CADTH Evidence Driven.

SUMMARY REPORT

Drugs for Chronic Hepatitis C Infection

What is hepatitis C?

- Hepatitis C is a liver disease that is caused by infection with hepatitis C virus (HCV). The virus is spread by contact with contaminated blood or blood products. Most HCV infections in Canada are associated with intravenous drug abuse; other risk factors are blood transfusions received before 1992, tattoos and body piercings, and needle-stick injuries and similar exposures for health care workers.
- About 25% of infected people will clear the virus spontaneously. The remainder will develop chronic hepatitis C (CHC) infection. About 242,000 Canadians have CHC infection.

Does chronic hepatitis C infection need to be treated?

Of those with chronic infection, 15% to 20% will develop end-stage liver disease over 20 years of infection. Others may be infected for a lifetime and never develop symptoms. Patients generally decide along with their doctor whether, and when, to initiate treatment. The decision may be based on their risk of progression, the harms of treatment, or other factors.

How has chronic hepatitis C treatment changed in recent years?

The landscape of CHC treatment has changed dramatically in the past few years. Treatment is more effective, more tolerable, and also more costly than ever before.

For many years, standard treatment for CHC was pegylated interferon (once weekly as a subcutaneous injection) plus ribavirin (twice daily by mouth), given for 24 to 48 weeks. This therapy was generally successful in about 40% of patients with the most common type of infection. Up to 50% of patients experienced flu-like symptoms, fatigue, muscle aches, nausea and vomiting, rash, headaches, and mood changes (depression, anxiety, mania, suicidal ideation); 10% to 15% of patients had to stop treatment because of side effects.

In 2011, the first direct-acting antiviral agents (DAAs) became available in Canada. These drugs increased the success rate to between 60% and 90%, but they still needed to be used in combination with interferon and ribavirin (and had associated side effects).

In 2014, the first interferon-free, all-oral regimens became available in Canada. These new regimens generally have success rates of more than 90% and offer the shorter treatment durations desired by patients. These regimens are also associated with high costs.

What has CADTH done?

Over the past five years, CADTH has responded to many requests for evidence on hepatitis C treatment. We have conducted many rapid evidence reviews on specific aspects of treatment, as well as a report on emerging therapies. Through the CADTH Common Drug Review (CDR), we have published reimbursement recommendations for all new drugs as they enter the Canadian market.

In 2015, CADTH conducted a Therapeutic Review. This was a systematic review of all interferon-free regimens available in Canada as of May 2015 — a review of the whole category of drugs at this time. Patient input was sought and incorporated throughout the review. A network meta-analysis was used to compare regimens indirectly, as no head-to-head trials have been published. An economic evaluation was completed, and the CADTH Canadian Drug Expert Committee (CDEC) made recommendations based on all available evidence. Although this Therapeutic Review doesn't include the newest drugs, it is a useful foundation for this complicated treatment area.

Table 1 provides more information from the CADTH Common Drug Review and comparison with the 2015 Therapeutic Review.

All CADTH work on hepatitis C is available at **cadth.ca/hepatitisc**.

CADTH

- People with any stage of CHC infection should be considered for treatment, but priority should be given to patients with more severe disease.
- Therapy should be managed by a medical specialist with expertise in liver diseases.

What is the goal of treatment?

Successful treatment will achieve a sustained virologic response (SVR). SVR means that the virus is undetectable a certain amount of time after treatment has finished (e.g., SVR24 means that no virus is detectable 24 weeks after the end of treatment). SVR is sometimes called a "cure" and is recognized as an acceptable surrogate for important complications such as cirrhosis, liver transplant, or hepatocellular carcinoma.

What factors are important when considering treatment options?

Genotype: There are six different strains, or genotypes, of HCV. Genotype 1 is the most common in Canada, and also traditionally the most difficult to treat. Many of the newer treatments have been studied and approved to treat genotype 1, so that now there are more treatment options for genotype 1 than for others.

Severity of liver disease: This is usually reported in terms of fibrosis — the amount of liver damage or scarring that is present. Liver biopsy is the traditional gold standard for measuring fibrosis, but other non-invasive methods are available. Fibrosis measured by liver biopsy is reported as a METAVIR score. METAVIR scores range from F0 to F4, where F0 means there is no visible scarring and F4 means there is advanced scarring or cirrhosis.

Prior treatment experience: People who have been treated unsuccessfully in the past may be less likely to clear the virus with subsequent treatment. Patients may be classified as treatment-naive or treatment-experienced. Treatment-experienced patients may be classified as having:

- prior relapse — previous treatment cleared the virus to undetectable levels but did not achieve SVR
- prior partial response — previous treatment significantly reduced viral load but did not achieve undetectable levels
- prior null response — previous treatment did not significantly reduce viral load.

Previous treatment may include pegylated interferon and ribavirin (PR), or a DAA plus PR regimen, or an all-oral interferon-free DAA regimen.

Presence of comorbidities: Some conditions make CHC infection more difficult to treat, such as coinfection with HIV, decompensated liver disease, or liver transplant. These patients have not been well-studied.

