Clinical and Cost-effectiveness of Interferon-based Therapies for Chronic Hepatitis C Virus Infection

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CADTH takes sole responsibility for the final form and content.
REPORT IN BRIEF
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Technology and Condition
Interferon alfa (IFN) and pegylated interferon alfa (PegIFN) in combination with ribavirin (RBV) for the treatment of chronic hepatitis C virus (CHC) infection.

Issue
Approximately 240,000 Canadians are infected with hepatitis C virus; although less than half are aware of it. The number of deaths and complications from CHC are expected to increase in the next 10 to 20 years, as is the cost of treating these complications. There is uncertainty about the costs and consequences of antiviral therapy, and a need to assess the value in funding these drugs.

Methods and Results
Clinical data on beneficial and adverse outcomes of antiviral therapy were extracted from randomized controlled trials and a previous CADTH systematic review. The net health impact was estimated using a decision-analytic model in terms of quality-adjusted life-years (QALYs) and life-years (LYs) saved, from the perspective of Canadian ministries of health. The analysis compared PegIFN+RBV to IFN+RBV and to no antiviral therapy. The simulated population (base case) had an average age of 43 years, with a mixture of liver disease states, hepatitis C virus genotypes, and gender, consistent with the Canadian CHC population.

Implications for Decision Making
- Antiviral therapies may improve health, but are not cost saving. Compared to no therapy, PegIFN+RBV was associated with 0.70 additional QALYs and C$11,800 of additional lifetime treatment costs per patient. IFN+RBV was associated with 0.51 additional QALYs and C$11,500 of additional lifetime costs per patient.
- Treating mild CHC can be less effective and consumes additional resources. Compared to no therapy, PegIFN+RBV was associated with 0.30 additional QALYs and C$14,900 of additional lifetime costs per patient.
- Genotype, age, and disease progression rate affect the efficiency of treatment. The additional health system costs to obtain a QALY increase as the disease progression rate decreases, and as the age of initiating therapy increases. Treating genotypes 2 and 3 infections cost less per QALY than patients with other genotypes.
- Important factors that affect optimal treatment decisions are still unknown. There are knowledge gaps about CHC, factors affecting a patient’s prognosis, and the effect of treatment on disease progression across patient subgroups.

1 Introduction

Hepatitis C virus (HCV) infection is a cause of chronic liver disease. It is transmitted through contact with infected blood or body fluids. An estimated 204,000 to 282,000 Canadians (0.8% of the population) are infected with HCV; although only 40% are aware of it.1,2 Genotype 1 is the most common in Canada, followed by genotypes 2 and 3.3,4 No vaccine is available to prevent HCV infection. About 3,000 to 6,000 Canadians are newly diagnosed every year, with 80% of cases resulting from injection drug use.5 Among newly infected adults, 15% to 25% will develop a short-term infection and spontaneously clear the virus. The remaining 75% to 85% will develop persistent viremia and chronic HCV infection (CHC).6-11 Most people with CHC remain largely asymptomatic for the first two or three decades after infection, but 9% to 30% will develop liver complications, such as cirrhosis and hepatocellular carcinoma.6,9-13

Treatments for CHC range from lifestyle counselling to the use of antiviral prescription drugs. The antiviral therapies approved in Canada are based on interferon alfa (IFN) (Table 1). IFN alfa-2a and IFN alfa-2b are proteins that differ by one amino acid. The conjugation of IFN with a polyethylene glycol molecule to form pegylated IFN (PegIFN) reduces the elimination rate, allowing less frequent dosing. IFN and PegIFN are administered by subcutaneous injection. Both are approved in Canada as monotherapy and as combination therapy with oral ribavirin (RBV).

