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VIRAL HEPATITIS

Sofosbuvir: a new milestone in HCV treatment?

The standard of care for HCV genotype 1 (the most common HCV genotype) is a protease inhibitor combined with PEG-IFN and ribavirin for 24–48 weeks. "Although a sustained virologic response (SVR) is achieved in up to 75% of patients, tolerability of these regimens is poor, dosing is complex and development of resistance is common among patients who do not achieve SVR," says Eric Lawitz. Now, two phase II trials from the USA have revealed that sofosbuvir—a uridine nucleotide analogue that selectively inhibits the HCV NS5B polymerase—is safe and effective in the treatment of patients with HCV infection.

> "Sofosbuvir...is safe and effective in the treatment of patients with HCV infection"

In the PROTON study, Eric Lawitz and colleagues evaluated the effect of different sofosbuvir doses (200 mg and 400 mg, $n = 48$ per dose) in treatment-naive patients infected with HCV genotype 1. Patients received sofosbuvir in combination with PEG-IFN and ribavirin or PEG-IFN and ribavirin alone (placebo; $n = 26$) for 12 weeks followed by 12 weeks of PEG-IFN and ribavirin alone. Open-label sofosbuvir (400 mg) was also given to 25 patients with HCV genotypes 2 or 3 for 12 weeks with PEG-IFN and ribavirin.

Sofosbuvir led to high (~90%) SVR rates in patients infected with HCV genotypes 1, 2 or 3, compared with 56% in the placebo group. However, a few cases of relapse in the 200 mg sofosbuvir group indicated that this dose was inadequate. Sofosbuvir was well-tolerated: no additional adverse events were noted in the sofosbuvir groups compared with the placebo group.

"PROTON provided the basis for the ATOMIC study—an open-label randomized trial in which 400 mg sofosbuvir was given to patients infected with HCV genotype 1," explains Lawtiz. In ATOMIC, Kris Kowdley and co-workers randomly assigned patients to receive sofosbuvir (400 mg) with PEG-IFN and ribavirin for 12 weeks ($n = 52$), 24 weeks ($n = 109$), or 12 weeks sofosbuvir with PEG-IFN and ribavirin followed by 12 weeks of sofosbuvir alone or combined with ribavirin ($n = 155$).

No statistically significant difference was found in the number of patients who achieved SVR24 between the three treatment groups (~90% of patients in each treatment group), indicating no additional treatment benefit from continuing treatment beyond 12 weeks. Sofosbuvir was well-tolerated, although the number of adverse events was higher in patients who continued treatment for 24 weeks compared with those who received the drug for 12 weeks (14% versus 6%). No viral resistance was observed in any patient.

Further investigation of 12-week regimens of sofosbuvir with PEG-IFN and ribavirin in patients with HCV genotype 1 has been undertaken in a phase III trial. The ATOMIC authors also suggest that 12-week regimens of sofosbuvir should be tested in a broader population of patients with HCV genotype 1, including those with cirrhosis.

Katherine Smith

Original articles Lawtiz, E. *et al.* Sofosbuvir in combination with peginterferon α-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet* doi:10.1016/S1473-3099(13)70033-1 | Kowdley, K. V. *et al.* Sofosbuvir with pegylated interferon α-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet* doi:10.1016/S0140-6736(13)60247-0

CORRECTION

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In the version of the article initially published online, the drug sofosbuvir was spelled incorrectly. The error has been corrected for the print, HTML and PDF versions of the article.