Review of Treatments in Hepatitis C Virus Genotype 1 Individuals

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Hepatitis C is a treatable liver disease. Although the prevalence of hepatitis C virus (HCV) in Canada is low, approximately a quarter of those infected are unaware of their status. This makes diagnosis and treatment difficult. Of the 6 genotypes of hepatitis C, genotype 1 is the hardest to treat and requires the longest duration of therapy as well. Since 2002, a combination of once weekly injection of pegylated interferon and twice daily oral ribavirin has been the standard of therapy in Canada. In 2012, two new protease inhibitors boceprevir and telaprevir were approved for use in combination with standard therapy and have been shown to improve cure rates as compared to standard therapy alone. Similar protease inhibitors as well as polymerase inhibitors are currently in the pipeline to help improve cure rates specifically for HCV genotype 1 patients.

Introduction

Approximately 1% of Canadian population has chronic hepatitis C and of those, 60% are injection drug users (1). Hepatitis C virus (HCV) genotypes 1-3 are more prevalent in Canada (1). Standard therapy has a good response rate in HCV genotypes 2 & 3 (70-80%) with genotype 1 being the least responsive (<50%) (1,2,3). Other genotypes are more prevalent outside Canada (4). Treatment with pegylated interferon (PegIFN) and ribavirin (RBV) has been standard of care therapy since 2002 in Canada and 1998 in US. This therapy includes a weekly subcutaneous injection of PegIFN and twice daily oral tablets of RBV and is associated with some significant side effects such as anemia which may require erythropoietin or transfusion treatments in some patients (1). Therefore, new oral only treatments are being tested which will allow shorter duration of therapy, improved sustained virologic response (SVR) rates, improved adherence and a lower pill burden. SVR is defined as undetectable HCV RNA levels at least 24 weeks after the end of treatment (1). Response to therapy, as measured by SVR, depends on factors such as HCV genotype, viral load, ethnicity, age, gender, and co-morbidities (HIV, depression, etc.) (5). Complications of untreated infection include decompensated liver disease, hepatocellular carcinoma and liver transplantation (1). Newer therapies are being developed to hopefully provide a lower pill burden and improved SVR. This review will discuss therapies for treating HCV genotype 1 infection.

Methods and results

Medline was searched using keywords “hepatitis C”, “protease inhibitors”, “randomized controlled trials” giving 78 results; keywords “hepatitis C”, “polymerase inhibitors”, and “randomized controlled trials” gave 19 results; and all of the above keywords along with “future therapies” gave 4 results. Embase was searched for the keywords “Hepatitis C”, “protease inhibitors”, “polymerase inhibitors”, and 93 results were obtained while keywords “hepatitis C” and “future therapy” obtained in 30 results. No date or language restrictions were applied to any of the searches. Of all these results, 23 relevant randomized controlled trials (RCTs) that were pivotal trials and reviews that discussed these pivotal trials were selected for this review.

Discussion

I. Standard Therapy

Interferons (IFNs) are glycoproteins produced by immune system in response to bacterial or viral antigens (2). IFN-α has two recombinants: rIFN- α2a and rIFN- α2b (2). They bind to cell receptors to induce the production of proteins and increase the host’s immune system activity against the virus (6). These effector proteins inhibit different stages of the viral replication cycle, specifically the translation of viral mRNA into viral proteins (2). HCV has acquired resistance by inhibiting the protein kinases in the host required for IFN activity (6). Therefore, monotherapy with IFN has low SVR (10-15%) and patients can rebound after cessation of therapy (7). Overall, SVR increases to 30-40% when given with RBV for 6-12 months but response varies by genotype (7). Genotype 1 patients require longer treatment of 12 months while those with genotypes 2 and 3 only require a 6-month course (7). RBV is a nucleoside analogue that has multiple modes of
action in HCV treatment (8). It can directly inhibit RNA polymerase or get incorporated and lead to mutagenesis of the HCV genome (8). It can also have indirect effects by modifying the immune response of host towards the virus by decreasing the number of activated T cells that express γ−interferon (a cytokine), inhibiting the host cell enzyme inosine monophosphate dehydrogenase (IMPDH) and increasing the production of interleukin (IL)-18 (a proinflammatory cytokine) (8).

