Review Article

Interferon-Free Treatments for Chronic Hepatitis C Genotype 1 Infection

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Abstract

Hepatitis C virus (HCV) infection affects as many as 185 million people globally, many of whom are chronically infected and progress over time to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and eventually death without a liver transplant. In the United States, HCV genotype 1 constitutes about 75% of all infections. While interferon and ribavirin therapy was the cornerstone of treatment for many years, interferon-free treatments have become the standard of care with the emergence of new direct-acting agents, resulting in more effective treatment, shorter duration of therapy, better tolerability, lower pill burden, and ultimately better adherence. This review will summarize the evidence for the currently available combination therapies as well as emerging therapies in phase 3 trials for treatment of HCV genotype 1.
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Introduction

Hepatitis C virus (HCV) is the most common cause of chronic hepatitis, which leads to severe complications over time.[1] In the mid-1970's, it was shown that most post-transfusion cases of hepatitis were neither due to hepatitis A nor B virus, the only known hepatitis viruses at the time. Hence, it was referred to as the "non-A non-B hepatitis" until its discovery in 1989.[2] Hepatitis C has a great disease burden and cost in the Western world, as it is the leading cause of cirrhosis, liver cancer, and a primary indication for liver transplantation.[1] Over the 27 years since its discovery, many advancements have been made in understanding the virus and developing effective and safe treatments.

Keywords: Hepatitis C; HCV; Genotype 1; Direct acting antiretroviral agents.
Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; ART, anti-retroviral therapy; AUC, area under the curve; DAAs, direct-acting agents; DLD, decompensated liver disease; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; RAV, resistance associated variant; RNA, ribonucleic acid; SVR, sustained virologic response; ULN, upper limit of normal.
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It is estimated that 3–4 million individuals are newly infected with HCV each year.[3] As many as 185 million persons worldwide and approximately 3.4–4.4 million individuals in the United States are chronically infected with HCV.[3,4] These numbers are perhaps an underestimate, since it is difficult to account for infected individuals who are homeless or incarcerated. Once exposed to HCV, individuals will develop acute infection in as early as 2 weeks and as late as 26 weeks (Fig. 1).[5,6] While spontaneous clearance of HCV is relatively rare, it can occur in 18%–34% of acutely infected patients.[7] The remainder of infected individuals, if left untreated, will progress to chronic infection over a period of 6 months. About 25% of chronically infected persons will develop cirrhosis. Progression to cirrhosis was thought to be a slow process, occurring over 25–30 years; but new data suggest that this progression may occur faster, over 5 to 10 years in some individuals, especially those over 58 years of age.[8] Once cirrhosis is established, progression seems to slow down, and 25% of patients will develop hepatocellular carcinoma (HCC) and/or decompensated liver disease (DLD), and eventually death.[8] In fact, more than 350,000 people die annually worldwide from HCV-related complications.[9]

Virology

HCV is an enveloped positive-sense viral ribonucleic acid (RNA) that belongs to the *Hepacivirus* genus of viruses in the *Flaviviridae* family.[2] The viral RNA uses the host's hepatocyte ribosomes for translation into a polyprotein that is processed into 10 polypeptides, each with distinct functions.[10] The lack of proofreading in HCV replication machinery results in a great number of viral mutations, contributing to a high level of variation.[11] Multiple HCV variants in the same infected individual are referred to as "quasispecies". These variations differ greatly based on geographic origin and lead to various HCV genotypes. There are seven major HCV genotypes, each with about 30% sequence divergence, whose prevalence varies geographically (Table 1).[3,12] Each genotype is grouped into a number of subtypes, each with about 20% sequence divergence, denoted by letters a, b, etc.[13,14] In the United States, HCV genotype 1 constitutes about 75% of all infections followed by HCV genotypes 2 and 3 constituting the remaining 25%.[3] Disease association is largely similar across all genotypes, but treatment response varies.[13]

Clinical manifestations

Acute hepatitis C is asymptomatic in 70%–85% of infected individuals.[15] Those infected persons who show signs and

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Fig. 1. Progression of hepatitis C.

Abbreviations: DLD, decompensated liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

symptoms are more likely to clear the virus naturally.[7] These symptoms can include malaise, jaundice, and influenza-like symptoms.[15] Elevated aminotransferase levels are often present in the setting of acute infection. Chronic hepatitis C is also asymptomatic in most individuals. Alanine aminotransferase (ALT) levels typically fluctuate independent of symptoms in the setting of chronic infection.[16] Insulin resistance often occurs in chronically infected persons.[17] Steatosis is usually present in those chronically infected with HCV genotype 3.[18] In individuals with advanced disease progression, symptoms of decompensated cirrhosis, such as esophageal varices, ascites, coagulopathy, encephalopathy, or HCC, can be present. Some individuals can also display extrahepatic symptoms, such as cryoglobulinemia, vasculitis, porphyria cutanea tarda, and membranous glomerulonephritis.[19,20]

Screening and diagnosis

The diagnosis of HCV is based on two broad categories of serological assays to detect antibodies against hepatitis C and molecular assays to detect or quantify HCV RNA. For acute hepatitis C, detectable HCV RNA by polymerase chain reaction (PCR), even in the setting of negative anti-HCV antibodies, is considered definitive proof of the infection. It generally takes about 12 weeks for the anti-HCV antibody to become detectable, whereas HCV RNA can be detected in blood as early as 1 week after exposure. Newly detectable HCV RNA and anti-HCV antibodies with documentation of negative tests within the prior 6 months are also suggestive of acute HCV infection. It sometimes becomes difficult to distinguish between acute and chronic HCV infection if prior documentation of negative tests are absent. If the antibody is nonreactive, then chronic HCV infection is unlikely. A positive HCV RNA result is evidence of HCV infection. Usually, if both HCV RNA and anti-HCV antibody are detectable, the patient has chronic HCV infection.[21]

HCV testing is recommended for all adults born from 1945 through 1965. The testing is also recommended for those who inject drugs, have certain medical conditions, including persons who received clotting factor concentrates produced before 1987 or who were on hemodialysis long-term, have HIV, or have persistently abnormal ALT levels. Recipients of transfusions or organ transplants before July 1992 and those who were notified that they received blood from a donor who later tested positive for HCV infection should be screened. Children born to HCV-positive women and healthcare providers exposed to needle sticks or HCV positive blood should be tested for HCV.[21]

Table 1. Prevalence of hepatitis C virus (HCV) genotypes worldwide

HCV genotype	Prevalence of HCV	Geographic Location
1a	36%–55%	United States
1b	23%–25%	Europe, Japan, and China
2	13%–16%	Europe, United States, and Central Africa
3	8%–13%	Southeast Asia
4	1%–2%	Middle East and Northern Africa
5	< 1%	South Africa
6	< 1%	Southeast Asia
7	< 1%	Unknown

HCV life cycle

The HCV virions exist as lipoviroparticles, which are able to enter hepatocytes by endocytosis trapped inside of endosomes. The low pH environment of endosomes results in uncoating of the virion and the release of viral RNA into the cytoplasm. The viral RNA is readily translated in the rough endoplasmic reticulum into a polypeptide consisting of 10 structural and nonstructural (NS) proteins. The structural proteins include the capsid protein C and the envelope glycoproteins E1 and E2. The nonstructural proteins include the porin p7, the autoprotease and assembly factor NS2, the serine protease and RNA helicase NS3, the NS3 protease cofactor NS4A, the organizer of replication complex and membranous web NS4B, the regulator of replication and viral assembly NS5A, and the RNA-dependent RNA polymerase NS5B. The resulting HCV polypeptide is co- and post-translationally cleaved by cellular proteases and viral NS2/3 and NS3/4A proteases to release the 10 HCV proteins.[13]

The next step in the HCV life cycle is the formation of the replication complex consisting of NS3, NS4A, NS4B, NS5A, and NS5B proteins. The HCV RNA template binds to NS5A protein in the replication complex.[22] NS5B protein replicates the template, and NS3 protein separates the nascent and template RNA strands. Cholesterol and fatty acid biosynthesis are important to HCV replication by forming membrane-associated RNA replication complexes. Assembly of HCV requires lipid droplets.[10] NS5A protein is also important in the assembly of the replication complex.[10,23] NS2 protein coordinates virion assembly through interactions with the glycoproteins, p7, NS3, and NS5A. Lastly, the mature virus is released from cells through the Golgi apparatus as lipoviral particles.[10]

Pathogenesis

The HCV replication cycles in the hepatocytes cause cell necrosis by multiple mechanisms, including immune mediated cytolysis. The virus can also cause hepatic steatosis (more likely with HCV genotype 3), oxidative stress, and insulin resistance. This continuous necroinflammatory response most likely causes progressive fibrosis and scarring of the liver, which leads to cirrhosis over time.[18,24]

Treatment

The combination of peginterferon and ribavirin was considered the standard of care for patients with HCV for many years.[25] This combination did not have a high rate of virologic cure, particularly in patients with HCV genotype 1, and 48 weeks of treatment was typically required.[26–29] Poor response to interferon-based therapy was associated with cirrhosis, non-CC *interleukin-28B* (*IL28B*) genotype (also known as *IFNL3* gene, encoding interferon lambda-3), black race, human immunodeficiency virus (HIV) coinfection, steatosis, and insulin resistance.[28,30–34] In addition, severe adverse effects as well as administration via subcutaneous injection resulted in poor patient adherence. The introduction of direct-acting agents (DAAs), boceprevir and telaprevir, in 2011, led to interferon-sparing combinations, resulting in shorter duration of therapy with a higher rate of virologic cure (Table 2).[35] These first-generation protease inhibitors were costly, had a pill burden with a thrice-daily schedule, and added more adverse effects, which made it challenging for the patients to remain adherent and leading to high rates of resistance and clinical failure.[36] As more classes of DAAs were introduced, agents from two or more classes could be combined to eliminate the need for peginterferon, which was previously needed to reduce the emergence of resistance to protease inhibitors. These new interferon-free therapies are better tolerated by patients and are more effective in achieving a high rate of virologic cure.[4] The results of clinical trials have confirmed that non-CC *IL28B* genotype, which is associated with poor response to peginterferon-containing regimens,[37] is not associated with poor response to interferon-free treatments.[38–40] However, patients with cirrhosis and/or HCV genotype 1a remain difficult to treat compared to patients without cirrhosis and those with HCV genotype 1b.

