ONTARIO PHARMACISTS ASSOCIATION
Drug Information & Resource Centre

PHARMACISTS MANITOBA

Therapeutic Options

FOCUS ON CHRONIC HEPATITIS C

BACKGROUND

Chronic hepatitis C is a prominent medical burden of our world today. Over 185 million people around the world have been infected with the hepatitis C virus (HCV).[1] One third of these people become chronically infected and 350 000 die each year from HCV.[1] Within Canada, an estimated 242,500 individuals are infected with HCV, and approximately 21% of these individuals remain undiagnosed.[2] Other sources have more bleakly reported that up to 70% of Canadians infected with HCV are unaware of their infection.[3]

Treatment of chronic HCV infection can be curative, and the landscape of treatment options has grown extensively over the last few years.[1,4] Major advances in treatment include the highly effective direct-acting antiviral agents (DAAs) and the approval of interferon-free, all-oral regimens.[3] The pace of change is not expected to slow down, as several novel drugs with different mechanisms of action are on the horizon.[4]

Managing and treating a patient with chronic HCV can be complex and often requires a multidisciplinary approach that includes experienced physicians, nurses, psychologists, social workers, addiction specialists, and other allied health professionals.[3] This review aims to equip pharmacists with knowledge of current treatment recommendations for HCV genotypes 1, 2 and 3, with an emphasis on newer treatment options and regimens.

ETIOLOGY AND PATHOPHYSIOLOGY

HCV is a single-stranded RNA virus from the *Flaviviridae* family, known for its ability to undergo frequent viral mutations and for lacking a proofreading polymerase.[5] The virus replicates within hepatocytes and is not directly cytopathic, similar to hepatitis B.[5] HCV presents as an immense challenge to the immune system because it replicates in large amounts and is constantly mutating.[5]

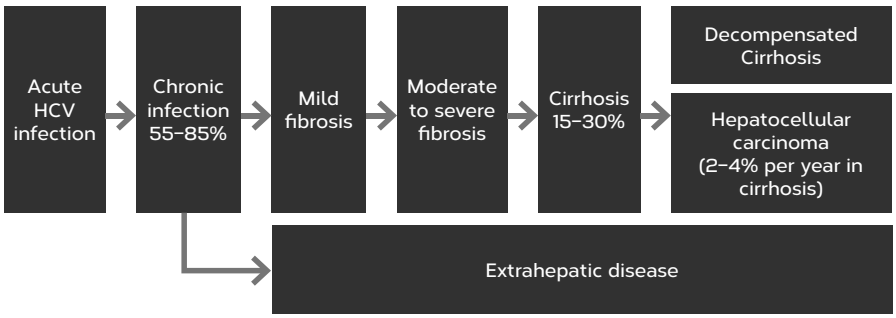
HCV is divided into six different genotypes, numbered 1 to 6. Each varies in nucleotide sequence by 30-50%.[5] Genotype 1 can be further classified into subtypes, such as 1a and 1b. Differentiating between genotypes and subtypes is important for treatment options, particularly with some of the new antiviral regimens.[3] Of those individuals infected with HCV in Canada, 65% are infected with genotype 1, making it the most prevalent genotype (56% genotype 1a, 33% genotype 1b, and 10% are a mixed or unspecified genotype).[3] Genotypes 2 and 3 constitute 14% and 20% of HCV infections in Canada respectively, while genotypes 4, 5 and 6 cumulatively account for less than 1%.[3]

HCV is the most prevalent blood-borne pathogen.[5] The primary route for transmission of HCV is through percutaneous exposure to blood.[4] Approximately one-quarter of people infected with HCV will spontaneously clear the virus.[3] However, for a majority of cases (55-85%), an acute HCV infection will lead to a chronic infection (see Figure 1).[1,5]

SCREENING AND TESTING

Acute infections of HCV are typically asymptomatic, and HCV is rarely associated with extrahepatic manifestations.[4] For these reasons, HCV screening and testing is

Figure 1. Natural History of HCV Infection*



* Reprinted from Guidelines for the screening, care and treatment of persons with hepatitis C infection, 1.1, World Health Organization, Natural History of HCV Infection, page no. 30, Copyright (2015).[1]

recommended based on risk factors, including behaviours, exposures, and co-morbidities associated with HCV infection.[4] Certain patient groups with a high prevalence of HCV are encouraged to be tested as treatment reduces the risk of hepatocellular carcinoma, all-cause mortality, and potential for transmission.[4]

