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Treatment of Hepatitis C Virus (HCV) Genotype 1 Disease

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Opinion Statement

The landscape of therapeutic options for HCV infection has dramatically changed with the approval of all-oral direct-acting antiviral (DAA) regimens. DAAs target important steps in the HCV viral life cycle, resulting in higher response rates and fewer adverse events than were afforded with interferon and ribavirin, the prior standard of care. The achievement of sustained virologic response (SVR) rates in excess of 90% with use of DAA regimens has not only translated into HCV eradication for the hundreds of thousands treated but is also anticipated to decrease the incidence of major complications associated with chronic HCV infection. Additionally, the favorable side effect profile of DAAs has made HCV therapy feasible in difficult-to-treat populations, including those with previous exposure to interferon and ribavirin, cirrhosis, decompensated liver disease, HIV and HCV co-infection, and severe renal dysfunction/end stage renal disease. Given this tremendous progress, all patients infected with HCV infection should be treated.

Keywords

Hepatitis C Virus; HCV; genotype 1; sustained virologic response 12 weeks after completion of therapy; SVR12; resistance-associated variants; RAVs

Introduction

Hepatitis C virus (HCV) is a hepatotropic virus that causes chronic infection after exposure in a majority of individuals.[1] Chronic infection may lead to hepatic fibrosis, cirrhosis and hepatocellular carcinoma. Successful treatment of HCV has been shown to decrease progression to liver failure, need for liver transplantation and both liver-related and all-cause mortality, thereby attenuating the sequelae of chronic infection.[2] HCV affects nearly 185 million persons worldwide.[3] In the United States, an estimated 3–4 million persons are infected, a clear underestimate as epidemiologic studies have excluded those at highest risk for infection including those who are homeless, inject drugs and/or are incarcerated.[4]

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Conflict of Interest

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Of the 6 major genotypes, genotype 1, the most prevalent HCV genotype worldwide, was difficult to eradicate with SVR rates of less than 50% with interferon-based therapy.[5] The advent of DAAs has revolutionized the treatment of genotype 1 HCV infection. Administration of these regimens results in > 90% SVR12, SVR at 12 weeks after completion of therapy, rates and is associated with virologic cure.[6–12] This review will focus on the new therapeutic regimens for the treatment of genotype 1 HCV infection in treatment-naïve, treatment-experienced, compensated cirrhotics and decompensated cirrhotics.

TREATMENT

The American Association of the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) treatment guidance includes six DAA combinations for the treatment of genotype 1 infection.[13] The choice of regimen and duration of therapy are contingent upon viral subtype (1a or 1b), presence of resistance-associated variants (RAVs), and degree of hepatic fibrosis. Specifically, the treatment of genotype 1 infection includes agents from three DAA classes; protease inhibitors (PIs), NS5A inhibitors, and NS5B polymerase inhibitors (nucleoside and non-nucleoside). Approximately 10–15% of patients may have baseline NS5A RAVs,[13] thereby limiting efficacy in certain populations and facilitating the emergence of resistance.

Treatment Regimens

Tables 1 and 2 list the recommended regimens for treatment-naïve and treatment-experienced patients with genotype 1 HCV infection. This section of the review will discuss the data (by regimen) that informed the current treatment recommendations. All fixed-dose combination regimens will be discussed first followed by other recommended combinations.

Elbasvir/Grazoprevir—Elbasvir is a pan-genotypic NS5A inhibitor with activity against resistance-associated variants (RAVs), to which other NS5A inhibitors are vulnerable.[14] Grazoprevir is a macrocyclic, second generation, pan-genotypic NS3/4A protease inhibitor with activity against boceprevir and telaprevir RAVs.[15, 16] This combination is administered in a fixed-dose tablet (50 mg elbasvir/100 mg grazoprevir).