The primary outcome in HCV clinical trials is sustained virologic response 12 weeks after the end of treatment (SVR12), defined as undetectable HCV RNA serum levels. Historically, SVR 24 weeks after the end of treatment (SVR24) was used for the primary endpoint. However, studies have shown that SVR12 has a 98% positive predictive value and a 99% negative predictive value compared to SVR24.[41,42] As a result, the United States Food and Drug Administration (FDA) guidance for industry has indicated use of SVR12 as the primary efficacy end point in clinical trials.[43] Patients who have never received treatment before are considered treatment-naïve. Those patients who received treatment in the past and failed treatment are considered treatment-experienced, including null response (a decrease in HCV RNA level of < 2 log IU/mL while on treatment), partial response (a decrease in HCV RNA level of ≥ 2 log IU/mL while on treatment but a detectable level at the end of treatment), virologic breakthrough (a detectable HCV RNA level while on treatment after previously undetectable), and relapse (an undetectable level of HCV RNA during treatment but a detectable level after stopping treatment). Analyses of studies using interferon-based treatment have shown that SVR is associated with lower all-cause mortality in patients with HCV infection and advanced hepatic fibrosis and in patients with HCV-HIV coinfection, including both liver-related and nonliver-related mortality.[44–47]

Sofosbuvir and simeprevir

Sofosbuvir (Sovaldi®) is a once-daily, film-coated tablet manufactured by Gilead Sciences. It was approved by the FDA on December 6, 2013. Sofosbuvir is currently indicated for the treatment of HCV genotypes 1 through 4 as a component of a combination antiviral treatment regimen.[48] It is a phosphoramidate prodrug and needs to be converted to its active metabolite (GS-461203) within hepatocytes.[49] The phosphoramidate moiety of the prodrug improves bioavailability and transport into hepatocytes. It can be taken with or without food.[50] As a uridine nucleotide analogue, GS-461203 binds to the NS5B catalytic site, induces chain termination, and increases the number of errors in the growing RNA chain.[49] It has activity against HCV genotypes 1 through 6 *in vitro*.[50] The pharmacokinetic properties of sofosbuvir are shown in Table 3. Because 80% of sofosbuvir is eliminated via urine, it is not recommended for patients with a glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or end-stage renal disease (ESRD). Increases of 5-fold or greater in the area under the curve (AUC) of active metabolite have been observed in these patients in a pharmacokinetic study.[51] Furthermore, patients with creatinine clearance < 60 mL/min were excluded in clinical trials. However, an ongoing study is evaluating lower doses of sofosbuvir (such as 100 mg once daily) in patients with severe renal impairment or ESRD (NCT01958281 and NCT02563665). Sofosbuvir is generally well tolerated as part of interferon-free combination therapies. However, post-marketing surveillance has revealed a risk of serious and potentially fatal bradycardia when sofosbuvir is taken with amiodarone.[52]

Simeprevir (Olysio®) is a second-wave, first-generation NS3/4A serine protease inhibitor manufactured by Janssen. It was approved by the FDA on November 22, 2013. Simeprevir is currently indicated for the treatment of HCV genotype 1 or 4 as part of a combination antiviral treatment regimen.[53] It reversibly inhibits NS3/4A serine protease inhibitor by noncovalently binding to the active site, which

Table 2. Efficacy of historic treatments for HCV genotype 1

Year	Trials	Regimen	SVR24	Relapse	Treatment
1991	HIT*[26]	IFN for 24 weeks	2%–3%	~80%	Naïve
1991	HIT*,[26] IHIT*[27]	IFN for 48 weeks	7%–11%	~46%	Naïve
1998	HIT*,[26] IHIT*[27]	IFN + RBV for 24 weeks	16%–18%	~42%	Naïve
1998	HIT*,[26] IHIT*[27]	IFN + RBV for 48 weeks	28%–31%	~24%	Naïve
2001	IHIT 2001*[28]	PegIFN + RBV for 48 weeks	42%	~18%	Naïve
2009	IDEAL[29]	PegIFN + RBV for 48 weeks	~40%	20–31%	Naïve

* Included genotypes 1 and other genotypes.

Abbreviations: IFN, interferon alpha; PegIFN, pegylated interferon alpha; RBV, ribavirin; SVR, sustained virologic response.

Table 3. Pharmacokinetics of NS5B polymerase inhibitors

Agent	Sofosbuvir[49,71]	Dasabuvir[76]	Beclabuvir[110]
Dosage	400 mg daily	250 mg twice a day with food	75 mg twice a day
Half-life	0.5 h (parent drug), 27 h (active metabolite)	5.5–6 h	8 h
Protein-binding	60%	> 99%	Unknown
Elimination	Urine (80%), feces (14%)	Feces (94%), urine (2%)	Feces, urine (< 10%)
Pregnancy	Category B	Category B	Unknown
Substrate	P-glycoprotein, BCRP	CYP 2C8, P-glycoprotein, BCRP	CYP 3A4
Inhibition	—	UGT 1A1	OATP 1B1, P-glycoprotein

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; UGT, uridine diphosphate glucuronosyltransferase; OATP, organic anion-transporting polypeptides.

interferes with cleavage of the HCV polyprotein and as a result prevents viral replication.[54] It has activity against HCV genotypes 1, 2, 4, 5, and 6, with no activity against genotype 3 *in vitro*.[55] The pharmacokinetic properties of simeprevir are shown in Table 4. It should be taken with food to improve absorption.[54] It is mainly metabolized by CYP 3A and excreted primarily in the feces with less than 1% excreted in the urine.[56] Maximum daily doses of 10 mg of rosuvastatin and 40 mg of atorvastatin are recommended if used concomitantly with simeprevir.[57] Common adverse effects of simeprevir in clinical trials were fatigue, headache, nausea, insomnia, pruritus, rash, and photosensitivity. The combination of simeprevir and sofosbuvir has been evaluated in phase 3 studies.

In OPTIMIST-1,[58] an open-label phase 3 trial in the United States and Canada, 310 patients without cirrhosis were randomized to receive either 8 or 12 weeks of simeprevir 150 mg once daily plus sofosbuvir 400 mg once daily. The study included both treatment-naïve and –experienced patients. Patients treated previously with a DAA containing regimen were excluded. Overall, SVR12 was achieved in 83% (128/155) of patients who received 8 weeks of treatment and 97% (150/155) of patients who received 12 weeks of treatment. There was no on-treatment failure. The relapse rate was significantly higher in the 8-week arm with 17% (27/155) compared to 3% (4/155) in the 12-week arm. There was no difference in SVR12 based on genotype 1 subtype, presence of the baseline Q80K resistance mutation, or whether patients were treatment-naïve or –experienced. A post-hoc analysis showed that an SVR12 rate of 96% is achieved with 8 weeks of treatment in patients with a baseline HCV RNA level less than 4 million IU/mL. The most frequent adverse events were nausea, headache, and fatigue. No patients discontinued treatment due to an adverse event.

In OPTIMIST-2,[59] a single arm, open-label phase 3 trial in the United States and Canada, 103 patients with compensated cirrhosis were assigned to receive 12 weeks of simeprevir 150 mg once daily plus sofosbuvir 400 mg once daily. The study included both treatment-naïve and –experienced patients. Overall, SVR12 was achieved in 83% (86/103) of patients, including 88% (44/50) of treatment-naïve and 79% (42/53) of treatment-experienced patients. In the absence of the Q80K mutation, which only occurs in genotype 1a, SVR12 rate was 84% (26/31) in patients with genotype 1a and 92% (35/38) in patients with genotype 1b. However, lower rates of

Table 4. Pharmacokinetics of NS3/4A protease inhibitors

Agent	Simeprevir[54,56]	Paritaprevir[76]	Asunaprevir[109]	Grazoprevir[96]
Dosage	150 mg daily with food	150 mg daily with food	200 mg twice a day	100 mg daily
Half-life	10–13 h (healthy adults), 41 h (HCV infected adults)	5.5 h	17–23 h	31 h
Protein-binding	> 99%	97%–99%	> 99%	99.8%
Elimination	Biliary excretion (91%), CYP 3A	Feces (88%), urine (9%)	Feces (84%), urine (< 1%)	Feces (> 90%), urine (1%)
Pregnancy risk	Category B	Category B	Unknown	Unknown
Substrate	CYP 3A	CYP 3A, P-glycoprotein, BCRP, OATP 1B	CYP 3A, P-glycoprotein, OATP 1B, OATP 2B	CYP 3A, P-glycoprotein, BCRP, OATP 1B
Inhibition	CYP 1A2, intestinal CYP 3A4, OATP 1B and P-glycoprotein	BCRP, P-glycoprotein, OATP 1B	CYP 2D6 (moderate), P-glycoprotein (weak), OATP 1B (weak)	Intestinal BCRP

Abbreviations: BCRP, breast cancer resistance protein; OATP, organic anion-transporting polypeptides.

SVR12 were achieved in the presence of the Q80K mutation (74% (25/34) in patients with genotype 1a). There was no difference in SVR12 based on genotype 1 subtype. However, IL28B TT genotype was associated with lower rates of SVR12. On-treatment failure occurred in 3% (3/103) of patients. One of these patients discontinued treatment due to an adverse event. The remaining two patients with viral breakthrough had multiple reports of missed doses. The relapse rate was 13% (13/103), mostly occurring at follow-up week 4. The most common adverse events were headache, fatigue, and nausea. Serious adverse events, none of which were considered related to study treatment, occurred in five patients, and three patients discontinued study treatment as a result.