The Canadian Consensus Conference guidelines on the treatment of viral hepatitis C provide recommendations that are specific to HCV genotype, and are based on patients’ weight.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Generic Name (brand name)</th>
<th>Dose</th>
<th>Duration of Therapy</th>
<th>Cost* for 1 Course of Therapy (C$)</th>
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<tbody>
<tr>
<td>IFN alfa-2a (Roferon®-A)</td>
<td>6 MIU, 3 times/wk for 3 months then 3 MIU, 3 times/wk</td>
<td>24 wks</td>
<td>3,672</td>
<td></td>
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<tr>
<td>IFN alfa-2b (Intron A®)</td>
<td>3 MIU, 3 times/wk</td>
<td>48 to 72 wks</td>
<td>4,894 to 7,342</td>
<td></td>
</tr>
<tr>
<td>PegIFN alfa-2a (Pegasys®)</td>
<td>180 µg, 1 time/wk</td>
<td>48 wks</td>
<td>19,000</td>
<td></td>
</tr>
<tr>
<td>PegIFN alfa-2b (Unitron Peg™, known as Peg-Intron® until January 2003)</td>
<td>1 µg/kg/wk</td>
<td>48 wks</td>
<td>19,000</td>
<td></td>
</tr>
<tr>
<td>PegIFN alfa-2a plus RBV (Pegasys RBV™)</td>
<td>PegIFN: 180 µg/wk RBV: 800 to 1,200 mg/day, based on weight and genotype</td>
<td>24 to 48 wks</td>
<td>9,500 to 19,000</td>
<td></td>
</tr>
<tr>
<td>IFN alfa-2b plus RBV (Rebetron®)</td>
<td>IFN: 3 MIU, 3 times/wk RBV: 1,000 to 1,200 mg/day, based on weight</td>
<td>24 to 48 wks</td>
<td>9,026 to 19,948</td>
<td></td>
</tr>
<tr>
<td>PegIFN alfa-2b plus RBV (Pegetron®)</td>
<td>PegIFN: 1.5µg/kg/wk RBV: 800 to 1,200 mg/day, based on weight and genotype</td>
<td>24 to 48 wks</td>
<td>9,026 to 19,948</td>
<td></td>
</tr>
</tbody>
</table>

MIU=millions of international units; µg=micrograms; wk=week; wks=weeks; C$=Canadian dollars; *source for manufacturers’ list price is January 2004 edition of PPS Pharma Publications; excludes pharmacy mark-up and pharmacist’s professional fee; ‘products have been discontinued since Technology Report initiated.17
The manufacturers’ list prices for PegIFN+RBV and IFN+RBV range from C$9,000 to C$20,000 for 24 to 48 weeks of treatment respectively (Table 1). As of May 2006, IFN-based therapies are available in most publicly funded drug plans in Canada, often as a restricted benefit.

Systematic reviews have evaluated the impact of IFN-based therapies on surrogate endpoints, but have omitted an adequate analysis of mortality and serious morbidity. Although Canadian guidelines recommend PegIFN+RBV as standard treatment for CHC, there is no direct evidence that altering surrogate endpoints with IFN-based therapies reduces HCV-related complications and mortality. From an economic perspective, there is a paucity of data on the direct and indirect costs of HCV infection in Canada. The number of deaths and complications from CHC are expected to increase in the next 10 to 20 years, as is the cost of treating these complications.1,14

2 Objectives

Our objectives were to assess the clinical and cost-effectiveness of IFN-based combination drug therapies in adults experiencing CHC, who have not been treated previously with PegIFN or IFN-based therapies. The comparators for the clinical outcomes analysis were IFN alone, IFN+RBV, and PegIFN+RBV. The comparators for the cost-effectiveness analysis were no antiviral therapy (AVT), IFN+RBV, and PegIFN+RBV.

3 Methods

Clinical Outcomes Review

A search for systematic reviews and reports on drug therapy was conducted. Bibliographies of retrieved reports were manually searched. Reports of safety were identified. Ultimately, an original systematic review of the literature was not conducted. Instead, one reviewer selected reports of RCTs from the bibliography of a systematic review conducted by the Agency for Healthcare Research and Quality.18 References were included if the trial randomized at least one treatment arm to IFN+RBV and another to IFN alone, or randomized patients to receive PegIFN+RBV and IFN+RBV. Individual trial quality was not assessed. The manufacturers of Rebetron® and Pegetron™ were contacted for additional information.

