Research Article

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Telaprevir-based Triple Therapy for Retreatment of Chronic Hepatitis C Patients with Genotype Four Followed in Our Clinic

Kliniğimizde İzlenen Genotip Dört ile Enfekte Kronik Hepatit C'li Hastalarda Telaprevir Tabanlı Üçlü Tedavi

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ABSTRACT

Objective: Telaprevir-based triple therapy for chronic hepatitis C virus (HCV) patients with genotype 4 is not recommended potently by the guidelines. There are few studies in the literature related to this issue. This study showed the antiviral activity and safety of telaprevir-based regimens in the treatment of treatment-experienced genotype 4 chronic HCV-infected patients.

Materials and Methods: This retrospective study consisted of 12 genotype 4 HCV-infected patients. All patients received 12 weeks of telaprevir in combination with 24 weeks of pegylated interferon (PEG-IFN) alpha and ribavirin (RBV).

Results: The sustained virological response (SVR) rate was six of 12 (50%). Notably, the rate of SVR in prior relapsers was 75% (6 of 8). SVR could not be achieved in non-responders.

Conclusion: Telaprevir, a potent HCV NS3-4A protease inhibitor, has been used as monotherapy and in combination with PEG-IFN/RBV in patients infected with genotype 1, 2 and 3 HCV. Limited clinical data suggest that telaprevir has activity against genotype 4 HCV. In this study, it was observed that the addition of telaprevir to the standard regimen had a greater activity on treatment relapse patients with genotype 4.

Keywords: Chronic hepatitis c, telaprevir, genotype 4

ÖZ

Amaç: Telaprevir bazlı üçlü tedavi ders kitaplarındaki önerilere dayanılarak genotip 4 hepatit C virüslü (HCV) hastalarda önerilmemektedir. Literatürde genotip 4 HCV pegile interferon/ribavirin (PEG-İFN/RBV) tedavi deneyimli ve kalıcı viral yanıt alınamamış hastalarda telaprevir bazlı üçlü tedavinin etkinliğini belirleyen az sayıda çalışma bulunmaktadır. Çalışmada bu konuda literatüre katkıda bulunmayı amaçlanmıştır.

Gereç ve Yöntemler: Çalışma retrospektif olarak dizayn edilmiş olup daha önceden PEG-İFN/RBV tedavisi almış ve nüksetmiş ya da yanıtsız olarak değerlendirilmiş 12 genotip 4 HCV enfeksiyonlu hasta alındı. Hastaların tedavi bitiminden 24 hafta sonra kalıcı viral yanıtları (KVY) kaydedildi.

Bulgular: KVY'li tüm hastaların altısı (%50) alındı. KVY'si alınan hastaların tamamı PEG-İFN/RBV tedavisi sonrası nüks hastalar olduğu görüldü. PEG-İFN/RBV tedavisine cevapsız olan dört hastanın hiçbirinde KVY alınamadı.

Sonuç: Telaprevir, etkili bir NS3-4A proteaz inhibitörü olup PEG-İFN/RBV ile ya da tek başına genotip 1, 2, 3 HCV hastaların tedavisinde kullanılmaktadır. Genotip 4'te kullanımına yönelik yapılan çalışmalar sınırlıdır. Çalışmamız, telaprevir bazlı PEG-İFN/RBV tedavisinin genotip 4 relaps 15 hastalarında KVY'yi önemli oranda arttırdığını göstermektedir.

Anahtar Kelimeler: Kronik hepatit c, telaprevir, genotip 4

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Introduction

Hepatitis C virus (HCV) infection is a major global health issue. HCV is genetically heterogeneous with 6 major HCV genotypes (1). HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world (2).

In Turkey, chronic HCV infection is an important health problem. Genotype 1 accounts for 68-94% and genotype 4 (G4) accounts for 36% of HCV infections. The prevalence of HCV G4 has been increased in recent years (3,4). HCV genotype is considered to be an independent factor affecting the response to interferon treatment (5). Therefore, analysis of the genotype of HCV is also important in regulating response and duration of the treatment (5,6).

The features of G4 and management strategies for patients infected with this genotype are not equally easily developed as for genotypes 1, 2, and 3 (2).

Telaprevir (TVR), an orally bioavailable inhibitor of the nonstructural 3/4A HCV protease (2), combined with pegylated interferon plus ribavirin (PEG-IFN/RBV) substantially improved rates of sustained virologic response (SVR) in patients who were treated previously for HCV infection (7,8).

