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RAPID COMMUNICATION

Efficacy and safety of pegylated-interferon α-2a in hemodialysis patients with chronic hepatitis C

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Abstract

AIM: To evaluate the efficacy and safety of pegylated-interferon alpha-2a in hemodialysis patients with chronic hepatitis C.

METHODS: Thirty-six hemodialysis patients with chronic hepatitis C were enrolled in a controlled and prospective study. All patients were treatment naive, positive tested for anti-HCV antibodies, and positive tested for serum HCV-RNA. Twenty-two patients received 135 μg peglyated-interferon α-2a weekly for 48 wk (group A). The remaining patients were left untreated, eleven refused therapy, and three were not candidates for kidney transplantation and were allocated to the control group (group B). At the end of the treatment biochemical and virological response was evaluated, and 24 wk after completion of therapy sustained virological response (SVR) was assessed. Side effects were monitored.

RESULTS: Of 22 hemodialysis patients, 12 were male and 10 female, with a mean age of 35.2 ± 12.1 years. Virological end-of-treatment response was observed in 14 patients (82.4%) in group A and in one patient (7.1%) in group B (P = 0.001). Sustained virological response was observed in 11 patients (64.7%) in group A and in one patient in group B (7.1%). Biochemical response parameters normalized in 10/14 patients (71.4%) at the end of the treatment. ALT levels in group B were initially high in six patients and normalized in one of them (25%) at the end of the 48 wk. In five patients (22.7%) therapy had to be stopped at mo 4 due to complications of weakness, anemia, and bleeding.

CONCLUSION: SVR could be achieved in 64.7% of patients on hemodialysis with chronic hepatitis C by a treatment with peglyated-interferon α-2a. Group A had a significantly better efficacy compared to the control group B, but the side effects need to be concerned.

Key words: Peglyated-interferon; Hemodialysis; Chronic hepatitis C; Treatment; Efficacy; Safety

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INTRODUCTION

Hemodialysis patients are at high risk of infection by hepatitis C virus (HCV) because the hemodialysis unit is a medical environment where exposure to blood is frequent. Therefore, the prevalence of HCV infection, from less than 5% to over 70% in some countries, is greater than the prevalence of HCV infection in the general population[1]. HCV infection is an important cause of morbidity and mortality among patients with end-stage renal disease (ESRD)[2]. HCV infection in patients on maintenance hemodialysis was reported in 10%-59% of patients, in comparison to 0.3%-1.5% observed in the general population[3]. The prevalence of HCV infection is 10%-20% in dialysis patients in developed countries[4,5] and much higher in less developed countries[6]. The prevalence of anti-HCV antibodies among dialysis patients was 40.3% in Turkey[7], 30% in India[8], and 43.9% in Saudi Arabia[9]. In United States of America in 2000, 8.4% of haemodialysis patients were anti-HCV positive[10].

The main mechanisms involved in nosocomial infection with HCV in haemodialysis patients are filter re-use, the use of contaminated haemodialysis machines, and contamination of medical staff's hands. It has been shown that the incidence of HCV infection in haemodialysis patients increases if the medical staff member does not change her/his gloves before injecting each patient and if hepatitis C patients undergo haemodialysis in the same room[11].

The eradication of HCV infection is thought to be valuable for patients with ESRD, especially those who are candidates for kidney transplantation[12]. To prevent the development of these complications and to make these patients suitable for transplantation, standard interferon-α

was used in various doses or regimes for the treatment of these patients[13].

The supplement of a polyethyleneglycol molecule to interferon produces a biologically active molecule with a longer half-life time and more favorable pharmacokinetics; these characteristics enable for a more appropriate once-weekly dosing. When pegylated-interferon α-2a (PEG-IFN) alone is given to chronic hepatitis C patients with normal renal function for 48 wk, the sustained virological response (SVR) rate is approximately twice that with standard interferon[14,15].

This study evaluated the tolerability and efficacy of PEG-IFN in patients with chronic hepatitis C. Therefore, we carried out a controlled prospective longitudinal study to assess the biochemical and the virological response at 48 wk of treatment with PEG-IFN and its tolerability in hemodialysis patients with chronic HCV infection.