Selected studies were re-examined for data on mortality and serious morbidity that were estimated by serious adverse events (SAEs), withdrawals due to adverse events (AEs), quality of life, and virological endpoints. Two reviewers abstracted data independently. Disagreements were resolved by using forced consensus (unanimity minus one) with a neutral third party. Data were combined by meta-analysis. A Peto odds ratio (OR) was calculated for death. Relative risk (RR), absolute risk, or rate ratio (RateR) was calculated for other outcomes. Statistical heterogeneity across trials was assessed using a chi-square test for each outcome.

Economic Analysis Methods

The economic analysis consisted of a systematic review of published economic evaluations, and an original economic evaluation and budget impact analysis.

A search of published literature was conducted until January 2006. A filter was used to retrieve economic studies. There was no language restriction. Reports were included if they were full economic evaluations, addressed treatment-naïve adults with CHC, and compared IFN+RBV with PegIFN+RBV. Two reviewers
independently applied the inclusion criteria; disagreements were resolved through consensus. Subsequently, data were independently extracted by two reviewers. Uncertainties and disagreements were resolved by referring to the original paper and, if necessary, consulting a third party. No formal quality assessment of the studies was performed.

Cost-effectiveness and cost-utility analyses were conducted using a decision-analytic Markov model. The model simulated the natural history of CHC, the treatment of HCV infection, and the impact of treatment-related SAEs in treatment-naïve adults with CHC. Canadian data were used to populate the model, where available. The time horizon was lifetime. The economic evaluation and budget impact analysis were performed from the perspectives of a publicly funded Canadian drug plan and a clinic that treats patients with CHC.

Three treatment strategies were evaluated: no antiviral treatment; IFN alfa-2b (3 MIU three times per week) plus RBV (1,000 to 1,200 mg/day) as in the 2000 Canadian practice guidelines19 and PegIFN (180 μg per week for PegIFN alfa-2a; 1.5 μg/kg per week for PegIFN alfa-2b) plus RBV (800 to 1,2000 mg/day) as in the 2004 Canadian practice guidelines.20

Genotype-specific virological response rates for the dosages and therapy time-points were obtained through data extraction from RCTs identified in the clinical outcomes review21 and from additional literature searching and consultation with experts.22-29 Virological response rates from the multiple studies were combined through weighted pooling based on sample size.

Reported outcomes were undiscounted and discounted LYs and QALYs gained, 20-year risk of CHC-related liver complications, and undiscounted and discounted ICERs (cost per LY and cost per QALY gained). The costs and health outcomes were discounted at 5% annually, with sensitivity analyses of 0% and 3%. The simulated population (base case) had an average age of 43 years, with a mix of liver disease states, HCV genotypes, and gender, consistent with the Canadian CHC population. One-way and multi-way deterministic sensitivity analyses were conducted for model parameters, to assess the robustness of the base-case results.

4 Results

Clinical Outcomes Review

a) IFN+RBV versus IFN alone

After applying the inclusion criteria, 50 reports describing 51 trials that enrolled 7,474 participants were identified. Patients were treatment-naïve,24-26,30-38 non-responders to previous treatment,39-61 relapsers,39,62-65 non-responders and relapsers with treatment modified according to initial response,66-69 non-responders and relapsers randomized together,70-72 and naïve and relapsers randomized together.73 The characteristics of patients in three trials were unknown.74,75 Sixteen trials were reported in conference-abstract form only.

b) IFN+RBV versus PegIFN+RBV

Two trials met the inclusion criteria.22,23,77,78 All participants were newly diagnosed and treatment-naïve. A total of 2,502 patients were randomized, and 2,427 participants received at least one dose of medication.

All-cause mortality (fatal SAEs)

IFN+RBV versus IFN alone: All-cause mortality data were available from eight trials24,26,34,36,51,62,68,79 enrolling 2,400 patients. All trials were <72 weeks in duration. Mortality data were presented in three trials, and implied using SAE and follow-up data in the other trials. When data were pooled, no
statistically significant difference was detected between treatment arms in all-cause mortality (Peto OR=0.37, 95% CI: 0.08 to 1.67).

