

# Telaprevir combination therapy in patients infected with hepatitis C virus genotype 4

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## Abstract

**Background:** The sustained virological response (SVR) rate for genotype 4 (G4) HCV-infected patients after pegylated interferon (PegIFN) and ribavirin (RBV) treatment is approximately 60%. We aimed to investigate the efficacy and safety of telaprevir (TVR) in combination with PegIFN and RBV in patients infected with G4 HCV who were previously treated with PegIFN/RBV and failed to achieve SVR.

**Material and Methods:** The study included 10 patients: two prior relapsers, two prior partial responders, and six prior null responders to PegIFN/RBV treatment. The patients were given TVR/PegIFN/RBV for 12 weeks, followed by a 12-36 weeks PegIFN/RBV treatment. Rapid virological response (RVR), early virological response (EVR), extended rapid virological response (eRVR), SVR, and side effects of therapy were evaluated.

**Results:** The mean age of the patients was 48.90±12.52 years and seven were female. All of HCV isolates were typed as 4d. Interleukin (IL) 28B genotype was found CT in seven patients and two patients had cirrhosis. Treatment was stopped within four weeks because of the side effects in two patients. Three of the remaining eight patients (37.5%) achieved HVR, RVR, and eHVR. SVR was obtained in two of these patients, but one patient relapsed. SVR rates were 25% in all patients.

**Conclusion:** TVR combination therapy had limited antiviral activity in this patient population. Further investigation of TVR combination therapy in patients with HCV G4 infection is warranted.

**Key words:** *Helicobacter pylori*, babA2, cagA, gastric disorders.

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## Introduction

Chronic hepatitis C virus (HCV) infection is an important health problem in our country, Turkey, as it is around the world (1-3). HCV genotype 4 (G4) is common in the Middle East and Egypt. HCV G4 infection has recently spread to several European countries including Italy, France, Greece, and Spain due to changes in population structure, immigration, and transmission routes.

Prevalence rates of 10% to 24% have been reported in some areas (4). The most frequently observed HCV genotype in our country is G1b, with a rate of 68–94%, but in recent years there has been an increase in G4 infections (5-8). With a 48-week administration of the combination therapy of pegylated alpha and ribavirin (PegIFN/RBV), the sustained virological response (SVR)

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rate is 60% in patients infected with HCV G4 (4).

Telaprevir (TVR) is a linear peptidomimetic HCV NS3/4A serine protease inhibitor. In previously conducted studies, the combination of TVR and PegIFN/RBV has been shown to be successful in both treatment-naïve and treatment-experienced patients with chronic HCV G1 (1, 9). In a phase 2a clinical study, TVR alone, PegIFN/RBV or a PegIFN/RBV/TVR combination was administered for two weeks in treatment-naïve patients infected with chronic HCV G4 infection (10). Antiviral activity was found to be higher in the triple-combination group compared to the other groups.

In this study, we aimed to evaluate the efficacy and safety of the combination therapy of TVR with PegIFN/RBV in chronic hepatitis C (CHC) treatment, in patients infected with G4 who previously received PegIFN/RBV treatment but failed to achieve SVR.

## Material and methods

### Patients

In this retrospective study, closely monitored patients infected with HCV G4 who had previously received at least 80% of PegIFN/RBV therapy but did not achieve SVR were evaluated. The age range of the 10 patients (seven women, three men) was 24-62 years, and the average age was  $48,90 \pm 12,52$ . Patients with liver disease other than HCV infection, patients who were positive for anti-HIV, and patients with active cancer were excluded from the study. Liver biopsies were performed percutaneously and assessed according to the Ishak scoring system (11). All of the subjects provided written informed consent for both treatment and genetic analysis. The study was approved by the Ethics Committee for Clinical Research at Erciyes University, conforming to protocols in accordance with the Declaration of Helsinki (Decision number: 2015-60).

