Perspective

Treating HCV Infection: It Doesn't Get Much Better Than This

Direct-acting antiviral (DAA) regimens now allow treatment of previously untreated or treated (including prior DAA failures) patients with chronic hepatitis C virus (HCV) infection with 8 or 12 week regimens, largely without the use of ribavirin. Newer next-generation pan-genotypic regimens with activity against resistance-associated substitutions include glecaprevir/pibrentasvir (GLE/PIB), a combination of a nonstructural protein (NS)3 protease inhibitor and an NS5A inhibitor, and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX), a combination of an NS5B polymerase inhibitor, NS5A inhibitor, and NS3 protease inhibitor. Both regimens have indications in DAA-experienced patients. GLE/PIB is approved for treatment of patients with genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis and for the treatment of patients with genotype 1 infection previously treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor, but not the combination. SOF/VEL/VOX is approved for retreatment of patients without cirrhosis or with compensated cirrhosis with genotype 1, 2, 3, 4, 5, or 6 infection previously treated with an NS5A inhibitor-containing regimen, or with genotype 1a or 3 previously treated with a SOF-containing regimen without an NS5A inhibitor. This article summarizes an IAS-USA webinar given by Susanna Naggie, MD, MHS, on August 30, 2018.

Keywords: HCV, hepatitis C, direct-acting antiviral, retreatment, pan-genotypic, glecaprevir, pibrentasvir, sofosbuvir, velpatasvir, voxilaprevir

It is estimated that approximately 71 million people worldwide (1% of population) have active hepatitis C virus (HCV) infection.[1] As of 2015, there were an estimated 1.75 million new infections per year. Global annual mortality from hepatitis, driven by HCV and hepatitis B virus (HBV), is increasing. As of 2015, related mortality was virtually identical to that caused by tuberculosis as the leading infectious disease causes of death.[1] In order to eliminate HCV disease, it will be necessary to decrease transmission of the virus, reach the populations at the highest risk for transmission and infection, and ensure that these patients are engaged in care and treatment.

Chronic HCV Treatment

Figure 1 shows direct-acting antivirals (DAAs) available for treatment of chronic HCV infection. These include: the HCV nonstructural protein (NS)3-4A protease inhibitors grazoprevir, glecaprevir (GLE), and voxilaprevir (VOX); the NS5A inhibitors daclatasvir, elbasvir, ledipasvir, velpatasvir (VEL), and pibrentasvir (PIB); and the NS5B polymerase inhibitor sofosbuvir (SOF). DAA regimens include 2 or 3 targeted mechanisms in combination to overcome the rapid emergence of resistance that occurs with single-target therapy.

Before starting anti-HCV therapy, it is necessary to know whether or not a patient has cirrhosis, the patient's prior treatment experience (including prior exposure to DAAs), and whether resistance testing is required. In addition, patients' renal and liver function must be assessed, including calculation of the Child-Pugh (CP) score for all patients with cirrhosis. The potential for drug interactions must be considered, and the HBV status must be determined. Whether the genotype or subtype of the infecting virus is required is debatable. With pan-genotypic regimens there is the potential to forgo this testing and in some clinical situations this may be desirable. There are also situations in which knowledge of genotype prior to therapy may be useful. For example, in groups at high risk for reinfection, knowledge of the

