

KRONİK HEMODİYALİZ HASTALARINDA KRONİK HEPATİT C ENFEKSİYONUNUN İNTERFERON İLE UZUN SÜRELİ TEDAVİ SONUÇLARI

INTERFERON MONOTHERAPY FOR CHRONIC HEPATITIS C INFECTION IN CHRONIC HEMODIALYSIS PATIENTS AND LONG-TERM FOLLOW-UP RESULTS

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Özet

Kronik hepatit C enfeksiyonu, hemodiyaliz hastalarında sağlıklı insanlara göre daha sık görüldüğünden dolayı bu hasta grubunda kronik hepatit C önemli bir problemdir. Bu çalışmada kronik hepatit C enfeksiyonu olan hemodiyaliz hastalarında interferon tedavisinin güvenilirliği ve etkinliğini araştırdık. Bu çalışmaya klinik, serolojik ve biyokimyasal olarak kronik hepatit C enfeksiyonu tanısı konulan 22 hemodiyaliz hastası alındı. Çalışmaya alınan hastalara haftada 3 defa 3mü Interferon α 2b (Intron A: Schering Plough) tedavisi başlandı. Tedavinin süresi 12 ay olarak planlandı. Tedaviden önce, tedavinin 3. ve 12. aylarında, tedavinin bitiminden 6 ve 12 ay sonra PCR ile HCV-RNA ve serum ALT düzeyine bakılarak Interferon α 2b'nin etkinliği değerlendirildi. Tedavinin 3. ayında hastaların 16 (%72.7) sında HCV RNA negatif, serum ALT düzeyi normaldi. 2 (%9) hastada ciddi yan etki görülmesi nedeni ilaç kesildi. Yan etki nedeni ile tedavinin kesildiği bir hasta ile diğer 4 hastanın (toplam 5 (%22.7) hasta) HCV-RNA'si tedavinin 3. ayında pozitif. Bu nedenle 6 hastada tedavi kesildi. Tedavinin 4. ayında bir hastanın evinde aniden ölmesi nedeni ile 16 hastanın 15'i 12 aylık tedaviyi tamamladı. Tedavinin bitiminde 15 hastanın 11'inde HCV-RNA negatif 4'ünde ise pozitif idi. Tedavinin bitiminden 12 ay sonra hastaların %36.4'ünde HCV-RNA negatifliği devam ediyordu.

Anahtar kelimeler: Kronik Hepatit C Enfeksiyonu, Interferon α 2b, Hemodiyaliz

Summary

The prevalence of anti-HCV in haemodialysis patients is higher than the healthy population. Chronic Hepatitis C virus (HCV) infection is important problem for hemodialysis patients. We aimed to determine the efficacy and safety of interferon monotherapy in hemodialysis patients with chronic HCV. Twenty-two hemodialysis patients were included in this study and followed up for a median time of 24 months. 3 million units (MU) interferon- α 2b (Intron A:Schering Plough) monotherapy was started three times a week (t.i.w) for 12 months to all of the patients who were clinically, biochemically and serologically diagnosed to have chronic HCV infection. HCV-RNA was determined with PCR in before of therapy, in 3th and the end of the 12th months of treatment. At the same time HCV-RNA and ALT levels were determined to evaluate whether the effectiveness of the therapy is of long-term after the end of therapy and in 6th and 12th months following the treatment. In the third month of interferon treatment, HCV-RNA was negative in 16 (72.7%) of 22 patients, and serum ALT level was normal. The treatment was stopped in 2 (9%) of the patients due to severe side effects. One of these 16 patients was learned to have died suddenly in his house in the 4th month of the treatment. Of these 16 patients, 15 patients completed the treatment. HCV-RNA was detected to be positive in 4 and negative in 11 of these 15 patients in the end of treatment. However, sustained viral response (SVR) rate was 36.4 % in 12 months after the end of treatment.

Key words: Chronic Hepatitis C virus (HCV) infection, Interferon α 2b, Hemodialysis

Introduction

HCV infection like HBV infection is one of the most important health problem in the world. It is the important cause of morbidity and mortality in the world. Hemodialysis patients have disorders in the immune system. In these patients the period in which HCV becomes chronic is short. It is shown that the development period of HCC is 5 years and nine months [1-3]. Recent studies have shown that chronic active hepatitis or cirrhosis has developed in hemodialysis patients infected with HCV [4]. Besides, there are studies indicating that HCV infection becomes chronic in 95% of haemodialysis patients infected with hepatitis C virus [5]. HCV is a single stranded, positive sense RNA virus of 55-65 nm in size, containing approximately 10.000 nucleotide, 3010 amino acid and a single open reading frame [6-8].