Most HCV infections in middle- and high-income countries occur among people who inject drugs (PWID) with unsterile equipment and contaminated drug solutions.[1] Other modes of HCV transmission include from mother-to-child, contaminated devices shared for non-injection drug use, health care exposures, and sexual transmission.[1,4] In Canada, current or former PWIDs account for 60% of HCV cases, while infected immigrants account for 20% and individuals who received contaminated blood products account for 11%.[3]

Table 1 outlines patient populations that are at increased risk for HCV infection and for whom HCV testing is recommended. It is worth noting that a one-time HCV test is recommended for all people born between 1945-1965, regardless of their country of birth.[4]

Table 1. Populations at risk for HCV infection*

Population	Description
People who inject drugs (PWID)	• Highest risk of infection in this patient population • Global prevalence of HCV infection is 67%
People who use intranasal drugs	• Use of intranasal drugs, such as sharing of inhalation equipment for cocaine, is associated with an increased risk of HCV infection
People at risk of health care associated transmission	• People who received infected blood products • People who had invasive procedures in health-care facilities with inadequate infection control • Recipients of long-term hemodialysis • Health care and public safety workers after exposure to HCV-infected blood
People at risk through sexual transmission	• HIV-positive persons at higher risk of HCV infection through unprotected sex, particularly men who have sex with men (MSM) • Sexual transmission of HCV is less frequent among heterosexual couples
Mother-to-child transmission	• Risk of transmission 4-8% during birth in women with HCV infection and 17-25% in women with HIV and HCV co-infection
People with tattoos or piercings	• Higher prevalence of HCV infection among people who have tattoos compared to those without
People with certain health conditions	• HIV infection (HCV and HIV have similar routes of transmission, and approximately 4-5 million people globally are coinfected with the two viruses) • Unexplained chronic liver disease and chronic hepatitis (with elevated alanine aminotransferase levels) • Solid organ donors

*Adapted from WHO guidelines and hcvguidelines.org.[1,4]

TREATMENT

The primary goal of antiviral therapy for HCV is eradication of the virus, known as sustained virological response (SVR).[3] SVR is defined as an undetectable HCV RNA at least 12 weeks following the end of treatment.[3,4] Achieving SVR is associated with a reduction in all-cause mortality and liver-related morbidity, including end stage liver disease and hepatocellular carcinoma.[4] Treatment is recommended for all patients with chronic HCV infection, with greatest urgency for those with advanced fibrosis, compensated cirrhosis, liver transplant recipients, and patients with severe extrahepatic hepatitis C.[4]

Until recently, standard therapy for HCV genotypes 1, 4, 5, and 6 was 48 weeks of dual therapy with peginterferon alfa (PEG-IFN) and ribavirin, and 24 weeks of dual therapy for genotypes 2 and 3.[3] This dual therapy achieves SVR rates of 40-50% in patients with genotype 1; in patients with genotypes 2, 3, 5 and 6, it achieves SVR rates of approximately 80%.[3]

Within the past 2-3 years, several novel pharmacological therapies have arrived on the market with new polyprotein targets for the HCV genome.[3] The first DAAs approved by Health Canada in 2011 were the nonstructural (NS) 3/4A protease inhibitors, boceprevir and telaprevir.[3] These agents were approved for treatment of the HCV genotype 1.[3,6] While boceprevir is still available on the Canadian market, telaprevir (Incivek™) was discontinued by the manufacturer in early 2015.[7] The introduction of these two drugs represented a breakthrough in HCV treatment because they substantially increased the rates of SVR in treatment-naïve patients as well as in those previously treated.[3] However, these agents are associated with higher rates of serious adverse effects, have many drug-drug interactions, and require complex regimens including co-administration with PEG-IFN and ribavirin.[3,4]