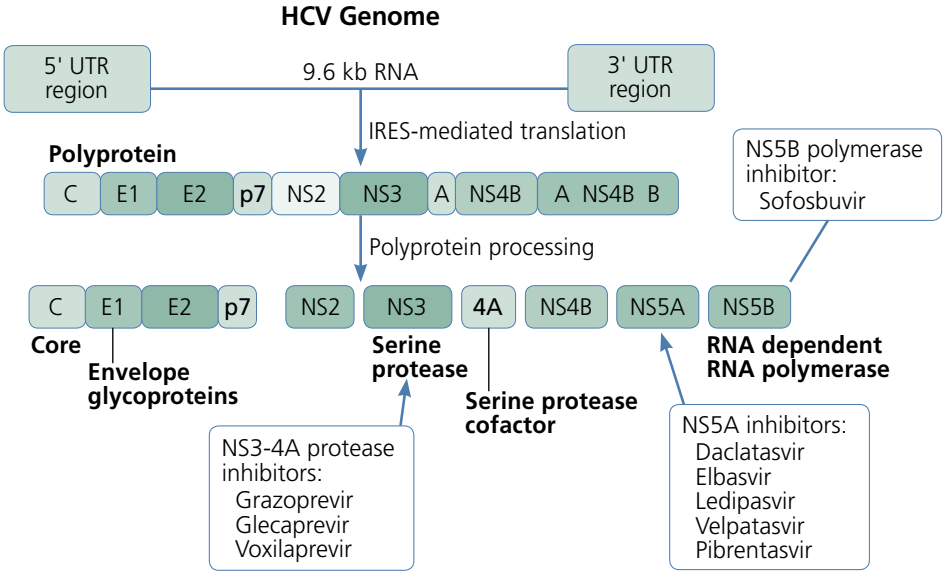

Figure 1. Direct-acting antivirals and viral targets in the HCV genome. IRES indicates internal ribosome entry site; NS, nonstructural protein. Adapted from Naggie et al.[17]

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underlying genotype or subtype may be useful in differentiating relapse from reinfection.

The American Association for the Study of Liver Disease (AASLD) and Infectious Diseases Society of America (IDSA) guidelines website (https://www.hcvguidelines.org)[2], updated on May 24, 2018, includes an active interface that allows users to enter items including genotype or subtype and presence or absence of cirrhosis and provides HCV regimen recommendations based on the information entered. The website also includes easier access to recommendations for treatment and management of key populations, including persons who inject drugs, men who have sex with men, and persons in correctional facilities.

Table 1 shows the AASLD/IDSA recommended regimens for treatment-naive or peginterferon/ribavirin (PEG/RBV)-experienced patients with HCV genotypes 1, 2, and 3 without cirrhosis or with compensated cirrhosis. As shown, these regimens are 8 or 12 weeks in duration and largely eliminate the need for ribavirin. Selection of particular regimens may depend on the presence of severe renal dysfunction, in which case sofosbuvir (SOF) is to be avoided; the presence of liver dysfunction (CP score B or C), in which case NS3 protease inhibitors are to be avoided; the need to consider other therapies instead of the combination of elbasvir/grazoprevir in patients with genotype 1a infection with NS5A resistance-associated substitutions (RASs); and the need to consider potential interactions with drugs a patient may be taking for other conditions, such as HIV or HBV infection. All anti-HCV DAAs carry a black box warning for the potential reactivation of HBV infection, which has been primarily described in patients with positive HBV surface antigen who are not on active nucleoside analogue therapy. Recommendations for some patients with genotype 3 infection are somewhat more complicated. For patients with cirrhosis or prior PEG/RBV treatment, NS5A RAS testing is recommended. For those with high fold change RASs detected or in whom prior treatment with NS5A inhibitors or SOF-containing regimens has failed, triple-combination regimens are recommended.

Recently Approved Pan-Genotypic Regimens

Glecaprevir/Pibrentasvir

Glecaprevir/pibrentasvir (GLE/PIB) is a pan-genotypic regimen, combining a next-generation NS3 inhibitor with a next-generation NS5A inhibitor. It was approved in 2017 for treatment of patients with genotype 1, 2, 3, 4, 5, or 6 infections without cirrhosis (8 weeks) or with compensated cirrhosis (12 weeks), and for the treatment of patients with genotype 1 infection previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not the combination (16 weeks).[3]

