Sustained Virologic Response with Triple Therapy in a Hemodialysis Patient with Chronic HCV Infection

Kronik HCV Enfeksiyonu Olan Bir Hemodiyaliz Hastasında Üçlü Tedavi ile Kalıcı Viral Yanıt

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ABSTRACT

Chronic hepatitis C virus (HCV) infection is more prevalent and has been proven to be an independent risk factor over mortality among hemodialysis patients than normal population. Since sustained virologic response (SVR) is so beneficial and may be maintained in 90-100% of post-transplant cases, treatment of chronic HCV infection is strongly suggested for all patients undergoing renal transplantation. A 45-year-old male patient had been offered to have renal transplantation due to chronic renal failure, and referred to our clinic because of chronic HCV infection (HCV-RNA positive). He had received hemodialysis three times a week since 2007. The patient was diagnosed with chronic HCV infection fifteen years ago and was given a 48-week lasting IFN therapy in 2000 and a subsequent therapy of PEG-IFN- α 2a for 48 weeks in 2004. Although both therapies had yielded end of treatment responses, subsequent relapses occurred. The patient was given a combination treatment involving PEG-IFN- α 2a (135 μ g/wk) for 24 weeks and ribavirin (200 mg/day) for 24 weeks and telaprevir (3 x 750 mg) for the first 12 weeks, and a weekly control visit in our clinic. The therapy was generally well tolerated and SVR was achieved. Triple therapy might be used as a treatment option in hemodialysis patients with genotype 1 chronic HCV infections.

Key words: Hemodialysis, chronic renal failure, chronic hepatitis C, triple therapy

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ÖZET

Kronik hepatit C virüsü (HCV) enfeksiyonu hemodiyaliz hastalarında, normal popülasyona göre daha sık görülür ve bu hastalar için mortalite açısından bağımsız bir risk faktörüdür. Bu hastalarda kalıcı viral yanıt elde edilmesi çok faydalı olduğu ve elde edilecek yanıtın transplantasyon sonrasında da %90-100 oranında devam edeceği için transplantasyon planlanan tüm kronik HCV enfeksiyonu olan hemodiyaliz hastalarına hepatit C tedavisi kuvvetle önerilmektedir. Kırk beş yaşında beyaz, erkek hasta, kronik böbrek yetmezliği nedeniyle renal transplantasyon planlandığı ve kronik HCV enfeksiyonu olduğu için HCV tedavisi planlanması açısından kliniğimize başvurdu. Hasta 2007 yılından itibaren haftada üç kez hemodiyalize giriyordu. Hastaya 15 yıl önce kronik HCV enfeksiyonu tanısı konulmuş ve bu nedenle 2000 yılında 48 hafta interferon, 2004 yılında da 48 hafta pegile-interferon monoterapisi verilmişti. Her iki tedavi sonunda da tedavi sonu yanıt alınmasına karşın relaps gelişti. Hastaya 24 hafta pegile-interferon- α 2a (135 μ g/hafta), 24 hafta ribavirin (200 mg/gün) ve 12 hafta telaprevir (3 x 750 mg) tedavisi verildi ve hastaya haftalık kontrol önerildi. Tedavi genel olarak iyi tolere edildi ve kalıcı viral yanıt gelişti. Genotip 1 kronik HCV enfeksiyonu olan hemodiyaliz hastalarında üçlü tedavi bir tedavi seçeneği olarak uygulanabilir.

Anahtar kelimeler: Hemodiyaliz, kronik böbrek yetmezliği, kronik hepatit C, üçlü tedavi

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection is more prevalent among hemodialysis patients than it is in normal population^[1,2]. While HCV prevalence varies between 8.5-75% among hemodialysis patients worldwide, it is estimated 31.4-51% in Turkey^[3]. Chronic HCV infection has been proved to be an independent risk factor over mortality of hemodialysis patients^[4]. It has also been shown that post transplantation allograft nephropathy and diabetes mellitus are more commonly seen complications for chronic renal failure (CRF) in patients suffering from chronic HCV infection^[5]. For transplantation cases, interferon (IFN) treatments are not recommended as they increase the risk of allograft rejection. Since sustained virologic response (SVR) is so beneficial and may be maintained in 90-100% of post-transplant cases, treatment of chronic HCV infection is strongly suggested for all patients undergoing renal transplantation. Providing SVR should decrease the risks of chronic allograft nephropathy and de novo membrano proliferative glomerulonephritis^[6-8].

