New Direct-Acting Antiviral Therapies for Treatment of Chronic Hepatitis C Virus Infection

Ara A. Kardashian, MD, and Paul J. Pockros, MD, FACP, FAASLD, FAGA

Dr Kardashian is a fellow in the Division of Gastroenterology and Hepatology at Scripps Clinic in La Jolla, California. Dr Pockros is the director of the Liver Disease Center at Scripps Clinic and is the director of clinical research at Scripps Translational Science Institute in La Jolla, California.

Address correspondence to:
Dr Paul J. Pockros
Division of Gastroenterology and Hepatology
Scripps Clinic
10666 North Torrey Pines Road
La Jolla, CA 92037
Tel: 858-554-8879
Fax: 858-554-8065
E-mail: Pockros.paul@scrippshealth.org

Keywords
Hepatitis C virus, direct-acting antiviral agents, nucleoside inhibitors, protease inhibitors, special populations

Abstract: The treatment of hepatitis C virus infection has been advancing at breakneck speeds over the past few years. This article provides an update on the newest drugs available and those currently in development, including newer-generation protease inhibitors, RNA-dependent RNA polymerase, and nonstructural component inhibitors. Also discussed in this article are the regimens developed and the genotypes they target. Treatment of cirrhotic patients and patients who have failed prior therapy is also addressed, as are special populations, such as patients with harder-to-treat genotypes, patients with HIV coinfection, patients who have undergone liver transplantation, and patients with chronic kidney disease. Future developments and economic considerations are also mentioned.

New direct-acting antiviral (DAA) therapies for hepatitis C virus (HCV) infection have come to the market over the past few years. This article discusses the various agents and regimens currently available for the treatment of HCV infection. Historically, treatment consisted of pegylated interferon and ribavirin. Recently, protease inhibitors (PIs) have achieved improved results with fewer side effects. However, the current crop of DAA options provides the most benefits with the fewest deleterious side effects. This article breaks down the treatment options currently available by genotype (with a focus on the newest studies), addresses treatment failures, and broaches the topic of special populations, including HCV-HIV coinfection and liver transplantation recipients.

Targets of Therapy

HCV-encoded proteins involved with replication are the main targets of the new DAA agents. These include nonstructural (NS) components, such as RNA-dependent RNA polymerase (NS5B), the protein NS5A (which has a role in the formation of the replication complex), and the proteins NS3 and NS4A (serine protease and cofactor, respectively).

NS3/4A PIs include first-generation agents (telaprevir [Incivek, Vertex] and boceprevir [Victrelis, Merck], both withdrawn from

Table 1. Treatment Regimens for Genotype 1a and 1b Hepatitis C Virus Infection[31,32]

Genotype 1a	
Treatment Naive	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	12 weeks
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin 1000/1200 mg	12 weeks
Treatment Naive + Cirrhosis	
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	24 weeks
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin 1000/1200 mg	24 weeks
Treatment Failure: PEG-IFN and Ribavirin	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	12 weeks
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin 1000/1200 mg	12 weeks
Treatment Failure: Sofosbuvir	
Without advanced fibrosis: defer treatment	
Treatment Failure: PEG-IFN, Ribavirin, PI	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Treatment Failure: PEG-IFN and Ribavirin + Cirrhosis	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	24 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg daily + WB ribavirin 1000/1200 mg	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	24 weeks
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin 1000/1200 mg	24 weeks
Treatment Failure: Sofosbuvir + Cirrhosis	
Advanced fibrosis: ledipasvir 90 mg/sofosbuvir 400 mg daily ± WB ribavirin 1000/1200 mg	24 weeks
Treatment Failure: PEG-IFN, Ribavirin, PI + Cirrhosis	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	24 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg daily + WB ribavirin 1000/1200 mg	12 weeks
Genotype 1b	
Treatment Naive	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID	12 weeks
Sofosbuvir 400 mg + simeprevir 150 mg	12 weeks
Treatment Naive + Cirrhosis	
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	12 weeks
Sofosbuvir 400 mg + simeprevir 150 mg	24 weeks
Treatment Failure: PEG-IFN and Ribavirin	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID	12 weeks
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin 1000/1200 mg	12 weeks
Treatment Failure: Sofosbuvir	
Without advanced fibrosis: defer treatment	