GLE/PIB is a coformulated regimen (3 pills once a day), with activity against resistance mutations to previously administered NS3 and NS5A inhibitors, including NS3 RAS at codons 80, 155, 168 and NS5A RAS at codons 28, 30, 31, 93. The drugs are not renally excreted, and can be used in patients with severe renal dysfunction or end-stage renal disease. Since the regimen contains a protease inhibitor, it should not be used by patients with severe liver disease (CP B or C) due to higher exposure to the protease inhibitor and potential risk of hepatotoxicity. Protease inhibitors are also associated with a greater number of drug-drug interactions. Use with acid-suppressing medications remains a matter of debate, since pharmacokinetic studies reported reduced GLE exposure in the setting of concomitant dosing with proton pump inhibitors; however, use of acid-suppressing agents was permitted in phase II and III studies and available data do not indicate a reduction in sustained virologic response (SVR) rates in patients taking these agents.[4]

The GLE/PIB clinical development program focused on an 8-week treatment course of treatment-naive patients and patients with PEG/RBV failure without cirrhosis, a 12-week course in patients with cirrhosis, approval for use in renal impairment, HIV coinfection, and the post-liver transplantation setting. The regimen was not extensively evaluated in the DAA salvage setting and in this setting 12 to 16 weeks of therapy was assessed.

Figure 2 shows pooled SVR rates in studies of GLE/PIB by HCV genotype with 8 (n=828) or 12 (n=1076) weeks of treatment in patients without cirrhosis. Patients were treatment-naive or had previous treatment failures with PEG/RBV with or without sofosbuvir or with SOF/RBV.[5,6] As shown, SVR

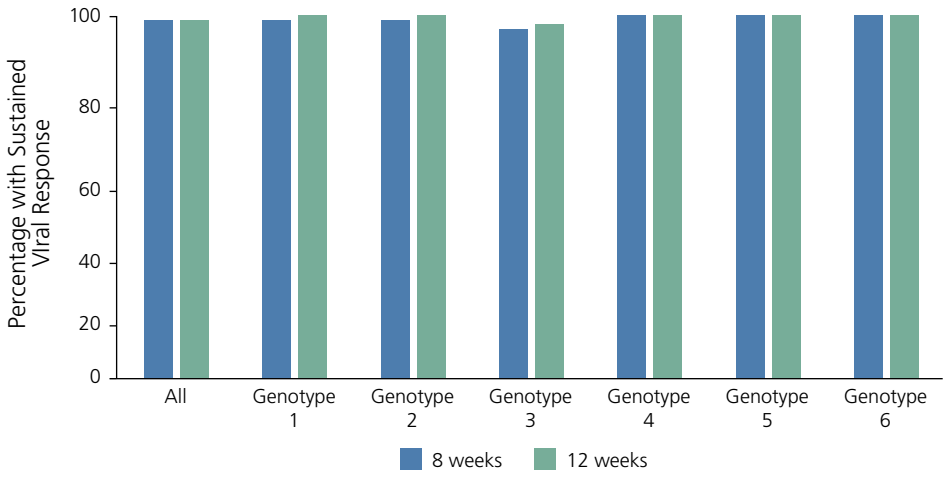

Figure 2. Pooled sustained viral response rates in studies of glecaprevir/pibrentasvir by hepatitis C virus genotype with 8 or 12 weeks of treatment in patients without cirrhosis. Patients were treatment-naive or had treatment failures with peginterferon/ribavirin with or without sofosbuvir or with sofosbuvir/ribavirin (treatment-experienced). Adapted from Puoti et al and Zeuzem et al.[5,6]

Table 1. American Association for the Study of Liver Disease/Infectious Diseases Society of America Recommended Regimens and Lengths of Treatment for Treatment of Hepatitis C Virus (HCV) Infection, 2018.[2]