*IFN+RBV versus PegIFN+RBV*: Among 2,502 patients enrolled, two patients who received IFN+RBV died (hypertensive heart disease and a motor vehicle accident), and one patient who received PegIFN+RBV died (suicide). The occurrence of all-cause mortality was not significantly different statistically between the two treatment arms (Peto OR=0.30, 95% CI: 0.03 to 3.14).

**All-cause serious morbidity (non-fatal SAEs)**

*IFN+RBV versus IFN alone*: SAE data were available from eight trials that included <30% of all participants in the 51 trials selected. The SAE data from the eight trials are presented in two reports.79,80 SAE rates were not significantly different between combination and monotherapy (RR=1.02, 95% CI: 0.84 to 1.24). The most commonly reported SAEs in the larger trials were psychiatric events, gastrointestinal events, serious infection, cardiovascular events, anemia, and thyroid disorder.

*IFN+RBV versus PegIFN+RBV*: Based on data from 2,502 participants, a significantly higher rate of non-fatal SAEs was associated with PegIFN+RBV than with IFN+RBV (RateR=1.24, 95% CI: 1.01 to 1.51) during 48 weeks of therapy and 28 weeks of follow-up.77,78 Patients who received PegIFN+RBV were significantly more likely to experience SAEs classified as “serious infection” (RateR=2.36, 95% CI: 1.21 to 4.59) and events classified as “all other SAEs” (RateR=1.43, 95% CI: 1.09 to 1.88).

**Withdrawals due to AEs**

To be evaluated as potential withdrawals due to AE, patients must have received at least one dose of medication.

a) **IFN+RBV versus IFN alone**

The likelihood of withdrawal due to AEs was estimated from 30 trials.24-26,31,33,34,36-39,41,47,49-53,55-57,59,60,62-64,68,71-73,76 Compared with patients who received IFN alone, patients who received IFN+RBV were significantly more likely to withdraw from trials because of AEs (RR=1.25, 95% CI: 1.03 to 1.52), equating with an absolute difference in risk of 2%. This implies that an extra patient would be required to withdraw due to AEs after starting therapy for every 50 treated with IFN+RBV, compared with IFN alone.

b) **IFN+RBV versus PegIFN+RBV**

Data pooled from two trials22,23 showed neither a significant increase nor decrease in withdrawals due to AEs (fixed effects estimate RR=0.97, 95% CI: 0.75 to 1.24).

**Quality of life**

a) **IFN+RBV versus IFN alone**

No trials reported on the effect of treatment on quality of life.

b) **IFN+RBV versus PegIFN+RBV**

A Food and Drug Administration (FDA) summary78 of one published trial22 reported that health-related quality of life was assessed using a self-administered questionnaire. The type of instrument used and the methods of administration were not provided. The quality of life reportedly decreased during treatment, and returned to baseline at the end of the post-treatment observation period, without significant differences detected between treatment arms.77
Virological endpoints

a) IFN+RBV versus IFN alone

A sustained viral response (SVR) is viral clearance six months after completion of AVT. SVR and early viral response were reported in 31 and 46 trials respectively. Statistical heterogeneity was detected in the meta-analyses, but was reduced when only those trials that enrolled IFN-naïve patients were pooled. The RR of not achieving SVR in these patients (n=2,443; seven trials) was reduced by 27% (95% CI: 23 to 30) (RR=0.73, 95% CI: 0.70 to 0.77). In absolute terms, these results indicate that an additional patient avoided persistent viremia for every 4.6 (95% CI: 4.1 to 5.0) patients treated with IFN+RBV instead of IFN alone. The RR of not achieving early viral response, based on 3,083 patients enrolled in 12 trials, was reduced by 30% (RR=0.70, 95% CI: 0.65 to 0.74).

b) IFN+RBV versus PegIFN+RBV

In the two trials, the RR of not achieving a sustained virological response was reduced by 13% (RR=0.87, 95% CI: 0.80 to 0.94). In absolute terms, this meant that an additional patient avoided persistent viremia for every 14 patients treated with PegIFN+RBV instead of IFN+RBV.

