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Bulevirtide for Chronic Hepatitis Delta

Wedemeyer H, Schöneweis K, Bogomolov P, et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. Lancet Infect Dis 2023;23:117–129.

Hepatitis delta virus (HDV) co-infection with hepatitis B virus (HBV) is the most aggressive form of viral hepatitis. HDV needs HBV surface antigen to enter hepatocytes, replicate, and spread. Pegylated interferon therapy for 48 weeks has been the only off-label therapeutic approach, but with response rates lower than 30%, late viral relapses, and significant side-effects, finding new therapeutic options in HDV has been an un-met need. Bulevirtide, a first-in-class entry inhibitor for HBV and HDV infection, received conditional authorization by the European Medicines Agency in July 2020, although questions remained regarding its use in clinical practice. For example, the optimal treatment duration is yet to be defined.

Wedemeyer et al report a phase 2 trial of 120 HDV/HBV patients randomized to receive daily subcutaneous bulevirtide at different doses (2, 5, and 10 mg) for 24 weeks with tenofovir compared with tenofovir alone. The primary end point was a 2 $\log_{10}$ IU/mL decline or undetectable HDV-RNA at week 24.

The proportion of patients achieving the primary end point in the groups assigned bulevirtide 2, 5, and 10 mg were 54%, 50%, and 77%, respectively, vs only 1 patient in the tenofovir monotherapy group. However, only a minority of patients (3%–4%) achieved undetectable HDV-RNA. The presence of cirrhosis (50% of patients at baseline) did not affect the primary outcome. The proportions of patients achieving viral response along with alanine transaminase (ALT) normalization were 21% to 37%. Additional benefits seen in the bulevirtide treatment groups included reductions in mean liver stiffness values, and in the number of HDV antigen and HDV-RNA–positive hepatocytes in 22 paired liver biopsies. Bulevirtide was generally well tolerated, with asymptomatic bile salt elevations detected in a significant proportion of patients.

In this study, only a small proportion of patients achieved undetectable HDV-RNA, and 90% experienced an HDV-RNA rebound after bulevirtide withdrawal. Finally, only 6% of patients maintained a sustained response at 48-week follow-up (24 weeks after drug discontinuation). A variety of questions arise from this study. Would bulevirtide be more effective in combination with other anti-virals or immuno-modulators? Should longer treatment durations with bulevirtide be the standard of care? Affordability issues within national health systems may prevent this. In patients with advanced liver disease, could the risks of viral and ALT flares after treatment discontinuation be especially deleterious? Predictors of response and criteria for bulevirtide discontinuation are therefore needed.

Because a decline in ALT levels occurred regardless of bulevirtide dose and not always in parallel with viral changes, does bulevirtide alter virus-specific immune responses involved in liver damage? Finally, hard end points, such as clinical decompensation and transplant–free survival, are strongly needed to assess the effect on the natural history of the disease.

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