Regimen	Weeks	Rating[a]
Recommended regimens for treatment-naive or PEG/RBV-experienced patients with HCV genotype 1 without cirrhosis		
Elbasvir/grazoprevir (except GT1a with NS5A RAS)	12	I, A
Glecaprevir/pibrentasvir	8	I, A
Ledipasvir/sofosbuvir	8[b]-12	I, A/B
Sofosbuvir/velpatasvir	12	I, A
Recommended regimens for treatment-naive or PEG/RBV-experienced patients with HCV genotype 1 with compensated cirrhosis		
Elbasvir/grazoprevir (except GT1a with NS5A RAS)	12	I, A
Glecaprevir/pibrentasvir	12	I, A
Ledipasvir/sofosbuvir	12[c]	I, A
Sofosbuvir/velpatasvir	12	I, A
Recommended regimens for treatment-naive or PEG/RBV-experienced patients with HCV genotype 2 with or without compensated cirrhosis		
Glecaprevir/pibrentasvir	8/12	I, A/B
Sofosbuvir/velpatasvir	12	I, A
Recommended regimens for treatment-naive patients with HCV genotype 3 with or without compensated cirrhosis		
Glecaprevir/pibrentasvir	8/12	I, A/B
Sofosbuvir/velpatasvir (NS5A RAS testing)[de]	12	I, A
Recommended regimens for PEG/RBV-experienced patients with HCV genotype 3 with or without compensated cirrhosis		
Sofosbuvir/velpatasvir (NS5A RAS testing)[e]	12	I, A
Elbasvir/grazoprevir + sofosbuvir (cirrhosis)[f]	12	I, B
Sofosbuvir/velpatasvir/voxilaprevir (cirrhosis)[f]	12	IIb, B

Adapted from http://hcvguidelines.org/, December 18, 2018.

Abbreviations: PEG/RBV, peginterferon/ribavirin; NS5A, nonstructural protein 5a; RAS, resistance-associated substitution; GT, genotype.

[a]See https://www.hcvguidelines.org/contents/methods/table-2 for explanation.

[b]Treatment-naive only with baseline HCV RNA <6 million IU/mL.

[c]PEG/RBV failure requires addition of RBV for ledipasvir/sofosbuvir which is an alternative.

[d]RAS testing is only recommended for patients with cirrhosis.

[e]A different regimen is recommended if high fold RAS is present.

[f]Not an FDA-approved use.

rates did not differ between 8-week and 12-week courses. The SVR rate was 97% in genotype 3 disease with 8 weeks of treatment, and although this is a very high rate, it still raised concerns about the shorter treatment course for this genotype, particularly among treatment-experienced patients with genotype 3 infection. A separate study (ENDURANCE-3) in patients with treatment-naive genotype 3 infection without cirrhosis showed noninferiority of an 8-week course and a 12-week course with a 12-week course of daclatasvir/SOF, with SVR rates of 95%, 95%, and 97% respectively.[5] It is important to note that 50% (n=5) of the virologic failures with GLE/PIB occurred in patients with an A30K mutation at baseline. Although the A30K does not confer resistance to PIB, it appears to lower the barrier to the development of the Y93H, which in combination confer a 69-fold resistance to PIB.

In Part 3 of the SURVEYOR-2 treatment salvage study, treatment-experienced patients with genotype 3 infection achieved SVR at 12 weeks (SVR12) in 91% (20/22) of patient) with a 12-week course and in 96% (21/22) of patients with a 16-week course.[7] Among treatment-naive patients with cirrhosis, SVR12 was 98% (39/40 patients) with a 12-week course, whereas a 16-week course in treatment-experienced patients with cirrhosis resulted in an SVR12 of 96% (45/47 patients). These findings contributed to the recommendation of a 12-week course in treatment-naive patients with cirrhosis and a 16-week course in PEG/RBV-experienced patients with or without cirrhosis.

The EXPEDITION-4 study enrolled 104 patients with renal impairment (all with glomerular filtration rate [GFR] <30 mL/min; 82% on dialysis) and genotypes 1 to 6 infection and reported an SVR12 of 98% with 12 weeks of treatment.[8,9] The current recommendations are 8 weeks for treatment-naive patients without cirrhosis and 12 weeks for those with cirrhosis, which is consistent with the recommendations in patients without renal dysfunction.

