European Journal of Internal Medicine 26 (2015) 292–296

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Efficacy and safety of pegylated interferon base treatment in patients with chronic hepatitis C on dialysis

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ARTICLE INFO

Article history:
Received 12 January 2015
Received in revised form 7 March 2015
Accepted 28 March 2015
Available online 13 April 2015

Keywords:
Hepatitis C
Pegylated interferon
Dialysis
Renal insufficiency

ABSTRACT

Introduction: Patients with chronic hepatitis C (CHC) and end-stage renal disease (ESRD) on dialysis are difficult to treat and show higher dropout rates during treatment. The aim of this study was to analyze the treatment outcomes in patients with CHC and underlying end-stage renal disease on dialysis in Korea.
Methods: A retrospective multi-center study of 35 patients with CHC and underlying ESRD on regular dialysis from 13 centers were analyzed. We investigated the tolerability and efficacy of pegylated interferon therapy with or without ribavirin on dialysis patients.
Results: Twenty patients (57%) were genotype 1. Sixteen patients (46%) were treated with pegylated interferon monotherapy. Nineteen patients (54%) were treated with pegylated interferon and ribavirin. The overall sustained virological response (SVR) rate was 65.7% in all subjects. Thirteen patients (37%) dropped out before completion of treatment, and six patients (46.2%) showed SVR despite premature termination of treatment. Twenty patients (90.9%) achieved SVR among the 22 patients who completed the scheduled course. The most common side effects were anemia and neutropenia. The patients receiving ribavirin treatment showed a higher dropout rate (52.6% vs. 18.8%, $p = 0.04$) and higher SVR rate (68.4% vs. 62.5%, $p = 0.07$) compared to the pegylated interferon mono-treatment group.
Conclusions: The difficulty in treating HCV patients with ESRD was attributed to higher dropout rate. However, despite the high dropout rate (37%), the SVR rate in genotype 1 was 65% and in genotypes 2 and 3 was 66%. Patients who completed the treatment showed a high SVR rate of 89.5%.

1. Introduction

The incidence rate of hepatitis C virus (HCV) infection among patients on hemodialysis is high, with a prevalence ranging between 3.3% and 16.8% according to the geographic area [1]. The overall incidence rate of HCV infection has been reported to be 1.47 per 100 patients per year [2]. According to the 'Dialysis Outcome and Practice Patterns Study' survey, the mean prevalence of anti-HCV positivity was 13.5% in patients on maintenance dialysis [3]. The prevalence rate of HCV in hemodialysis patients in South Korea has been reported to be 5–15% [4,5]. However, hepatitis C infection is very rarely treated among hemodialysis patients. One multicenter international study reported that only 1% (48/4589) of HCV-infected patients on hemodialysis were receiving antiviral medication [6].

HCV patients with underlying end-stage renal disease (ESRD) on hemodialysis are difficult to treat and are associated with poor tolerance of interferon, more complications, and a higher dropout rate, which may ultimately affect the treatment outcomes [7,8]. The efficacy and safety of interferon-based therapy in HCV patients with hemodialysis remain

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http://dx.doi.org/10.1016/j.ejim.2015.03.011
0953-6205/

unclear, although a number of small clinical trials have been undertaken. Currently, there have only been two reported randomized trials on HCV patients with ESRD on hemodialysis. These studies showed a SVR for genotype 1 of 64% in the group receiving conventional pegylated interferon and ribavirin (PR) combination therapy, and a SVR of 33% in the pegylated interferon monotherapy group. The SVR of the genotype 2 groups was 74% in the PR group and 44% in the monotherapy arm [9]. Although there is satisfactory evidence for pegylated interferon base treatment in patients with chronic hepatitis C (CHC) on dialysis from randomized controlled trials, the clinical data is very limited. Many physicians still hesitate to treat CHC in patients with ESRD because of the low treatment efficacy and high rate of adverse events. The aim of our study was to analyze the efficacy and safety of clinical pegylated interferon base treatment in patients with CHC on dialysis.

2. Methods

We retrospectively analyzed the data from 35 ESRD with CHC patients who were treated with pegylated interferon from 13 medical centers in Korea. We collected data including sex, age, genotype, ribavirin dose, laboratory findings, duration of treatment, and complications. Thirty-four patients were maintained on hemodialysis and one patient was maintained on peritoneal dialysis for ESRD during the treatment period. Hemodialysis was carried out routinely three times a week.

The diagnosis of CHC was based on positive HCV RNA by RT PCR, with or without elevated serum alanine aminotransferase (ALT) levels. Seventeen patients were treated with peginterferon alfa-2a and 18 patients were treated with peginterferon alfa-2b. The dosage of peginterferon was varied between 50 μg and 180 μg. Sixteen patients were treated without ribavirin. Nineteen patients were treated with ribavirin. The median dose of ribavirin was 182 ± 185 mg (80–800 mg). Treatment was discontinued when patients had uncontrolled complications. Genotype 1 patients received pegylated interferon base treatment for 48 weeks, and patients with genotypes 2 and 3 received 24 weeks of treatment.