(continued on the next page)

Table 1. *(continued)* Treatment Regimens for Genotype 1a and 1b Hepatitis C Virus Infection[31,32]

Treatment Failure: PEG-IFN, Ribavirin, PI	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Treatment Failure: PEG-IFN and Ribavirin + Cirrhosis	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	24 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg daily + WB ribavirin 1000/1200 mg	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	12 weeks
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin 1000/1200 mg	24 weeks
Treatment Failure: Sofosbuvir + Cirrhosis	
Advanced fibrosis: ledipasvir 90 mg/sofosbuvir 400 mg daily ± WB ribavirin 1000/1200 mg	24 weeks
Treatment Failure: PEG-IFN, Ribavirin, PI + Cirrhosis	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	24 weeks
Ledipasvir 90 mg/sofosbuvir 400 mg daily + WB ribavirin 1000/1200 mg	12 weeks

PEG-IFN, pegylated interferon; PI, protease inhibitor; WB, weight-based. WB ribavirin: <75 kg=1000 mg, ≥75 kg=1200 mg.

the US market in 2014) and second-generation agents (simeprevir [Olysio, Janssen], paritaprevir, and asunaprevir; only asunaprevir is not yet approved in the United States). Largely replaced by newer DAA agents, the first-generation agents have significant side effects such as anemia and rash, and their use is complicated by drug-drug interactions, the need for multiple daily doses, and low barriers to resistance. The benefits of second-generation agents include reduced dosing, improved side effect profiles, and fewer drug-drug interactions. Additionally, the therapeutic efficacy is improved for treatment of HCV genotype 1 infection. Of note, paritaprevir is pharmacologically boosted with low-dose ritonavir.

NS5A inhibitors (ledipasvir, ombitasvir, and daclatasvir) are active against all genotypes, particularly HCV genotype 1 when given with other DAA agents. Currently, these agents are only available in fixed-dose combinations: ledipasvir with sofosbuvir (Harvoni, Gilead) and ombitasvir with paritaprevir and ritonavir administered with dasabuvir (Viekira Pak, AbbVie).

RNA-dependent RNA polymerase (NS5B) inhibitors include sofosbuvir (Sovaldi, Gilead; a nucleotide polymerase inhibitor) and dasabuvir (a nonnucleoside polymerase inhibitor). As previously mentioned, these agents are available in combination with NS5A inhibitors or alone (sofosbuvir only) to be used in other drug combinations. The side effects of sofosbuvir and ribavirin combination therapy are generally mild; they include fatigue, headache, nausea, insomnia, and anemia, and are generally attributed to ribavirin rather than sofosbuvir.

The fixed-dose combinations currently available include ledipasvir/sofosbuvir (90 mg/400 mg) and ombitasvir/paritaprevir/ritonavir (2 pills of 12.5 mg/75 mg/50 mg of each agent, respectively) plus dasabuvir (250 mg).

Hepatitis C Virus Genotypes 1a and 1b Infection

Three regimens are currently available for treatment of HCV genotype 1 infection (Table 1). These include simeprevir plus sofosbuvir with or without ribavirin, ledipasvir/sofosbuvir, and ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin.