Sofosbuvir has a high barrier to resistance. No resistant variants have been detected in clinical trials when used as part of a dual or triple therapy.[60,61] In the ELECTRON trial,[62] however, when sofosbuvir was used as monotherapy to treat HCV genotype 2 or 3, one patient developed S282T resistance mutation. This mutation has not been isolated in patients with HCV genotype 1. Simeprevir, on the other hand, seems to have a lower barrier to resistance. Although the presence of baseline Q80K polymorphism was originally associated with a decreased rate of SVR12 when simeprevir was used in combination with peginterferon and ribavirin,[63,64] it was not observed in the COSMOS phase 2 trial when simeprevir was used with sofosbuvir.[65] Nonetheless, Q80K polymorphism seemed to result in decreased SVR12 in OPTIMIST-2.[59] Therefore, screening for Q80K polymorphism is recommended at baseline when using this combination in patients with HCV genotype 1a. It is not clear if extending treatment to 24 weeks will increase efficacy in cirrhotic patients with HCV genotype 1a in the presence of the Q80K mutation. Thus, it may be reasonable to avoid this combination in patients with the Q80K mutation. Although data are lacking, cross-resistance across the HCV protease inhibitor class is a concern. Hence, simeprevir-containing combinations should be avoided in patients who have failed other first-generation HCV protease inhibitors, such as boceprevir and telaprevir.[66]

Sofosbuvir and ledipasvir

Sofosbuvir-ledipasvir (Harvoni™) is a once daily, fixed-dose, film-coated, one-pill combination manufactured by Gilead Sciences. It was approved by the FDA on October 10, 2014. It is currently indicated for the treatment of HCV genotype 1, 4, 5, or 6.[67] Ledipasvir is a first-generation NS5A inhibitor with a dual mechanism of action and is only available in combination with sofosbuvir. It binds to domain 1 of the NS5A protein and blocks its ability to regulate HCV replication within the replication complex, and it inhibits assembly and release of viral particles.[68] It has activity against HCV genotype 1, 4, and 5, with limited activity against genotype 2 and 3 *in vitro*.[69] The pharmacokinetic properties of ledipasvir are shown in Table 5. It can be taken with or without food.[67] However, the absorption of ledipasvir is pH-dependent, and administration of antacids within 4 h should be avoided.[70] While both sofosbuvir and ledipasvir are P-glycoprotein substrates, neither of them is a CYP substrate, resulting in minimal drug interactions. Ledipasvir is also an inhibitor of P-glycoprotein.[71] Common adverse effects of sofosbuvir-ledipasvir in clinical trials were fatigue and headache, and less commonly nausea, diarrhea, and insomnia.[38–40] Bilirubin and lipase elevations were also observed. This combination has been evaluated in several phase 3 studies.

In ION-1,[38] an open-label, phase 3 trial in the United States and Europe, 865 treatment-naïve patients with HCV genotype 1 were randomized to one of the four groups to take sofosbuvir-ledipasvir 400 mg–90 mg by mouth once daily with or without ribavirin for either 12 weeks or 24 weeks. A minimum creatinine clearance of 60 mL/min was required. SVR12 was achieved in 99% (211/214) of patients who received sofosbuvir-ledipasvir without ribavirin for 12 weeks. Furthermore, SVR12 was achieved in 97% of patients with cirrhosis, which constituted 16% of the patients in the study. Only two patients in the study had relapse, and they both had cirrhosis. There was no relapse in groups that received ribavirin. Overall, 10 patients discontinued treatment prematurely owing to adverse events (four received sofosbuvir-ledipasvir for 24 weeks and six received sofosbuvir-ledipasvir plus ribavirin for 24 weeks), and all 10 patients achieved SVR. All 10 patients received at least 8 weeks of therapy before discontinuation. No patient in the groups receiving 12 weeks of treatment discontinued therapy prematurely. Of the 33 patients who had a serious adverse event, only eight were in the 12-week groups, one who received sofosbuvir-ledipasvir and seven who received sofosbuvir-ledipasvir plus ribavirin. The most common adverse events were fatigue, headache, insomnia, and nausea. Groups that received ribavirin had higher rates of events associated with ribavirin therapy: fatigue, insomnia, asthenia, rash, cough, pruritus, and anemia. Laboratory abnormalities included changes in hemoglobin level (~−2 g/dL) and hyperbilirubinemia, both of which are associated with ribavirin therapy.

Table 5. Pharmacokinetics of first-generation NS5A inhibitors

Agent	Ledipasvir[71]	Ombitasvir[76]	Daclatasvir[92]
Dosage	90 mg daily	25 mg daily with food	60 mg daily*
Half-life	47 h	21–25 h	12–15 h
Protein-binding	99.8%	99.9%	99.0%
Elimination	Feces (86%), urine (1%)	Feces (90%), urine (2%)	Feces (88%), urine (7%)
Pregnancy	Category B	Category B	Unknown
Substrate	P-glycoprotein, BCRP	P-glycoprotein	CYP 3A, P-glycoprotein
Inhibition	P-glycoprotein, BCRP	—	P-glycoprotein, OATP 1B, BCRP

* 30 mg daily with 3A inhibitors, 90 mg daily with 3A inducers.

Abbreviations: BCRP, breast cancer resistance protein; OATP, organic anion transporter peptide.

Similarly, ION-2 was an open-label, phase 3 trial in the United States that randomized 440 treatment-experienced patients with HCV genotype 1 to one of four groups.[39] The patients were previously treated with peginterferon and ribavirin, 53% of which had received the treatment with a first-generation protease inhibitor, mostly telaprevir or boceprevir. Nonresponders made up 44% of the patients, and the remainder had either relapse or virologic breakthrough on their previous therapy. About 20% of the study patients had cirrhosis. A minimum creatinine clearance of 60 mL/min was required. While SVR12 was achieved in 94% (102/109) of all patients who received 12 weeks of treatment with sofosbuvir-ledipasvir without ribavirin, only 86% of patients with cirrhosis achieved SVR12 in this group. Adding ribavirin to the regimen did not improve outcomes in cirrhotic patients. However, this outcome was improved to 100% with 24 weeks of treatment. The rate of relapse was 6% with 12 weeks of treatment, but relapse was reduced to 0% with 24 weeks of treatment. Overall, 11 patients had a relapse, 10 of which occurred within 4 weeks after the end of treatment. No patient had a relapse after 12 weeks post-treatment. None of the patients discontinued treatment prematurely due to adverse events. Patients in the groups that received ribavirin had higher rates of adverse events associated with ribavirin therapy: fatigue, nausea, insomnia, arthralgia, cough, rash, irritability, dyspnea, and anemia. The rates of laboratory abnormalities were similar in all groups with the exception of hyperbilirubinemia, which developed in more patients who received sofosbuvir-ledipasvir plus ribavirin than in those who received only sofosbuvir-ledipasvir. Changes in hemoglobin level (~−2.5 g/dL) were associated with ribavirin therapy, as the groups that did not receive ribavirin only experienced non-significant changes in hemoglobin level (~−0.5 g/dL).

ION-3 was an open-label, phase 3 trial in the United States that randomized 647 treatment-naïve noncirrhotic patients infected with HCV genotype 1 to one of the three groups to take sofosbuvir-ledipasvir 400 mg-90 mg by mouth once daily with or without ribavirin for 8 weeks or without ribavirin for 12 weeks.[40] A minimum creatinine clearance of 60 mL/min was required. SVR12 rate was 94% (202/215) in patients who received treatment without ribavirin for 8 weeks. However, 11 patients (5%) in this group had a relapse, 10 of whom were infected with HCV genotype 1a. Data submitted to the FDA showed that nine out of 11 patients with relapse in this group had a viral load of ≥ 6,000,000 IU/mL at baseline. In the group that also received ribavirin, nine patients (4%) had a relapse, seven of whom were infected with HCV genotype 1a. As a result, the FDA has approved the 8 week regimen only for treatment-naïve noncirrhotic patients who have a baseline viral load < 6,000,000 IU/mL. Three patients discontinued treatment prematurely due to adverse events, including one patient in the group receiving 8 weeks of treatment with sofosbuvir-ledipasvir plus ribavirin reported to have a road accident. No single serious adverse event occurred in more than one patient. The most common adverse events were fatigue, headache, and nausea. Patients who received ribavirin experienced greater changes in hemoglobin level (~−1.9 g/dL) than those who did not receive ribavirin (~−0.2 g/dL). Only three patients who received 8 weeks of sofosbuvir-ledipasvir with ribavirin had hyperbilirubinemia. Otherwise, the rates of laboratory abnormalities were similar among groups.

ION-4 was a single-group, open-label, phase 3 trial in the United States, Puerto Rico, Canada, and New Zealand, involving 335 patients co-infected with HIV-1 and HCV genotype 1 or 4.[72] All patients were required to receive a protocol-approved antiretroviral regimen for HIV-1 (emtricitabine/tenofovir disoproxil fumarate plus efavirenze, raltegravir, or rilpivirine) for at least 8 weeks prior to the screening for the study and to have evidence of HIV-1 viral suppression (HIV-1 RNA < 50 copies/mL) with a CD4+ count >100 cells/mcL. A minimum creatinine clearance of 60 mL/min was required. Patients received sofosbuvir-ledipasvir 400 mg–90 mg by mouth once daily for 12 weeks. Only eight patients (2%) were infected with HCV genotype 4. Overall, 20% of patients had cirrhosis, 45% were treatment-naïve, and 55% were treatment-experienced (of whom 36% had failed previous DAAs). SVR12 was achieved in 96% (322/335) of patients. This rate was 94% among patients with cirrhosis and 97% among treatment-experienced patients. All 13 patients who had relapsed previous treatment with sofosbuvir and ribavirin had SVR. One patient died after 4 weeks of treatment. Two patients had a virologic breakthrough during treatment that was suspected to be due to poor adherence. Ten patients had a relapse, all of whom were black with seven patients having the TT allele in the *IL28B* gene. Exploratory univariate analysis identified black race and the presence of the TT allele to be associated significantly with relapse. None of the patients discontinued treatment prematurely because of an adverse event. Most adverse events were mild to moderate, most commonly headache, fatigue, diarrhea, and nausea. Rare grades 3 and 4 serum laboratory abnormalities were reported, including elevations in lipase, creatine kinase, and serum glucose. No significant drug interactions were identified in this study.

