Granulocyte-Colony Stimulating Factor for Antiviral-Associated Neutropenia: Systematic Review and Economic Evaluation

This document highlights key findings from a CADTH health technology assessment report entitled Granulated-Colony Stimulating Factor for Antiviral-Associated Neutropenia: Systematic Review and Economic Evaluation.

Hepatitis C affects more than 250,000 Canadians, with 5,000 newly infected each year. Some 60% are infected with a genotype 1 virus and another 11% to 16% with genotype 2 (of a total of six genotypes). A large proportion of infections is related to injection drug use and occurs among vulnerable populations, including people with low income and unstable housing. Hepatitis C is the leading indication for liver transplantation in Canada.

The standard treatment for people with hepatitis C in Canada is antiviral therapy (pegylated interferon, or PEG IFN, in combination with ribavirin). The goal of treatment is to achieve a sustained virological response (SVR), which is thought to represent a clinical cure.

Up to 30% of patients, however, can experience side effects that result in the need to reduce the dose of PEG IFN or discontinue therapy. Neutropenia, a blood disorder characterized by an abnormally low number of a type of white blood cells called neutrophils is the most common reason for reducing the dose of PEG IFN.

The use of granulocyte-colony stimulating factor (G-CSF) has been proposed as an alternative means to control neutropenia without having to reduce the PEG IFN dose. However, there is uncertainty about its effectiveness and its cost-effectiveness.

**Key Findings**

- The evidence to assess whether a higher rate of SVR is achieved with G-CSF is weak, and no conclusion can be reached on the basis of this systematic review.
- The rate of adverse events associated with G-CSF is low.
- If preliminary findings are confirmed by further clinical data, G-CSF could be perceived as more cost-effective than PEG IFN dose reduction.
FOR HEALTH CARE PROVIDERS

- Between 30% and 50% of patients on HCV therapy experience a fall in neutrophil counts within the first two weeks of therapy.
- Neutrophil counts can fall to levels that have been associated with an increased risk of bacterial infections. However:
  - Much of the research on this topic is based on people receiving chemotherapy for cancer.
  - The studies included in this clinical review found that patients with neutropenia as a result of antiviral therapy were at low risk of infection; and when infections occurred, most were of minor consequence and did not lead to hospitalization or modification of antiviral therapy.
  - Canadian guidelines suggest that dose reductions are unnecessary until the neutrophil count falls below $0.5 \times 10^9/L$.

### TABLE 1: ANTIVIRAL TREATMENT OF HEPATITIS C IN CANADA

<table>
<thead>
<tr>
<th>Brand Name, Manufacturer</th>
<th>PEG IFN Formulation, PEG IFN Dose</th>
<th>Ribavirin Dose</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegasys RBV, Hoffmann-La Roche Ltd., Canada</td>
<td>PEG IFN-alpha-2a, 180 µg sc weekly</td>
<td>1,000 mg to 1,200 mg/day given orally in 2 divided doses; dose depends on whether patient weighs less or more than 75 kg</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Pegetron, Schering-Plough Canada, Inc.</td>
<td>PEG IFN-alpha-2b, 1.5 µg/kg sc weekly</td>
<td>800 mg to 1,200 mg/day given orally in 2 divided doses; dose depends on patient’s weight (800 mg if &lt; 64 kg; 1,000 mg if 64 kg to &lt; 85 kg; 1,200 mg if ≥ 85 kg)</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Genotype 2 or 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegasys RBV, Hoffmann-La Roche Ltd., Canada</td>
<td>PEG IFN-alpha-2a, 180 µg sc weekly</td>
<td>800 mg/day given orally in 2 equal doses</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Pegetron, Schering-Plough Canada, Inc.</td>
<td>PEG IFN-alpha-2b, 1.5 µg/kg sc weekly</td>
<td>800 mg/day given orally in 2 equal doses</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

PEG IFN = pegylated interferon; RBV = ribavirin; sc = subcutaneously.
and that discontinuation occur only if neutrophil counts fall below $0.3 \times 10^9$/L.

- G-CSF seems to be well tolerated, with the most common reported adverse effect being mild to moderate bone pain. Other adverse effects included rash, body aches, headache, and an enlarged spleen.

**FOR POLICY MAKERS AND ADMINISTRATORS**

- The economic evaluation found that G-CSF has the potential to be cost-effective for genotype 1 patients with neutropenia.
  - The cost per additional SVR using G-CSF instead of dose reduction was $115,870 for patients with genotype 1 and $134,628 for those with genotype 2 or 3.
  - The cost per quality-adjusted life-year gained was $16,247 for genotype 1 and $18,877 for genotype 2 or 3 patients.
- In Canada, publicly funded drug plans generally cover G-CSF only for patients with cancer who develop neutropenia. Yukon, Ontario, Québec, and New Brunswick provide compensation on a case-by-case basis for patients with chronic HCV who develop neutropenia.
- The certainty of these findings requires confirmation from further study, because they are based on weak underlying clinical assumptions.

**GLOSSARY OF IMPORTANT TERMS**

- **Neutropenia**: A decrease in the number of neutrophils in the body. Neutropenia lowers the body's barrier to bacterial infection.
- **Neutrophil**: A type of white blood cell that helps to kill and digest microorganisms.
- **Sustained virological response (SVR)**: The absence of serum Hepatitis C virus ribonucleic acid (RNA) 24 weeks after treatment; thought to represent clinical cure.

**PROJECT INFORMATION**

Hepatitis C affects more than 250,000 people in Canada. The standard therapy (pegylated interferon, or PEG IFN, combined with ribavirin) is effective at achieving a
sustained virological response in many people with the virus. However, the dosage must be reduced or therapy discontinued in up to 30% of patients, most commonly because of neutropenia, or reduced levels of neutrophils. Granulocyte-colony stimulating factor (G-CSF) can be used as an alternative to reducing the dosage of PEG IFN when neutrophil levels fall. CADTH initiated a review of the effectiveness and cost-effectiveness of G-CSF compared with dosage reduction to provide necessary evidence on this question.

Donna Dryden of the University of Alberta Evidence-based Practice Center coordinated the project. Konrad Fassbender of the Division of Palliative Care Medicine, Department of Oncology, University of Alberta, was the lead for the technology assessment.

CADTH’s full-length Technology Report, *Granulocyte-Colony Stimulating Factor for Antiviral-Associated Neutropenia: Systematic Review and Economic Evaluation*, as well as a Technology Overview and this Research Highlights tool, are available at [www.cadth.ca](http://www.cadth.ca).

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The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada’s federal, provincial, and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

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