MATERIALS AND METHODS

Study design and patients

The present controlled and prospective study was carried out in the Department of Infectious Diseases in Dicle University Hospital, and in one Private Dialysis Center in Diyarbakir, Turkey. In total, 58 among the 161 patients with total hemodialysis in this center were anti-HCV positive (36%). Of the 58 patients, 38 were HCV-RNA positive (65%). Two patients were excluded because they had decompensated liver disease (n = 1), coinfection with hepatitis B virus (n = 1), or because they were lost to follow-up. Thirty-six HCV-RNA positive patients were informed about the benefits and possible risks of PEG-IFN treatment. Fourteen patients were excluded from the study, eleven refused the therapy, and three were not candidates for kidney transplantation and were allocated to the control group (group B). The remaining 22 patients were allocated to the PEG-IFN treatment group (group A). All patients underwent chronic hemodialysis treatment for ESRD during the study period. Hemodialysis was carried out routinely 2-3 times weekly in the patient population. All patients were anti-HCV antibody positive and had detectable HCV-RNA by polymerase chain reaction for at least 6 mo. It has been reported that liver biopsy (histology) is not suggested in the patient with chronic hepatitis C and end-stage renal diseaese because of high bleeding risk.

Inclusion criteria

PEG-IFN therapy was performed in patients meeting the following inclusion criteria: (1) Age < 65 years; (2) absence of pregnancy and agreement to avoid pregnancy during therapy; (3) informed consent; (4) lack of autoimmune, thyroid, psychiatric, or malignant disorders; (5) negative HIV antibody test; and (6) thrombocyte count > 70 000/mm^3 and white blood cell count > 3000/mm^3.

Exclusion criteria

Patients meeting at least one of the following criteria were excluded: (1) Age < 18 or > 65 years; (2) presence of coinfection with HBV or HIV; (3) receiving immunosuppressive therapy or other treatments, namely antihistaminics, non-steroidal anti-inflammatory drugs, aciclovir, or amiodarone; (4) previous treatment for HCV infection; (5) alcohol consumption > 40 g/d; (6) active drug addiction; (7) evidence of hepatocellular carcinoma (α-fetoprotein > 100 ng/mL); (8) hemophilia; or (9) contraindication to interferon therapy.

Study protocol

Patients (group A) enrolled in the study received 135 μg PEG-IFN (40 kDa) (PEGASYS; F. Hoffmann-La Roche, Basel, Switzerland) weekly for 48 wk at the end of dialysis session. All treated patients were evaluated at the end of wk 12 of treatment. The antiviral treatment was continued if the patient had at least a 2-log decline from baseline HCV-RNA level. Patients were followed up and evaluated for 24 wk after completion of treatment. Therapy was monitored weekly by complete blood count and liver function tests (alanine aminotransferase [ALT; U/L], aspartate aminotransferase [AST; U/L]) for 3 mo, then monthly. HCV-RNA testing was carried out before treatment and then every 3 mo. Anti-HCV antibody was measured by a third generation commercial ELISA (Innotest HCV Ab IV; Innogenetics NV, Ghent, Belgium). Liver biopsy was not performed in hemodialysis patients. Serum HCV-RNA was quantified using a reverse transcriptase-polymerase chain reaction assay (Amplicor HCV ver. 2.0; Roche Diagnostic Systems, Branchburg, NJ) with a dynamic range being between 600 and 500 000 IU/mL. All samples were blindly tested in duplicate.

Virological and biochemical response criteria

In group A virological early response (virological EAR), virological end-of-treatment response (virological EOR), and sustained virological response (SVR) were defined as negative HCV-RNA by PCR at 12 and 48 wk of the therapy, and 6 mo after completion of therapy, respectively. In the treatment group, biochemical early response (biochemical EAR), biochemical end-of-treatment response (biochemical EOR), and sustained biochemical response (biochemical SR) were defined as the normalization of serum ALT activity at wk 12 and 48 and 6 mo after completion of therapy, respectively. Although group B patients did not receive PEG-IFN, biochemical and virological recovery at 12, 48, and 72 wk after the beginning of the study were categorized as early response (EAR), end-of-treatment response (EOR), and sustained response (SR), too.

Statistical analysis

Student's t test was used to compare mean values between groups, and the χ^2 test and Fisher's exact test were performed to analyze qualitative data. Parametric data are expressed as mean ± SD. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed by using SPSS version 10.0 (SPSS Inc; Chicago, IL).

RESULTS

Enrollment started in November 2004 and the study was finished in July 2006. Seventeen of 22 patients finished therapy. The mean serum viral load before treatment was

Table 1 Demographic and clinical features of study patients

Variables	Group A (n = 22)	Group-B (n = 14)	P
Age (yr)	35.2 ± 12.1	37.1 ± 14.6	0.629
Male (%)	12 (54.5)	10 (71.4)	0.448
BMI (kg/m^2)	25.6 ± 3.3	26.1 ± 3.9	0.78
ALT (IU/L)-Range	59.2 ± 22.4-(33-109)	44.8 ± 20.9-(21-71)	0.489
Viral load (x 10^5 copy/mL)	7.9 ± 4.8	8.1 ± 4.5	0.89
Genotype 1b (%)	86.4	92.9	0.56
HD duration (mo)	52.4 ± 24.7	49.8 ± 21.1	0.95

