The hepatitis C genotype 1 paradox: Cost per treatment is increasing, but cost per cure is decreasing

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Significant attention has been focused on the perceived increase in the cost of antiviral treatment for hepatitis C genotype 1 infection since the approval of the first direct-acting antiviral agents in 2011. Using Canadian list prices, the present analysis points out a paradox: while the cost per antiviral regimen is increasing, the cost per cure is decreasing, especially with interferon-free therapy. In a publicly funded health care system, the lowest cost per cure is a more valuable measure of value for public money than the cost per regimen.

Key Words: Antiviral therapy; Hepatitis C; Health economics

Hepatitis C is a major global public health problem affecting approximately 80 million individuals worldwide (1). Hepatitis C is the leading cause of cirrhosis, liver failure and hepatocellular carcinoma in Western countries (2), and is the leading indication for liver transplantation.

Unlike chronic hepatitis B virus and HIV infections, for which there are highly effective lifetime suppressive antiviral therapy, but for which curative therapy remains elusive, chronic hepatitis C virus (HCV) infection is curable with a finite course of antiviral therapy. Importantly, antiviral treatment-induced virological cure of chronic hepatitis C, also known as sustained virological response (SVR), virtually eliminates liver-related mortality and markedly reduces the risk of hepatocellular carcinoma (3).

From 2001 to 2011, HCV infection was treated with pegylated interferon-alfa plus ribavirin (PR). The duration of therapy was 24 weeks for viral genotypes 2 and 3, and 48 weeks for genotypes 1, 4 and 6. The SVR rates in response to PR varied according to viral genotype and was typically 40% to 45% in genotype 1 (4,5), the most common genotype globally and in Canada (1). However, among genotype 1-infected patients with cirrhosis, who have the greatest need for cure, SVR rates with PR are as low as 13% (6).

The past five years have witnessed rapid advances in understanding the replication of HCV, leading to the development of four classes of direct-acting antivirals (DAAs) acting on three antiviral targets: the NS3 protease, the NS5A replication complex and the NS5B polymerase. In mid-2011, the first two DAAs were licensed, boceprevir (BOC) and telaprevir (TVR), both of which inhibit the NS3 protease. These drugs were evaluated and approved only for HCV genotype 1 in combination with PR. In previously untreated patients with genotype 1 infection, randomized trials demonstrated that PR+BOC significantly improved SVR rates to 63% from 38% with PR (7), and PR+TVR significantly improved SVR rates to 75% from 44% with PR (8). SVR rates were lower in patients with cirrhosis, approximately 55% with BOC+PR (9) and 62% with TVR+PR (8). However, BOC and TVR have high pill burdens, must be taken with food, exhibit significant drug-drug interactions and cause significant anemia (hemoglobin <100 g/L) in approximately 50% of patients. TVR can cause serious

Le paradoxe de l'hépatite C de génotype 1: le coût par traitement augmente, mais le coût par cure diminue

On s'est beaucoup attardé sur l'augmentation perçue du coût des antiviraux pour l'infection de l'hépatite C de génotype 1 depuis l'approbation des premiers antiviraux à action directe en 2011. Compte tenu de la liste des prix au Canada, la présente analyse fait ressortir un paradoxe : le coût par traitement antiviral augmente, mais le coût par cure diminue, particulièrement dans le cas du traitement sans interféron. Dans un système de santé financé par les fonds publics, le moindre coût par cure est une mesure plus intéressante de la valeur pour l'argent public que le coût par traitement.

and, occasionally, life-threatening skin rashes, including DRESS (drug reaction with eosinophilia and systemic symptoms) and Stevens-Johnson syndrome (8). Side-effect management uses significant human and laboratory resources, as well as blood supplies, and occurs more frequently in clinical practice than in the controlled environment of phase 3 clinical trials (10). Almost all patients who fail treatment with PR+BOC or PR+TVR have viruses with treatment-emergent resistance mutations in the NS3 region (7,8).

The next major advance in HCV therapeutics came in December 2013, when Health Canada approved the NS5B nucleotide inhibitor sofosbuvir (SOF), which has pangenotypic activity, is given as one pill once daily without regard to food, has a very high barrier to resistance and exhibits no clinically significant drug-drug interactions. When coadministered with PR for 12 weeks in patients with genotype 1 infection, SVR rates were 89%, although the SVR rate was reduced to 80% in patients with cirrhosis (11). All treatment failures were due to relapse without treatment-emergent resistance mutations (11).

In October 2014, Health Canada approved a fixed-dose combination tablet containing SOF plus the NS5A inhibitor ledipasvir (LDV) for the treatment of genotype 1. SOF/LDV is given once daily for eight or 12 weeks in most patients, with SVR rates of approximately 96% (12,13) and no clear reduction of activity in cirrhosis (SVR rate 94%). SOF/LDV is the only approved therapy for patients who have failed PR plus an NS3 protease inhibitor, with no reduction of efficacy compared with those who failed previous therapy with PR without an NS3 protease inhibitor (14). In patients with cirrhosis who have failed previous PR-based therapy, SOF/LDV should be given for 24 weeks to minimize relapse (14).

Since the approval of the first DAAs in 2011, concern has been raised about the rising cost of HCV treatments. Even more concern was expressed when SOF was approved, especially in the United States, where the list price is USD\$1,000 per pill (15). Many of the criticisms of price do not examine the cost per cure compared with other DAA-containing treatments.

