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Recommendations for Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1

Supporting Informed Decisions

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ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CHC	chronic hepatitis C
DAA	direct-acting antiviral
HCV	hepatitis C virus
ICUR	incremental cost-utility ratio
NMA	network meta-analysis
PR	peginterferon plus ribavirin
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RGT	response-guided therapy
RNA	ribonucleic acid
SVR	sustained virologic response

BACKGROUND

Hepatitis C infection is caused by an enveloped, single-stranded linear ribonucleic acid (RNA) virus of the Flaviviridae family. It is estimated that 250,000 Canadians have chronic hepatitis C virus (HCV) infection; however, the exact number affected is unknown, as 30% to 70% of patients are unaware that they have been infected, and limited population level surveillance has been carried out in Canada to document prevalent cases.[1,2] There are six major HCV genotypes; genotype 1 infections account for most HCV infections in Canadians (roughly 60%).[3] Of those infected, approximately 25% clear the infection spontaneously (ranging from 15% to 45%) and the remainder develop chronic infection.[4-6] Of those with chronic infection, available evidence suggests that 15% to 20% will develop end-stage liver disease over 20 years of infection.[7] Given the long duration of infection in many individuals, it is possible that a higher proportion of patients will develop progressive liver disease during their lifetimes; however, long-term follow-up data beyond 20 to 30 years of infection are limited. While the incidence of HCV infection in the US and Canada appears to be stable or declining, it is expected that liver-related morbidity and mortality will increase during the coming decades, as those who are already infected get older and develop progressive liver disease.[1,2,8-10] A Metavir score may be used to grade the severity of liver disease in terms of liver fibrosis. Scores range from F0 to F4, where F0 means there is no visible liver scarring, F1 indicates portal fibrosis without septa, F2 means portal fibrosis with rare septa, F3 indicates numerous septa without cirrhosis (i.e., advanced fibrosis), and F4 means advanced liver scarring (i.e., cirrhosis).

Since the early 2000s, pegylated interferon plus ribavirin (PR) has been the standard therapy to treat chronic hepatitis C (CHC) infection. The goal of treatment is viral eradication, reported as sustained virological response (SVR), which is associated with improved long-term clinical outcomes.[11,12] Approximately half of patients with genotype 1 CHC could expect to achieve SVR with PR therapy.

Greater understanding of the hepatitis C viral replication cycle has resulted in the development of direct-acting antiviral (DAA) agents that target several non-structural proteins essential to viral replication. The market entry of protease inhibitors (boceprevir and telaprevir) in 2011 changed the landscape of CHC therapy. For patients with an inadequate response to PR therapy, re-treatment with a protease inhibitor added to PR compared with PR alone can triple the likelihood of treatment success.[13,14] Unless stated otherwise, patients described as treatment experienced (i.e., patients with prior relapse, partial or null response) are those who have received PR therapy and failed to achieve a SVR. Recently, two new DAAs have been approved by Health Canada, simeprevir (a third protease inhibitor) and sofosbuvir (a nucleotide polymerase inhibitor). Currently Health Canada approval of the four DAAs indicated for the treatment of genotype 1 CHC is contingent upon their use in combination with PR. The Health Canada–recommended duration of a course of therapy for patients with genotype 1 CHC is dependent upon patients' previous experience with PR therapy and the presence of cirrhosis, and ranges from 28 to 48 weeks for boceprevir regimens, 24 to 48 weeks for telaprevir and simeprevir regimens, and 12 weeks for sofosbuvir. Sofosbuvir does not have a Health Canada–recommended dosing regimen for patients previously treated with PR.

The treatment burden is high for regimens that require 48 weeks of therapy. Patients have expressed the need for new treatments with higher cure rates and shorter durations, better side effect profiles, and treatments that are affordable and accessible. The introduction of the new DAA agents (simeprevir

and sofosbuvir) may address some unmet needs through potentially higher cure rates, more favourable adverse event profiles, and/or shorter treatment durations; however, treatment costs remain a concern.

Evidence informed recommendations were developed by the Canadian Drug Expert Committee (CDEC) to address the following policy questions.

1. How should simeprevir be listed for reimbursement in comparison with other protease inhibitors (boceprevir and telaprevir[a]) for the treatment of CHC genotype 1?
2. How should sofosbuvir be listed for reimbursement in comparison with the available protease inhibitors (simeprevir, telaprevir, and boceprevir) for the treatment of CHC genotype 1?
3. 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?
4. Should re-treatment with a DAA plus PR regimen be reimbursed for patients with CHC genotype 1 who did not achieve a cure, due to virologic failure or intolerance, with a prior DAA plus PR regimen?

