Retreatment of Chronic Hepatitis C Infection with Telaprevir : Turkey Experience

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Abstract

Background/Aims : **Patients with genotype 1 chronic hepatitis C virus (HCV) who do not have a sustained virologic response to therapy with peginterferon alfa and ribavirin have a low likelihood of success with retreatment.**

Materials and Methods : **Voluntary patients aged 18 and older with genotype-1 chronic HCV and with no exclusion criteria were included. Treatment was organized as following : telaprevir was administered at a dose of 750 mg every 8 hours ; Peg-IFN α-2a was administered at a dose of 180 mcg per week and ribavirin was administered at a dose of 1000-1200 mg per day. HCV-RNA levels were measured before treatment, at 4, 12, 24 weeks of treatment, after treatment and after 24 weeks of treatment. Sustained virologic response was defined as undetectable HCV-RNA after 24 weeks of treatment.**

Results : **Sustained virologic response was obtained in 37 patients (74%). Breakthrough (BT) or early relapse was seen in 6 patients (12%) in total. Treatment had to be discontinued because of treatment related adverse events in 7 patients (14%).**

Conclusion : **Triple combination therapy including telaprevir is significantly better than classical Peg-IFN α and ribavirin therapy in patients with chronic hepatitis-C infection.** (Acta gastroenterol. belg., **2016**, 79, **18-22**).

Key words : Hepatitis C, Telaprevir, triple treatment, sustained virologic response.

Introduction

Worldwide, an estimated 80 (64-103) million people have chronic hepatitis C virus (HCV) infection, and in many of these people, cirrhosis and complications of end stage liver disease will develop (1). Chronic HCV infection is the leading cause of liver disease and is the leading indication for liver transplantation in the United States and Europe (2). Currently available treatment for HCV infection is peginterferon alfa injections combined with oral ribavirin for 24 or 48 weeks (depending on the HCV genotype) (3). Approximately 60% of patients who are infected with hepatitis C virus (HCV) genotype 1 are not cured by 48 weeks of peginterferon alfa combined with ribavirin (4).

For patients in whom a sustained virologic response is not achieved, retreatment options are limited to a second trial of the same medications, with potential modification of the dose or duration of the regimen. These retreatment strategies are associated with clinically significant morbidity and generally have a very limited chance of a successful outcome (5,6). Therefore, the development of effective regimens to retreat patients with chronic HCV infection who did not have a sustained response to previous therapy is an urgent priority. Telaprevir is an inhibitor of the nonstructural (NS3/4A) HCV protease, with oral bioavailability, and specifically targets HCV with the goal of improving the chance of a sustained virologic response (7). It has been approved for treatment of genotype 1 chronic hepatitis C.

In two recent phase 2 trials, telaprevir substantially enhanced rates of sustained virologic response when it was combined with peginterferon plus ribavirin in patients who had received previous therapy (8,9). Moreover, high rates of early viral suppression and low rates of relapse after cessation of telaprevir therapy suggested that therapy could potentially be shortened to 24 weeks in patients who have a rapid virologic response – that is, patients in whom HCV RNA is undetectable at week 4 of treatment (10,11).

In this study, we assessed the efficacy and safety of the addition of telaprevir to a regimen of peginterferon plus ribavirin in patients with chronic HCV genotype 1 infection who did not have a sustained virologic response to previous treatment.

Material and Methods

Patients

In total, 50 patients who were diagnosed, followed and treated for definite chronic hepatitis-C infection at our institution between January 2013 and September 2014 were included in the study. The study was initiated by obtaining required ethical committee approval. Voluntary patients aged 18 and older with genotype-1 chronic HCV and with no exclusion criteria were included. All the patients had failed previous HCV treatment. Patients previously had received peginterferon alfa and ribavirin. Overall, 58% of the patients had a previous relapse, 20% had a partial response, and 22% had no response. Only eighteen of the patients received liver biopsies prior to treatment ; six patients had minimal or no fibrosis (Ishak F0,1,2), five patients had portal fibrosis (Ishak F3), one patient with bridging fibrosis (Ishak F4) and six patients had cirrhosis (Ishak F5.6). In particular, patients with compensated cirrhosis were included. No patient had

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findings of decompensated liver failure such as ascites or jaundice at the time of the study.