Simeprevir Plus Sofosbuvir

The first of these combinations, simeprevir plus sofosbuvir with or without ribavirin, was evaluated in the COSMOS trial. Patients (prior nonresponders to pegylated interferon and ribavirin who were treatment naive) achieved a 94% sustained virologic response after 12 weeks of treatment (SVR12) with or without ribavirin (compared with a SVR after 24 weeks [SVR24] of 91%) and low viral relapse rates. Most side effects consisted of fatigue, headache, and nausea, and were thought to be related to ribavirin more than to the other 2 agents used. Well-compensated cirrhotic patients were also able to tolerate the regimen. The use of ribavirin did not appear to confer a higher SVR12 rate (91% with ribavirin and 95% without ribavirin).[1]

Ledipasvir/Sofosbuvir Combination

The combination of ledipasvir and sofosbuvir is available as a fixed-dose combination tablet. This all-oral combination was evaluated in previously untreated HCV genotype 1–infected patients in ION-1. With an endpoint of SVR12, the study examined ledipasvir/sofosbuvir with or without ribavirin for 12 or 24 weeks. Patients treated with ledipasvir/sofosbuvir with or without ribavirin for 12 weeks achieved a SVR12 rate of 99% and 97%, respectively; treatment extended to 24 weeks resulted in a SVR12 rate of 98% and 99% for the same categories.

Table 2. Treatment Regimens for Genotypes 2, 3, 4, 5, and 6 Hepatitis C Virus Infection[31,32]

Genotype 2	
Treatment Naive	
Sofosbuvir 400 mg + WB ribavirin daily	12 weeks
Treatment Naive + Cirrhosis	
Sofosbuvir 400 mg + WB ribavirin daily	16 weeks
Treatment Failure: PEG-IFN and Ribavirin	
Sofosbuvir 400 mg + WB ribavirin daily	12-16 weeks
(Alternative) Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
Genotype 3	
Treatment Naive	
Sofosbuvir 400 mg + WB ribavirin daily	24 weeks
(Alternative) Sofosbuvir 400 mg + WB ribavirin daily for 24 weeks + PEG-IFN weekly for 12 weeks	24/12 weeks
Treatment Failure: PEG-IFN and Ribavirin	
Sofosbuvir 400 mg + WB ribavirin daily	24 weeks
(Alternative) Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
Genotype 4	
Treatment Naive	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + WB ribavirin 1000/1200 mg	12 weeks
Sofosbuvir 400 mg + WB ribavirin daily	24 weeks
(Alternative) Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
(Alternative) Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin	12 weeks
Treatment Failure: PEG-IFN and Ribavirin	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + WB ribavirin 1000/1200 mg	12 weeks
Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
Sofosbuvir 400 mg + WB ribavirin daily	24 weeks
Genotype 5	
Treatment Naive	
Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
WB ribavirin daily + PEG-IFN weekly	48 weeks
Treatment Failure	
Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
(Alternative) PEG-IFN weekly + WB ribavirin daily	48 weeks
Genotype 6	
Treatment Naive	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
(Alternative) Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks
Treatment Failure	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	12 weeks
(Alternative) Sofosbuvir 400 mg + WB ribavirin daily + PEG-IFN weekly	12 weeks

PEG-IFN, pegylated interferon; WB, weight-based. WB ribavirin: <75 kg=1000 mg, ≥75 kg=1200 mg.

Cirrhotic patients accounted for 16% of the study population; although not powered, efficacy rates were similar to those of noncirrhotic patients. In conclusion, ledipasvir/sofosbuvir without ribavirin for a duration of 12 weeks provided effective treatment.[2]

For patients with previously treated HCV genotype 1 infection (20% of whom had cirrhosis), the same regimens were examined in another phase 3 trial, ION-2. Twelve weeks of therapy with or without ribavirin yielded SVR12 rates of 96% and 94%, respectively. When the treatment was extended to 24 weeks, both groups (with or without ribavirin) achieved a SVR12 rate of 99%. For cirrhotic patients treated for 12 weeks, the SVR12 rate was 82% and 86% for treatment with or without ribavirin, respectively. Cirrhotic patients treated for 24 weeks showed no difference from noncirrhotic patients, and the difference compared with 12 weeks of treatment was statistically significant.[3]

A shorter duration of treatment was examined in previously untreated noncirrhotic patients in ION-3. Noninferiority of an 8-week course of ledipasvir/sofosbuvir was shown (SVR12 of 94%) compared with 12 weeks (SVR12 of 95%) and with ledipasvir/sofosbuvir plus ribavirin for 8 weeks (SVR12 of 93%).[4]

Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir

Also currently available is the combination of ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin. Twelve weeks of therapy in previously untreated noncirrhotic patients with HCV genotype 1 infection led to a SVR24 rate of 96% compared with 88% with 8 weeks of treatment in a phase 2b trial. Response to triple DAA therapy with ribavirin for 12 weeks was a SVR24 rate of 96% for previously untreated patients and 93% for patients nonresponsive to prior therapy. Lastly, relapse occurred in 1% of previously untreated patients receiving treatment for 12 weeks, but in 12% with 8 weeks of treatment.[5]

This phase 2b test was validated in SAPPHIRE-I, a phase 3 trial with previously untreated noncirrhotic patients with HCV genotype 1 infection. In this trial, SVR12 was examined. Compared with a historical control (SVR24 of 78% for the combination of peginterferon, ribavirin, and telaprevir), this new combination of ombitasvir (25 mg)/paritaprevir (150 mg)/ritonavir (100 mg) daily plus dasabuvir (250 mg) twice daily with weight-based ribavirin had an increased SVR12 rate (96.2%: 95.3% for HCV genotype 1a infection and 98% for HCV genotype 1b infection). Virologic failure was 0.2%, whereas treatment relapse was 1.5%.[6]

A subsequent trial evaluated the same regimen with or without the inclusion of ribavirin (PEARL-III [HCV genotype 1b infection], PEARL-IV [HCV genotype 1a infection]). After 12 weeks of treatment, the SVR12 rate was 99.5% in HCV genotype 1b–infected patients treated with ribavirin and 99.0% in those without ribavirin. HCV genotype 1a–infected patients had SVR12 rates of 97.0% and 90.2% with or without ribavirin, respectively. While noninferiority of the nonribavirin regimen was shown in HCV genotype 1b infection, this was not the case in HCV genotype 1a infection. Virologic failure was higher in HCV genotype 1a–infected patients treated without ribavirin; no difference was seen in patients with HCV genotype 1b infection. Overall, while a ribavirin-free regimen is acceptable for patients with HCV genotype 1b, ribavirin does provide additional benefit for those with HCV genotype 1a infection.[7]

In the previously treated and treatment-naive compensated cirrhotic population, the above combination with ribavirin was used in a phase 3 trial (TURQUOISE-II). With an efficacy endpoint of SVR12, 91.8% and 95.9% of patients infected with HCV genotype 1 achieved success with 12 and 24 weeks of treatment, respectively. Specifically with regard to HCV genotype 1a infection with prior treatment failure, 12 weeks of treatment yielded a SVR12 rate of 80.0%, whereas 24 weeks of treatment improved the SVR12 rate to 92.9%. Significantly, more patients relapsed with 12 weeks of treatment compared with 24 weeks (5.9% vs 0.6%).[8]

Retreatment of pegylated interferon and ribavirin failure in HCV genotype 1–infected, noncirrhotic patients was subsequently addressed in the phase 3 SAPPHIRE-II trial. Approximately half of the patients were null responders. Treatment consisted of the combination ombitasvir/paritaprevir/ritonavir plus dasabuvir with ribavirin. Overall, 96.3% achieved SVR12; the HCV genotype 1a and 1b subgroups had SVR12 rates of 96.0% and 96.7%, respectively.[9]

Hepatitis C Virus Genotypes 2 and 3 Infection

Table 2 shows the regimens for HCV genotypes 2 and 3 infection. The VALENCE study evaluated HCV genotype 2– and 3–infected patients (21% with cirrhosis, 58% with prior interferon treatment) with the regimen of sofosbuvir and ribavirin; however, the duration of therapy varied. For patients with HCV genotype 2 infection, a SVR12 rate of 93% was achieved with 12 weeks of therapy. However, the SVR12 rate was 85% in patients with HCV genotype 3 infection who were treated for 24 weeks (91% for noncirrhotic patients, 68% for cirrhotic patients).[10]

Hepatitis C Virus Genotypes 4, 5, and 6 Infection and HIV Coinfection

Data supporting the use of DAA agents in HCV genotypes 4, 5, and 6 infection are sparse; therefore, the US Food and Drug Administration (FDA) chose not to provide

labeling guidance for all-oral regimens in these populations (Table 2). However, combined guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America have provided recommendations for ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin based on 2 small phase 3 trials that have recently been published (Table 3).[11,12] Both of these regimens are FDA-approved for HIV-coinfected patients, with labeling that is identical to that for monoinfected patients.