In the phase III C-EDGE study, treatment-naïve cirrhotic and non-cirrhotic patients were randomized to immediate or delayed therapy with elbasvir/grazoprevir.[17] Overall, SVR12 was achieved in 95% of the cohort, 92% in genotype 1a and 99% in genotype 1b. The presence of baseline NS5A RAVs was important, with an SVR rate of only 58% in patients with genotype 1a with RAVs conferring greater than 5-fold resistance (amino acid positions 28, 30, 31, 58, and 93). Based on these data, the AASLD/IDSA guidance suggests extending therapy to 16 weeks and adding ribavirin in all patients with baseline NS5A RAVs (treatment-naïve and treatment-experienced, regardless of cirrhosis status).[13]

Treatment-experienced: In the phase III C-EDGE treatment-experienced trial, patients previously treated with pegylated interferon and ribavirin were randomized to 12 or 16 weeks with or without weight-based ribavirin.[18] Overall SVR12 for noncirrhotic patients was 94% and 97% in the 12 week arms, with and without ribavirin, and 93% and 96% in the

16 week arms, with and without ribavirin. NS5A RAVs also conferred lower SVR rates in treatment-experienced genotype 1a patients in an integrated analysis of phase II and III trials, with an SVR of 90% and 99%, with and without RAVS, respectively.[19]

In patients who failed a protease inhibitor, pegylated interferon, and ribavirin combination, the recommendation is to administer grazoprevir/elbasvir with ribavirin for 12 weeks. This guidance is based on the phase II C-SALVAGE trial which evaluated 12 weeks of grazoprevir/elbasvir and ribavirin in genotype 1 protease inhibitor-pegylated interferon-ribavirin experienced patients. The overall SVR12 was 96%.[20]

Cirrhosis: The C-EDGE treatment-naïve study enrolled 92 participants with cirrhosis and the SVR12 rate was 97% in this cohort.[17] In the treatment-experienced C-EDGE TE study which included 35% cirrhotics (see above), the overall SVR12 in cirrhotics was 95% in the group who received grazoprevir/elbasvir without ribavirin for 12 weeks. The regimen was further demonstrated to be well tolerated and safe, with the placebo group having comparable numbers of serious adverse events when compared to those on active drug.[18] SVR12 was 94% in the C-SALVAGE study of protease inhibitor-pegylated interferon and ribavirin experienced patients.[20]

Decompensated Cirrhosis: In an open label study of grazoprevir/elbasvir for 12 weeks in patients with Child-Turcotte-Pugh, CTP, B cirrhosis, the SVR12 rate was 90% and 1 patient died of liver failure. However, given the concerns related to hepatotoxicity with protease inhibitors, this combination should not be used in decompensated liver disease.[21]

Ledipasvir/Sofosbuvir—Ledipasvir/sofosbuvir (400 mg sofosbuvir/90 mg ledipasvir co-formulated in a single tablet) was approved by the FDA in October 2014 for the treatment of genotype 1 infection. ION-1, a phase III trial of ledipasvir/sofosbuvir with and without weight-based ribavirin for 12 or 24 weeks in previously untreated patients, resulted in rates of SVR12 of 97–100%.[22] Given an increase in adverse events with ribavirin administration and limited improvement in efficacy with 24 weeks, 12 weeks of therapy was suggested as the optimal treatment duration. ION-3, another study of ledipasvir/sofosbuvir with or without ribavirin for 8 or 12 weeks, was conducted in 647 treatment-naïve non-cirrhotic patients.[23] In this trial, 8 weeks of therapy was non-inferior to 12 weeks and there was no additional benefit with the addition of ribavirin. In post-hoc analyses, the 8-week regimen was most efficacious for treatment-naïve patients with mild to moderate hepatic fibrosis (METAVIR stage F0–F3) and with a baseline HCV RNA of <6 million IU/mL. Participants meeting these criteria at baseline achieved an SVR12 of 97%.

Real world data from HCV-TARGET also confirm the effectiveness of this regimen.[24] In HCV-TARGET, rates of SVR12 in patients receiving 8, 12, or 24 weeks of a ledipasvir/sofosbuvir containing regimen were 96%, 97% and 95%, respectively. Predictors of SVR12 included higher albumin (≥3.5 g/dL), lower total bilirubin (≤1.2 g/dL), absence of cirrhosis and absence of proton pump inhibitor (PPI) use. In patients who were on a PPI, regardless of dose, there was an approximate 2-fold decrease in odds of achieving an SVR (OR 0.57, 95% CI 0.25–0.67). Given that an acidic environment is required for absorption of ledipasvir, co-administration of high-dose PPI therapy is not recommended with ledipasvir.[25]

