

Telaprevir-based triple therapy for re-treatment Chronic HCV patients with Genotype 1, including the Null-Response: A single center experience from Turkey

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Abstract

Background: Telaprevir with peginterferon/ribavirin (TVR/PR) leads to significantly higher sustained virological response (SVR) rates with partial response or relapse after prior treatment with peginterferon alpha (PegIFN)/ribavirin (RBV) in patients infected with hepatitis C. We studied the efficacy of TVR/PR in patients with prior treatment failure, including those with a null response (<2 Log₁₀ decline in HCV RNA), to peginterferon/ribavirin.

Objectives: It was aimed to evaluate efficacy, safety and side effects of the addition of telaprevir to a regimen of peg-interferon plus ribavirin in patients with chronic HCV genotype 1 infection who did not have a sustained virologic response to previous treatment.

Method: This study is in a retrospective design with patients receiving TVR based triple therapy for chronic hepatitis C in a single center of a Middle Anatolia. The patient who did not have the response with the previous peg-interferon alpha with ribavirin treatment included the study.

Virological response results were assessed at weeks 4, 12, and 24 during the triple treatment. If the HCV RNA levels was > 1000 IU/mL at week 4 or negative at week 4 but >1000 IU/mL at week 12, treatment was discontinued. Rapid virological response (RVR), early virological response (EVR), extended rapid virological response (eRVR), and virological response at 24th week of treatment were evaluated. The adverse events were evaluated during the therapy.

Results: Twenty-six patients infected with genotypes 1a or 1b hepatitis C virus were included the study. All of the patients had been previously treated with PegIFN plus RBV. Sustained virologic response occurred in 21 out of 22 previous relapse patients (95.5%) and 2 out of the 4 non-responder or partial responder patients (50%). The most common side effects were fatigue, insomnia, myalgia and anaemia.

Conclusions: In conclusion, the response to TVR treatment rate was high in previous relapsers but it was low in non-responder or partial responder patients.

Introduction

Chronic hepatitis c infection and complications are an important health problem in Turkey as well as all over the world [1]. The predominant genotype in Turkey is 1b, which was reported over 90% in the previous studies [2,3]. Approximately 60% of the patients, infected with hepatitis C virus (HCV) genotype 1 are not achieved sustained virologic response (SVR) by 48 weeks of peg-interferon alpha (PegIFN) combined with ribavirin (RBV) [4]. Telaprevir (TVR) is an orally bioavailable drug for non-structural 3/4A HCV protease inhibition [5]. When TVR is combined with PegIFN plus RBV, sustained virologic response (SVR) rates are increased significantly in patients with treatment experience [6,7].

In this study, we aimed to evaluate the efficacy, safety and side effects of the triple therapy of TVR, Peg IFN plus RBV treatment in patients with chronic HCV genotype 1 infection who did not have a SVR.

Methods

This retrospective study consisted of 26 patients with genotype 1a and 1b HCV infection from January 2013 to December 2014.

The inclusion criteria were being between the ages of 18 and 70 years, having chronic HCV genotype 1 infection, not having SVR to the previous therapy of PegIFN plus RBV. HCV genotype 1 infection with evidence of chronic hepatitis, confirmed by a liver biopsy

before screening for the study. The exclusion criteria were having decompensated liver disease, having other causes of significant liver disease, or active cancer.

The lower detection limit of the HCV polymerase chain reaction (PCR) was 15 IU/ml (COBAS TaqMan HCV Qualitative, v2. 0, Roche). HCV RNA levels were measured by screening at baseline and during weeks 4, 8, 12, 24, 36 and 48 at follow-up visits and 24 weeks after the end of treatment.

The non - response was defined as a reduction of less than 2 log₁₀ in HCV RNA after 12 weeks of therapy. Partial response was defined as a reduction of 2 log₁₀ or more in HCV RNA after 12 weeks of therapy but with detectable HCV RNA. Relapse was defined as undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter. Viral breakthrough was defined as an increase of at least 1 log₁₀ in HCV RNA or an HCV RNA level of more than 100

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IU per milliliter in patients whose viral load had previously been less than 15 IU per milliliter during treatment.

