Ledipasvir–sofosbuvir for hepatitis C genotype 4 infection

In *The Lancet Infectious Diseases*, Anita Kohli and colleagues report the results of a single-centre, open-label cohort, phase 2a trial of a ledipasvir plus sofosbuvir fixed-dose combination (FDC) for adult patients with genotype 4 hepatitis C virus (HCV).[1] The primary endpoint was the proportion of patients achieving a sustained viral response at 12 weeks after the termination of study drugs (SVR12). They enrolled 21 patients, including 13 [62%] who were treatment naive and eight [38%] who were interferon treatment-experienced, to receive ledipasvir plus sofosbuvir for 12 weeks. Patients previously treated with a direct acting antiviral, patients with decompensated cirrhosis, and patients with co-infections (eg, HIV or hepatitis B virus) were excluded. Most patients (12 [57%] of 21 individuals) had early stage fibrosis (F0–F2), with only a third of patients (seven of 21 individuals) having compensated cirrhosis. SVR12 was achieved by 95% of patients (95% CI 76–100). The only patient who did not achieve SVR12 was deemed to be non-compliant. The safety profile of the FDC in this study is similar to those seen in studies of patients with HCV genotype 1.[2–4] Viraemia was rapidly reduced in these patients, with 95% having undetectable HCV RNA by week 4 of treatment according to the Roche assay (with a lower limit of quantification of 43 IU/mL). However, guidelines recommend use of an assay with a lower limit of quantification of 25 IU/mL or lower; thus, based on this study, 71% of patients achieved the lower limit of quantification of less than 12 IU/mL. These results in patients with HCV genotype 4 are promising in view of the efficacy and safety data.

Although this is a proof-of-concept study with a high proportion of patients achieving SVR12, the results of the study have restricted applicability. The population studied was mostly treatment-naive patients with early staged fibrosis (F0–2). The highest priority patients, those with advanced fibrosis or compensated cirrhosis (F3 and F4),[5] were represented by 43% of patients in the study, and patients with co-infections were excluded.[1] Additionally, the investigators used a Fibrosure test plus aspartate aminotransferase-to-platelet to assess fibrosis; however, there are substantial limitations to this approach. One major limitation is its lower specificity in the differentiation of F0–1 from F2. Therefore, the investigators grouped these patients together as F0–2. Reporting of the number of patients with mild fibrosis (F1) and possible moderate fibrosis (F2) would have been beneficial.[6] Additionally, genotyping for the *IL28B* polymorphism was not done. A previous study,[7] which contained 182 patients with HCV genotype 4 who were treatment naive, examined the predictive value of *IL28B* polymorphisms and treatment outcomes—ie, SVR. Patients were treated with pegylated interferon and ribavirin for 48 weeks and the patient population included patients with fibrosis stage 0–2 (55%) and 3–4 (45%), in accordance with the Metavir scoring system. The results of this study[7] showed that *IL28B* polymorphisms strongly predict virological response in patients with HCV genotype 4. *IL28B* genotyping would have been useful data to collect, although polymorphisms probably would not have affected the results.

Existing recommendations for treatment of HCV genotype 4 include the ledipasvir plus sofosbuvir FDC for 12 weeks based on the preliminary data from this trial;[1] the combination of paritaprevir, ritonavir, or ombitasvir with ribavirin for 12 weeks based on preliminary results of the PEARL-I trial;[8] or sofosbuvir plus ribavirin for 24 weeks based on several other studies.[9–11] The proportion of patients achieving SVR12 in the PEARL-I trial was higher in the group treated with ribavirin (100%) than in the group without ribavirin (90%), which suggests that ribavirin should be added to the regimen.[8] The studies of sofosbuvir plus ribavirin showed that 24 weeks of treatment led to increased numbers of patients achieving SVR12 (92–100%) compared with 12 weeks of treatment (79–84%); therefore suggesting that 24 weeks of treatment should be used.[9,10] These results are similar to those of Kohli and colleagues' study, with overall SVR between 92–100%.

The advantages of treatment with the ledipasvir plus sofosbuvir FDC for patients with HCV genotype 4 compared with other recommended regimens include the short treatment duration (12 weeks), simple dosing (one pill per day), and the fact that ribavirin is not needed. Further studies of the ledipasvir plus sofosbuvir FDC for patients with HCV genotype 4 should include patients with co-infections, increased numbers of patients with advanced disease (Metavir scores of F3 or F4), and transplant patients.

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*Michael A Smith, *Rima A Mohammad*
University of the Sciences in Philadelphia, Philadelphia College of Pharmacy, Philadelphia, PA, USA (MAS); and University of Michigan College of Pharmacy, UMHS Pharmacy Services, Ann Arbor, MI 48109-2054, USA (RAM)
rimam@umich.edu

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