Pegylating the IFN increases SVR. Of the two types of pegylated IFNs, PegIFN α2a (Pegasys®; 180 mcg once/week subcutaneously) was shown to attain slightly higher SVR when compared to PegIFN α2b (Unitron PEG®; 1.5 μg/kg once/week subcutaneously) in some studies; however, both have been used in standard therapy along with weight based RBV (1000 or 1200 mg/day) (6,9,10). Treatment with PegIFN-α2a (180 μg/wk) and standard RBV (weight based, 1000 or 1200 mg/day) for 48 weeks has been shown to produce an overall SVR rate of 63% in patients with HCV genotype 1 as compared to only a 24 week therapy with odds ratio of 2.19 [CI, 1.52 to 3.16; P < 0.001] (11). Therefore, a combination therapy of PegIFN and RBV for 48 weeks has been the standard of care for HCV genotype 1 for over a decade. On the other hand genotypes 2, 3 and 4 patients did not have any statistically significant differences in SVR rates when treated for 24 vs 48 weeks or with a low dose vs weight based RBV regimen (11). The side effects associated with IFN therapy include flu-like symptoms, anorexia, nausea, depression, suicidal ideation, retinopathy, renal failure, fatal hepatotoxicity, etc (12). The side effects associated with RBV therapy include anemia, neutropenia, fatigue, headache, insomnia, myalgia, fever, etc (8,13). Use of PegIFN is not indicated in patients with comorbidities such as major uncontrolled depression, decompensated cirrhosis, etc (5). Patients with co-existing mild to moderate depression require psychiatric evaluation, antidepressant treatment and monitoring before and during PegIFN therapy. Reassessment should be done for patients who develop severe depression and require hospitalization (14). Therefore, newer therapies were required to address some of these shortcomings of the standard therapy.

II. Current Therapies

HCV has a single stranded RNA genome which encodes for a polyprotein that is cleaved into four functional proteins essential for viral replication (5). HCV NS3/4A serine protease inhibitors stop replication of viral RNA by inhibiting the cleavage of this polyprotein and have shown improved outcomes and SVR in both treatment-naïve and previously treated patients (5). Two recently approved triple therapies in Canada include boceprevir (Victrelis®) or telaprevir (Incivek®) in combination with standard therapy to improve SVR in patients with HCV genotype 1. They are novel peptidomimetic NS3 protease inhibitors that bind to and form reversible covalent complexes with the RNA NS3/4A protease (15,16).

SPRINT 1 showed that in treatment-naïve patients, after a four week lead-in therapy with PegINF α2b and RBV, addition of boceprevir (800 mg three times a day) starting at week 5 for 24 weeks resulted in almost double SVR rates as compared to standard therapy alone (17). SPRINT 2 also enrolled treatment-naïve patients and tested 48 week standard therapy (along with placebo) vs response guided therapy (which is based on whether HCV RNA levels are undetectable from weeks 8 through 24) vs patients that received boceprevir along with standard therapy for 44 weeks after the 4 week lead-in period (18). If HCV RNA levels were undetectable, therapy was stopped at 24 weeks but if they were detectable at any time during weeks 8-24, patients received standard therapy along with placebo until week 48 (18). They concluded that SVR rates were similar in both short (24 weeks) and long (44 weeks) duration of boceprevir therapy (18). RESPOND 2 assessed the efficacy of the combination of boceprevir with standard therapy for retreatment of difficult to treat patients with chronic HCV genotype 1 infection including those with advanced liver disease (3). Triple therapy with boceprevir 800 mg three times a day attained higher SVR rates (3).

The three PROVE studies showed that in patients with genotype 1 infection, the addition of telaprevir (750 mg every 8 hours) to standard therapy for as short as 12 weeks produces viral suppression and increases the SVR rates even in patients that have failed previous therapies (19). They also showed that the addition of RBV was necessary to decrease the rates of resistance and viral breakthrough (19). The ADVANCE and ILLUMINATE trials are randomized, double-blinded studies that enrolled treatment-naïve patients who received PegINF α2a and RBV, combined with 8-12 week therapy of telaprevir (750 mg every 8 hours with a high calorie meal) (20,21). They found that the combination therapy provided significant improvement in SVR rates and decreased in HCV RNA levels (20,21). The REALIZE trial assessed the safety and efficacy of telaprevir combination therapy in patients that previously failed on standard therapy or those with a high viral load, severe liver fibrosis, and cirrhosis (22). They found an improvement in SVR rates regardless of a lead-in phase with standard therapy (22). Side effects of protease inhibitors include rash, anemia, fatigue, nausea, pruritis, gastrointestinal and flu-like symptoms. (3,17,20,21,22). Comparison of triple therapies with boceprevir or telaprevir is shown in Table 1.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
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<tbody>
<tr>
<td>Regimen</td>
<td>4 week lead-in with peginterferon alfa-2b (1.5 μg/kg) plus ribavirin (800–1400 mg daily)</td>
<td>No lead-in required</td>
</tr>
<tr>
<td>Combination with</td>
<td>peginterferon alfa-2b (1.5 μg/kg) plus ribavirin (800–1400 mg daily)</td>
<td>peginterferon alfa-2b (180 μg/week) plus ribavirin (1000 mg/day for patients weighing &lt; 75 kg or 1200 mg/day for patients weighing &gt; 75 kg)</td>
</tr>
<tr>
<td>Duration of drug</td>
<td>24 weeks of boceprevir</td>
<td>12 weeks of telaprevir</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>24 weeks if HCV RNA levels undetectable from week 8 through 24.</td>
<td>24 weeks if HCV RNA levels undetectable from week 4 through 12.</td>
</tr>
<tr>
<td></td>
<td>If HCV detectable anytime during weeks 8 through 24, continue PegINF/RBV therapy only until week 48</td>
<td>If HCV detectable anytime during weeks 4 through 12, continue PegINF/RBV therapy only until week 48</td>
</tr>
<tr>
<td>Dose</td>
<td>4 tablets of 200 mg three times a day</td>
<td>2 tablets of 375 mg every 8 hours</td>
</tr>
<tr>
<td>Side effects</td>
<td>Anemia, headache, fatigue, nausea, flu-like symptoms, dysgeusia, rash, itchy and dry skin</td>
<td>Anemia, nausea, diarrhea, pruritis, dysgeusia, rash, itchy and dry skin, anorectal symptoms</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Effect of food</td>
<td>Food enhances absorption by 60% and the type (low/high fat) or timing of the meal (before/during/after) does not matter</td>
<td>Serum concentration decreases by 39% when given with a low-fat meal (249 kcal, 3.6 g fat), but increases by 20% with a high-fat meal (928 kcal, 56 g fat)</td>
</tr>
<tr>
<td>Plasma binding</td>
<td>75%</td>
<td>59-76%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Aldo-ketoreductase (AKR)-mediated pathway into inactive metabolites</td>
<td>P-gp substrate; undergoes extensive metabolism in the liver (hydrolysis, oxidation, and reduction) via CYP3A4</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>Mean elimination half life is 3 hours only</td>
<td>After a single dose = 4.0 to 4.7 hours; steady state = 9 to 11 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>79% excreted through feces and 9% through urine</td>
<td>Major route of elimination is feces (90%) and minor routes are exhaled air (9%) and urine (1%)</td>
</tr>
<tr>
<td>Dose adjustment</td>
<td>Not required for renal or hepatic impairment</td>
<td>Not required in renal or mild hepatic impairment; use not recommended in moderate to severe hepatic impairment</td>
</tr>
</tbody>
</table>

Table 1. Comparison chart of triple therapies with boceprevir and telaprevir.

### III. Future therapies

Similar to the recently approved boceprevir and telaprevir, other oral protease inhibitors (danoprevir, vaniprevir, BMS-650032) are currently in the development phase and are also given in combination with standard therapy (5). INFROM-1 investigated the use of danoprevir in combination with mericitabine, a nucleoside polymerase inhibitor, with and without interferon and RBV (5). They showed a favourable result in the IFN and RBV free cohort but the sample size was very small (5). Triple therapy with other promising nucleoside polymerase inhibitors is also under investigation (5). Host cell factors such as cyclophilin A (cypA), micro-(mi)RNA-122, and phosphatidylinositol 4-kinase...
type III-a (PI4KIII-a) are also being investigated as alternative targets as they are required for HCV replication (23). DEBIO-025 (alisporivir), an analogue of cyclosporine A, inhibits cyclophylin A but does not cause immune suppression and is being investigated as a potential drug to combine with PegIFN/RBV therapy (24). Patients coinfected with Hepatitis C and HIV-1 who received DEBIO-25 1200 mg twice a day for 14 days showed a significant reduction in viral load (24). Other cyclosporine A analogues (NIM811 and SCY-635) are also under preclinical and clinical development (25). Pharmacogenomic biomarkers, such as IL-28B polymorphism, are being investigated as pre-treatment predictors of response to PegIFN/RBV therapy (26). SYREN trial showed that in patients that previously failed on standard therapy, response to high dose PegIFN/RBV (PegIFN either 360 μg once/ week or 180 μg twice/week; RBV either 1.0-1.2 g/d or 1.2-1.6 g/d according to body weight for 72 weeks) can be predicted based on the patients’ genotype and the single nucleotide polymorphism on IL-28B (26). The current combination therapy for HCV infection targets different steps in the viral replication cycle to achieve adequate suppression and delay the emergence of resistance (27). However, the overall benefits of therapy with newer direct antivirals are limited due to the inherent safety and tolerability of PegIFN/RBV therapy (27). Therefore, the development of IFN and RBV-free therapy can potentially improve tolerability and duration of HCV treatment. Investigation into combination once daily therapy of an oral protease inhibitor (BI 2011335) with an oral polymerase inhibitor (BI 207127) is currently underway (28). SOUND-C2 is evaluating their use without either IFN or RBV (28). An interim analysis of the data showed that 68% of genotype 1 HCV patients achieved viral cure after 28 weeks of treatment (28).

Conclusion

Hepatitis C treatment has come a long way and although, the current triple therapy for HCV genotype 1 provides higher SVR rates and shorter duration of therapy, future therapies offer oral only combinations with a smaller pill burden. This can have a huge impact on compliance and cure rates specifically in genotype 1 patients. However, the applicability of these data to other genotypes remains to be seen as most of the newer studies recruit participants that are HCV genotype 1 in a higher proportion. Therefore, more studies in genotypes 2–6 are required to see the potential benefits of newer therapies in these patients.

Acknowledgments

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References


