EDITORIAL

Ushering in an Era Where No Group Who Wants to Be Treated Should Be Excluded

The landscape on the treatment of hepatitis C virus (HCV) has shifted from interferon (IFN)-based therapy to the era of all oral direct acting antiviral (DAA) therapy in December 2013 with the approval of sofosbuvir and ribavirin for HCV genotypes 2 and 3.[1] In addition, the off-label use of sofosbuvir and simeprevir with or without ribavirin provided an oral option for patients infected with HCV genotypes 1 and 4.[2,3]

The transition to non–IFN-based therapy makes the treatment more tolerable, opening an avenue for patients who previously were not treatment candidates for IFN including those with clinically decompensated liver disease, ongoing substance abuse, uncontrolled psychiatric disease, notably depression, and those who could not tolerate IFN side effects.[2,4–6] In fact, the Food and Drug Administration's approval of sofosbuvir and ribavirin was partly based on the POSITRON study, a blinded, placebo-controlled study that evaluated 12 weeks of treatment with sofosbuvir and ribavirin in patients who had medical contraindications precluding therapy or who had decided against treatment with an IFN-based regimen.[7] In the population of patients for whom IFN treatment was contraindicated, the rate of sustained virologic response (SVR) at 12 weeks after treatment was 78% among patients receiving sofosbuvir and ribavirin ($P < .001$).[7]

Comorbidities have historically affected the decision to treat HCV infection in clinical trials as well as real-world settings, especially in those with psychiatric contraindications and ongoing substance abuse, limiting the use of IFN in the pre-DAA era.[4,5] Ribavirin is also associated with psychiatric side effects, albeit with a lesser extent than that of IFN, and thus also restricting its use in those with underlying psychiatric issues.[8] A study that used the U.S. Veterans Affairs National Patient Care Database among 126,926 HCV-infected veterans showed that the prevalence of all psychiatric comorbidities and substance abuse was higher in the HCV-infected patients than that in uninfected subjects.[9] The prevalence of major depression, alcohol use disorder, and drug use disorder among those with and without HCV infection was 11.1% vs 7.2%, 35.4% vs 12.3%, and 30.3% vs 8.4%, respectively.[9] As a result, a significant number of U.S. veterans were not eligible to undergo hepatitis C treatment in the pre-DAA period, and they also have been excluded from large registration trials for oral DAA therapies. Therefore, the overall safety, efficacy, and tolerability of oral DAA therapy among veterans are not well-established.

In this issue of *Clinical Gastroenterology and Hepatology*, Ho et al[10] report the results of the Phase 4, prospective, open-label study to evaluate the efficacy of 12-week treatment of sofosbuvir and ribavirin in veterans with compensated cirrhosis caused by HCV genotype 2 (VALOR-HCV). This study focused on veterans with multiple comorbidities, who historically have been excluded from HCV treatment trials. In a cohort of 66 patients (47 treatment naive and 19 treatment experienced), all had at least 1 comorbidity, 59% with psychiatric disorders, 35% with depression or major depression, 24% with post-traumatic stress disorder, 30% with anxiety or an anxiety disorder, and 29% with ongoing substance use.[10] The overall SVR rate was 79%, with higher SVR rate in treatment-experienced patients (84%) than that in treatment-naive patients (77%, not statistically significant). Interestingly, those with history of psychiatric disorders had a comparable SVR rate than those who did not (82% vs 74%). Among those with current substance abuse, their SVR rate was also high at 89%. Last, the compliance to therapy, defined as >80% adherence to sofosbuvir, was 83%. Of importance, adherence to sofosbuvir was the primary driver and an independent predictor of achieving SVR; the success rate was ~3 times higher in those with >80% adherence to treatment compared with those with <80% adherence rate.[10]

