Hepatitis C Virus Genotype 3: Hope for Nonresponders and Patients With Cirrhosis

Abstract

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Background: In clinical trials, treatment with a combination of the nucleotide polymerase inhibitor sofosbuvir and the antiviral drug ribavirin was associated with high response rates among patients with hepatitis C virus (HCV) genotype 2 infection, with lower response rates among patients with HCV genotype 3 infection.

Methods: We conducted a study involving patients with HCV genotype 2 or 3 infection, some of whom had undergone previous treatment with an interferon-based regimen. We randomly assigned 91 patients with HCV genotype 2 infection and 328 with HCV genotype 3 infection, in a 4:1 ratio, to receive sofosbuvir–ribavirin or placebo for 12 weeks. On the basis of emerging data from phase 3 trials indicating that patients with HCV genotype 3 infection had higher response rates when they were treated for 16 weeks, as compared with 12 weeks, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

Results: Of the 419 patients, who were enrolled and treated, 21% had cirrhosis and 58% had received previous interferon-based treatment. The criterion for a sustained virologic response was met in 68 of 73 patients (93%; 95% confidence interval [CI], 85–98) with HCV genotype 2 infection who were treated for 12 weeks and in 213 of 250 patients (85%; 95% CI, 80–89) with HCV genotype 3 infection who were treated for 24 weeks. Among patients with HCV genotype 3 infection, response rates were 91% and 68% among those without and those with cirrhosis, respectively. The most common adverse events were headache, fatigue, and pruritus.

Conclusions: Therapy with sofosbuvir–ribavirin for 12 weeks in patients with HCV genotype 2 infection and for 24 weeks in patients with HCV genotype 3 infection resulted in high rates of sustained virologic response. (Funded by Gilead Sciences; VALENCE ClinicalTrials.gov number, NCT01682720.)

COMMENTS

Hepatitis C virus (HCV) affects approximately 130–170 million people across the globe.¹ The prevalence of the 7 genotypes described varies geographically. Genotype 1 is most common genotype in the west, whereas genotype 3 is the predominant type in the Indian subcontinent.² The treatment of HCV has evolved over the past 3 decades—from interferon monotherapy, peginterferon to a combination of peginterferon and ribavirin (RBV) and now the directly acting antivirals (DAAs). The sustained viral response rates have been reported to be >90% with these later drugs. The present approach is combining drugs with additive or synergistic effects to get the maximum results.

The standard of care till recently was peginterferon and ribavirin. The response rates have been reported to be around 55% (genotype 1) and 80% (genotype 3) in registration trials, but in real life scenarios they are lower. The response rates in relapsers and nonresponders are 40% and 5%, respectively.³ This is changing, and newer drugs—namely DAAs and host-target agents (HTA)—which act by inhibiting viral replication, have been shown to be promising. The latest guidelines (2014) released by AASLD, for treatment naive and nonresponder genotype 3 HCV, recommend an oral regimen of sofosbuvir (400 mg) and weight based RBV (1000 mg for <75 kg; 1200 mg for ≥75 kg) for a duration of 24 weeks.⁴ Alternatively, peginterferon can be added to this regimen and duration reduced to 12 weeks.

Genotype 3 is more commonly associated with steatosis, progression to cirrhosis and hepatocellular carcinoma.⁵ Various factors influencing the sustained viral response (SVR) include host factors (age, gender, obesity, insulin resistance, significant alcohol intake, compliance, serum ferritin, vitamin D3, and IL-28B polymorphism), disease factors (high degree of fibrosis and necroinflammation), and viral factors (genotype, baseline viral load and viral kinetics). Many of these factors are not modifiable and a subgroup of patients—who are decompensated, have cytopenias, side-effects to drugs or post transplantation—cannot be considered for peginterferon and ribavirin. In addition, patients on treatment need to be regularly monitored for side-effects. This has led to a need for developing drugs which are pan-genotypic and have better SVR and fewer side-effects.