Economic Analysis

a) Systematic review

The electronic search yielded 148 records; 78 papers were selected for review. Of these, nine studies met the inclusion criteria. Treatment duration was 48 weeks in all studies. Eight studies indicated the cost of the drugs, which was higher for PegIFN+RBV than IFN+RBV. All studies used a health-care payer perspective with or without direct costs to the patient. Seven studies used a lifetime horizon. Seven studies applied a discount rate of 3% for costs and health outcomes, one study discounted costs at 6% and health outcomes at 1.5%, and one study did not specify. All studies conducted analysis using a Markov model that included treatment response data from two clinical trials. Three studies included the disutility of AEs associated with the treatments. Sensitivity and subgroup analyses were performed in all studies.

None of the nine studies concluded that PegIFN+RBV is cost saving for patients with CHC compared with IFN+RBV. All studies suggested that PegIFN+RBV was associated with better outcomes and more costs, and could be considered cost-effective below a stated threshold. The results of sensitivity and subgroup analysis were robust (below the cost-effectiveness threshold) in all the cases analyzed in five studies, and generally cost-effective in the other studies.

b) Economic evaluation: base case

PegIFN+RBV was associated with a higher SVR rate than IFN+RBV. For every 1,000 patients treated, 607 and 453 patients would be expected to achieve an SVR when treated with PegIFN+RBV and IFN+RBV respectively.

Compared with no AVT, the model predicted that the 20-year risk of CHC-related liver disease and death would be reduced by 33% to 36% in relative terms by IFN+RBV and by 45% to 49% by PegIFN+RBV. During patients’ lifetimes, compared with no AVT, IFN+RBV was associated with 19 fewer liver transplants and 158 fewer deaths due to liver disease per 1,000 patients treated. PegIFN+RBV was associated with 26 fewer liver transplants and 212 fewer deaths due to liver disease per 1,000 patients treated. In terms of risk reduction over 20 years, CHC-related deaths were reduced from 20.1% with no AVT to 13.0% with IFN+RBV and to 10.6% with PegIFN+RBV.

The discounted remaining life expectancy for the 43-year-old patient in the analysis was 14.2 years for no AVT, 15.0 years for IFN+RBV, and 15.2 years for PegIFN+RBV (Table 2). The discounted remaining
quality-adjusted life expectancies for the three strategies were 10.3 QALYs, 10.8 QALYs, and 11.0 QALYs respectively. Therefore, compared to no AVT, patients gained 0.8 LYs (0.5 QALYs) with IFN+RBV and 1.0 LYs (0.7 QALYs) with PegIFN+RBV.

<table>
<thead>
<tr>
<th>Table 2: Base case – undiscounted and discounted lifetime results</th>
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<tr>
<td><strong>Undiscounted</strong></td>
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<tr>
<td></td>
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<tr>
<td>no AVT</td>
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<tr>
<td>IFN+RBV</td>
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<tr>
<td>PegIFN+RBV*</td>
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<td><strong>Discounted at 5%</strong></td>
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<tr>
<td>no AVT</td>
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<tr>
<td>IFN+RBV</td>
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<tr>
<td>PegIFN+RBV*</td>
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*ICER versus next non-dominated strategy (no AVT); CS=Canadian dollars; numbers in parenthesis=weakly dominated strategy; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year; SVR=sustained viral response; LY=life-year; N/A=not applicable.

The total lifetime costs of CHC consist of costs related to antiviral treatment and costs associated with the treatment of CHC-related complications. The total undiscounted lifetime cost of no AVT (C$30,907) was less than the total cost of treatment with PegIFN+RBV (C$33,170) and IFN+RBV (C$35,328) (Table 2). On a discounted basis, the total lifetime cost of PegIFN+RBV (C$24,636) and IFN+RBV (C$24,366) was approximately double that of no AVT (C$12,819). The differences in the discounted and undiscounted results reflect differences in the timing of costs. The discounted cost of treating CHC-related diseases 10 to 20 years in the future is 60% and 38% respectively of today’s ( undiscounted) costs.

