

Hepatitis C Genotype 3 Infection

Pathogenesis and Treatment Horizons

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KEYWORDS

- Hepatitis C • Genotype 3 • Hepatocellular carcinoma • Hepatic steatosis
- Accelerated fibrosis

KEY POINTS

- Hepatitis C genotype 3 infection is associated with increased late-stage liver events, accelerated hepatic fibrosis, and hepatocellular carcinoma.
- Infection with genotype 3 infection has been linked to hepatic steatosis thought to be related to direct viral protein effect on hepatocytes.
- With the advent of direct-acting antiviral therapies, infection with genotype 3 has been found to be more difficult to treat as compared with other genotypes.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a global epidemic affecting approximately 170 million people. It is a major cause of cirrhosis, observed in approximately one-quarter of those chronically infected.¹ The mortality related to decompensated cirrhosis is high, with a 5-year survival of approximately 50%.² Furthermore, HCV is the leading indication for liver transplantation in the Western world.³ Six major genotypes (GTs) have been identified worldwide, with GTs 1, 2, and 3 accounting for most identified infections within the United States.⁴

It has been clear for many years that the different GTs respond differently to interferon-alfa-based medical regimens. Sustained virologic response (SVR) rates with pegylated interferon and ribavirin for GT 1 infection were less than 50%, and 48 weeks of therapy were required.⁵ Infection with GTs 2 and 3, accounting for approximately one-third of patients in the United States, was easier to treat with SVR rates exceeding 70% with only 24 weeks of therapy recommended.⁶ With the advent of noninterferon-based therapies (direct-acting antiviral agents

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[DAA]), however, GT 3 infection has become more difficult to treat. GT 3 subjects with some regimens require an extended duration of therapy, and lower SVR rates are observed, particularly in patients with cirrhosis and who have been previously treated with interferon-alfa-based regimens.

Unlike the long-standing well-known different treatment responses for the various GTs, until recently, it has been thought that the natural history of the different GTs was similar. However, evidence has been emerging that there are differences. Infection with GT 3 infection, in particular, has been associated with an increase in mortality when compared with GT 1. Specifically, there is an increased risk of hepatocellular carcinoma and a higher risk of late-stage liver events.^{6–8} Central to the aggressive natural history and relative resistance to treatment of GT 3 HCV infection is its association with hepatic steatosis leading to increased necroinflammatory activity via oxidative stress.⁶

A factor implicated in lower treatment response rates is the presence of baseline and treatment-emergent resistance-associated variants (RAVs), also called resistance-associated substitutions. NS5A RAVs are particularly problematic. When detected, these markers denote those who are at increased risk of virologic relapse and may identify those patients who require a longer duration of therapy or benefit from the addition of ribavirin. Lower response rates are observed in patients with cirrhosis and in patients who are treatment experienced. Patients who are cirrhotic and treatment experienced have the lowest treatment response rates.⁹

This article reviews current data on the natural history and treatment approaches to HCV GT 3.

DEMOGRAPHICS

GT 3 infection is the second most common hepatitis C GT, accounting for approximately 30% of infections. Worldwide, an estimated 54.3 million individuals are infected with HCV GT 3.¹⁰ The prevalence of GT 3 infection is highest in Southeast Asia, accounting for approximately 40% of infections, primarily in India and Pakistan.¹¹ Within the United States, the prevalence of GT 3 infection is slightly lower, accounting for approximately 12% of infections. GT 3 infection is unique in that it has been associated with accelerated hepatic fibrosis and hepatic steatosis.¹²

Changes in host metabolism and insulin resistance have been identified in HCV-infected individuals, thus leading to hepatic steatosis.¹³ GT 3 infection has been associated with a higher incidence of hepatic steatosis when compared with all other GTs (73% vs 50%).^{14–17} The mechanism is thought to involve a direct viral protein effect on hepatocytes. In vitro studies have found that protein expression in GT 3 leads to a three-fold increase in intracellular triglyceride accumulation when compared with other GTs.¹⁸ The development of hepatic steatosis results in accelerated development of hepatic fibrosis.¹⁹ In one study, patients with HCV infection with significant steatosis were noted to have elevated fibrosis scores when compared with those with less steatosis. When compared with individuals infected with GT 1 and 4, subjects infected with GT 3 have been found to have a faster rate of hepatic fibrosis progression over time.²⁰

