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Journal Article: **Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D Network** N Engl J Med 2024;391:133-43. ; T. Asselah, V. Chulanov, P. Lampertico, H. Wedemeyer, A. Streinu-Cercel, V. Pantea,S. Lazar, G. Placinta, G.S. Gherlan, P. Bogomolov, T. Stepanova, V. Morozov, V. Syutkin, O. Sagalova, D. Manuilov, R.-C. Mercier, L. Ye, B.L. Da, G. Chee, A.H. Lau,A. Osinusi, M. Bourliere, V. Ratziu, S. Pol, M.-N. Hilleret, and F. Zoulim

Commentary:

More than 40 years since its discovery, there is no FDA-approved therapy for chronic hepatitis D virus (HDV) infection, the most aggressive form of chronic viral hepatitis. The off-label use of 48-week pegylated interferon-α (pegIFN) therapy is suboptimal in achieving sustained HDV RNA negativity after therapy is completed (~25%), which is similar to the sustained virological response rate achieved with pegIFN-based therapy for hepatitis C in the early 2000s. Bulevirtide (BLV), an entry inhibitor, was recently approved in Europe as the first direct acting drug for chronic hepatitis D. Asselah et al conducted a phase 2b open-label trial comparing four treatment arms: (i) pegIFN alone, (ii) pegIFN + 2mg BLV daily, (iii) pegIFN + 10mg BLV daily, and (iv) BLV 10mg daily alone and reported **sustained HDV negativity** (ALT normalization) rates of **25%** (42%), **26%** (38%), **46%** (46%) and **12%** (22%), respectively, 48 weeks after treatment was completed. PegIFN + 10 mg BLV was superior to BLV alone. The study was not powered to compare the pegIFN + BLV arms to pegIFN alone. Interestingly, most patients who had sustained HDV negativity did not clear hepatitis B surface antigen (HBsAg).

The 46% HDV negativity rate with pegIFN + 10 mg of BLV suggests a welcome advance in HDV therapy. In addition, HDV negativity and ALT normalization rates observed at end of treatment suggest fascinating opportunities to develop response guided therapy (RGT) strategies to optimize sustained HDV negativity. Further research could focus on developing RGT stopping rules and to identify patients who can reach sustained HDV negativity with longer courses of BLV monotherapy and combination therapy with pegIFN. Since HDV packaging and secretion from infected cells relies on HBsAg, achieving sustained HDV negativity without clearing HBsAg may potentially indicate HDV cure.