A Proposal for Managing the Harvoni Wave
June 22, 2015

Clinical Background

Hepatitis C is an infectious disease caused by the Hepatitis C Virus (HCV) that damages the liver over time. The disease affects an estimated 300,000 Canadians and approximately 150 million people worldwide. Hepatitis C can be fatal in its end stages, taking the form of liver cancer or cirrhosis of the liver.

To date, seven Hepatitis C virus types (Genotypes) have been discovered. Genotype 1, which is the most prevalent, affects approximately 67% of HCV-infected Canadians. The second most prevalent genotype is Genotype 3, affecting approximately 22% of Canadian patients. Genotype 2 affects approximately 6% of Canadian patients and remains the easiest genotype to treat. Genotypes 4-7 are confined mostly to Africa and Southeast Asia, with Genotype 7 being confirmed in only one case worldwide.

Treatment of Hepatitis C can be complex, and can depend on many factors such as virus genotype, severity of symptoms, and condition of the liver. As some patients will clear the infection without medication, treatment may or may not be necessary in all those with the disease. Where treatment is necessary, typically in patients with signs of liver inflammation, the goal of treatment is to cure the disease.

Treatment development timeline

Historically, treatment of chronic Hepatitis C has been challenging. The disease was first discovered and published in 1989, and interferon became the first FDA-approved drug treatment in 1992. This initial treatment had a cure rate of approximately 9% of patients with Genotype 1 and 30% of patients with Genotypes 2 and 3.

Treatment continued to develop throughout the 1990s with the approval of alpha-interferon, and soon after, alpha-interferon in combination with ribavirin, which had much higher cure rates of 30% for Genotype 1 and 60% for Genotypes 2 and 3.

In 2001, peg-interferon – a modified form of interferon that stays in the bloodstream for longer – was approved by the FDA and, when combined with ribavirin as Pegasys or PegIntron with RBV, established cure rates of 50% for Genotype 1 and 82% for Genotypes 2 and 3. The cocktail also had some side effects such as severe anemia and depression that caused concern among the Hepatitis C community.

In the late 2000s, an additional class of drugs was approved for use with the cocktail treatment: protease inhibitors such as Incivek (telaprevir) and Victrelis.
(boceprevir). This combination therapy achieved cure rates of up to 79% for Genotype 1, and up to 86% for prior non-responders, but came at the expense of severe side effects that prevented many patients from completing treatment.

In 2012, a new class of drugs called Direct Acting Antivirals (DAAs) was showing great promise touting cure rates of 90-100% for Genotype 1 – some without the use of interferon. These DAAs have also cut treatment time in half from 24-48 weeks down to 12-24 weeks, and displayed much less severe side effects. The DAAs that have been approved for use in conjunction with peg-interferon and ribavirin are Galexos (simeprevir) and Sovaldi (sofosbuvir) and have achieved cure rates of 80-90% for Genotype 1 and 96% for Genotype 4.

In 2014, Harvoni (sofosbuvir, ledipasvir) was approved to treat Genotype 1 without peg-interferon or ribavirin, and Viekira Pak (known in Canada as Holkira Pak) was approved to treat Genotype 1 with and without ribavirin, and both have achieved cure rates of 90-100%\textsuperscript{2}. Table 1 lists the most commonly prescribed treatments in Canada.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Name(s)</th>
<th>Genotype(s) Treated</th>
<th>Approximate Treatment Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegasys/Copegus</td>
<td>Peg-interferon alpha 2a + ribavirin</td>
<td>All Genotypes</td>
<td>$20,000</td>
</tr>
<tr>
<td>PegIntron/Rebetrol</td>
<td>Peg-interferon alpha 2b + ribavirin</td>
<td>All Genotypes</td>
<td>$35,000</td>
</tr>
<tr>
<td>Incivek</td>
<td>Telaprevir with peg-interferon + ribavirin</td>
<td>Genotype 1</td>
<td>Up to $77,000</td>
</tr>
<tr>
<td>VICTRELIS</td>
<td>Boceprevir with peg-interferon + ribavirin</td>
<td>Genotype 1</td>
<td>Up to $70,000</td>
</tr>
<tr>
<td>Galexos</td>
<td>Simeprevir with peg-interferon + ribavirin</td>
<td>Genotype 1</td>
<td>Up to $85,000</td>
</tr>
<tr>
<td>Sovaldi</td>
<td>Sofosbuvir with peg-interferon + ribavirin</td>
<td>Genotypes 1-4</td>
<td>Up to $135,000</td>
</tr>
<tr>
<td>Harvoni</td>
<td>Sofosbuvir with ledipasvir</td>
<td>Genotype 1</td>
<td>Up to $154,000</td>
</tr>
<tr>
<td>Holkira Pak</td>
<td>Ombitasvir, dasabuvir, paritaprevir, ritonavir</td>
<td>Genotype 1</td>
<td>Up to $128,000</td>
</tr>
</tbody>
</table>

