Three-month pegylated interferon-alpha-2a therapy for chronic hepatitis E virus infection in a haemodialysis patient

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Abstract

Hepatitis E virus (HEV) can induce chronic hepatitis in immunosuppressed patients. There is no established treatment for HEV infection. Pegylated interferon-alpha-2a (Peg-IFN-α-2a) has been successfully used for treating HEV infection in liver transplant patients with chronic hepatitis. A kidney transplant patient with chronic HEV infection evolved to end-stage kidney disease and started haemodialysis. Three months after immunosuppressive therapy was stopped, HEV RNA was still detected both in serum and in stools. Before considering a retransplantation, we decided to initiate Peg-IFN-α-2a therapy to eradicate the virus. A 3-month course of Peg-IFN-α-2a was scheduled, and the latter was started at the weekly dose

References


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of 135 µg. Serum HEV RNA became negative by Week 3 of Peg-IFN-α-2a therapy, and remained negative until the last follow-up, i.e. 6 months after anti-viral therapy was stopped. Hence, we report the first known case of a 3-month course of Peg-IFN-α-2a inducing a sustained virological response in this HEV-positive and RNA-positive haemodialysis patient who had failed to be cleared of the virus after immunosuppressant withdrawal.

Keywords: chronic hepatitis; haemodialysis; hepatitis E virus; pegylated interferon

Introduction

To date, it is acknowledged that hepatitis E virus (HEV) may induce not only acute hepatitis [1] but also chronic hepatitis, at least in organ transplant patients [2], haematological patients receiving chemotherapy [3] and patients infected by the human immunodeficiency virus (HIV) [4]. Furthermore, chronic hepatitis may progress rapidly to cirrhosis [5,6]. There is no established treatment for chronic HEV infection. However, very recently, we have shown that reducing immunosuppressive drugs that target T-cells can be considered a first-line therapeutic option for treating solid-organ transplant patients with chronic HEV infection [7]. We have also shown that pegylated interferon-alpha-2a (Peg-IFN-α-2a) can effectively treat liver transplant patients with chronic HEV infection [8]. Herein, we report, for the first time, the efficacy of a 3-month Peg-IFN-α-2a therapy in a haemodialysis patient with chronic HEV infection.

Case report

A 24-year-old man received a first deceased-donor kidney allograft for Alport disease. After an induction therapy that used rabbit anti-thymocyte globulins (RATG), his initial immunosuppressive therapy was based on cyclosporine A and steroids. At 3 months after transplantation, he experienced a steroid-sensitive acute rejection. At 14 months post-transplantation, because of biopsy-proven chronic allograft nephropathy, cyclosporine A was replaced by sirolimus. Serum creatinine level was 134 µmol/L.

At 49 months after transplantation, he presented with acute HEV infection (Figure 1). Anti-HEV IgG and IgM, which were negative at transplantation, were found to be positive. At diagnosis, HEV RNA concentration was 6.65 log copies/mL. Retrospective analysis of frozen sera revealed that HEV RNA had been negative at transplantation and at 4 months before the acute phase. Phylogenetic analysis of HEV RNA revealed that the strain belonged to the...
genotype 3f (GenBank No. EU220999). At HEV infection diagnosis, hepatitis C virus (HCV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV) serologies, and hepatitis A virus (HAV) IgM, as well as HCV RNA, HBV DNA and HIV RNA were all negative, as at transplantation, and stayed negative thereafter. Similarly, there was no evidence of cytomegalovirus, Epstein–Barr virus and herpes simplex virus infections. Anti-nuclear autoantibodies, anti-liver–kidney microsomal antibodies, anti-smooth muscle cell antibodies and anti-mitochondrial antibodies were not detected.

HEV infection evolved to chronic hepatitis, as defined by the presence of persistently elevated liver enzyme levels and detectable HEV RNA in the serum. HEV RNA concentration at 6 months post-HEV infection was 4.84 log copies/mL. At the acute phase of HEV infection, serum creatinine level was 118 μmol/L. During the following 6 years, serum creatinine level increased progressively. At 68 months post-transplant, due to impaired kidney function, sirolimus was replaced by low-dose tacrolimus (targeting a trough level of between 3 and 5 ng/mL) and mycophenolate sodium (720 mg/day). By 113 months post-transplantation, the patient progressed to end-stage kidney disease and required haemodialysis (three times weekly). At that time, tacrolimus and mycophenolate sodium were withdrawn. Steroids were stopped 1 month later.

When haemodialysis was initiated, liver enzyme levels were still elevated, and serum HEV RNA concentration was still positive at 5.22 log copies/mL. Three months after immunosuppressant withdrawal, serum HEV RNA was still positive at 5.15 log copies/mL.

