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Direct-Acting Antivirals for Chronic Hepatitis C Genotype 1 — Project Protocol

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report. CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

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ABBREVIATIONS

CDEC	Canadian Drug Expert Committee
CHC	chronic hepatitis C
DAA	direct-acting antiviral agent
HCV	hepatitis C virus
PR	pegylated interferon plus ribavirin
RGT	response-guided therapy
RCT	randomized controlled trial
SDT	standard duration therapy

1 INTRODUCTION AND RATIONALE

Hepatitis C infection is caused by an enveloped, single-stranded linear RNA virus of the Flaviviridae family. It is estimated that 0.8% or 242,000 Canadians have chronic hepatitis C virus (HCV) infection; however, the exact number affected is not known, as 30% to 70% of patients are unaware that they have been infected.[1] In 2009, 11,357 cases of HCV were reported through the Canadian Notifiable Disease Surveillance System, with most cases resulting from injection drug use.[2] There are six major HCV genotypes, which show a similar natural history and no clear correlation between the infecting genotype and disease severity or the rate of disease progression. Genotype, however, strongly correlates with treatment response. Genotype 1 infections are the least treatment-responsive and account for most HCV infections in Canadians (55% to 65%).[3-5]

Of those infected, approximately 25% clear the infection spontaneously (ranging from 15% to 45%) and the remainder develop chronic infection.[6-8] Of those with chronic infection,15% to 25% will develop progressive liver disease, end-stage liver disease, hepatocellular carcinoma, or will require a liver transplant.[9,10] A Metavir score may be used to grade the severity of liver disease in terms of liver fibrosis or cirrhosis. Scores range from F0 to F4, where F0 means there is no visible liver scarring and F4 means there is advanced liver scarring or cirrhosis. Male gender, ethanol use, HIV coinfection, obesity, and increasing age are associated with an increased risk of liver disease progression. While incident cases of HCV in North America and Canada[11,12] continue to decline, it is expected that liver-related morbidity and mortality will continue to increase over the coming decades as those who are already infected age.[1,13]

Since the early 2000's, pegylated interferon plus ribavirin (PR) was the gold standard of therapy to inhibit viral replication in patients with chronic hepatitis C (CHC). Approximately half of patients with genotype 1 CHC, the most prevalent type of CHC in Canada, could expect to achieve sustained virologic response with PR therapy. Greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral agents (DAAs) that target several types of non-structural proteins used to support viral replication.

The market entry of protease inhibitors (boceprevir, telaprevir) in 2011 has changed the landscape of CHC therapy. For patients with an inadequate response to PR therapy, retreatment with a protease inhibitor added to PR can triple the likelihood of treatment success.[14,15] Recently, two new DAAs have been approved by Health Canada (simeprevir and sofosbuvir), and approval for a third agent, faldaprevir, is expected in the near future.

Although the treatment of CHC is expected to evolve rapidly, there is an immediate need to assess the comparable benefits, harms, and cost-effectiveness of the antiviral agents and regimens recently approved for use in Canada. Accordingly, this therapeutic review will focus on DAAs approved by Health Canada for use in combination with PR for the treatment of CHC genotype 1 (Table 1).

While the prevalence of other genotypes of hepatitis C is estimated to be on the rise in Canada, at this point in time the only DAA to have a pan-genotypic indication is sofosbuvir. Given that genotype 1 is the most prevalent form of CHC in Canada and that all Health Canada-approved DAA agents are indicated for this genotype, this therapeutic review will focus solely on genotype 1 CHC.