Unlike sofosbuvir, ledipasvir has a low barrier to resistance. NS5B resistance-associated variant (RAV) S285T was not detected in ION-1, ION-2, ION-3, or ION-4.[38–40,72] One patient with relapse in ION-4 had NS5B RAV L159F, but this patient also had NS5A RAVs. Among treatment-experienced patients in ION-4, three patients had the L159F variant at baseline, but all achieved SVR12. Both patients with relapse in ION-1 had NS5A-resistant variants at baseline (L31M in genotype 1a and Y93H in genotype 1b).[38] Of the 11 patients who had a relapse in ION-2, seven patients received 12 weeks of treatment without ribavirin.[39] NS5A-resistant variants were present at baseline in four of these patients. The remaining four patients with a relapse received 12 weeks of treatment with ribavirin. NS5A-resistant variants were present at baseline in two of these patients. Nevertheless, all 11 patients who had a relapse had NS5A-resistant variants at the time of the relapse. Of the 23 patients who had a relapse in ION-3, 15 patients had NS5A resistant variants at the time of relapse, nine of whom had the variants at baseline.[40] Of the 10 patients who had a relapse in ION-4, four patients had NS5A resistant variants at baseline and eight patients had them at the time of relapse. The two patients who had a virologic breakthrough, possibly due to poor adherence, did not have resistance-associated NS5A variants at baseline but did have such emergent variants at the time of failure.

Ombitasvir-paritaprevir-ritonavir and dasabuvir

Ombitasvir-paritaprevir-ritonavir and dasabuvir, copackaged as Viekira Pak™ by Abbvie, are together known as the "3D" combination since three DAAs are included. The combination was approved by the FDA on December 19, 2014. It is currently indicated for the treatment of HCV genotype 1, including

patients with compensated cirrhosis.[73] Ombitasvir-paritaprevir-ritonavir is a coformulated fixed-dose tablet (12.5 mg/75 mg/50 mg), and dasabuvir is a separate tablet (250 mg).[74] Ombitasvir is a first-generation NS5A inhibitor with pangenotypic antiviral activity.[75] The pharmacokinetic properties of ombitasvir are shown in Table 5. It is a P-glycoprotein substrate, and it is eliminated primarily through the feces with only 2% eliminated through the urine.[76] Paritaprevir is a NS3/4A serine protease inhibitor. The pharmacokinetic properties of paritaprevir are shown in Table 4. It is a substrate of P-glycoprotein as well as CYP 3A, and it is an inhibitor of P-glycoprotein.[76] It is primarily eliminated through the feces with only 9% eliminated through the urine. Ritonavir, which does not have activity against HCV, is a potent inhibitor of CYP 3A4 enzyme and is used as a pharmacokinetic booster to increase paritaprevir plasma levels.[77] Dasabuvir is a non-nucleoside NS5B inhibitor. The pharmacokinetic properties of dasabuvir are shown in Table 3. It is a substrate of P-glycoprotein and CYP 2C8, and it is primarily eliminated through the feces.[76] Since the half-life of dasabuvir is only about 6 h, it must be taken twice a day. The 3D combination should always be taken with a meal since food increases the absorption of the included agents.[78] In patients with mild, moderate, or severe renal insufficiency, no dosing adjustment is required; although this regimen has not been adequately studied in patients with renal dysfunction since patients with a creatinine clearance < 60 mL/min were excluded from most studies. RUBY-I study is an ongoing trial investigating the safety and efficacy of this regimen in patients with severe renal impairment or ESRD.[79] It is contraindicated in patients with hepatic decompensation (Child-Pugh B and C), patients receiving medications highly dependent on CYP 3A metabolism for which significant increases in plasma levels is dangerous, patients on moderate or strong inducers of CYP 3A or strong inducers of CYP 2C8, patients on strong inhibitors of CYP 2C8 (since this may result in increased levels of dasabuvir and QT prolongation), or known hypersensitivity to ritonavir.[80] This combination was well tolerated in clinical trials. The most common (greater than 10%) adverse effects have been fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. Its concomitant use with ethinyl estradiol-containing medications can lead to significant elevations in hepatic aminotransferase levels.[81]

The addition of ribavirin to the 3D combination is recommended for all patients except those with HCV genotype 1b without cirrhosis.[73] Ribavirin can cause significant adverse effects, including hemolytic anemia. It is also highly teratogenic and embryocidal, and extreme care must be given to avoid pregnancy during therapy and for 6 months after finishing the treatment; this pertains both to treatment of women receiving ribavirin and women whose male partners are receiving ribavirin therapy.[82] Treatment with ribavirin is contraindicated in pregnant women and men whose female partners are pregnant, hemoglobinopathies, and co-administration with didanosine. Furthermore, ribavirin must be dosed carefully based on body weight, changes in hemoglobin, and renal function.[82]

In PEARL-II,[83] a multicenter, open-label phase 3 trial in Europe and the United States, 179 patients with HCV genotype 1b, without cirrhosis, who had previously received and failed treatment with peginterferon and ribavirin were randomized to receive 3D combination either with ribavirin (group 1) or without ribavirin (group 2) for 12 weeks. Ribavirin was dosed based on body weight twice daily: 1,000 mg daily if body weight < 75 kg or 1,200 mg daily if body weight ≥ 75 kg. Patients with a creatinine clearance < 60 mL/min were excluded. SVR12 rate for group 1 was 97% (85/88) and 100% (91/91) for group 2. No patients from either group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients who did not achieve SVR12, two patients discontinued the study drug due to an adverse event, and one patient was lost to follow-up after 4 weeks. The most commonly reported adverse events were fatigue, headache, and nausea, which occurred significantly more frequently in group 1 than in group 2. Patients in group 1 also experienced significantly more events of insomnia, anemia, rash, and increased blood bilirubin levels, which are known to be associated with ribavirin treatment.

In PEARL-III,[84] a multicenter, double-blind, placebo-controlled phase 3 trial in Europe, Russia, and the United States, 419 treatment-naïve patients with HCV genotype 1b without cirrhosis were randomized in a 1:1 ratio to receive either ribavirin twice daily according to body weight or matching placebo for 12 weeks. All patients received open-label 3D combination for 12 weeks. Notably, patients with a creatinine clearance < 60 mL/min were excluded. SVR was 99.5% (209/210) in the ribavirin group and 99% (207/209) in patients who did not receive ribavirin. Only one patient in the study, who was in the group receiving ribavirin, had virologic failure during treatment. The two patients in the group not receiving ribavirin who did not achieve SVR12 were lost to follow-up at week 12. The most common adverse events were headache and fatigue. Adverse events were more frequently reported in the group receiving antiviral regimens that contained ribavirin.

Similar to PEARL-III, PEARL-IV was a multicenter, double-blind, placebo-controlled phase 3 trial in Canada, the United States, and the United Kingdom.[84] Instead of patients with HCV genotype 1b, it randomized 305 treatment-naïve patients with HCV genotype 1a without cirrhosis in a 1:2 ratio to receive either ribavirin twice daily according to body weight or matching placebo for 12 weeks. All patients received open-label 3D combination for 12 weeks. Again, patients with a creatinine clearance < 60 mL/min were excluded. The SVR rate was 97% (97/100) in the ribavirin group and 90% (185/205) in patients who did not receive ribavirin. Logistic-regression analysis showed that *IL28B* CC genotype was associated with an increased rate of SVR12. The most common adverse events were headache and fatigue. Adverse events were more frequently reported in the group receiving antiviral regimens that contained ribavirin.

SAPPHIRE-I was a multicenter, double-blind, placebo-controlled phase 3 trial in North America, Europe, and Australia.[85] It randomized 631 treatment-naïve patients with HCV genotype 1, no cirrhosis, and a plasma HCV RNA level of at least 10,000 IU/mL in a 3:1 ratio to receive a 12-week treatment course with 3D regimen plus ribavirin (group A) or a matching placebo regimen (group B). Patients in group B were eligible to receive treatment at the end of study. Patients with a creatinine clearance < 60 mL/min were excluded. About 68% of the patients had HCV genotype 1a, and 31% had IL28B CC genotype. The overall SVR12 rate was 96.2% (455/473) in group A, including 95.3% (307/322) among patients with HCV genotype 1a and 98% (148/151) among patients with HCV genotype 1b. The rates were similarly high in all subgroups. Furthermore, logistic-regression analysis showed that patient characteristics, including *IL28B* genotype, did not significantly affect the rate of SVR12. The most common

adverse events were fatigue and headache; the frequency of which did not differ significantly between the two study groups.

Similar to SAPPHIRE-I, SAPPHIRE-II was a multicenter, double-blind, placebo-controlled phase 3 trial in North America, Europe, and Australia.[86] Instead of treatment-naïve patients, it randomized 394 patients with HCV genotype 1, without cirrhosis, a plasma HCV RNA level of at least 10,000 IU/mL who had previously failed treatment with peginterferon and ribavirin in a 3:1 ratio to receive a 12-week treatment course with 3D regimen plus ribavirin (group A) or a matching placebo regimen (group B). Patients in group B were eligible to receive treatment at the end of study. Patients that had received a HCV protease inhibitor, and those with a creatinine clearance < 60 mL/min were excluded. About 58% of the patients had HCV genotype 1a and 11% had IL28B CC genotype. The overall SVR12 rate was 96% (286/297) in group A, including 96% (166/173) among patients with HCV genotype 1a and 97% (119/123) among patients with HCV genotype 1b. The rates were similarly high in all subgroups, including *IL28B* genotype, prior relapsers, prior partial responders, and prior null responders. The investigators reported adverse events in 91.2% of patients in the active-regimen group and 82.5% of patients in the placebo group; severe adverse events occurred in 2% of patients in the active treatment group and in 1% of the patients in the placebo group. The two most common adverse events were headache and fatigue. Pruritus was the only adverse events that occurred in more than 10% of patients in either group that had a higher frequency in the active-regimen group than the placebo group.