During the year of drug treatment, PegIFN+RBV cost C$1,995 more than IFN+RBV (C$18,595 versus C$16,600). Costs are higher mainly because more patients treated with PegIFN+RBV show an early response to therapy; therefore, they continue treatment longer than those who receive IFN+RBV. This accounts for 90% of the higher cost; <1% of the difference in cost is due to treating the adverse effects associated with PegIFN plus RBV.

In the long term, PegIFN+RBV reduced the costs required to treat CHC-related complications. The costs associated with treating liver complications were C$14,575 (PegIFN+RBV), C$18,728 (IFN+RBV), and C$30,907 (no AVT). The savings with PegIFN+RBV were split among treatment for mild to moderate CHC and liver cirrhosis (37%), decompensated cirrhosis (27%), and liver transplants (36%). Compared with no AVT, the discounted ICER for PegIFN+RBV was C$11,532 per LY gained and C$16,969 per QALY gained (Table 2). The discounted cost per SVR was C$19,464.

c) Economic evaluation: sensitivity analysis

The cost per QALY results were robust in most of the sensitivity analyses. In many cases, PegIFN+RBV was more effective and had a lower ICER than IFN+RBV. In the sensitivity analysis that simulated the treatment of mild CHC patients, the ICER for PegIFN+RBV was higher than in the base case ($56,300 versus $17,000 per QALY). This should be interpreted cautiously because patients with mild CHC may have better treatment response rates than those used in the analysis. In other analyses, the ICER for PegIFN+RBV increased from C$17,000 per QALY in the base case to C$21,600 per QALY when the expected SVR rate was reduced by 15%, and to C$35,600 per QALY when the expected SVR rate was reduced by 40%. IFN+RBV dominated PegIFN+RBV when the SVR was reduced by ≥19%.
Treatment with PegIFN+RBV in patients with HCV genotypes 2 and 3 was associated with lower ICERs than treatment in patients with other genotypes (C$3,200 per QALY versus C$28,800 per QALY). This may be explained by a higher SVR rate and predicted better long-term outcomes in the group with genotypes 2 and 3. In a conservative scenario combining unfavourable health state costs with a 21% lower SVR rate for PegIFN+RBV, the ICER of PegIFN+RBV was C$50,000 per QALY compared with IFN+RBV. Greater SVR reductions resulted in higher ICERs for PegIFN+RBV. In this conservative scenario, PegIFN+RBV was dominated by IFN+RBV when the SVR rates of PegIFN+RBV were reduced by \( \geq 25\% \).

The ICER results for PegIFN+RBV were most sensitive to disease progression rate and age at the start of treatment. Lower rates of disease progression increased the cost per QALY of PegIFN+RBV. Patients whose disease progresses more slowly have smaller health gains from AVT and lower costs for treating CHC-related complications because they have fewer of them in their lifetime. ICER results increased with the age at which treatment is started. The cost per QALY for PegIFN+RBV increased from C$17,000 at age 43 years in the base case, to about C$50,000 at age 61 years, and C$100,000 at age 68 years. This reflects the fact that patients are more likely to die of other causes before developing serious liver disease.

5 Limitations

Clinical Outcomes Review

The analysis of clinical outcomes was based on a previously conducted systematic review. Although measures were taken to minimize bias in the selection of RCTs during the original review, the possibility of such a bias cannot be discounted.

Our results, based on limited pooled data, are not robust. Mortality data were presented in three trials, all of which were <72 weeks long. SAE data were based on <30% of participants in all the trials selected, and were presented in only two reports. The definition, monitoring, and collection of outcomes were usually not reported in the papers reviewed. This lack of information leads to uncertainty in the findings reported.