Table 1: Health Canada-Approved Pharmaceutical Therapies for the Treatment of Chronic Hepatitis C	
Product, Manufacturer	**Health Canada Indication**
Pegylated interferon (pegIFN-containing products)	
pegIFN alfa-2a (PEGASYS), pegIFN alfa-2a plus RBV (PEGASYS RBV)	For the treatment of CHC in adult patients with cirrhosis and adult patients with compensated cirrhosis, including HCV/HIV co-infection patients with stable HIV disease with or without antiretroviral therapy.
pegIFN alfa-2b plus RBV (PEGETRON**)**	Treatment of adult patients (18 years or older) with CHC who have compensated liver disease and are positive for HCV-RNA, including patients who have not received previous treatment or who failed prior treatment with interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy.
NS3/4 Protease inhibitors	
boceprevir (VICTRELIS) (VICTRELIS TRIPLE)	Treatment of CHC genotype 1 infection, in combination with peginterferon alpha/ribavirin, in adult patients (18 years or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy.
telaprevir (INCIVEK)	Treatment of CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.
simeprevir (GALEXOS)	Treatment of CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with ribavirin.
Nucleotide polymerase inhibitor	
sofosbuvir (SOVALDI)	Treatment of CHC infection in adult patients with compensated liver disease, including cirrhosis, as follows: • for the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon and ribavirin • for the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin.

CHC=chronic hepatitis C; pegIFN=pegylated interferon; RBV=ribavirin.

2 PROTOCOL DEVELOPMENT

To inform the final scope of the therapeutic review and protocol development, a proposed scope was posted to the CADTH website for stakeholder feedback. In addition, patient-group input was solicited. Throughout the planning and consultation process, patients, clinicians, and other stakeholders have clearly expressed the need for more effective, safer, and less burdensome therapies for CHC. Considering the extensive ongoing research into new treatments for CHC, including pan-genotypic DAAs, all-oral fixed-dose combinations, and interferon-free treatment regimens, we expect that an update to this therapeutic review may be required in the near future. Studies of these anticipated treatments are ongoing but, as yet, these treatments have not been approved for use by Health Canada. Thus, the current therapeutic review protocol is limited to currently approved treatments for patients with CHC genotype 1. As new research is published, and these therapies are filed for regulatory approvals or approved for use by Health Canada, they may be incorporated into future CADTH therapeutic reviews.

3 DELIVERABLES

The following deliverables are planned:

- A science report, including both a systematic review of comparative efficacy and safety of Health Canada-approved DAAs for CHC, as well as an assessment of their cost-effectiveness based on a cost-utility economic analysis
- Canadian Drug Expert Committee (CDEC) Recommendations and/or Advice based on the science report and stakeholder feedback.

4 POLICY QUESTIONS

There are three proposed policy questions for this project. These reflect the information needs of CADTH jurisdictional clients. Policy questions will also feed deliberations by CDEC members when they develop therapeutic review recommendations.

1. How should the new DAAs (simeprevir and sofosbuvir) be listed for reimbursement in comparison with other available DAAs (boceprevir, telaprevir) for the treatment of CHC genotype 1?
2. Should reimbursement of the DAAs for CHC genotype 1 be guided by fibrosis staging and be limited to fibrosis stages greater than or equal to F2?
3. Should retreatment with a DAA be reimbursed for patients with CHC genotype 1 who did not achieve a cure, due to virologic failure or intolerance, on another DAA triple-therapy regimen?

5 RESEARCH QUESTIONS

There are eight research questions for this project. These were developed to address the aforementioned policy issues.

1. What is the comparative efficacy and safety of DAA and PR combination treatments for CHC genotype 1 patients who are treatment-naive?
2. What is the comparative cost-effectiveness of DAA and PR combination treatments for CHC genotype 1 patients who are treatment-naive?
3. What is the comparative efficacy and safety of DAA and PR combination treatments for CHC genotype 1 patients who have relapsed or had a partial or null response to prior PR therapy?
4. What is the comparative cost-effectiveness of DAA and PR combination treatments for CHC genotype 1 patients who have relapsed or had a partial or null response to prior PR therapy?
5. For questions 1 to 4, how do the comparative efficacy, safety, and cost-effectiveness vary across population subgroups based on fibrosis level (Metavir score F0, F1, F2, F3, or F4), genotype subtype (1a/1b), and Q80k polymorphism (present/absent)?
6. What is the comparative efficacy and safety of DAA and PR combination treatments for CHC genotype 1 patients who are coinfected with HIV?
7. What is the comparative efficacy and safety of DAA and PR combination treatments for CHC genotype 1 patients who have had a liver transplant?
8. What is the comparative efficacy, safety, and cost-effectiveness of DAA and PR combination treatments for CHC genotype 1 patients who have had an inadequate response (due to virologic failure or intolerance) to prior DAA-plus-PR therapy?

