Telaprevir Experience From Turkey

Suheyla Komur 1,*; Behice Kurtaran 1; Ayse Seza Inal 1; Husnu Pullukcu 2; Aslihan Ulu 1; Ferit Kuscu 1; Tansu Yamazhan 2; Yesim Tasova 1; Hasan Salih Zeki Aksu 1

1 Department of Infectious Diseases, Cukurova University, Adana, Turkey
2 Department of Infectious Diseases, Ege University, Izmir, Turkey
3 Numune Training and Research Hospital, Adana, Turkey
*Corresponding Author: Suheyla Komur, Department of Infectious Diseases, Cukurova University, Adana, Turkey. Tel: +90-5052677498, Fax: +90-3223387664, E-mail: skomur@gmail.com

Received: November 27, 2014; Revised: January 8, 2015; Accepted: January 22, 2015

1. Background

Chronic hepatitis C virus (HCV) infection affects approximately 3% of the population and is a major cause of liver cancer, cirrhosis and hepatocellular carcinoma worldwide (1, 2). Dual therapy with peginterferon and ribavirin has been regarded as the standard regimen for patients with genotype 1 chronic hepatitis C (CHC) for a decade (3, 4). Triple drug regimens (TDR) containing a protease inhibitor, peginterferon-α and ribavirin were found to significantly increase sustained virologic response rates compared to standard dual drug regimen, especially in genotype 1 (5). In Turkey, telaprevir has been used since March 2013 and created great excitement for treatment-experienced patients. The data regarding this therapy is being newly reported in our country.

2. Objectives

We aimed to evaluate the efficacy of telaprevir-based TDR in relapse or non-responder patients.

3. Patients and Methods

We evaluated 28 patients with genotype 1 CHC treated with telaprevir based TDR, in three medical centers in Turkey, retrospectively. Demographic data of patients, virological response and treatment outcomes were analyzed.

3.1. Treatment

Telaprevir was administered every eight hours after meals. Ribavirin dosage was adjusted according to body-weight (1000, 1200 mg for ≤ 75 kg and > 75 kg, respectively). Nineteen patients (76%) received Peginterferon-α-2a and six patients received Peginterferon-α-2b. Treatment
was discontinued for patients with HCV-RNA > 1000 IU/mL at week 4, detectable HCV-RNA at week 12 or a more than 2 log10 IU/mL increase in HCV-RNA levels from the lowest level during therapy. In addition, all antivirals stopped if a serious adverse event occurred.

4. Results

Of 28 patients intended to treat, 25 (89.2%) patients completed the treatment. One patient discontinued treatment due to unresponsiveness since eight week. In two patients, all antivirals were stopped due to severe rash and detection of hepatocellular carcinoma in 7th and 13th weeks, respectively. Since these two patients did not complete the treatment, 26 patients were included in the analysis of virological outcomes and adverse effects.

The mean age of patients was 54.7 ± 11.1 (29-70) years and 69.2% (18) were male. Overall, 21 (80.7%) patients had relapse and five patients were non-responder. All patients were genotype 1. Twelve patients had liver biopsy. Of 12 patients with biopsy results, one patient had compensated cirrhosis. The mean histologic activity index was 8.2 (5-12) and fibrosis score was 2.1 (1-4) according to the Ishak fibrosis score. The mean value of baseline HCV-RNA was 1965202 (90400 - 7890000) IU/mL. RVR and EVR were detected in all patients except one. In patients with HCV-RNA > 1000 IU/mL at week 4, therapy was discontinued. In 21 patients, HCV-RNA had negative results in 4th week of treatment, positive but ≤ 50 IU/mL in other four patients, so these four patients were treated for 48 weeks. Regarding the treatment outcomes of Telaprevir based TDR, 20/26 (76.9 %) patients achieved SVR and 5/26 patients had relapse. The SVR rates for relapsers and non-responders were similar. In addition, gender, treatment durations, HCV-RNA, fibrosis score and ALT levels were similar between patients who achieved SVR and those who did not.

4.1. Adverse Events

Data about adverse events was recorded during the therapy. One patient presented with a severe maculopapular, so that her therapy was discontinued at seventh week of her therapy. At least one adverse effect was reported in all patients. Pruritus, rash, dysgeusia and anorectal discomfort were main adverse effects. Anemia (57.7%), leukopenia (38.4%) and thrombocytopenia (26.9%) were common hematological adverse effects. Blood transfusion was required for seven patients. Ribavirin dose reduction was performed in 11 patients. Due to several adverse effects such as anemia, thrombocytopenia, severe pruritus, rash and anorectal discomfort, 10 patients were hospitalized and four had to break treatment for a few days.

5. Discussion

This study was the first report from Turkey including Telaprevir based TDR results. The enhanced therapeutic efficacy with combination of telaprevir and standard therapy has been demonstrated in several randomized multicenter trials in patients with genotype 1 CHC (6, 7). In our country, SVR rates reported between 41.2 - 64.4% with standard HCV treatments (8) and our SVR rates with telaprevir based TDR was higher in this study. Our results were similar to other trials (6, 7). Our clinical experience in treating patients with cirrhosis with telaprevir based TDR was limited. Only one patient with compensated cirrhosis was treated and achieved SVR. In PROVE 3 study, response rates were higher in patients with relapse than nonresponders (6). In our study, SVR rates in relapers and nonresponders were similar, but this could be due to our small sample size.