Studies of GT 3-infected subjects have noted a correlation of elevated viral load with increased hepatic fibrosis.²¹ Moreover, in patients with GT 3 infection, eradication of virus has been found to improve and, in some cases, resolve steatosis. This has not been observed in GT 1 infection.^{6,14,19,22} Within the posttransplant setting, patients with GT 3 have been found to have histologic recurrence of hepatic steatosis following orthotopic liver transplantation.²³

When patients with GT 3 infection were compared with those with GT 1, 2, or 4 infection, those with GT 3 were found to have an increased progression to cirrhosis at a younger age when compared with GT 1–infected individuals. In this study, GT 3–infected subjects were also found to have a higher incidence of hepatocellular carcinoma.²⁴ These findings corroborated previous retrospective data showing an increased risk of hepatocellular carcinoma in GT 3–infected individuals when compared with all other GTs (34% vs 17%).⁷ GT 3 infection is also associated with increased rates of decompensated cirrhosis, liver-related hospitalization, and death when compared with GT 1– and GT 2–infected individuals.⁸

TREATMENT

Interferon-Alfa-Based Regimens

Historically, treatment recommendations for GT 2 and GT 3 infection were coupled together. In the era of interferon-alfa-based regimens, for many years, a 24-week course of pegylated interferon and low-dose ribavirin (800 mg) was recommended for GT 2 and GT 3, whereas 48 weeks of therapy was recommended for GT 1 with pegylated interferon and weight-based ribavirin (1000–1200 mg per day in divided doses).^{25,26} When peginterferon alfa-2a plus ribavirin was compared with peginterferon alfa-2a alone versus interferon alfa-2b alone, treatment response rates were noted to be improved with peginterferon alfa-2a plus ribavirin (56%), versus 44% and 36%, respectively. When treatment response rates for GT 1 infection were compared with response rates for GT 2 or 3 infection collectively, response rates were better for GT 2 and 3 (76% vs 46%).²⁷

In a subsequent trial, peginterferon alfa-2a and weight-based ribavirin therapy yielded a higher overall SVR rate of 63%. When individuals with GT 1 infection were compared with those with GT 2 and 3 infection, SVR rates with 48 weeks of therapy were 52% versus 80%. In this study, for GT 2– and 3–infected individuals, SVR rates were 84% versus 80% with 24 versus 48 weeks therapy, respectively. Additionally, although patients with GT 1 infection had higher response rates with standard weight-based ribavirin compared with a low, flat dose, response rates with weight-based ribavirin dosing did not benefit GT 2 and 3 infection compared with the low, flat dose.²⁸ Similar response rates were reported in another trial with peginterferon alfa2b and ribavirin with SVR rates of 42% for GT 1–infected patients versus 80% for patients with GT 2 and 3 infection after 48 weeks of therapy.²⁹ Only weight-based ribavirin dosing was investigated with this peginterferon alfa product. Nevertheless, the general recommendation for GT 2 or 3 infection was treatment with a 24-week course of peginterferon alfa plus a flat dose of 800 mg ribavirin. Although initially it was thought that GT 2 and 3 had similar response rates to one another, it soon became clear that GT 3–infected patients had lower SVR rates, largely secondary to an increased rate of virologic relapse.^{30,31}

It should also be noted that treatment with interferon-alfa-based therapies is limited by an unfavorable side effect profile, including influenza-like symptoms, psychiatric effects, such as depression, and cytopenias, among others, prohibiting widespread use of these regimens. Additionally, ribavirin use is associated with hemolytic anemia, lymphopenia, hyperuricemia, and rash. Ribavirin is also teratogenic, necessitating the use of contraception while on therapy and for 6 months thereafter. Furthermore, ribavirin is cleared by the kidney, mandating caution with use in patients with renal impairment.²⁵ Yet, pegylated interferon alfa once weekly and ribavirin 800 mg daily for 24 weeks constituted the standard of care for HCV GT 3 in the United States until late 2013. In some parts of the world, this regimen

remains the standard because of lack of availability of newer regimens and cost considerations.

Direct-Acting Antiviral Agents

In recent years, oral direct DAAs were approved for treatment of HCV. The first agents were the protease inhibitors, boceprevir and telaprevir, approved in the United States in 2011 in combination with pegylated interferon alfa and ribavirin for treatment of GT 1. These agents added significant toxicity to the standard interferon-alfa-based regimen, although higher SVR rates were observed in GT 1. Unfortunately, the new regimens were still suboptimal for GT 1, and they were not approved for therapies of other GTs, including GT 3. New oral regimens with DAAs were sought.