In TURQUOISE-II,[87] a multicenter, open-label, phase 3 controlled trial, 380 patients with HCV genotype 1, a plasma HCV RNA level of at least 10,000 IU/mL, and compensated cirrhosis (Child-Pugh class A) were randomized to receive either 12 (group A) or 24 weeks (group B) of treatment with 3D regimen plus ribavirin. Patients with prior therapy with DAAs (e.g., telaprevir and boceprevir) and those with creatinine clearance < 60 mL/min were excluded. About 69% of patients had HCV genotype 1a, 58% were treatment-experienced, and 42% were treatment-naïve. For group A, the overall SVR12 rates were 92% (191/208), 89% (124/140) among all patients with HCV genotype 1a, 92% (59/64) among treatment-naïve patients with HCV genotype 1a, and 86% (65/76) among treatment-experienced patients with HCV genotype 1a. For group B, the overall SVR12 rates were 96% (165/172), 94% (114/121) among all patients with HCV genotype 1a, 93% (52/56) among treatment-naïve patients with HCV genotype 1a, and 95% (62/65) among treatment-experienced patients with HCV genotype 1a. For patients with HCV genotype 1b, SVR12 rates were 99% (67/68) in group A and 100% (51/51) in group B. No specific adverse event led to premature discontinuation by more than one patient, and no pattern in the types of adverse events leading to discontinuation was observed.

The CORAL-I Study,[88] which was a single-arm, phase 2 trial, enrolled 34 liver transplant recipients (at least 12 months prior to screening) with recurrent HCV genotype 1 and a plasma HCV RNA level of at least 10,000 IU/mL to receive 3D regimen plus ribavirin for 24 weeks. Patients had no evidence of cirrhosis, and those with a creatinine clearance < 55 mL/min were excluded. About 85% of the patients had HCV genotype 1a, 24% had IL28B CC genotype, and 71% were previously treated with peginterferon and ribavirin. The median time since liver transplantation was 3.3 years, and 85% of patients were receiving a tacrolimus-based immunosuppressive regimen. The overall SVR12 rate was 97% (33/34), including 97% (28/29) among patients with HCV genotype 1a and 100% (5/5) among patients with HCV genotype 1b. The most common adverse events were fatigue, headache, and cough. Only one patient discontinued treatment, which was due to rash, memory impairment, and anxiety.

The 3D regimen has a low barrier to resistance. Due to a very low rate of virologic failure, resistance-associated variants were not observed in PEARL-II and PEARL-III.[83,84] In PEARL-IV,[84] two of the three patients who received ribavirin but did not achieve SVR12 had virologic failure. A total of 18 patients had virologic failure, 16 of whom were not receiving ribavirin. Of these 16 patients, six had a virologic rebound while on treatment, and 10 had a relapse after treatment. All 18 patients who had virologic failure had at least one resistance-associated variant. The most frequently detected variants were D168V in NS3, M28T and Q30R in NS5A, and S556G in NS5B. In SAPPHIRE-I,[85] one patient had virologic failure while on treatment, and seven patients had a relapse. Each of these patients had at least one resistance-associated variant, most frequently D168V in NS3, M28T and Q30R in NS5A, and S556G in NS5B for HCV genotype 1a and Y56H and D168V in NS3, L31M and Y93H in NS5A, and S556G in NS5B for HCV genotype 1b. In SAPPHIRE-II,[86] seven patients had a relapse, all of whom were adherent to treatment. Five of these patients had resistance-associated variants at the time of relapse, most frequently D168V in NS3, M28V and Q30R in NS5A, and S556G in NS5B for HCV genotype 1a and Y56H and D168A in NS3, Y93H in NS5A, and C316N and S556G in NS5B for HCV genotype 1b. In TURQUOISE-II,[87] virologic failure occurred in 13 patients receiving 12 weeks of treatment (group A), with one patient failing while on treatment, the remaining 12 relapsing, and four patients receiving 24 weeks of treatment (group B). Seven of the 12 patients with a relapse in group A had HCV genotype 1a and a prior null response. Only two of the 17 patients who had virologic failure did not have resistance-associated variants at the time of virologic failure. The remaining 15 patients had resistance-associated variants in two or more of the drug targets, most commonly D168V in NS3 and Q30R in NS5A for HCV genotype 1a and D168V in NS3, Y93H in NS5A, and G316Y and M414I in NS5B for HCV genotype 1b. In CORAL-I study,[88] the only patient who had a relapse (on day 3 of treatment) had resistance-associated variants R155K in NS3, M28T and Q30R in NS5A, and G554S in NS5B at the time of relapse but not at baseline.

Sofosbuvir and daclatasvir

Daclatasvir (Daklinza™) is a once-daily, oral tablet manufactured by Bristol-Myers Squibb. It is available as 30 mg or 60 mg tablets. It was approved by the FDA on July 24, 2015. Daclatasvir is currently indicated for the treatment of HCV genotypes 1 and 3 in combination with sofosbuvir.[89] It is a first-generation HCV NS5A inhibitor, which prevents the replication of RNA and assembly of the virion by inhibiting conformational change of NS5A protein through impairing phosphatidylinositol-4-kinase III α activation.[90] It has activity against HCV genotypes 1 through 6 *in vitro*.[91] The pharmacokinetic properties of daclatasvir are shown in Table 5. It can be taken with or without food. While co-administration with proton pump inhibitors results in decreased daclatasvir exposure, the interaction is not clinically significant.[92] Although high-fat meals reduce its absorption, no dosage adjustments

are recommended.[92] This effect is not observed with low-fat, low-caloric meals (approximately 277 total kcal).[89] Daclatasvir is a substrate of CYP 3A. Therefore, a dose reduction to 30 mg of daclatasvir is needed when used in combination with a strong CYP 3A inhibitor, such as ketoconazole, atazanavir, ritonavir, or cobicistat. No dosage adjustments are needed when used in combination with moderate CYP 3A inhibitors. The use of daclatasvir in combination with strong CYP 3A inducers is contraindicated. A dose increase to 90 mg of daclatasvir is needed when used in combination with a moderate CYP 3A inducer, such as dexamethasone, efavirenz, or nevirapine.[92] About 88% of the drug is eliminated in feces, and 7% is excreted in the urine. Therefore, renal adjustment of daclatasvir dosage is unnecessary. Daclatasvir is highly protein bound and is unlikely to be removed by dialysis. When used in combination with sofosbuvir, daclatasvir is generally well tolerated. The most common adverse effects are headache, fatigue, and nausea. Daclatasvir, in combination with sofosbuvir, has been evaluated for treatment of HCV genotype 1 in phase 3 trials.

In ALLY-2,[93] an open-label, multi-center phase 3 trial in the United States, 203 patients co-infected with HIV-1 and HCV genotypes 1 through 4 were randomly assigned to one of the three arms. The study included both HCV treatment-naïve and –experienced patients. Patients who were HCV treatment-naïve were assigned in a 2:1 ratio to receive either 12 weeks or 8 weeks of daclatasvir 60 mg once daily, with dose adjustment for concomitant medications, plus sofosbuvir 400 mg once daily. Patients previously treated for HCV were assigned to receive 12 weeks of treatment at the same doses. The standard 60 mg dose of daclatasvir was adjusted to 30 mg in patients receiving ritonavir-boosted protease inhibitors and to 90 mg in those receiving efavirenz or nevirapine. Patients with creatinine clearance less than 50 mL/min were excluded. About 83% of the patients had HCV genotype 1, and 29 patients (14%) had compensated cirrhosis. Among previously treated patients, 94% had received an interferon-containing regimen, and 22% had received a HCV protease inhibitor. The rate of SVR12 was 96.4% in treatment-naïve patients with HCV genotype 1 who received 12 weeks of treatment, 75.6% with 8 weeks of treatment, and 97.7% in treatment-experienced patients who received 12 weeks of treatment. There was no difference in the rate of SVR12 based on any subgroups except for baseline viral load in the 8-week treatment group. Patients with baseline viral load < 2 million IU/mL had SVR12 rate of 100% (18/18) compared to 62% (20/32) in patients with baseline viral load ≥ 2 million IU/mL. Although a small number of patients had cirrhosis, there was similar rate of SVR12 (92%) among these patients. The combination of daclatasvir and sofosbuvir was well tolerated. None of the patients discontinued treatment due to an adverse event. The most common adverse events were fatigue, nausea, and headache. Two patients died during post-treatment follow-up.

ALLY-1 was an open-label, phase 3 trial that enrolled 113 patients infected with HCV (any genotype) who either had advanced cirrhosis or had recurrence of HCV infection post-liver transplant.[94] Both treatment-naïve and –experienced patients were included. The study consisted of 60 patients with advanced cirrhosis and 53 patients post-liver transplant. All patients received 12 weeks of daclatasvir 60 mg once daily plus sofosbuvir 400 mg once daily plus ribavirin initially 600 mg per day, adjusted to 1,000 mg per day based on hemoglobin levels and renal function. Overall, 83% (50/60) of patients with advanced cirrhosis and 95% (39/41) of patients post-transplant achieved SVR12. In patients with HCV genotype 1, SVR12 rate was 82% (37/45) in patients with advanced cirrhosis and 95% (39/41) in patients post-transplant. There was no difference based on gender, age, IL28B, or HCV RNA level in the advanced cirrhosis cohort with HCV genotype 1. Overall, the combination was tolerated well. Only one patient in each arm discontinued treatment due to adverse effects. Most common adverse effects included headache, fatigue, anemia, diarrhea, nausea, and arthralgia.

