A Glimmer of Hope for an Orphan Disease

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Hepatitis D virus (HDV) is a small satellite virus that is present almost exclusively in persons with chronic hepatitis B virus (HBV) infection because of its dependence on HBV surface antigen (HBsAg) for transmission and infectivity. Among HBsAg-positive persons, approximately 5% are infected with HDV, which corresponds to approximately 12 million persons (95% confidence interval, 8.7 million to 18.7 million) worldwide.[1] The estimated prevalence of HDV infection in the United States is low (0.11% of persons).[2] Accordingly, chronic HDV infection qualifies for the Food and Drug Administration Orphan Drug Designation Program, a status that is typically granted for diseases that affect fewer than 200,000 persons.

Chronic hepatitis D is associated with faster progression to cirrhosis and liver failure and a higher rate of liver cancer than the other forms of chronic viral hepatitis. Persistently high HDV levels are associated with worse clinical outcomes.[3] Currently, no therapy has been approved in the United States for the treatment of chronic HDV infection. Although pegylated interferon alfa-2a is effective at suppressing viral replication and reducing liver inflammation, only a minority of patients benefit from treatment, and responses are rarely sustained after therapy is stopped. Therefore, more effective, safe therapies are urgently needed.

Bulevirtide, a synthetic lipopeptide derived from the pre-S1 region of the large envelope protein of HBsAg, irreversibly binds to sodium taurocholate cotransporting polypeptide, the hepatocyte entry receptor for both HDV and HBV. By blocking viral entry, bulevirtide prevents new infection. In July 2020, bulevirtide, at a dose of 2 mg administered subcutaneously once daily, received conditional marketing authorization from the European Medicines Agency (EMA) for use in patients with compensated chronic HDV infection. The EMA authorization was based on early phase studies that showed the ability of bulevirtide to suppress HDV viremia and normalize alanine aminotransferase (ALT) levels.[4]

Results of an ongoing, multicenter, phase 3 trial assessing the safety and efficacy of this new agent are now reported in the *Journal*. Patients with chronic HDV infection were randomly assigned to receive bulevirtide at a dose of 2 mg per day (2-mg group) or 10 mg per day (10-mg group) subcutaneously once daily for 144 weeks or to receive no therapy for the initial 48 weeks followed by bulevirtide at 10 mg once daily for 96 weeks (control group).[5] All patients are scheduled to be followed for 96 weeks after the completion of therapy, in order to establish the durability of the response to treatment. The primary end point was a combined response at week 48 of an undetectable HDV RNA level, or a level that declined by at least 2 $\log_{10}$ IU per milliliter from baseline, and normalization of the ALT level.

A primary end-point response occurred in 45% of patients in the 2-mg group and 48% in the 10-mg group, as compared with 2% in the control group. The percentage of patients with a combined response was similar across subgroups defined according to baseline characteristics, including the presence of cirrhosis and the concomitant use of nucleoside or nucleotide analogue therapy. At week 48, HDV viremia was undetectable in 12% of patients in the 2-mg group and 20% in the 10-mg group, as compared with 0% in the control group. In the 2-mg and 10-mg groups, 19% and 4% of patients, respectively, did not have a meaningful decline (a decline of ≥1 $\log_{10}$ IU per milliliter) in the HDV level. Resistance testing in this subgroup of patients did not reveal any amino acid substitutions in the HBV pre-S1 region or a meaningful change in the maximal effective concentration that suggested a reduced susceptibility to bulevirtide. No declines in HBsAg level were noted. Pruritus occurred in 14% of patients in the 2-mg and 10-mg groups combined, and 16% of patients in the 2-mg group and 30% of patients in the 10-mg group had injection-site reactions.

The goal of HDV therapy is to improve patient survival by preventing progression to cirrhosis, liver failure, and liver cancer.[6] On the basis of surrogate end points used for other chronic viral infections, sustained suppression of HDV viremia should represent the best marker of treatment

efficacy. If undetectable HDV viremia is required for clinical benefit, then only 12% of patients in the 2-mg group and 20% of patients in the 10-mg group had a clinical benefit. The durability of this response after the end of bulevirtide treatment is unknown. The absence of any reduction in the HBsAg level arouses concern about the durability of the response and the possibility of achieving cure with treatment of finite duration, because the presence of HBsAg is typically associated with HDV persistence. In addition, whether a decline in HDV viremia from baseline of 2 $\log_{10}$ IU per milliliter or more and normalization of the ALT level, as assessed at week 48 of treatment, would translate into a clinical benefit is uncertain. Although this end point was accepted by regulatory authorities, it was based on expert opinion and on follow-up data from a small study of interferon therapy that suggested that the end point was associated with a clinical benefit.[7] Whether this end point would be applicable to other agents with different mechanisms of action remains unproven. Key questions remain unanswered. Would the clinical benefit in patients with only a 2-$\log_{10}$ IU per milliliter decline in HDV viremia level be similar to that in patients with undetectable viremia? Would continued use of bulevirtide increase the percentage of patients in whom HDV viremia becomes undetectable, or would the incidence of virologic breakthrough increase over time? Of note, virologic breakthrough occurred in three patients in the trial.

Moreover, what are the appropriate dose and duration of bulevirtide therapy? It should be noted that the trial lacked power to detect a difference in the primary end-point response between the 2-mg and 10-mg groups. The EMA approved the 2-mg dose of bulevirtide and recommended that therapy can be continued as long as clinical benefit is maintained; however, the EMA did not define "clinical benefit."[4] In addition, the long-term safety of bulevirtide needs to be defined.

Perhaps bulevirtide combination therapy may overcome some limitations of bulevirtide monotherapy. Bulevirtide plus pegylated interferon alfa-2a showed synergy in the suppression of HDV viremia during treatment and resulted in HBsAg clearance in a small minority of patients.[8] However, sustained off-treatment suppression of HDV viremia was observed only in patients with HBsAg clearance. There is tantalizing evidence that long-term suppression of HDV viremia may lead to clinical improvement and cure. A patient who received uninterrupted treatment with bulevirtide for 3 years had resolution of esophageal varices with histologic improvement and, more important, maintained undetectable viremia with normal ALT levels for 72 weeks after treatment — findings that suggest the possibility of cure without HBsAg loss.[9] Caution should be exercised when interpreting findings from this case report because spontaneous HDV clearance can occur. Nevertheless, the results of the trial by Wedemeyer and colleagues offer a glimmer of hope for an orphan disease, and the final results of the trial are eagerly awaited.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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