As described in the CADTH Therapeutic Review Framework, the depth and scope of a CADTH Therapeutic Review is determined by CADTH in consultation with the jurisdictions. CADTH Therapeutic Reviews are evidence-based, and use the highest level of publicly available evidence. Therapeutic Reviews are conducted to coincide with key Common Drug Review (CDR) submission(s) relevant to the scope of the therapeutic review.

The recommendations listed in this report are intended to be used in conjunction with the Therapeutic Review Clinical and Economic Report as well as the recommendations made for individual drugs. Individual drug reviews and recommendations are made through the CDR process.

PREAMBLE TO THE RECOMMENDATIONS

The treatment strategies for CHC continue to evolve rapidly. It is anticipated that future DAA regimens will be all-oral regimens that will not include interferon. Compared with currently available regimens, these new regimens are anticipated to offer higher cure rates and important safety benefits in addition to the shorter treatment durations desired by patients. However, the timing of marketing authorization for these new regimens in Canada is unknown at this time.

CADTH had originally planned a future expansion of the current therapeutic review to include evidence for the anticipated all-oral regimens once clinical trial results for all regimens of interest become available in the public domain. CDEC confirmed the need for an expanded therapeutic review to assess the clinical and cost-effectiveness of future regimens. However, in the interim, the public drug plans require recommendations and advice regarding the currently approved and available treatments.

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated absolute benefits, harms, and cost-effectiveness of the therapies compared with each other, along with patient group input, were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that clinical practice guidelines related to the treatment of hepatitis C have been developed by several groups.[16] Clinical practice

[a] Vertex Pharmaceuticals Incorporated will be discontinuing the sale and distribution of INCIVEK® (telaprevir) in the United States by October 2014.[15]

guidelines are generally based on clinical judgment and consideration of individual patient characteristics, but do not take into account the cost or cost-effectiveness of these treatments.

The evidence for developing CDEC recommendations was derived from the following reports:

1. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Direct-acting antiviral agents for chronic hepatitis C genotype 1 [Internet]. Ottawa: The Agency; 2014 Oct. (CADTH Therapeutic Review vol.2, no.2b). [cited 2014 Oct 3]. Available from: http://www.cadth.ca/en/products/therapeutic-reviews/chronic-hep-c/reports
2. Patient input to CADTH therapeutic review: direct-acting antivirals for chronic hepatitis C genotype 1 [Internet]. Ottawa: The Agency; 2014. [cited 2014 Oct 3]. Available from: http://www.cadth.ca/en/products/therapeutic-reviews/chronic-hep-c/patient-input

ADDRESSING STAKEHOLDER FEEDBACK TO THE DRAFT RECOMMENDATIONS

Following stakeholder feedback to the draft recommendations, posted to the CADTH website on August 5, 2014, minor changes were made to the recommendation document to enhance clarity. In addition, key components of stakeholder feedback were addressed as follows:

- CADTH responded to the CDEC request to explore the possibility of employing novel methods to incorporate single-arm data into the network meta-analysis (NMA); thus, allowing the inclusion of data from the NEUTRINO trial on sofosbuvir into the NMA and the base-case economic analysis. CADTH considered that the most appropriate method to include single-arm trials into the NMA would require patient-level data; however, CADTH was unable to obtain these data from the manufacturer of sofosbuvir. Alternative methods to incorporate single-arm trials into NMAs using aggregate data were considered of insufficient known validity at this time, and were not undertaken by CADTH.
- CDEC considered the expressed preference of patient groups, clinicians, and industry that all infected patients should have access to treatment regardless of fibrosis stage. CDEC reaffirmed that the high cost of currently available treatments in conjunction with the long latency of liver complications supports an approach of judicious use of available therapies at this time.
- Based on jurisdictional feedback, CDEC provided additional context with regard to their recommendation for patients who did not achieve a cure with a DAA plus PR regimen due to virologic failure or intolerance.

SUMMARY OF RECOMMENDATIONS

1. CDEC recommends simeprevir daily for 12 weeks, in combination with PR for 24 to 48 weeks, as the protease inhibitor of choice for treatment-naive patients or for treatment-experienced patients with prior relapse.
2. No definitive recommendation regarding the place in therapy for sofosbuvir, relative to available protease inhibitors, can be made by CDEC at this time.
3. CDEC recommends that DAA plus PR treatment should be offered only to persons with CHC who have fibrosis stages F2, F3, or F4.
4. CDEC recommends that persons in whom a DAA plus PR regimen has failed not be re-treated with another DAA plus PR regimen.

