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Mini Review

Telaprevir-Based Therapy for Chronic Hepatitis C in Japan: A Summary of Clinical Study Results

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Abstract

We summarized the clinical study results of Telaprevir (TVR) in combination with peginterferon and ribavirin for Japanese patients with genotypes 1 and 2 Hepatitis C Virus (HCV) infection. The Sustained Virological Response (SVR_{24}) rates of relapsers and non-responders with genotype 1 HCV infection were 88.1% (96/109) and 34.4% (11/32), respectively. On the other hand, the SVR_{24} rates of relapsers and non-responders with genotype 2 HCV infection were 88.0% (95/108) and 50.0% (5/10), respectively. These results demonstrated that high SVR rates are achieved with TVR-based triple therapy in difficult-to-treat patients with genotype 2 as well as genotype 1 HCV infection. The majority of Japanese patients with HCV is older and has a lower weight than patients in the United States and Europe. A post-marketing surveillance study of patients with genotype 1 HCV infection showed the SVR rates of naïve patients, relapsers, and non-responders treated at a dose of 2250 mg/day and less than 2250 mg/day of TVR were as follows: 92.1% (680/738) and 90.7% (223/246) in naïve patients; 91.9% (719/782) and 88.9% (297/334) in relapsers; and 74.8% (243/325) and 60.4% (81/134) in non-responders, respectively. These results suggest that the lower dose regimen of TVR maybe a treatment alternative in older and lower weight Japanese patients.

Keywords: Telaprevir; Hepatitis C virus; Genotype 1; Genotype 2; Sustained virological response; Japanese patient

Abbreviations

TVR: Telaprevir; Peg-IFN: Peg Interferon alfa-2b; RBV: Ribavirin; DAA: Direct Acting Antiviral; HCV: Hepatitis C Virus; SVR: Sustained Virological Response; RVR: Rapid Virological Response; ETR; End-Of-Treatment Response

Introduction

Hepatitis C Virus (HCV) is estimated to infect approximately 185 million people worldwide. In Japan, there are estimated to be about 2 million HCV carriers. Genotype 1b and genotype 2 accounts for approximately 70% and 30% of chronic HCV infections in Japan, respectively. In 2011, the first-generation direct-acting antiviral agent Telaprevir (TVR) with Peg Interferon (Peg-IFN) and Ribavirin (RBV) was approved for treatment of chronic HCV genotype 1 patients in the United States and Europe. In Japan, TVR was approved in September 2011 and has been marketed since November 2011. Furthermore, in September 2014, only in Japan, TVR for 12 weeks plus Peg-IFN and RBV for 24 weeks (T12/PR24) was approved for patients with genotype 2 HCV infection who experienced relapses or were non-responders to a prior IFN-based regimen. Recently, a number of Direct Acting Antiviral Agents (DAAs) (second-generation protease inhibitors, NS5B polymerase inhibitors, and NS5A inhibitors) are being studied in advanced clinical trials, and some DAAs have been marketed. These DAAs have a different resistance profile from the first-generation protease inhibitor TVR. We summarized the clinical study results of T12/PR24for Japanese patients with genotypes 1 and 2 HCV infection.

Clinical study results

The patients were excluded if they had cirrhosis. In treatment-naïve patients with genotype 1 HCV infection, Sustained Virological Response (SVR_{24}) was achieved more frequently withT12/PR24 than with Peg-IFN and RBV for 48 weeks (PR48) (73.0% vs. 49.2%, P=0.0020) [1]. Relapsers were defined as patients who had been previously treated for Chronic Hepatitis C (CHC) and had undetectable HCV RNA during IFN or Peg-IFN therapy (including combination with RBV). Non-responders were defined as patients who were previously treated for CHC and had never had undetectable HCV RNA for more than 24 weeks with IFN or Peg-IFN therapy (including combination with RBV).The SVR_{24} rates in relapsers and non-responders with genotype 1 HCV infection were 88.1% (96/109) and 34.4% (11/32), respectively [2]. The SVR_{24} rates for the treatment-naïve patients and non-responders who received more than the 40% RBV cumulative dose were 80.6% (54/67) and 45.5% (10/22), respectively [1, 2]. The SVR_{24} rate for the relapsers who received more than the 20% RBV cumulative dose was 92.8% (90/97) [2]. Anemia and skin disorder were frequent adverse events that led to discontinuation of all the study drugs. Discontinuation rates of all the study drugs due to anemia and skin disorder were 7.5% (20/267) and 4.5% (12/267) in T12/PR24, and 4.8% (3/63) and 3.2% (2/63) in PR48, respectively [1,2]. The SVR_{24} rates for relapsers and non-responders with genotype 2 HCV infection were 88.0% (95/108) and 50.0% (5/10), respectively. The SVR_{24} rates after completing the treatment protocol for relapsers and non-responders were 98.4% (61/62) and 100% (5/5), respectively. The SVR_{24} rates did not differ significantly between patients with rs8099917 TT and non-TT [3]. The overall safety profiles of TVR-

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Table 1: Comparison of telaprevir-based therapy results in patients with Genotype 1 and 2 HCV infection [2,3].