Hence, because of persisting detectable HEV RNA in serum and stools, and histological signs of active hepatitis (A2F1 according to the Metavir classification [9], and before considering re-transplantation, we decided to initiate Peg-IFN-α-2a therapy to eradicate the virus. Consequently, a 3-month course of Peg-IFN-α-2a (Pegasys®, Roche, Basle, Switzerland) was started at a weekly dose of 135 μg. Serum HEV RNA concentration remained unchanged after Week 1 of Peg-IFN-α-2a therapy (5.22 vs. 4.97 log copies/mL), but had become negative by Week 3 of Peg-IFN-α-2a therapy and remained negative until Month 3. HEV RNA became undetectable in the stools by Month 2 of Peg-IFN-α-2a treatment. Liver enzyme levels returned to the normal range by Week 3 of therapy. However, by Month 3 of Peg-IFN-α-2a, at the time scheduled to stop the anti-viral therapy, the patient presented with acute rejection of the failed kidney allograft and required a transplantectomy.

At the last follow-up, i.e. 6 months after Peg-IFN-α-2a therapy had been stopped, HEV RNA was still negative in the serum and stools, and liver enzyme levels remained within the normal range. The clinical and biological tolerances to Peg-IFN-α-2a were good.

Discussion

HEV infection is considered an emerging disease in industrialized countries [1]. Within the last couple of years, many cases of chronic HEV infection have been reported in immunocompromised patients and those infected by HIV [2–4,10]. Among solid-organ transplanted infected by HEV, ~60% evolve to chronic hepatitis [7]. Furthermore, rapid evolution to cirrhosis has been reported after kidney, kidney–pancreas and liver transplantsations [5,6,10]. In two liver transplant recipients, HEV-induced cirrhosis required re-transplantation; in one of these cases, chronic HEV infection re-occurred on the second liver transplant [10]. Hence, the severity of HEV infection in immunocompromised patients prompted us to try to eradicate the virus in the present patient before considering re-transplantation.

Until now, no specific therapy against HEV infection has been established. Among 16 solid-organ transplant patients with chronic hepatitis, four were cleared of the virus after significantly reducing immunosuppressive drug doses [7]. Interestingly, all four were liver transplant patients. Recently, 3 months of Peg-IFN-α-2a therapy has been found to effectively sustain a virological response in two out of three liver transplant patients with chronic HEV infection [8]. This recent finding prompted us to use Peg-IFN-α-2a in our haemodialysis patient who failed to be cleared of the virus despite immunosuppressants being stopped for a 3-month period. The choice of Peg-IFN-α-2a dosage (i.e. 135 μg/week) was based on the dose previously used in HCV-positive haemodialysis patients [11–13]. By Week 3 of Peg-IFN-α-2a therapy, HEV RNA was no longer detected in the serum. By Month 2 of anti-viral therapy, HEV RNA was no longer detected in the stools. As scheduled, Peg-IFN-α-2a therapy was stopped at Month 3. Additionally, a sustained virological response was observed, i.e. there was no relapse of HEV replication during the 6 months after Peg-IFN-α-2a treatment had been stopped. We hope this sustained virological response will be maintained after re-transplantation. Only one case of HEV reactivation has been reported after allogeneic stem cell transplantation in a patient with acute lymphoblastic leukaemia [14]. No incidences of HEV reactivation have been observed in solid-organ transplant patients who are cleared of the virus despite intensive immunosuppressive therapy [7,8]. In HCV-positive and RNA-positive haemodialysis patients, when a sustained HCV RNA clearance occurs after interferon therapy, no HCV relapses developed after transplantation despite intensive immunosuppressive treatment [15,16].

In HCV-positive and RNA-positive haemodialysis patients, HCV therapy still relies on standard interferon therapy [17]. However, it has recently been shown that pegylated interferon can be used safely in this setting [12,18]. In the present case, the clinical and biological tolerances of Peg-IFN-α-2a were excellent. However, as previously described in HCV-positive haemodialysis patients who were treated by interferon therapy, an acute rejection did occur on the failed kidney allograft that required a transplantectomy [19]. This may be related to the use of a rather high dosage of pegylated interferon in a haemodialysis patient.

In conclusion, a 3-month course of Peg-IFN-α-2a induced a sustained virological response in this HEV-positive and RNA-positive haemodialysis patient who had failed to be cleared of the virus after immunosup-
Pulmonary alveolar proteinosis in kidney transplant

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Abstract
Pulmonary alveolar proteinosis (PAP) has been associated with the immunosuppressant sirolimus in transplant patients. PAP is a progressive lung disease characterized by the accumulation of surfactant-like material in the lungs leading to decreased pulmonary function with shortness of breath and cough as common symptoms. We report a rare case of sirolimus-associated PAP in a kidney trans-