CDEC Values and Preferences

CDEC sought to balance patient perspectives, clinical evidence, and economic evidence. The committee considered the values of efficacy, safety, cost-effectiveness, and patient preferences as particularly important in making these recommendations.

In considering patient perspectives, CDEC noted patients' desire for the most effective treatment, and their strong preference for DAAs with shorter treatment durations and less toxicity, access to treatment for individuals with less advanced disease, and access to re-treatment. CDEC noted that the high cost of newly available treatments and the rapid evolution of CHC therapy were important considerations in drafting recommendations.

RECOMMENDATIONS

Recommendation 1:
CDEC recommends simeprevir daily for 12 weeks, in combination with PR for 24 to 48 weeks, as the protease inhibitor of choice for treatment-naive patients or for treatment-experienced patients with prior relapse.

Reasons for Recommendation 1

1. For treatment-naive and treatment-experienced patients, simeprevir was more effective in achieving SVR compared with PR (direct and indirect evidence), and showed no statistically significant differences in efficacy compared with other protease inhibitors based on indirect evidence. Indirect evidence suggests that simeprevir may have a lower risk of anemia compared with other protease inhibitors.
2. For treatment-naive patients, simeprevir is the most cost-effective option, when compared with other protease inhibitors.

3. For treatment-experienced patients with prior relapse, given the uncertainty in the clinical estimates resulting in modest differences in the ICURs between simeprevir and telaprevir compared with PR, these two protease inhibitors were considered to have similar cost-effectiveness in patients with prior relapse; whereas, boceprevir was dominated. In addition, indirect evidence suggests that simeprevir may have a lower risk of anemia compared with both telaprevir and boceprevir.

Of Note:

1. Simeprevir should not be used in patients with genotype 1a with Q80K polymorphism. For patients with genotype 1a with Q80K polymorphism, there is insufficient RCT evidence reporting the efficacy of other protease inhibitors to enable CDEC to make a recommendation regarding an optimal therapy at this time. CDEC noted that there is no theoretical basis to suspect that the presence of Q80K polymorphism would affect sofosbuvir efficacy, given that sofosbuvir is a polymerase inhibitor rather than a protease inhibitor.
2. For partial and null responders to PR, there is insufficient evidence to identify an optimal therapy, and therefore CDEC is unable to make a recommendation at this time.

Recommendation 2:
No definitive recommendation regarding the place in therapy for sofosbuvir, relative to available protease inhibitors, can be made by CDEC at this time.

Reason for Recommendation 2

There is insufficient clinical evidence to determine the comparative clinical and cost-effectiveness of sofosbuvir compared with protease inhibitors when used in combination with PR.

Of Note:

Based on the recent review of sofosbuvir through the CDR process, CDEC recommended listing sofosbuvir with clinical criteria and conditions; see *CDEC Final Recommendation*, available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_sovaldi_august_20_2014.pdf. However, there is no generally accepted methodological approach to compare sofosbuvir with the three available protease inhibitors because the pivotal clinical trial employing the Health Canada–approved sofosbuvir regimen (NEUTRINO) was a single-arm trial. Methods to conduct indirect treatment comparisons using single-arm data are not well developed. CADTH considered that the most appropriate method to include single-arm trials into the NMA would require patient-level data; however, CADTH was unable to obtain these data from the manufacturer of sofosbuvir. CADTH and CDEC further considered that methods to incorporate single-arm trials into NMAs using aggregate data are of insufficient known validity at this time.

Recommendation 3:
CDEC recommends that DAA plus PR treatment should be offered only to persons with CHC who have fibrosis stages F2, F3, or F4.

Reasons for Recommendation 3

1. No liver-related morbidity is expected in the short-term for patients with no fibrosis or a low fibrosis stage (stages F0 and F1).
2. In all analyses, treatment of patients with higher stages of fibrosis was more cost-effective.

Of Note:

1. CDEC recognized patient group input regarding the desire for early access to treatments irrespective of fibrosis stage. However, the high cost of currently available therapies, in conjunction with the long latency of liver complications of CHC infection, supports an approach for judicious use of available therapies at this time.

Recommendation 4:
CDEC recommends that persons in whom a DAA plus PR regimen has failed not be re-treated with another DAA plus PR regimen.

Reason for Recommendation 4

There is insufficient evidence to evaluate efficacy or cost-effectiveness of re-treatment with an alternative DAA plus PR regimen following failure of a first DAA plus PR regimen.