Unlike sofosbuvir, daclatasvir has a low barrier to resistance. While monotherapy with daclatasvir selects for resistant variants in both genotype 1a and 1b, most of these variants are susceptible to NS3 protease inhibitors and NS5B polymerase inhibitors, so daclatasvir as part of a combination therapy remains effective.[95] In ALLY-2,[93] none of the patients in the study had a HCV virologic breakthrough. Overall, 12 patients had a relapse, 10 of whom were in the 8-week treatment arm, and nine patients had HCV genotype 1a. Baseline NS5A resistance-associated polymorphisms did not seem to affect significantly response. Only three of the 12 patients with relapse had daclatasvir-resistance polymorphism at baseline. In ALLY-1,[94] nine patients had a relapse in the advanced cirrhosis group, whereas only three patients had a relapse in the post-transplant group. One patient with advanced cirrhosis had a breakthrough. All 13 patients who had virologic failure had NS5A resistance variants present at the time of failure. Only four of these patients had these variants at baseline. No NS5B-S282 variants were detected at baseline or failure.

Elbasvir and grazoprevir

Elbasvir-grazoprevir (Zepatier™) is a once daily, fixed-dose, film-coated one-pill combination manufactured by Merck & Co. It was approved by the FDA on January 29, 2016 for the treatment of HCV genotypes 1 and 4.[96] Grazoprevir is a second-generation NS3/4A protease inhibitor, which has shown high potency against HCV genotypes 1, 2, 4, 5, and 6, with less potency against genotype 3.[97] It also has activity against variants that are resistant to earlier first-generation NS3/4A protease inhibitors.[98] The pharmacokinetic properties of grazoprevir are shown in Table 4. Less than 1% of grazoprevir is renally excreted; and, hence, dose adjustments in the setting of chronic kidney disease is not necessary.[99] It is a substrate of CYP 3A, P-glycoprotein, and the organic anion transporter protein 1B and an inhibitor of intestinal breast cancer resistance protein.[100] Thus, co-administration with strong CYP 3A inducers or efavirenz is contraindicated.[96] Elbasvir is a second-generation NS5A inhibitor. It has activity against genotype 1, 2a, 3, 4, 5, and 6, including variants that are resistant to first-generation NS5A inhibitors, such as daclatasvir and ledipasvir.[101,102] However, testing for the presence of NS5A resistance-associated polymorphisms is recommended prior to the initiation of treatment in patients with HCV genotype 1a.[96] The pharmacokinetic properties of elbasvir are shown in Table 6. Elbasvir is a substrate of CYP 3A and P-glycoprotein. No clinically meaningful pharmacokinetic interactions between elbasvir-grazoprevir with tacrolimus, mycophenolate mofetil, and prednisone have been identified, but cyclosporine seems to increase exposure to elbasvir-grazoprevir.[103] Co-administration with famotidine or pantoprazole does not affect the pharmacokinetics of elbasvir-grazoprevir.[104] There are no drug interactions between elbasvir-grazoprevir

Table 6. Pharmacokinetics of second-generation NS5A inhibitors

Agent	Elbasvir[96]	Velpatasvir[96,120]
Dosage	50 mg once daily	100 mg once daily
Half-life	24 h	16–19 h
Protein-binding	99.9%	Unknown
Elimination	Feces (> 90%), urine (1%)	Feces (99%), urine (1%)
Pregnancy risk	Unknown	Unknown
Substrate	CYP 3A, P-glycoprotein	P-glycoprotein
Inhibition	—	Intestinal BCRP, P-glycoprotein

Abbreviation: BCRP, breast cancer resistance protein.

and either tenofovir or raltegravir.[105] However, boosted HIV-1 protease inhibitors are not recommended for use in combination with elbasvir-grazoprevir due to potential drug-drug interactions. The combination elbasvir-grazoprevir has been evaluated in phase 3 trials.

C-EDGE Treatment-Naïve was an international, single-blind, phase 3 trial that randomized 421 adult patients infected with HCV genotypes 1, 4, and 6 in a 3:1 ratio to receive treatment with a fixed-dose combination tablet of grazoprevir 100 mg/elbasvir 50 mg or a matching placebo once daily, without regards to food, for 12 weeks.[106] The study was conducted in Australia, the Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and the United States. About 91% of the patients had HCV genotype 1, of which 50% were genotype 1a, and 22% of patients had cirrhosis. The majority of the patients from Australia, Sweden, and the United States had HCV genotype 1a. Patients with creatinine clearance less than 50 mL/min were excluded. SVR12 was achieved in 92% of the patients with HCV genotype 1a and 99% of patients with genotype 1b. Furthermore, SVR12 was achieved in 97% of cirrhotic patients and 94% of non-cirrhotic patients. One patient with HCV genotype 1a had a breakthrough. A relapse occurred in nine patients with HCV genotype 1a and one patient with genotype 1b. Elbasvir-grazoprevir was well-tolerated with a similar safety profile between the active and placebo groups. Serious adverse events were reported in about 2.8% of patients in both groups, none of which was considered drug related. Although two patients in the treatment group died, neither death was considered drug related. The most common adverse events were headache (17%), fatigue (15%), and nausea (9%), which were similar in frequency in both groups. Three patients discontinued treatment, two patients with elevated aminotransferase levels and one patient with palpitations and anxiety on day 4 of treatment. One patient in the placebo group discontinued placebo pills because of a rash on day 2. Two patients discontinued treatment due to elevations in aminotransferase level.

C-SURFER was a double-blind, phase 3 trial consisting of a randomized study of safety and an observational study of efficacy in the United States, Argentina, Australia, Canada, Estonia, France, Israel, South Korea, Lithuania, the Netherlands, Spain, and Sweden.[106] The study randomized 224 HCV genotype 1 infected adult patients with chronic kidney disease stage 4–5, of whom 76% were hemodialysis dependent, to receive either grazoprevir 100 mg/elbasvir 50 mg once daily or placebo for 12 weeks. Patients receiving placebo were given active treatment for 4 weeks after the end of the treatment period (week 16). About 80% of the patients were HCV treatment-naïve, and the remaining 20% had previously received an interferon regimen. Only 6% of the patients had cirrhosis. Six of 122 patients in the treatment group were excluded from the modified full analysis for reasons other than virological failure. SVR12 rate was 99.1% (115/116). The frequencies of adverse events were similar between the two groups; most commonly headache, nausea, and fatigue. There were no drug-related serious adverse events. Two cases of congestive heart failure occurred in the treatment group within 14 days of the end of treatment, one of which was judged to be drug-related. There were no treatment discontinuations due to an adverse event in the treatment group. One patient in the treatment group died from cardiac arrest, but it was not considered related to study drugs. Although first-generation HCV protease inhibitors have been shown to cause a reversible decline in renal function,[107] no differences in renal function were noted between the groups in this study.

C-EDGE CO-INFECTION was an open-label, single-arm, multicenter, phase 3 trial in Europe, the United States, and Australia.[108] The study enrolled 218 treatment-naïve adult patients co-infected with HCV and HIV-1 to receive grazoprevir 100 mg/elbasvir 50 mg fixed-dose combination tablet once daily for 12 weeks without food restriction. About 86% of the patients were infected with HCV genotype 1, 13% with genotype 4, and the remaining 2 patients (1%) with genotype 6. With the exception of seven patients, most patients received anti-retroviral therapy (ART) with undetectable HIV RNA. ART-naïve patients had to have CD3 or CD4 T-cell counts of at least 500 cells/mcL and HIV RNA viral load of less than 50,000 copies/mL to be included. Otherwise, patients had to have CD3 or CD4 T-cell counts of at least 200 cells/mcL and undetectable HIV RNA levels. Patients with decompensated liver disease, cirrhosis who were Child-Pugh class B or C, and hepatitis B virus co-infection were excluded. SVR12 was achieved in 96.3% of patients infected with HCV genotype 1 and in all 35 patients with cirrhosis. The treatment was generally well tolerated. The most common adverse events were fatigue, headache and nausea. Six patients experienced serious adverse events, but they were not considered to be related to treatment. Two patients had a late increase in ALT/AST > 5x upper limit of normal (ULN) after treatment week 4, and this increase normalized without discontinuation of treatment. There was no notable change in CD3 or CD4 T-cell count at treatment week 12 or follow-up week 12.

Elbasvir-grazoprevir has a high barrier to resistance.[102] In C-EDGE Treatment-Naïve,[106] virologic analysis of the 10 patients with HCV genotype 1a who had virologic failure showed that NS3 RAVs were present in six patients (most commonly Q80K and D168A), and NS5A RAVs were present in all 10 patients (most commonly M28V/A/G, Q30H/L/R, L31M, and Y93H). However, an association of genotype 1a RAVs with virologic failure was present only in patients with baseline viral levels greater than 800,000 IU/mL. In C-SURFER,[106] only one patient relapsed. This noncirrhotic patient with diabetes had a baseline HCV genotype 1b viral load > 800,000 IU/mL and relapsed 12 weeks after the end of

treatment. Analysis showed that this patient had an NS5A L31M mutation at baseline. In C-EDGE CO-INFECTION,[108] four noncirrhotic patients with genotype 1a relapsed after having undetectable HCV RNA levels at the end of treatment. Two of these patients had D168A variant in the NS3 region, and three had Q30R/K variants in the NS5A region. In patients with HCV genotype 1, SVR12 was achieved in 87% of patients who had baseline NS5A resistance-associated variants compared to 98% in patients without resistance-associated variants. Baseline NS3 resistance-associated variants, as well as Q80K polymorphism in genotype 1a, did not seem to affect SVR12.