Studies with DAAs in GT 3 were first reported using sofosbuvir, an oral nucleotide analogue inhibitor of the HCV NS5B polymerase. Sofosbuvir, when used in combination with ribavirin within the context of an interferon-free regimen, was found to be effective in GT 2 and 3 patients, although there were lower SVR rates in GT 3–infected individuals. The FISSION trial randomized patients with GT 2 or 3 infection to therapy with sofosbuvir, 400 mg daily, plus ribavirin, 800 mg, in divided doses daily for 12 weeks or peginterferon alpha-2a plus ribavirin (the previous standard) for 24 weeks. In this study, overall SVR rates at 12 weeks following treatment completion were statistically equivalent between the two regimens, specifically 67% in each group. However, when GT 3 patients were evaluated separately, response rates were lower, 56% in patients receiving sofosbuvir plus ribavirin versus 63% in patients receiving peginterferon plus ribavirin. Fatigue, headache, nausea, and insomnia were seen in both treatment groups. However, the incidence of side effects was markedly less in the sofosbuvir regimen treatment arm.³² The POSITRON trial evaluated 207 patients with GT 2 or 3 infection who were interferon intolerant or ineligible. Subjects were treated with 12 weeks of sofosbuvir and weight-based ribavirin. SVR rates were slightly higher than those reported in the FISSION trial (61.2%). Adverse events were minimal, namely fatigue, insomnia, and anemia, a side effect profile characteristic of ribavirin therapy.³³

The FUSION trial assessed patients with HCV GT 2 or 3 and history of interferon treatment failure. Patients were treated with sofosbuvir and ribavirin for 12 or 16 weeks. GT 2 SVR rates were 86.1% in the 12-week arm and 93.8% in the 16-week arm. In comparison, lower SVR rates were noted in the GT 3 12- and 16-week treatment arms (29.7% and 61.9%, respectively). The adverse event profile was similar to the one in the POSITRON trial, with no appreciable difference in the 12- and 16-week regimens.³³ Because a longer course increased SVR rates in GT 3 patients, further extension of therapy was evaluated in the VALENCE trial in this population. Sofosbuvir and weight-based ribavirin were administered for 12 weeks in patients with GT 2 infection and 24 weeks in patients with GT 3. In this study, 93% of patients with GT 2 infection achieved SVR. Overall, 85% of patients with GT 3 infection achieved SVR, the highest rate yet.¹² In particular, SVR rates were 95% in treatment-naïve patients without cirrhosis and 92% in treatment-naïve subjects with cirrhosis. Patients that had failed therapy with pegylated interferon and ribavirin in the past, however, had lower SVR rates (87% in patients without cirrhosis and 62% in patients with cirrhosis). This phase 3 treatment program highlighted the difficulty in eradicating GT 3 infection, particularly in treatment-experienced patients with cirrhosis. In December 2013, the Food and Drug Administration approved a regimen of sofosbuvir and weight-based ribavirin for 24 weeks in GT 3 patients. Although an interferon-free regimen was now available for GT 3, the regimen was suboptimal, with lower SVR rates in treatment-experienced

patients with cirrhosis. Furthermore, a 24-week course with ribavirin was required. The impetus to develop new strategies remained.

The BOSON trial involved randomization of HCV GT 3–infected subjects to peginterferon alfa plus sofosbuvir and ribavirin for 12 weeks versus sofosbuvir plus ribavirin for 16 or 24 weeks. Patients who received peginterferon alfa had higher SVR rates (93%) when compared with those who received sofosbuvir and ribavirin (71% for 16 weeks and 84% for 24 weeks, respectively). Among the treatment-experienced cirrhotic cohort, interferon therapy was found to result in an improved SVR rate (86%) versus 47% and 77% for the 16- and 24-week sofosbuvir and ribavirin treatment arms, respectively.³⁴