Of Note:

1. The potential for cross-resistance among protease inhibitors may increase the likelihood of failure upon re-treatment with another protease inhibitor, since protease inhibitors all target the same pathway.
2. Although the Health Canada–approved indication for sofosbuvir (a polymerase inhibitor) appears to include treatment-experienced genotype 1 patients, the approved product monograph does not provide a dosing recommendation for such patients and does not discuss any trials that support the use of sofosbuvir in such patients.
3. CDEC considered that it may be reasonable for patients with intolerance to one DAA to attempt an alternative DAA in combination with PR. However there is no evidence to guide the choice of the second DAA plus PR regimen.

PATIENT GROUP INPUT

Committee discussions were informed by submissions to CADTH by five patient groups: The Positive Living Society of British Columbia, The Canadian Liver Foundation, The Canadian Treatment Action Council, The Hepatitis C Education and Prevention Society (HepCBC), and The Pacific Hepatitis C Network. The following points summarize the concerns of patients and caregivers as documented in the patient group submissions.

- Patients noted that living with HCV infection damages, sometimes severely, their quality of life. Frequently reported symptoms included fatigue, "brain fog," and depression, though these appear to be experienced to widely different degrees. Patient groups emphasized that the social, financial, psychological, and familial difficulties are as important as the physical symptoms experienced by people living with HCV. Stigma (coming even from health care professionals) was singled out as pervasive and debilitating.
- Prior users of PR therapy reported the difficulty of adhering to therapy given the many onerous side effects (especially depression and cognitive impairments) and the long treatment duration required.
- Patients acknowledged that boceprevir and telaprevir, in combination with PR, resulted in improved rates of cure compared with PR alone, but emphasized that each was associated with a number of unwelcome and sometimes onerous side effects that made adherence very difficult and sometimes impossible. Among the side effects reported by patients were anemia (associated mainly with boceprevir), rash (associated mainly with telaprevir), fatigue, muscle aches, joint pain, and insomnia. The long treatment periods required for telaprevir and boceprevir therapy, and the added pill burden they imposed compounded the difficulty of adherence.
- Patients expressed eager anticipation for simeprevir and sofosbuvir because of the reported high cure rates and more attractive adverse event profiles, shorter treatment periods, and less onerous pill burden.
- Being cured of the disease, as indicated by a patient's SVR over time, is of primary importance, but patients also expressed the desire for shorter treatment periods and treatments that exact less of a toll on their health and quality of life.
- While several patient groups acknowledged that some patients without significant liver damage may prefer to wait for newer treatments, all patient groups expressed the conviction that all patients with infection should have access to treatment if desired, irrespective of fibrosis stage. They emphasized that treatment is more effective the earlier it is provided and that waiting for treatment is difficult for many patients and caregivers.
- Several patient groups expressed the belief that patients co-infected with HIV should not be denied coverage despite the exclusion of HIV co-infected patients from many of the clinical trials.
- All of the patient groups want patients for whom a particular treatment has failed to have the opportunity to be treated with a different therapy.

SUMMARY OF THE EVIDENCE

Clinical Evidence

CDEC considered the results of a systematic review conducted to assess the comparative clinical efficacy and safety of boceprevir, telaprevir, simeprevir, and sofosbuvir, in combination with PR, for patients with genotype 1 CHC. Trials were selected for inclusion in the systematic review and subsequent analyses if they were randomized or non-randomized, controlled or uncontrolled, prospective clinical trials published in English, involved adults with genotype 1 CHC, had a treatment group consisting of a Health Canada-approved DAA regimen, and reported any of the protocol-specified outcomes related to efficacy or safety. Comparisons of interest included DAA plus PR versus another DAA plus PR regimen, or versus PR alone.

The review included 26 unique trials. Twenty-four studies were in mono-infected patients (15 studies in treatment-naive patients, nine studies in treatment-experienced patients), and two studies were in HIV co-infected patients. Of the included studies, 15 were double-blind randomized controlled trials (RCTs),[13,14,17-29] seven were open-label or partially blinded RCTs,[30-36] and four were uncontrolled studies.[37-40] No published trials were identified in the literature search that directly compared the DAA regimens of interest, or that enrolled patients post-liver transplant, or in whom prior DAA plus PR therapy had failed.

The outcomes of interest were SVR, relapse, treatment completion, mortality, liver disease progression, liver transplant, and hepatocellular cancer, quality of life, and safety events (serious adverse events; total adverse events; discontinuation due to adverse events; and specific adverse events outlined in the protocol, including three key adverse events, anemia, rash and depression). Direct pairwise analyses were conducted for all outcomes comparing DAA regimens with PR. A Bayesian network meta-analyses (NMAs) was conducted for treatment-naive and treatment-experienced patients for the outcomes of SVR, rash, anemia, and depression. An indirect treatment comparison using the Bucher method was conducted in patients with HIV co-infection.