Post–Liver Transplant Patients

Recurrent HCV genotype 1 infection in post–liver transplant patients was treated in a phase 2 study (CORAL-I) with combination ombitasvir/paritaprevir/ritonavir plus dasabuvir with ribavirin for a duration of 24 weeks. The SVR12 rate was 97%, with no graft rejection reported. Previously, a regimen of pegylated interferon and ribavirin had been used; it had been poorly tolerated and associated with a SVR24 rate of less than 50% (Table 3).[13]

Future Treatment Regimens

The goals of future treatment regimens will be to solidify and improve on the gains that have been achieved thus far. This will likely lead to regimens that are pangenotypic, administered for fewer than 12 weeks, ribavirin-free, less costly, and well tolerated in special populations. The first of these regimens will likely involve daclatasvir, a pangenotypic NS5A inhibitor that has completed phase 3 trials in HCV genotype 2– and 3–infected patients (in combination with sofosbuvir) and in HCV genotype 1–infected patients (in combination with asunaprevir and beclabuvir). In a phase 2 study, daclatasvir plus sofosbuvir (with or without ribavirin) for 24 weeks achieved SVR rates of 93% to 100% in HCV genotype 2–infected, treatment-naive patients and 89% in HCV genotype 3–infected, treatment-naive patients.[14] The ALLY-3 study is a recently published phase 3 trial that evaluated the same regimen for 12 weeks in only patients with HCV genotype 3 infection.[15] The regimen demonstrated good efficacy in both treatment-naive (SVR12 of 90%) and treatment-experienced patients (SVR12 of 86%). The SVR12 rates in noncirrhotic patients with the 12-week regimen were 96%, but only 63% in cirrhotic patients, indicating that a longer duration is needed with cirrhosis (which has been seen with the other all-oral DAA therapies). Daclatasvir plus sofosbuvir was safe and well tolerated. This regimen is approved in Europe and Japan and currently under regulatory review in the United States.

An all-oral triple combination has also completed phase 3 study using daclatasvir together with the NS3 PI asunaprevir and a nonnucleoside NS5B polymerase inhibitor, beclabuvir, coformulated as a twice-daily fixed-dose combination (daclatasvir-trio, Bristol-Myers Squibb). The regimen of daclatasvir-trio plus ribavirin was studied in patients with HCV genotype 1 infection and compensated cirrhosis and showed SVR12 rates of 98% in treatment-naive patients and 93% in treatment-experienced patients.[16] With daclatasvir-trio alone, the SVR12 rate was 93% in treatment-naive patients and 87% in patients without cirrhosis regardless of whether they were treatment naive or experienced.[17] Neither thrombocytopenia nor prior null response had an impact on SVR12. Daclatasvir-trio with or without ribavirin was generally safe and well tolerated. However, the regimen will likely require ribavirin to minimize relapse, and there have been 2 cases of reported immunoallergic hepatotoxicity related to asunaprevir in the Japanese population.[18]

Another all-oral DAA combination that is currently in development is grazoprevir, a pangenotypic NS3/4 PI, plus elbasvir, a NS5A inhibitor, with or without ribavirin (Merck). This regimen has been extensively studied in a large phase 2 study (C-WORTHY) in treatment-naive HCV genotype 1–infected patients with cirrhosis and in null responders with or without cirrhosis. The regimen demonstrated SVR12 rates averaging 95% with or without ribavirin in either 12- or 18-week regimens.[19] A second phase 2 study has been published showing equally high SVR rates in HIV-coinfected patients treated with 8 or 12 weeks of the same regimen with or without ribavirin.[20] Merck is currently exploring the use of these 2 compounds in combination with a nucleoside polymerase inhibitor as a fixed-dose combination in HCV genotypes 1, 2, 3, and 4 patients for durations as short as 6 weeks. The ultimate goal is to achieve SVR rates greater than 95% in multiple genotypes with shorter durations of therapy. However, such a regimen is not expected to be available until 2016.