	Genotype 1		Genotype 2	
	Relapsers	Non-responders	Relapsers	Non-responders
	N = 109	N = 32	N = 108	N = 10
Baseline characteristics				
Men, n (%)	66 (60.6)	17 (53.1)	53 (49.1)	8 (80.0)
Age (years), median (range)	57.0 (20–65)	57.5 (40–65)	59.0 (29–65)	59.0 (46–65)
Weight (kg), median (range)	62.50 (41.0–92.5)	61.30 (44.9–92.5)	60.45 (40.8–111.1)	67.15 (53.3–103.2)
Hemoglobin (g/dL), median (range)	14.70 (12.0–17.8)	14.50 (12.3–16.6)	14.20 (12.0–18.0)	14.95 (13.6–15.9)
Efficacy				
RVR n/N (%)	95/109 (87.2)	23/32 (71.9)	94/108 (87.0)	7/10 (70.0)
ETR n/N (%)	103/109 (94.5)	19/32 (59.4)	102/108 (94.4)	6/10 (60.0)
SVR n/N (%)	96/109 (88.1)	11/32 (34.4)	95/108 (88.0)	5/10 (50.0)
SVR by study drug discontinuation, n/N (%)				
No discontinuation	65/69 (94.2)	9/20 (45.0)	61/62 (98.4)	5/5 (100)
Telaprevir only	19/20 (95.0)	2/7 (28.6)	21/23 (91.3)	0/1 (0.0)
All study drugs	12/20 (60.0)	0/5 (0.0)	13/23 (56.5)	0/4 (0.0)

Sustained Virological Response (SVR) was defined as undetectable hepatitis C virus RNA, 24 weeks after treatment completion. RVR: Rapid Virological Response, ETR: End-Of-Treatment Response, HCV: Hepatitis C Virus.

based regimens were similar for Japanese patients with genotype 1 and 2 HCV infection who experienced treatment failure.

Post-marketing findings in patients with genotype 1 HCV infection

The majority of Japanese patients infected with HCV is much older and have a lower weight than Western patients. A randomized controlled trial by Kawakami et al. [4] confirmed that a dose reduction of TVR therapy (1500mg/day, 750mg every 12 hours) is as effective as the approved regimen (2250mg/day, 750mg every 8 hours) in genotype 1 patients. SVR_{12} rates were 92.3% in both regimens. Safety results regarding anemia and renal damages were improved with 1500mg/day compared with 2250mg/day. Therefore, the frequency of TVR discontinuation due to anemia or renal damage was notably lower with1500mg/day than 2250mg/day (0% and 23%, respectively). Adherence to Peg-IFN and RBV treatment was higher with 1500mg/day. Oze et al. [5] also conducted a randomized trial to evaluate the antiviral efficacy and safety after administration of TVR at a dose of 2250 mg/day or 1500mg/day with Peg-IFN and RBV. SVR_{12} rates were 85% in both groups. Regarding safety, more than moderate rash, severe anemia, increase in serum creatinine levels, and decrease in estimated glomerular filtration rate were lower with 1500mg/day than with 2250mg/day. Consequently, the rate of TVR discontinuation was lower with 1500mg/day. A post-marketing surveillance study reported the SVR rates of naïve patients, relapsers, and non-responders treated with 2250 mg/day and less than 2250 mg/day of TVR as follows: 92.1% (680/738) and 90.7%(223/246) in naïve patients; 91.9% (719/782) and 88.9% (297/334) in relapsers; and 74.8% (243/325) and 60.4% (81/134) in non-responders, respectively [6]. The TVR dose of 2250 mg/day is one of the risk factors for Grade 3 anemia and serious renal dysfunction. These results suggest that a TVR regimen of 1500mg/day or less than 2250 mg/day is an effective and safe alternative for the treatment of elderly and low bodyweight Japanese genotype 1 HCV patients. In the case of genotype 2 treatment failure patients, greater effectiveness and safety of TVR triple therapy are suggested in the post-marketing surveillance study than in clinical study results.

Conclusion

A TVR-based regimen is an effective treatment option for Japanese patients with genotype 1 as well as genotype 2 HCV infection who previously experienced treatment failure. The severe adverse events could be avoided by TVR dose reduction. In addition, the administrated TVR regimen of 1500mg/day or less than 2250 mg/day has a similar SVR rate compared with the 2250-mg/day regimen in elderly (>65) and low bodyweight Japanese genotype 1 HCV patients.

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