Additional subgroup, meta-regression, and sensitivity analyses were conducted for the NMA, based on prior PR treatment response (prior relapse, partial or null response to PR), fibrosis severity, genotype subtype and presence of HCV Q80K polymorphism, proportion of patients with cirrhosis, and type of peginterferon used.

Except for two trials, all studies excluded patients with HIV co-infection. The average age of patients enrolled ranged from 40 to 55 years and the proportion of patients with cirrhosis ranged from 0% to 17% in treatment-naive, 9% to 53% in treatment-experienced, and 0% to 5% in the HIV co-infected population studies. The duration of follow-up ranged from 16 to 72 weeks.

Treatment-Naive

In the treatment-naive population, the included RCTs compared PR plus one of boceprevir (two studies),[17,30] telaprevir (four studies),[18,19,33,34] simeprevir (three studies),[21-23] or sofosbuvir (one study),[20] with 48 weeks of PR therapy. Two RCTs compared telaprevir 750 mg every eight hours plus PR with telaprevir 1,125 mg every 12 hours plus PR.[31,32] One telaprevir RCT compared different response-guided therapy (RGT) regimens.[35] There was one uncontrolled, single-arm clinical trial for sofosbuvir

(NEUTRINO),[37] and another RCT that compared different sofosbuvir regimens.[36] Twelve studies that enrolled 4,160 patients were included in the NMA.

In treatment-naive patients, direct and indirect evidence suggested that simeprevir, telaprevir, and boceprevir, at Health Canada–recommended dosages and in combination with PR RGT, were more effective in achieving SVR than 48 weeks of PR alone. In addition, sofosbuvir plus PR RGT was more effective in achieving SVR than PR alone (based on the PROTON study, which employed a longer PR treatment than recommended by Health Canada), in both direct and indirect comparisons. Based on the NMA, there were no statistically significant differences between DAA regimens for SVR. The comparative effectiveness of sofosbuvir at the Health Canada–recommended dosage regimen could not be assessed due to the lack of any RCT employing this regimen.

Subgroup analyses by fibrosis severity showed that simeprevir, telaprevir, and boceprevir were more effective than PR based on direct and indirect evidence, in patients with less severe fibrosis (F0 to F2). No statistically significant differences were found between DAA regimens in the NMA, including a supplementary analysis with sofosbuvir that used the PROTON study as a proxy of patients with less severe fibrosis. Among patients with more severe fibrosis (F3 to F4), simeprevir and telaprevir, but not boceprevir, were more effective than PR, based on both direct and indirect analyses. No significant differences were detected between DAA regimens based on the NMA.

Patients with genotype 1a and the Q80K polymorphism who received simeprevir showed no statistically significant difference in terms of SVR versus PR in both direct and indirect comparisons. None of the boceprevir, telaprevir, or sofosbuvir studies reported results for patients with the Q80K polymorphism.

Treatment-Experienced

Among treatment-experienced patients, six RCTs compared PR plus boceprevir (two studies),[13,24] telaprevir (two studies),[14,25] or simeprevir (two studies)[26,27] with 48 weeks of PR therapy. These six studies were included in the NMA. In addition, there were two uncontrolled studies for telaprevir[39,40] and one uncontrolled study for boceprevir.[38] There were no trials of sofosbuvir plus PR in treatment-experienced patients therefore sofosbuvir could not be included in the NMA.

Among all treatment-experienced patients (N = 2,020), those with prior relapse (N = 1,287), or prior partial response (N = 370), simeprevir, boceprevir, and telaprevir were more effective than PR in achieving SVR, based on both direct and indirect evidence. Based on indirect evidence, no statistically significant differences between DAA plus PR regimens were found except for boceprevir 32 weeks RGT, which was less effective in achieving SVR than telaprevir 12 weeks plus PR 48 weeks in patients with prior relapse. Limited data were available for patients with prior null response (N = 184) and only telaprevir was more effective than PR based on direct and indirect evidence.

In direct pairwise comparisons, boceprevir, telaprevir, and simeprevir were more effective than PR in subgroups with less (F0 to F2) and more severe fibrosis (F3 or F4). Similar results were observed in the NMA except for boceprevir 32 weeks RGT, which was not statistically significantly different than PR among treatment-experienced patients with more severe fibrosis.

Subgroup analysis in patients with genotype 1a and the Q80K polymorphism suggested that simeprevir was not statistically significantly different from PR (in all treatment-experienced and relapsed patients), based on direct and indirect evidence.

Of note, the findings of some subgroup analyses, particularly among treatment-experienced patients, were interpreted with caution due to the limited number of patients and the uncertainty in the findings.