In the phase 3 C-EDGE study, a 12-week course of grazoprevir and elbasvir was used in HCV genotype 1–infected patients with the SVR12 rate of 92% for genotype 1a and 99% for genotype 1b.[21] This same combination with sofosbuvir was evaluated in the C-SWIFT trial in treatment-naive HCV genotype 1–infected patients both with cirrhosis (6- and 8-week treatment) and without cirrhosis (4- and 6-week treatment). For noncirrhotic patients, the SVR12 rate was 33% in the 4-week group (with 20 relapses) but 87% in the 6-week group. In cirrhotic patients, 6- and 8-week courses provided SVR12 rates of 80% and 94%, respectively.[22]

Salvage therapy with this combination plus ribavirin has also been studied in C-SALVAGE. Patients with HCV genotype 1 infection who had failed DAA agents were re-treated with this combination for 12 weeks and

Table 3. Treatment Regimens for Special Populations With Hepatitis C Virus Infection[31,32]

HCV/HIV Coinfection[a]	
Ledipasvir 90 mg/Sofosbuvir 400 mg Daily	
Avoid with tenofovir/ritonavir combination, cobicistat, elvitegravir, tipranavir	
Paritaprevir 150 mg/Ritonavir 100 mg/Ombitasvir 25 mg Daily + Dasabuvir 250 mg BID	
Use with raltegravir, enfuvirtide, tenofovir, emtricitabine, lamivudine, atazanavir	
Avoid with efavirenz, rilpivirine, darunavir, ritonavir-boosted lopinavir	
Must be on antiretroviral therapy	
Simeprevir	
Avoid with efavirenz, etravirine, nevirapine, cobicistat, HIV protease inhibitors	
Ribavirin	
Avoid with didanosine, stavudine, zidovudine	
Decompensated Cirrhosis	
Genotype 1, 4; Treatment Naive	
Ledipasvir 90 mg/sofosbuvir 400 mg daily + ribavirin 600 mg (increase as tolerated)	12 weeks
Genotype 1, 4; Anemia/Ribavirin Intolerant	
Ledipasvir 90 mg/sofosbuvir 400 mg daily	24 weeks
Genotype 1, 4; Treatment Failure: Sofosbuvir	
Ledipasvir 90 mg/sofosbuvir 400 mg daily + ribavirin 600 mg (increase as tolerated)	24 weeks
Genotype 2, 3; Treatment Naive	
Sofosbuvir 400 mg + WB ribavirin daily	up to 48 weeks
Posttransplant	
Genotype 1, 4; Including Compensated Cirrhosis; Treatment Naive and Failure	
Ledipasvir 90 mg/sofosbuvir 400 mg daily + WB ribavirin 1000/1200 mg	12 weeks
(Alternative) Ledipasvir 90 mg/sofosbuvir 400 mg daily	24 weeks
Genotype 1; Including Compensated Cirrhosis but Without Cirrhosis	
Sofosbuvir 400 mg + simeprevir 150 mg ± WB ribavirin	12 weeks
(Alternative) Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily + dasabuvir 250 mg BID + WB ribavirin 1000/1200 mg	24 weeks
Genotype 2; Treatment Naive and Failure	
Sofosbuvir 400 mg + WB ribavirin daily	24 weeks
Genotype 3; Treatment Naive and Failure	
Sofosbuvir 400 mg + WB ribavirin daily	24 weeks
Genotype 3; Decompensated Cirrhosis	
Sofosbuvir 400 mg + ribavirin 600 mg (increase as tolerated)	24 weeks
Pretransplant	
Unclear	
Retreatment of Sofosbuvir Failure	
Unclear	

WB, weight-based. WB ribavirin: <75 kg=1000 mg, ≥75 kg=1200 mg.