Examination of post-marketing data has also elucidated the influence of host factors including race on rates of SVR in ledipasvir/sofosbuvir treated patients. In a large Veterans' Affairs treatment cohort, African-American race conferred a 30% decrease in achievement of SVR with 8 weeks of therapy, a finding that was attenuated with receipt of 12 weeks.[26] Similarly, in a post-hoc analysis of ION trials, African-American race was associated with higher relapse rates (8.6% vs 1.5% and 1.1%) with 8 weeks versus 12 or 24 weeks of therapy.[27] In sum, these data support the use of ledipasvir/sofosbuvir for 12 weeks in treatment-naïve patients and 8 weeks in treatment-naive patients with patient (non-African-American race, female sex, HIV-uninfected and IL28B CC genotype[26–28]) and disease characteristics (absence of cirrhosis and low viral load) associated with a favorable response.[13]

Treatment-experienced: ION-2 was a phase III, randomized open-label study[29] where pegylated interferon and ribavirin treatment-experienced patients with or without prior exposure to protease inhibitors were randomized to ledipasvir/sofosbuvir with or without ribavirin for 12 or 24 weeks. Rates of SVR12 were high across all treatment groups (94%, 96%, 99% and 99%, respectively for 12 and 24 weeks of therapy with or without ribavirin). Non-cirrhotic treatment-experienced patients had high rates of SVR12 (100% and 95%) however patients with cirrhosis required at least 24 weeks of therapy.

Real world cohort data from HCV-TARGET and Trio also substantiate high rates of SVR12 in treatment-experienced patients (to interferon based or DAA therapy) in receipt of ledipasvir/sofosbuvir.[24, 30] In treatment-experienced patients without cirrhosis enrolled in HCV-TARGET, rates of SVR12 were 98.8% with ledipasvir/sofosbuvir and 97.6% with ledipasvir/sofosbuvir with ribavirin.[24] Of note, treatment-experienced patients were much more likely to receive 24 weeks of therapy. This may be in the setting of more advanced liver disease though the data available does not provide this level of granularity. In Trio, patients who were treatment-experienced were just as likely to experience an SVR12 with ledipasvir/sofosbuvir as in treatment-naïve patients.[30]

Cirrhosis: Twenty percent of the patients in the treatment-naïve ION-1 trial were cirrhotic and SVR12 rates in these patients were high (94% – 100%).[22] In ION-2, those patients with cirrhosis had lower rates of SVR12 with 12 weeks of treatment with or without ribavirin (82% versus 86%, respectively), suggesting that a longer duration of therapy is required in treatment-experienced cirrhotics.[29] In SIRIUS, a multicenter trial of ledipasvir/sofosbuvir and ribavirin for 12 weeks versus ledipasvir/sofosbuvir for 24 weeks in treatment-experienced cirrhotics, SVR12 rates were 96% (95% CI: 89–99%) and 97% (95% CI: 91–100%), respectively.[31] Given these conflicting data, a post-hoc analysis was conducted which included data from the ELECTRON studies, LONESTAR, the ION phase III programs, and SIRIUS.[22, 29, 31–33] In this pooled data, there were few differences between patients treated for 12 or for 24 weeks though cirrhotic patients who were previously treated had an SVR12 of 90% with ledipasvir/sofosbuvir without ribavirin for 12 weeks, suggesting some added benefit to longer duration of therapy or addition of ribavirin. Based on these data, the AASLD/IDSA guidance document recommends 12 weeks of

ledipasvir/sofosbuvir for treatment-naïve cirrhotics and either 12 weeks with ribavirin or 24 weeks without ribavirin in treatment-experienced cirrhotics.[13]