The EXPEDITION-2 study enrolled 151 patients with HIV/HCV coinfection, including 15 with cirrhosis, and 19% with prior treatment. Those without cirrhosis (n=136) received an 8-week course of therapy and achieved 100% SVR12 and those with cirrhosis received a 12-week course of therapy and achieved 93% (14/15) SVR12.[10] These data led to the approval of GLE/PIB in patients with HIV/HCV coinfection. With regard to drug-drug interactions with GLE/PIB, antiretroviral drugs that should not be used concomitantly include boosted atazanavir, boosted darunavir, efavirenz, and etravirine. Data are unclear for cobicistat-boosted elvitegravir due to increased exposures to GLE in the setting of the pharmacologic booster or cirrhosis and the

Table 2. Glecaprevir/Pibrentasvir Safety Profile in Individuals With (n=228) or Without (n=1977) Cirrhosis.[18]

Adverse Event (AE)	No cirrhosis n (%)	Cirrhosis n (%)
Any AE	1316 (67)	213 (74)
AE ≥10%		
- Headache	363 (18)	47 (16)
- Fatigue	272 (14)	58 (20)
Any serious AE	31 (2)	17 (6)
Drug-related serious AE	1 (<0.1)	0
AE leading to discontinuation	8 (0.4)	0
Drug-related AE ≥ grade 3	4 (0.2)	0
Fatal AE	2 (0.1)	0
Death	5 (0.3)	1 (0.3)

enrollment of only 1 participant on this regimen in the registration trial. Agents that can be used concomitantly include rilpivirine, raltegravir, dolutegravir, bictegravir, and nucleoside reverse transcriptase inhibitors (nRTIs).

Safety data for GLE/PIB are summarized in Table 2. The most common adverse events of any grade in both patients with and without cirrhosis were headache and fatigue, which are commonly reported with all DAA therapies.

Sofosbuvir/Velpatasvir/Voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is a pan-genotypic regimen with activity against NS3 RASs at codons 80, 155, and 168 and NS5A RASs at codons 28, Q30, and 31. Similar to other protease inhibitor-containing regimens, it is not safe for use in patients with CP B or C liver disease and poses increased risk for drug-drug interactions. Since it contains SOF, it is not approved for use in patients with GFR below 30 mL/min or end-stage renal disease. VEL exposure is reduced with concomitant use of acid-suppressing agents, thus when possible concomitant dosing should be avoided and at a minimum a strict dosing schedule followed per the package insert. It is approved as a 12-week course for retreatment of patients without cirrhosis or with compensated cirrhosis with genotype 1, 2, 3, 4, 5, or 6 infection previously treated with an NS5A inhibitor-containing regimen, or with genotype 1a or 3 previously treated with a SOF-containing regimen without an NS5A inhibitor.

The clinical development program for SOF/VEL/VOX focused on an 8-week treatment course in treatment-naive patients and PEG/RBV-experienced patients and on use in salvage of patients with prior DAA treatment failure. There was no registration trial in patients with HIV infection, liver transplantation, or renal disease. Although there is no expectation that patients with HIV infection would respond differently to new DAA regimens, their exclusion in registration trial programs like SOF/VEL/VOX limit the information provided to clinicians in light of the potential drug-drug interactions that are unique to this population.

In the POLARIS 2 trial, the 8-week treatment course failed to meet noninferiority compared with a 12-week course of SOF/VEL in treatment-naive or PEG/RBV-experienced patients.[11] This failure to meet the predefined noninferiority margins was due to a lower-than-expected SVR rate of 92% in participants with genotype 1a infection. Based on those findings, the regimen was not approved in the United States as an 8-week course in treatment-naive or PEG/RBV-experienced patients. A relapse rate of approximately 4% was observed in the genotype 1a group. Although the reason for the higher failure rate in genotype 1a is not clear, the increased prevalence of the baseline Q80K mutation has been identified as a potential risk factor. The RAS, which is prevalent in US populations, decreases the barrier to resistance for treatment emergent RASs without conferring resistance to VOX in and of itself.