6 METHODS

6.1 Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy. Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946-) with In-Process records & daily updates via Ovid; Embase (1974-) via Ovid; the Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are telaprevir, boceprevir, sofosbuvir, simeprevir, Incivek, Incivo, Victrelis, Sovaldi, Galexos, and Olysio.

No filters will be applied to limit the retrieval by study type. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication date but will be limited to English language results. Regular alerts will be established to update the search until recommendations by the Canadian Drug Expert Committee (CDEC), based on this review, are finalized. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* checklist (http://www.cadth.ca/resources/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, and databases (free). Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacting appropriate experts.

6.2 Selection Criteria

6.2.1 Clinical

Two reviewers will independently screen titles and abstracts relevant to the clinical research questions regarding drug therapies for the treatment of patients with CHC genotype 1 infection. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 2). The two reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table 2: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Population	Patients with CHC genotype 1 infection (adult populations)
Interventions	• Telaprevir in combination with PR • Boceprevir in combination with PR • Simeprevir in combination with PR • Sofosbuvir in combination with PR
Comparators	• Comparisons between dual therapy (PR) vs. triple therapy (PR + DAA) • Comparisons between DAA triple-therapy options
Outcomes	SVR, treatment completion, histological changes, relapse, quality of life, liver failure, hepatocellular carcinoma, liver transplants, and mortality (all-cause and liver related). Serious adverse events, adverse events, withdrawals due to adverse events, rash, fatigue, anemia, pruritus, anorectal discomfort, neutropenia, depression, suicidal ideation, and flu-like symptoms.
Study design	Published, randomized or non-randomized, controlled or uncontrolled, prospective interventional studies.
Exclusion Criteria	
Studies will be excluded if they: are in languages other than English; do not meet the aforementioned selection criteria; provide results of a qualitative study; are follow-up, extension, or observational studies. Duplicate publications, narrative reviews, and editorials will also be excluded. Abstracts will be excluded unless they present supplementary data for an RCT that has another full-text publication that may be used to assess the risk of bias.	

CHC = chronic hepatitis C; DAA = direct-acting antiviral; PR=pegylated interferon + ribavirin; RCT=randomized controlled trial; SVR=sustained virologic response; vs. = versus.

6.2.2 Criteria for inclusion in systematic review based on employed dosage regimens

- All studies must include a Health Canada-approved dosage regimen for the population enrolled, which includes:
  - DAA agent (daily dose, dosing interval, and duration of therapy must all meet Health Canada-approved regimens; e.g., telaprevir 750 mg every eight hours or 1,125 mg every 12 hours for 12 weeks would both be eligible for inclusion)
  - Peginterferon 2a or 2b (weekly dose)
  - Ribavirin (weight-based dosing, with a total daily dose of 600 mg to 1,400 mg)
- Randomized controlled trials (RCTs) and non-randomized studies in which the duration of PR therapy is consistent with the Health Canada-recommended duration for the population (or a subpopulation) enrolled will be eligible for inclusion.
- RCTs that employ alternate durations of PR therapy may be included in the systematic review if they meet the following criteria:
  - If Health Canada recommends response-guided therapy (RGT), then standard duration therapy (SDT) will be eligible for inclusion if the PR therapy duration is the same as RGT treatment options (e.g., if the RGT regimen is 24 or 48 weeks of PR treatment, then SDT for 24 weeks or 48 weeks would be eligible for inclusion).
  - If Health Canada recommends SDT, then studies employing response-guided PR therapy for up to 48 weeks would be eligible for inclusion.
- Regimens with a lead-in period may be accepted if the total duration of the DAA and PR agent fall within the ranges specified.