Daclatasvir, beclabuvir, and asunaprevir

Daclatasvir-asunaprevir-beclabusvir, or DCV-TRIO, is a fixed-dose, film-coated tablet under development by Bristol Myers Squibb. It contains three direct-acting agents: 30 mg daclatasvir, 200 mg asunaprevir, and 75 mg beclabuvir. Daclatasvir is currently FDA-approved for the treatment of HCV genotype 3 in combination with sofosbuvir.[89] Asunaprevir is a second-wave first-generation protease inhibitor that inhibits NS3 serine protease, ultimately preventing the cleavage of the HCV polypeptide into individual proteins.[109] The pharmacokinetic properties of asunaprevir are shown in Table 4. It has *in vitro* activity against HCV genotypes 1, 4, 5, and 6, with less potency against HCV genotypes 2 and 3.[109] Unlike NS5A inhibitors, NS3 protease inhibitors are more specific to genotype as the viral protease active site can vary according to genotype. In addition, asunaprevir has a low barrier to resistance, such that it should be used in combination with other DAA similar to daclatasvir. Beclabuvir is a non-nucleoside NS5B inhibitor and acts by binding allosterically to the NS5B RNA polymerase, ultimately inhibiting the elongation of the nascent viral RNA chain.[110] This process differs from nucleoside NS5B inhibitors that bind directly to the active site of the RNA polymerase. This difference in mechanism between the non-nucleoside and nucleoside NS5B inhibitors is what determines the degree of barrier to resistance. Nucleoside NS5B polymerase inhibitors have a high barrier to resistance since the RNA polymerase active site must maintain a particular amino acid sequence for viral replication, whereas non-nucleoside NS5B inhibitors like beclabuvir have a low barrier to resistance since they bind elsewhere to RNA polymerase. As such, beclabuvir is best used in combination with other DAAs.[111] The pharmacokinetic properties of beclabuvir are shown in Table 3. Beclabuvir has *in vitro* activity against HCV genotypes 1, 3a, 4a, and 6, with reduced potency against HCV genotype 2.[112] Daclatasvir, asunaprevir, and beclabuvir all undergo CYP 3A metabolism and are excreted mainly in the feces. Additionally, all and have increased exposure with renal insufficiency.[110,113] Patients enrolled in trials taking the combination tablet were instructed to take it with food. DCV-TRIO fixed-dose combination was evaluated recently in two phase 3 trials.

The UNITY-1 trial was a multi-national, phase 3 trial in the United States, Canada, France, and Australia, with an open-label, single-group, uncontrolled design.[114] It enrolled 415 non-cirrhotic patients with HCV genotype 1 and a plasma HCV RNA level of at least 10,000 IU/mL to receive DCV-TRIO twice daily for 12 weeks. Three-hundred twelve patients were treatment-naïve, and 103 were treatment-experienced. Patients with a creatinine clearance < 50 mL/min were excluded. Previous exposure to NS5A, NS3 protease, or nonnucleoside NS5B polymerase inhibitors was not permitted. Overall, 91% (379/415) of patients achieved an SVR12. In the treatment-naïve group, 92% (287/312) of patients achieved SVR12, while in the treatment-experienced group, 89% (92/103) achieved SVR12. Fewer patients achieved SVR12 with HCV genotype 1a in both the treatment-naïve (90%) and –experienced (85%) group compared to HCV genotype 1b (98% and 100%, respectively). The rates of SVR12 were similar across all subgroups. The most common side effects, which occurred in more than 10% of patients, included headache, fatigue, diarrhea, and nausea.

The UNITY-2 trial was a multinational, phase 3 trial in the United States, Canada, France, and Australia, with a two-cohort, four-arm, design.[115] It enrolled 202 compensated-cirrhotic patients with chronic HCV genotype 1 and a plasma HCV RNA level of at least 10,000 IU/mL to receive open-label DCV-TRIO twice daily for 12 weeks. Additionally, patients were randomized in double-blind fashion to receive ribavirin or matching placebo twice daily. One-hundred twelve patients were treatment-naïve, and 90 patients were treatment-experienced. Patients previously exposed to NS5A, NS3 protease, or nonnucleoside NS5B polymerase inhibitors and those with a creatinine clearance < 50 mL/min were excluded. Overall, 93% (188/202) of patients achieved SVR12. In treatment-naïve groups, SVR12 rate was 98% (54/55) in the group receiving ribavirin and 93% (53/57) in the group receiving placebo. The treatment-experienced group on ribavirin achieved an SVR12 rate of 93% (42/45), and the placebo group achieved an SVR12 rate of 87% (39/45). Fewer patients with HCV genotype 1a achieved SVR12, as shown in the UNITY-1 trial; however, improved SVR12 rates in the HCV genotype 1a population were seen with the addition of ribavirin. Patients with HCV genotype 1a in the treatment-naïve group that received ribavirin had an SVR12 of 97% (38/39) compared to 90% (36/40) in those without ribavirin; and in the treatment-experienced group, SVR12 was 91% (32/35) and 86% (30/35), respectively. Evaluation of statistical significance was not reported. SVR12 rates were similar across all subgroups. The most common side effects, which were reported in more than 10% of patients, included headache, nausea, diarrhea, fatigue, insomnia, and pruritus. Three serious, treatment-related adverse events occurred and included anemia, aminotransferase and bilirubin elevations, and ribavirin overdose.

DCV-TRIO has a low barrier to resistance. In UNITY-1 trial,[114] virologic failure occurred in 34 patients while data were missing for two patients. Eight patients had virologic breakthrough, and 21 patients had relapse (15 treatment-naïve patients and six treatment-experienced patients). The majority of treatment failures were in patients infected with HCV genotype 1a. Of the 31 patients with HCV genotype 1a infection with available baseline and failure genetic sequencing, 30 patients had RAVs emerge in NS5A (most frequently Q30), 29 had RAVs emerge in NS3 (most frequently R155), and 12 had RAVs emerge in NS5B (most frequently P495). Both patients with HCV genotype 1b who had virologic failure had a different genotype at the time of failure. In UNITY-2 trial,[115] emergent RAVs in those patients with virologic failure occurred primarily in patients infected with HCV genotype 1a. Twelve patients infected with HCV genotype 1a with virologic failure had emergent RAVs: 11 NS5A (Q30), 10 NS3 (R155K), and two NS5B (P495). Only one patient with HCV genotype 1b had an emergent NS5A RAV.

Sofosbuvir and velpatasvir

Velpatasvir (formerly known as GS-5816) is a second-generation NS5A protease inhibitor and is under development in combination with sofosbuvir by Gilead Sciences. It has shown pangenotypic antiviral activity *in vitro*.[116] The pharmacokinetic properties of velpatasvir are shown in Table 6. No clinically important drug interactions between sofosbuvir and velpatasvir have been identified in pharmacology studies. Velpatasvir is primarily eliminated in the feces with < 1% of the dose excreted in the urine.[117] The combination of sofosbuvir and velpatasvir was evaluated in phase 3 trials.

ASTRAL-1 was a double-blind, multi-center, phase 3 trial in the United States, Canada, Europe, and Hong Kong.[118] The study enrolled 741 patients with HCV genotype 1, 2, 4, 5, or 6, 68% of whom were treatment-naïve. The remaining patients were previously treated with peginterferon or peginterferon plus ribavirin with or without a protease inhibitor, 51% of whom had a virologic relapse or breakthrough and 48% who were non-responders. Patients, with the exception of those with HCV genotype 5, were randomized to receive sofosbuvir 400 mg/velpatasvir 100 mg once daily or placebo for 12 weeks. Patients with creatinine clearance of less than 60 mL/min and those who had received previous treatment with any NS5B inhibitors or NS5A inhibitors were excluded. Overall, 121 patients had cirrhosis, 210 patients had HCV genotype 1a, and 118 patients had HCV genotype 1b. SVR12 was achieved in 99% of all patients, including 98% of patients with HCV genotype 1a and 99% of patients with HCV genotype 1b. The treatment was well tolerated, with only one patient discontinuing treatment due to an adverse events. Common adverse events included headache (29%), fatigue (20%), nasopharyngitis (13%), nausea (12%), insomnia (8%), diarrhea (8%), asthenia (7%), arthralgia (6%), cough (6%), back pain (5%), and myalgia (4%), all of which occurred in the placebo arm with similar frequencies.

In ASTRAL-4,[119] an open-label, multicenter, phase 3 trial in the United States, 267 patients with decompensated cirrhosis (Child-Pugh-Turcotte class B) were randomly assigned at a 1:1:1 ratio to one of three arms to receive fixed-dose sofosbuvir 400 mg/velpatasvir 100 mg once daily for 12 weeks, sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or sofosbuvir-velpatasvir for 24 weeks. About 60% of patients had HCV genotype 1a, and 18% had genotype 1b, with 55% of patients having received prior treatment with either peginterferon and ribavirin or a protease inhibitor regimen. Patients with creatinine clearance of less than 50 mL/min, those who had received previous treatment with any NS5A inhibitor or nucleotide analogue NS5B inhibitor, and patients who had undergone liver transplantation were excluded from this study. Among patients with HCV genotype 1, SVR12 rate was 88% with 12 weeks of sofosbuvir-velpatasvir, 96% with 12 weeks of sofosbuvir-velpatasvir plus ribavirin, and 92% with 24 weeks of sofosbuvir-velpatasvir. This regimen was well tolerated. A total of nine patients discontinued treatment due to an adverse events, one of whom had received 12 weeks of treatment, four had received 12 weeks of ribavirin-containing treatment, and four had received 24 weeks of treatment. The most common adverse events in all groups were fatigue (29%), nausea (23%), and headache (22%). Anemia, diarrhea, and insomnia were also common among patients who received ribavirin. Reductions in hemoglobin, lymphocytes, and platelets were common in all patients but more frequently in patients who were receiving ribavirin. Nine patients died during the study, mostly due to complications of end-stage liver disease, none of which were considered to be related to therapy.