A multicenter study reported that SVR rate was significantly higher with 48 weeks than 24 weeks therapy in nonresponders (9). In Turkey, the duration of Telaprevir based TDR is 24 weeks; first 12 weeks all three agents and peginterferon and ribavirin for the remaining 12 weeks. Totally, 48-week treatment is recommended for patients not achieved RVR. For this reason, treatment of our four patients with a positive RNA at fourth week was extended to 48 weeks.

Treatment response is influenced by several factors related to the virus (genotype and viral load) or host (fibrosis, age, gender, body weight, duration of the infection) (4). There was no association between SVR and gender, mean HCV-RNA/ALT levels and fibrosis. However, our small sample size might provide inadequate statistical analysis.

In clinical trials, increased serious cutaneous adverse events have been reported with Telaprevir based TDR (10). In literature, pruritus, eczematous or cutaneous eruption is observed in 56%; besides, severe cutaneous adverse reactions were reported in 3.7% of patients. Pruritus and rash were found in 65.4% and 26.9% of our patients, respectively. Rash was most often observed within the first 4 - 6 weeks, reported in literature (11). In telaprevir phase III trials, the rate of discontinuation of antiviral drugs due to skin manifestation was low (6). In our study, only one patient presented with generalized rash in the seventh week of treatment and her treatment was stopped. In the management of dermatological adverse effects, education of patient about good skin care practices is important. In case of severe cutaneous reaction, discontinuation is strongly recommended. Cutaneous and systemic symptoms usually improve after discontinuation and support care (6, 7, 11). All of our patients with skin disorders, except one, were able to continue treatment using topical corticosteroid and oral antihistamine therapy.

Telaprevir based TDR appears to increase the frequency and severity of anemia. In ADVANCE and PROVE 1 trials, anemia was more common in the Telaprevir arms than the control; however, anemia was transient and resolved after discontinuation of Telaprevir (12, 13). In our study, anemia was a common adverse effect, but rapidly reversed in all patients when Telaprevir discontinued after 12 weeks.

Blood transfusions and reductions in ribavirin doses
not less than 600 mg/gun were applied. We found no association between SVR and anemia or ribavirin dose reduction. ADVANCE and ILLUMINATE trials reported that ribavirin dose reduction did not appear to affect SVR rates (13, 14). Telaprevir was generally well tolerated, but hospitalization during treatment period was required for 10 patients. Patients were hospitalized due to severe or symptomatic anemia, rash or impaired general condition and close follow-up of adverse effects. The hospitalization rate seems higher according to general practice in CHC treatments (15).

Telaprevir has been promising for difficult to treat patients with CHC. In most of these patients, curative results were obtained. Our findings suggested that despite more severe and frequent adverse effects of Telaprevir, successful results can be obtained by close follow-up.

Acknowledgements
The authors wish to thank our nurse Mrs Havva Ozkilic for her excellent assistance in collecting patients’ data.

Authors’ Contributions
Study concept and design: S. Komur. Acquisition of data: S. Komur, B. Kurtaran, H. Pullukcu and F. Kuscu. Analysis and interpretation of data: A. Ulu and AS. Inal. Drafting of the manuscript: S. Komur and H. Aksu. Critical revision of the manuscript for important intellectual content: T. Yamazhan and Y. Tasova. Statistical Analysis: A. Ulu and AS. Inal. Study supervision: S. Komur, B. Kurtaran and F. Kuscu.

References
1. Lavanchy D. The global burden of hepatitis C. Liver Int. 2009;29 Suppl 1:74–81.
2. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis. 2000;20(1):37–55.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2011;55(2):245–64.
4. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. American Association for Study of Liver D. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(4):1433–44.
5. Park C, Jiang S, Lawson KA. Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: a meta-analysis. J Clin Pharm Ther. 2014;39(1):14–24.
6. McHutchison JG, Manns MP, Murr AJ, Terrault NA, Jacobson IM, Afdhal NH, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010;362(14):1292–303.
7. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364(25):2407–28.
8. Akinci E, Ünal Kayaaslan B, Tanrıci BaşıBuğ A, Surri Eren S, ÖnçüRGÜ P, Bodur H. Genotip 1iko Kronik Hepatit C Hastalarında Kalıcı Virolojik Yanıtın Değerlendirilmesi. Viral Hepatit Dergisi. 2013;19(2):80–4.
9. Shimada N, Suhota A, Atsukawa M, Abe H, Ide T, Takaguchi K, et al. A 48-week telaprevir-based triple combination therapy improves sustained virological response rate in previous non-responders to peginterferon and ribavirin with genotype 1b chronic hepatitis C. A multicenter study. Hepatol Res. 2014;44(4):3386–96.
10. Chopra A, Klein PL, Drinnan T, Lee SS. How to optimize HCV therapy in genotype 1 patients: management of side-effects. Liver Int. 2013;33 Suppl 1:30–4.
11. Cacoub P, Bourlhere M, Lubbe J, Dupin N, Buggisch P, Dusheiko G, et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. J Hepatol. 2012;56(2):455–63.
12. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski MS, Everson GT, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009;360(18):1827–38.
13. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Rzwej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(4):1433–44.
14. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(1):1024–24.
15. Maaouny B, Port K, Markova AA, Serrano BC, Rogalska-Taranta M, Sollik I, et al. Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. PLoS One. 2013;8(2).