[a] Otherwise treat these patients the same as those without HIV infection.

achieved a SVR12 rate of 96.2%. In this study, 43% of the patients were cirrhotic, and 84% had prior virologic failure. Pretreatment evaluation revealed that 41% of the 73 patients who were tested harbored resistance-associated variants of NS3.[23]

For HCV genotype 1 infection with cirrhosis, the C-SALT study showed a SVR12 rate of 90% after 12 weeks of grazoprevir and elbasvir. Additionally, for the noncirrhotic group, the SVR12 rate was 100%. The only difference was that cirrhotic patients received elbasvir 50 mg while noncirrhotic patients received 100 mg.[24]

Importantly, this combination of grazoprevir plus elbasvir has now also been studied in patients with chronic kidney disease. In the C-SURFER trial, 12 weeks of treatment resulted in a SVR12 rate of 94%; this included patients who received at least 1 dose of the medication.[25]

Gilead is also developing a pangenotypic NS5A inhibitor, GS-5816, which has demonstrated high SVR12 rates with 8 weeks of therapy in treatment-naive, noncirrhotic patients with HCV genotype 3 infection.[26] The 100-mg formulation of the compound has been combined with 400 mg of sofosbuvir in a fixed-dose combination that is undergoing phase 3 studies in multiple HCV genotypes. Also being explored is the efficacy of ledipasvir/sofosbuvir or ledipasvir/sofosbuvir plus ribavirin in treatment-experienced patients with HCV genotype 3 infection for 12 weeks, which has shown SVR12 rates of 73% and 89% in patients with or without cirrhosis, respectively. Although this regimen is not currently approved for HCV genotype 3 infection in the United States, some providers have reported using it off-label. Ledipasvir/sofosbuvir for 12 weeks without ribavirin is also the first reported safe, effective, all-oral regimen for patients with HCV genotype 6 infection that has been studied.[27]

Although the cost per SVR for patients with HCV genotype 1 infection is lower than it was with prior DAA combination regimens,[28] there will need to be more cost reduction realized by payors before these regimens can be widely available. Currently, most payors are only covering treatment for patients with advanced fibrosis or cirrhosis (F3-4), which is actually more costly than treating patients with earlier stages of fibrosis.[29] There has already been substantial discounting of the drug regimens upon approval of the third all-oral treatment in the United States.[30] There will likely be 5 all-oral therapies available in the United States by early 2016, and competition in the marketplace will bring down the cost of therapy and thus reduce barriers to access. Therapies for HCV genotype 3 infection will be more effective than the current therapies, and a number of pangenotypic regimens are being developed. Regimen durations shorter than 8 weeks have not succeeded thus far but may be seen in the future.

Dr Kardashian has no relevant conflicts of interest to disclose. Dr Pockros has received research grants from and has served on the advisory boards of Gilead, AbbVie, Janssen, Merck, and BMS. He has also received speaking fees from Gilead, AbbVie, and Janssen. Scripps Health receives CME grants from Gilead, AbbVie, Janssen, Merck, and BMS.