Other Outcomes

Analysis of other outcomes showed that those who received a DAA regimen were less likely to relapse and more likely to complete therapy than those who received PR for both treatment-naive and treatment-experienced patients. Few deaths were reported during the trials and the incidence was similar across treatments. Health-related quality of life was reported in only two studies (telaprevir, sofosbuvir) and these data were limited by missing data and potential bias due to incomplete blinding. The follow-up periods in the included trials were too short (up to 72 weeks) to assess the impact of SVR on mortality and liver disease progression.

Harms

In terms of safety, boceprevir and telaprevir showed an increased risk of anemia relative to PR in treatment-naive and treatment-experienced patients, and an increased risk of rash versus PR in treatment-experienced patients. Indirect comparisons between DAA regimens showed an increased risk of anemia with boceprevir and telaprevir versus simeprevir, but statistical significance was not consistently achieved across all dosage comparisons. Similarly, in treatment-experienced patients, no consistent increased risk of rash was found between boceprevir or telaprevir and simeprevir. Pruritus and anorectal discomfort were reported more frequently among patients who received telaprevir than PR. All other adverse events included in the systematic review showed a similar incidence between DAA and PR treatment groups. Comparative safety data for sofosbuvir were limited.

HIV Co-infection

In patients with CHC and HIV co-infection, two RCTs comparing boceprevir or telaprevir with PR met the inclusion criteria. Both boceprevir and telaprevir were more effective in achieving SVR than PR, based on direct comparisons. The indirect treatment comparison (Bucher method) found no statistically significant difference between the two DAA regimens for SVR, relapse, anemia, depression, and rash.

Economic Evidence

CDEC considered the results of an economic model developed to assess the comparative cost-effectiveness of DAA and PR combination treatments and PR alone for CHC genotype 1 patients who are treatment-naive or treatment-experienced. The model was in the form of a cost-utility analysis with treatments compared in terms of the incremental cost per quality-adjusted life-year (QALY) gained during a lifetime horizon. The target population was Canadians infected with genotype 1 CHC, with an average age of 50 years and weight of 80 kg. Cohorts were defined by treatment status (naive versus experienced), and fibrosis stages (F0 to F4). The treatment-experienced cohort was further categorized by type of prior response with respect to PR therapy (prior relapsers and partial responders). No analysis was performed in null responders because there were insufficient data to perform a NMA stratified by fibrosis stage in that population.

The currently available treatments that are approved and available in Canada were included in the primary analysis, with the exception of sofosbuvir in combination with PR. Because the trial supporting the Health Canada dosing recommendation for sofosbuvir (NEUTRINO) could not be included in the NMA, and considering the number of assumptions required, sofosbuvir was not included in the primary baseline analysis, but its cost-effectiveness was assessed in an exploratory analysis.

The costs per course of therapy considered in the analysis are presented in Table1.

Table 1: Drug Costs per Course of Therapy

Drug	Strength	Duration (weeks)	Cost for One Course of Therapy ($)	Reference
HCV Protease Inhibitor				
Boceprevir (Victrelis)	200 mg	24 to 44	25,200 to 46,200[a]	Ontario MoH (2014)
Simeprevir (Galexos)	150 mg	12	36,502[b]	Manufacturer's information
Telaprevir (Incivek)	375 mg	12	34,968[b]	Ontario MoH (2014)
Nucleotide Polymerase Inhibitor				
Sofosbuvir (Sovaldi)	400 mg	12	55,000[c]	Manufacturer's information
Combination PegIFN alfa plus RBV Therapy				
PegIFN alfa 2a plus RBV (PEGASYS RBV)	180 mcg/200 mg	24 to 48	9,500 to 19,000[d]	Saskatchewan Drug Benefit (2014)
PegIFN alfa 2b plus RBV (PEGETRON)	50 mcg/200 mg	24 to 48	9,297 to 18,594[d]	Saskatchewan Drug Benefit (2014)
	150 mcg/200 mg		10,273 to 20,547[d]	Saskatchewan Drug Benefit (2014)
	80 mcg/200 mg 100 mcg/200 mg 120 mcg/200 mg 150 mcg/200 mg		9,297 to 20,547[d]	Saskatchewan Drug Benefit (2014)

HCV = hepatitis C virus; IFN = interferon; MoH = Ministry of Health; PegIFN = pegylated interferon; RBV = ribavirin.
[a] Total cost of treatment regimen will also include 24 to 48 weeks of PegIFN and RBV
[b] Cost will vary depending on treatment status (naive versus experienced) and fibrosis stage
[c] Total cost of treatment regimen will also include 12 weeks of PegIFN and RBV
[d] Dosing varies by weight and HCV genotype.