Patients were treated with TVR orally at a dose of 750 mg three times a day (every 8 hours) with food, PegIFN-2a by the subcutaneous route at a dose of 180 µg per week or PegIFN-2b by the subcutaneous route at a dose of 1.5 µg/kg per week, and RBV at a daily oral dose of 1000 mg (patient weight < 75 kg) or 1200 mg (patient weight ≥ 75 kg).

All the treatment had to be discontinued if patients had less than a 2 log10 decrease in HCV RNA at week 12 or in cases of detectable HCV RNA at week 24th or 36th. Patients who discontinued telaprevir because of the stopping rule were considered to have had virologic failure.

Baseline, 4th (Rapid viral response; RVR) 12th (Early viral response; EVR), 4th through 12th (extended rapid viral response; eRVR) and 24th and 48th weeks' (End of treatment viral response ETR) virologic response and sustained viral response (SVR) after the end of the treatment's 24th week were prospectively monitored.

All adverse events were collected throughout the treatment period and at 4 weeks after the last dose of the study drug were administered. The rash was graduated of mild, moderate, severe.

Results

The demographic characteristic of the patient is shown in Table 1. 26 Turkish patients were participated in the study and 81 percent of them was female. According to the response of previous treatment; any of the patient was naïve and four of them were non-responder. Baseline median HCV viral load was 6.78 log10 IU/mL (range 3.79 log10 – 6.94 log10). Before the treatment, 42 percent of the patients had > 6 log10 IU/ML of HCV RNA level, and 88 percent of them had the subtype of HCV genotype 1b. Four patients with compensated liver cirrhosis were eligible. Liver biopsy was performed in sixteen patients.

The baseline characteristics of the patients and their disease level were similar in the three study groups.

Responses of the triple treatment are shown in Table 2. 22 of the 26 patients were previous relapsers and 21 of them had SVR. Breakthrough was occurred in one patient after the 4.th week of the treatment. Three of the patient in relapsers had bridging fibrosis or cirrhosis and all of them had SVR. Four of the patients had no response or partial response to previous therapy end two of them had SVR at the end of the triple treatment.

Adverse events observed during TVR treatment are shown in Table 3. The most common adverse events were fatigue, headache, insomnia, and myalgia.

Discussion

In previous studies reported that when the Peg-IFN + RBV and TVR treatment compared to the standard therapy, the rate of SVR can significantly improve in the patients infected with HCV genotype 1 [6-9] Although the treatment success was increased in TVR added regimens when RBV removed the treatment with TVR, SVR rates was lower than the standard therapy [6,10].

In this study, all the patients were infected with HCV genotype 1. In a study involving the patient infected with genotype 4, the SVR rates were 50% in all patients [11]. Also, another study which was conducted patients with genotype 1 and 4, SVR rates was maximum 53% [6]. In PROVE study, that was included the HCV genotype 1 infected patients

Table 1. Baseline Characteristics of the Patients.

Age (median)	58.5
Gender (%)	
Male	19
Female	81
Race or ethnic group — no. (%)	All were Turkish
Cirrhosis (%)	22
Previous type of response — no. (%)	
Naïve	-
Relapsers	22
Nonresponders	4
Alanine aminotransferase — IU/liter	42.5
Serum albumin — g/liter	4.1
Platelet count — per mm³	2,19X10 ⁵
Baseline HCV RNA (log10 IU/mL)	6.78
HCV RNA>6 log10 IU/mL	11 (42.3 %)
HCV genotype 1 subtype	
1a	11.5 %
1b	88.5 %
Stage of fibrosis or cirrhosis	
Minimal fibrosis	11 (42 %)
Moderate	3 (11 %)
Cirrhosis	4 (15 %)

Table 2. Response rates of all the patients.

Previous relapsers	
Undetectable viral load at 4th week (RVR)	22/22 (100%)
Undetectable viral load at 4ththrough 12th(eRVR)	21/22 (95.5%)
Undetectable viral load at 12th week (EVR)	21/22 (95.5%)
End of treatment viral response (ETR)	21/22 (95.5%)
Viral response after the end of treatment's 24th week (SVR)	
All patients	21/22 (95.5%)
Patients with undetectable viral load at 4th week	21/22 (95.5%)
Patients with bridging fibrosis or cirrhosis	3/3 (100%)
Virologic failure	-
No response or partial response to previous therapy	
Undetectable viral load at 4th week (RVR)	2/4 (50%)
Undetectable viral load at 4th through 12th (eRVR)	2/4 (50%)
Undetectable viral load at 12th week (EVR)	4/4 (100%)
End of treatment viral response (ETR)	2/4 (50%)
Viral response after the end of treatment's 24thweek (SVR)	
All patients	2/4 (50%)
Patients with undetectable viral load at 4thweek	2/4 (50%)
Patients with bridging fibrosis or cirrhosis	-

the rate of SVR was higher (the SVR rate was 67% in the treated group with TVR for 12 week and PegIFN + RBV for 48 week [12].

