



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL

TITLE: Sofosbuvir for the Treatment of Patients with Genotype 4 Hepatitis C: A Review of the Clinical Efficacy, Cost-effectiveness, and Guidelines

DATE: 05 December 2014

CONTEXT AND POLICY ISSUES

Over 150 million people worldwide are infected with hepatitis C virus (HCV) and approximately 350,000 deaths occur each year.¹ In Canada, the estimated prevalence is 0.8%, or more than 240,000 Canadians infected.² The majority of HCV-infected individuals (up to 85%) are unaware of their health status, due to the absence of symptoms during early stages.¹ There are seven major genotypes of HCV, and each genotype may respond differently to treatment.³ The HCV genotypes 1, 2, and 3 are widely distributed throughout the world; the most common genotype in North America is 1 (~70%) followed by genotype 2 and 3 (30%).⁴ HCV genotype 4, 5 and 6 are less common in North America (<1%).⁴ HCV genotype 4 is found in the Middle East and Africa, genotype 5 in South Africa, and genotype 6 and 7 in Southeast Asia.⁴ Although it has been suggested that certain genotypes may be associated with a more severe disease progression, it remains to be confirmed by larger prospective clinical trials.⁴ Before 2011, the main treatment regimen for HCV genotypes 1, 4, 5 and 6 was peginterferon and ribavirin for 48 weeks, and for HCV genotypes 2 and 3 it was peginterferon and ribavirin for 24 weeks.⁵ In 2011, the approval of two new NS3/4A protease inhibitors, telaprevir and boceprevir, to be used in combination with peginterferon and ribavirin, has led to advanced treatment which offers shorter treatment duration and an increase in sustained virological response (SVR) rates.⁵ However, this treatment regimen failed to achieve a SVR in 25% to 35% of treatment-naïve patients even with up to 48 weeks of treatment.^{6,7} In addition, this treatment combination are associated with high pill burden, drug-drug interactions, complex treatment algorithms, and severe adverse events such as anemia and rash.^{8,9}

Sofosbuvir (Sovaldi), a nucleotide analogue inhibitor of the HCV NS5B polymerase, has shown highest SVR rates compared to historical SVR rates seen in HCV-infected patients.¹⁰ It was approved by the US Food and Drug Administration and Health Canada in December 2013 for the treatment of chronic HCV infection in patients with genotypes 1, 2, 3 or 4.^{11,12} Of note, in July 2014, the Canadian Drug Expert Committee (CDEC) has recommended sofosbuvir to be listed for the treatment of HCV genotypes 1, 2, or 3, while genotype 4 was not considered at that time.¹³

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The aim of this report is to review the clinical efficacy, cost-effectiveness, and guidelines for use of sofosbuvir for the treatment of adults with HCV genotype 4.

RESEARCH QUESTIONS

1. What is the clinical efficacy of sofosbuvir for the treatment of adults with genotype 4 chronic hepatitis C?
2. What is the cost-effectiveness of sofosbuvir for the treatment of adults with genotype 4 chronic hepatitis C?
3. What are the evidence-based guidelines for the treatment of adults with genotype 4 chronic hepatitis C?

KEY FINDINGS

Sofosbuvir in combination with peginterferon and ribavirin is recommended for treatment of naïve-patients, who are eligible and not eligible to receive interferon, as well as those who are peginterferon/ribavirin non-responders. There was no evidence of comparative clinical efficacy and cost-effectiveness of sofosbuvir for the treatment of HCV genotype 4 identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and November 7, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Population	Adults with Genotype 4 chronic hepatitis C
Intervention	Sofosbuvir in combination with peginterferon and ribavirin (PR)
Comparator	Placebo in combination with PR, placebo/no treatment, PR alone, other direct acting antivirals + PR
Outcomes	Sustained virologic response, Relapse, Health related quality of life (HRQoL) measured with a validated scale, Mortality (all cause and liver related), Hepatic-related morbidity outcomes (e.g., histological changes, hepatocellular carcinoma, liver failure, liver transplant), serious adverse events, withdrawal due to adverse events, adverse events, harms of special interest (rash, fatigue, anemia, neutropenia, pruritus, depression, sleep loss, nausea, photosensitivity)

Study Designs

Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, and guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009, duplicate publications of the same study, or included in a selected health technology assessment or systematic review.