More recently, sofosbuvir plus daclatasvir, an NS5A inhibitor, have also been studied in patients with HCV GT 1, 2, or 3. In patients with GT 3, subjects were randomized to a 4-week lead-in arm with sofosbuvir followed by sofosbuvir plus daclatasvir for 23 weeks versus sofosbuvir plus daclatasvir for 24 weeks versus sofosbuvir, daclatasvir, and ribavirin for 24 weeks. A total of 85% of patients treated with daclatasvir and sofosbuvir alone demonstrated SVR versus 100% treated with sofosbuvir, daclatasvir, and ribavirin.³⁵ In ALLY 3, treatment-naïve or experienced subjects received 12 weeks of therapy with sofosbuvir plus daclatasvir. The overall SVR rate was 89%, in treatment-naïve patients 90%, and in treatment-experienced patients 86%. In patients without cirrhosis, a 97% SVR was observed in treatment-naïve patients and a 94% SVR in the treatment experienced cohort. Response rates for patients with cirrhosis were lower, however, with SVR rates of 58% for treatment-naïve and 69% for treatment-experienced subjects.³⁶ Adverse events were minimal, with the most common side effects reported being fatigue, headache, and nausea. This 12-week, interferon and ribavirin-free regimen is appealing for GT 3 patients. Data from the ALLY-3+ study were published evaluating the response of daclatasvir in combination with sofosbuvir and ribavirin for 12 or 16 weeks. This study included only GT 3–infected patients with advanced fibrosis or cirrhosis who were either treatment naïve or experienced, although patients previously exposed to NS5A inhibitors were excluded. The overall SVR rate was 92% (91% in those treated with 12 weeks and 92% in those treated for 16 weeks). In patients with advanced fibrosis alone, a 100% response rate was observed with both 12 and 16 weeks of therapy. Response rates were slightly lower for patients treated who had underlying cirrhosis (88% with 12 weeks of therapy vs 89% for 16 weeks of therapy). In the treatment-experienced cirrhotic cohort, 12 weeks of therapy yielded an 88% response rate versus an 86% response rate with 16 weeks of therapy. The primary side effects observed were insomnia, headache, and fatigue, although none resulted in treatment discontinuation. Ribavirin dose reduction was undertaken in 12% of patients.³⁶

An extended duration of therapy with 24 weeks of daclatasvir and sofosbuvir with or without ribavirin has also been assessed as part of the European Multicenter Compassionate Use Program. This study enrolled patients infected with HCV at risk of decompensation within 12 months. Most of the patients in this study were cirrhotic (91%) with GT 3–infected patients comprising 17% of those studied. Response rates for GT 3–infected patients overall were 92%, with 85% who received sofosbuvir and ribavirin achieving SVR compared with 100% in those who received sofosbuvir, daclatasvir, plus ribavirin. The most common side effects were headache, nausea, fatigue, and anemia, the latter of which was observed in the ribavirin-containing arms³⁷

Ledipasvir, an NS5A inhibitor, has also been studied in GT 3–infected patients in combination with sofosbuvir. The ELECTRON-2 trial assessed response rates of sofosbuvir plus ledipasvir with or without ribavirin for 12 weeks in GT 1– and 3–infected individuals. Response rates of 100% were observed in treatment-naïve GT 3 patients

receiving ribavirin, although response rates were lower in treatment-naïve patients not administered ribavirin (64%).³⁸ Of note, this study included 15% GT 3–infected patients with cirrhosis, but the response rates for this subpopulation were not reported.

Another treatment recently approved includes sofosbuvir plus velpatasvir, an NS5A inhibitor with pan-genotypic activity. In one study, treatment-naïve, GT 3–infected patients without cirrhosis were treated with sofosbuvir and velpatasvir with or without ribavirin for 8 weeks. In this study, patients who received 100 mg of velpatasvir had response rates of 96% without ribavirin and 100% with ribavirin.³⁹ In a subsequent trial, GT 1– and 3–infected patients, treatment naïve or treatment experienced, were administered 12 weeks of sofosbuvir plus velpatasvir with or without ribavirin. This study, which included subjects with cirrhosis, demonstrated response rates of 100% in GT 3–infected patients without cirrhosis with 100 mg of velpatasvir with or without ribavirin. In patients with cirrhosis, 100% response rates were achieved with adjunctive ribavirin compared with SVR rates of 88% without ribavirin.⁴⁰

