The dollars and sense of chronic hepatitis C infection management

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Hepatitis C ranks among the most burdensome infectious diseases in Canada. Traditionally, therapies have met with limited success that has, in part, been related to significant side effects due to the use of injectable interferon, the need for prolonged treatment periods of up to 48 weeks and moderate efficacy even under optimal conditions. As a result, a large cohort of untreated hepatitis C virus (HCV)-infected Canadians remains; these patients are at risk for major complications, most notably the development of cirrhosis and hepatocellular carcinoma. Recent years have witnessed dramatic advances in the management of patients with chronic HCV infection. New direct-acting agents have been developed and licensed in Canada; they have high efficacy (ie, >90%) for inducing sustained virological response (SVR) when used in combination therapy, in some cases for as little as eight to 12 weeks. In addition, oral-only regimens are now possible, especially for genotype 1 infections, which are responsible for approximately two-thirds of all HCV infections in Canadians (1,2). However, these agents are remarkably expensive. Outstanding and detailed evidence-based reviews have recently been published describing the epidemiology, clinical aspects and treatment options for HCV-infected Canadians, and the interested reader is referred to these reports for further review (1,2). In the present note, we briefly review therapies for HCV infection and focus on issues surrounding the use of these new therapeutic options in Canada.

Burden of HCV infection
Although the exact prevalence and incidence of HCV infection is not known, current estimates indicate that approximately 250,000 Canadians (approximately 1% of the population) are infected with HCV (3). Kwong et al (4) investigated the burden associated with 51 infectious diseases in Ontario from 2005 to 2007 and found that HCV infection was associated with the greatest disease burden. Among patients with HIV infection, coinfection with HCV is associated with a major increased risk for adverse outcomes (5,6). Genotypes 1a and 1b are the most prevalent HCV genotypes in Canada, representing approximately two-thirds of cases, with the remainder being largely genotypes 2 and 3; genotypes 4, 5 and 6 are rare (1). Among patients initially infected with HCV, approximately 15% to 20% will spontaneously clear the infection. However, those with chronic infection are at risk for major complications, including cirrhosis, liver failure and hepatocellular carcinoma (3,7,8).

The evolution of HCV therapy
Management of HCV has undergone major changes over the past several decades (9). Injection of interferon-α (INF-α) was first used to treat patients with HCV infection in the 1980s, but even with prolonged courses, success rates for cure remained very low (<10% to 20%) (10). The addition of ribavirin to INF-α and subsequently to pegylated INF-α therapy for 48 weeks led to improved rates of response to approximately 30% and 40% to 50% overall in the later 1990s and early 2000s, respectively (9). Compared with genotype 1, genotypes 2 and 3 were found to respond at much higher (70% to 80%) rates even when shorter 24-week treatments were evaluated (11). Several clinical trials were published in 2011 demonstrating the benefit of adding one of the HCV NS3/4A protease inhibitors (telaprevir or boceprevir) in combination with pegylated INF-α and ribavirin for genotype 1 infection (1,9). However, side effects and toxicity along with a low barrier to the development of resistance has left these agents by the wayside.

The newer HCV NS3/4A protease inhibitors simeprevir and ritonavir-boosted paritaprevir, the HCV nucleotide and nonnucleoside NS5B polymerase inhibitors sofosbuvir and dasabuvir, and the NSSA inhibitors ledipasvir and ombitasvir have been the most recent and important additions to the HCV therapeutic armamentarium in the past few years (9). In combination therapy, these agents have not only demonstrated outstanding efficacy (>90%) in the treatment of genotype 1 HCV infection, but have the advantages of high efficacy in treatment-experienced and cirrhotic patients, and are of relatively short duration (eight to 12 weeks in most cases). Perhaps most importantly, these agents have now made interferon-free treatment regimens possible.

The combination of sofosbuvir and ledipasvir or paritaprevir/ritonavir, ombitasvir and dasabuvir orally once daily ± ribavirin has been evaluated in a number of recent randomized clinical trials in genotype 1 HCV-infected patients (12-21). In general, these regimens are well tolerated and result in SVR ≥95% (approaching 100% in some cases) in a wide range of treatment-experienced/naïve and cirrhotic/noncirrhotic patients when administered in courses as short as eight to 12 weeks. While these trials have focused on genotype 1 HCV infection, these combination therapies have demonstrated high efficacy in some other genotypes, and newer agents are on the horizon that will likely lead to highly efficacious oral therapies for all HCV infections.

The cost of SVR
With the approval of new regimens, we now have access to relatively simple, well-tolerated, highly efficacious oral therapies for many HCV-infected patients (1). A daily single-dose tablet (Harvoni, Gilead, USA) of sofosbuvir (400 mg)/ledipasvir (90 mg) for eight to 12 weeks may be used for management of genotype 1 HCV. A two-tablet once-daily dose combination (Holfrika Pak, AbbVie, USA) of paritaprevir (150 mg)/ritonavir (100 mg) and ombitasvir (25 mg) taken with dasabuvir (250 mg) orally twice daily for 12 weeks (24 weeks in treatment-experienced cirrhotic patients with genotype 1a) is available for management of genotype 1 HCV-infected patients. With the
exception of treatment-experienced patients with cirrhosis, genotype 2 and 3 HCV-infected patients may be treated with sofosbuvir (Sofvaldi, Gilead) plus ribavirin for 12 and 24 weeks, respectively.