Critical Appraisal of Individual Studies

The Appraisal of Guidelines Research & Evaluation (AGREE II) instrument¹⁴ was used to evaluate the quality of the included guidelines. For the critical appraisal of studies, a numeric score was not calculated. Instead, the strength and limitations of the studies were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 206 citations. Upon screening titles and abstracts, five potential relevant articles were retrieved for full-text review. One additional relevant report was retrieved from other sources. Of the six potentially relevant articles, two guidelines^{15,16} were included in this review. No health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations could be identified. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics on the grading of recommendations and levels of evidence used to develop the corresponding guidelines are summarized in Appendix 2.

The UK consensus guideline was published in 2014.¹⁵ The working group consist of experts in hepatology and infectious diseases. The guidelines were developed for clinicians to provide guidance on treatment choice and are based on an expert review of phase 2 and 3 studies published in full reports or abstract reports from large phase 2 or 3 clinical trials published in 2013. The evidence to formulate recommendations was ranked against a series of criteria, in which the SVR rate was the first and dominant criterion.

The American Association for the Study of Liver Diseases (AASLD) guideline was published in 2014.¹⁶ The guidelines were developed by a panel of HCV experts in the fields of hepatology and infectious diseases. The goal of the guidelines is to provide recommendations to health care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the US, using up-to-date available evidence. Recommendations were graded according to the strength of the recommendation and quality of the supporting evidence.

Summary of Critical Appraisal

The strengths and limitations of included studies are summarized in Appendix 3.

Although they were explicit in scope and purpose, and clarity of recommendations, both guidelines^{15,16} had limitations in the applicability domain according to the AGREE II instrument. The UK consensus guideline also suffered from several limitations, covering rigour of

development, applicability and editorial independence.¹⁵ Particularly, for rigour of development, systematic methods were not used to search the evidence, the strengths and limitations of the body of evidence were not clearly described, the methods of formulating the recommendations were not clearly described, and a procedure for updating the guideline was not provided. The American Association for the Study of Liver Diseases (AASLD) guideline met all items in stakeholder involvement and rigour of development.¹⁶

Summary of Findings

Two guidelines were identified that provided recommendations for the use of sofosbuvir in the treatment of patients infected with HCV genotype 4. Details of the recommendations are provided in Appendix 4. The UK consensus guideline¹⁵ provided brief recommendations for treatment of naïve and experienced HCV genotype 4 patients with sofosbuvir in combination with interferon alpha and ribavirin. The AASLD guideline¹⁶ provided more detailed recommendations with treatment dosages and treatment duration. Recommendations in the AASLD guideline were for treatment of naïve-patients, who are eligible and not eligible to receive interferon, as well as those who are peginterferon/ribavirin non-responders.

Limitations

Neither of the two guidelines was from Canada. The UK consensus guideline did not provide a rating of the recommendations and evidence. The recommendations of both guidelines on the use of sofosbuvir for treatment of HCV genotype 4 were based on expert opinions and evidence from one single-group, open-label study,¹⁰ in which only 9% (28/327) of HCV genotype 4 patients were present in the total studied population.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or economic evaluations were identified for this report. Two guidelines, one from the UK and one from the US, were identified. Both guidelines had recommendations for the use of sofosbuvir in the treatment of HCV genotype 4 patients. The AASLD US guideline rated its recommendations as of level IIa and the evidence of level B and C. The recommendations of both guidelines were based on expert opinions and the evidence from a single-group, open-label study (NEUTRINO), in which the administration of sofosbuvir plus ribavirin and peginterferon for 12 weeks in patients with HCV genotypes 1, 4, 5, or 6 resulted a SVR rate of 90%.¹⁰ Due to lack of comparator, NEUTRINO study was not included in this report. In the NEUTRINO study, most patients were of HCV genotype 1 (89%, 291 of 327); 9% (28 of 327) had genotype 4, and 2% (7 of 327) had genotype 5 or 6.¹⁰ The SVR rate for genotype 4 was 96% (27 of 28 patients). One patient of genotype 5 and six patients of genotype 6 had a sustained virologic response. Because it was a single-arm trial, the lack of a control group limits the ability to attribute any benefit solely to the intervention being investigated, as external or historical controls may not be similar to the populations are similar. Additionally, single-arm trials are at an increased risk of bias due to the lack of blinding. Due to the paucity and limitations of the current evidence, the recommendations in the identified guidelines should be applied with caution.

