TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

CASE REPORT

Successful treatment of fibrosing cholestatic hepatitis with pegylated interferon, ribavirin and sofosbuvir after a combined kidney–liver transplantation

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Keywords
fibrosing cholestatic hepatitis, hepatitis C virus, kidney transplantation, liver transplantation, sofosbuvir.

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Conflicts of interest
The authors have declared no conflicts of interest.

Received: 28 June 2014
Revision requested: 26 July 2014
Accepted: 19 August 2014
Published online: 29 September 2014

doi:10.1111/tri.12428

Summary

Fibrosing cholestatic hepatitis (FCH) is a classical but rare and severe form of recurrent hepatitis C virus (HCV) after liver transplantation. Classical anti-HCV therapy, that is pegylated-interferon (peg-interferon) and ribavirin, has been shown to have limited efficacy in treating FCH. Herein, we report on the first case of successful use of peg-interferon, ribavirin, plus sofosbuvir to treat HCV-induced FCH in a combined liver–kidney transplant patient. Antiviral therapy was given for 24 weeks. HCV clearance occurred within 4 weeks after starting therapy and was maintained until 4 weeks after the end of therapy. Antiviral tolerance was good. We conclude that the use of sofosbuvir-based anti-HCV therapy can be successfully used to treat FCH after a liver or combined kidney–liver transplantation.

Introduction

Fibrosing cholestatic hepatitis (FCH) is a classical but rare and severe form of recurrent hepatitis C virus (HCV) after liver transplantation, occurring in up to 15% of HCV-positive RNA-positive patients [1]. It is responsible for severe cholestasis and rapid fibrosis, leading to death. Classical anti-HCV therapy, that is, pegylated-interferon (peg-interferon) and ribavirin, has been shown to have limited efficacy in treating FCH [2]. Within the last couple of years, the use of second-generation direct anti-HCV drugs has dramatically improved the sustained virological-response rate in naïve, relapsing, and nonresponding patients, whatever their HCV genotype [3–6]. To the best of our

knowledge, sofosbuvir- or daclatasvir-based anti-HCV drugs have been successfully used in only three patients presenting with FCH after liver transplantation [7–9]. Herein, we report on the first case of successful use of peg-interferon, ribavirin, plus sofosbuvir to treat HCV-induced FCH in a combined liver–kidney transplant patient.

Case report

A 66-year-old non-HLA sensitized man received a combined liver and pre-emptive kidney transplantation for HCV-induced cirrhosis and membranoproliferative glomerulonephritis. At transplantation, the MELD score was 10. HCV RNA concentration was 5.78 log IU/ml and was genotype 1a. The patient's IL28B polymorphism was C/C. He was co-infected with hepatitis B (HBV) and D viruses (HDV). However, HBV DNA and HDV DNA were negative. Before transplantation, he failed to respond to a 12-month course of peg-interferon plus ribavirin. The organ donor was anti-HCV negative RNA-negative. After transplantation, he was given an induction therapy of basiliximab, followed by a triple immunosuppressive therapy of tacrolimus, mycophenolic acid plus low-dose steroids. Postsurgical events after the transplantations were unremarkable, and the patient was discharged on day 12.

At 3 months post-transplantation, he presented with fatigue, jaundice and weight loss (−7 kg). Liver biochemistry parameters showed increased alanine aminotransferase (ALT) levels, from 25 to 209 IU/l (normal range: 0–40); increased aspartate aminotransferase (AST) levels, from 22 to 222 IU/l (normal range: 0–50); increased gamma-glutamyl transpeptidase (GGT) levels, from 60 to 5522 IU/l (normal range: 0–60); and increased total bilirubin levels from 10 to 265 μmol/l (normal range: 0–21; Fig. 1). Serum creatinine level was unchanged at 81 μmol/l, that is, eGFR (estimated by the Modification in Diet for Renal Disease equation) was 88 ml/min. INR was 1.2. Tacrolimus trough level was 10 ng/ml. HCV RNA concentration was >8 log IU/ml. HBV, HDV, hepatitis E virus, cytomegalovirus, HHV6 and Epstein–Barr virus infections were ruled out by nucleic-acid tests. Biliary-tract abnormalities were ruled out by a magnetic-resonance cholangiogram and endoscopic-retrograde cholangiography. A liver ultrasound, using Doppler, excluded portal-vein thrombosis. No anti-HLA donor-specific antibodies (DSAs) were detected.