- For patients with HIV coinfection or those who are treated following liver transplantation, dosing regimens other that those described previously may be eligible for inclusion given that potential drug interactions between antiretroviral and immunosuppressant agents may require dosage adjustments of HCV medications.

6.2.3 Economic

One reviewer will screen titles and abstracts relevant to the economic research questions on the use of available drug therapies for the treatment of patients with CHC that might inform data inputs in the health economic model. Full papers will be obtained for those that appear to be potentially relevant.

6.3 Data Extraction and Critical Appraisal of Clinical Studies

One reviewer will perform data extraction for each article, using a data extraction form developed a priori and covering the following items:

- Baseline characteristics, demographics, and treatment history of trial participants
- Interventions evaluated, including dose, duration, and relevant concomitant medication
- Efficacy and safety results for specified outcomes
- Type of analysis (intention-to-treat [ITT] or per-protocol)
- Withdrawals.

All extracted data will be checked for accuracy by a second reviewer. Any disagreements will be resolved through discussion until consensus is reached.

Quality assessment of the included studies will be performed independently by two reviewers using the Cochrane Risk of Bias tool.[16]

6.4 Data Analysis and Synthesis

6.4.1 Clinical

Included studies will be classified based on study populations and relevant comparisons. Prior to quantitative pooling of study-specific outcomes, a thorough qualitative analysis will be undertaken to assess clinical heterogeneity. If substantial heterogeneity exists in certain comparisons or subsets of studies, then narrative summaries of findings will be reported. Where appropriate, meta-analysis of direct comparisons and network meta-analyses (NMA) for the purpose of indirect treatment comparisons may be performed.

Analyses will be separated into subpopulations based on prior treatment experience with PR, as follows:

- Treatment-naive
- Relapsed
- Prior partial response
- Prior null response.

In addition, patients with an inadequate response to DAA triple therapy, liver transplant patients, or those with HIV coinfection will be examined separately.

Subgroup analyses will be conducted where appropriate, based upon the presence of:

- Liver fibrosis (Metavir stage F0, F1, F2, F3, F4)
- Genotype subtype 1a, 1b
- Q80k polymorphism.

A hierarchical approach will be taken for data synthesis, with the base case analyses (meta-analysis and/or network meta-analysis [NMA]) limited to RCTs that compare one DAA-plus-PR therapy to another, or to PR dual therapy, in a Health Canada-approved dosing regimen. Secondary analyses of RCTs may include alternate dosage regimens as specified in Section 6.2. Non-randomized or non-comparative studies will be synthesized narratively. Any studies or data identified from stakeholder feedback to the included studies list (posted on the CADTH website) will be assessed for inclusion in the analyses and economic model. Any data identified subsequently (through search alerts or other means) may not be incorporated into the analyses or economic model but will be summarized narratively.

6.4.2 Economic

A Markov model will be constructed and the primary analysis will be in the form of a cost-utility analysis. The primary outcome will be the number of quality-adjusted life-years (QALY) with DAA-plus-PR therapies and PR dual therapy compared in terms of the incremental cost per QALY (incremental cost-utility ratio [ICUR]). The parameter uncertainty will be assessed through both deterministic and probabilistic sensitivity analyses.

6.5 Data Availability

In accordance with the CADTH *Therapeutic Review Framework*: *"The primary source of data is in the public domain. All stakeholders will be given the option of identifying and providing unpublished data on the condition that, if used, it would be included in publicly available reports and documents, related to the therapeutic review."* If the necessary clinical data required to address the research questions are not made publicly available by the manufacturers at the time of project initiation, there may be limited information available to address all of the research or policy questions listed in the protocol.

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