Who should be offered drug treatment for chronic hepatitis C infection?

This is one of the most difficult questions facing clinicians and decision-makers in this area. If the treatments were free of side effects and cost, it would be simpler to offer treatment to everyone. In reality, we can't always predict who will develop progressive liver disease and who won't, and all treatments have side effects. For some individual patients, watchful waiting might make sense — in other words, deciding with their doctor to defer treatment, perhaps wanting to avoid side effects or waiting for new options to become available. For other patients, this is not feasible.

When we think about treating large groups of people, we need to consider which options will help us achieve the greatest good for the greatest number of people. To do this, we need to look at both cost-effectiveness and budget impact. Estimates of cost-effectiveness predict how much health improvement we'll see for each dollar spent — in other words, value for money. Budget impact, on the other hand, looks at how many dollars need to be spent, and whether the funds are available or would have to be taken away from something else.

CADTH's latest review showed that interferon-free treatment regimens are cost-effective in many situations. However, the budget impact is likely to be substantial. Public payers may have to consider the overall costs of treatment and the effects on system sustainability.

CADTH CDEC recommends that all patients should be considered for treatment. However, given the potential impact on health system sustainability of treating all patients with CHC infection on a first-come, first-served basis, priority for treatment should be given to patients with more severe disease.

What does the evidence say about interferon-free treatment regimens?

Recommendations from the 2015 CADTH Therapeutic Review demonstrate that the evidence is more robust for genotype 1 infection than for other types. For genotype 1, patients and clinicians have a choice of regimens that have demonstrated greater efficacy than interferon-based regimens and are cost-effective.

For genotypes 2 through 4, evidence is more limited. The CADTH Therapeutic Review found that:

- Interferon-free regimens generally showed greater efficacy than interferon-based therapy.
- There were no significant differences between the interferon-free regimens.
- Interferon-free regimens were rarely cost-effective.

CADTH CDEC gave considerable weight to input from patient groups, which said that interferon-based therapy was unacceptable because of its side effects profile, and the committee consequently prioritized interferon-free regimens in its recommendations. However, it noted the potential impact on health system sustainability of treating all patients with CHC genotypes 2 through 4 infection with these regimens.

For genotypes 5 and 6, there was not enough evidence to make a recommendation.

Evidence on safety was limited, as much of the available evidence comes from small, uncontrolled studies. CADTH CDEC noted the October 2015 warning from the US FDA regarding serious liver injury with ombitasvir/paritaprevir/ritonavir + dasabuvir with or without ribavirin (Holkira Pak).

Note that the CADTH Therapeutic Review included emerging treatments, and therefore several had not yet been approved by Health Canada or submitted to CDR. Some of these regimens have been recommended by clinical practice guidelines and were found to be cost-effective in CADTH's review. Conversely, some regimens that have been approved by Health Canada had insufficient evidence to include in the analysis.

Since the release of the 2015 CADTH Therapeutic Review, researchers have found more evidence on retreatment of patients after DAA-based therapy. A separate CADTH rapid review on this topic is available.

For a detailed summary of all CADTH's reimbursement recommendations, including both CDR (single drug review) and Therapeutic Review (category review) recommendations, as well as explanations of where these recommendations differ, refer to Table 1.

Who should manage treatment?

With newer all-oral regimens, treatment may be increasingly available outside of specialized centres. CADTH CDEC recommends that therapy should be managed by medical specialists with experience in the treatment of CHC infection. The physician managing treatment requires specialized knowledge on monitoring therapy and ensuring patient adherence with therapy.

Table 1: Summary of CADTH Recommendations

This table outlines reimbursement recommendations from the CADTH Common Drug Review (single drug review) and recommendations from the 2015 Therapeutic Review (category review), and gives explanations for cases in which the recommendations differ. Refer to the full Recommendations Report for more detail.

Treatment Regimen	Patient Populations Recommended for Reimbursement		Comments
	Common Drug Review (Individual Drug Reviews)	Therapeutic Review (Category Review)	
All Genotypes (1 to 6)			
sofosbuvir/velpatasvir (Epclusa) for 12 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
Genotype 1			
simeprevir (Galexos) + PR for 12 weeks	Treatment-naive or PR-experienced, with or without cirrhosis, fibrosis stage ≥ 2	Not recommended	In the Therapeutic Review, this regimen was not recommended for clinical reasons; i.e., lower rates of SVR as compared with PR-free regimens, preference for PR-free regimens.
simeprevir + sofosbuvir for 12 or 24 weeks	Not reviewed	Not recommended	This regimen has not been filed for review through the Common Drug Review process.
sofosbuvir (Sovaldi) + PR for 12 weeks	Not recommended	Not recommended	Recommendations are aligned.
ledipasvir/sofosbuvir (Harvoni) for 12 weeks	Treatment-naive or PR/PI-experienced, with or without cirrhosis	Treatment-naive or PR/PI-experienced, with or without cirrhosis	Recommendations are aligned.
ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak) ± ribavirin for 12 or 24 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Treatment-naive or PR-experienced, with or without cirrhosis	Recommendations are aligned.
elbasvir/grazoprevir (Zepatier) ± ribavirin for 8 to 16 weeks	Treatment-naive or PR/PI-experienced, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
asunaprevir (Sunvepra) + daclatasvir + PR for 24 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
Genotype 1b			
asunaprevir (Sunvepra) + daclatasvir	Treatment-naive or PI/PR experienced, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
Genotype 2			
sofosbuvir + ribavirin for 12 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Treatment-naive or PR-experienced, with or without cirrhosis	Recommendations are aligned.