Currently, the standard therapy approach for HCV genotype 1 patients with normal renal functions involves pegylated interferon (PEG-IFN), ribavirin, and protease inhibitor combinations^[9]. However, the use of ribavirin in chronic renal failure patients may lead to anemia and it is contraindicated^[10]. Monotherapy with PEG-IFN was the most suggested option in hemodialysis patients with chronic HCV infection before. However, studies in recent years have reported a com-

bination therapy of IFN and low dose ribavirin as a safe option with high rates of SVR^[11]. SVR rates have been reported to be as much as 56% and promising in a meta-analysis of ten studies in which a combination of PEG-IFN and ribavirin were administered to hemodialysis patients with chronic HCV infection^[12].

In May 2011, Food and Drug Administration (FDA) approved the treatment of chronic HCV genotype 1 cases by protease inhibitors (telaprevir and boceprevir)^[9]. With the contribution of these agents, SVR rates have reached to as much as 65-75% among patients. Nevertheless, there are limited and inadequate data regarding the efficacy and safety of protease inhibitor-sin hemodialysis patients with chronic HCV infection.

In this paper it is aimed to present a hemodialysis patient with chronic HCV infection relapsed with IFN and PEG-IFN monotherapies previously and achieved SVR with triple therapy as a first case report in Turkey

CASE

A 45-year-old Caucasian male patient had been offered to have renal transplantation due to chronic renal failure and referred to our clinic because of chronic HCV infection. The HCV-RNA level of the patient measured by real time Polymerase Chain Reaction (QUIAGEN, QI Asymphony, + Rotor Gene Q, Germany) was $9.362 \times 10^5/\text{mm}^3$. He had received hemodialysis three times a week for six years due to a post-streptococcal glomerulonephritis developed in 2007. The patient was diagnosed with chronic HCV (genotype 1b) infection fifteen years ago and was given a 48-week lasting IFN (3 x 3 mu/week) therapy

in 2000. A subsequent therapy of PEG-IFN- α 2a (1 x 135 μ g/week) for 48 weeks was also conducted in 2004. Although therapies had yielded end of treatment responses, subsequent relapses occurred.

At the first physical examination, no pathologic finding could be detected except for arteriovenous fistula on his right arm. Table 1 demonstrates the laboratory results upon first presentation. A renal USG was performed and resulted in multicystic kidney.

According to patient's history, he had not received any drugs for chronic renal failure. He only had a 6-month lasting iron replacement therapy due to deficiency in the past.

As the patient rejected liver biopsy, it was decided to start chronic HCV infection treatment before organ transplantation. Since there is no special recommendation for the treatment duration for hemodialysis patients, we planned a combination treatment involving PEG-IFN α -2a (135 μ g/wk) for 24 weeks and ribavirin (200 mg/day) for 24 weeks and telaprevir (3 x 750 mg) for the first 12 weeks as recommended for genotype 1 chronic HCV patients. In addition, a weekly control visit was recommended.

The therapy was successful and well tolerated through the first four weeks without any complications. The patient experienced a rectal bleeding at the fourth week of treatment.

A grade 1 hemorrhoid was detected in physical examination and managed by local medications without any surgical application.

A progressive decrease of hemoglobin levels was monitored at the start of therapy (Figure 1). Therefore, at the fourth week, erythropoietin (EPO) 5000 U/wk was started. Hemoglobin levels reached above 10 g/dL between the fourth and seventh weeks. Since the hemoglobin level was detected as low as 7.6 g/dL at the eighth week, EPO dose was increased (15000 U/wk) and ribavirin dose decreased (200 mg/wk). Since

Table 1. Laboratory results at admission

AST : 23 IU/L	Hb : 13.7 g/dL
ALT : 16 IU/L	WBC : 6800 /mm ³
ALP : 112 U/L	PLT : 183.000 /mm ³
GGT : 179 U/L	HBsAg : Negative
T Bil : 0.67 mg/dL	Anti-HBsAg : Positive
D Bil : 0.15 mg/dL	Anti-HIV : Negative
Urea : 90 mg/dL	AFP : 3.66 mg/dL
Creatinin : 9.73 mg/dL	HCV-RNA : 9.362 x 10 ⁵ copy/mm ³ (genotype: 1b)

Figure 1

Hemoglobin levels during therapy.

the elevation in hemoglobin levels were provided, ribavirin doses were increased gradually (200 mg per week), and by the fourteenth week, a constant dose of 200 mg/day was pursued until the end of therapy. Graphic 1 demonstrates the hemoglobin levels regarding the weeks. Telaprevir treatment was complemented to twelve weeks and ceased. EPO treatment was ceased by the seventeenth week when the hemoglobin level was above 11 g/dL. The HCV-RNA detections were found to be negative at the fourth, eighth and twelfth weeks, at the end of treatment, and twenty-four weeks after the end of the therapy. There was no decrease in thrombocyte and leukocyte levels to influence the course of the therapy.

