Regular Article

The Safety Profile of Telaprevir-Based Triple Therapy in Clinical Practice: A Retrospective Cohort Study

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This study was designed to evaluate the safety profile of adding telaprevir to therapy using pegylated interferon-alfa-2b and ribavirin (PR) using real world patient data obtained from a nationwide Japanese interferon database. This retrospective cohort study compared telaprevir-based triple therapy (T/PR) with PR therapy. The study population comprised patients with genotype 1 chronic hepatitis C represented in the database between December 2009 and August 2015. The primary endpoint was dropout from treatment due to adverse events during the relevant standard treatment duration based on guidelines from the Japan Society of Hepatology. The dropout odds ratio (OR) and 95% confidence interval (95% CI) were calculated using univariate logistic regression analysis. Covariates were detected using a stepwise logistic regression analysis, and the adjusted OR and 95% CI were calculated. A total of 25989 patients were registered, and 4619 patients (T/PR: 1334, PR: 3285) were appropriate for primary endpoint analysis. The dropout rate due to adverse events was lower in the T/PR group (13.4%) than in the PR group (22.6%) (OR: 0.530; 95% CI, 0.444–0.633). After adjustment for the covariates detected by stepwise selection, the OR was 0.529 (95% CI, 0.441–0.634). Our study showed that there was a difference in dropout rate between real world T/PR and PR therapy in Japan. Although the addition of telaprevir to PR therapy may improve treatment continuity under the care of hepatologists, this study could not fully determine which therapy was safer or the factors influencing this result. Therefore, additional research will be required to confirm this.

Key words telaprevir; real world database; hepatitis C; retrospective cohort study; interferon; ribavirin

About 130–150 million people are infected with the hepatitis C virus (HCV) worldwide, and approximately 700000 people die annually of liver diseases related to HCV infection.[1)] Pegylated interferon-alfa and ribavirin (PR) have been used to treat chronic HCV for more than a decade.[2)] Recently, the development and approval of direct-acting antiviral agents (DAAs) have dramatically changed antiviral therapy against HCV. Telaprevir is a first-generation NS3/4A viral protease inhibitor that has been used in combination with pegylated interferon-alfa-2b and ribavirin (T/PR) for genotype 1 chronic hepatitis C since 2011. This has increased the sustained virologic response (SVR) to 60–70%, as compared with the 40–50% achieved with PR therapy.[3,4)] Furthermore, this approach has enabled the use of shorter therapies (24 weeks), in contrast to the 48 weeks required for PR therapy. A new treatment has also been developed using a combination of DAA agents without PR. This interferon-free therapy has achieved SVR levels of over 90%.[5–7)] Consequently, T/PR therapy for the treatment of chronic HCV has been replaced by interferon-free therapy. However, HCVs possessing variant proteins that are resistant to some DAAs have been identified, and this has led to treatment failure. A previous study showed that T/PR therapy could provide a last treatment option for patients in whom previous DAA-based treatments have failed owing to HCV resistance.[8)] Additionally, it has been suggested that combining DAA with PR was important to overcoming this problem.[9)]

Although the advantages of T/PR therapy have been recognized, HCV patients in real world settings have experienced more adverse events with this therapy than was predicted from the drug development trials.[10)] This difference between clinical experience and clinical trials may reflect the older age of the real world patients and their more advanced fibrosis.[10,11)] Additionally, although T/PR therapy has been reported to be associated with more frequent and serious adverse events than PR therapy is,[12,13)] it remains unclear whether the addition of telaprevir to PR leads to higher rates of treatment dropout in clinical practice. The shorter treatment duration may help to reduce the dropout rate. Therefore, it is essential to evaluate the safety profile of T/PR therapy in clinical practice.

The present retrospective cohort study was conducted to obtain a more detailed safety profile of T/PR therapy using a nationwide Japanese interferon database. This study compared the dropout rates during the standard treatment periods for T/PR and PR therapy.

METHODS

Study Design A retrospective cohort study was performed using a nationwide database consisting of standardized case report forms collected from 38 local governments across Japan between December 2009 and August 2015. The database contained information from hepatitis B virus (HBV) and HCV-infected patients who had received a medical expense subsidy for interferon therapy that commenced in April 2008 or later. The available information included the following: sex, date of birth, age, interferon treatment duration, treatment experience, diagnosis, drug use, HCV serotype or/and geno-

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type, serum HCV RNA level, SVR rate (complete response, relapse, or ineffective), adverse events, and blood test results (alanine aminotransferase [ALT] level, aspartate aminotransferase level, and platelet count). Serum HCV RNA levels were quantitated using a Cobas® Amplicor HCV Monitor, version 2.0 (Roche Molecular Systems, Pleasanton, CA, U.S.A.) or a Cobas® TaqMan HCV Test (Roche Molecular Systems).

