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Case Report

Sustained virological response after only 5 weeks treatment with daclatasvir/pegylated interferon and ribavirin as part of a clinical trial in a cirrhotic human immunodeficiency virus (HIV) - hepatitis C virus (HCV) co-infected patient with liver decompensation during treatment

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This study presents a case of a sustained virological response to 24 weeks early cessation of hepatitis C direct acting antiviral (DAA) treatment with daclatasvir/peginterferon (PEG-IFN)/ribavirin (RBV), mandated by liver decompensation, in a clinical trial subject with advanced liver disease and human immunodeficiency virus (HIV)/hepatitis C virus (HCV) co-infection.

Key words: Human immunodeficiency virus (HIV), hepatitis C, daclatasvir, liver decompensation, sustained virological response, HIV/hepatitis C co-infection.

INTRODUCTION

We present a case of sustained virological response on a shortened duration directly-acting antiviral regimen for treatment of hepatitis c in the context of liver de-compensation in a clinical trial subject with a history of advanced liver disease and HIV/Hepatitis C co-infection.

CASE REPORT

A 57 year old white British bisexual man was referred to the Hepatology department for investigation of raised alanine aminotransferase (ALT) and raised gamma-glutamyl transferase (GGT) discovered on a routine health screen. He was known to have essential hyper-tension, diet-controlled type 2 diabetes mellitus, gout and vitamin d deficiency. His alcohol intake had always been minimal at less than 8 units per month, and there was no history of intravenous drug use. Losartan 50 mg was prescribed to him once daily by his general practitioner (GP), and he did not use over the counter preparations or herbal medications.

Further investigations revealed the patient to be

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co-infected with newly diagnosed HIV (Antibody positive) and Hepatitis C (Antibody positive) genotype 1A. CD4 count was 255 cells/mm3 (7%), HIV-RNA 118,825 copies/ml (Log 5.07), HCV RNA 5,074,501 IU/mL (Log 6.71) and Hepatitis B sAB 538 IU/L. Liver functions tests were bilirubin 6 µmol/L, alkaline phosphatase (ALT) 58 units/L, aspartate transaminase (AST) 48 units/L, albumin 43 g/L. International Normalized Ratio (INR) was 1.0 and creatinine 78 µmol/L. Hepatitis A antibody, autoimmune screen, ferritin, and caeruloplasmin were negative, and alpha-fetoprotein was normal. Examination was unremarkable with no stigmata of chronic liver disease. An ultrasound doppler scan of the abdomen showed the liver to be normal in size and reflectivity, slightly coarse in echotexture, with no associated duct dilatation. The spleen and other intra-abdominal organs were reported as normal.

A single core biopsy of the liver showed cirrhosis with marked portal-portal and portal-central bridging fibrosis with nodule formation: fibrosis score 6/6 (Ishak score). Oesophago-gastro-duodenoscopy revealed portal hypertensive gastropathy without esophageal varices. Child-Pugh score was 5 (Class A). The patient was referred to HIV services and in view of his low CD4 count, tenofovir, emtricitabine and efavirenz, was commenced on achieving an undetectable HIV RNA result after 4 weeks.

The patient was screened for inclusion into a clinical trial evaluating the efficacy and safety of pegylated interferon lambda-1a (PEG-IFN), in combination with ribavirin (RBV) and daclatasvir (DCV). The patient was to receive PEG-IFN and RBV and DCV for 12 or 24 weeks based on stopping rules (rapid virological response achieved at 4 weeks (RVR)). As daclastavir can interact with efavirenz causing reduced DCV exposure (Bifano et al., 2013), the DCV dose was increased from 60 to 90mg. At week one, the HCV-RNA viral load decreased from 6,743,260 to 33 IU/ml (a 5.3 log drop) and the HCV was 'target not detected' at week 2.

The patient was feeling well until week 4 when he complained of fatigue and dysgeusia. Examination revealed slight gynaecomastia but no other positive findings. AST was 118 IU/L (3 x upper limit of normal and 2.45 x baseline). At the patient week 5 study visit, he was more lethargic and had been vomiting for 2 days. He was pyrexial (38.5°C) and mildly icteric. There was no evidence of ascites or clinical signs of encephalopathy. Liver function tests showed an increasing transaminitis; ALT 201 units/L, AST 691 units/L, bilirubin 55 µmol/L, albumin 37 g/L. International Normalized Ratio (INR) was 2.2 and creatinine 146 µmol/L. Child-Pugh score was 8 (Class B). Our assessment was that of decompensated liver disease, and so his study medications were stopped after 5 weeks and 3 days of treatment.

Urine microscopy and culture revealed a sensitive *Escherichia coli* infection, and the patient was admitted in the hospital for treatment with amoxicillin/clavulanic acid. His INR, liver synthetic function and renal function were closely monitored. Within 5 days, the liver function tests (LFT) had returned to the normal range and the patient was discharged from hospital. Although, the patient had been withdrawn from the study, we continued to monitor his HCV-RNA, which had remained undetectable after cessation of the study drugs. 24 weeks after treatment was terminated, the patient's HCV-RNA remained undetectable, indicating a sustained viral response after only 5 weeks of treatment with PEG-IFN, RBV and DCV.

DISCUSSION

There has been considerable evolution in the treatment options for Hepatitis C in the past 3 years, particularly for those with HIV-HCV co-infection who had been difficult to treat with PEG-IFN/RBV. DAAs have considerably improved options in terms of efficacy and better tolerability, as well as much shorter treatment durations. Daclatasvir is the first approved DAA belonging to the NS5A replication complex inhibitors class. With a high potency drug, DCV has become an important component of combination regimens for all HCV genotypes (Kim et al., 2014). The combination of DCV/PEG-IFN/RBV is generally well tolerated and has achieved higher SVR_{24} rates compared with placebo/peginterferon-alfa/ribavirin in mono-infected G1 and G4 patients (Hezode et al., 2014). Daclatasvir has been studied in combination with other DAAs such as asunaprevir (Lok at al., 2012), and sofosbuvir (SOF) (Sulkowski et al., 2012) with or without RBV and PEG-IFN, achieving SVR_{12} rates of >90% in G1A mono-infection. Phase 3 studies of DCV-SOF combination therapy for HIV-HCV co-infected patients are underway (ALLY2 - Clinical trials NCT02032888). Patients with cirrhosis remain challenging as they tolerate DAA therapy less well and decompensation is well described (Chastain and Naggie, 2013). Our patient had normal liver function with extensive fibrosis on biopsy and Child-Pugh score 5 prior to commencing DCV/PEG-IFN/RBV. Subsequent development of hepatic decompensation, probably precipitated by urinary tract infection, put him at risk of liver failure and death. Patients with extensive fibrosis should be monitored closely as they are at higher risk of serious adverse events.

Duration of therapy with most DAAs is currently around 12 weeks with excellent SVR_{12} and SVR_{24} rates after 12 weeks therapy. The ALLY 2 study will compare SVR_{12} rates in treating naïve patients treated with either 8 weeks or 12 weeks of DCV- SOF, examining whether HCV cure can be achieved with even shorter duration therapies. This study indicates that early viral load is a good predictor of long term outcome (Araújo et al., 2011), with a swift suppression of HCV-RNA leading to achievement of SVR_{24}, despite advanced liver disease

and more than halving the duration of therapy.

CONCLUSION

This study reports a case of decompensated liver disease in a patient on DCV/PEG-IFN/RBV for 5 weeks who achieved suppressed HCV-RNA within 2 weeks of therapy, and went on to achieve SVR_{24} after treatment was terminated.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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