Data from the ASTRAL-3 trial were published showing favorable response rates for GT 3–infected individuals. In this study, treatment-naïve and -experienced patients with GT 3 infection were treated with sofosbuvir and ribavirin for 24 weeks versus sofosbuvir and velpatasvir for 12 weeks. This trial, which included subjects with cirrhosis, demonstrated a 95% response rate in the velpatasvir arm versus 80% in the regimen containing sofosbuvir and ribavirin alone. Side effects were minimal in the velpatasvir-containing arm, consisting primarily of headache and fatigue, with no treatment discontinuations attributed to adverse events.⁴¹ In regard to patients with GT 3 infection and decompensated cirrhosis, the ASTRAL-4 study assessed 12 weeks of velpatasvir and sofosbuvir with or without ribavirin compared with velpatasvir and sofosbuvir alone for 24 weeks. Response rates for 12 weeks of therapy without ribavirin were 50% as compared with 85% for 12 weeks of therapy with ribavirin. For those patients who received 24 weeks of therapy without ribavirin, response rates of 50% were observed.⁴² A recent paper assessing patient-related outcomes in individuals with both compensated and decompensated cirrhosis treated with velpatasvir and sofosbuvir found a significant improvement in patient-related outcome scores during treatment and following SVR. These scores were more significant among those patients who had decompensated cirrhosis.⁴³

Another study assessed sofosbuvir in conjunction with grazoprevir, an NS3/4A protease inhibitor, and elbasvir, an NS5A inhibitor. Treatment regimens with grazoprevir and elbasvir can be used in patients with renal dysfunction, including those on hemodialysis.⁴⁴ Sofosbuvir, however, is not recommended in patients with severe renal insufficiency or who are on dialysis. These agents, when used in treatment-naïve GT 3 patients without cirrhosis for either 8 or 12 weeks of therapy, were found to yield response rates of 93% and 100%, respectively. Of those patients who had underlying cirrhosis, response rates were 91% after 12 weeks of treatment.⁴⁵

Emerging Therapies for Genotype 3

Glecaprevir/pibrentasvir

Glecaprevir, an NS3/NS4A inhibitor, and pibrentasvir, an NS5A inhibitor, are two emerging therapies currently being studied. These drugs have minimal renal excretion, thus being a viable option for patients with significant renal dysfunction, including individuals who are on hemodialysis. In the EXPEDITION-IV study, a total of 104 patients with renal insufficiency were treated, 82% of whom were on hemodialysis. In the modified intention-to-treat analysis, 100% of patients achieved SVR 12 after treatment for 12 weeks. Eleven percent of the patients in this study had GT 3 infection, with 19% of the overall cohort having cirrhosis, none of whom were decompensated. No major

side effects were observed, with most treatment-related side effects being pruritus (20%), fatigue (14%), and nausea (12%).⁴⁶

Grazoprevir/ruzasvir/uprifosbuvir

Grazoprevir/ruzasvir/uprifosbuvir is a combination of an NS3/NS4 inhibitor (grazoprevir), a new pangenotypic NS5A inhibitor (ruzasvir), and a new NS5B polymerase inhibitor (uprifosbuvir). In Part B of C-CREST-1&2, this combination was studied in patients with HCV GTs 1, 2, or 3 infection. Patients were either treatment naive or treatment experienced with prior interferon-based therapies. Treatment was administered for 8, 12, or 16 weeks, with or without ribavirin. This study included a total of 337 GT 3–infected patients, 35% of whom had cirrhosis. Sustained virologic rates for 8, 12, and 16 weeks of therapy were 95%, 97%, and 96%, respectively. Regarding ribavirin, in the 8-week group, response rates of 94% without ribavirin and 98% with ribavirin were noted. In the 12-week arms, individuals who did not receive ribavirin had response rates of 97% versus 99% with ribavirin. In the 16-week group, numerically higher response rates were found in those who did not receive ribavirin (98%) as compared with those who did (96%). Response rates in patients with compensated cirrhosis were not significantly different, and included SVR rates of 100% at 12 weeks with ribavirin and 100% at 16 weeks without ribavirin. In patients who were both treatment-experienced and had cirrhosis, 100% response rates were achieved at 12 weeks with and without ribavirin and at 16 weeks without ribavirin. Pretreatment RAVs were found in 4% of patients treated for 8 weeks and 5% of those treated for 12 weeks, with response rates in that population of 50% in the 8-week arm and 71% in the 12-week arm. Minor common side effects included headache (22%), fatigue (19%), and nausea (13%), with one death during the study period caused by bacterial sepsis unrelated to study-drug.⁴⁷