Table 2 Virological response rates

	Group A (n = 22)	Group-B (n = 14)	P
Early response			
Virological (%)	82.4	0	< 0.001
End-of-treatment response			
Virological (%)	82.4	0	< 0.001
Sustained response			
Virological (%)	64.7	0	< 0.001

2.4 × 10^5 copy/mL. At the beginning of therapy, ALT levels were found to be elevated in fourteen patients (63.6%). In nine of these patients, ALT activity decreased to normal levels within 12 wk of treatment (biochemical EAR 64.3%). At the end of the treatment, four patients still had high ALT levels (biochemical EOR 71.4%). In this group, the mean serum ALT activity at initiation was 59.2 ± 22.4 IU/L (range, 33-109 IU/L). This significantly decreased to 29.9 ± 13.7 IU/L and 21.8 ± 10.9 IU/L at wk 12 (P = 0.017) and at the end of the treatment (P = 0.001), respectively. At the beginning of the study, ALT levels were high in six patients in group B. One of the patients' levels became normal at 12 wk resulting in a biochemical EOR of 16.7%. In the control group, the mean ALT level was 44.8 ± 20.9 IU/L at the beginning. This value declined to 33.8 ± 21.7 IU/L at wk 12 (P = 0.786) and 33.1 ± 18.9 IU/L at wk 48 (P = 0.760).

The mean pretreatment serum HCV-RNA levels were 7.9 ± 4.8 × 10^5 copy/mL and 8.1 ± 4.5 × 10^5 copy/mL in group A and group B, respectively (Table 1).

The viral load was statistically similar between the groups (P = 0.890). All patients treated with PEG-IFN showed at least a 2-log decline from baseline HCV-RNA level. But HCV-RNA became undetectable in 82.4% of the patients at wk 12 of therapy. Virological EOR and SVR occurred in 82.4% and 64.7% of the patients (Table 2). Virological EOR and SVR 0% of the control group.

Therapy with PEG-IFN was associated with a higher rate of virological response than the control group (P < 0.001). All of the subjects had genotype 1. In the treatment group, three patients had genosubtype 1a and 19 had genosubtype 1b. In group B one subject had genotype 1a, and 13 had genotype 1b. There was no significant difference between the groups with respect to genotype distribution (P = 0.560).

Most adverse events were mild to moderate in severity, and all adverse events were typical of those previously reported for PEG-IFN. The drug was suitably tolerated by patients. Flu-like syndrome, throbocytopenia, leucopenia, and anemia were the most frequent side-effects and were experienced in nine patients (53%). These side-effects included flu-like syndrome in eight (47%), fatigue in six (35%), anemia in four (23.5%), thrombocytopenia in three (17.6%), and leucopenia in three of them (17.6%). We had to stop the treatment in five patients (22.7%) in fourth month at the begin of the treatment due to complications (two of anemia, two of weakness, one of gastrointestinal bleeding). The side-effects led to discontinuation of the treatment in five patients. Seventeen of 22 patients finished the treatment in spite of side-effects due to PEG-IFN. No patient had a serious infection during the treatment period.

DISCUSSION

In patients with normal renal function, pegylation increases the size of the molecule, delays its clearance, and enhances the therapeutic effect of standard IFN. It is possible to hypothesize that, in patients with renal failure; the clearance of PEG-IFN would be even more delayed, resulting in higher serum levels of the drug and in a longer half-life time.

The results of this study confirm the efficacy and safety of PEG-IFN therapy in hemodialysis patients with chronic hepatitis C. Treatment for 48 wk with PEG-IFN resulted in sustained virologic responses in 64.7% of patients. HCV infection increases the risk of death in patients on chronic hemodialysis, along with hepatocellular carcinoma and liver cirrhosis[16]. Many controlled and uncontrolled trials have focused on the treatment of chronic hepatitis C patients on chronic haemodialysis with IFN therapy[17], because treatment with PEG-IFN is rarely recommended.

Fabrizi *et al* have found a mean SVR of 37% in chronic hepatitis C patients on dialysis after IFN therapy. Sustained biochemical and virological response rates in patients under classical IFN therapy were reported as 0%-67% and 15.8%-64%, respectively[6]. Sporea *et al* have found, in treatment of these patients with standard IFN the sustained biochemical response of 46.1% and sustained virological response of 38.4% respectively 6 mo after interferon treatment[17]. The promising results at the standard IFN therapy in chronic haemodialysis patients with chronic hepatitis C, have shown that viral clearance occurs in 27%-64% of patients after 12 mo of treatment with standard IFN[18,19].