Anti-HCV prevalence in dialysis patients is higher than that in the healthy community [9-11]. The high incidence of hepatitis C infection in haemodialysis units, relative similarity of HCV subtypes in patients receiving treatment in the same haemodialysis units, and the lack of transfusion history in most HCV patients make us think that HCV is spread from patient to patient in haemodialysis units [1,6,11]. The only agent recommended by FDA for the treatment of hepatitis C is interferon- α [7,12].

In non-uremic patients, the response to long-term treatment with interferon- α is higher than that to short-term treatment [7]. There are few studies of long term interferon treatment in hemodialysis patients [13]. This study is carried out to determine the effectiveness of 3 MU recombinant interferon- α 2b treatment three times a week for 12 months, to determine the tolerability and side effects of interferon.

Method

This study was carried out on 22 patients (11 male, 11 female) receiving haemodialysis. The average age of the patients ranged between 20-72 years (44.4 ± 15.9), and dialysis period was between 12-48 months. The histories of the patients were taken to see their age, dialysis period, if they had taken alcohol and hepatotoxic drugs before. Tests were made to detect metabolic illness and autoimmune hepatitis to make clear if chronic hepatitis aetiology had a reason other than HCV infection. All the patients were performed anti-

HCV with second generation ELISA method (Enzyme-Linked Immune Assay) and those with negative anti-HCV were excluded from the study. AST and ALT levels of the patients in the last 6 months were inspected.

Detailed histories were taken and careful physical examination was made. In addition, all the patients were made abdominal USG and Liver paranchimal tissue, portal vein and splenic vein were evaluated. Protein electrophoresis, bilirubin, protrombin time and serum albumin levels were analyzed. Cirrhosis and portal hypertension were accepted to be reason to exclude patients from the study. Besides, dialysis sufficiency, ure kinetic model (Kt/V) and nutritional state were evaluated with serum albumin and body mass index (BMI). AST/ALT ratios were made in all of the patients.

HCV-RNA of patients was determined with PCR who were clinically, serologically and biochemically diagnosed to have chronic hepatitis-C virus infection. Five ml blood was taken from a surface vein at the antecubital areas of the patients in sterile conditions with plastic injector, the serum of the patients was separated and frozen at -80°C . Serum samples were transported in suitable conditions in ice pack. 3 mu interferon- α -2b treatment was started three times a week to all of the 22 patients who were clinically, biochemically and serologically diagnosed to have active chronic hepatitis C virus infection.

HCV-RNA was determined in the third month of the the treatment. Serum levels of ALT,AST were determined. In this way the response to treatment was investigated. At the same time HCV-RNA and ALT levels were determined to evaluate whether the effectiveness of the therapy is of long-term after the end of therapy and in the 6 th and 12 th months following the treatment.

Statistical Analysis

The mean and standard deviation of all the data were taken, ALT levels before treatment, after treatment and 6 months following the end of treatment were compared using Wilcoxon signed Ranks. The comparison of the group responding treatment and not responding treatment at the end of treatment Kt/V, albumin and BMI was made using Mann Whitney U test. Non-parametric statistical analyses were made using SPSS 7.5 computer programme.

Results

HCV-RNA was found to be positive with PCR and anti-HCV was found to be positive with second-generation ELISA in all the patients. HCV subtypes were made in 5 of the patients. Type 1b was detected in those 5 patients.

Serum ALT level before treatment was about 175 ± 109.1 IU/L (70-444). AST/ALT < 1 for all patients. Prothrombin time about 13.2 ± 0.7 (12-14.2) seconds. Average serum albumin level was 3.76 ± 0.47 (3-4.7) g/dl. Globulin level was 2.88 ± 0.4 (1.9-3.5) g/dl. Kt/V was about 1.22 ± 0.11 (1-1.4), and BMI was about 22.5 ± 2.9 (19-30).

In the third month of interferon treatment, HCV-RNA became negative in 16 (72.7 %) of 22 patients, and serum ALT level was normal. HCV-RNA and serum ALT level were positive and high in 4 (18 %) patients, respectively. These patients were considered as to be non responder and their treatment was stopped. The treatment was stopped in 2 (9%) of the patients due to severe side effects. One was female and the other was male. In the second month of the treatment, high fever (39-40°C) and arthralgia not responding paracetamol and methamizol developed in the male patient. These side effects disappeared after stopping the treatment. Cutaneous necrosis developed as a result of the side effect of interferon treatment in the female patient, and it healed after stopping the treatment. Treatment of 16 patients whose HCV-RNAs became negative in the third month of interferon treatment was continued. One of these 16 patients was learned to have died suddenly in his house in the 4th month of the treatment. The treatment of the rest 15 patients was continued with same doses of interferon α -2b for 12 months. HCV-RNA was assessed again in these 15 patients after the completion of the treatment by PCR method. HCV-RNA was detected to be positive in 4 of these 15 patients. HCV-RNA was negative in 11 of the patients. Serum ALT level of these 15 patients before the treatment was about 177.8 ± 115.5 (70-444) IU/L. Serum ALT levels decreased to about 33.1 ± 29.8 (8-130) IU/L after the treatment (z:-3.4; p:0.001).