The study protocol was approved by the Ethics Committee of the National Center of Global Health and Medicine of Japan (No. 738; October 1, 2009), and performed in accordance with the Declaration of Helsinki.

Case Definition The study included patients recorded in the database between December 2009 and August 2015 who had genotype 1 chronic hepatitis C and were treated with T/PR or PR. Patients were excluded from the study if they had an HCV genotype other than 1, were infected with HBV only, had cirrhosis, were treated with a therapy other than T/PR or PR, were younger than 16 years, or dropped out for reasons other than adverse events; patients lacking a complete set of data were also excluded.

Study Endpoints The primary endpoint was dropout from the treatment due to adverse events occurring during the relevant standard therapy period, which was 24 weeks for T/PR therapy and 48 weeks for PR therapy. The secondary endpoints were dropout from the treatment due to adverse events occurring within 12 weeks (period 1), between 13 and 24 weeks (period 2), between 25 and 48 weeks (period 3), after 48 weeks (period 4), and within all of these periods (period 1+2+3+4). These periods were selected because T/PR therapy involved the administration of all three drugs for the first 12 weeks followed by dual drug therapy (without telaprevir) for the final 12 weeks,[3,4] while PR therapy was continued for 48 weeks.[2] The database classified the reason for dropout into 9 common categories: malaise, interstitial pneumonia, cerebral hemorrhage, anemia, anorexia, thrombocytopenia, psychoneurosis, retinopathy, and any other reason. The number of dropouts during each time period for each reason was analyzed.

Statistical Analysis Descriptive statistics were calculated, including the mean and standard deviation (S.D.) of continuous variables, and the number and percentage (%) for categorical variables. The odds ratios (OR) for dropout, 95% confidence intervals (95% CI), and p values were calculated using univariate logistic regression analysis.[14] Covariates for dropout were identified using a stepwise selection method in which terms were selected and eliminated if they reached the 0.150 level of significance. Each continuous variable (age, platelet count, ALT level) was classified into two levels by following the guidelines of The Japan Society of Hepatology before identification.[15] The following variables were assessed using this stepwise selection method: age ($\geq$65 years *vs.*$<$65 years); sex (male *vs.* female); platelet count ($<15\times10^4/\mu$L *vs.* $\geq15\times10^4/\mu$L); ALT level ($\geq$30 IU/L *vs.*$<$30 IU/L); HCV viral load (high [$\geq$5.0 logIU/mL or $\geq$100 KIU/mL] *vs.* low [$<$5.0 logIU/mL or $<$100 KIU/mL]); and treatment experience (re-treatment *vs.* initial). Adjusted ORs were calculated using multivariate logistic regression analysis.[14] Logistic model performances were evaluated using the Hosmer–Lemeshow test.[14] p values of less than 0.050 were considered to indicate statistical significance.

All statistical analyses were conducted using SAS software, version 9.4 for Windows (SAS institute Inc., Cary, NC, U.S.A.).

RESULTS

Patient Characteristics Figure 1 shows a patient identification flow diagram. A total of 25989 patients were included in the database between December 2009 and August 2015. Of these patients, 18092 were excluded for the following reasons: 10242 were infected with an HCV genotype other than 775 were infected with HBV alone, 1060 had cirrhosis, 10780 were not treated with T/PR or PR, 9 were younger than 16 years, 1801 dropped out owing to reasons other than adverse events, and 2236 lacked essential data. These exclusions also included duplicate entries for some patients. The remaining 7867 patients were appropriate for inclusion in the analysis of each secondary endpoint. Of these, 3248 were excluded because they had treatment durations $>$24 weeks in the T/PR group or $>$48 weeks in the PR group. Finally, 4619 met the criteria for evaluation of the primary endpoint. The baseline characteristics of these patients are presented in Table 1.