Economic Analysis

The rate of CHC disease progression varied in published studies; reliable data on factors affecting a patient’s prognosis and the effect of treatment on long-term health outcomes were lacking. The model did not address the impact of treating specific subgroups of patients. The model assumed that CHC patients who die from causes other than CHC-related liver complications have the same death rate as that of the general population. Patients with CHC often have risk factors or comorbidities that predispose them to die sooner. Using the same death rate as that of the general population may bias the results in favour of treatment.

Although patient cohorts were modelled using average transition probabilities, SVR and disease progression rates may depend on individual patient characteristics. Using average transition probabilities may have biased the model in favour of treatment for some subgroups.

6 Health System Implications

Clinical Outcomes Review

Clinicians and patients must make IFN-based treatment decisions based on limited mortality and morbidity data. They will need to decide if an increased chance of becoming HCV-negative is worth the short-term consequence of increased toxicity with PegIFN combination therapy.
Increasing rates of serious and life-threatening events will require monitoring, and their management will increase costs and affect health-service use in the short term. Whether a higher SVR rate will translate into reduced incidences of end-stage liver disease and hepatocellular carcinoma has not been proven. If no (or little) reduction occurs, then the cost of treatment (in terms of clinical gain) becomes prohibitively high.

**Economic Analysis**

For publicly funded drug plans in Canada, it is expected that PegIFN+RBV would replace IFN+RBV, should it also be covered by drug plans. Because of better SVR rates, an increase of about 10% in the number of CHC patients who will be treated with PegIFN+RBV can be expected. The incremental cost of covering PegIFN+RBV is estimated at C$337,000 per 100 patients currently treated with IFN+RBV. For a HCV clinic, additional costs in the first year are about C$30,000 per 100 patients currently treated with IFN+RBV. Additional human and financial resources may be required, which may exacerbate the shortage of physicians working in this area.

Some reports indicate that support and monitoring by additional nursing resources is likely to improve treatment adherence, and thereby improve SVR. The sensitivity analysis indicates that the cost-effectiveness of PegIFN+RBV treatment is sensitive to age at treatment initiation, and that at ≥61 years of age, the cost per QALY increases to >C$50,000. This factor can be considered by decision makers who use cost per QALY thresholds for funding decisions.

7 Conclusions

**Clinical Outcomes Review**

Information on long-term quantity and quality of life related to IFN-based treatment is lacking. Pooled data from available sources showed no detectable differences in the occurrence of death in any treatment group in short-term studies.

Serious morbidity was not significantly different between therapy with IFN alone and IFN+RBV. Patients who received IFN+RBV were significantly more likely to withdraw from trials because of AEs. The RR of persistent viremia was reduced by 27% in patients who received IFN+RBV. Compared with IFN+RBV, PegIFN+RBV was associated with a significantly higher rate of SAEs that can increase the need for urgent medical attention. Withdrawals due to AEs and the effect of treatment on quality of life were not significantly different between the two treatment arms. The RR of persistent viremia was reduced by 13% with PegIFN+RBV.

**Economic Analysis**

Compared with no AVT and IFN+RBV, PegIFN+RBV was more effective in improving health outcomes in terms of achieving SVR, reducing the risk of CHC-related liver diseases and death, and demonstrating gains in LYs and QALYs. Treatment with PegIFN+RBV was not cost saving when evaluated over patients’ lifetimes and is expected to increase drug budgets that already fund IFN+RBV. The total discounted lifetime cost of treatment is similar for the two treatment regimens, given the lower costs of CHC-related liver complications for patients treated with PegIFN+RBV.

PegIFN+RBV was more effective and more costly, but had a lower ICER than IFN+RBV in the base case, and in most of the sensitivity analyses. The results for PegIFN+RBV were most sensitive to the natural disease progression rate and the age at the start of treatment.
References


78. Antiviral Drugs Advisory Committee, U.S. Food and Drug Administration. An update on the approval of BLA 103949/5002, PEG-Intron™ (peginterferon alfa-2b) powder for injection, indicated for use alone or in combination with Rebetol (ribavirin, USP) for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age: summary of the clinical review [FDA briefing information]. Bethesda (MD): The Committee; 2002 Nov 14. Available: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3819b1_03_FDA-Clinical%20review.PDF.