The availability of highly efficacious, oral, interferon-free regimens for treatment of HCV infections represents the most important medical advance in infectious diseases in the recent years. However, there is one notable drawback: cost. Although pricing is negotiable and, therefore, variable, estimates of medication cost for typical treatment courses for Harvoni, Holkira Pak or Sofvaldi range from $35,000 to $60,000 (22,23). These agents set a new precedent for high cost for curative therapies in infectious diseases.

HCV therapy in 2015

There are several issues and controversies surrounding contemporary HCV management in Canada. However, the high drug acquisition costs of the new agents may be viewed as the most pressing (24). While the Canadian public health care system provides comprehensive coverage for medically necessary hospital and physician services, this is not necessarily the case for outpatient drug costs. Support for medication costs varies according to province and for individuals who may have additional private insurance. Given that 1% of Canadians may be infected with HCV and the drug acquisition costs of many tens of thousands of dollars per course, the potential for massive expenditures and stresses on the ability of the system to pay is readily evident.

An important consideration that must be balanced against the high drug acquisition cost of these new agents is that they will likely translate to long-term cost benefits. Myers et al (3) estimated that the lifetime cost (excluding antiviral therapy) of HCV infection as of 2013 was $64,694. Among patients with HCV infection, treatment with resulting SVR dramatically reduces the incidence of liver failure, hepatocellular carcinoma, liver transplantation and mortality (25). To our knowledge, concise economic evaluations of the new combination regimens for the Canadian population at large have yet to be published, but a long-term cost neutrality or benefit is likely. It is, therefore, reasonable to expect that, despite the current high up-front cost, the public system should provide comprehensive coverage for use of the agents without delay. We are currently experiencing a major demographic shift with regard to aging of the population. Deferral of costs of HCV care to the ‘next generation’ of taxpayers is unjust, if not unethical.

Provincial programs are currently struggling with funding decisions for comprehensive provision of the new HCV treatment regimens (26). While we await decisions with great interest, we expect that many programs will attempt to rationalize and restrict these therapies. Some may require use of interferon-based treatments unless contraindicated. This may particularly be the case in situations in which the superiority of the new agents has not been clearly demonstrated, such as in non-genotype 1 HCV infections. In other cases, new agents may be restricted to patients at highest risk for complications, such as those with liver transplants, HIV or hepatitis B coinfection, or evidence of significant hepatic fibrosis. While it may be justified to prioritize patients at greatest benefit to be treated first, a reasonable argument may be made that all patients with HCV infection eventually be offered therapy with new interferon-free regimens when they have been shown to be effective. Arguing in favour of this, in part, is the concept of treatment as prevention, adopted from the HIV literature, in which an overall societal benefit (ie, through reduction in transmission) may be observed by treating a high proportion of the total infected population (27). Prevention of an incident case of HCV infected has been estimated to be associated with a cost savings of $6,300, 0.85 life-years gained and 0.38 fewer cases of HCV infection (28). Further support in favour of treating all patients with oral regimens for HCV infection may be based on the fact that HCV infection is now a readily curable disease. As a result, all Canadians should have the right to access these proven therapies irrespective of cost within our system that claims to offer publicly funded therapy for all medically necessary conditions. Numerous precedents exist within our system for patients demanding and receiving considerably more expensive treatments that have far less individual or societal benefit (29).

While drug acquisition cost is an immediate and readily evident issue surrounding HCV management, there are several other non-economic issues that we must consider. To have overall success in reducing the burden of HCV infection in Canada, we will need to identify patients with active HCV infection, engage them in active care and successfully manage them through to demonstration of SVR. Conservative estimates are that approximately 30% of HCV-infected patients remain undiagnosed in Canada (3). In addition, many others who may know their HCV status may not be aware of the new opportunities for treatment. Systems will, therefore, need to be developed to enhance screening and for registering patients with HCV infection (30). The best outcomes for HCV therapy are expected when a multidisciplinary team approach is undertaken with involvement of specialized physicians and allied health providers (31). Given the expected tidal wave of patients with HCV who will be seeking therapy, either a massive expansion of specialized multidisciplinary clinics or development of new delivery models are needed without delay. Models to deliver care to marginalized populations and to rural/remote areas will need to be developed to reach these important but historically under-treated populations.

SUMMARY

We have observed major advances in opportunities for HCV treatment in the recent years; however, there are a number of economic and practical challenges to reducing the burden of HCV infection in Canadians. As an infectious diseases community, we will need to advocate on behalf of HCV-infected patients for access to optimal therapies to cure their infection. Due to focus of care in subspecialized clinics in many cases, infectious diseases specialists at large in Canada, with a few exceptions, have traditionally had a limited role in the management of HCV-infected patients. Given the prevalence of HCV infection and current availability of highly effective therapies, we believe that HCV management can no longer be considered to be a ‘subspecialty’ within infectious diseases. The onus is on all adult infectious diseases specialists to actively contribute to reducing the burden of HCV infection in Canada.

REFERENCES


