Randomised controlled trial

ABT-450/r-ombitasvir and dasabuvir with ribavirin eliminates viraemia in most patients with HCV infection with cirrhosis

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Commentary on: Poordad F, Hezode C, Trinh R, *et al.* ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370:1973–82.

Context

The prevalence of hepatitis C virus (HCV) reached its peak in 1994 and is expected to decrease significantly over the next few years. However, HCV-related cirrhosis continues to increase. Razavi *et al*[1] predicted that decompensated cirrhosis will reach its peak in 2019. This translates into increased healthcare costs secondary to complications of cirrhosis.

Patients with cirrhosis due to HCV infection are less likely to achieve a sustained virological response (SVR), even in the era of direct-acting antivirals (DAA). Only 62% of genotype-3 cirrhotics treated with sofosbuvir and ribavirin for 24 weeks achieved SVR compared with 87% of non-cirrhotics.[2] Treatment of advanced cirrhosis brings increased risks of complications.

As fewer cirrhotics are generally included in interferon-free trials, expected outcomes are extrapolated from a small number of participants. Poordad and colleagues explored rates of SVR and adverse events associated with ABT-450/r-ombitasvir, dasabuvir and ribavirin among a cohort of exclusively patients with cirrhosis.

Methods

This randomised controlled trial included 380 patients with Child-Pugh class-A cirrhosis. Patients were given protease inhibitor ABT-450 boosted with ritonavir, the NS5A inhibitor ombitasvir, the non-nucleoside polymerase inhibitor dasabuvir and ribavirin (3D-RBV regimen) for 12 or 24 weeks. Both previously untreated and treated patients were included, but patients with prior exposure to DAAs were excluded. Patients were classified by their treatment history. Untreated patients were additionally stratified by HCV subgenotype and IL28B genotype. Treated patients were separated by HCV subgenotype and previous treatment response.

The primary endpoint was SVR 12 weeks after end of treatment. The authors ascertained non-inferiority and superiority of the 12-week and 24-week groups against the estimated historical control group (telaprevir-based regimen; 47%, 95% CI 41% to 54%). The comparison between the 12-week and 24-week SVR rates was the key secondary endpoint. The percentage of patients with virological failure and relapse was also determined in each treatment arm. Modified intent-to-treat analysis was performed.

Findings

In the 12-week arm, 91.8% (97.5% CI 87.6% to 96.1%) of participants achieved SVR 12, compared with 95.9% (97.5% CI 92.6% to 99.3%) in the 24-week arm. These results met non-inferiority and superiority to historical controls. Superiority was demonstrated among all subgroups, including prior null responders. SVR rate difference between the 12-week and 24-week arms did not reach statistical significance (p=0.09). Prior null-response to pegylated-interferon/ribavirin treatment, subgenotype 1a and self-reported history of injection-drug use were associated with lower likelihood of SVR in multivariable logistic regression.

Virological failure occurred in 0.5% and 1.7% patients of the 12-week and 24-week arms, respectively. Relapses were more common in the 12-week arm (5.9% vs 0.6%). Overall, 15 of the 17 patients who failed or relapsed had resistance-associated mutations to at least two drug targets.

Adverse events were common (91.3%), but only 8 patients (2.1%) discontinued as a result, with 21 patients (5.5%) experiencing serious adverse events. Severe anaemia (grades 3–4) occurred in 1.1% of patients. Grades 3–4 total hyperbilirubinaemia was the most common laboratory abnormality (9.7%).

Commentary

This is an important study focusing on a difficult to treat population. SAPPHIRE-1 and SAPPHIRE-2 demonstrated that the 3D-RBV regimen achieved more than 95% success with just 12 weeks of treatment.[3 4] Even if not a head-to-head comparison with non-cirrhotics, TURQUOISE-2 suggested that similar results could be expected in patients with cirrhosis if treatment is extended to 24 weeks.

In addition to cirrhosis, 36.1% of TURQUOISE-2 participants were prior null responders. Although prior null response was associated with a higher chance of virological failure in multivariable analysis, most null responders still achieved SVR in this trial.

This study has some limitations. Only patients with Child-A cirrhosis were included and, despite the fact that eligibility criteria allowed for inclusion of patients with low platelets (≥60 000/mm^3) or albumin (≥28 g/dL), median platelet count was only slightly lower than the inferior limit of normal (150 000 cells/mm^3), with median albumin falling within normal range. Actual results may differ in patients with more advanced cirrhosis.

Despite the common occurrence of adverse events, the 3D-RBV regimen resulted in a low rate of serious adverse events and may consequently become a viable treatment option for patients with cirrhosis in the near future.

Competing interests VM-L has lectured for Gilead Sciences.

Provenance and peer review Commissioned; internally peer reviewed.

References

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