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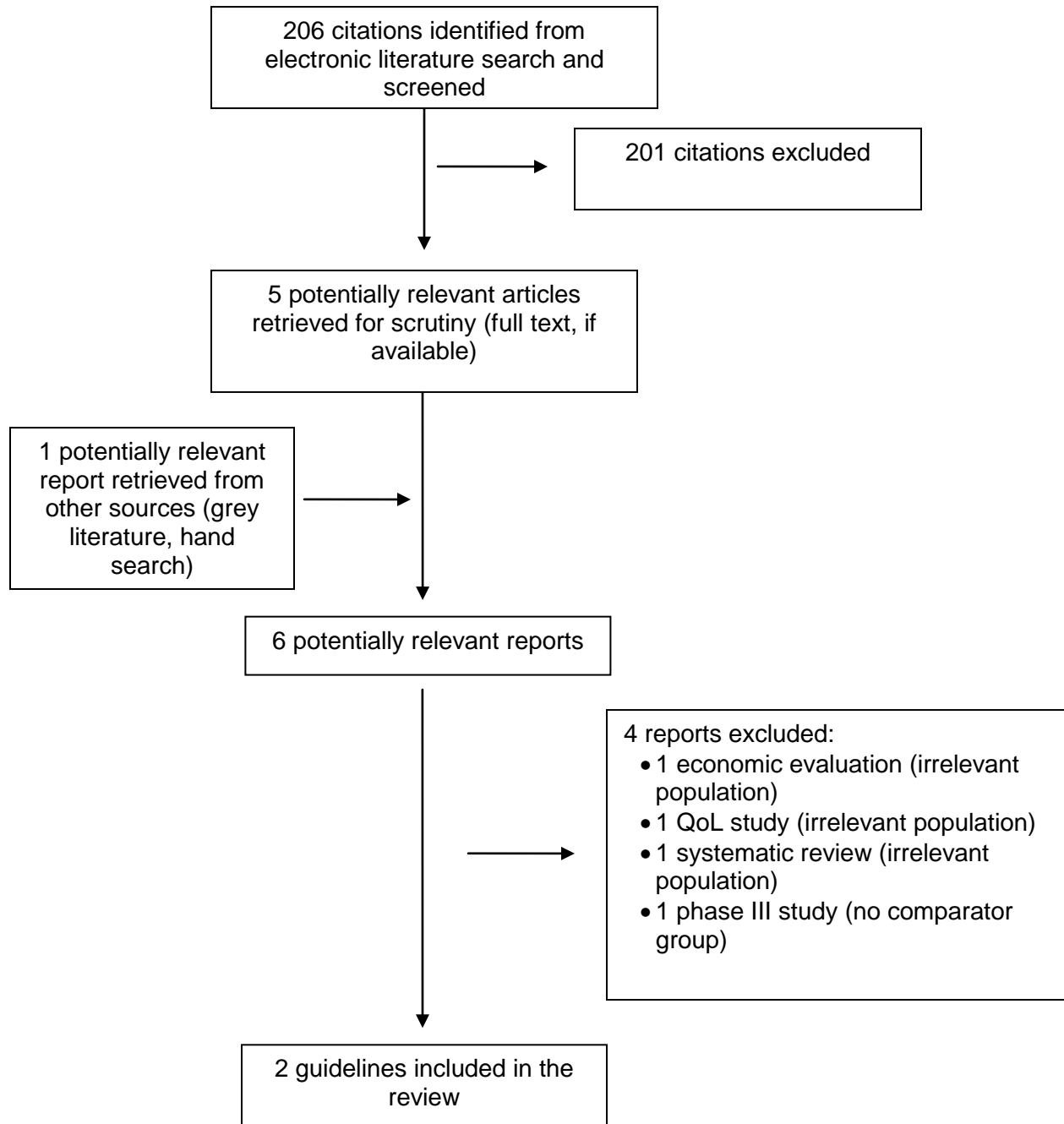
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute	Recommendation	Level of Evidence
2014 UK consensus guideline ¹⁵	The evidence to formulate recommendations was ranked against a series of criteria. The first and dominant criterion of assessment of a drug regimen was the sustained virologic response (SVR) rate. If the SVR rates were equivalent (within the limitations of the evidence), then those regimens that are interferon sparing or interferon free and or reduce other side effects were considered superior.	
The American Association for the Study of Liver Diseases (AASLD) guideline ¹⁶	<p>Class I: Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective</p> <p>Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment</p> <p>Class IIa: Weight of evidence and/or opinion is in favor of usefulness and efficacy</p> <p>Class IIb: Usefulness and efficacy are less well established by evidence and/or opinion</p> <p>Class III: Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful</p>	<p>Level A: Data derived from multiple randomized clinical trials, meta-analyses, or equivalent</p> <p>Level B: Data derived from single randomized trial, nonrandomized studies, or equivalent</p> <p>Level C: Consensus opinion of experts, case studies, or standard of care</p>

