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Editorials

Bulevirtide in Chronic Hepatitis D: Progress in Treatment, Gaps in Care

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For years, chronic hepatitis D left clinicians with few satisfactory treatment options. Bulevirtide has changed that. By blocking viral entry through the sodium taurocholate cotransporting polypeptide receptor, it offers a way to control hepatitis D virus (HDV) infection without relying solely on interferon. The advance is substantial, particularly for patients with compensated liver disease. But a better drug is only part of better care. We still have to find people with unrecognized infection, support treatment that may need to continue for years, and decide what to do when treatment ends (1).

The final MYR301 results make the last question difficult to ignore. After up to 144 weeks of bulevirtide, virological response was observed in 73%-92% of patients across treatment groups. At 96 weeks after treatment discontinuation, the corresponding rates had fallen to approximately 30%–33%. Of 64 patients whose HDV RNA was undetectable at the end of treatment, only 23 (36%) remained continuously undetectable during follow-up (2). Suppression while taking a drug and durable control after withdrawal are plainly different outcomes.

There is, however, a useful lead. In an exploratory analysis, sustained undetectability was observed in 9% of those with less than 48 weeks of continuous on-treatment HDV RNA undetectability, 50% of those with 48 to less than 96 weeks, and 90% of those with at least 96 weeks (2). The numbers are encouraging, but the subgroups are small, support treatment, and these thresholds are not validated stopping criteria. Discontinuation also carries clinical risks: 20 of 142 patients (14%) experienced serious hepatic adverse events after treatment in MYR301 (2). The US prescribing information now warns of severe exacerbations of hepatitis D or B after withdrawal and recommends monitoring HBV DNA and HDV RNA for at least six months (3). Stopping treatment should never mean stopping care.

Nor should a virological endpoint be mistaken for proof of a longer, healthier life. Real-world cohorts have reported encouraging responses, including among patients with cirrhosis, but the evidence remains concentrated in patients with compensated disease (4). Whether bulevirtide reduces decompensation, hepatocellular carcinoma, liver transplantation, or liver-related death requires longer and more definitive follow-up. For now, antiviral treatment must sit alongside the familiar essentials of liver care: assessment of disease stage, indicated cancer surveillance, and appropriate management of the underlying hepatitis B infection (1,3).

Treatment choices are changing as well. In MYR204, HDV RNA was undetectable 24 weeks after treatment in 46% of patients who received 48 weeks of 10-mg bulevirtide plus peginterferon alfa-2a followed by bulevirtide alone for 48 weeks, compared with 12% after 96 weeks of bulevirtide monotherapy (5). This revives interest in finite treatment for selected patients. It does not remove the adverse effects or contraindications of interferon, and it does not establish one regimen as suitable for everyone. The next task is to match treatment intensity and duration to the individual patient.

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That person has too often been absent from discussions dominated by viral load. An MYR301 analysis identified improvements in some patient-reported health measures during bulevirtide treatment (6). Yet daily subcutaneous injections bring difficulties of their own. In a German survey, 25% of patients reported difficulties with injection administration and 27% reported problems with refrigeration; injection difficulties were associated with poorer virological outcomes, although causation cannot be inferred (7). A small prospective study has also explored pharmacist-led education alongside adherence and quality-of-life assessments (8). These observations give nurses and other members of the care team a practical role: checking injection technique, addressing missed doses and storage problems, recognizing treatment burden, and helping patients remain engaged in follow-up. Such work may appear routine, but long-term therapy depends on it.

Diagnosis is the other unfinished task. The World Health Organization favors offering anti-HDV testing to people who are HBsAg-positive, followed by HDV RNA testing when antibodies are detected; reflex testing can reduce missed opportunities (9). In a recent Spanish care cascade program, 42% of anti-HDV-positive individuals had neither a recorded risk factor nor elevated alanine aminotransferase. Even with strong linkage to care, fewer than half of viremic patients started bulevirtide, often because of patient-related or reimbursement barriers (10). A positive test, therefore, is not the same as access to treatment.

Evidence from the Iran–Afghanistan border makes this point especially relevant to our setting. In a community-based survey of three villages in Nehbandan County, Askari and colleagues found anti-HBc positivity in 114 of 489 evaluable participants (23.3%). Among 41 HBsAg-positive participants tested for anti-HDV, five (12.2%) were anti-HDV-positive (11). In an earlier facility-based study across eastern Iran and western Afghanistan, Javanmard and colleagues identified anti-HDV antibodies in 37 of 350 HBsAg-positive patients (10.6%), with marked variation across study sites (12). The studies sampled different populations and should not be combined or read as estimates of population-wide HDV prevalence. In the Nehbandan survey, testing for HBsAg was restricted to anti-HBc-positive samples; in both studies, anti-HDV seropositivity alone could not establish active HDV infection without RNA testing. Together, these findings argue for integrated HBV/HDV testing and reliable referral rather than headline prevalence figures.

Finally, decisions about treatment response and discontinuation will be no better than the tests on which they rely. Inter-assay differences in HDV RNA quantification remain important, especially at low viral loads (13). In Iran and elsewhere, reliable laboratory follow-up, patient education, and accessible specialist services need to develop alongside access to bulevirtide. Our measures of success should therefore extend beyond the proportion of patients with suppressed HDV RNA to include diagnosis, treatment initiation, continuity of care, appropriate surveillance after withdrawal, quality of life, and ultimately fewer serious liver outcomes. That is how a therapeutic breakthrough becomes a lasting improvement in care.

Statements

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