Should alanine aminotransferase flares mean stopping antiviral therapy in patients with cirrhosis?

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The HIDIT-2 study by Heiner Wedemeyer and colleagues[1] is the latest and most thorough attempt to control co-infection with hepatitis B virus (HBV) and hepatitis D virus (HDV) with drugs approved for HBV. Within the population of patients with chronic HBV infection, the 15–20 million patients with HDV co-infection[2] are an especially difficult clinical challenge: in addition to the absence of an approved therapy, these patients also have the most rapid progression to cirrhosis,[3] resulting in a large proportion of patients with cirrhosis before exposure to antiviral therapy. Previous studies have examined the therapeutic potential of pegylated interferon either alone[4] or in combination with nucleoside and nucleotide analogues[5,6] in patients co-infected with HBV–HDV, but only enrolled fairly small numbers of patients with cirrhosis. In the HIDIT-2 study, Wedemeyer and colleagues continue to build on previous work[7,8] in combining nucleoside and nucleotide analogues with peginterferon in more patients with cirrhosis who are co-infected with HBV–HDV and extending this combination therapy from 48 weeks to 96 weeks.

As the authors noted, the overall rate of HDV RNA negativity after 48 weeks of therapy in the HIDIT-2 study was improved compared with in the HIDIT-1 study[7] (38% *vs* 24%), which might be related to the switch from the use of adefovir dipivoxil in HIDIT-1 to tenofovir disoproxil fumarate in HIDIT-2. However, extending therapy to 96 weeks in the HIDIT-2 trial did little to increase the rate of HDV RNA negativity observed at week 48. Unfortunately, even with this extended treatment regimen, HDV RNA relapse during follow-up in the HIDIT-2 study still occurred in 19 (40%) of 48 patients, underscoring the difficulty in effectively treating patients with this co-infection.

During treatment of HBV infection, aminotransferase flares are associated with reductions or loss of serum HBsAg and the persistent control of infection with a finite course of therapy.[9–11] If aminotransferase flares become a frequent feature of effective treatment, understanding how patients with cirrhosis tolerate these flares[12–14] is important to help manage these patients during such therapies.

With a uniquely large proportion of patients with cirrhosis (48/120 [40%]) and an extended exposure to 96 weeks of peginterferon, alanine aminotransferase flares were reported in 12 (25%) patients with cirrhosis in the HIDIT-2 study. These flares resolved spontaneously and were similar to those observed in patients without cirrhosis. Only two patients with cirrhosis developed bilirubin elevations: 4·2 mg/dL in one patient who also had a grade 1 international normalised ratio elevation (1·5–1·7), and 3·3 mg/dL in another patient, which was transient. These findings suggest that alanine aminotransferase flares during therapy might be either well tolerated or manageable in these patients. This idea is supported by additional data provided: peginterferon dose reduction was only required during transaminase flares in a few cases. Although thrombocytopenia was reported in 20% of patients, only three instances were severe and all recovered, and stable or improved fibrosis scores were reported in 36 (78%) patients in whom this analysis was possible.

Additional detail regarding liver function in patients with cirrhosis in the HIDIT-2 trial was unfortunately not provided and should include analysis of the timing and geometry of alanine aminotransferase flares and maxima in patients with and without cirrhosis and the relationship between these events and the timing of deflections in INR and bilirubin during these flares (even when below the upper limit of normal). Comparison of these parameters between patients with F5 or F6 cirrhosis might also be informative.

This kind of expanded analysis from both the HIDIT-1 and HIDIT-2 trials and in future studies of patients with HBV–HDV co-infection can help improve our understanding of how alanine aminotransferase flares might be safely managed in patients with cirrhosis so that omitting antiviral therapy can be avoided.

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Long-term protection against varicella with two-dose combination measles-mumps-rubella-varicella vaccine

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In 2014, WHO estimated that approximately 4·2 million severe complications leading to hospital admission and 4200 related deaths occur globally each year because of varicella (also known as chickenpox).[1] By comparison with other vaccine-preventable diseases in childhood, such as measles and diphtheria, mortality and morbidity from varicella are lower.[2] However, the frequency of infection and indirect costs such as from parents taking time off from work, mean varicella has a substantial, albeit underestimated, economic impact.[2] Varicella monovalent vaccines first became widely available in the mid to late 1990s. By the mid-2000s two new vaccines that combined varicella and measles-mumps-rubella (MMR) were licensed on the basis of non-inferior immunogenicity of the constituent components to the separate vaccines. However, despite the potential for these four-in-one MMRV vaccines to simplify immunisation programme schedules and improve varicella vaccine uptake,[3] by 2015 only an estimated 31 countries had adopted routine universally funded varicella vaccination, with either MMRV or monovalent varicella vaccines.[2]

In 2014, the first randomised (phase 3a) trial of a two-dose short course of MMRV vaccine against varicella in children aged 12–22 months, from ten varicella-endemic European countries, followed up over a 3-year period was published.[4] In *The Lancet Infectious Diseases*, Michael Povey and colleagues[5] report results from the phase 3b extension of this study with a total median follow-up time of 9·8 years. Vaccine efficacy was assessed in three groups of children who, 42 days apart, received two doses of measles-mumps-rubella-varicella (MMRV) vaccine (Priorix Tetra, GSK; per-protocol cohort at study end, n=2279), MMR vaccine (Priorix, GSK) followed by monovalent varicella vaccine (Varilrix, GSK; n=2266), or two doses of MMR vaccine as the control group (n=744). Vaccine efficacy against all varicella was 95·4% (95% CI 94·0–96·4) in children who received two doses of MMRV, and 67·2% (62·3–71·5) for MMR vaccine followed by varicella vaccine (MMR+V). For moderate or severe varicella, vaccine efficacy was notably higher, at 99·1% (97·9–99·6) for MMRV, and 89·5% (86·1–92·1) for MMR+V.

Over the near 10-year study period, varicella was reported in 76 (3%) children in the MMRV group, 469 (21%) in the MMR+V group, and 352 (47%) in the MMR control group, providing strong evidence of the endemic circulation of varicella-zoster virus in the participating countries in the absence of widespread vaccination. A decline in vaccine efficacy over time was not evident. Estimates at the 10-year follow-up were similar to those at 3 years, and annual vaccine efficacy was stable at more than 91·4% for the MMRV group and more than 59·4% for MMR+V group. The vaccines also had a good safety profile over years 3–10, with no difference in proportions of patients with serious adverse