A liver biopsy was performed and showed features of FCH, that is, active chronic hepatitis with focal bridging fibrosis and a pericentral cholestatic reaction with lymphocytic inflammation (Fig. 2). As kidney function was not

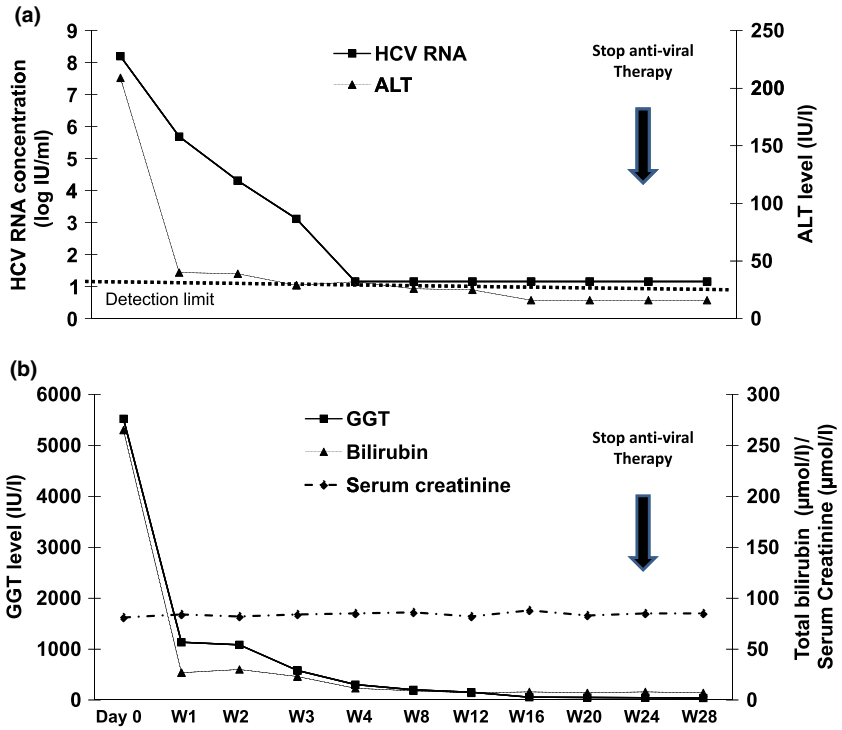

Figure 1 (a) Outcome of hepatitis C virus (HCV) RNA concentration and alanine aminotransferase levels during therapy. (b) Outcome of gamma-glutamyl-transpeptidase, serum creatinine and total bilirubin levels during therapy.

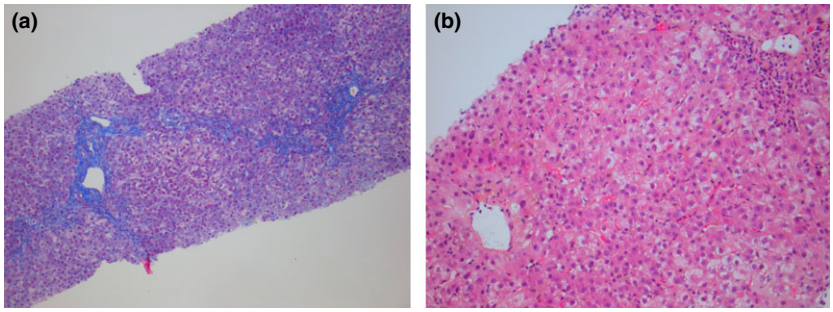

Figure 2 (a) Active chronic hepatitis with focal bridging fibrosis. (b) An intense pericentral cholestatic reaction with lymphocytic inflammation.

impaired, no kidney biopsy was performed. Despite the risk of interferon-induced acute kidney-allograft rejection, the patient was given peg-interferon (135 μg/week), ribavirin (400 mg b.i.d.) and sofosbuvir (400 mg/day orally, in the mornings). The treatment was scheduled for 24 weeks. Antiviral therapy remained unchanged as well as the immunosuppressive therapy.

Within 4 weeks of starting the antiviral therapy, HCV RNA had decreased to below the detection limit (<1.18 log IU/ml, Roche Cobas Taqman assay; Fig. 1). ALT and AST levels had returned to within normal ranges by day 15, and bilirubin level had decreased to 11.5 μmol/l by month 1. As scheduled, antiviral therapy was stopped at week 24. At that time, HCV RNA was still undetectable and liver-enzyme levels were within their normal ranges. Serum creatinine level was 85 μmol/l, and no proteinuria was detected. No DSAs were detected. At 4 weeks after ceasing antiviral therapy, HCV RNA was still undetectable. Liver enzymes levels remained within the normal ranges, and serum creatinine level was 84 μmol/l.

