EDITORIAL

# Hepatitis C Drugs: Is Next Generation the Last Generation?

**See "High efficacy of ABT-493 and ABT-530 in patients with HCV genotype 1 or 3 infection and compensated cirrhosis," by Gane E, Poordad F, Wang S, et al, on page 000.**

Much has been written about the "hepatitis C virus (HCV) drug revolution." For an individual who started to work on the newly discovered HCV in 1990, at the time happy to describe rates of sustained virologic response (SVR) on the order of 6% with standard interferon (IFN)-$\alpha$ administered 3 times per week for 6 months,[1] the current HCV treatment landscape could look miraculous. It is simply the result of an enormous intellectual, scientific, and financial effort of the publicly funded academic and the industrial sectors to solve a major public health problem, building on the experience accumulated in the fight against the human immunodeficiency virus.

This unprecedented effort led to the approval of IFN-free treatment regimens based on combinations of direct-acting antiviral (DAA) drugs. Four classes of HCV DAAs are available in the United States and Europe, including inhibitors of the HCV RNA-dependent RNA polymerase (the nucleotide analog sofosbuvir and the non-nucleoside inhibitor dasabuvir), nonstructural 5A (NS5A) protein inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, and velpatasvir), and inhibitors of the NS3-4A protease (simeprevir, paritaprevir, and grazoprevir). These drugs are available either as fixed-dose combinations, including sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) and grazoprevir/elbasvir, or as single agents that can be combined (sofosbuvir, daclatasvir, and simeprevir). The HCV DAA combinations should be administered for 8, 12, 16, or 24 weeks, with or without weight-based ribavirin, according to baseline parameters, including the HCV genotype and subtype, the stage of fibrosis, prior HCV treatment history, comorbidities, and co-administered medications. Their practical use is guided by recommendations published and regularly updated by the international liver societies.[2,3]

In phase II and III clinical trials with the currently approved drug combinations, SVR rates of >90% were achieved in most patient groups, with generally minor side effects. Real-world studies involving large numbers of patients from various continents confirmed the high SVR rates and the excellent safety and tolerability profiles of the newly approved HCV DAA combinations.[4–7] However, a number of issues remained unsolved:

- The ideal treatment duration and to what extent treatment can be shortened to <12 weeks;
- Many groups of patients still require cotherapy with ribavirin, a medication with moderate side effects, to achieve high rates of cure;
- Genotype 3 remains a difficult-to-cure genotype, with limited treatment options and lower SVR rates than the other genotypes;
- The ideal timing of therapy and ideal drug regimen in patients with decompensated cirrhosis, including those awaiting liver transplantation;
- Whether pre-liver transplantation treatment has a clear clinical benefit;
- Limited treatment options for patients infected with genotypes 2, 3, 4, 5, and 6 who have advanced renal insufficiency, given sofosbuvir-based regimens should be avoided in patients with severe chronic kidney disease and in those with end-stage renal disease on hemodialysis; and
- The optimal retreatment of patients who failed an IFN-free, DAA-based regimen, some patients seeming to be incurable with the current drug regimens.

Thus, new, better performing combinations are still needed.

Two recent articles published in *Gastroenterology* report encouraging results with new DAA combination regimens in phase II trials.[8,9] In the first study, treatment-naïve and previously treated patients with HCV genotype 1 or 3 infection received the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) plus voxilaprevir or GS-9857 (100 mg) for 4 to 8 weeks. Voxilaprevir is a pan-genotypic second-generation NS3-4A protease inhibitor with potent in vitro antiviral activity against variants resistant to first-generation protease inhibitors, that is, with a higher barrier to resistance than these compounds. The study tested the hypothesis that the combination of 3 potent DAAs from different classes (ie, without cross-resistance) would yield very high SVR rates without the need for ribavirin and with a short treatment duration. Although the number of patients included in each treatment arm was small, 4 weeks of treatment did not seem to be a viable option and 6 weeks were suboptimal in all groups. In contrast, 8 weeks of the triple combination of sofosbuvir, velpatasvir, and voxilaprevir yielded high SVR rates in treatment-experienced patients infected with genotype 1 or 3, including those with compensated cirrhosis.[8] These results confirm previous studies showing that achieving SVR in >95% of patients requires ≥8 weeks of treatment, regardless of the DAA combination used. Adding ribavirin has been shown to allow for shortening treatment duration while maintaining high infection cure rates with any HCV drug regimen.[10] However, the administration of ribavirin is associated with an increased burden of side effects and a





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reduced quality of life. Thus, as shown in the study published in *Gastroenterology*, 8 weeks without ribavirin seems to be a reasonable compromise for treatment with this triple drug combination.[8] Among patients infected with HCV genotype 3, all treatment-experienced patients (including 19 of 19 with cirrhosis previously exposed to pegylated IFN-$\alpha$ and ribavirin, and 4 of 4 DAA-experienced with or without cirrhosis) achieved SVR. The overall safety and tolerability of the triple combination of sofosbuvir, velpatasvir, and voxilaprevir were excellent in the study.[8]