The primary outcome of this study was measuring the sustained virological response (SVR) for treatment efficacy. SVR was defined as the disappearance of HCV viremia (HCV RNA) by PCR for at least 6 months after the completion of therapy. Secondary end-points included the dropout rate as a measure of tolerability and the end-of-treatment virological response (ETR). The ETR was defined as the absence of HCV viremia by PCR at the end of the treatment with or without completing treatment depending upon the viral genotype. We also assessed the treatment response with the rapid virological response (RVR) and the complete early virological response (EVR) at 4 and 12 weeks as assessed by undetectable HCV RNA.

3. Results

3.1. Characteristics of patients and treatment methods

Our study included 35 dialysis patients (22 men and 13 women) with HCV infection with a mean age of 48.9 ± 10.8 years old. The number of patients with genotypes 1, 2, and 3 were 20 (57%), 14 (40%), and 1 (3%) respectively. There were 17 patients who were treated with peg-interferon α-2a, and 18 patients who were treated with peg-interferon α-2b. Nineteen patients had ribavirin as their initial treatment and the average dosage was 131 mg/day (Tables 1, 2).

3.2. Treatment response and dropout rates

Sixteen patients (46%) were treated only with pegylated interferon. Nineteen patients (54%) were treated with interferon and ribavirin. RVR at 4 weeks was achieved in 24 patients (68%). EVR and ETR were achieved in 27 patients (77%). Twenty-three patients (85%) had SVR among the 27 patients who had ETR. The overall SVR rate was 65.7% in all subjects (genotype 1: 65.0%, non-genotype 1: 66.7%). Thirteen patients (37.1%) dropped out before the completion of treatment. However, of these patients, six (46.2%) showed SVR despite premature termination of treatment (genotype 1: 55.5%, non-genotype 1: 25.0%). Twenty-two patients completed the scheduled treatment. Twenty patients (90.9%) achieved SVR among the 22 patients who completed the scheduled course of treatment (Tables 3, 4).

Table 1
Characteristics of the study population.

Characteristics	
Sex (M:F)	22:13
Age (year)	48.9 ± 10.8
Genotype 1/2/3	20/14/1
Interferon (Peg α-2a/Peg α-2b)	17/18
With/without ribavirin	19/16
Ribavirin dose (mg)	182 ± 185

3.3. Factors affecting the sustained virological response (SVR)

Only RVR seemed to have a statistically significant effect on SVR ($p = 0.03$) (Table 5). The positive predictive value of RVR was 95.0%, and the negative predictive value was 66.7%. HCV genotype, pre-treatment viral load, sex, and age were not independent risk factors for SVR. The rate of SVR did not differ between different types of pegylated interferon (pegylated interferon α-2a and pegylated interferon α-2b).

3.4. Outcome with and without ribavirin

The dropout rate was higher in the ribavirin group than in the interferon mono-treatment arm (52.6% vs. 18.8%, $p = 0.04$). Combination treatment with ribavirin showed a marginal benefit in SVR as compared to interferon monotherapy (68.4% vs. 62.5%, $p = 0.07$) (Table 6).

3.5. Tolerability and safety

Thirteen patients (37.1%) dropped out of the treatment. Anemia was the most frequent cause of discontinuation of therapy (17.1%). Mean hemoglobin level drop from 12.4 mg/dl at the initiation of ribavirin treatment to 9.9 mg/dl after the 12 weeks of ribavirin therapy (Fig. 1). Four patients discontinued treatment due to neutropenia and thrombocytopenia (11.4%). The mean glomerular filtration rates and serum creatinine levels did not change during treatment.

4. Discussion

It has been reported that interferon and ribavirin combination therapy allows for a SVR rate of ~45% in genotype 1-infected patients treated for 48 weeks, and a SVR rate of 76–85% in patients with genotypes 2 and 3 treated for 24 weeks in the general population [10–12]. In this study, we found that the SVR rate in hemodialysis patients with HCV infection was 65.7%, which, as suspected, was not lower than the rate in the overall population.

A recent meta-analysis of 14 observational studies on dialysis patients with HCV infection reported that the summary estimate for the adjusted relative risk of mortality was 1.35 (1.25–1.47, 95% confidence interval) [13]. Other multicenter studies have also showed that the association between HCV infection and mortality was significant (RR, 1.17; $p < 0.0159$) [14]. Therefore, the treatment of HCV in patients on hemodialysis is crucial for better prognoses. Due to the risk of allograft rejection, the use of interferon is contraindicated in renal transplant patients. Hence, the treatment of patients with ESRD and CHC is feasible only prior to kidney transplantation [15].

However, physicians are reluctant to treat HCV infection in patients with underlying ESRD on hemodialysis in clinical practice. Clinicians