### Study design

Patients were evaluated according to their baseline viral load (HCV RNA  $< 800.000$  IU/mL or  $\geq 800.000$  IU/mL), interleukin (IL) 28B rs12979860 C/T polymorphism (CC, CT, or TT), stage of fibrosis, and type of prior response to PegIFN/RBV (null response, partial response, or relapse) (12, 13). For patients who agreed to receive treatment, a special out-of-indication form and patient consent document were submitted to the Ministry of Health and approval was obtained. The patients were

given TVR/PegIFN/RBV for 12 weeks, followed by a 12-36 week PegIFN/RBV treatment (12-16).

### Efficacy assessments

Quantitative HCV RNA was measured before the treatment and at weeks 4, 12, 24, 48 and after treatment at weeks 12 and 24. Responses of therapy were assessed according to the guidelines (12, 13). Rapid virological response (RVR), early virological response (EVR), extended rapid virological response (eRVR), SVR, end-of-treatment response (ETR) and side effects of therapy were evaluated.

### Safety assessments

The patients were assessed clinically and the essential biochemical, hematologic laboratory tests were performed at weeks 1, 2, and 4 of treatment and on a monthly basis thereafter. Side effects were recorded at each visit and the precautions were taken. Patients with serious side effects were controlled frequently; if necessary, they were hospitalized and/or triple therapy was discontinued.

### Blood samples and laboratory tests

Routine biochemical tests were performed on venous blood samples with an automated device and anti-HCV antibody examined using an enzyme immunoassay method (Architect System; Abbott Laboratories, Chicago, IL, USA). Quantitative HCV RNA measurement was performed with real-time polymerase chain reaction (COBAS Ampliprep/COBAS TaqMan 48, Roche Molecular Systems, Mannheim, Germany). HCV genotyping was investigated by pyrosequencing method (Pyromark, Qiagen, Germany). A nested PCR approach was adopted to amplify the 472 bp stretch in the E1core gene between 843 and 1315 nucleotides using primers PR108, PR109, PR110, PR111 as described by Murphy et al (17). A heminested PCR approach was adopted to amplify the 380 bp stretch in the NS5B gene between positions 8256 and 8636 using primers PR3, PR4, and PR5 as described by Laperche et al (18). The sequencing was done using Big dye sequencing chemistry with primers; PR3, PR5, PR108, PR109. 3130 ABI sequencer (ABI Prism, Applied Biosystems, USA) was used to generate the sequences. Phylogenetic analysis was performed using MEGA software 5.02 (19). Genotyping for the IL-28B rs12979860 C/T polymorphism was

performed by a polymerase chain reaction-based restriction fragment length polymorphism assay (20).

## Results

### Patients

The study included 10 patients: two prior relapsers, two prior partial responders, and six prior null responders to PegIFN/RBV treatment. All of the genotypes were found as G4. Molecular characterization of HCV G4 isolates obtained from all patients. All the isolates were typed as 4d. The demographic characteristics and treatment outcomes of the patients included in this study are shown in Table 1.

### Efficacy

There were two patients who failed to complete the first four weeks of treatment due to side effects (case four and case 10). In three (37.5%) of the remaining eight patients, RVR, eRVR, and EVR were achieved. SVR was obtained in two of these patients, but one patient had relapsed. SVR could not be obtained in the patients who did not have RVR. SVR rates were 25% in all patients.

SVR was obtained in two relapser. In these patients, the HCV RNA level was below 800,000 IU/mL, the fibrosis scores were zero and five, IL-28B genotypes were CT and TT respectively. In one partial responder, RVR, eRVR and ETR were detected but relapse occurred three months after the treatment. The fibrosis score was two and IL-28B genotype was CT in this patient. In five null responders, triple therapy was discontinued due to HCV RNA levels above 1,000 IU/mL at the first four weeks of treatment. The HCV RNA level was higher than 800,000 IU/mL in these cases. The fibrosis score was zero in two patients, two in one patient, three in one patient, and six in one patient. IL-28B genotype was TT in one patient and was CT in the others.

### Adverse events

Common side effects were fatigue, headache, anorexia, malaise, anemia, pruritus, dry skin, rash, dyspepsia, nausea, pyrexia, stomachache, and anorectal discomfort. Anorectal discomfort was observed in seven patients. All therapies were discontinued in these two patients at the second week of treatment. One of these patients had anal hemorrhage and hemorrhoid. Dryness of the skin was in seven patients, pruritus was six patients, and mild rash

was four patients. The RBV dose was reduced in four patients who developed anemia, and erythrocyte transfusion was performed in two patients.