DISCUSSION

HCV infection after renal transplantations has been proved to be an independent risk factor regarding graft rejections and mortality rates. In addition to liver diseases, extra-hepatic complications of new-onset DM, de novo allograft nephropathy, and sepsis are highly encountered among renal transplant patients with chronic HCV infections^[13]. Therefore, all patients undergoing transplantation should be considered for chronic HCV treatment.

Previously, IFN monotherapy was suggested for hemodialysis patients with chronic HCV infection. Ribavirin was eliminated primarily by renal route and it was hard to clear ribavirin by hemodialysis. Since ribavirin may cause hemolytic anemia and worsen the baseline anemia of hemodialysis patients, its usage is defined as a contraindication^[13,14]. However, according to more recent studies, low dose ribavirin and high dose EPO may be used in a safe and tolerable manner as an adjunct of IFN monotherapy. This combination can increase SVR rates in hemodialysis patients with chronic HCV infections from 30% up to 50%^[12,15].

There is not a defined standard dose for ribavirin but it is usually applied as 400 mg/day to 600 mg/week doses. Deltenre et al. have compared ribavirin doses of 1000 mg/week in hemodialysis patients and 800-1200 mg/weeks in patients with normal renal functions in their study. They reported lower ribavirin serum concentrations in the first month of therapy for 1000 mg receiving group which disappeared later. At the end of the study, a positive correlation was detected between the first month ribavirin serum concentration and SVR rates and a dose of 1400 mg/week ribavirin was offered as optimal for hemodialysis patients^[5].

Hakim et al. implemented a therapy of IFN monotherapy for the first month followed by ribavirin addition after four weeks in their study. The ribavirin dose was started as 200 mg/week and increased gradually (200 mg with two week interval). The SVR rate of this study was reported to be 6.7%^[16]. In light of these studies, ribavirin dose was started as 200 mg/day in our patient. However, due to a fall of Hb level as low as 7.6 g/dL at the eighth week, ribavirin dose was reduced. With the recovery of Hb levels, we increased ribavirin doses gradually. Poordad et al. reported lower SVR rates among patients receiving < 50% of the total milligrams of ribavirin protocol assignment than those receiving ≥ 50%. Our patient received ≥ 50% of the total ribavirin dose^[17].

Previous studies have indicated that EPO dose may be increased up to 90.000 IU/week in order to prevent ribavirin induced anemia^[5]. Due to some cost and payment restrictions, (according to social insurance instructions) EPO could be described as 15.000 IU/week in the presented patient. With the rise of hemoglobin level above 11 g/dL at the seventeenth week, EPO treatment was ceased.

Given the results of its well tolerable and pharmacokinetically safe usage by previous studies, PEG-IFN- α 2a dose was preferred and started as 135 μ g/week^[18]. Regarding IFN monotherapy in hemodialysis patients with chronic HCV infection, there are limited data in Turkey provided from studies of small series, and SVR rates vary between 46.1-75% in these series. Apart from our case report, we could not encounter a study subjecting ribavirin or protease inhibitor usage in hemodialysis patients in Turkey^[3,19-22].

There are limited data and experience regarding the use of telaprevir and boceprevir (protease inhibitors) in patients with chronic renal failure. However, it is supposed that renal failure leads to an insignificant pharmacokinetic interference with telaprevir^[9]. In a study, 750 mg telaprevir has been given to HCV negative patients with severe renal diseases (creatinine clearance ≤ 30 mL/min). As a result, mean telaprevir C_{max} and AUC values have been detected to be 10-21% higher than healthy controls^[9]. In our case, telaprevir was started as 750 mg per eight hours and stopped at the twelfth week of therapy. The most common side effects of telaprevir involve rash, anemia and anorectal symptoms. Particularly cutaneous symptoms like rash may be a cause of treatment termination^[23].

In our case, a grade 1 hemorrhoid was detected after the development of a rectal bleeding at the fourth week and managed by local topical hydrocortisone agents. Subsequently, the patient healed and reported no other anorectal complication. No cutaneous rash was detected during the follow-up of patient.

There are very limited data regarding the efficacy of triple therapy in hemodialysis patients with chronic HCV infection. According to the sole study we found in the international literature, after triple therapy, early virologic response was provided in three of four patients. These chronic HCV patients had been previously treated and not responded^[9]. A rapid, early and sustained virologic response was also achieved in our patient. Triple therapy was also well tolerated.

In conclusion triple therapy might be used as a treatment option in hemodialysis patients with genotype 1 chronic HCV infections. Nevertheless, there is a need for more comprehensive studies in order to reveal safety and efficacy of triple therapy in that patient group.

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