A Markov cohort approach was taken for the analysis. The model was divided into a treatment module and a natural history module. The treatment module was such that it could easily be modified to reflect different treatment algorithms; whereas, the natural history module was a robust model that reflected the natural history of CHC and was validated against other models existing in the literature. In the model, health states related to treatment and adverse events (anemia, depression, rash), fibrosis stages (F0 to F4), and clinical states (e.g., cirrhosis, hepatocellular carcinoma) were used to reflect the natural history of CHC. CHC-infected individuals with fibrosis F0 to F3 are initially assumed to have no cirrhosis, but to progress over time to different clinical states of CHC, and/or development of cirrhosis. Those developing

cirrhosis may develop decompensated liver disease and/or hepatocellular carcinoma and may die from the complications of liver disease or require a liver transplant.

Fibrosis progression parameters were obtained from a systematic review conducted by Thein et al. in 2008,[7] and transition probabilities to advanced liver disease were obtained from a published study that provided separate estimates for both SVR and non-SVR CHC patients.[11] The cost of managing CHC and health utilities were mostly derived from published Canadian studies. A variety of deterministic and probabilistic sensitivity analyses were conducted.

The economic analysis suggests that for all populations assessed (treatment-naive, prior relapsers, and prior partial responders), at least one of the new DAA-based therapies appears to be economically attractive, compared with PR therapy. The drug that is the most cost-effective varies by population, but was generally consistent across fibrosis stages. This can be explained by the fact that, although the NMA for SVR stratified by fibrosis stage showed that there were generally no statistically significant differences between DAA regimens, the magnitude of effect for each DAA compared with PR, and the drug with the greatest effect versus PR, varied across populations. It is also important to note that simeprevir was not included in the analysis of prior partial responders, because of insufficient reporting of SVR stratified by fibrosis stage in that subgroup in the clinical trials.

For treating genotype 1 CHC treatment-naive patients, the economic analysis suggests that simeprevir is likely to be the most cost-effective option, at $32,230 per QALY gained compared with PR therapy. The incremental cost per QALY for telaprevir versus PR was $36,661, and the incremental cost per QALY for boceprevir versus PR was $73,429.

Treating genotype 1 prior relapsers with telaprevir is likely to be the most cost-effective option, at $19,808 per QALY gained compared with PR therapy. The incremental cost per QALY for simeprevir versus PR was $22,608 and the incremental cost per QALY for boceprevir versus PR was $31,341.

For genotype 1 prior partial responders, treatment with boceprevir is likely to be the most cost-effective option, at $23,131 per QALY gained compared with PR therapy. The incremental cost per QALY for telaprevir versus PR was $37,803 (simeprevir was not included in the analysis).

In the analyses stratified by fibrosis stage, ICURs of DAA-based therapies compared with PR tended to be lower in patients with advanced fibrosis (F3 to F4) compared with patients with no or mild fibrosis (F0 to F2), meaning that therapy appears to be more cost-effective in patients with more advanced disease. In treatment-naive patients, simeprevir was the most cost-effective treatment option, compared with PR, across all fibrosis stages. In patients with prior relapse and no or mild fibrosis (F0 to F2), both simeprevir and telaprevir were economically attractive, while boceprevir was ruled out due to extended dominance by PR and simeprevir. In patients with advanced fibrosis (F3 and F4), telaprevir was the most cost-effective treatment option, compared with PR. In patients with partial response and no or mild fibrosis, both boceprevir and telaprevir were economically attractive (simeprevir was not included in the analysis). In patients with F3 and F4 fibrosis, boceprevir was the most cost-effective treatment option compared with PR, while telaprevir was dominated or extendedly dominated by PR alone and boceprevir.

Besides treatment efficacy and fibrosis stage, the main factors affecting the cost-effectiveness of DAAs versus PR were the baseline age and the cost of antiviral therapy. The sensitivity analyses also suggest

that the cost-effectiveness results are highly sensitive to drug acquisition costs; however, the analyses do not account for any confidential prices that have been negotiated for CHC therapies.

Results of both the multiple one-way sensitivity analyses and probabilistic sensitivity analysis suggest that simeprevir is likely to remain cost-effective for treatment-naive patients. Telaprevir is likely to remain cost-effective for treatment-experienced patients with prior relapse, but, the differences in ICURs between simeprevir and telaprevir as compared with PR were modest. Due to the large credible intervals for the efficacy data derived from the NMA for prior partial responders, there is significant uncertainty associated with the ICURs for this population.