Both sofosbuvir and velpatasvir have a high barrier to resistance. In ASTRAL-1,[118] two patients had virologic relapse by post-treatment week 4, both of whom had NS5A-resistant variants at baseline. However, 99% of patients with baseline NS5A-resistant variants achieved SVR12. In ASTRAL-4,[119] a total of 22 patients had virologic failure, nine of whom had HCV genotype 1. In the arm receiving sofosbuvir-velpatasvir for 12 weeks, three patients with genotype 1a and two patients with genotype 1b had relapse, while one patient with genotype 1a in the arm receiving 12 weeks of sofosbuvir-velpatasvir plus ribavirin had relapse. In the arm receiving 24 weeks of sofosbuvir-velpatasvir, two patients with HCV genotype 1a and one patient with genotype 1b had relapse. Among patients with HCV genotype 1 and baseline NS5A resistance-associated variants, the rate of SVR12 was 80% and 90% with 12 and 24 weeks of sofosbuvir-velpatasvir, respectively, and 100% with the addition of ribavirin. All patients with baseline NS5B resistance-associated variants achieved SVR12.

Conclusions

The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) have jointly developed a HCV Guidance, which provides up-to-date recommendations for testing, managing, and treating hepatitis C (Table 7).[21] The recommended regimens for treatment-naïve noncirrhotic patients with HCV genotype 1 are 12 weeks of simeprevir plus sofosbuvir, 12 weeks of sofosbuvir-ledipasvir, 12 weeks of ombitasvir-paritaprevir-ritonavir plus dasabuvir without ribavirin for HCV genotype 1b and with ribavirin for HCV genotype 1a, and 12 weeks of daclatasvir plus sofosbuvir. For treatment-naïve patients with cirrhosis, the recommended regimens are simeprevir plus sofosbuvir for 24 weeks, sofosbuvir-ledipasvir for 12 weeks, ombitasvir-paritaprevir-ritonavir plus dasabuvir without ribavirin for 12 weeks for HCV genotype 1b and with ribavirin for 24 weeks for HCV genotype 1a, and daclatasvir plus sofosbuvir for 24 weeks.

The recommended regimens for treatment-experienced noncirrhotic patients with HCV genotype 1 are 12 weeks of simeprevir plus sofosbuvir, 12 weeks of sofosbuvir-ledipasvir (with ribavirin if prior treatment failure with sofosbuvir plus ribavirin), 12 weeks of ombitasvir-paritaprevir-ritonavir plus dasabuvir without ribavirin for HCV genotype 1b and with ribavirin for HCV genotype 1a, and 12 weeks of daclatasvir plus sofosbuvir. For treatment-experienced patients with cirrhosis, the recommended regimens are simeprevir plus sofosbuvir for 24 weeks, sofosbuvir-ledipasvir for 24 weeks (with ribavirin if prior treatment failure with sofosbuvir plus ribavirin), sofosbuvir-ledipasvir with ribavirin for 12 weeks (if prior treatment failure with telaprevir, boceprevir, or simeprevir), ombitasvir-paritaprevir-ritonavir plus dasabuvir with ribavirin for 12 weeks for HCV genotype 1b and for 24 weeks for HCV genotype 1a, and daclatasvir plus sofosbuvir for 24 weeks.

Over the past few years, we have seen great advancements in the treatment of HCV. New treatments have shown high cure rates in clinical trials. For most treatment-naïve patients without cirrhosis, ribavirin-free treatments are effective. However, treatment-experienced patients with cirrhosis

Table 7. Recommendations by American Association for the Study of Liver Diseases and Infectious Diseases Society of America

Genotype	Cirrhosis	Treatment-naïve	Treatment-experienced
GT1b	No Cirrhosis	Recommended: GZR/EBR × 12 weeks (I, A) LDV/SOF × 12 weeks (I, A) OBV/PTV/r + DSV × 12 weeks (I, A) SMV + SOF × 12 weeks (I, A) DCV + SOF × 12 weeks (I, B)	Recommended:* GZR/EBR × 12 weeks (I, A) LDV/SOF × 12 weeks (I, A) OBV/PTV/r + DSV × 12 weeks (I, A) SMV + SOF × 12 weeks (I, A) DCV + SOF × 12 weeks (IIa, B) Recommended:** LDV/SOF + RBV × 12 weeks (IIb, C) Recommended:*** LDV/SOF × 12 weeks (I, A) DCV+SOF × 12 weeks (IIa, B) GZR/EBR + RBV × 12 weeks (IIa, B)
	Compensated Cirrhosis	Recommended: GZR/EBR × 12 weeks (I, A) LDV/SOF × 12 weeks (I, A) OBV/PTV/r + DSV × 12 weeks (I, A) Alternative: SMV + SOF ± RBV × 24 weeks (I, A) DCV + SOF ± RBV × 24 weeks (IIa, B)	Recommended:* GZR/EBR × 12 weeks (I, A) LDV/SOF + RBV × 12 weeks (I, A) LDV/SOF × 24 weeks (I, A) OBV/PTV/r + DSV × 12 weeks (I, A) Alternative:* DCV + SOF ± RBV × 24 weeks (IIa, B) SMV + SOF ± RBV × 24 weeks (IIa, B) Recommended:** LDV/SOF + RBV × 24 weeks (IIb, C) Recommended:*** LDV/SOF + RBV × 12 weeks (I, A) LDV/SOF × 24 weeks (I, A) DCV + SOF ± RBV × 24 weeks (IIa, B) GZR/EBR + RBV × 12 weeks (IIa, B)
	Decompensated Cirrhosis	Recommended: LDV/SOF + RBV low-dose × 12 weeks (I, A) DCV + SOF + RBV low-dose × 12 weeks (I, B) RBV ineligible: DCV + SOF × 24 weeks (II, C) LDV/SOF × 24 weeks (II, C)	Prior SOF failure: LDV/SOF + RBV low-dose × 24 weeks (II, C)
GT1a	No Cirrhosis	Recommended: GZR/EBR × 12 weeks (I, A)**** LDV/SOF × 12 weeks (I, A) OBV/PTV/r + DSV + RBV × 12 weeks (I, A) SMV + SOF × 12 weeks (I, A) DCV + SOF × 12 weeks (I, B) Alternative: GZR/EBR + RBV × 16 weeks (IIa, B)*****	Recommended:* GZR/EBR × 12 weeks (I, A)**** LDV/SOF × 12 weeks (I, A) OBV/PTV/r + DSV + RBV × 12 weeks (I, A) SMV + SOF × 12 weeks (I, A) DCV + SOF × 12 weeks (IIa, B) Alternative:* GZR/EBR + RBV × 16 weeks (I, B)*****
	Compensated Cirrhosis	Recommended: GZR/EBR × 12 weeks (I, A)**** LDV/SOF × 12 weeks (I, A) Alternative: OBV/PTV/r + DSV + RBV × 24 weeks (I, A) SMV + SOF ± RBV × 24 weeks (I, A) DCV + SOF ± RBV × 24 weeks (IIa, B) GZR/EBR + RBV × 16 weeks (IIa, B)*****	Recommended:* GZR/EBR × 12 weeks (I, A)**** LDV/SOF × 24 weeks (I, A) LDV/SOF + RBV × 12 weeks (I, A) Alternative:* OBV/PTV/r + DSV + RBV × 24 weeks (I, A) GZR/EBR + RBV × 16 weeks (I, B)***** DCV + SOF ± RBV × 24 weeks (IIa, B) SMV + SOF ± RBV × 24 weeks (IIa, B)

(*continued*)

Table 7. Recommendations by American Association for the Study of Liver Diseases and Infectious Diseases Society of America (*continued*)

Genotype	Cirrhosis	Treatment-naïve	Treatment-experienced
	Decompensated Cirrhosis	Recommended: LDV/SOF + RBV low-dose × 12 weeks (I, A) DCV + SOF + RBV low-dose × 12 weeks (I, B) RBV ineligible: DCV + SOF × 24 weeks (II, C) LDV/SOF × 24 weeks (II, C)	Prior SOF failure: LDV/SOF + RBV low-dose × 24 weeks (II, C)

(Class of recommendation, level of evidence)

*prior treatment failure with PEG-IFN and RBV; **prior treatment failure with SOF + RBV; ***prior treatment failure with (telaprevir, boceprevir, or SMV) + PEG-IFN + RBV or SMV + SOF (no prior NS5A treatment); ****if no baseline high fold-change NS5A RAVs; *****if baseline high fold-change NS5A RAVs.

Abbreviations: EBR, elbasvir; DCV, daclatasvir; DSV, dasabuvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; OBV, ombitasvir; PEG-IFN, pegylated-interferon; PTV/r, paritaprevir/ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

remain difficult to treat and, hence, the need for ribavirin-containing regimens for these patients. Emerging therapies could potentially eliminate the need for ribavirin in the coming years. While most DAAs have a low barrier to resistance, using them in combination seems to overcome this limitation. Further evaluation is needed to establish the role of resistance testing in clinical practice. As more regimens become available, more patients may have access to medications over time as they become more affordable, presenting great opportunities to decrease the burden of HCV infection, to decrease morbidity and mortality, and ultimately to improve the quality of life of patients.

Conflict of interest

None

Author contributions

Wrote the following sections: abstract, introduction, virology, HCV life cycle, treatment, sofosbuvir and simeprevir, sofosbuvir and ledipasvir, sofosbuvir and daclatasvir, elbasvir and grazoprevir, sofosbuvir and velpatasvir, and conclusions (AF), wrote the following sections: clinical manifestations, screening and diagnosis, pathogenesis, and ombitasvir-paritaprevir-ritonavir and dasabuvir (MM), wrote the following section: daclatasvir, beclabusvir, and asunaprevir (RB).

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