OBJECTIVES

Failure to achieve sustained virological response (SVR) with hepatitis C virus (HCV) direct-acting antiviral-based regimens is commonly associated with emergence of variants carrying resistance-associated substitutions (RASs) [1]. The optimal retreatment regimen for such patients is unknown. The aim of this randomized open-label study was to evaluate sofosbuvir + grazoprevir + elbasvir + ribavirin in patients with Hepatitis C virus Genotype 1 or 4 with RASs at failure of a sofosbuvir + ledipasvir or + daclatasvir or + simievirin regimens (ANRS HC34 REVENGE study).

PATIENTS & METHODS

Randomized, double arm, multicenter, open-label, Phase IIb pilot study conducted in France.

Main inclusion criteria:
- Adult >18 years
- Infection with HCV genotype 1 or 4, confirmed by detectable HCV RNA at pre- inclusion
- Failure to a prior therapy with Sofosbuvir + Ledipasvir or Daclatasvir or Ledipasvir, with documented presence of NS5A or NS5B RASs (Resistance-Associated Substitutions) at the time of failure (presence of RASs on at least one sample since the time of failure).
- Fibrosis at any stage

Main exclusion criteria:
- Child B or C cirrhosis (or Child A patients with history of Child B)
- Patients with documented presence of RASs conferring resistance to sofosbuvir
- Positive HBsAg
- Chronic HIV or HCV co-infection
- Transplant recipients
- Any active or ongoing malignancy disease, including hepatocellular carcinoma, which will be specifically screened for before inclusion
- Treatment with contra-indicated associated drugs

Antibacterial efficacy was evaluated using the secondary endpoint of SVR4 (SVR 4 weeks post-treatment). On-treatment responder and safety were also assessed.

FLOW CHART AND BASELINE CHARACTERISTICS

Twenty-six patients chronically infected with HCV genotype 1 (n=20) or 4 (n=6) were randomized and treated. All of the 26 patients achieved HCV RNA below lower limit of quantification (LLQ) or TLDN during treatment and 18 patients had a rapid response (week 4). SVR4 was achieved by 23/26 patients with sufficient follow-up. One patient underwent at week 16 died before week 20 (up to Safety J). No relapse was observed.

CONCLUSIONS

Our findings suggest that retreatment patients who failed a DAA-based regimen with NS5A/NS5B RASs with the combination of SOF + GZR + EBV + RBV for 16 weeks is efficacious and this combination appears to be a therapeutic option in DAA failure. Safety needs to be monitored cautiously in these patients with a severe disease. Moreover, in these patients who received two lines of treatment, HCV recurrence occurred in 3/26 patients. Among the 3 HCV, 2 were recurrence of HCC.

REFERENCES