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Guidelines		
UK consensus guideline, 2014 ¹⁵	<p><u>Scope and purpose</u></p> <ul style="list-style-type: none"> Objectives and target patients population were explicit The health question covered by the guidelines is specifically described The population to whom the guidelines is meant to apply is specifically described <p><u>Stakeholder involvement</u></p> <ul style="list-style-type: none"> The guideline development group includes individuals from all relevant professional groups The target users of the guideline are clearly defined <p><u>Rigour of development</u></p> <ul style="list-style-type: none"> The criteria for selecting the evidence are clearly described The health benefits, side effects, and risks have been considered in formulating the recommendations There is an explicit link between the recommendations and the supporting evidence The guideline has been externally reviewed by experts prior to its publication <p><u>Clarity of recommendation</u></p> <ul style="list-style-type: none"> The recommendations are specific and unambiguous The different options for management of the condition or health issue are clearly presented Key recommendations are easily identified <p><u>Editorial independence</u></p> <ul style="list-style-type: none"> Competing interests of guideline development group members have been recorded and addressed 	<p><u>Stakeholder involvement</u></p> <ul style="list-style-type: none"> The views and preferences of the target population have not been sought <p><u>Rigour of development</u></p> <ul style="list-style-type: none"> Systematic methods were not used to search for evidence The strengths and limitations of the body of evidence are not clearly described The methods of formulating the recommendations are not clearly described A procedure for updating the guideline is not provided <p><u>Applicability</u></p> <ul style="list-style-type: none"> The guideline does not describe facilitators and barriers to its application The guidelines does not provide advice and/or tools on how the recommendations can be put into practice The potential resource implications of applying the recommendations have not been considered The guideline does not present monitoring and/or auditing criteria <p><u>Editorial independence</u></p> <ul style="list-style-type: none"> It is unclear if the views of the funding body have influenced the content of the guideline
The American Association for the Study of Liver Diseases (AASLD) guideline, 2014 ¹⁶	<p><u>Scope and purpose</u></p> <ul style="list-style-type: none"> Objectives and target patients population were explicit The health question covered by the guidelines is specifically described The population to whom the guidelines is meant to apply is specifically described <p><u>Stakeholder involvement</u></p> <ul style="list-style-type: none"> The guideline development group 	<p><u>Applicability</u></p> <ul style="list-style-type: none"> The guideline does not describe facilitators and barriers to its application The guidelines does not provide advice and/or tools on how the recommendations can be put into practice The potential resource implications of applying the recommendations have not been considered

