 and 3, and PEG and RIB therapy for 48 weeks for genotype 1.

Strategy 8 was PEG plus RIB for 14 weeks for genotype 2 achieving rapid viral response, and 24 weeks for the remaining genotype 2 patients; PEG plus RIB for 14 weeks for genotype 3 with low viral load (<800,000 IU/mL) and rapid viral response (week 4 <600 IU/mL); 24 weeks for remaining genotype 3 patients; and PEG plus RIB for 48 weeks for genotype 1 patients.

Strategy 9 was the same as strategy 8 for genotypes 2 and 3; PEG plus RIB for 24 weeks for genotype 1 with low viral load (<600,000 IU/mL) and rapid viral response (week 4 <50 IU/mL), 72 weeks for genotype 1 with slow virological response (week 12 >50 IU/mL), and 48 weeks for the remaining genotype 1 patients.

All strategies had 24 weeks' follow-up.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.
Study population
The study population comprised a hypothetical cohort of patients with HCV. The typical patient was 45 years of age with chronic hepatitis C (CHC), without decompensated cirrhosis or hepatocellular carcinoma and with no co-infections with hepatitis B or the human immunodeficiency virus.

Setting
The setting was secondary care. The economic study was carried out in Sweden.

Dates to which data relate
The clinical data were derived from studies published between 1987 and 2006. Some data on resource use were taken from a study published in 2001. The price year was 2004.

Source of effectiveness data
The clinical and epidemiological data used in the decision model were age-specific mortality rates for the general Swedish population, estimates of progression of CHC, and the effectiveness of the interventions (e.g. rates of sustained virological response).

Modelling
A decision tree with attached Markov models was constructed to simulate the clinical and economic outcomes associated with improvements in HCV treatments over time. The model started with patients receiving treatment for CHC with possible progression to more severe health states. A simplified graphical representation of the model was reproduced. The time horizon of the model was lifetime. Annual cycles were considered.

Sources searched to identify primary studies
Clinical data were mainly derived from the literature. Specifically, the mortality rates came from Swedish statistics. Data on CHC progression were mainly derived from a long-term study. Treatment effectiveness was obtained from clinical trials. However, limited information on these studies was provided. Some assumptions were also made to simplify the model.

Methods used to judge relevance and validity, and for extracting data
The approach used to derive the clinical estimates was not reported. The authors chose clinical trials to estimate the treatment effect, owing to their high internal validity. There was no information on the methods used to combine the data.

Measure of benefits used in the economic analysis
The summary benefit measure was the quality-adjusted life-years (QALYs). These were estimated using a modelling approach. Survival data were combined with health-related utility values derived from the literature using the Short-Form 36 questionnaire. Some details of the calculation of utility scores were reported. The benefits were discounted at an annual rate of 3%.

Direct costs
The analysis of the costs was performed from the viewpoint of the third-party payer. It included the costs associated with outpatient resources, drugs and annual costs related to CHC health states. The unit costs and the quantities of resources used were presented separately. The costs were broken down by health states. A breakdown of the cost items was given for most cost categories. Data on outpatient resource use and costs were mainly derived from the accounting system of the Karolinska University Hospital at Huddinge. The drug costs came from the National Medicine Information System, based on recommended dosage per week. The costs for specific health states were derived from a
published study. Discounting was relevant, as long-term costs were evaluated, and an annual rate of 3% was used. The price year was 2004.

**Statistical analysis of costs**
No statistical analyses of the costs or resource quantities were performed.

**Indirect Costs**
Productivity costs were not considered.

**Currency**
Swedish kronor (SEK). The exchange rate from euros (EUR) was EUR 1 = SEK 9.1.

**Sensitivity analysis**
A deterministic sensitivity analysis was carried out on key model inputs such as annual costs of disease, treatment costs and several transition probabilities. The alternative values appear to have been defined arbitrarily.

**Estimated benefits used in the economic analysis**
The introduction of IFN monotherapy (strategy 2) led to an improvement in QALYs over no treatment (strategy 1) of 0.888.

The introduction of RIB in combination with IFN (strategy 3) led to an improvement over IFN monotherapy (strategy 2) of 1.331 QALYs.

The introduction of genotyping (strategy 4) was as effective as the introduction of RIB in combination with IFN (strategy 3).

The introduction of PEG (strategy 5) led to an improvement over the introduction of genotyping (strategy 4) of 0.564 QALYs.

With the exception of strategy 9, which led to an increase of 0.069 QALYs, all of the proposed treatments were as effective as strategy 5.