References

1. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet*. 2014;384(9956):1756-1765.
2. Afdhal N, Zeuzem S, Kwo P, et al; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014;370(20):1889-1898.
3. Afdhal N, Reddy KR, Nelson DR, et al; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014;370(16):1483-1493.
4. Kowdley KV, Gordon SC, Reddy KR, et al; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014;370(20):1879-1888.
5. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med*. 2014;370(3):222-232.
6. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1594-1603.
7. Ferenci P, Bernstein D, Lalezari J, et al; PEARL-III Study; PEARL-IV Study. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med*. 2014;370(21):1983-1992.
8. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014;370(21):1973-1982.
9. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med*. 2014;370(17):1604-1614.
10. Zeuzem S, Dusheiko GM, Salupere R, et al; VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med*. 2014;370(21):1993-2001.
11. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA*. 2015;313(12):1232-1239.
12. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA*. 2015;313(12):1223-1231.
13. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med*. 2014;371(25):2375-2382.
14. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al; AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. 2014;370(3):211-221.
15. Nelson DR, Cooper JN, Lalezari JP, et al; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*. 2015;61(4):1127-1135.
16. Muir AJ, Poordad F, Lalezari J, et al. Daclatasvir in combination with asunaprevir and beclabuvir for hepatitis C virus genotype 1 infection with compensated cirrhosis. *JAMA*. 2015;313(17):1736-1744.
17. Poordad F, Sievert W, Mollison L, et al; UNITY-1 Study Group. Fixed-dose combination therapy with daclatasvir, asunaprevir, and beclabuvir for noncirrhotic patients with HCV genotype 1 infection. *JAMA*. 2015;313(17):1728-1735.
18. Fujii Y, Uchida Y, Mochida S. Drug-induced immunoallergic hepatitis during combination therapy with daclatasvir and asunaprevir. *Hepatology*. 2015;61(1):400-401.
19. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015;385(9973):1075-1086.
20. Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015;385(9973):1087-1097.

21. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic HCV genotype 1, 4, or 6 infection: a randomized trial [published online April 24, 2015]. *Ann Intern Med*. doi:10.7326/M15-0785.
22. Poordad F, Lawitz E, Gutierrez JA, et al. C-SWIFT: Grazoprevir/elbasvir sofosbuvir in cirrhotic and noncirrhotic, treatment-naïve patients with hepatitis C virus genotype 1 infection, for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. *J Hepatol*. 2015;(62):S192.
23. Forns X, Gordon S, Zuckerman E, et al. Grazoprevir/elbasvir plus ribavirin for chronic HCV genotype 1 infection after failure of combination therapy containing a direct-acting antiviral agent [published online April 17, 2015]. *J Hepatol*. doi:10.1016/j.jhep.2015.04.009.
24. Jacobson I, Poordad F, Firpi-Morell R, et al. Efficacy and safety of grazoprevir and elbasvir in hepatitis C genotype 1-infected patients with Child-Pugh class B cirrhosis (C-SALT Part A). *J Hepatol*. 2015;(62):S193.
25. Roth D, Hezode C, Zuckerman E, et al. C-SURFER: grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease. *J Hepatol*. 2015;(62):S263.
26. Gane EJ, Hyland RH, An D, et al. Once-daily sofosbuvir with GS-5816 for 8 weeks with or without ribavirin in patients with HCV genotype 3 without cirrhosis results in high rates of SVR12: the ELECTRON-2 study. *Hepatology*. 2014;60(4 suppl):236A.
27. Gane EJ, Hyland RH, An D, et al. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. *Hepatology*. 2014;60(4 suppl):LB-11.
28. Younossi Z, Saab S, Ahmed A, Gordon SCA. Decision-analytic Markov model To evaluate the health outcomes of ledipasvir/sofosbuvir (LDV/SOF) for patients with chronic hepatitis C (HCV) genotype 1 (GT1) infection. *Hepatology*. 2014;60(4 suppl):1043A.
29. Ahmed A, Gordon SC, Saab S, Younossi Z. Evaluation of the health outcomes for ledipasvir/ sofosbuvir in early vs. delayed treatment according to fibrosis stage of patients with chronic hepatitis c virus (HCV) genotype 1 infection: results from a decision-analytic Markov model. *Hepatology*. 2014;60(4 suppl):1041A.
30. Pollock A. Sales of Sovaldi, new Gilead hepatitis C drug, soar to $10.3 billion. *New York Times*. Feb 3, 2015.
31. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed February 2, 2015.
32. Pockros PJ. Direct-acting antivirals for the treatment of hepatitis C virus infection. UpToDate. Accessed February 28, 2015.