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Telaprevir Experience From Turkey

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Background: In patients with chronic hepatitis C, triple drug regimens containing a protease inhibitor, peginterferon and ribavirin were found to significantly increase sustained virologic response rates compared to dual drug regimen containing pegylated interferon and ribavirin, especially in genotype 1.
Objectives: In Turkey, telaprevir has been used since March 2013. We aimed to evaluate results of patients with chronic hepatitis C treated with telaprevir, peginterferon and ribavirin.
Patients and Methods: We evaluated 28 patients with genotype 1 chronic hepatitis C infection treated with triple drug regimen containing telaprevir, in three medical centers in Turkey, retrospectively. Demographic data of patients, treatment indications, adverse events and outcomes were recorded.
Results: Of 28 patients intended to treat, 25 (89.2%) patients completed the treatment. Overall, 21 (82.1%) patients had relapse and five patients were non-responder. Regarding the treatment outcomes of Telaprevir based regimen, 20/26 patients achieved sustained virological response. Pruritus, rash, dysgeusia, anorectal discomfort and anemia were main adverse effects. Blood transfusion and ribavirin dose reduction required for 7 and 11 patients, respectively. Due to several adverse effects, 10 patients were hospitalized.
Conclusions: Although more frequent and severe adverse effects, telaprevir has been promising for patients with treatment-experienced hepatitis C.

Keywords: Genotype 1; Hepatitis C; Telaprevir; Turkey

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, treatment indications, laboratory findings (complete blood count, AST, ALT), liver biopsy documentations and adverse effects were recorded. Standard definitions for prior treatment categories were used. HCV-RNA levels at 4, 12 and 24th weeks, virological response and treatment duration were analyzed. Rapid virological response (RVR) was defined as detection of HCV-RNA negative in fourth week and early virological response (EVR) was defined as detection of HCV-RNA negative in 12th week. End of treatment response (ETR) was defined as an undetectable HCV-RNA at completion of therapy. A sustained virological response (SVR) was defined as the absence of HCV-RNA 24 weeks after the end of treatment (3).

3.1. Treatment

Telaprevir was administered every eight hours after meals. Ribavirin dosage was adjusted according to bodyweight (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 nonresponders 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 relapsers 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 effects 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.

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Authors' Contributions

Study concept and design: S. Komur. Acquisition of data: S. Komur, B. Kurtaran, H. Pullukcu amd 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 H. Pullukcu. Administrative, technical and material supports: B. Kurtaran and AS. Inal. Study supervision: B. Kurtaran and F. Kuscu.

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