Analyses of the cost of HCV therapy do not always account for the costs of monitoring patients, which include not only laboratory tests, but also physician and nursing time. Interferon-containing therapy is

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TABLE 1
Comparison of anti-hepatitis C virus (HCV) regimen cost and cost per sustained virological response (SVR) for HCV genotype 1-infected patients with cirrhosis

Antiviral regimen	SVR, %	Cost*/regimen	Antiviral drug cost*/SVR
PR 48 wk + BOC 44 wk	55	66,200	120,364
PR 48 wk + TVR 12 wk	62	55,000	88,710
PR + SOF × 12 wk	80	60,000	75,000
SOF + LDV × 12 wk	94	67,000	71,277

*Presented as \$CAD. BOC Boceprevir; LDV Ledipasvir; PR Pegylated interferon- α plus ribavirin; SOF Sofosbuvir; TVR Telaprevir; wk Weeks

typically supported by skilled nurses who spend significant time with each patient throughout their course of treatment. Additionally, cost analyses do not routinely include the cost of managing side effects, which typically include extra clinic visits, extra laboratory tests and medication to manage side effects. When significant anemia occurs, erythropoiesis-stimulating agents and/or red blood cell transfusions are often administered. Both are very costly, and the use of blood products to manage HCV treatment-induced anemia diverts blood supplies away from other patients who require blood products, especially trauma and cancer patients.

COST PER CURE VERSUS COST PER TREATMENT

Table 1 compares four different antiviral regimens that are approved by Health Canada for patients with cirrhosis due to HCV genotype 1 infection who have not previously been treated with antiviral therapy. In the table, the cost of each of the complete regimens is listed, as well as the published SVR rates from the clinical trial programs (8,9,11,13). The drug costs used are Canadian list prices and do not reflect discounts that are negotiated in confidential public listing agreements. The cost per SVR is calculated by dividing the cost per regimen by the SVR rate of that regimen. Similar calculations can be performed as new interferon-free regimens are introduced in Canada once their list prices are known.

The cost per SVR data illustrate that the lowest cost per antiviral regimen does not necessarily select an antiviral regimen that provides the best value for whomever is paying for therapy. Even when the costs of antiviral drug therapy is covered by private insurers, physician and laboratory monitoring costs are still covered by public health care in Canada.

The BOC- and TVR-based regimens require a 48-week total course in cirrhotic patients and, therefore, require more laboratory and clinical monitoring than the two SOF-based regimens, which are given for 12 weeks. BOC- and TVR-based regimens also cause more anemia requiring intervention with ribavirin dose reduction, erythropoiesis-stimulating agents and/or red blood cell transfusions. A recently published study from a large United States centre evaluated 147 patients treated with PR+TVR and reported a cost per SVR for PR+TVR of USD\$189,338 (16). It should be noted that the list price of PR+TVR in the United States is approximately double the Canadian list price.

COST OF TREATMENT FAILURE

It is also important to consider the additional costs that follow non-SVR. Every patient who is treated for HCV who fails to achieve SVR requires medical follow-up, in which case ongoing health care costs are incurred with medical visits, laboratory monitoring, transient elastography (FibroScan [Echosens, France]), ultrasounds to screen for liver cancer (in those with advanced fibrosis) and, ideally, future antiviral therapy. In some cases, patients who fail HCV therapy may progress to liver failure and/or develop liver cancer, both of which are very costly to manage, especially if a liver transplant is required. Every HCV-related liver transplant that is prevented by curing HCV results in one less person with end-stage liver disease dying while on the transplant wait list.

A less expensive HCV therapy, with an SVR rate of 70%, means that the 30% of treated patients who fail to achieve SVR enter a medical follow-up pathway; however, a more expensive therapy, with a 95% SVR rate, results in only 5% of patients entering the medical follow-up pathway. Careful analysis needs to be undertaken to determine whether the less expensive initial course of therapy leads to increased long-term costs, resulting in a 'penny wise, pound foolish' scenario.

CONCLUSIONS

While it is true that the cost per antiviral regimen for treating HCV genotype 1 infection has increased starting with the first DAAs, SVR rates have increased to approximately 95% with interferon-free therapy, side effects of treatment are minimal without interferon, and the cost per cure has decreased from approximately \$120,000 to \$71,000 in cirrhotic patients using list prices. The cost per cure with currently available interferon-free therapy will likely be <\$50,000 after public listing agreements have been negotiated. In contrast, the lifetime drug costs of antiretroviral therapy for one HIV-infected patient is approximately \$600,000 (\$15,000 per year × 40 years). Current HCV therapies are costly, but the cost per cure in genotype 1 infection with interferon-free therapy is lower than it is with interferon-containing triple therapy, which is currently publicly funded in all Canadian provinces. Provincial health ministries managing publicly funded drug plans have a responsibility to spend public money wisely, and to consider all health care costs – not only drug costs – in making decisions regarding which medications to fund for their citizens. When it comes to HCV therapy, public payers should preferentially fund regimens with the lowest cost per SVR and should stop funding therapies with high costs per SVR. The lower 'sticker price' of the first-generation DAAs is deceptive; they are far more costly than they initially appear.

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