Hepatitis C Therapy: Game Over!


Treatment of chronic hepatitis C virus (HCV) infection has improved considerably in the last 5 years with the introduction of direct-acting antiviral (DAA) agents that target key steps of the HCV replication cycle.1 DAAs are able to halt HCV replication by inhibiting the activity of 3 nonstructural (NS) viral proteins: the NS3 protease, the NS5B polymerase, and the NS5A protein. Combinations of 2 or 3 DAAs have been shown to be highly effective and safe in phase III clinical trials and large real life cohorts, providing sustained virologic response (SVR) rates of >90%.2,3 Although the greatest challenge that clinicians, stakeholders, and patients with HCV are facing currently is how to expand access to treatment to all HCV patients, there are therapeutic areas where gaps in knowledge remain, and areas where treatment optimization is required.4 With respect to previously untreated patients, shortening the duration of treatment below the standard of care 12 weeks is a relevant aim because it provides clinical and public health benefits. Shorter treatment durations could be particularly useful for large-scale strategies aimed at eliminating HCV in marginalized HCV populations, that not only are at the core of new incident HCV cases, but also might suffer from reduced adherence to medications.5 Last, a shorter course of therapy would likely decrease the direct health care costs of treatment, thus positively impacting on access to DAAs.6 Current HCV treatment guidelines support 8 weeks of treatment only in HCV-1 treatment-naïve patients receiving sofosbuvir/ledipasvir who do not have cirrhosis and have a baseline HCV-RNA of <6,000,000 IU/mL.7,8 In the current issue of Gastroenterology, and Lawitz et al6 and Gane et al8 provide evidence that by combining 3 classes of DAAs, the NS5B polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the new protease inhibitor GS-9857 (voxilaprevir), 6 to 8 weeks of treatment could be the new standard of care for treatment-naïve patients infected with HCV-1, -2, -3, and -4.9,10 In the study by Lawitz et al,8 SVR rates in HCV-1 patients after 8 weeks of treatment were 100% in noncirrhotic patients and 94% in cirrhotic patients. In patients with HCV genotypes 2, 3, 4, and 6, Gane et al3 analyzed the efficacy of 6 weeks of treatment in noncirrhotic patients and 8 weeks of treatment for cirrhotic patients. SVR rates in non cirrhotic patients were 67% for HCV-2, 100% for HCV-3, and 60% for HCV-4; the corresponding figures for patients with cirrhosis who received 8 weeks of therapy were 100%, 94%, and 80%. With all the caveats related to the relatively small sample size that calls for validation in a larger phase III study, these data obtained in treatment-naïve patients compare well with those reported with 12 weeks of treatment with sofosbuvir/velpatasvir a recently approved pangenotypic fixed dose regimen.10,11 It is also relevant to note that HCV-3 patients with cirrhosis, still considered the most difficult to cure group of patients,12 achieve 94% SVR rates with 8 weeks of total treatment without any need for ribavirin. This figure increases to 100% when treatment for 6 weeks was given to HCV-3–infected noncirrhotic patients. The optimal efficacy in HCV-3–infected patients is a major breakthrough given the high prevalence of this genotype worldwide and the relatively disappointing SVR rates that have been reported by real life studies on this genotype.12 Moreover, the high SVR rates reported by Lawitz et al and Gane et al independent of genotype and disease stage in treatment naïve patients could also finally represent the end of the ribavirin era in the treatment of HCV.13 Clearly, both studies were not designed to assess this question, but the high SVR rates in HCV-3 patients with advanced fibrosis, a group of patients in whom ribavirin is recommended by most international guidelines, coupled with the disappointing results of the 8 week sofosbuvir/velpatasvir/GS-9857 plus ribavirin arm in HCV-1 patients with cirrhosis included in the Lawitz et al study (SVR 81%) seem to support this concept. Even more meaningful are the findings in treatment experienced patients, who represent an important unmet clinical need.