Study Design

Demographic characteristics such as name, family name, age, gender, primary disease duration, prior treatments and responses and concomitant diseases, as well as genotypic features, were recorded. Treatment was prescribed as the following : telaprevir (Incivo ; Janssen pharmaceutical companies, New Jersey, USA) was administered at a dose of 750 mg every 8 hours ; Peg-IFN α-2a (Pegasys ; Roche, Basel, Switzerland) was administered at a dose of 180 mcg per week and ribavirin (Copegus ; Roche, Basel, Switzerland) was administered at a dose of 1000-1200 mg per day. HCV-RNA levels were measured before treatment, at 4, 12, 24 weeks of treatment, immediately after treatment, and after 24 weeks of treatment. Patients were evaluated at following time points ; biweekly during the first three months of treatment and thereafter monthly.

In each visit, patients were given a detailed exam and were questioned about possible side effects. Also, peripheral complete blood count and ALT levels were measured. Adverse events, treatment modifications for these adverse events and additional medications were recorded during therapy.

Virologic Assessments

Sustained virologic response was defined as undetectable HCV-RNA after 24 weeks of treatment. Exacerbation was defined as HCV-RNA being negative after the start of treatment but then detectable during treatment. Relapse was defined as undetectable HCV-RNA at the end of treatment with HCV-RNA positivity thereafter. In accordance with treatment discontinuation rules, telaprevir was discontinued if HCV-RNA levels were greater than 1.000 IU/mL at 4 and 12 weeks after the start of treatment. In patients treated for 48 weeks, Peg-IFN α + ribavirin had to be discontinued if patients had positive HCV-RNA at weeks 24 and 36.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS 16.0 Chicago, USA) for Windows. Data were assessed using the Shapiro-Wilk test whether they normally distributed or not. Because data were not normally distributed, intergroup comparisons were performed with Mann-Whitney U test. Groups were compared by obtaining percentage changes of time-dependent variables compared to baseline. Categorical variables were compared using Fisher Freeman Halton test. Statistical significance level was accepted as $\alpha = 0.05$.

Ethical Considerations

The Ethics Committee of Uludağ University Faculty of Medicine, Bursa, Turkey approved this study (date : December 17, 2013). The patients were included into the study after obtaining informed written consent.

Results

Patients Characteristics

Twenty two (44%) patients were men and 28 (56%) were women. The youngest patient was 22 and the oldest patient was 71 years old. The mean age was 57.62 ± 10.21 and the median age was 59.5. A total 13 patients (26%) were cirrhotic and 37 (74%) were non-cirrhotic. Threshold for viral load was accepted to be 800.000 IU/mL of HCV-RNA. Accordingly, patients were accepted as having high viral load if HCV-RNA was above 800.000 IU/mL and having low viral load if HCV-RNA was under 800.000 IU/mL. There were 17 patients (34%) with a low viral load and 33 patients (66%) with a high viral load. The minimum baseline HCV-RNA level was 57.592 IU/mL, the maximum was 23.167.984 IU/mL. All patients had genotype-1 disease. The mean total leukocyte (WBC) was 7010.22 ± 1921.67, the median total leukocyte was 6.990 K/μL, the mean haemoglobin was 13.49 ± 1.39 g/dL and the median haemoglobin was 13.7 g/dL before treatment. The mean platelet count was 197.189 ± 65.595/mm^3 and the median was 297.000 mm^3. The mean ALT was 54.6 ± 48.7 IU/mL and the median ALT was 38 IU/mL.

Thirteen of the patients (26%) were cirrhotic ; six were men and seven were women. The mean age was 60.5 ± 11.2. The mean total leukocyte (WBC) was 6898.33 ± 2106.509 K/μL, the mean haemoglobin was 13.33 ± 1.497 g/dL before treatment. The mean platelet count was 168.905 ± 65.204 mm^3. The mean ALT was 59.92 ± 37.783 IU/mL. The mean albumin was 3.86 ± 0.33 g/dL, creatinine was 0.74 ± 0.16 mg/dL and INR 1.13 ± 0.15.