Decompensated Cirrhosis: Ledipasvir/sofosbuvir in patients with decompensated liver disease was explored in the SOLAR-1 and SOLAR-2 studies.[34, 35] In SOLAR-1, ledipasvir/sofosbuvir and ribavirin for 12 or 24 weeks was administered to two cohorts: 1) cirrhotics with moderate or severe hepatic impairment (CTP B or C) and 2) cirrhotic (CTP A, B, and C) and non-cirrhotic liver transplant recipients.[34] In cohort A, SVR12 rates ranged from 86–89%. In cohort B, SVR12 rates ranged from 96–98% in patients without cirrhosis or those with decompensated cirrhosis. Those with hepatic impairment after liver transplant had a stepwise decrease in SVR12: 85–88% in CTP B and 60–75% in CTP C cirrhosis. SOLAR-2 explored the same questions in a European cohort and also found that therapy had acceptably high rates of SVR12 though there was a higher rate of treatment-related complications and mortality.[35] Of note, both studies demonstrated a decline in CTP and Model for End-Stage Liver Disease (MELD) scores in a majority of patients. Given the use of the MELD score for liver allograft allocation, treatment of patients on the liver transplant list should be individualized in the setting of priority for transplant, wait time, risk of death, potential for receipt of HCV organs and the effectiveness of therapy in the post-transplant setting.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir (PrOD)—Daily fixed-dose combination of paritaprevir (150mg)/ritonavir (100mg)/ombitasvir (25mg) with dasabuvir (600mg) as part of an extended release regimen or plus twice-daily dosed dasabuvir (250mg) is a regimen also suggested by the AASLD/IDSA guidance document. In the PEARL phase III and IV programs, treatment-naïve HCV genotype 1a and 1b patients without cirrhosis were randomized to PrOD with or without ribavirin.[36] Rates of SVR12 with and without administration of ribavirin were 97.0% and 90.2% for genotype 1a and 99.5% and 99.0% for genotype 1b patients, respectively, highlighting the need for ribavirin in genotype 1a patients. Though this regimen was well tolerated and low discontinuation rates were observed, there were several cases of hyperbilirubinemia, consistent with paritaprevir's inhibition of the bile transporter OATP1B1.

Treatment-experienced: In SAPPHIRE II, treatment-experienced patients were randomized to PrOD with ribavirin or placebo.[37] The overall rate of SVR12 achieved was 96.3%. Based on prior treatment response, few differences were noted in rates of SVR12 (95.3% for prior relapsers, 100% for prior partial responders, and 95.2% for prior null responders), suggesting that 12 weeks of therapy is likely the appropriate duration in non-cirrhotic treatment-experienced HCV infected patients. This regimen was further studied in PEARL-II, a study which enrolled treatment-experienced HCV genotype 1b patients.[38] Enrolled patients received PrOD with or without ribavirin. Rates of SVR12 were high in both treatment groups (96.6% and 100% with or without ribavirin, respectively). In both studies, patients had few adverse events.

Cirrhosis: The PrOD regimen with the addition of ribavirin was evaluated in the TURQUOISE II study, a phase III trial inclusive of treatment-naïve and experienced

genotype 1 infected patients with compensated cirrhosis.[39] In this study that randomized patients to 12 or 24 weeks of therapy, rates of SVR12 were 91.8% and 95.9%, respectively. In addition to establishing efficacy of the regimen, the study found the regimen to be safe, with a low rate of discontinuation (2.1%). Of note, there were differences based on viral subtype (genotype 1a null responders achieving higher rates of SVR with 24 weeks of therapy, 92.9%, versus 80% with 12 weeks of therapy), leading to the recommendation of 24 weeks of therapy with weight based ribavirin in treatment-experienced cirrhotics.

Treatment-naïve and -experienced patients with genotype 1b and compensated cirrhosis were studied in the TURQUOISE III study.[40] In this phase III study, patients received PrOD without ribavirin for 12 weeks and 100% achieved an SVR. These data suggest that the PrOD regimen without ribavirin may be used in genotype 1b infection despite the presence of advanced fibrosis.

In patients with decompensated liver disease and even some with well-compensated disease, several cases of hepatic decompensations, including those resulting in liver transplantation and death, were reported within the first four weeks of therapy, presumably due to acute liver injury from the regimen. Thus the FDA issued a warning about hepatotoxicity and suggested avoidance of this regimen in patients with decompensated cirrhosis and caution in those with compensated cirrhosis.