Currently, between 1% and 15% of patients, depending on the HCV genotype and treatment regimen, remain without a virologic cure.6,7 Retreatment strategies have been evaluated with the currently approved drugs in only a small numbers of patients. Optimal regimens still need to be defined, particularly for patients infected with HCV strains harboring NSSA-resistance–associated substitutions (RASs), which can lead to treatment failure with some of the current drugs commonly used in HCV therapy. This hot topic seems to be resolved, according to the results of studies performed by Gane et al7 and Lawitz et al.6 These authors included individuals infected by different HCV genotypes (1-4 and 6) who had failed therapies based on ≥2 DAAs, including patients with cirrhosis and a substantial number with NSSA RASs. All received treatment with sofosbuvir, velpatasvir, and GS9857, for 12 weeks. The results are impressive: All patients, except one with cirrhosis infected by genotype 3, achieved virologic cure.8 This is the largest retreatment study, all genotypes except genotype 5 were represented, therapy duration was fixed at 12 weeks regardless of the HCV genotype or the presence of cirrhosis or NSSA RASs, and it used a ribavirin-free regimen. The only caveat is that

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the regimen, which included a protease inhibitor, has not been studied in decompensated cirrhosis. The reason being that protease inhibitors are metabolized by the liver and as such reach higher than expected blood concentration in patients with decompensated liver cirrhosis, which can cause severe toxicity and side effects.

Retreatment based on currently approved drugs has been investigated in small-scale studies, using various strategies: first, extension of treatment with the same combination, with or without ribavirin. This approach was assessed in 2 studies. Forty-one patients who failed ledipasvir/sofosbuvir for 8 to 12 weeks were retreated with the same combination for 24 weeks. The overall SVR-12 rate was 71%. The presence of baseline NSSA RASs, which were more likely to develop with longer prior ledipasvir/sofosbuvir therapy, was associated with treatment failure (SVR of 60%) in NSSA RASs, and with Y93H/N even lower (SVR of 30%). In the second study, genotype 1 to 3 patients who failed the pangenotypic combination of sofosbuvir/velpatasvir, were retreated with the same combination plus ribavirin for 24 weeks. SVR rates in genotypes 1 and 2 were 97% and 91%, respectively, whereas SVR decreased to 76% in genotype 3. There were no virologic failures in genotype 3 patients without RASs, but in those with NSSA RASs, SVR rates were 77%, although the number of patients is small.

Another strategy is to retreat with an alternative regimen. This approach was examined in 16 patients who received sofosbuvir and simeprevir for 12 weeks after failing an NSSA-based regimen; 88% (14/16) achieved SVR, including 12 with genotype 1 infection, and both patients infected with genotype 4 infection. In another study, 22 patients who failed DAA therapy, including 16 patients exposed to an NSSA inhibitor, were retreated with sofosbuvir, ombitasvir/paritaprevir/ritonavir, and dasabuvir for 12 to 24 weeks, with or without ribavirin depending on HCV subtype and the presence of cirrhosis. SVR was achieved in all patients except 1 noncirrhotic patient with genotype 1a infection who had failed telaprevir + peginterferon plus ribavirin, and was retreated for 12 weeks. All 17 patients with baseline NSSA RASs achieved SVR. However, it is contraindicated in patients with decompensated cirrhosis.

Another option is to combine 2 or 3 highly potent DAs with different mechanisms of action to retain antiviral activity against existing RASs. This approach was examined in only noncirrhotic genotype 1 patients who failed a DAA-containing regimen in an open-label, phase II trial. Forty-four patients were randomized to receive ABT493 300 mg, a pangenotypic NS3/4 protease inhibitor, and ABT 530 120 mg, a pangenotypic NSSA inhibitor, with or without ribavirin 800 mg for 12 weeks. SVR rates were high. Only 2 patients relapsed, one in each arm, suggesting that ribavirin did not improve SVR. Finally, the combination of sofosbuvir/velpatasvir/GS9857 administered for four different treatment durations (6 to 12 weeks) with or without ribavirin has been investigated in the largest number of patients (n = 211). The cohort included cirrhotic patients infected by all genotypes and harboring NSSA RASs, even multiple-class RASs. Therapy duration of 6 or 8 weeks was suboptimal for retreatment. The appropriate duration was 12 weeks for all genotypes, and ribavirin did not increase SVR rates. The current American Association for the Study of Liver Diseases/Infectious Diseases Society of America HCV recommendation for retreatment with a sofosbuvir-based regimen and dual DAA therapy is 24 weeks’ duration. Weight-based ribavirin dosing, unless contraindicated, should be added, and nucleotide-based triple or quadruple DAA regimens may be considered, if available.

In conclusion, the main message that can be brought home by the studies from Gane et al and Lawitz et al is that the combination of sofosbuvir/velpatasvir/GS9856 has several advantages, because it enables to shorten treatment duration in treatment naïve patients and provides a valuable option to previous DAA failures. These 3 potent pan-genotypic DAs have been coformulated into a fixed dose combination tablet given at a fixed duration for all genotypes with an excellent safety profile, being ribavirin free. The next step is to evaluate these 3 drugs for 12 weeks in a phase III program in a large number of patients.

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