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Long-term Pegylated Interferon-α-2a Treatment for Chronic Hepatitis C in an Elderly Renal Transplant Recipient

Case Report and Literature Review

Ming-Hua Zheng, MD, PhD and Yong-Ping Chen, MD

Abstract: Combination treatment of pegylated interferon (PEG-IFN) plus ribavirin for renal transplant recipients (RTRs) with hepatitis C virus (HCV) infection remains controversial, as it has been associated with a high risk of rejection, resulting in graft loss and a reduction in patient survival.

We present a special case of an elderly RTR who experienced treatment of HCV infection 8 years after renal transplant. There was no rejection episode during or after PEG-IFN treatment. The patient first received a 24-week therapy and a further 60-week course due to relapse. Cessation of both courses corresponded to an achieved end-of-treatment response. However, HCV infection reappeared shortly after cessation of the 60-week treatment period.

This case highlights the safety of PEG-IFN therapy for elderly RTR and the potential importance of combination pretreatment for patients undergoing renal transplantation.

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Abbreviations: AE = adverse effect, ALT = alanine aminotransferase, CHC = chronic hepatitis C, ETR = end of treatment response, HCV = hepatitis C virus, PEG-IFN = pegylated interferon, RTR = renal transplant recipient, SVR = sustained virological response.

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INTRODUCTION

It is well known that hepatitis C virus (HCV) infection is the major cause of chronic liver disease after renal transplantation. The prevalence of anti-HCV varies between 10% and 49% in patients who undergo renal transplantation.[1] Age, particularly >50 years, is considered to be an independent risk factor for the progression of fibrosis and development of cirrhosis in patients with chronic hepatitis C (CHC), which results in worse patient- and allograft-survival rates than observed in younger patients.[2] However, treatment with pegylated interferon (PEG-IFN) plus ribavirin for renal transplant recipients (RTRs) with HCV infection remains controversial, as it has been associated with a high risk of rejection, resulting in graft loss and reduced patient survival.[3]

CASE PRESENTATION

A 60-year-old man presented to the First Affiliated Hospital of Wenzhou Medical University for routine examination. The patient suffered from uremia secondary to chronic renal failure at the age of 50 years in May 1998. Afterwards, he underwent renal transplantation in November of the same year. Following the procedure, immunosuppression was performed with ciclosporin with a follow-up as an outpatient every 2 weeks. Subsequently, the patient acquired HCV infection through hemodialysis perioperatively; the renal allograft showed stable function and liver function remained stable after the transplantation procedure. Clinical data of renal and liver function and the concentration of ciclosporin during the follow-up from 2000 to 2007 are summarized in Figure 1. A renal biopsy was performed in 2004 and 2008 and both biopsies showed slight IgA nephropathy with no evidence of allograft rejection.

All findings of physical examination were unremarkable. However, results from laboratory tests showed aspartate aminotransferase was 66 IU/L (normal range 5–60 IU/L) and alanine aminotransferase (ALT) rose to 103 IU/L (normal range 5–55 IU/L). The ALT level showed elevation at subsequent follow-ups, which was suggestive of progressive liver dysfunction. Suspecting iatrogenic hepatitis, the immunosuppressant was changed from ciclosporin to FK-506 (tacrolimus); however, there was no improvement in liver function. The HCV-RNA assay showed the presence of an HCV genotype 1b infection with a serum virus load of 7.7×10^6 IU/mL (normal range $\leq 5 \times 10^2$ IU/L). He was diagnosed with CHC and started receiving PEG-IFN-α-2a therapy. Written informed consent was obtained before treatment. The patient's pretreatment laboratory tests, including thyroid function and white blood cell count, were all in the normal range (see Supplementary online file, http://links.lww.com/MD/A137).