Sofosbuvir/Velpatasvir—Sofosbuvir (400 mg) and velpatasvir (100 mg), an NS5A inhibitor with pan-genotypic activity and a high barrier to resistance, have been studied in a phase 2 and 3 program and demonstrated clinical efficacy in HCV genotypes 1,2,4,5 and 6. This highly active combination with or without the addition of ribavirin was studied in treatment naïve patients with genotype 1 infection for 8 or 12 weeks.[41] Treatment with 12 weeks of therapy achieved a 100% rate of SVR12. Eight weeks of therapy, with or without ribavirin, achieved SVR12 rates of 81% and 90%, respectively, with all virologic failures representing post-treatment relapse. These data, on this well tolerated regimen, suggest that 12 weeks of treatment is an appropriate duration of therapy and that use of ribavirin is not essential for achievement of HCV eradication when a 12-week duration of therapy is being used.

Treatment-experienced: Treatment-experienced patients with genotype 1 or 3 infection were randomized to 12 weeks of therapy with one of four drug combinations (25 mg or 100 mg velpatasvir, 400 mg sofosbuvir, with or without weight-based ribavirin), with genotype 1 patients achieving rates of SVR12 of 96% to 100%.[42] Of note, the study included protease inhibitor (PI) failures and the high rates of SVR achieved suggest that PI failures can be successfully treated with this regimen. These findings were extended in a phase 3 trial in 5 distinct HCV genotypes.[43] In this study that included over six hundred patients, overall rates of SVR12 were found to be high (99%, 95% CI: 98%–>99%). For the subtypes of genotype 1 disease, sofosbuvir/velpatasvir was found to be highly efficacious (genotype 1a: SVR 98%; genotype 1b: SVR 99%). Additionally, markers of poor treatment response in the interferon/ribavirin era had no bearing on the achievement of SVR12. Furthermore, 99% of patients with NS5A RAVs at baseline achieved an SVR12 with this safe and well-tolerated regimen.

Cirrhosis: Cirrhotic patients were included in phase 2 and 3 studies of this drug combination.[42, 43] In the phase 2 study, 1/3 of patients included in the genotype 1 cohort were cirrhotic. Rates of SVR were high across all groups, with 97% of the treatment-experienced patients in the genotype 1 cohort achieving an SVR. In the phase 3 program, 19% of patients included in the study had compensated cirrhosis. Though the rates of SVR in the genotype 1 cohort were not specifically reported, patients with genotype 1a and 1b disease had excellent rates of SVR (98% and 99%, respectively) and all comers with cirrhosis also had high rates of SVR achieved (99%, 95% CI 95–>99%), suggesting that 12 weeks is an adequate treatment duration in patients even with cirrhosis.[43]

Decompensated Cirrhosis: Sofosbuvir/velpatasvir was evaluated in a phase 3 study in treatment naïve and treatment-experienced patients with decompensated liver disease secondary to genotype 1–6 HCV infection (ASTRAL-4).[44] In this study with 78% patients infected with genotype 1 HCV, rates of SVR were 83% for 12 weeks of sofosbuvir/velpatasvir, 94% for 12 weeks of sofosbuvir/velpatasvir and ribavirin, and 86% for 24 weeks of sofosbuvir/velpatasvir. For the genotype 1 cohort, the rates of SVR12 were found to be marginally higher, 88%, 96% and 92%, respectively, with the relatively lower rates of SVR representing relapse after the end of therapy. The study also highlighted the findings that the presence of baseline NS5A RAVs influenced rates of SVR, with an SVR of 80% in those with baseline RAVs and in receipt of 12 weeks of therapy. As rates of SVR were higher in those receiving ribavirin or 24 weeks of therapy, the authors concluded that the addition of ribavirin or increased duration of therapy may be necessary in the setting of baseline NS5A RAVs. Lastly, in addition to the demonstrated safety of this regimen, though more adverse events and discontinuations were seen in this sick population, early improvements were also demonstrated, with a clear improvement in the MELD score and decrease in the CTP score in a majority of patients.

Daclatasvir + Sofosbuvir—Daclatasvir is an NS5A replication complex inhibitor with activity against a spectrum of HCV genotypes.[45] Sofosbuvir, a nucleotide analog, is a pan-genotypic NS5B polymerase inhibitor.[46] This combination was studied in treatment-naïve and treatment-experienced HCV-infected patients with genotype 1, 2, or 3.[47] In this study, 126 treatment-naïve patients were randomized to daclatasvir (60 mg) + sofosbuvir (400 mg) once daily with or without ribavirin (weight-based) for 12 or 24 weeks, the majority of genotype 1a were noncirrhotic (87%). Overall, 98% achieved SVR, and treatment-naïve genotype 1 patients who received 12 weeks without ribavirin had as favorable a response as those receiving ribavirin or those receiving longer duration of therapy (SVR 100% vs. 95% vs. 100%).