The second generation protease inhibitor, simeprevir, was approved in 2013 for treatment of genotype 1, in combination with PEG-IFN and ribavirin.[3] Also approved in 2013 was the first HCV nucleotide polymerase inhibitor, sofosbuvir.[3] Similar to simeprevir and the first generation protease inhibitors, sofosbuvir is to be used in combination with PEG-IFN and ribavirin for treatment of genotypes 1 and 4, or with ribavirin alone for genotypes 2 and 3.[3]

In 2014, a single combination-tablet regimen of sofosbuvir with the NS5A inhibitor ledipasvir was approved by Health Canada for treatment of patients with HCV genotype 1.[3] Also in 2014, a combination pack containing paritaprevir, low-dose ritonavir, the NS5A inhibitor ombitasvir, and dasabuvir was approved for use with or without ribavirin in patients with HCV genotype 1.[3] These new antiviral agents have allowed for all-oral antiviral regimens with minimal risk of toxicity, short treatment courses, and few contraindications.[3] They also have markedly improved effectiveness, indicating that regimens free of PEG-IFN are beneficial for

patients with HCV. While these new agents are now considered first-line therapy, availability across Canada continues to be a barrier.[3] See Table 2 for a complete list of all antiviral therapies for HCV available in Canada.

Treatment regimens with newer antiviral therapies are outlined in Table 3 for treatment-naïve patients with HCV genotypes 1, 2, and 3. It is important to note that recommendations differ for treatment-experienced patients who have failed therapy with PEG-IFN and ribavirin.[3,4] The recommendations in Table 3 have been compiled from individual product monographs, the 2015 Consensus guidelines from the Canadian Association for the Study of the Liver, and from guidelines created by the Infectious Diseases Society of America (IDSA) and the American Association for the Study of Liver Diseases (AASLD) (http://hcvguidelines.org).[3,4] Pharmacists involved in the care of patients with HCV are encouraged to regularly consult with these resources, particularly the website maintained by the IDSA and AASLD, as the website is regularly updated with new developments and therapies.

Health Canada has approved the indications of all the new antiviral agents listed in Table 3, with the exception of simeprevir in the treatment of HCV genotype 1a and 1b. Simeprevir has a notice of compliance with conditions granted by Health Canada for its use in combination with sofosbuvir.[10] This status was granted because of promising clinical evidence, mainly from the phase II COSMOS study.[12] Phase III study data of simeprevir use should be available by mid-to-late 2015.[4]

There are many benefits of the PEG-IFN-free regimens listed above in Table 3. They are all-orally administered and use fixed-dose regimens (unlike older therapies that modify treatment based on HCV RNA levels).[3] The safety profiles of all the recommended regimens for genotypes 1a and 1b are excellent, particularly those that avoid ribavirin.[4] Data from multiple phase III trials have shown discontinuation rates less than 1% in patients without cirrhosis, and reported adverse events were considered mild.[4] Discontinuation rates for patients with cirrhosis were higher but still low overall (approximately 2%).[4]

Despite the evidence for safety, potential drug interactions must also be considered. In March 2015, the FDA released a Drug Safety Communication, warning that patients can experience a serious and life-threatening symptomatic bradycardia when the antiarrhythmic medication amiodarone is taken with either ledipasvir and sofosbuvir (Harvoni™) or sofosbuvir (Sovaldi™) in combination with another DAA.[13] This caution is based on postmarket reports of adverse events, including the death of one patient secondary to cardiac arrest, and three patients who required the placement of pacemakers.[13]

The new DAAs also have a significant number of drug interactions with other medications commonly used by patients.[4] Acid suppressing agents may reduce the concentration of ledipasvir (Harvoni™); moderate or strong inducers of CYP3A4 are contraindicated with all currently available HCV protease inhibitors; and administration of QT prolonging drugs is not recommended with the combination of paritaprevir, ritonavir, ombitasvir and dasabuvir (Holkira™

Table 2. Hepatitis C drug therapies available in Canada

Active Ingredient(s)	Brand Name
Peginterferon alfa-2a	Pegasys™
Ribavirin	Ibavyr™ Moderiba™
Peginterferon alfa-2a and ribavirin	Pegasys RBV™
Peginterferon alfa-2b and ribavirin	Pegetron™
Boceprevir	Victrelis
Boceprevir, peginterferon alfa-2b and ribavirin	Victrelis Triple™
Simeprevir	Galexos™
Sofosbuvir	Sovaldi™
Ledipasvir and sofosbuvir [a]	Harvoni™
Paritaprevir, ritonavir, and ombitasvir[b] with dasabuvir[c]	Holkira™ Pak