First Author, Publication Year	Strengths	Limitations
	<p>includes individuals from all relevant professional groups</p> <ul style="list-style-type: none"> • The views and preferences of the target population have been sought • The target users of the guideline are clearly defined <p><u>Rigour of development</u></p> <ul style="list-style-type: none"> • Systematic methods were used to search for evidence • The criteria for selecting the evidence are clearly described • The strengths and limitations of the body of evidence are clearly described • The methods of formulating the recommendations are clearly described • The health benefits, side effects, and risks have been considered in formulating the recommendations • There is an explicit link between the recommendations and the supporting evidence • The guideline has been externally reviewed by experts prior to its publication • A procedure for updating the guideline is not provided <p><u>Applicability</u></p> <ul style="list-style-type: none"> • The guideline presents monitoring and/or auditing criteria <p><u>Clarity of recommendation</u></p> <ul style="list-style-type: none"> • The recommendations are specific and unambiguous • The different options for management of the condition or health issue are clearly presented • Key recommendations are easily identified <p><u>Editorial independence</u></p> <ul style="list-style-type: none"> • Competing interests of guideline development group members have been recorded and addressed 	<p><u>Editorial independence</u></p> <ul style="list-style-type: none"> • It is unclear if the views of the funding body have influenced the content of the guideline

APPENDIX 4: Guidelines and Recommendations on Use of Sofosbuvir for Treatment of HCV Genotype 4

Guideline Society, Country, Author, Year, Indication	Recommendations
<p>UK consensus guideline, 2014¹⁵</p> <p>Hepatitis C management and direct-acting anti-viral therapy</p>	<ul style="list-style-type: none"> • “HCV genotype 4 patients could be treated with 12 weeks of interferon alpha 2a or 2b, with ribavirin and sofosbuvir” p.1371 • “On an individual basis, HCV genotype 4, 5 or 6 treatment-experienced patients could be treated with either 12 weeks of interferon alpha 2a or 2b, with ribavirin and sofosbuvir” p.1371
<p>The American Association for the Study of Liver Diseases (AASLD) guideline, 2014¹⁶</p> <p>Recommendations for testing, managing, and treating hepatitis C</p>	<ul style="list-style-type: none"> • <i>Recommended regimen for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN.</i> <i>Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons.</i> Rating: Class IIa, Level B • <i>Recommended regimen for treatment-naïve patients with genotype 4 who are not eligible to receive IFN.</i> <i>Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for IFN-ineligible persons. IFN-ineligible is defined as one or more of the below:</i> <ul style="list-style-type: none"> - Intolerance to IFN - Autoimmune hepatitis and other autoimmune disorders - Hypersensitivity to PEG or any of its components - Decompensated hepatic disease - Major uncontrolled depressive illness - A baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000/μL or baseline hemoglobin below 10g/dL - A history of pre-existing cardiac disease patients with HCV genotype 4 infection Rating: Class IIb, Level B • <i>Recommended regimen for HCV genotype 4, PEG/RBV non-responder patients.</i> <i>Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 4 infection.</i> Rating: class IIa, Level C • <i>Alternative regimen for HCV genotype 4, PEG/RBV non-responder patients.</i> <i>Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 weeks is recommended for retreatment of HCV genotype 4 infection.</i> Rating: class IIa, Level B • <i>Recommended regimen(s) for treatment-naïve and treatment-experienced HIV/HCV-coinfected patients with genotype 4, 5, or 6 HCV:</i> <i>Treat as recommended for persons with HCV mono-infection.</i>

HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; PEG = peginterferon; RBV = ribavirin