Treatment-experienced: Guidance for treatment-experienced noncirrhotic patients primarily comes from the ALLY-2 study of HIV/HCV coinfected individuals where treatment-experienced (pegylated interferon, protease inhibitor + pegylated interferon, and sofosbuvir + ribavirin) genotype 1 patients received 12 weeks of daclatasvir and sofosbuvir. Overall, SVR12 was achieved in 43 (98%) of 44 treatment-experienced patients with genotype 1 infection, the majority of whom were non-cirrhotic.[48]

Cirrhosis: The optimal duration of therapy in cirrhosis is unclear as pivotal trials enrolled few cirrhotic patients. Daclatasvir + sofosbuvir and ribavirin for 12 weeks (up to 24 in liver transplant) were evaluated in the phase III ALLY-1 study in treatment-naïve and experienced patients with advanced cirrhosis or after liver transplantation.[49] In patients with genotype 1 infection and cirrhosis, SVR12 rates were modest (82%, 95% CI: 67.9%-92%). However, in those patients with relatively compensated disease, CTP A disease, SVR12 rates were 93%. This combination was safe, with no treatment-related serious adverse events. Given these results and findings from European cohort studies which demonstrated higher SVR rates with 24 weeks of therapy (with and without ribavirin[25, 50]), extension of therapy to 24 weeks (with consideration for ribavirin) is recommended for all compensated cirrhotic patients.[13]

Decompensated Cirrhosis: In ALLY-1 patients with CTP C disease achieved a rate of SVR12 of 56%. In contrast, in those genotype 1 patients who underwent liver transplantation, 95% achieved SVR12.[49]

Simeprevir + Sofosbuvir—Though simeprevir, a multigenomic NS3/4A protease inhibitor administered once daily, and sofosbuvir were approved for use with interferon and ribavirin in 2013, they were not evaluated in combination with one another until after marketing. The COmbination of SiMeprevir and sOfoSbuvir in HCV infected patients (COSMOS) study was the first to do so and provided the FDA with the necessary preliminary data to approve this regimen for use in patients who were interferon and ribavirin naïve or intolerant.[51] In this small study of treatment naïve and experienced patients randomized to 12 or 24 weeks of simprevir + sofosbuvir with or without ribavirin, SVR12 was achieved in over 90% of patients in both cohorts.[51] The OPTIMIST-1 study further explored the efficacy of sofosbuvir + simeprevir in treatment naïve and experienced patients.[52] Treatment with 12 weeks of sofosbuvir + simeprevir therapy was found to be superior to the rate of SVR achieved in historical controls. Eight weeks of therapy however was found to be non-superior to historical controls, even in treatment naïve patients (SVR12 85%, 95% CI: 77% – 92%). In real world data from HCV-TARGET, treatment response varied based on viral subtype, with higher rates of SVR noted in genotype 1b infection (97.5%).[24]

Cirrhosis: In COSMOS, simeprevir + sofosbuvir was administered for 12 or 24 weeks, with cirrhotics achieving high rates of SVR12 (89% and 96%, respectively) regardless of the addition of ribavirin to the therapeutic regimen.[51] Simeprevir + sofosbuvir was administered to genotype 1 infected cirrhotics, treatment naïve or treatment-experienced, in the phase 3 OPTIMIST-1 study for 12 weeks.[52] SVR12 was 83% in all comers, superior to historical controls but not in the range of SVR12 being achieved with other DAA combinations. Of note, treatment naïve patients derived more benefit from this combination (SVR12 88% versus 79%). Additionally, in HCV-TARGET data, patients with cirrhosis had high rates of SVR12 (84%, 95% CI 80–87%).[24] Of note, the study did include patients with a history of hepatic decompensation (45% of cirrhotics), a group with historically low rates of achievement of SVR.