The SVR rate of this VALOR-HCV study compares favorably with that achieved in the majority of registration trials with 12 weeks of sofosbuvir and ribavirin,[1,11] suggesting that treatment for HCV in these populations, notably in those with compliance, can be successful and that they should not be excluded from clinical trials or prohibited from receiving DAA therapies in clinical practice. In addition, the study design of this study mimics the real-world approach in that no special interventions were implemented to achieve this SVR rate despite including those with ongoing drug use and psychiatric problems, who were perceived to be a difficult group to treat and normally not considered for registration trials. Furthermore, the SVR rate of the VALOR-HCV study is also comparable with the HCV-TARGET Registry, an international, prospective observational study evaluating effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 at 44 academic and 17 community medical centers in North America and Europe.[11] The initiation of the HCV treatment with DAA agents was at the discretion of the site investigator. The overall SVR rate for 12-week treatment in cirrhotic patients in the TARGET study was 79%; numerically higher SVR rates were noted in the treatment-experienced cohort (87%) compared with the treatment-naive cohort (23 of 32, 72%).[11] In addition, a recently published German cohort study included 27

HCV genotype 2 infected individuals with cirrhosis who received 12 weeks of sofosbuvir and ribavirin at the discretion of the treating physician, and this study also demonstrated that SVR could be achieved at a similar rate of 74% (20 of 27).[12]

The results of the VALOR-HCV study highlight the high SVR rates that can be achieved in a cirrhotic population who may have been deemed ineligible for treatment, yet they are in the highest need of successful viral eradication to reduce disease progression and prevent other complications. As for the safety profile, 7 patients discontinued study treatment prematurely, of whom 3 were having adverse event (AE), but only 1 was considered to be therapy-related. No patient discontinued the therapy because of anemia; however, the levels of hemoglobin did fall in the study cohort, with 24% developing anemia (considered as AEs) and one (2%) considered as serious AE. Ribavirin dose reduction or discontinuation did not impact the SVR rates, and none required the use of growth factor, ie, erythropoietin. This demonstrates that this therapy combination is well-tolerated in patients with cirrhosis. Despite these findings, there are ribavirin-free DAA combinations that are now available for HCV genotype 2, including sofosbuvir/daclatasvir and sofosbuvir/velpatasvir. These new all oral DAA therapies without ribavirin have yielded SVR rates of essentially 100% in small cirrhotic cohorts.[13] Although we are waiting for the "real world" data with these DAA combinations, it appears that those with psychiatric disorders and substance abuse disorders should be able to achieve SVR rates comparable with the clinical trial data, with only patient adherence dictating the efficacy rates.

A recent report examined the efficacy of grazoprevir and elbasvir in those who inject drugs or are on opioid substitution therapy. Again, these are individuals who previously would be excluded from registration trials.[14] The study found an overall SVR rate of 92% by intention-to-treat analyses, with no differences in the SVR rate noted between those who had positive drug screens and negative drug screens.[14] In this international study, only 6 of 296 individuals were reinfected. These are individuals who are at risk to transmit the virus, and effective therapies will be required from a public health perspective to reduce the incidence of new cases of HCV infection.

The VALOR study and other studies mentioned here should provide reassurance that as long as compliance by the patient can be reasonably assured by the evaluating clinicians, therapy for chronic HCV should move forward irrespective of other comorbidities in those with hepatitis C and reasonable life expectancy. Strategies that may be used for higher-risk patients such as those with depression, post-traumatic stress disorder, and/or substance use include the use of integrated care models by mental health providers.[15]

Adherence to therapy has been important since the era of pegylated IFN and ribavirin[16] and the previously defined 80-80-80 rule for IFN and ribavirin-based therapy.[17] Adherence to treatment substantially raised the SVR rate in treated patients, regardless of substance abuse status or underlying psychiatric issues, and the Valor study, among others, demonstrates adherence to DAAs is also important to achieve SVR. Future studies to identify the predictors of non-adherence and to further refine the integrated care approach tailored to those with high risk for noncompliance should strongly be considered in routine clinical care. This is an exciting time for hepatitis C treatment and is the time to start considering treatment for all,[18,19] with no group who wants to be treated and can comply with therapy being excluded.

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Conflicts of interest

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