On February 27th, 2008, the patient was started on a 24-week course of PEG-IFN-α-2a, 135 μg/wk administered subcutaneously. Ribavirin was added at a dose of 400 mg/d. However, consistent with the association of hemolytic anemia as a known severe adverse effect (AE) of ribavirin use, the

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From the Department of Infection and Liver Diseases, Liver Research Center, The First Affiliated Hospital of Wenzhou Medical University (MHZ, YPC); and Institute of Hepatology, Wenzhou Medical University, Wenzhou, China (MHZ, YPC).
Correspondence: Ming-Hua Zheng, Department of Infection and Liver Diseases, Liver Research Center, The First Affiliated Hospital of Wenzhou Medical University, No. 2 Fuxue Lane, Wenzhou 325000, China (e-mail: blueman1320@163.com).
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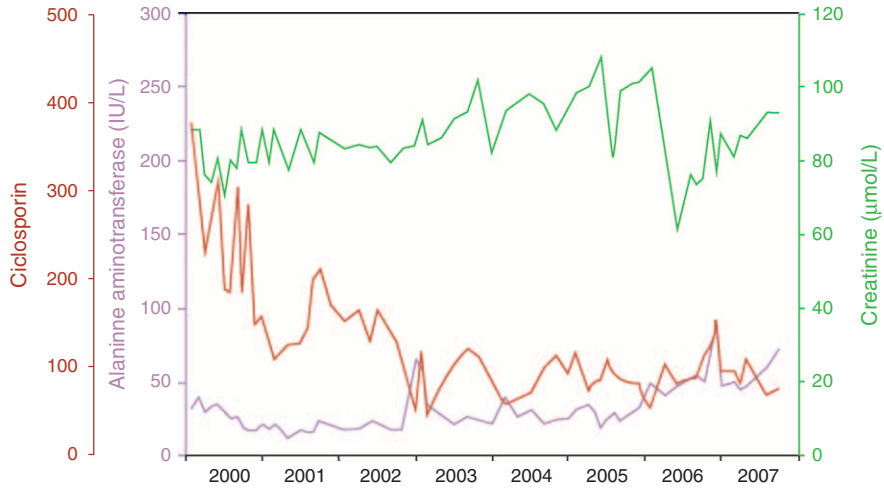

FIGURE 1. Major laboratory results during 8-year follow-up after renal transplantation. The green line represents the level of creatinine, the brown line the level of alanine aminotransferase, and the purple line the level of ciclosporin.

patient's hemoglobin level decreased to 72 g/L (normal range 120–160 g/L) at week 2. Ribavirin therapy was stopped and PEG-IFN-α-2a therapy continued. The level of hemoglobin subsequently stabilized at 110 g/L by week 7. At week 12, HCV-RNA was undetectable and remained negative until week 24. Given the time taken to attain undetectable HCV-RNA, the patient achieved early virus response (defined as ≥2 log10 reduction of serum HCV RNA after 12 weeks of antiviral therapy[3]) and end-of-treatment response (ETR, which was defined as undetectable HCV RNA by qualitative assay at the end of 24 or 48 weeks of treatment).[3] There was a remarkable improvement in the ALT level (23 IU/L) at week 24 and allograft function was steady with creatinine of 97 μmol/L. FK-506 was used as maintenance immunosuppression therapy throughout the duration.

In spite of this satisfactory profile, a viral relapse with HCV-RNA of 6.3×10^7 IU/mL occurred 4 months after the end of PEG-IFN-α-2a therapy (Figure 2) and the patient was admitted to the hospital for treatment of recurrent hepatitis. PEG-IFN-α-2a 135 μg/wk was reinitiated. Ribavirin was not administered due to the patient's history of hemolytic anemia. The patient was difficult to treat, as he was 60 years' old presenting with HCV genotype 1b relapse. Therefore, the treatment duration was extended to 72 weeks and he attained undetectable HCV-RNA level at week 8. PEG-IFN-α-2a monotherapy continued until week 60, when the patient presented with severe depression and anxiety, and PEG-IFN-α-2a treatment was stopped. Viral relapse occurred 3 weeks after the cessation of PEG-IFN-α-2a treatment. However, he maintained normal renal function with a creatinine level of 97 μmol/L in spite of prolonged PEG-IFN-α-2a therapy. Clinical data from both 24-week and 60-week treatment regimes are summarized in Figure 2.