**Table 1. Most common treatments in Canada for chronic HCV infection.**

**Side Effects and Adverse Drug Reactions**

Each of the above treatments has accompanying side effects and, in some cases, adverse drug reactions (ADRs). The ADRs are typically more severe in the traditional cocktails as opposed to the newer DAA medications.
The most commonly reported ADRs in patients receiving Pegasys RBV treatment were psychiatric reactions like depression (20%) and flu-like symptoms like fatigue (65%). These ADRs led to approximately 11% of patients discontinuing therapy. Some ADRs such as anemia led to dose modifications (22%)\textsuperscript{5}.

Among the DAAs taken in combination with peg-interferon and ribavirin (Sovaldi and Galexos), the most commonly reported ADRs were fatigue (<20%), anemia (<20%), and rash/photosensitivity (28%). Discontinuation due to ADRs occurred in 2% of patients\textsuperscript{6,7}.

In patients taking Harvoni, ADR incidence and severity decreased further, with the most commonly reported ADRs being fatigue and headache (<10%), and the proportion of patients discontinuing Harvoni due to ADRs being 1%\textsuperscript{8}.

**The Economics of Hepatitis C Treatments**

The newer DAAs, such as Harvoni, have begun to dominate the Hepatitis C treatment market. As was previously shown, these medications can cure Hepatitis C at higher rates, with lower incidence of ADRs, and in half the course of treatment compared to the traditional cocktails. However, this new class of treatment is much more expensive than the traditional cocktails. The traditional cocktails – such as Pegasys RBV – cost approximately $20,000, on average, whereas Harvoni costs approximately $77,000 for the average course of treatment.

If 300,000 Canadians are currently living with chronic Hepatitis C and 67% of them have Genotype 1 – the only Genotype cured by Harvoni – and those patients rush to get Harvoni over the next five years, drug payors will be faced with an enormous bill to pay. At $77,000 for a course of treatment and 200,000 patients, the total cost of Harvoni treatment will be approximately $15 billion. It may seem unlikely that all those with the disease will take Harvoni in the next five years, but recent uptake trends suggest the opposite.

Starting in late 2014, most doctors have been gravitating to prescribing Harvoni as opposed to the cocktails or even the other DAAs, and the trend is accelerating. Furthermore, patients that have avoided the cocktails for fear of ADRs or lack of efficacy are being drawn to Harvoni. Harvoni is already topping the list of costliest drugs at insurance companies across the country, taking the third spot on Great West Life’s total drug spend list only five months after the drug hit the Canadian market (2.5% of total drug spend).

**Pharmacogenetics of Hepatitis C Treatments: Efficacy and Adverse Reactions**

Historically, the traditional cocktails were perceived as low-efficacy drugs where generally the treatment was almost worse than the disease. Half of patients on the cocktails remained uncured after treatment, and many suffered serious adverse
drug reactions. On the other hand, a subset of the population were cured with little to no adverse drug reactions.

Why was it that some patients were cured without side effects, while others were not? The answer lies mainly in genetics.

Pharmacogenetics – the study of how a patient’s genes will interact with a drug – is a scientific field that has been developed over half a century and now explains much of the variability in drug response across the medical field. Pharmacogenetics, also known as Personalized Medicine or Precision Medicine, has the ability to predict drug efficacy, dosage, and adverse drug reactions in a particular patient, using their genetics.

There is now very strong evidence of pharmacogenetics of the traditional Hepatitis C cocktails, both in predicting cure rate and risk of adverse drug reactions. In fact, PegIntron has gone so far as to include pharmacogenetic information in its drug label to ensure proper administration of the drug (Figure 1). Hundreds of published scientific studies have been validated at a very high clinical level, and have been implemented by the FDA, as well as many clinical institutions across North America.