Decompensated Cirrhosis: Although not recommended in decompensated cirrhosis because of a substantial increase in drug levels and concern of PI toxicity, this regimen has been used in real-world cohorts (HCV-TARGET) where cirrhosis and hepatic decompensation were associated with a 70% decreased likelihood of achieving SVR.[24]

Patients with NS5A-experience—The optimal approach to patients who do not achieve SVR with NS5A-containing regimens is unknown. RAVs to NS5A inhibitors are polymorphisms located at amino acid positions 28, 30, 31, and 93. Though many RAVs confer low-level resistance, those conferring high-level resistance (>100 fold) have been demonstrated to result in higher relapse rates in patients in phase II/III clinical trials of ledipasvir/sofosbuvir regimens.[53] Because of insufficient data in patients who have failed NS5A-containing regimens, the AASLD/IDSA consensus document suggests deferring therapy in those patients who do not have cirrhosis or other indications for immediate retreatment for regimens with proven activity for this group.[13] If however, patients require urgent therapy, testing for NS5A and NS3/4A RAVs is suggested with subsequent tailoring of the chosen therapeutic regimen based on the resultant findings.

Recently published phase II clinical trial results generated enthusiasm for new HCV therapeutic regimens with the ability to eradicate chronic HCV infection in patients with high-level baseline resistance to NS5A inhibitors. Bourliere and colleagues administered sofosbuvir, velpatasvir, and GS-9857 (voxilaprevir), a macrocyclic NS3/4A protease inhibitor, to NS5A treatment-experienced (DAA-experienced) patients. In 127 participants (all genotypes) with NS5A RAVs, 94% had an SVR12.[54] Based on phase 3 data, sofosbuvir/velpatasvir/voxilaprevir and another regimen, glecaprevir/pibentasvir, were submitted to the FDA and are expected to be reviewed in 2017.

In summary, the advent of all-oral DAA therapies has resulted in extremely high SVR12 rates in the majority of uncomplicated patients. Nuances in host (baseline HCV resistance, race/ethnicity) and viral factors (HCV viral load) impact the selection and duration of regimen. Challenges remain in harder-to-treat patient populations, including those who have failed NS5A-containing regimens. New agents in development may provide opportunities for cure in these patient populations.

Conclusions

Treatment regimens for genotype 1 HCV infection are highly efficacious and safe. Though once a difficult-to-treat infection in many patient subgroups, HCV can now effectively be eradicated in most patients with all oral therapy, the choice and length of which are guided by viral subtype, host characteristics, and disease characteristics. Given the wide spread availability of therapy, ease of administration, and limited requirement for monitoring, HCV eradication should be a realized goal for the next decade.

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Table 1

AASLD/ IDSA Recommended HCV Regimens for Treatment-Naïve Patients (adapted from the American Association of the Study of Liver Diseases/ Infectious Diseases Society of America treatment guidance)

	Drug/ Dose	Duration
Treatment Naïve, Non-Cirrhotic		
Genotype 1a		
	Elbasvir (50 mg)/ grazoprevir (100 mg) *	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg) + weight-based ribavirin§	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
	Daclatasvir (60 mg) + sofosbuvir (400 mg)	12 weeks
	Simeprevir (150 mg) + sofosbuvir (400 mg)	12 weeks
	*Elbasvir (50 mg)/ grazoprevir (100 mg) + weight-based ribavirin§^*	*16 weeks*
Genotype 1b		
	Elbasvir (50 mg)/ grazoprevir (100 mg) *	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg)	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
	Daclatasvir (60 mg) + sofosbuvir (400 mg)	12 weeks
	Simeprevir (150 mg) + sofosbuvir (400 mg)	12 weeks
Treatment Naïve, Compensated Cirrhotic		
Genotype 1a		
	Elbasvir (50 mg)/ grazoprevir (100 mg) *	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
	*Elbasvir (50 mg)/ grazoprevir (100 mg)/weight-based ribavirin§^*	*16 weeks*
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg) + weight-based ribavirin§	*24 weeks*
	Daclatasvir (60 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin§	*24 weeks*
	Simeprevir (150 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin§ ∞	*24 weeks*
Genotype 1b		
	Elbasvir (50 mg)/ grazoprevir (100 mg)	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg)	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
	Daclatasvir (60 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin§	*24 weeks*
	Simeprevir (150 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin§	*24 weeks*

[*] In the absence of baseline NS5A resistance associated variants (RAVs) at amino acid positions 28, 30, 31, and 93.