DISCUSSION

Pageaux et al[4] demonstrated that PEG-IFN-α-2a/2b may be a safe and effective treatment in RTRs with HCV. The ETR was 75% and the sustained virological response (SVR) was 50%. Most importantly, there was no renal graft rejection reported in any of the patients included, as the mean delay between transplantation and PEG-IFN-α-2a/2b administration was about 16 years. It suggested that the graft was well-tolerated and likely reduced the risk of rejection related to PEG-IFN use. There also appeared to be a steady reduction in the incidence of acute rejection with elderly RTRs. It is possible that age-related immunosenescence may make elderly patients more vulnerable to the effects of immunosuppression and long-time graft survival.[5] This patient described here was a 60-year-old man, who received PEG-IFN-α-2a therapy 8 years after transplantation and FK-506. The drug was well tolerated and he remained well controlled during the treatment period. His creatinine values at time of biopsy and throughout follow-up periods prior to treatment with PEG-IFN-α-2a suggested normal renal function.

A limited number of studies describing the efficacy of antiviral treatment in elderly patients with CHC showed that age was a negative predictive factor regarding SVR. Antonucci et al[6] suggested that the probability of a good response to PEG-IFN plus ribavirin combined therapy was decreased for patients around 40 years old who were infected with genotype 1 HCV. Moreover, Dai et al[7] performed a prospective study in 210 chronic HCV patients aged 50 years or more: 140 in the 50–64 years group and 70 in the older group, confirming that the SVR was lower in the older patient group.

HCV genotype was also a major predictor of SVR in elderly patients. Huang et al[2] investigated 70 elderly patients (Group A) with HCV infection and 140 sex- and HCV genotype-matched controls (Group B). They were allocated to receive PEG-IFN-α-2a therapy. The SVR was substantially lower in group A than in group B (67.1% vs 78.6%; $P = 0.07$). The inferiority of the SVR in group A was observed among patients with HCV genotype 1 (51.9% vs 75.9%; $P = 0.03$), but not among patients with HCV genotype 2 or 3 (76.7% vs 80.2%; $P = 0.65$). This study suggests that older patients with HCV infection, especially those in the subgroup infected with HCV genotype 1, had a lower SVR.

Other reasons that may contribute to a reduced treatment response rate may be associated with a greater frequency of AE and reduced tolerance to the standard-of-care regimen. PEG-IFN-related AE was the principal cause for patients to decline or stop treatment. Almost all patients treated with PEG-IFN had experienced ≥1 AEs during the course of therapy. The most common AEs were influenza-like side effects such as fatigue, headache, fever, and rigors, which occurred in more than half of