During the 2000s, prescribing physicians had very little knowledge of pharmacogenetics. Without their patient’s genetics, doctors simply could not predict efficacy or risk of adverse reactions to a particular treatment. Doctors were working in the dark, but with pharmacogenetics, it is now evident that the low cure rates of the traditional cocktails were due in part to patients’ genetics.

Perhaps a different perspective is needed. Understandably, the traditional cocktails earned a nasty reputation, and doctors avoided using them unless completely necessary. However, there was always a subset of patients that did respond well – or would have responded had they not been avoiding the drug – to the cocktails with little to no adverse drug reactions. Considering the large price tag of Harvoni, perhaps the cocktails should be given a second chance, with the help of pharmacogenetics.

Personalized Prescribing Inc. has now developed a pharmacogenetic test and accompanying interpretive report that can determine patient genetic compatibility with the traditional cocktails, regarding both drug efficacy and toxicity. Physicians no longer need to be working in the dark when prescribing these medications, hoping that their patients will respond well to the treatment. The report aids physicians to better predict and prescribe the correct cocktail early in the treatment process. The report also allows physicians and their patients to be prepared for predicted adverse reactions with the appropriate remedy.
Figure 1. Cure rates across different genetic populations of HCV patients based on the IL28B marker. IL28B is a human gene that, as shown above, affects the likelihood of cure in patients taking PegIntron RBV or Pegasys RBV. The IL28B Genotype is not to be confused with the HCV viral Genotype (1-7).

Pharmacogenetics Testing as Special Authorization

Over the coming months, payors will take notice of the enormous cost of Harvoni, and will be looking for ways to manage it. The most obvious management technique is through Special Authorization with pharmacogenetics.

Anticipated Outcomes across Responder Groups

Now, with pharmacogenetics, we can identify the “Super Responders”: the proportion of the population who are expected to be cured by the traditional cocktails and have a lower risk of developing adverse drug reactions (approximately 35% of patients)\(^9\).\(^5\). Super Responders would be directed with a great degree of confidence to the traditional cocktails such as Pegasys RBV or PegIntron RBV.

Currently, the World Health Organization (WHO) has updated recommendations on the treatment of HCV infection. Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin. (Strong recommendation, moderate quality of evidence)\(^1\)
Patients that are identified as “Poor Responders” – those who would not likely be cured by the traditional cocktail, or would have severe adverse drug reactions (approximately 33% of patients) – would be approved for Harvoni.

The patients identified as “Moderate Responders” would be the proportion of the population who are likely to be cured by the cocktail, but are predicted to have moderate ADRs (approximately 32% of patients). This group would be dealt with in accordance to the philosophy and standards of the payor. Patients in this group could be approved for the cocktail with frequent monitoring by the physician, or could be approved for Harvoni (Figure 2).

**Figure 2.** Proportion of responder groups and their recommended courses of therapy, as predicted by pharmacogenetic testing.

With this pharmacogenetic test, doctors can prescribe the traditional cocktails with confidence. Patients approved to take the traditional cocktails may experience greater adherence, knowing that their treatment has been tailored to their genetics. Finally, payors can manage the significant uptake of Harvoni without breaking the bank, whilst ensuring a safe and effective treatment outcome for all patients (Figure 3).
Economic analysis of cost savings through pharmacogenetic testing as special authorization for Hepatitis C treatment. A minimum of approximately 20% of cost spent on Harvoni can be saved with pharmacogenetic testing as special authorization.

**Highlights**

- Hepatitis C affects approximately 300,000 Canadians
- Treatments have been available since 1992, with varying cure rates and adverse drug reactions
- Next-generation drugs, such as Harvoni, have been approved recently that promise high cure rates and low adverse drug reactions, but come with a steep price tag (avg $77,000; max $154,000)
- Pharmacogenetics can now identify patients likely to be cured by traditional cocktail drugs with low adverse drug reactions, at a much lower price (~$20,000 for Pegasys)
- Pharmacogenetic testing can be used by drug payors through special authorization to direct patients to the appropriate treatment, without compromising patient safety
- Cost savings with pharmacogenetic testing as special authorization is predicted to be approximately 20% of total medication cost
References