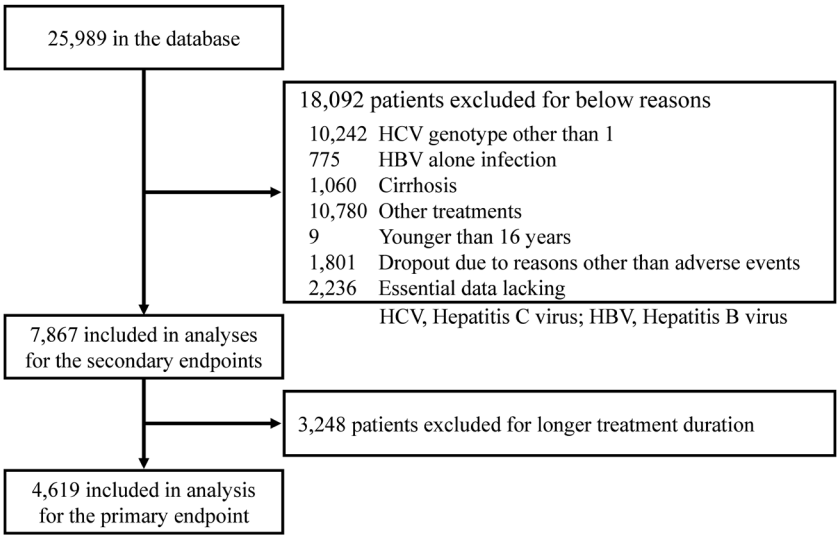

Fig. 1. Flow Diagram for Study

The Primary Endpoint and Multivariate Logistic Regression Analysis The rate of treatment dropout due to adverse events occurring during the standard therapy duration was 13.4% in the T/PR therapy group and 22.6% in the PR therapy group (OR, 0.530; 95% CI, 0.444–0.633; $p<0.001$). The stepwise selection method identified the following covariates: age (adjusted OR, 2.075; 95% CI, 1.780–2.420; $p<0.001$); sex (adjusted OR, 1.570; 95% CI, 1.353–1.821; $p<0.001$); platelet count (adjusted OR, 1.235; 95% CI, 1.063–1.435; $p=0.006$); and HCV viral load (adjusted OR, 2.250; 95% CI, 1.502–3.370; $p<0.001$) (Table 2). After adjusting for these covariates, the OR for the primary endpoint was 0.529 (95% CI, 0.441–0.634; $p<0.001$). The Hosmer–Lemeshow test showed a good fit for this model ($p=0.589$).

Table 1. Clinical Characteristics

	T/PR	PR
N	1334	3285
Age, years (mean±S.D.)	57.50±10.00	58.52±10.15
≥65, *n* (%)	329 (24.7)	1017 (31.0)
Treatment duration, weeks (mean±S.D.)	21.00±5.93	39.19±13.28
Sex (male), *n* (%)	752 (56.4)	1795 (54.6)
Platelet count, $\times10^4/\mu$L (mean±S.D.)	16.56±5.34	16.68±5.54
<15, *n* (%)	578 (43.3)	1386 (42.2)
ALT, IU/L (mean±S.D.)	64.90±53.22	70.99±61.32
≥30, *n* (%)	1029 (77.1)	2682 (81.6)
Treatment experience, *n* (%)		
Initial	643 (48.2)	2582 (78.6)
Re-treatment	687 (51.5)	674 (20.5)
Unknown	4 (0.3)	29 (0.9)
HCV viral load, *n* (%)		
High (≥5.0 logIU/mL or ≥100 KIU/mL)	1294 (97.0)	3063 (93.2)
Low (<5.0 logIU/mL or <100 KIU/mL)	40 (3.0)	222 (6.8)

The serum HCV RNA level was quantitated using the Cobas® Amplicor HCV Monitor, version 2.0 (Roche Molecular Systems, Pleasanton, CA, U.S.A.) or Cobas® TaqMan HCV Test (Roche Molecular Systems). T/PR, telaprevir+pegylated interferon-alfa-2b+rivabirin; PR, pegylated interferon-alfa-2b+rivabirin; ALT, alanine amino transferase; HCV, hepatitis C virus; S.D., standard deviation.

The Secondary Endpoints and Multivariate Logistic Regression Analyses In period 1, the OR for dropout was 0.274 (95% CI, 0.109–0.687; $p=0.006$). The covariates were not identified by the stepwise selection method in period 1. In period 2, the OR for dropout was 0.025 (95% CI, 0.017–0.037; $p<0.001$). After adjusting for the covariates identified by the stepwise selection method, the OR was 0.019 (95% CI, 0.013–0.029; $p<0.001$). In period 3, the OR for dropout was 0.283 (95% CI, 0.149–0.539; $p<0.001$). After adjusting for the covariates identified by the stepwise selection method, the OR was 0.261 (95% CI, 0.137–0.498; $p<0.001$). In period 4, the OR for dropout was 0.729 (95% CI, 0.099–5.353; $p=0.756$). After adjusting for the covariates identified by the stepwise selection method, the OR was 0.763 (95% CI, 0.103–5.647; $p=0.791$). In all of these periods, the OR for dropout was 0.822 (95% CI, 0.695–0.972; $p=0.022$). After adjusting for the covariates identified by the stepwise selection method, the overall OR was 0.888 (95%CI, 0.745–1.060; $p=0.189$) (Table 3).