Efficacy

In the context of treatment progress and outcomes, sustained virologic response was obtained in 37 patients (74%). Breakthrough (BT) or early relapse was seen in 6 patients (12%) in total. Treatment had to be discontinued because of treatment related adverse events in 7 patients (14%) (Table 1).

HCV-RNA levels were negative at 4 and 12 weeks after the start of treatment in 41 patients of the total group. HCV-RNA levels were positive at 4 weeks but negative at 12 weeks in six patients. HCV-RNA levels were negative at 4 weeks but positive at 12 weeks in three patients. HCV-RNA levels were negative at 4 weeks in 31 patients of non-cirrhotic group and only one was positive at 12 weeks. HCV-RNA levels were positive at 4 weeks but undetectable at 12 weeks in six patients. HCV-RNA levels were negative at 4 weeks in all of the patients in the cirrhotic group. It was positive at 12 weeks in two patients.

Table 1. — **Distribution of treatment outcomes by the groups**

		Sustained virologic responce (n:37)	Relapse/ Breakthrough (n:6)	Treatment discontinuation (n:7)
Gender	Male (n:22)	17 (77.2%)	2 (9%)	3 (13.6%)
	Female (n:28)	20 (71.4%)	4 (18.1%)	4 (14.2%)
Fibrosis	Cirrhotic (n:13)	8 (61.5%)	1 (7.6%)	4 (30.7%)
	Non-cirrhotic (n:37)	29 (78.3%)	5 (17.2%)	3 (8.1%)
Viral load	Low viral load (n:17)	14 (82.3%)	0 (0%)	3 (17.6%)
	High viral load (n:33)	23 (69.6%)	6 (18.1%)	4 (12.1%)

When analyzed by gender, sustained virologic response was achieved in 77.2% of men and 71.4% of women. Relapse/BT was seen only in 2 of the men and 4 of the women. The rate of treatment discontinuation was 13.6% in men and 14.2% in women. There was no gender difference for sustained virologic response, relapse/BT and treatment discontinuation rates ($p = 0.899$). The rate of sustained virologic response was 61.5% (8 of 13 patients) and relapse/BT was 7.6% (1 of 13 patients) in the cirrhotic group. The rate of discontinuation due to adverse events was 30.7% in the cirrhotic group as compared with 8.1% in the non-cirrhotic group. Sustained virologic response was achieved in 78.3% ($n = 29$) and relapse/BT was seen in 17.2 % ($n = 5$) of non-cirrhotic patients (Table 1). There was no statistically significant difference between the groups with or without cirrhosis for the rates of sustained virologic responce, relapse/BT or treatment discontinuation ($p = 0.144$).

When patients were evaluated in the context of viral load, the rate of sustained virologic response was 82.3% in patients with low viral load whose HCV-RNA levels were 800.000 IU/mL or below. This rate was 69.6% in patients with high viral load. Relapse/BT was not seen in patients with a low viral load, but it was seen in 6 patients (18.1%) with high viral load. The rates of discontinuation were 17.6% in low viral load patients as compared with 12.1% in high viral load patients (Table 1). Similarly, no statistically significant difference was found for the rates of sustained response, relapse/BT or treatment discontinuation between groups with low or high viral load ($p :0.200$).

Ribavirin dose reduction was performed in 32 patients. None of the patients had a change in dose of telaprevir or peginterferon alfa. The ribavirin dose was reduced, and in patients in whom anemia did not improve, they received erythrocyte transfusions and erythropoietin injections.

Adverse Events

Weakness was the most common adverse event (70%), followed by nausea (64%), anemia (64%), headache (32%), insomnia (30%), rash (28%), pruritus (24%), and hemorrhoids (20%) (Table 2). Decreased haemoglobin levels were seen most often at 8 and 12 weeks of treatment in both the cirrhotic and non-cirrhotic group. It began to increase after the 12th week (Fig. 1). We observed that the haemoglobin level decreased by as much as 5 gr/dL. This decrease in haemoglobin level was significantly higher in the cirrhotic group than the non-cirrhotic group during the period after the end of treatment ($p = 0.021$). From all of our patients, 15 received at least one erythrocyte transfusion. In 2 patients, 8 units of erythrocytes were transfused. Also, 17 patients were treated with erythropoietin (epoetin beta) 10.000 IU/mL injections. In total, 65 injections were administered and only one patient received 10 injections.