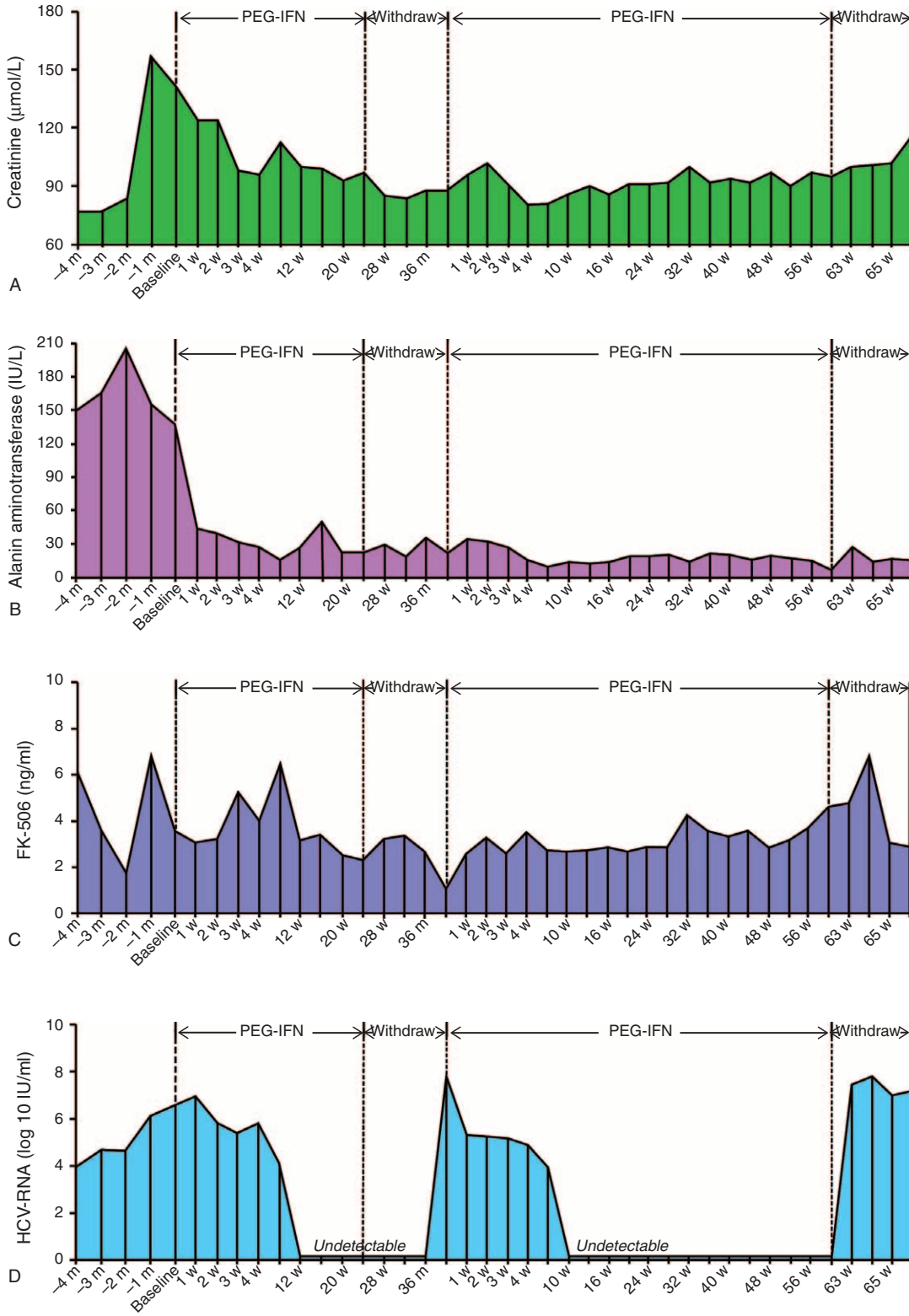

FIGURE 2. Major laboratory results during 2-year pegylated interferon-α-2a treatment. (A) Creatinine, (B) alanine aminotransferase, (C) FK-506, (D) HCV-RNA.

the patients, and psychiatric side effects (eg, depression, irritability, and insomnia), which occurred in 22% to 31% of patients.[3] Preexisting underlying diseases, such as diabetes mellitus and chronic kidney disease, further reduced the tolerance to PEG-IFN-related AEs in elderly patients.

Elderly patients tend to have lower hemoglobin levels and poorer creatinine clearance, 2 factors that must be taken into account in the context of ribavirin administration. It has been well established that older patients have a statistically significant higher ribavirin dose reduction and discontinuation rate. The superior efficacy of the combination therapy compared with PEG-IFN monotherapy in nontransplantation patients has supported its preferred use in RTRs with acceptable renal function.[8] The recurrence of HCV infection in the patient may be partially explained by cessation of ribavirin treatment.

Compared with the limited experiences in elderly RTRs with CHC,[2,4,7] this case report adds 2 valuable points. First, reducing the dose of PEG-IFN is the key measure to increase the safety profile of the treatment during the long-term treatment for elderly CHC patients. Dose reduction of PEG-IFN is associated with a reduction of the AEs and improved tolerance in this special patient population. Second, it appears that as the duration of the stability of transplanted renal function prior to PEG-IFN treatment increases, the possibility of rejection or graft loss is reduced in RTR patients.

CONCLUSION

In summary, this case study reports on the safety of PEG-IFN therapy for elderly RTRs. However, older patients tend to experience AEs more frequently and consequently present with reduced tolerance to treatment, leading to suboptimal efficacy, particularly in patients infected with HCV genotype 1. Thus, it is important to take into account favorable and unfavorable indicators of response to optimize the treatment dose and duration. Large-sample, prospectively designed randomized controlled trials are needed in this special population.

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