In patients infected with HCV G4, triple-combination with TVR had better results compared to PEG-IFN/RBV dual therapy (9).

For G4 HCV patients in whom SVR is not achieved with PEG-IFN/RBV, re-treatment options are limited to re-exposure to the same medications, with potential modification of the dose or duration of the regimen.

It was proposed to assess efficacy, safety and side effects of triple therapy and especially TVR in our HCV patients who were diagnosed with G4 (subtype 4d) and previously received PEG-IFN/RBV treatment.

This was an uncommon clinical trial to evaluate the antiviral activity of TVR in G4 HCV-infected patients.

Materials and Methods

Patients

This retrospective study consisted of 12 patients who were followed up in our clinic between January 2013 and February 2014. Patients, who were anti-HCV- and HCV RNA-positive and presented with the signs and symptoms of chronic hepatitis diagnosed by liver biopsy, were included in the study. All the patients were infected with HCV alone. No other accompanying infectious diseases were found. Liver biopsies were scored with reference to the ISHAK staging system (10). Those with F4-5 fibrosis were considered having cirrhosis. Patients classified as child-pugh B and C were considered as having cirrhosis.

We considered TVR in combination with PEG-IFN alpha-2a or 2b plus RBV in patients who had relapse after an initial response and not responded or partially responded to previous therapy. The results of TVR plus PEG-IFN/RBV treatment were recorded at baseline, 4th rapid virological response (RVR), 12th early virological response (EVR), 4th through 12th (eRVR) and 24th and 48th week [end of treatment viral response (EOTVR)] virologic response and SVR after 24th week at the end of treatment.

The study were retrospective, at the same time ethical approval is expected for the meeting by the Erciyes University of Local Ethics Committee.

Results

The mean age of the patients was 55±10.8 years (range: 31-73). Among HCV patients infected with HCV G4, the diagnosis was confirmed by a liver biopsy before screening for the study. Four patients with compensated liver cirrhosis were eligible. All treatments were discontinued in patients with a decrease in HCV ribonucleic acid (RNA) level of less than 2 log10 from baseline to week 12. Only one patient had no EVR, and his treatment was stopped. Eleven patients completed their treatment. The demographic characteristics of patients are shown in Table 1.

Responses of the patients are shown in Table 2. SVR was achieved in 50% of patients (6 out of 12).

The number of prior relapsers was 8, and the SVR rate among them was 75% (6 out of 8). One of these patients showed an improvement between the 20th and 24th weeks of treatment. This patient had no RVR, but he had only EVR. One of the relapsers had no RVR, EVR and SVR.

Four patients were non-responders to previous therapy and two of them had RVR and entecavir, but they had an improvement between the 20th and 24th weeks of treatment. SVR was not achieved in any of the nonresponders. One of these patients died because of liver failure at the 20th week of treatment. He had RVR, eRVR and EVR, but liver decompensation occurred in this patient (Figure 1).

Discussion

G4 HCV is uncommon in the U.S. and Europe, although this genotype is most prevalent in Middle East and North Africa. G4 HCV was classified as "difficult-to-treat," because it had not been extensively studied in clinical trials of protease inhibitor therapies formerly (11,12). In a study performed in Kayseri, G4 was observed in 24 of 100 patients (13), and the suboptimal SVR rates achieved with Peg-IFN/RBV in a study done by Kamal and Nasser (2).

Table 1. Demographic characteristics of the patients

Age (mean ± SD)	55±10.8
Gender	
Male	5 (42%)
Female	7 (58%)
Cirrhosis	4 (33%)
Relapse	3 (75%)
Nonresponder/partial responder	1 (25%)
Previous therapy	
Naïve	None
Relapse	8 (67%)
Nonresponder/partial responder	4 (33%)
Baseline HCV RNA (log10 IU/mL) minumum-maximum	5.76±0.6 (4.75-6.72)

SD: Standard deviation, HCV: Hepatitis C virus, RNA: Ribo nucleic acid

However, recently, there are some studies about protease inhibitor used in G4 HCV-infected patients. In these studies, SVR was achieved with ledipasvir in combination with sofosbuvir or ombitasvir, paritaprevir and ritonavir in about 90% of subjects. However, it is not possible to reach these new drugs in all countries.