In 13 patients, treatment was discontinued. In 6 patients, treatment discontinuation was due to insufficient response to treatment. The patients were able to complete the first three-month period with telaprevir. However, the treatment was discontinued because of the detectable HCV-RNA level measured.

Of 7 patients whose treatments were discontinued because of drug-related adverse events, 4 were cirrhotic and 3 were non-cirrhotic. Of cirrhotic patients, treatment was discontinued because of decompensation due to ascites and icterus in 2 patients. In one patient, it was discontinued because of severe weakness and haematuria at month 9 of treatment. In another patient, treatment had to be discontinued because of weight loss of about 8-9 kg due to extreme lack of appetite and weakness. Although this patient received treatment only for 1 month, HCV-RNA was still negative after 60 weeks. In one of the non-cirrhotic patients, the haemoglobin level decreased by 5 gr/dl and treatment was discontinued at patient's own request because of severe weakness. In another patient, a diffuse skin rash, which covered over 75% of the patient's body, developed during the first month of treatment. Then, treatment was immediately discontinued and systemic and topical steroids were given. In this patient, all lesions completely resolved. Additionally, one patient expired because of an acute myocardial infarction which developed after the first month of treatment.

Discussion

Chronic hepatitis C infection can cause numerous pathologies varying from minimal histopathological changes to diffuse fibrosis and cirrhosis as well as hepatocellular carcinoma in the presence of a cirrhotic liver.

Table 2. — **The most common adverse events**

	n (%)
Weakness	35 (70)
Nausea	32 (64)
Anemia	32 (64)
Hb : 8.5-10	15 (30)
Hb : < 8.5	17 (34)
Headache	16 (32)
Insomnia	15 (30)
Rash	14 (28)
Pruritus	12 (24)
Hemorrhoids	10 (20)
Influenza like illness	9 (18)
Weight loss	9 (18)
Cough	8 (16)
Ascites	2 (4)
Icterus	2 (4)
Hematuria	1 (2)
Cardiac disorder	1 (2)

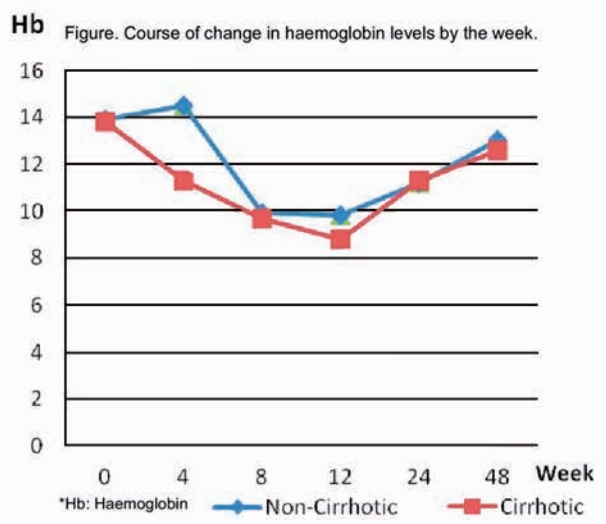

Fig. 1. — Course of change in haemoglobin levels by the week.

Therefore, hepatitis C infection represents a significant community health problem. All patients with chronic hepatitis-C are potential candidates for anti-viral treatment and all suitable patients should be treated (12). Although the reported incidence which derives from community surveys by different liver societies varies by region, the prevalence of hepatitis C is between 1.3 and 2.1%. Until recently, Pegile-interferon α and ribavirin combination had been used as a standard treatment regimen in chronic HCV. However, the likelihood of treatment success remains at about 40-50% in patients infected with genotype 1 (13). This means that there are a considerable number of chronic HCV patients treated unsuccessfully or insufficiently, considering the fact that the genotype is the predominant and most common genotype in our country and over the world.