Limitations of the Evidence

The therapeutic review of the comparative efficacy, safety, and cost-effectiveness of DAA regimens was limited by important gaps in the available evidence, including the lack of RCTs comparing different DAA regimens head to head, sofosbuvir at the Health Canada-recommended dosage regimen or sofosbuvir in treatment-experienced patients, and DAAs in the populations of special interest (patients with HIV co-infection, liver transplant, or those who failed to achieve SVR with DAA plus PR therapy). Furthermore, limited data were available for several DAAs at the Health Canada–recommended dose, or for specific subgroups, such as those with severe fibrosis, Q80K polymorphism, or prior partial or null response. As a result, some NMAs were either missing approved treatments, or were conducted using few studies and a limited number of patients, thereby producing results with considerable uncertainty. Of particular concern is the limited comparative data with sofosbuvir. Consequently, sofosbuvir was assessed in an exploratory economic analysis, and ICURs generated from these analyses, although informative, are uncertain.

Comparative efficacy was based on findings for fibrosis subgroups from the NMA. Ideally, the NMA should have been stratified by individual fibrosis stages (F3 should have been analyzed separately from F4). This was not possible with the data available.

The economic analyses do not account for any confidential prices that may have been negotiated for CHC therapies.

DISCUSSION POINTS

- CDEC discussed that the progression of liver fibrosis occurs slowly over many years. The committee heard from clinical experts that it is difficult to predict which patients will experience further progression of liver fibrosis and how quickly progression may occur. Thus, in clinical practice patients who have fibrosis stages of F0 or F1 were often monitored without treatment, especially given the lower efficacy and treatment burden of older regimens, which patients were reluctant to incur. Therefore, CDEC considered watchful waiting in patients with lower fibrosis stages (F0 and F1) to be a reasonable approach, but that patients with the highest stages of liver fibrosis (especially F3 and F4) are a priority for treatment.
- CDEC discussed that few of the trials in the systematic review included patients who were co-infected with HIV. However, the committee considered that HIV co-infected patients should have the same access to treatment and criteria for treatment as patients who are not co-infected. This was supported by clinical expert opinion.

- The committee considered that treatment of CHC with antiviral drugs will not by itself be sufficient to address the public health impact of CHC.
- CDEC discussed the unmet medical need for patients with extrahepatic manifestations of HCV infection (cryoglobulinemic vasculitis, membranoproliferative glomerulonephritis, and porphyria cutanea tarda). However, given the limited clinical data available, CDEC did not review the use of DAA therapy in this patient population and was unable to make specific recommendations for these patients.
- CDEC noted that currently there is limited evidence to inform treatment strategies for patients in whom DAA containing regimens have failed. Sofosbuvir and other DAAs with viral targets other than the protease region may offer treatment options for patients in whom a protease inhibitor plus PR regimen has failed; however, clinical evidence for this option is lacking.
- CDEC noted that there are practical limitations in identifying intolerance specific to the DAA versus the PR component of the treatment regimen. The committee considered that clinical expertise would be required to make this distinction.

RESEARCH GAPS

The Committee proposed that the following be addressed through research as a high priority:

- Head-to-head RCTs to assess the comparative efficacy and safety of DAAs.
- Provision of clinical trial evidence regarding the efficacy of DAA regimens, other than simeprevir plus PR, in patients infected with HCV genotype 1a with a Q80Kpolymorphism.
- RCTs to determine the optimal treatment for populations of special interest, including HIV co-infected, post-transplant, and patients in whom DAA plus PR treatment has failed.
- Epidemiologic studies of the prevalence of CHC and the impact of antiviral treatment on the burden of disease in the Canadian population.
- Studies to facilitate the prediction of patients most likely to develop progressive liver disease.
- Studies of long-term outcomes with respect to the impact of DAA regimens on hepatic related morbidity (end-stage liver disease, hepatocellular carcinoma, liver transplant) and mortality.
- Studies of reinfection, adherence, and toxicities in real-world settings.

September 16, 2014 Meeting:
CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius, (Vice-Chair), Dr. Silvia Alessi-Severini,
Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets: Dr. Kerry Mansell

Conflicts of Interest: None

July 15, 2014 Meeting:
CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi,
Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt,
Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk,
Dr. James Silvius, and Dr. Adil Virani.

Regrets:
None

Conflicts of Interest:
None

External Clinical Experts
Two external clinical experts in hepatology attended the July 2014 CDEC meeting and participated in the discussion but did not vote on the draft recommendations. Four clinical experts in hepatology attended the September 2014 CDEC meeting and participated in the discussion but did not vote on the final recommendations.

About This Document:
The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy, and public members.

The CDEC Therapeutic Review Recommendations or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The Therapeutic Review Framework describes the Therapeutic Review process in detail.[41]

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