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Case Report

CASE REPORT

'Double-hit' pegylated interferon-alpha successfully treats Hepatitis B and Hepatitis D co-infection

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Abstract

Hepatitis delta (HDV) infection is either acquired simultaneously with, or as a superinfection to, existing Hepatitis B (HBV). It leads to a serious form of chronic viral hepatitis and accelerated liver-related morbidity and mortality including hepatocellular carcinoma. Current treatment regimes propose Pegylated interferon-alpha for 48 weeks however sustained virological response (SVR) rates remain low. We report a patient who initially responded to Pegylated interferon treatment for HBV-HDV co-infection. Although initial improvement in viraemia from both virsues was seen, SVR was not achieved with ongoing progression of liver injury biochemically. However, the summative effect of a second course of Pegylated interferon 2 years later led to HDV cure (SVR 12 months post-treatment), very low level HBV carrier status (with persistently undetectable viral load) and ongoing biochemical normalization. This case illustrates a successful treatment strategy for persistent HBV-HDV co-infection where proposed treatment regimes elicit an initial response but SVR is not achieved.

INTRODUCTION

Hepatitis delta infection is caused by the Hepatitis D virus (HDV) which requires the Hepatitis B virus (HBV) for replication [1]. Therefore, Hepatitis delta infection is either acquired simultaneously with, or as a superinfection to, existing HBV. Transmission routes are the same as for HBV, including percutaneous and sexual contact with blood products that are infected (and rarely vertical transmission from mother to child). Acute simultaneous HDV-HBV co-infection causes a hepatitis ranging in severity from mild to fulminant, however a complete recovery is usually seen, and <5% progress to chronic. In contrast, HDV superinfection on a background of established chronic HBV carries a much poorer prognosis in up to 90% of cases, accelerating the development of cirrhosis by almost a decade compared with chronic HBV alone.

HDV-HBV co-infection is seen in at least 5% of chronic HBV cases worldwide resulting in >15–20 million estimated cases [2, 3], although this is thought to be an underestimation of the true prevalence. However, following a global vaccination programme for HBV, the overall number of HDV cases has decreased over the last four decades.

HDV-HBV co-infection is regarded as the most serious form of chronic viral hepatitis, leading to accelerated liver-related morbidity and mortality including hepatocellular carcinoma. Although HDV infection can be prevented successfully by HBV immunisation, current treatment options for established HDV infections have disappointing success rates. Current treatment regimes propose Pegylated interferon-alpha [2, 4] for 48 weeks [2] however sustained virological response (SVR) rates remain low [2–4] with no real advancement in treatment options over the last two decades [5].

We report a patient who was successfully treated for HBV-HDV co-infection with two courses of Pegylated interferon leading to biochemical and virological response.

CASE REPORT

A 42-year-old male with known HBV (diagnosed in Romania in 2011) presented to North Middlesex Hospital with deranged

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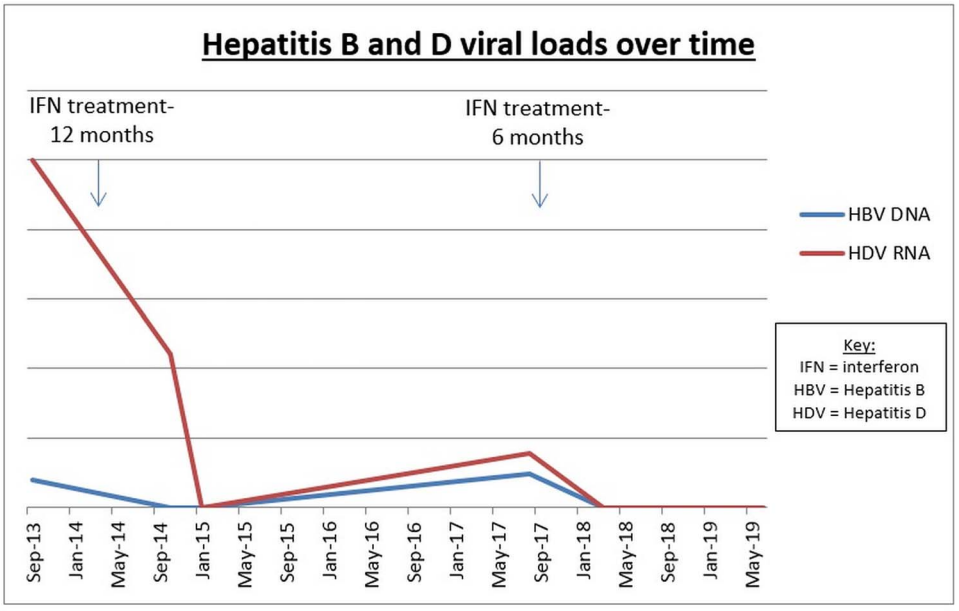

Figure 1: Hepatitis B and D viral loads over time.