In patients who relapsed to a short course (8 weeks) of antiviral therapy with grazoprevir, uprifosbuvir, and either elbasvir or ruzasvir in an earlier trial, C-CREST Part C studied retreatment with grazoprevir, ruzasvir, and uprifosbuvir and ribavirin for 16 weeks. A total of 24 patients were enrolled, eight of whom had GT 3 infection. RAVs to NS3 were found in all eight patients, and seven of eight had NS5A RAVs. All patients with GT 3 infection who were retreated achieved SVR 12. The results of this study are reflective of efficacy of retreatment despite treatment failure when a truncated duration of therapy was used.⁴⁸

The issue of resistance

Testing for RAVs is recommended in patients prone to treatment failure or relapse, particularly those who have cirrhosis, are treatment naive, or both. When detected, they may help to identify patients who may require a longer duration of therapy and/or addition of ribavirin to optimize SVR rates.⁹

Emerging Therapies for Direct-Acting Antiviral Failures

Sofosbuvir/velpatasvir/voxilaprevir

Sofosbuvir, velpatasvir, and voxilaprevir, a new pangenotypic NS3/NS4 inhibitor, have been examined in patients with GT 3. In the POLARIS-1 study, 263 patients who previously were exposed to NS5A inhibitors were treated with a 12-week course of the three medications. Thirty percent had GT 3; 46% of the overall cohort was cirrhotic. SVR 12 was noted in 96% of the overall treatment cohort, and 93% of cirrhotics. SVR rates in patients with GT 3, specifically, were 95%. Adverse events were mild and included headaches (25%), fatigue (21%), diarrhea (18%), and nausea (14%). RAVs were noted in 83% of patients overall, with 79% having NS5A RAVs. A total of 96% of subjects with any RAV achieved SVR 12, and 94% with NS5A RAVs

achieved SVR 12. This regimen, which should soon be available, seems to be a viable solution for patients who have failed an NS5A inhibitor.⁴⁹

Whereas POLARIS-1 enrolled patients who were treatment experienced to NS5A inhibitors, POLARIS-4 enrolled patients who were treatment experienced with NS3/4A protease inhibitors and NS5B inhibitors. In this study, patients with GTs 1 to 6 were randomized in a one-to-one fashion to sofosbuvir, velpatasvir, or voxilaprevir versus sofosbuvir and velpatasvir alone for 12 weeks. Forty-six percent of the overall cohort had compensated cirrhosis. Among those with GT 3 infection, 54 were randomized to sofosbuvir, velpatasvir, and voxilaprevir with 94% achieving SVR 12 as compared with 85% of the 52 patients randomized to sofosbuvir and velpatasvir for 12 weeks. Treatment side effects were similar to those seen in POLARIS-1 with no discontinuations related to adverse drug-related events.⁵⁰

Glecaprevir/pibrentasvir

This regimen has been studied in patients with DAA failure. In the SURVEYOR-II, Part 3 trial, 131 GT 3–infected patients were randomized to 12 or 16 weeks of therapy. Patients who were treatment naive or experienced, with or without cirrhosis, were included. RAVs were identified at baseline in 21%, most being NS5A RAVs (18% overall). Treatment-experienced patients without cirrhosis randomized to 12 or 16 weeks of therapy achieved SVR 12 rates of 91% and 96%, respectively. Treatment-naive patients with cirrhosis treated for 12 weeks achieved SVR 12 rates of 98%, and treatment-experienced patients with cirrhosis had response rates of 96%. The most common side effects reported were fatigue and headache, with no treatment discontinuations attributed to study drug. The combination of these two agents, which should soon be available, will provide a viable option for GT 3 patients with prior treatment experience.

CURRENT TREATMENT RECOMMENDATIONS

It should be noted that the landscape for HCV therapy is rapidly changing given the advent of newer DAA therapies. A guidance document with treatment recommendations from the American Association of the Study for Liver Diseases and the Infectious Diseases of America is frequently updated to reflect the changing landscape.

Currently, for treatment-naive GT 3–infected patients without cirrhosis, 12 weeks of daclatasvir plus sofosbuvir are recommended. An alternate recommended regimen for this population is velpatasvir and sofosbuvir for 12 weeks (**Table 1**).

For patients who are treatment naive with cirrhosis, 12 weeks of velpatasvir plus sofosbuvir are recommended. As an alternative regimen, 24 weeks of therapy with daclatasvir plus sofosbuvir with or without weight-based ribavirin is recommended.