There was not any difference between BMI (z:-1.12; p:0.27), Kt/V (z:-0.92; p:0.39) and albumin values (z:-1.20; p:0.23) of 8 patients whose HCV-RNA was positive and 11 patients whose HCV-RNA was negative at the end of 12-month treatment. Following the treatment, serum ALT levels were in normal limits (5-40 U/ml) in 13 (59%) of 22 patients. Serum ALT level became normal in

11 patients whose HCV-RNA was negative and in 2 of 4 patients whose HCV-RNA was positive. HCV-RNA was negative and serum ALT level was in normal limits in 12 months after the end of treatment in 6 of 11 patients whose HCV-RNA was negative.

Long-term virological response of 22 patients was 36.3%. Three of 11 patients who had negative HCV-RNA at the end of the treatment could not be followed up because of some reasons, thus they were not included in the evaluation. Pretreatment serum ALT levels of 15 patients (about 177.8 ± 115.5) who completed their interferon treatment decreased considerably (about 44.8 ± 49.9) after 6-months follow up period (z:-3.4; p:0.001).

Discussion

HCV has become the main reason of chronic hepatitis in haemodialysis patients by development of vaccines for hepatitis-B prophylaxis in chronic haemodialysis patients and use routinely in these group of patients [1,4,14,15]. In studies made using ELISA-1 (First Generation ELISA) anti-HCV prevalence among haemodialysis patients are as follows: 8-36% in North America, 39% in South America, 1-54% in Europe, 17-51% in Asia, 1.2-10% in New Zeland and Australia [4,10,11].

It has been reported that treatment can be started without biopsy in order not to increase mortality and morbidity risk, and cost by diagnosing chronic hepatitis C infection biochemically, serologically and clinically, that this is favourable for cost-effect, and that almost always histological improvement occurs with viral eradication. In addition, cirrhosis has ben reported to be eliminated by AST/ALT [16,17]. Due to both above reasons and its being an invasive procedure, the patients did not accept biopsy; thus we did not carry it out.

In a study by Huraib S et al., in which they treated 17 hemodialysis patients with chronic hepatitis C for a year with 3 MU interferon- α -2b (Intron A:Schering Plough) three times a week, they evaluated biochemical and virologic response twice, at the end of treatment and 6 months after treatment. They found HCV-RNA to be negative with PCR method in 76% of the patients following 12th week of treatment, in 71% six months after treatment, and in 88% at the end of treatment. They reported that biochemical response rate was 83% at the end of treatment and 67% 6 months after treatment. Only one patient was reported not

to tolerate treatment because of letargia and myalgia [4].

Umlauft F et al. treated 33 hemodialysis patients with positive HCV-RNA for 4 months with 5 mu interferon- α 3 times a week, and found HCV-RNA to be negative in 25 (76%) of 33 patients during the treatment. They detected HCV-RNA to be negative in 24 of 33 patients at the end of treatment, and in 7 (21%) patients after 1 year follow-up. This indicates that long-term virological response rate was 21% [18]. The long-term virological response obtained in our study (36.3%) is higher than that obtained by Umlauft F. et al. (21%). This may arise from the fact that our treatment period was longer than theirs.

The above-mentioned studies reveal that long treatment periods increase virological and biochemical response rate. However, in cases in which interferon dose is increased, side effects also increase [15]. HCV-RNA became negative in 16 (72.7%) of 22 patients in the third month of treatment. Serious side effects occurred in 2 (9%) patients and their treatment was stopped. We found virological response rate to be 50%, and biochemical response rate to be 59% at the end of treatment. We followed-up these patients for 12 months. We found virological response to be 50%, and biochemical response to be 54.5% 6 months after treatment. We could not continue the follow-up of 3 of 11 patients giving virological response due to some reasons 12 months after treatment. But, in the follow-up of the other 8 patients, their serum ALT levels were permanently normal, and their HCV-RNA, controlled with PCR method 12 months after the study was negative. The reason for these encouraging results may be as follows: half-time of interferon is longer in haemodialysis patients [15], viral load decreases with dialysis, interferon reverses cell-mediated immun deficiency in uremia, and perhaps patient concordance is satisfactory as a result of the controlled nature of treatment in dialysis units [4]. As in our patient group, efficiency of dialysis and lack of malnutrition may increase the rate of response.

As a result, interferon- α -2b treatment was found to be quite effective and showed high tolerability in haemodialysis patients with chronic hepatitis C virus infection. Especially patients in chronic haemodialysis programme who are infected with HCV and thought be made renal transplantation should be treated with interferon. Besides, we conclude that patients with active HCV

infection should receive the same treatment to prevent HCV contamination in haemodialysis units.

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