No acute kidney- or liver-allograft rejection episodes were observed within the treatment period. Indeed, although no systematic liver and kidney biopsies were performed during and after therapy; liver enzymes levels have returned to normal ranges, and no kidney function impairment or *de novo* DSA or *de novo* proteinuria were observed. The main side effect was haemolytic anaemia: at 3 months post-antiviral therapy, this required ribavirin dose to be reduced from 800 to 400 mg/day, and one blood transfusion. At that time, haemoglobin level had decreased from 9.5 to 7.8 g/dl. In addition, the dose of darbepoetin, which was initiated 1 month after starting ribavirin, was increased from 100 to 300 μg/week. No infection episode occurred during antiviral therapy.

Discussion

FCH is a rare but life-threatening form of HCV recurrence after liver transplantation [1]. It is responsible for rapid and severe fibrosis that can lead rapidly to death [1]. The use of peg-interferon and ribavirin in this setting has shown limited efficacy [2]. The addition of boceprevir or telaprevir, two first-generation direct-acting anti-HCV drugs, increased the efficacy, but tolerance was poor [10]. More recently, second-generation direct-acting anti-HCV drugs, such as sofosbuvir and daclatasvir, have been shown to be highly efficient when combined with ribavirin, with or without peg-interferon, at treating all HCV genotypes in both naïve and previously treated patients [6].

To the best of our knowledge, sofosbuvir- or daclatasvir-based antiviral therapy has been successfully used to treat FCH after liver transplantation in three patients. A first patient, who experienced FCH at 3 months after a second liver transplantation, was given peg-interferon, ribavirin, plus reduced-dose daclatasvir (20 mg/day) for 24 weeks, followed by peg-interferon and ribavirin consolidation therapy for 4 additional weeks. HCV RNA clearance occurred at week 3 and remained undetectable until the end of therapy [7]. A second patient, who developed FCH at 6 months after a first liver transplantation, was given sofosbuvir and daclatasvir for 24 weeks. HCV RNA became undetectable at week 4 and a sustained virological response was observed [8]. The third patient, who experienced FCH at 15 months after liver transplantation, was given sofosbuvir and ribavirin for 24 weeks. HCV RNA clearance was observed at week 12, and HCV RNA was still undetectable at week 2 after completion of his anti-HCV therapy [9].

Herein, we report, for the first time, a case of FCH that occurred 3 months after combined kidney–liver transplantation that was successfully treated by peg-interferon, ribavirin, plus sofosbuvir given for 24 weeks. HCV clearance occurred within 4 weeks after starting therapy and was maintained until the end of therapy. Similar to previous reports, in which patients were given sofosbuvir and daclatasvir or peg-interferon, ribavirin and low-dose daclatasvir, HCV clearance occurred within the first month after starting therapy. Conversely, HCV clearance occurred only within 12 weeks when a patient was given sofosbuvir plus ribavirin. The very severe form of FCH that developed in our patient, prompted us to use a triple therapy that

combined peg-interferon, ribavirin and sofosbuvir. Because of the rapid virological response observed at 1 week after starting anti-HCV therapy, and because daclatasvir is not yet commercially available in France, we did not ask for compassionate use of daclatasvir. The use of peg-interferon in a patient who has received a kidney-allograft is open to criticism: it is usually contraindicated in this setting because of an increased risk of acute rejection [11]. Nevertheless, the combination of peg-interferon plus ribavirin has been successfully and safely used in kidney transplant patients [12,13], and in those who have received a combined kidney–liver transplantation [14]. In the case we report, no acute-rejection episode was observed and kidney function was unchanged during therapy. The sole side effect was anaemia, which required a blood transfusion and the use of erythropoietin. In addition, no adverse drug–drug interactions were observed between sofosbuvir and tacrolimus.

To date, the use of a combination of two second-generation direct-acting anti-HCV drugs seems to be the optimal and safer treatment for FCH. In the near future, pegylated interferon may not be used anymore. In addition, whenever, it is possible, pegylated-interferon should be avoided in patients having received a kidney transplant. However, its use in combination with one direct acting agent and ribavirin can be considered when the use of two direct acting agents is not possible.

In summary, based on the present and previous case reports, the use of sofosbuvir- or daclatasvir-based anti-HCV therapy can be successfully used to treat FCH after a liver- or combined kidney–liver transplantation.

Authorship

CD: collected the data and wrote the paper. LL, GD, LR, JMP and CB: participated to the patients' management and reviewed the paper. FM: performed the liver transplantation. FS: performed the kidney transplantation. MD: did the pathological analysis. JI: did the virological analysis and reviewed the paper. NK: participated to the patients' management and wrote the paper.

Funding

The authors have declared no funding.

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