In patients who are treatment experienced with interferon and without cirrhosis, 12 weeks of daclatasvir plus sofosbuvir or the combination of velpatasvir plus sofosbuvir for 12 weeks are recommended. For patients who are treatment experienced with cirrhosis, 12 weeks of velpatasvir plus sofosbuvir and weight-based ribavirin or elbasvir/grazoprevir plus sofosbuvir for 12 weeks are recommended. An alternate to these regimens is 24 weeks of daclatasvir plus sofosbuvir with weight-based ribavirin.

In patients who are treatment experienced with a sofosbuvir-containing regimen, who do not require urgent treatment, and who do not have evidence of cirrhosis, treatment deferral is recommended. For those who require urgent treatment regardless of cirrhosis status, 24 weeks of daclatasvir plus sofosbuvir with weight-based ribavirin is recommended. An alternate to this is 12 weeks of velpatasvir and sofosbuvir with weight-based ribavirin.

Table 1
Current American Association of the Study for Liver Diseases treatment recommendations for genotype 3 infection

	Noncirrhotic	Cirrhotic
Treatment naive	DCV + SOF × 12 wk VEL + SOF × 12 wk	DCV + SOF ± R × 24 wk VEL + SOF × 12 wk
Treatment experienced (interferon)	DCV + SOF × 12 wk VEL + SOF × 12 wk	DCV + SOF + R × 24 wk VEL + SOF + R × 12 wk ELB/GRA + SOF × 12 wk
Treatment experienced (sofosbuvir)	Defer therapy (nonurgent) If urgent DCV + SOF + R × 24 wk VEL + SOF + R × 12 wk ELB/GRA + SOF × 12 wk	DCV + SOF + R × 24 wk VEL + SOF + R × 12 wk ELB/GRA + SOF × 12 wk
	Decompensated cirrhosis	LDV + SOF + r × 24 wk DCV + SOF + r × 24 wk VEL + SOF + R × 12 wk

Abbreviations: DCV, daclatasvir; ELB/GRA, elbasvir/grazoprevir; SOF, sofosbuvir; SOF + r, sofosbuvir with low-dose ribavirin; SOF + R, sofosbuvir with weight-based ribavirin; VEL, velpatasvir.

Table 2
Treatment response rates by regimen

	Treatment-Naive Noncirrhotic, %	Treatment-Experienced Noncirrhotic, %	Treatment-Naive Cirrhotic, %	Treatment-Experienced Cirrhotic, %
SOF + R × 24 wk (VALENCE)	95	92	87	62
SOF + PR × 12 wk (BOSON)	96	91	94	86
SOF + DCV × 12 wk (ALLY-3)	97	94	58	69
	Overall	Noncirrhotic	Overall	Cirrhotic
SOF + DCV × 24 wk		N/A		100
	Treatment	Naive	Treatment	Experienced
SOF + LDV + R × 12 wk (ELECTRON-2)		100		82
	Treatment-naive noncirrhotic	Treatment-naive cirrhotic	Treatment-experienced noncirrhotic	Treatment-experienced cirrhotic
SOF + VEL × 12 wk (ASTRAL -3)	98	93	91	89
	Treatment-naive noncirrhotic 8 wk	Treatment-naive noncirrhotic 12 wk		Treatment-naive cirrhotic 12 wk
SOF + ELB/GRA × 8–12 wk	100	100		91

Abbreviations: DCV, daclatasvir; ELB, elbasvir; GRA, grazoprevir; LDV, ledipasvir; PR, Peg interferon + ribavirin; SOF, sofosbuvir; SOF + R, sofosbuvir with weight-based ribavirin; VEL, velpatasvir.

In individuals with decompensated cirrhosis, ledipasvir with sofosbuvir, and ribavirin (600 mg daily), or daclatasvir with sofosbuvir and ribavirin (600 mg) are recommended for 12 weeks. Ribavirin dosage should be increased as tolerated. An alternate is velpatasvir plus sofosbuvir and weight-based ribavirin for 12 weeks⁵¹

SUMMARY

GT 3 HCV is associated with a more aggressive clinical course when compared with other HCV GTs. This provides the impetus to actively treat patients with GT 3. Unfortunately, GT 3 has proven to be the most difficult to eradicate with the new DAAs.⁶ In particular, treatment-naïve and treatment-experienced patients with cirrhosis have the lowest response rates. With the current regimens, it seems that longer courses and the addition of ribavirin may improve response rates (**Table 2**). Effective, well-tolerated regimens are now available. For patients who have failed therapy with DAAs, new regimens should be available in the near future. Antiviral therapy for patients with GT 3 should be implemented when possible.

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