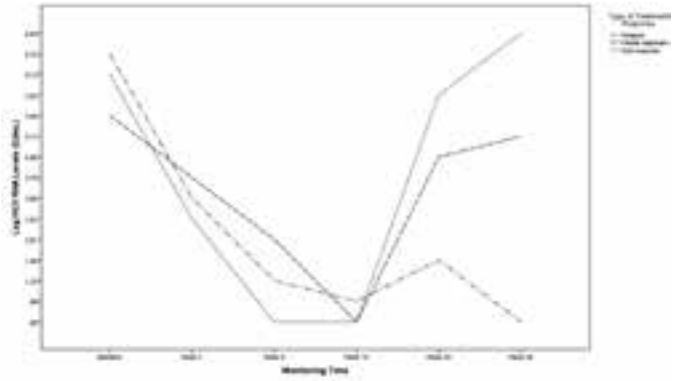

Figure 1. Type of treatment response

Table 2. Response rates of all of the patients	
Previous relapsers	
Undetectable viral load at 4th week (RVR)	6/8 (75%)
Undetectable viral load at 4th through 12th (eRVR)	6/8 (75%)
Undetectable viral load at 12th week (EVR)	6/8 (75%)
End of treatment viral response	6/8 (75%)
Viral response after the end of treatment's 24th week (SVR)	
All patients	6/8 (75%)
Patients with undetectable viral load at 4th week	6/6 (100%)
Patients with bridging fibrosis or cirrhosis‡	2/3 (66%)
Virologic failure	2/6 (33%)
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	2/4 (50%)
Viral response after the end of treatment's 24th week (SVR)	
All patients	0/4 (0%)
Patients with undetectable viral load at 4th week	0/2 (0%)
Patients with bridging fibrosis or cirrhosis	0/1 (0%)
Virologic failure	4/4 (100%)

Several studies indicate that in G1 HCV patients who were treated with protease inhibitors-based triple drugs, SVR rates were higher than in those who received Peg-IFN/RBV treatment (8). In a study which included HCV patients with G4, triple-combination therapy with TVR had better results compared to PEG-IFN/RBV therapy. Antiviral activity was found to be higher in the triple-combination group compared to the other groups (9). In our cities a study conducted by Aygen et al. (14), nine patients who had G4 HCV were evaluated. These patients had undetectable HCV RNA levels at 24th week. In this study, SVR rates were not evaluated, but EOTVR response rate was found to be 80.2%.

In our study, the SVR was 50% (6 out of 12). SVR rates were higher in patients who achieved RVR and eRVR during treatment. RVR and eRVR rates may indicate if the patient will achieve SVR with this treatment.

Moreover, the SVR was higher in relapsers than in nonresponders. Most of the relapsers (75%; 6 out of 8) achieved SVR. All SVR-achieved relapsers achieved RVR and eRVR as well. Although 2 out of 4 nonresponders achieved RVR and eRVR, SVR could not be obtained in those patients. On 12th weeks of treatment, 11 patients had undetectable HCV RNA levels. Five patients showed improvement over the 20th week.

The determination of HCV genotypes and subtypes is very important to indicate the response to antiviral therapy (5,6).

With the introduction of specific HCV-1 protease inhibitors boceprevir and TVR in 2011, HCV-4 became the "most difficult to treat" genotype especially in patients previously treated with partial responder (15,16). All patients who included in our study were G4d (13).

Conclusion

Although this study was with a small sample size, it has showed that TVR plus PEG-IFN/RBV has highly antiviral activity (SVR: 50%) against HCV G4 in relapsers and nonresponders to standard therapy. This treatment may be preferred in patients who have relapse after standard therapy.

This triple treatment can attain SVR better than standard therapy but the combination treatment could lead to some serious side effects from interferon and ribavirin. Recently, there have been profound changes in the treatment of hepatitis C. New medicines are quite successful and have fewer side effects, and they are promising drugs for overcoming the disease (17). However it is not always possible for everyone to reach these drugs. TVR treatment should be considered when other drugs can not be reached.

Ethics

Ethics Committee Approval: The study were retrospective, at the same time ethical approval is expected for the meeting by the Erciyes University of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Zehra Beştepe Dursun, Concept: Zehra Beştepe Dursun, Design: Zehra Beştepe Dursun, İlhami Çelik, Data Collection or Processing: Zehra Beştepe Dursun, Analysis or Interpretation: Zehra Beştepe Dursun, İlhami Çelik,

Literature Search: Zehra Beştepe Dursun, Writing: Zehra Beştepe Dursun.

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

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