LFTs in September 2013. He did not drink alcohol or have any risk factors for non-alcohol related fatty liver disease (NAFLD). Subsequent investigations revealed a diagnosis of HBV-HDV co-infection, and histopathology was consistent with advanced fibrosis (Ishak stage 5) with severe portal inflammation. Viral loads of both viruses were detectable with HBV DNA of 39 iU/ml (e-antigen negative/e-antibody positive at presentation) and a rising HDV RNA of 6.5×10^6 iU/ml going up to 8.8×10^6 iU/ml.

Treatment with Pegylated interferon-alpha 3 was initiated in April 2014, and an initial encouraging response was documented with HDV RNA down to 220 iU/ml after 14 weeks of treatment. After 6 months, HBV DNA was undetectable and after 8 months, HDV RNA was also undetectable. The patient completed 12 months of treatment before unfortunately being lost to follow up and therefore SVR was not assessed.

Two years later, aged 45, he presented to Luton & Dunstable University hospital with a transaminitis (ALT 61). Although the liver looked radiologically unremarkable, a subsequent Fibroscan indicated F2 fibrosis (7.2 kPa). In addition, viral loads of both viruses had become detectable again (HDV RNA 77 iU/ml, HBV DNA 30 iU/ml). The suspicion that both viruses working in tandem were causing progressive liver damage prompted treatment with a second course of Pegylated interferon-alpha 2a (Pegasys).

Following this second course (which the patient stopped at 6 months due to non-compliance) he was essentially cured of his Hepatitis delta infection (HDV RNA undetectable, HDV IgM negative) with an SVR 12 months after completion of treatment (see graph 1). Furthermore, although Hepatitis B surface antigen remains positive and therefore functional cure has not been achieved, he became a very low level chronic HBV carrier (HBV DNA undetectable) as a result of the treatment. Finally, persistent biochemical normalization has been achieved.

DISCUSSION

This is an interesting case because although the initial full course of treatment improved viraemia from both viruses, SVR was not achieved with persistent infection re-presenting as a transaminitis with Fibroscan evidence of ongoing fibrosis. Of note, advanced fibrosis was diagnosed histologically just 3 years prior to the Fibroscan which indicated F2 fibrosis in 2017. This may indicate improvement in fibrosis following initial treatment course (taking the differences in diagnostic modality into consideration), or may be as a result of potential overstating of fibrosis histologically (taking into account the significant improvement in fibrosis over only 3 years as indicated by the histology and subsequent Fibroscan). However, the summative effect of the second course, albeit for a subtherapeutic duration, appears to have achieved very low level HBV carrier status (with persistently undetectable viral load) and Hepatitis delta infection cure as well as biochemical normalisation.

A case described in the literature describes how functional cure of chronic HBV (with HBsAg clearance) as well as SVR of HDV infection was achieved after 12 years of treatment with interferon-alpha [6]. However, subsequent literature including a meta-analysis comparing interferon-alpha, lamivudine and pegylated interferon-alpha for the treatment of HBV-HDV co-infection concluded that pegylated interferon-alpha led to superior SVR rates [4]. Two subsequent studies [7, 8] highlighted that longer courses of Pegylated interferon have superior SVR rates, however treatment is generally poorly tolerated, which is likely to impact compliance with longer courses. Furthermore, there is still a significant proportion of patients who do not achieve SVR after initial response to treatment with Pegylated interferon despite length of treatment as highlighted by these studies.

Although research into a superior therapy for HDV-HBV co-infection is ongoing, the lack of enzymatic proteins to target in the HDV means that conventional antiviral therapy has limited efficacy [5]. This case illustrates the cumulative effect of a 'double hit' of Pegylated interferon-alpha treatment as a successful treatment strategy for persistent HBV-HDV co-infection in patients who do not achieve SVR following initial treatment until a superior management option becomes available.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

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ETHICAL APPROVAL

Ethical approval is not required.

CONSENT

Written consent obtained.

GUARANTOR

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