Meanwhile, the 8-week course was approved in Europe, where SVR rates were 97%. In a post-hoc analysis by the European Medicines Agency,[12] baseline variables associated with virologic failures included the presence of the Q80K mutation, IL28B T allele, and higher HCV RNA level and higher body mass index at baseline, all of which are more common in the United States.

Table 3. Sofosbuvir/Velpatasvir/Voxilaprevir Safety Profile in Individuals With (n=405) or Without (n=1056) Cirrhosis.[19]

Adverse Event (AE)	No cirrhosis n (%)	Cirrhosis n (%)
Any AE	790 (75)	308 (76)
AE ≥10%		
- Headache	277 (26)	--
- Fatigue	233 (22)	--
- Diarrhea	188 (18)	--
- Nausea	162 (15)	--
Any serious AE	26 (2.5)	7 (0.7)
Drug-related serious AE	0	0
AE leading to discontinuation	1 (0.1)	1 (0.2)
AE ≥ grade 3	21 (2)	8 (0.7)
Death	2 (0.2)	1 (0.2)

With regard to drug-drug interactions with SOF/VEL/VOX, antiretroviral drugs that should not be used concomitantly include boosted atazanavir, efavirenz, and etravirine; data are unclear for boosted darunavir and cobicistat-boosted elvitegravir due to increased voxilaprevir exposures in non-infected volunteer studies.[13] Agents that can be used concomitantly with SOF/VEL/VOX include rilpivirine, raltegravir, dolutegravir, bictegravir, and nRTIs. Headache and fatigue are the most common adverse events of any grade, with gastrointestinal adverse events also being common (Table 2).

Salvage Treatment in DAA-Experienced Patients

Retreatment in 2019 is primarily focused on patients with prior DAA failures. The considerations for retreatment should primarily consider whether the prior treatment regimen included an NS5A inhibitor. Prior failure of an NS5A-containing regimen increases the risk of treatment emergent NS5A RASs, which are fit and can be long-lived. Furthermore, the presence of these treatment emergent RASs may increase the risk of relapse with some salvage regimens.

Data from small numbers of DAA-experienced patients treated with GLE/PIB indicated poorer outcomes in patients with previous failure with the combination of a protease inhibitor and an NS5A inhibitor.[14] This was in large part because these individuals were more likely to have RASs in both gene targets. Higher SVR rates were seen in patients in whom only an NS5A inhibitor had previously failed (88% with 12 weeks of treatment, 94% with 16 weeks of treatment). The best outcomes occurred in those in whom only a protease inhibitor had previously failed (SVR in 100% with 12 and 16 weeks of treatment).[15] Such findings supported the US Food and Drug Administration approval of a 16-week course of treatment for patients with genotype 1 infection previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both in combination.

With regard to SOF/VEL/VOX, a trial in patients with prior non-NS5A inhibitor failure (POLARIS 4) showed SVR12 rates of 97% among 182 patients treated with 12 weeks of SOF/VEL/VOX versus 90% among 151 patients with 12 weeks of SOF/VEL.[16] However, analysis by genotype indicated that SOF/VEL performed as well as SOF/VEL/VOX in genotypes 1b, 2, and 4, whereas SVR12 rates were higher with SOF/VEL/VOX in genotypes 1a (98% vs 89%) and 3 (94% vs 85%). These data supported the approval of SOF/VEL/VOX in genotypes 1a and 3, although retreatment of other genotypes would be recommended with SOF/VEL for 12 weeks.

In a study in patients with NS5A inhibitor failure (POLARIS 1), 12 weeks of SOF/VEL/VOX resulted in SVR12 rates of 97% among 142 patients without cirrhosis and 93% among 121 with cirrhosis,[16] with relapses being observed among patients with genotype 3 infection and cirrhosis. The 12-week regimen is approved for all genotypes in patients without cirrhosis. Current recommendations are to add RBV in DAA experienced patients with cirrhosis and genotype 3 infection.

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