**Cost results**
The introduction of IFN monotherapy (strategy 2) led to an additional cost over no treatment (strategy 1) of SEK 29,391.

The introduction of RIB in combination with IFN (strategy 3) led to a reduction of SEK 22,598 over IFN monotherapy (strategy 2).

The introduction of genotyping (strategy 4) led to a reduction of SEK 44,038 over RIB in combination with IFN (strategy 3).

The introduction of PEG (strategy 5) led to an additional cost of SEK 6,153 over the introduction of genotyping (strategy 4).

All proposed treatments were less expensive than strategy 5, but strategy 9 (the most effective) led to an increment of SEK 8,269.

**Synthesis of costs and benefits**
Incremental cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

Moving from strategy 1 to strategy 2 led to an incremental cost per QALY gained of SEK 33,098.

Moving from strategy 2 to strategy 3, as well as moving from strategy 3 to strategy 4, was dominant due to higher (or similar) benefits and lower costs.

The incremental cost per QALY gained with strategy 5 over strategy 4 was SEK 10,910.

All new treatments except strategy 9 dominated strategy 5, which was similarly effective but more expensive.

The incremental cost per QALY gained with strategy 9 over strategy 8 was SEK 119,841.

The results of the sensitivity analysis showed that the base-case results were insensitive to variations in the annual cost of disease, treatment costs and most probability values. A sensitivity analysis in which it was assumed that patients with compensated cirrhosis and hepatocellular carcinoma were able to receive liver transplantation produced lower cost-utility ratios.

**Authors’ conclusions**

Newer treatments for chronic hepatitis C (CHC) over time have generally achieved a better effect at slightly higher costs, or the same effect at lower costs, suggesting that improvements in treatment have been highly cost-effective. The current genotype-guided peginterferon (PEG) plus ribavirin (RIB) treatment was a cost-effective strategy. Furthermore, of the proposed treatments, the treatment strategy involving a reduced duration of treatment for certain patient sub-groups with genotypes 2 or 3 was cost-saving, whilst having similar effectiveness to the current strategy. It was pointed out that all treatments achieved their increases in benefits at a cost that was well below the commonly used threshold of SEK 600,000 per quality-adjusted life-year (QALY).

**CRD COMMENTARY - Selection of comparators**

The selection of the comparators represents a key aspect of this study, which aimed to cover all previous, current and future treatments for patients with HCV. A description of all strategies was given. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data came mainly from published sources. However, no systematic search for these data was reported, which suggests that the primary studies might have been identified selectively. The treatment effect was appropriately taken from clinical trials of previous treatments, while disease progression was derived from a study with long follow-up. However, the fact that very limited information about the primary sources was given prevents an objective assessment of the validity of these data.

**Validity of estimate of measure of benefit**

QALYs are an appropriate benefit measure that captures the impact of the interventions on both survival and health-related quality of life, which are two relevant dimensions of health for patients with CHC. Discounting was performed, as recommended by Swedish guidelines. Some information on the sources of the utility scores was provided.

**Validity of estimate of costs**

The analysis of the costs was consistent with the perspective adopted in the study. The authors stated that the indirect costs might be relevant in advanced CHC, but were not included because of the lack of reliable data. However, their inclusion would have further favoured the cost-effectiveness of the interventions. A breakdown of the costs was reported for disease costs, for which the unit costs and quantities of resources used were given. The sources of the costs were reported for all items. Disease costs were derived from a published study, which was not described. Statistical analyses of the costs were not carried out, but the cost estimates were varied in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.
Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. The sensitivity analysis partially addressed the issue of the external validity of the analysis, as the use of alternative estimates was investigated. The authors noted that clinical data regarding proposed treatments came often from small or non-randomised studies, which have a limited internal validity.

Implications of the study
The study results support the current treatment for CHC, which consists of genotype-guided PEG plus RIB treatment. The proposed treatments have the potential for being similarly cost-effective.

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None stated.

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Other publications of related interest
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Indexing Status
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MeSH
Antiviral Agents /economics /therapeutic use; Cost-Benefit Analysis; Disease Progression; Drug Administration Schedule; Efficiency; Female; Genotype; Health Care Costs /statistics & numerical data; Hepatitis C, Chronic /economics /genetics /therapy; Humans; Interferons /economics /therapeutic use; Male; Markov Chains; Models, Economic; Quality of Life; Ribavirin /economics /therapeutic use; Treatment Outcome

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