Recently, protease inhibitors, which suppress the replication of HCV by blocking the protease enzyme that breaks down proteins, have been introduced as a therapeutic modality, so a new era has begun in HCV treatment. New treatment standard for HCV patients with genotype-1 is a triple combination therapy including a protease inhibitor + Pegile-interferon α + ribavirin (14). In our study, sustained response was achieved in 74% of patients treated with combination therapy. Our response rate is similar to the other studies in the literature. Treatment had to be discontinued because of drug-related adverse events in 14% of our patients. Also, telaprevir therapy could not be completed because of adverse events in the other clinical studies and telaprevir phase trials.

In the present study, patients were assessed for negative predictive factors such as increased HCV-RNA levels, cirrhosis presence, male gender with regard to sustained virologic response. In our cohort, twenty six percent of patients were cirrhotic. The number of females and males were similar (n = 22 and 28, respectively). The rates of patients with low and high viral load were 34% and 66%, respectively. Sustained virologic response rate was 61.5% in the cirrhotic group and 78.3% in the non-cirrhotic group and there was no statistically significant difference between the groups. This may be due to the small number of patients in the study. More studies with patients in cirrhotic and non-cirrhotic groups is likely to demonstrate a statistically significant difference. Even so, although cirrhosis presence is a negative predictive factor, sustained response rates are not lower in non-cirrhotics compared to cirrhotics. It is very important to complete the full course of therapy. Although the difference was not significant, treatment had to be discontinued because of adverse events in 30.7% of cirrhotic patients. The treatment discontinuation rate was only 8.1% in non-cirrhotic patients. Similarly, although sustained virologic response rate was relatively lower in patients with a high viral load compared to patients with low viral load (69.6% and 82.3%, respectively), this was not statistically significant. Our results indicate that all patients should be given a chance of treatment even if they have negative predictive factors for treatment response.

Patients treated with telaprevir + Pef-IFN α + ribavirin combination should be followed closely, especially during the first 3 months of therapy. In our study, adverse events related to drug and laboratory changes was seen most frequently during the first 3 months of therapy. No neutropenia or thrombocytopenia was observed in included patients. Anemia was the clinical condition in which patients, treatment modifications and therapy duration were mostly influenced. When anemia occurred, the ribavirin dose was reduced and also erythrocyte transfusions, as well as erythropoietin injections were given. Cirrhotic patients should be more closely followed than non-cirrhotic patients during the therapy. More

severe anemia may occur in cirrhotics compared to non-cirrhotics. Also, decompensation may arise in cirrhotics during therapy. We need to be careful in this regard. Many patients have the complaint of severe weakness, especially, during the first three month of treatment. These complaints disappear after the third month of therapy and treatment becomes well-tolerated. Therefore, treatment regimen, possible adverse events and their management should be explained to all patients who are candidates for triple therapy before the beginning of treatment, and also, patients should be assessed for compliance of treatment and follow-up. One potential limitation of our study is that 24 weeks after the end of treatment was the assigned time frame to assess for subsequent evaluation of HCV-RNA levels. However, long-term observation for actual success and recurrence rates of the treatment is required. Morever, another limiting factor was the small number of the patients that participated in the study.

Triple combination therapy including telaprevir is significantly better than classical Peg-IFN α and ribavirin therapy in patients with chronic hepatitis-C infection. Although there are some side effects of telaprevir, successful results can be obtained with close follow-up. Since the close of 2013, several new direct acting antiviral agents for the treatment of chronic HCV have been approved by the Food and Drug Administration (FDA). These new treatments have fairly high cost, but have a high cure rate of 80-100%. The cost of the new interferon-free regimens ranged from $63,000 to $168,000 per patient (15). New treatments are now administered for the treatment of chronic HCV in developed countries with high income levels. In many countries of the world with low income levels, they are not able to meet the high drug costs. On the other hand, HCV prevalence is higher in the underdeveloped countries of the world. Although telaprevir is somewhat outdated in the area of interferon free treatment, it could still be considered for countries that do not have access to the new direct acting antiviral agents.

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