When patients are grouped according to previous treatment responses, the SVR rates of relapsers were higher than no responder and partial responders [9]. In our study, the rates of SVR were 95% in relapsers and 50% in the others. Like these results, Muir *et, al.* reported these rates 97% in relapsers, 75% in breakthroughs, 55% in partial responders and 37% in non-responders consequently [8]. The SVR of the non-responders and partial responders were higher than in the study which was reported by Aygen *et, al.* (56% and 66% respectively). Nonetheless, the rate of response in relapsed patients was higher in this study again [13]. The high level of SVR in our study may be because all patients have type 1 genotype and the proportion of relapsed patients is high.

In the previous relapsers group, three patients had bridging fibrosis and cirrhosis and all of these patients had SVR in our study. In a study evaluating the triple treatment of the majority of non-responder

Table 3. Incidence of the Most Common Adverse Events.

General disorder	N (%)
Fatigue	22 (80)
Influenza-like illness	8 (31)
Pyrexia	6 (23)
Chills	8 (31)
Gastrointestinal disorder	
Nausea	18 (69)
Diarrhea	4 (15)
Hemorrhoids	4 (15)
Skin and subcutaneous tissue disorders	
Pruritus	6 (23)
Any rash-related event	8 (31)
Alopecia	7 (26)
Nervous system disorders	
Headache	13 (50)
Dizziness	14 (53)
Psychiatric disorders	
Insomnia	18 (69)
Depression	10 (38)
Musculoskeletal disorders	
Myalgia	15 (57)
Arthralgia	12 (46)
Respiratory disorders	12 (46)
Cough	8 (31)
Blood and lymphatic system disorders	
Anemia	15 (58)

patients, SVR rates of cirrhotic patients were found to be around 20% at 12 and 24 weeks of TVR treatment regimens [6]. In a multicentre study evaluating the response of TVR and boceprevir treatment, this rate was reported as 44% in patients with cirrhosis. However, the previous treatment responses of these cirrhotic patients were not indicated throughout this study [14]. In our study, this rate may be higher due to insufficient number of patients and being relapser in the previous treatment.

The viral breakthrough rates were reported as 7% to 24 in the previous studies [6,10]. In a study performed in 81 patients, of the 15 of the patients (18%) had a viral breakthrough. And they reported that 11 of these 15 patients were previous nonresponder [8]. In PROVE 1 study viral breakthrough rate was reported as 7% and first 12 week of the treatment. And, they also reported the observation of Telaprevir-resistance-associated mutations in these patients [12]. We observed a breakthrough in one of the patients we followed; however, we did not have a chance to evaluate the resistance- mutations in this patient. Any of the patients had viral breakthrough in nonresponders group, but this result may be associated with the insufficient number of patients.

The results of the treatment response observed were similar to the results of other treatments reported from our country. A study done by Komur *et al.* [15] from a neighboring city reported the rate of SVR as 77 percent. Aygen *et al.* reported the SVR rates as 88% at relapsers [13].

The most common adverse events were fatigue, headache, insomnia, and myalgia. 58 percent of the patient developed anemia as a hematologic disorder. However, none of the patients had to leave treatment due to side effects.

The results of this study show in patients who had a previous relapse to an initial standard therapy after treatment with telaprevir that achieving high rates of sustained virologic response after the end of the treatment's 24th week (95.5%).

In addition, probably appropriate patient selection must be done by testing IL28B polymorphism and previous history of adverse events due to dual therapy with PEG IFN plus RBV in terms of cost-effectiveness and the quality of life of the patients due to triple therapy.

In conclusion, with the recent advances in hepatitis C therapy options, telaprevir may not be recommended as a standard therapy for this indication anymore. In some countries, the new-generation DAAs will not be available/reimbursed, and TVR and BOC base triple therapy will therefore be the alternative for the newer all-oral treatments.

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