Patients with end-stage renal disease and chronic hepatitis C might have severe chronic hepatitis despite normal serum liver enzyme activity[20]. In our study, serum ALT levels were normal in 36.4% of the patients at the beginning of the study. Similarly, Perez *et al* reported normal ALT levels in 49% of patients at the beginning of treatment[20]. In the treatment group in our study, serum ALT levels became normal in 71.4% of the patients by the end of the therapy, whereas 16.7% of the patients in the control group had a biochemical response of end of therapy. In contrast, the side-effects of IFN treatment are very important for the patients with ESRD. In several situations, the IFN treatment could not be continued in those patients. Liver biopsy was avoided because of the risk of bleeding in these patients[21].

Recently, a pharmacokinetic study was carried out with

PEG-IFN in subjects with various degrees of stable renal failure who were not yet dialysis dependent. Adsorption and distribution of PEG-IFN were similar in subjects with stable chronic renal impairment versus individuals with normal renal function[22]. The dose of 135 μg of PEG-IFN in patients with ESRD gave similar serum concentrations to a dose of 180 μg in patients with normal renal function. On the trials of PEG-IFN in patients with end-stage renal disease have been designed using weekly doses of 135 μg (as opposed to 180 μg)[7].

HCV genotype 1 is very common in Turkey. Similarly, all of the patients in the present study had genotype 1. Although the response to IFN treatment is not excellent in genotype 1, our results were outstanding[23]. Most of the patients in our study were infected with genotype 1b (86.4% group A, 92.9% group B).

Recently, Kokoglu *et al* reported the results of a controlled study in which PEG-IFN 135 μg/wk for 48 wk was used in hemodialysis patients with HCV infection. They found 83.4% virological EOR and 71.4% biochemical EOR[7]. Sporea *et al* reported on a 50% SVR in hemodialysis patients receiving PEG-IFN 180 μg/wk[24]. In another study, virological response was 40% with PEG-IFN. The difference in virological response could be related to the duration of treatment in the last study (24 wk) and the molecular weight of PEG-IFN (17 kDa)[25]. We found in our study 82.4% virological EOR and 71.4% biochemical EOR.

PEG-IFNs are likely to become a valuable addition for HCV therapy in ESRD when combined with reduced ribavirin doses. However, the pharmacokinetics and tolerability of PEG-IFN and ribavirin combination therapy need to be studied in prospective studies[26]. To date, PEG-IFN and ribavirin combination therapy is the treatment of choice for patients with HCV infection. Ribavirin is metabolized by the kidneys and its clearance reduces in patients with ESRD. High ribavirin serum levels markedly increase the risk of hemolytic anemia and the use of ribavirin in uremic patients, who are often already anemic, could cause severe and life-threatening anemia. Thus, a combination therapy with ribavirin is not an option for treatment of chronic HCV infection in hemodialysis patients[27].

We found in the present study 64.7% SVR and we can expect that in these subjects the use of PEG-IFN would lead to a higher rate of SVR than that observed with standard IFN, probably with a higher rate of adverse effects[11]. PEG-IFN therapy had a successful efficacy in the present study but tolerability was not perfectly. We had to stop the treatment in five patients (22.7%) due to complications (two of anemia, two of weakness, one of gastrointestinal bleeding).

In conclusion, the results of the present study show PEG-IFN (40 kDa) administered at a dose of 135 μg weekly for 48 mo was efficacious but not perfectly tolerable in dialysis patients with HCV infection.

COMMENTS

Background

Our study showed that PEG-IFN (40 kDa) administered at a dose of 135 μg weekly for 48 mo was efficacious but not perfectly tolerable in dialysis patients with chronic hepatitis C.

Research frontiers

The present study was carried out in South-east Anatolien/Diyarbakir, Turkey, in hemodialysis patients with chronic hepatitis C.

Related publications

Yu JW, Wang GQ, Sun LJ, Li XG, Li SC. Predictive value of rapid virological response and early virological response on sustained virological response in hepatitis C virus (HCV) patients treated with pegylated interferon α-2a and ribavirin. *J Gastroenterol Hepatol*. 2007 Jun; 22(6): 832-836. Sporea I, Popescu A, Sirli R, Golea O, Totolici C, Danila M, Vernic C. Pegylated-interferon α 2a treatment for chronic hepatitis C in patients on chronic hemodialysis. *World J Gastroenterol*. 2006 Jul 14; 12(26): 4191-4194.

Innovations and breakthroughs

Many studies published that PEG-IFN treatment is efficacious and tolerable in hemodialysis patients with chronic hepatitis C. In our study we found similar efficacy, but this treatment was not perfectly tolerable in dialysis patients with HCV infection.

Peer review

Ayaz *et al* investigated the effects of PEG-IFN for treatment of HCV infection in hemodialysis patients. Eleven of 17 patients had a SVR at wk 24 after end-of-treatment. In 5 patients treatment had to be stopped because of side effects. The currently available data on this topic are scarce and therefore this is an important study which should be published.

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