Treatment Regimen	Patient Populations Recommended for Reimbursement		Comments
	Common Drug Review (Individual Drug Reviews)	Therapeutic Review (Category Review)	
Genotype 3			
sofosbuvir + ribavirin for 24 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Treatment-naive or PR-experienced, **with** cirrhosis	In the Therapeutic Review, this regimen was not recommended for patients without cirrhosis for economic reasons; i.e., daclatasvir + sofosbuvir is more cost-effective in these patients.
daclatasvir (Daklinza) + sofosbuvir for 12 weeks	Treatment-naive or PR-experienced, **without** cirrhosis	Treatment-naive or PR-experienced, **without** cirrhosis	Recommendations are aligned. The 24-week regimen (for patients **with** cirrhosis) was not recommended.
elbasvir/grazoprevir + sofosbuvir for 12 weeks	Treatment-naive, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
Genotype 4			
simeprevir + PR for 12 weeks	Not reviewed	Not recommended	Genotype 4 was not included in the manufacturer's submission to the Common Drug Review.
sofosbuvir + PR for 12 weeks	Treatment-naive, **without** cirrhosis	Treatment-naive, **without** cirrhosis	Recommendations are aligned.
ombitasvir/paritaprevir/ritonavir (Technivie) + ribavirin for 12 weeks	Treatment-naive or PR-experienced, **without** cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
elbasvir/grazoprevir ± ribavirin for 12 to 16 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.
asunaprevir + daclatasvir + PR for 24 weeks	Treatment-naive or PR-experienced, with or without cirrhosis	Not reviewed	The Therapeutic Review predated the approval of this regimen.

CDR = Common Drug Review; PI = protease inhibitor; PR = pegylated interferon and ribavirin; SVR = sustained virologic response.

CADTH

References

1. Drugs for chronic hepatitis C infection: recommendations report [Internet]. Ottawa: CADTH; 2015 Nov. [cited 2016 May 19]. (CADTH Therapeutic Review; vol.3, no.1d). Available from: www.cadth.ca/drugs-chronic-hepatitis-cinfection
2. Re-treatment for patients with NS5A resistant-associated variants of hepatitis C virus: a review of clinical effectiveness [Internet]. Ottawa; CADTH; 2016 Jul. [cited 2017 Mar 29]. (CADTH Rapid Response). Available from: www.cadth.ca/re-treatment-patients-ns5a-resistant-associated-variants-hepatitis-c-virus-review-clinical
3. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: simeprevir (Galexos - Janssen Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2014. [cited 2016 May 19]. Available from: www.cadth.ca/simeprevir-6
4. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: sofosbuvir (Sovaldi - Gilead Sciences Canada Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2016 May 19]. Available from: www.cadth.ca/sofosbuvir-7
5. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: ledipasvir/sofosbuvir (Harvoni - Gilead Sciences Canada Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2016 May 19]. Available from: www.cadth.ca/ledipasvir-sofosbuvir-5
6. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: ombitasvir/paritaprevir/ritonavir and dasabuvir (Holkira Pak - AbbVie Corporation). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2016 May 19]. Available from: www.cadth.ca/ombitasvirparitaprevir-ritonavir-and-dasabuvir
7. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: elbasvir/grazoprevir (Zepatier - Merck Canada Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2016 May 19]. Available from: www.cadth.ca/elbasvirgrazoprevir
8. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: daclatasvir (Daklinza - Bristol Myers Squibb Canada Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2016 May 19]. Available from: www.cadth.ca/daclatasvir-0
9. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: ombitasvir/paritaprevir/ritonavir (Technivie - AbbVie Corporation). Indication: chronic (genotype 4) hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2016 May 19]. Available from: www.cadth.ca/ombitasvir-paritaprevir-ritonavir
10. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: sofosbuvir/velpatasvir (Epclusa - Gilead Sciences Canada Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2017 Mar 29]. Available from: www.cadth.ca/sofosbuvir-velpatasvir
11. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: asunaprevir (Sunvepra - Bristol Myers Squibb Canada Inc.). Indication: chronic hepatitis C [Internet]. Ottawa: CADTH; 2016. [cited 2017 Mar 29]. Available from: www.cadth.ca/asunaprevir

Questions or comments about CADTH or this Summary?

Learn more:
cadth.ca/hepatitisc

Contact us:
requests@cadth.ca

Follow us on Twitter:
@CADTH_ACMTS

Subscribe to our E-Alert and *New at CADTH* newsletter:
cadth.ca/subscribe.

ABOUT CADTH

CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Ce document est également disponible en français.

July 2017

CADTH Evidence Driven.

cadth.ca