Does interferon-sparing tenofovir disoproxil fumarate-based therapy have a role in the management of severe acute hepatitis delta superinfection?

Zahir Osman Eltahir Babiker, Celia Hogan, Andrew Ustianowski and Edmund Wilkins

Department of Infectious Diseases & Tropical Medicine, North Manchester General Hospital, Delaunays Road, Manchester M8 5RB, UK

Infection with hepatitis delta virus (HDV) always occurs in association with hepatitis B virus (HBV) and is a cause of significant morbidity and mortality. We present a case of severe acute HDV infection superimposed on a previously unrecognized HBV infection, in which an interferon-sparing antiviral therapy consisting of tenofovir disoproxil fumarate (TDF) and lamivudine was initiated and subsequently maintained. Evidence of successful suppression of HDV ribonucleic acid (RNA) was obtained after 65 weeks of TDF-based treatment. This was mirrored by a significant reduction in the levels of HBV DNA and HBV surface antigen. HDV RNA subsequently rebounded after our patient stopped antiviral therapy of his own accord. Interferon-sparing TDF-based antiviral therapy was safe and effective in achieving HDV RNA suppression in acute HDV superinfection. Further research into the utility of interferon-sparing TDF-based regimes in the treatment of acute HDV infection is needed.

Introduction

We present a case of acute hepatitis delta virus (HDV) infection superimposed on a previously unrecognized chronic hepatitis B virus (HBV) infection and subsequent suppression of HDV ribonucleic acid (RNA) after 65 weeks of receiving a regimen of interferon-sparing therapy consisting of tenofovir disoproxil fumarate (TDF) and lamivudine (LAM). At present, there are no established treatment recommendations for acute HDV infection. Interferon-based therapy may not be possible in the acute stage of HDV infection owing to the increased risk of hepatic decompensation; therefore, there is a need to explore safe alternative options.

Case report

A previously fit and well 22-year-old man presented with a 4-day history of nausea, vomiting, abdominal pain and yellowish discoloration of his eyes. Physical examination confirmed he was jaundiced and tender over the right upper quadrant of his abdomen. Examination of other systems was unremarkable. He denied any use of injectable drugs but admitted to having unprotected sexual intercourse with a female sex worker in Eastern Europe 5 months prior to his presentation. He did not have tattoos. He was not on any long-term medication and did not have any known drug allergies. He denied excessive alcohol consumption.

Initial diagnostic work-up showed raised levels of bilirubin (209 µmol l⁻¹; reference range: 3–21 µmol l⁻¹), alanine transaminase (ALT) (3382 U l⁻¹; reference range 10–35 U l⁻¹), alkaline phosphatase (219 U l⁻¹; reference range 30–150 U l⁻¹) and international normalized ratio (INR) (1.2; reference range 0.9–1.1). The toxicology screen was negative. HBV surface antigen (HBsAg) was reactive on serum testing and the sample was referred to the regional virology laboratory for confirmation and further testing. Both hepatitis A immunoglobulin M (IgM) and hepatitis C virus (HCV) antibody tests were negative. HIV serology was negative. An ultrasound scan of the abdomen was unremarkable.

During the first week of hospital stay, liver function tests continued to deteriorate with serum bilirubin and ALT levels climbing gradually and reaching peaks of 538 µmol l⁻¹ and 4113 U l⁻¹, respectively. Renal function remained within normal limits but the INR rose to 1.3. In view of the worsening liver function, antiviral therapy with TDF and LAM was initiated and the regional liver transplant unit was contacted while waiting for the results of additional virological tests.

Abbreviations: ALT, alanine transaminase; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; HIDIT, HepNet/International Delta Hepatitis Intervention Trial; INR, international normalized ratio; LAM, lamivudine; RT-PCR, reverse transcriptase PCR; TDF, tenofovir disoproxil fumarate.
Further laboratory testing confirmed that our patient had chronic HBV infection with e-antibody-positive status. The pre-treatment HBV DNA level was only 120 U ml\(^{-1}\) (Abbott Diagnostics) with a corresponding quantitative HBsAg level of 2281 U ml\(^{-1}\) (in-house quantitative HBsAg assay, Centre for Infections, Colindale, UK). HCV RNA was negative by reverse transcriptase PCR (RT-PCR). Serology for cytomegalovirus and Epstein–Barr virus was consistent with previous infection. Hepatitis E virus IgM was weakly reactive but immunoglobulin G (IgG) was not detected. Initial auto-immune profile screening showed anti-nuclear antibody reactivity but was negative on repeat analysis.

HDV serology was strongly positive for IgM but less so for total IgG antibodies (DiaSorin). HDV RNA was detectable at baseline in plasma and upon repeat 2 months later (in-house qualitative RT-PCR assay, Micropathology, Coventry, UK).