The results of other studies have been presented with the same triple combination in difficult-to-cure populations. Treatment-experienced (including DAA-experienced) patients, including 50% with compensated cirrhosis, treated with sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks achieved SVR in 100% (63 of 63) of genotype 1, 100% (21 of 21) of genotype 2, 97% (34 of 35) of genotype 3, and 100% (9 of 9) of genotype 4 and 6 patients in a phase II trial.[11] In patients previously exposed to $\geq$6 weeks of DAAs who failed to achieve SVR and were retreated for 12 weeks with sofosbuvir, velpatasvir, and voxilaprevir, the SVR rates were 100% (24 of 24) without ribavirin and 96% (24 of 25) with ribavirin in another study.[12]

In the second study published in *Gastroenterology*, a combination of 2 second-generation drugs with potent pangenotypic antiviral activity and a high barrier to resistance was administered to patients infected with HCV genotype 1 or 3 with compensated cirrhosis.[9] The combination included the second-generation NS3-4A protease inhibitor glecaprevir or ABT-493 (200 or 300 mg) and the second-generation NS5A inhibitor pibrentasvir or ABT-530 (120 mg). The drugs were administered for 12 or 16 weeks with or without 800 mg of ribavirin once daily. Overall, 96% of patients infected with genotype 1 and 98% of patients infected with genotype 3 achieved SVR, with no difference in the latter between those who received ribavirin and those who did not. The combination was safe and tolerable in this study.[9]

The results of other phase II trials with this combination regimen have been presented. SVR rates $\geq$93% were reported with glecaprevir and pibrentasvir administered for 12 weeks in treatment-naïve and treatment-experienced patients without cirrhosis infected with genotype 1 to 6.[13–16] In another study, SVR was achieved in 97% (33 of 34) of genotype 1-, 98% (53 of 54) of genotype 2-, and 97% (28 of 29) of genotype 3-infected treatment-naïve and treatment-experienced patients without cirrhosis treated with the combination for 8 weeks.[17,18] Finally, genotype 1-infected patients with prior DAA failure retreated with glecaprevir and pibrentasvir for 12 weeks achieved SVR in 86% (19 of 22) and 91% (20 of 22) of cases, with and without ribavirin, respectively.[19]

These 2 "next-generation" HCV DAA combinations are likely to be approved in 2017 in the United States and Europe, after the results of on-going phase III trials have been presented. Pending confirmation in these larger-scale trials, the results presented so far suggest that a number of the remaining issues with the currently approved regimens, as outlined above, will be solved. Indeed, there is concordant evidence that, whatever the combination regimen, 8 weeks is the shortest treatment duration able to yield SVR rates >95%. Because 8 weeks of treatment is easily accepted by the patients and does not raise significant issues in terms of tolerance and adherence, it does not seem useful to further explore shorter durations.

Less and less ribavirin will be used in the future. However, ribavirin will probably remain useful in some very difficult-to-cure patients. For instance, ribavirin must systematically be used in patients with decompensated cirrhosis who receive sofosbuvir and an NS5A inhibitor (ledipasvir, velpatasvir, or daclatasvir). This will not change in the immediate future, because the 2 DAA combinations studied here contain an NS3-4A protease inhibitor and thus cannot be used in this population. Uncertainties will remain as to the best timing for antiviral therapy (before or after liver transplantation) and the reality of the clinical benefit of treatment for patients with decompensated cirrhosis awaiting transplantation.

Genotype 3 is considered as the most difficult-to-cure genotype with IFN-free, DAA-based regimens. This should no longer be the case with next-generation regimens if the excellent results reported in phase II studies, both in patients with and without cirrhosis, are replicated in phase III trials. Presently, safe therapies without sofosbuvir are available only for genotype 1- or 4-infected patients with severe chronic kidney disease (estimated glomerular filtration rate, <30 mL/min/1.73 $m^2$) or end-stage liver disease on hemodialysis. They include ombitasvir/paritaprevir/ritonavir with or without dasabuvir for genotype 1 or 4 patients, respectively, and grazoprevir/elbasvir for genotype 1 and 4 patients. The arrival of the pangenotypic glecaprevir/pibrentasvir fixed-dose combination will fill in the gap for patients infected with other genotypes, offering a number of sofosbuvir-free options for patients with severe renal impairment.

Based on the very small number of patients included in the phase II trials, reasonably high SVR rates seem to be achievable when retreating patients who failed a prior DAA-based treatment. However, relapses still occur in difficult-to-treat patients, who often have advanced liver disease, a history of multiple treatment courses, and a number of comorbidities, while taking medications that may interact with the HCV drugs, in particular the protease inhibitors. It is thus likely that some patients will remain incurable even with the new treatment regimens. More complex retreatment options may be offered by combining fixed-dose combinations with other drugs available as single agents. However, data are lacking with these combinations, the safety of which should be evaluated carefully.

The next generation of HCV drugs will be the last generation. Apart from, maybe, a few more compounds with characteristics similar to those of the current drugs currently at the late clinical developmental stages, no further HCV drug development effort is on-going. The drug industry is now hunting on other lands, with better promises for profits, given the diminishing market for patients to treat. Hepatitis C is already past for them. It is unfortunately not for us, because many millions of patients are still

unaware of their infection, at risk of severe hepatic and extrahepatic complications, and/or desperately waiting for access to therapy. With the current and next generation of HCV drugs, it will be technically possible to cure the vast majority of HCV-infected patients, particularly if more affordable agents become available. National plans should now be universally implemented to screen and diagnose HCV-infected patients, provide them with efficient care, educate those at high risk of reinfection about its prevention, and make the world almost free of hepatitis C by 2030.

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**Conflicts of interest**
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