[a]Provided as a single combination tablet

[b]Paritaprevir, ritonavir and ombitasvir provided as a single combination tablet in Holkira Pak[8]

[c]Dasabuvir provided as an individual tablet within Holkira Pak [8]

Table 3. Antiviral first-line therapy recommendations for treatment-naïve HCV genotypes 1, 2, 3[3,4]

Genotype	Antiviral regimen and duration*
Genotype 1a	ledipasvir/sofosbuvir x 8¶ or 12 weeks[9]
	paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin x 12 weeks[8]
	sofusbuvir plus simeprevir x 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)[10]
Genotype 1b	ledipasvir/sofosbuvir x 8¶ or 12 weeks[9]
	paritaprevir/ritonavir/ombitasvir plus dasabuvir x 12 weeks (with ribavirin for cirrhotic patients)[8]
	sofosbuvir plus simeprevir x 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)[10]
Genotype 2	sofosbuvir and ribavirin x 12 weeks[11]
Genotype 3	sofosbuvir and ribavirin x 24 weeks[11]

* In instances where duration varied among the guidelines, the duration listed in the Canadian product monograph was listed

¶ Shorter duration can be considered in treatment-naïve patients without cirrhosis with pre-treatment HCV RNA <6 million IU/mL

Pak).[3,4,8,9] While product monographs may be consulted, resources have also been developed as quick reference guides to check for and prevent drug interactions (eg. http://www.hep-druginteractions.org).[14] It is recommended for all patients that a comprehensive medication history be completed prior to initiation of antiviral therapy.[4]

PREVENTION OF HCV INFECTION

As there is no effective vaccine for HCV, reducing the risk of exposure is the primary method of preventing infection.[1] The World Health Organization has recommended a number of interventions to prevent transmission of HCV (Table 4).[1]

CONCLUSION

Treatment options for HCV are rapidly evolving with the goal of improving patients' health outcomes and quality of life. In this time of change, pharmacists can play an essential role in ensuring appropriate treatment regimens are selected for patients and minimizing adverse effects by avoiding potential drug interactions.

Table 4. Interventions to prevent HCV infection*

Setting	Recommendations*
Healthcare	• Hand hygiene • Safe disposal of sharps and waste • Adequate cleaning of equipment • Testing donated blood
Injection of Drugs	• Sterile needle and syringe programs • Condom programs (for sexual partners as well) • Targeted information, education, and communication • Completion of hepatitis B vaccination schedule
Sexual Transmission	• Correct and consistent condom use should be promoted • Routine sex worker screening

* Adapted from WHO guidelines, see original document for complete guidance on prevention of HCV infection[1]

REFERENCES:

1. Guidelines for the screening, care, and treatment of persons with hepatitis C infection. World Health Organization. April 2014. http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1
2. Hepatitis C - Quick Facts. Public Health Agency of Canada. Retrieved May 12, 2015. http://www.phac-aspc.gc.ca/hepc/index-eng.php
3. RP Myers, H Shah, KW Burak, C Cooper, JJ Feld. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol 2015;29(1):19-34.
4. Recommendations for Testing, Managing, and Treating Hepatitis C. AASLD and IDSA. http://hcvguidelines.org/full-report-view
5. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: a pathophysiologic approach. 8th ed. Columbus (OH): McGraw-Hill; 2012.
6. Product Monograph. Victrelis. Merck Canada. Feb 11, 2015.
7. Drug Product Database. INCIVEK™. April 21, 2015.
8. Product Monograph. Holkira ™ Pak. AbbVie Corporation. Dec 22, 2014.
9. Product Monograph. Harvoni™ Gilead Sciences Inc. Oct 14, 2014.
10. Product Monograph. Galexos™ Janssen Inc. Jan 29, 2015.
11. Product Monograph. Sovaldi™ Gildead Sciences Inc. December 4, 2014.
12. Lawitz E, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014 Nov 15;384(9956):1756-65.
13. FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug. U.S. Food and Drug Administration. March 24, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm
14. University of Liverpool. http://www.hep-druginteractions.org