[^] In presence of baseline NS5A RAVS at amino acid positions 28, 30, 31, or 93.

[§] Weight-based ribavirin dosing: 1000 mg/day in divided doses in patients with a body weight of <75 kg; 1200 mg/day in divided doses in patients with a body weight of ≥75 kg.

[∞] In the absence of baseline NS3/4A Q80K polymorphism.

Table 2

AASLD/ IDSA Recommended HCV Regimens for Treatment-Experienced Patients (adapted from the American Association of the Study of Liver Diseases/ Infectious Diseases Society of America treatment guidance)

	Drug/ Dose	**Duration**
Treatment-experienced, Non-Cirrhotic		
Genotype 1a		
	Elbasvir (50 mg)/grazoprevir (100 mg)*	12 weeks
	Elbasvir (50 mg)/grazoprevir (100 mg) + weight-based ribavirin@	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)%	12 weeks
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg) + weight-based ribavirin§	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)%	12 weeks
	Daclatasvir (60 mg) + sofosbuvir (400 mg)%	12 weeks
	Simeprevir (150 mg) + sofosbuvir (400 mg)	12 weeks
	Elbasvir (50 mg)/grazoprevir (100 mg) + weight-based ribavirin§^$	*16 weeks*
Genotype 1b		
	Elbasvir (50 mg)/ grazoprevir (100 mg)*	12 weeks
	Elbasvir (50 mg)/grazoprevir (100 mg) + weight-based ribavirin@	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg)	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
	Daclatasvir (60 mg) + sofosbuvir (400 mg)	12 weeks
	Simeprevir (150 mg) + sofosbuvir (400 mg)	12 weeks
Treatment-experienced, Compensated Cirrhotic		
Genotype 1a		
	Elbasvir (50 mg)/ grazoprevir (100 mg)*	12 weeks
	Elbasvir (50 mg)/grazoprevir (100 mg) + weight-based ribavirin@	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg) + weight-based ribavirin§≃#	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)#	12 weeks
	Elbasvir (50 mg)/ grazoprevir (100 mg) + weight-based ribavirin§^$	*16 weeks*
	Ledipasvir (90 mg)/sofosbuvir (400 mg)#	*24 weeks*
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg) + weight-based ribavirin§	*24 weeks*
	Daclatasvir (60 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin§#	*24 weeks*
	Simeprevir (150 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin§ ∞	*24 weeks*
Genotype 1b		

	Drug/ Dose	Duration
	Elbasvir (50 mg)/ grazoprevir (100 mg)	12 weeks
	Elbasvir (50 mg)/grazoprevir (100 mg) + weight-based ribavirin[@]	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg) + weight-based ribavirin[§≃]	12 weeks
	Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) or + twice-daily dosed dasabuvir (250 mg)	12 weeks
	Sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
	Ledipasvir (90 mg)/sofosbuvir (400 mg)[&]	*24 weeks*
	Daclatasvir (60 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin[§]	*24 weeks*
	Simeprevir (150 mg) + sofosbuvir (400 mg)+/− weight-based ribavirin[§]	*24 weeks*

[*] In the absence of baseline NS5A resistance associated variants (RAVs) at amino acid positions 28, 30, 31, and 93.

[@] Regimen specific for protease-inhibitor (boceprevir/telaprevir) and pegylated interferon + ribavirin failures. Patients with RAVs at amino acid positions 28, 30, 31, or 93 should have therapy extended to 16 weeks.

[^] In presence of baseline NS5A RAVS at amino acid positions 28, 30, 31, or 93.

[§] Weight-based ribavirin dosing: 1000 mg/day in divided doses if body weight of <75 kg; 1200 mg/day in divided doses if body weight of ≥75 kg.

[∞] In the absence of baseline NS3/4A Q80K polymorphism.

[≃] Regimen can be used for non-cirrhotic sofosbuvir treatment failures.

[&] Regimen with the addition of ribavirin can be used for cirrhotic sofosbuvir treatment failures

[%] Regimen can be used for non-cirrhotic PI failures, regardless of subtype.

[$] Regimen can be used for PI failures, regardless of cirrhosis status

[#] Regimen can be used for cirrhotic PI failures, regardless of subtype.