Title: Re-Treatment with Pegylated Interferon Plus Ribavirin for Patients with Relapsing Chronic Hepatitis C: Clinical and Cost-Effectiveness

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Context and policy issues:

Chronic hepatitis C infection is a significant medical and economic burden in Canada. The exact prevalence is unknown but chronic hepatitis C is estimated to affect 250,000 persons, or 0.8% to 1% of Canadians. The infection is slowly progressive and over several years may lead to cirrhosis, liver failure and hepatocellular carcinoma. The most effective treatment currently available is pegylated interferon alfa-2a or alfa-2b in combination with ribavirin. After a course of treatment, 54% to 61% of patients achieve a sustained viral response (SVR) (i.e., virus is no longer detectable six months after antiviral treatment was completed). However, a portion of patients who initially clear the virus will relapse after a period of time. The treatment options for these patients are unclear. Should they receive a repeat course of pegylated interferon with ribavirin? Are there benefits to switching to the other form of pegylated interferon (ie, from alfa-2a to alfa-2b, or vice versa)? What is the cost effectiveness of repeat courses of pegylated interferon in patients who relapse? Information on the clinical and economic impact of pegylated interferon plus ribavirin re-treatment in patients with chronic hepatitis C infection is needed to assist in coverage decisions.

Research questions:

There are two research questions:

1. What is the clinical efficacy of pegylated interferon plus ribavirin therapy in patients with chronic hepatitis C who have relapsed after responding to a previous course of pegylated interferon plus ribavirin treatment (i.e., patients who relapse on one pegylated interferon are tried on the other)?

2. What is the cost-effectiveness of pegylated interferon plus ribavirin therapy in patients with chronic hepatitis C who have relapsed after responding to a previous course of pegylated interferon plus ribavirin treatment?
Methods:

A limited literature search was conducted on key health technology assessment (HTA) resources, including PubMed, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and January 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

Summary of findings:

No HTA reports, systematic reviews, randomized clinical trials (RCTs) or economic evaluations were identified that met the criteria outlined in the research questions.

In the literature search, several RCTs were identified that assessed re-treatment options in patients who relapsed on standard interferon ± ribavirin but not those who relapsed on pegylated interferon plus ribavirin. Findings from these studies are therefore not relevant to answer the above research questions.

One uncontrolled, non-randomized study was found that assessed peginterferon alfa-2a plus ribavirin in patients who relapsed after a 24 week course of the same therapy. This was a follow up study to a phase III randomized clinical trial by Hadziyannis et al. which investigated the effect of 24 or 48 weeks of treatment with peginterferon alfa-2a in combination with either a low dose (800 mg/day) or a standard weight-based dose of ribavirin (1000 mg/day for patients weighing <75 kg or 1200 mg/day for patients weighing ≥75 kg) in treatment-naïve patients with chronic hepatitis C infection. The objective of the follow up study by Berg et al. was to evaluate the efficacy of a second-line 48-week course of combination therapy in patients who cleared the virus at the end of treatment but had a virological relapse during the 24 week follow up period.

From a total of 116 eligible patients, 64 (55%) participated in this follow up study. The majority of patients were Caucasian (91%), male (80%), and infected with hepatitis C virus genotype 1 (70%). Fifty two patients had previously received the low dose ribavirin and 12 had received the weight based dose. In the follow-up study, dosing of peginterferon and ribavirin varied. Thirty nine percent of patients continued with the same dose of peginterferon alfa-2a and ribavirin as in the initial trial.

Following re-treatment, the overall SVR rate was 55%. For genotype 1 the SVR rate was 51% (23/45) and for genotypes 2 and 3 it was 64% (9/14). Two patients withdrew and 10 had dose modifications due to adverse events. The most frequent adverse events leading to treatment modifications were fatigue (5%) and abdominal pain (3%). Authors concluded that re-treatment should be offered to patients with hepatitis C infection who relapse after an initial, 24-week course of combination peginterferon and ribavirin therapy. In interpreting these findings, the following should be considered: i) the cohort of patients studied was small and originated from a pool of patients who met pre-determined criteria, ii) although selected from a randomized population, the cohort lost the randomization effect due to the high level of attrition which occurred when patients elected to enrol in the follow up study, iii) the 24 week duration of treatment used as the primary therapy is only recommended for patients with genotype 2 and 3 hepatitis C virus whereas the majority of the patients in the follow-up cohort (70%) were infected with genotype 1. Overall, these limitations suggest findings may have been subject to the introduction of bias in the selection of patients. Generalizability of findings may also be
compromised by the initial duration of treatment used in view of the viral genotyping of patients included in the follow up cohort.

The Drug Effectiveness Review Project conducted a drug class review for pegylated interferons.\textsuperscript{2,6} It explored the comparative effectiveness and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin. The population criteria were broad and included all subgroups of adult patients with chronic hepatitis C (e.g., previous treatment failures, HIV co-infected, advanced liver disease). However, in the studies available, the patients enrolled were primarily treatment naïve. We examined the individual studies that enrolled relapsers and in all cases initial treatment was standard interferon with or without ribavirin.\textsuperscript{6,7} The review authors concluded that comparative evidence was lacking in relapsers and no conclusions could be drawn.\textsuperscript{2}

Conclusions and implications for decision or policy making:

Evidence available on the clinical benefit of peginterferon plus ribavirin re-treatment in patients with hepatitis C infection who relapse may only be considered preliminary at this time. It is also limited to peginterferon alfa-2a. This evidence suggests that about half of the patients with genotype 1 hepatitis C infection who relapse after 24 weeks of treatment could benefit from a 48 week re-treatment with peginterferon alfa-2a plus ribavirin. Given the supporting evidence is limited to a single small uncontrolled non-randomized study, with limited generalizability, there is considerable uncertainty around this conclusion. No clinical evidence on the re-treatment with peginterferon alfa-2b plus ribavirin was identified. Also, no evidence was retrieved on the cost-effectiveness of re-treatment of patients with chronic hepatitis C who relapsed after pegylated interferon plus ribavirin therapy. From a policy perspective, reimbursement decisions should account for the patient’s previous treatment history as well as the genotype of the hepatitis C virus.

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References:


