HCV Treatment of Special Populations: HIV Coinfected, Liver Transplant, and Renal Failure

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Introduction

The burden of hepatitis C viral (HCV) disease is considerable, with over 170 million people affected worldwide. In the United States, the prevalence is between 2 to 4 million. With new recommendations regarding birth cohort screening (all persons born between 1945–1965),[1] more and more people will be diagnosed and referred for treatment. The treatment of HCV has undergone major changes with the development of the direct acting antiviral agents (DAAs). Within the general population are "special populations" that represent unique challenges to HCV treatment. This article will focus on HCV treatment of three such populations, namely patients with HCV/human immunodeficiency virus (HIV) coinfection, those with chronic kidney disease, and liver transplantation recipients.

HCV/HIV Coinfected Patients

Globally, approximately 4 million patients have HCV/HIV coinfection.[2] With the availability of highly effective combination antiretroviral treatment regimens (cART), HIV-infected patients are now living longer; and progressive liver disease from HCV is becoming more prevalent, with its resultant morbidity and mortality.[3] Patients with HCV/HIV coinfection are considered a special population for several reasons: 1) Drug–drug interactions between HIV cART and HCV DAAs could lead to increased risk of drug toxicities, decreased antiviral efficacy, or both. 2) HIV infection leads to an aberrant immune response, which could affect treatment responses. 3) HIV and related opportunistic infections may alter drug absorption and exaggerate side-effect profiles, resulting in decreased efficacy and adherence.

Until December 2013, the only US Food and Drug Administration (FDA)-approved therapy for HCV in the setting of HIV was pegylated interferon (IFN) alfa-2a + ribavirin 800 mg/day. This dual therapy demonstrated lower treatment response rates than seen in monoinfected hepatitis C patients. The response rate was 26% to 40% for genotype 1 and 4 and 56% for genotype 2 and 3. In Phase 2 trials,[4-6] the addition of first-generation protease inhibitors such as telaprevir or boceprevir improved the sustained virologic response (SVR) to 74%[7] and to 63%,[8] respectively. These rates are comparable to those observed in monoinfected populations, and side-effect profiles were also similar. Phase 3 trials of these agents have been completed, and preliminary results of telaprevir efficacy suggest slightly lower SVR rates in treatment naïve HCV/HIV coinfected patients.[9] No outcome results from Phase 3 boceprevir trials are yet available. Drug–drug interactions require altered telaprevir dosing with some cART regimens (e.g., efavirenz-containing regimens). However, the use of these agents has been superseded by rapid developments in the DAA field.

At the end of 2013, Sofosbuvir—a new NS5b polymerase inhibitor—was approved for the treatment of hepatitis C, including in those with HIV. It has activity against all genotypes of HCV, though its antiviral activity is lower against genotype 3 than that against other genotypes. It does not affect the cytochrome P-450 pathway for other medications such as protease inhibitors used in highly active antiretroviral therapy regimens. A study by Rodrigues-Torres et al. showed the same HCV eradication rates in coinfected patients as in monoinfected HCV genotype 1 patients (91% SVR after 12 weeks of therapy).[10] No interaction was noted with emtricitabine/tenofovir, raltegravir, efavirenz, darunavir, or rilpivirine. PHOTON-1 demonstrated excellent response to sofosbuvir and ribavirin (all oral) regimen in coinfected treatment-naïve patients infected with genotype 1, 2, and 3.[11] Coinfected patients were treated with sofosbuvir/RBV for 12 to 24 weeks and yielded an SVR of 76% in genotype 1, 88% in genotype 2, and 92% in genotype 3.

Abbreviations: cART, combination antiretroviral treatment regimen; CKD, chronic kidney disease; DAA, direct acting antiviral agent; FDA, US Food and Drug Administration; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; SVR, sustained virologic response

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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.397

Simeprevir is a NS3/4a protease inhibitor, which was also approved for the treatment of HCV (genotype 1 only). The preliminary results from C212 study[7] showed a 74% SVR overall, and 89% of the HIV/HCV coinfected patients were able to reduce the duration to 24 weeks based on response-guided therapy, although drug–drug interactions were noted with efavirenz and darunavir/ritonavir.

Studies of sofosbuvir with daclatasvir (NS5a inhibitor) and ledipasvir (NS5a inhibitor), as well as a multidrug regimen (ABT-450/ritonavir/ABT-267/ABT-333 ± ribavirin), are in progress.

Recommendations for Treatment of HCV/HIV.*

Genotype 1	
Treatment-naïve or relapser patients	
First-line treatment	Pegylated IFN/ribavirin /sofosbuvir for 12 weeks
Alternate treatment	Sofosbuvir with ribavirin for 24 weeks (no IFN) or Sofusbuvir and simeprevir with or without weight-based ribavirin for 12 weeks
Treatment-experienced nonresponders	
First-line treatment	Sofosbuvir and simeprevir ± ribavirin for 12 weeks
Alternate treatment	Sofosbuvir + pegylated IFN and ribavirin for 12 weeks or Sofosbuvir and ribavirin for 24 weeks
Genotype 2	
Treatment-naïve or experienced patients	
First-line treatment	Sofosbuvir and ribavirin for 12 weeks (may extend to 16 weeks for prior nonresponders)
Genotype 3	
First-line treatment	Sofosbuvir and ribavirin for 24 weeks
Alternate treatment	Sofosbuvir, pegylated IFN, and ribavirin for 12 weeks
Genotype 4	
First-line treatment	Pegylated IFN, ribavirin, and sofosbuvir for 12 weeks or Sofosbuvir and ribavirin for 24 weeks
Genotype 5 or 6	
Recommended treatment	Sofosbuvir, pegylated IFN, and ribavirin for 12 weeks

*Derived from Sofosbuvir package insert. [cited 2013 December 30]; Available from:http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf. and American Association for the Study of Liver Diseases/Infectious Diseases Society of America HCV Treatment Guidelines.

Liver Transplant Patients

Liver transplant patients with HCV can be divided into two main categories:

1. Pretransplant patients with decompensated liver disease, or with hepatocellular carcinoma
2. Posttransplant patients with evidence of recurrent hepatitis C

In the first group, treatment of HCV with INF-based regimens historically has been fraught with complications, including the worsening of decompensation, cytopenias, infections, and the associated mortality. For that reason, most patients with cirrhosis were traditionally referred to liver transplant centers for listing for transplantation prior to attempting treatment. The success rate of treatment was also less frequent than that in noncirrhotic patients. With dual therapy with IFN and ribavirin, the rate of SVR was approximately 30% for genotype 1 and approximately 80% for genotype 2 and 3, respectively.[12] Introduction of telaprevir and boceprevir improved the SVR, but the patients still needed a 48-week treatment duration. In one study, SVR in decompensated patients with triple therapy was 35%, with a relapse rate of 25% (compared to 54% and 17% in the compensated group, respectively).[13] The COSMOS study with Sofosbuvir and Simeprevir showed a 93% rate of SVR after 12 weeks of treatment without ribavirin and a 96% rate of SVR with ribavirin in patients with compensated cirrhosis. However, data are not available on patients with decompensated liver disease. Pretransplant decompensated cirrhotic patients have been treated successfully with Sofosbuvir and Ribarivin for 48 weeks. However, the SVR data on this study are not available at this time.

Administration of sofosbuvir and ribavirin after liver transplantation (LT) in the setting of established HCV recurrence has been well tolerated and achieved an early SVR12 and SVR 24 rate of 70%. However, the data was not adequate for FDA approval in the posttransplant setting.[14] Simeprevir has not been studied in patients with decompensated liver disease; therefore, it is not recommended for use in this patient population. Because simeprevir is metabolized through the CYP3A, there is a potential risk that drug–drug interactions in the setting of typical posttransplant immunosuppression regimens may occur, although no dose adjustment is required.

Recommendation for Pretransplant Patients with Decompensated Liver Disease, or with Hepatocellular Carcinoma

First-line treatment	Sofosbuvir and ribavirin for up to 48 weeks (all genotypes), or until transplant

Treatment of Recurrent HCV After Liver Transplantation

For the patients who have already received liver transplantation, the recommendations for treatment are as follows:

Genotype 1	
Treatment-naïve patients (with or without cirrhosis)	
First-line treatment	Sofosbuvir and simeprevir with or without ribavirin for 12--24 weeks
Alternative treatment	Sofosbuvir and ribavirin ± pegylated IFN for 24 weeks
Genotype 2 and 3	
Treatment naïve patients (with or without cirrhosis)	
First-line treatment	Sofosbuvir and ribavirin for 24 weeks
Treatment-naïve patients (with decompensated cirrhosis)	
	Same as for pretransplant decompensated patients

Patients With Renal Disease

This set of patients constitutes the most difficult group with regard to treating their hepatitis C infection. In the

United States, a high proportion of these patients are African American because diabetes and hypertension, the leading causes of chronic kidney disease (CKD), are more prevalent in this population. Historically, renal patients have a lower response rate to the pegylated IFN/ribavirin therapy compared to patients with normal renal function. There are limited data regarding the use of pegylated IFN/ribavirin in patients with CKD. However, a recent study in Taiwan demonstrated a 68% SVR among genotype 1 patients treated with pegylated IFN 135 ug/week + ribavirin 200 mg/day.[15]

Patients with renal disease can be divided into two broad categories:

1. Patients with CKD stage I to III (creatinine clearance > 30 ml/min)
2. Patients with more advanced CKD, end-stage renal disease with or without renal replacement therapy requirements (creatinine clearance < 30 ml/min)

There has been a case series of four patients treated with telaprevir-based triple drug therapy, with three out of four patients responding to treatment. However, their SVR data are not available.[16] The authors have had successful experience in treating patients with advanced CKD with telaprevir- and boceprevir-based triple drug therapy, although the numbers are small. None of the protease inhibitors have been studied extensively enough in patients with advanced renal disease (CKD IV and V, CrCl < 30); thus, they are not approved for use in that setting. For patients who are started on sofosbuvir + ribavirin and whose CrCl falls below 30, we are altering the dosing to an every-other-day frequency and reducing ribavirin to 600 mg/day or less. However, results from studies of sofosbuvir, which are expected to be released in late 2014 in those with poor renal function, may alter this practice.

Recommendations for Treatment.

Patients with CKD stage I to III (creatine clearance > 30 ml/min)	
First-line treatment	Pegylated IFN, renally dosed ribavirin, and sofosbuvir
Alternate treatment	Pegylated IFN, renally dosed ribavirin, and simeprevir (for genotype 1b; and for 1a if no Q80K mutation)
Patients with CKD IV or V	
First-line treatment	Pegylated IFN and ribavirin 200 mg daily

Summary

The treatment of hepatitis C has evolved rapidly in recent years. The development of new DAAs has increased efficacy, decreased side effects, and shortened treatment duration. These therapies show particular promise in special populations previously not considered candidates for prior generations of HCV treatment. In parts of the world where access to the new DAA medications is limited due to cost issues, the first-generation protease inhibitors can still be used to good effect in combination with pegylated IFN and weight-based ribavirin, as per previous guidelines. The hope is that "special populations" will become a historic relic and that all patients with HCV will undergo effective and safe therapy in the near future. This vision has the promise of improved survival, decreased need for transplantation/retransplantation, and better quality of life.

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