The major trials reported from the west have included predominantly genotype 1 patients.⁶ The major trials

Keywords: SVR, peginterferon, ribavirin, side-effects

Received: 21.5.2014; Accepted: 21.5.2014; Available online: 10.6.2014

<http://dx.doi.org/10.1016/j.jceh.2014.05.009>

Table 1 Response Rates in Treatment Naïve and Treatment Experienced Genotype 3 Patients.

Trial name	Patient population	Treatment	Duration	SVR	
FISSION 7	US, Australia, New Zealand, Italy, Sweden, and the Netherlands	Naïve	12 weeks	CHC (n = 145)	61%
				Cirrhosis (n = 38)	34%
POSITRON 8	US, Canada, Australia, and New Zealand	Naïve	12 weeks	CHC (n = 176)	81%
				Cirrhosis (n = 31)	61%
FUSION 8	US, Canada, Australia, and New Zealand	Experienced	12–16 weeks	CHC	37%
				12 weeks (n = 38)	63%
				16 weeks (n = 40)	
				Cirrhosis	19%
VALENCE 9	77 sites in Europe	Naïve	24 weeks	CHC (n = 92)	93%
				Cirrhosis (n = 13)	92%
		Experienced	24 weeks	CHC (n = 100)	87%
				Cirrhosis (n = 45)	60%

involving genotype 3 treated with a combination of oral sofosbuvir and weight based ribavirin are highlighted in Table 1.^{7–9} These trials (including the current) have reported SVR rates in these patients to be lower than genotype 1, making it a more difficult to treat genotype with these new drugs. The optimal treatment duration and drug regimen for genotype 3 is still not clear, the trials have shown that increasing the duration of therapy from 12 weeks to 24 weeks is associated with better SVR, therefore the current optimal duration considered for genotype 3 is 24 weeks. The treatment duration in the current trial was initially planned for 12 weeks, and had a placebo arm.

Among the important predictors of SVR is the presence of underlying cirrhosis. In treatment naïve patients (genotype 3), SVR rates vary from 61%–91% in patients without cirrhosis to 34%–92% in patients with underlying cirrhosis. Similarly, in treatment experienced patients the SVR in patients without cirrhosis varies from 37% to 87%; whereas in patients with cirrhosis it is less (19%–60%).^{7–9} In both chronic hepatitis C (CHC) and cirrhosis patients, increasing the duration of treatment to 24 weeks is associated with an increased SVR. The high SVR associated with 24 weeks of therapy prompted the authors to extend the duration of treatment to 24 weeks and the recruitment for placebo group was stopped.

The results of trials involving DAA in genotype 1 have not shown any other host, viral, or disease factors to be predictive of SVR, apart from cirrhosis, which is associated with low SVR.⁶ The results of the current trial highlight other factors, in addition to the absence of cirrhosis, which are associated with higher SVR—viral load less than 6 log₁₀ IU/ml, female sex and age <50 years. These factors are also predictors of response to interferon treatment. Although these results

need further validation, these findings highlight the fact that genotype 3 is different from genotype 1, and host and viral factors may play a role in treatment responsiveness. The other factors which are predictors of SVR with interferon-based therapy—like IL-28B polymorphism, baseline BMI, ALT levels, compliance (>80%), ethnicity—were not found to be statistically different.

The mutations associated with reduced susceptibility to sofosbuvir (S282T) were not detected in any patient, providing assurance that 24 weeks of treatment does not lead to development of resistance.¹⁰ Only 2 patients discontinued treatment—due to intractable headaches and malaise in one patient and suicide attempt in another. In the absence of significant major side-effects, the combination of sofosbuvir and ribavirin is safe for longer durations of use.⁹

The results of the current trial open the gates to a brighter future for patients with genotype 3 HCV, both CHC and cirrhosis patients, whether they are treatment naïve or treatment experienced.⁹ The tolerability of these drugs needs to be further assessed in patients with decompensated cirrhosis, renal failure, thalassemia and post transplantation, which are notoriously difficult to treat, and therapy in such cases may be life saving. This study also paves the way for more research, especially in genotype 3 CHC, which though was initially considered to be easy to treat with high SVR, is now considered the most difficult to treat. With the development of new drugs like DAA and HTA acting at different viral targets, the future holds promise.

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