Sixty-five weeks following initiation of TDF-based therapy, HDV RNA became undetectable in plasma. This was checked using two different assays; an in-house qualitative RT-PCR assay (Micropathology, Coventry, UK) and an in-house semiquantitative TaqMan RT-PCR assay (Centre for Infections, Colindale, UK). Corresponding HBV DNA and quantitative HBsAg levels at that point were 32 and 253 U ml\(^{-1}\), respectively (Fig. 1). Repeat HDV serology confirmed loss of IgM reactivity and maturation of HDV total IgG antibodies. Transient liver elastography (FibroScan) revealed raised stiffness measure of 10.9 kPa. The patient declined an offer of a liver biopsy. Upper gastrointestinal endoscopy revealed benign antral gastric ulceration but there was no evidence of oesophageal varices.

Afterward, the patient was lost to follow-up for a 12-month period, during which he stopped taking antiviral therapy. On returning to the clinic, he was found to have a raised ALT of 140 U l\(^{-1}\), normal \(\alpha\)-fetoprotein levels, detectable HDV RNA (in-house semiquantitative TaqMan RT-PCR assay, Centre for Infections, Colindale, UK), an undetectable HBV DNA level of <10 U ml\(^{-1}\), and a low quantitative HBsAg level of 125 U ml\(^{-1}\). Our patient was again lost to follow-up after this appointment.

Discussion

We presented a case of acute HDV superinfection in a young adult with a previously unrecognized chronic HBV infection. He received interferon-sparing TDF-based therapy, which managed to suppress HDV RNA fully after 65 weeks of treatment. However, his HDV RNA rebounded after stopping treatment.

HDV, which has eight recognized genotypes with a distinct geographical distribution, is a defective RNA virus requiring the simultaneous presence of HBsAg for complete virion assembly and secretion (Bichko et al., 1994; Le Gal et al., 2006). It is of note that HDV p24 and p27 proteins suppress HBV replication by trans-repressing its enhancers and trans-activating the interferon-inducible MxA gene (Williams et al., 2009)

The pathogenesis of HDV infection is not fully understood. A direct cytopathic effect appears to be the hallmark of acute HDV infection, whereas immune-mediated hepatocyte damage seems to predominate in chronic infections. Furthermore, the pathogenic process is thought to be dependent on host-associated factors, HDV genotype, expression of specific hepatitis delta antigens (HDAg), and HBV genotype and its replicative capacity (Smedile et al., 1982; Casey et al., 1993; Tang et al., 1993; Smedile et al., 1991).

There are two clinically distinct patterns of acute HDV infection. HDV superinfection occurs in individuals with chronic HBV infection and usually presents as acute hepatitis in a previously unrecognized HBV carrier or as a flare up in known HBV carriers. By contrast, co-infection of HBV and HDV occurs in susceptible individuals giving rise to acute hepatitis that is clinically indistinguishable from acute HBV mono-infection. Furthermore, HBV and
HDV co-infection is usually transient and self-limiting whereas HDV superinfection tends to persist in 70–90% of cases (Smedile et al., 1981; Yurdaydın et al., 2010). At present, it is not known whether offering early treatment for patients with HDV superinfection would decrease the likelihood of persistence.

There has been a reported benefit in using foscarnet in cases with acute fulminant hepatitis delta infection (Hedin et al., 2008). There has been a reported benefit in using foscarnet in chronic hepatitis delta virus infection (Hedin et al., 2011). Furthermore, the HIDIT-1 trial showed that a significant decline in HBsAg levels was best achieved in patients receiving PEGylated interferon plus adefovir but not in patients on adefovir monotherapy. This particular finding points to a potential benefit in the adjunctive use of adefovir in eradicating HBV in chronic HBV/HDV dual infection. Similarly, a single-case study suggested that the addition of TDF and emtricitabine to PEGylated interferon might be beneficial in resolving chronic HDV infections associated with high HBV DNA levels (Mansour et al., 2010). A possible mechanism for this is that effective control of HBV DNA replication during the acute stage of HDV infection may result in HDV RNA suppression. Randomized controlled trials on the use of interferon-sparing TDF-based antiviral therapy in acute HDV infection are needed to test this hypothesis.

PEGylated interferon therapy for 72 weeks has been shown to have an efficacy of 20% in individuals with chronic HIV/HBV/HDV co-infection (Niro et al., 2006). A case series, in which 10 out of 16 patients with chronic HIV/HBV/HDV co-infection received interferon-sparing TDF-based regimens, showed significant reduction in HDV RNA levels over a median follow-up period of 6 years (Sheldon et al., 2008).

In conclusion, an interferon-sparing TDF-based regimen has helped our patient with a severe acute HDV superinfection by suppressing HDV RNA and reducing HBV DNA and HBsAg levels significantly over a 65-week period. The fact that HDV RNA rebounded following discontinuation of the TDF-based regimen is intriguing and suggests a potential benefit in using such a regime in similar cases. Further studies on the use of interferon-sparing TDF-based antiviral therapy in acute HDV infection are needed.

References