## Discussion

SVR rate in combination therapy with TVR or boceprevir was much lower in a real-life patient cohort than in clinical trials (53% for TVR and 40% for boceprevir, compared to 66–75% in clinical trials) (1). The SVR rates obtained with triple therapy are different, depending on how patients respond to double therapy (relapse, partial response, or null response) (21, 22). In one of our research, we showed that virological response rate at 24th week of treatment are high with TVR/PegIFN/RBV combination therapy in patients infected with CHC G1 and G4 but virologic eradication rate was found to be the highest in prior relapsers (3). Only two studies, one phase II study with limited number of patients and one with a patient with mixed HCV G1 and G4 infection, are found in the literature pointing the success of TRV combination therapies in CHC patients infected with HCV G4 (10, 23). In our study, the rates of RVR, eRVR, and EVR were found 37.5%. SVR was obtained in two of relapser patients, but one patient who was prior partial responder had relapsed.

In prior null responders, cure is difficult when retreating patients with high pre-treatment HCV RNA levels and advanced stage liver fibrosis (3, 22). Our null responder patients were unresponsive to the treatment. In our study, the basal viral load was high in five of treated patients, and one patient had bridging fibrosis or cirrhosis.

The IL28B rs 12979860 C/T polymorphism has been shown to play an important role in both double and triple therapies for CHC (12, 14). In our previous study, although 94.1% of cases had the CT or TT genotype, the virological response rate at the 24th week of treatment was high (3). All patients were IL28B genotype CT or TT in this study but SVR rate was low.

In this study all of HCV isolates were subtyped as 4d. We know that genotype 4d is resistant to antivirals. This study is the first study that evaluates antiviral activity of TVR/PegIFN/RBV combination therapy and SVR rates were found as 25% in all patients. The results of this study should be supported by further studies.

**Table 1.** The demographic characteristics and treatment outcomes of the patients.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (years)	30	62	54	46	54	58	49	53	24	59
Gender	F	M	M	M	F	F	F	F	F	F
Prior type of response	Relapse	Relapse	Partial response	Partial response	Null response	Null response	Null response	Null response	Null response	Null response
Baseline ALT level (IU/L)	51	142	35	30	26	56	31	55	30	81
Viral load at baseline (IU/mL)	432,000	782,000	684,000	2,860,000	1,060,000	1,190,000	7,600,000	4,660,000	2,170,000	7,430,000
Liver biopsy* Necroinflammation score	6	7	3	9	4	7	5	8	4	9
Fibrosis score	0	5	2	3	0	6	2	3	0	2
IL28B rs12979860 C/T gene polymorphism	CT	TT	CT	TT	CT	TT	CT	CT	CT	CT
Treatment outcome	SVR	SVR	Relapse	Therapy was discontinued**	Null response	Null response	Null response	Null response	Null response	Therapy was discontinued*

M: Male; F: Female; ALT: Alanin aminotransferase; SVR: Sustained virological response, \*Ishak scoring system, \*\* Because of side effects.

Important side effects are observed in triple therapies with TVR. There is an 8-12% increase in treatment discontinuation due to side effects (16, 22). All therapies were discontinued in two patients due to side effects.

This study shows that the TVR/PegIFN/RBV therapy has been found effective in relapser patients infected with HCV GT4 but the virological response could not be obtained in patients with partial responder and null responder patients. The rate of side effects with TVR observed in our study was high and the treatment discontinuation rate was 20%.

## Conclusion

In conclusion, TVR combination therapy had limited antiviral activity in especially null responder patients with HCV G4 infection. Further investigation of TVR combination therapy in patients with HCV G4 infection is warranted.

**Ethics Committee Approval:** Ethics Committee approval was received for this study from the ethics committee.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** No conflict of interest was declared by the author.

**Financial Disclosure:** The author declared that this study has received no financial support.

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