



Interferon-free treatment for genotypes 2 and 3 patients with hepatitis C

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Nowlan Selvapatt,¹ Philip Hendy²

Sofosbuvir and ribavirin in HCV genotypes 2 and 3

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This paper reviews the outcomes of the VALENCE study which evaluated an interferon-free treatment regime for patients with genotypes 2 and 3 hepatitis C virus (HCV).¹ While demonstrating promising efficacy in the treatment of genotype 2 infected patients and certain subtypes of patients with genotype 3 infection, it also provides a timely reminder that careful patient selection is required.

Sofosbuvir (trade name Sovaldi) is an oral direct acting antiviral agent (NS5B polymerase inhibitor) licensed in the UK for the treatment of hepatitis C. It is currently under review at the National Institute for Health and Care Excellence. The study was designed as a phase III blinded placebo controlled trial of treatment of genotype 2 and 3 HCV infected patients. Both treatment-naïve patients and those with previous interferon treatment were included, and presence of cirrhosis was not an exclusion criterion. It was originally designed for all patients to receive 12 weeks of treatment with either sofosbuvir plus ribavirin or with matching placebo.

The dose of sofosbuvir was 400 mg once daily given orally and ribavirin was given orally in a split dose, dose dependent on weight (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg). However, after initiation of the VALENCE study, published results from the FUSION study demonstrated significant benefit in extending treatment of genotype 3 HCV infection beyond 12 weeks.² The study was therefore altered from hypothesis generating to descriptive. The genotype 2 HCV treatment arm remained unchanged with 12 weeks of treatment, while the genotype 3 HCV treatment arm was made open label and extended to 24 weeks. The primary end point was sustained virological response at 12 weeks after completion of therapy (SVR₁₂) and HCV RNA below the limit of quantification (25 IU/mL).

A total of 475 patients were screened for enrolment and 421 underwent randomisation with 419 starting treatment. Enrolment was in a 4:1 ratio of genotype 3 to genotype 2. Overall 60% were men, 21% had cirrhosis and 58% had received previous interferon treatment, of whom 30% were primary non-responders. Overall, 99% of patients receiving sofosbuvir and ribavirin had undetectable HCV RNA by week 4. Of the 73 genotype 2 infected patients, 93% of patients achieved SVR₁₂.

There was greater variation in virological response in patients with genotype 3 infection. Among treatment naïve patients, SVR₁₂ was 95% in non-cirrhotics and 92% in cirrhotics. However, for those with past exposure to

interferon, SVR₁₂ was 87% in non-cirrhotics and 62% in cirrhotics. Treatment was well tolerated with only 1% discontinuation. There were 10 serious adverse events out of 250 treated patients in the 24-week treatment arm but nil adverse events in either of the 12-week treatment groups. In common with previous published data, no resistance to sofosbuvir was demonstrated on viral resistance testing.

Using multivariate regression analysis, the study investigators demonstrated four possible predictors of sustained viral response among genotype 3 infected patients: absence of cirrhosis; low viral load at baseline; female sex; and younger age. This requires further validation before utilisation as a pretreatment predictor score.

The authors acknowledge the limitations of this study. First, the trial was altered from a hypothesis generating exercise to a descriptive study without any formal hypothesis or statistical comparisons. Second, very few pretreatment biopsies were available meaning that questions regarding levels of fibrosis and steatosis and links to treatment response could not be adequately addressed. Overall, the study is well powered to deliver definitive conclusions regarding the drug efficacy for both genotype 2 and 3 HCV, but it is not sufficiently powered to make definitive conclusions regarding the subgroup of genotype 2 patients who exhibit pretreatment characteristics associated with a lower response rate.

Comment

This study reaffirms the potential for shortened duration of treatment

¹Department of Hepatology, Imperial College Healthcare, London, UK

²IBD Unit, St Mark's Hospital, London, UK

Correspondence to Dr Philip Hendy, IBD Unit, St Mark's Hospital, Watford Rd, Harrow, London HA1 3UJ, UK; philiphendy14@gmail.com

when compared with interferon based regimes, particularly for genotype 2 HCV. It also demonstrates the efficacy of this treatment regime for those numerous patients unable to take an interferon based regimen due to contraindications or intolerance. Importantly, it also provides a timely reminder that there are limitations to this therapy, with SVR₁₂ lower in certain difficult to

treat groups (especially patients with cirrhosis and previous exposure to interferon therapy). Future work should evaluate the addition of interferon and/or other direct acting agents, as well as longer treatment durations, for those patients with pretreatment characteristics associated with decreased treatment response. This study also highlights our lack of understanding of the

basis for differences in response to sofosbuvir between genotype 2 and 3 patients, especially given the similarities in viral kinetics between these two groups.

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