Reasons for Dropout The reasons for patient dropout during the study periods are summarized in Table 4. The most frequent reason in both study groups was "malaise," which applied to 46 patients (25.7%) in the T/PR group and 310 patients (41.7%) in the PR group. The second most frequent

Table 2. Multivariate Logistic Regression Analysis for the Primary Endpoint

Covariate	Adjusted OR for covariate (95% CI)	*p* value
Age (≥65 *vs.*<65)	2.075 (1.780–2.420)	<0.001
Sex (female *vs.* male)	1.570 (1.353–1.821)	<0.001
Platelet count(<$15\times10^4/\mu$L *vs.* ≥$15\times10^4/\mu$L)	1.235 (1.063–1.435)	0.006
HCV viral load (High *vs.* Low)	2.250 (1.502–3.370)	<0.001

Hosmer-Lemeshow p value=0.589. HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval; High HCV viral load, ≥5.0 logIU/mL or ≥100 KIU/mL; Low HCV viral load,<5.0 logIU/mL or <100 KIU/mL.

Table 3. Multivariate Logistic Regression Analyses for the Secondary Endpoints

	Covariate	Adjusted OR for covariate (95% CI)	*p* value
Period 1	None	—	—
Period 2	Age (≥65 *vs.*<65)	1.792 (1.200–2.675)	0.004
	Sex (female *vs.* male)	1.373 (0.946–1.992)	0.095
	Platelet count (<$15\times10^4/\mu$L *vs.* ≥15×10^4 /μL)	1.353 (0.928–1.972)	0.116
	HCV viral load (High *vs.* Low)	9.689 (4.433–21.174)	<0.001
Period 3	Age (≥65 *vs.*<65)	1.886 (1.473–2.415)	<0.001
	Sex (female *vs.* male)	1.644 (1.290–2.096)	<0.001
	HCV viral load (High *vs.* Low)	2.941 (1.285–6.730)	0.011
Period 4	Age (≥65 *vs.*<65)	1.565 (1.018–2.404)	0.041
	Platelet count (<$15\times10^4/\mu$L *vs.* ≥$15\times10^4/\mu$L)	1.715 (1.118–2.632)	0.014
	Treatment experience (Re-treatment *vs.* Initial)	0.625 (0.365–1.070)	0.086
All of these periods	Age (≥65 *vs.*<65)	1.932 (1.685–2.216)	<0.001
	Sex (female *vs.* male)	1.281 (1.121–1.465)	<0.001
	Platelet count (<$15\times10^4/\mu$L *vs.* ≥$15\times10^4/\mu$L)	1.211 (1.059–1.385)	0.005
	Treatment experience (Re-treatment *vs.* Initial)	0.824 (0.704–0.965)	0.016
	HCV viral load (High *vs.* Low)	1.465 (1.009–2.126)	0.045

HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval. High HCV viral load, ≥5.0 logIU/mL or ≥100 IU/mL; Low HCV viral load,<5.0 logIU/mL or <100 KIU/mL.

Table 4. Reasons for Dropout

	T/PR, *n* (%)	PR, *n* (%)
Malaise	46 (25.7)	310 (41.7)
Interstitial pneumonia	2 (1.1)	28 (3.8)
Cerebral hemorrhage	1 (0.6)	4 (0.5)
Anemia	28 (15.6)	115 (15.5)
Anorexia	41 (22.9)	183 (24.6)
Thrombocytopenia	5 (2.8)	45 (6.1)
Psychoneurosis	20 (11.2)	146 (19.7)
Retinopathy	11 (6.1)	51 (6.9)
Any other reason	112 (62.6)	305 (41.0)
Total dropout	179	743

The result includes duplicates in a same patient. T/PR, telaprevir+pegylated interferon-alfa-2b+ribavirin; PR, pegylated interferon-alfa-2b+ribavirin.

reason for dropout in both groups was "anorexia." The third was "anemia" in the T/PR group, and "psychoneurosis" in the PR group. Most dropout reasons were observed at the same frequency or more frequently in the PR group, with the exception of "any other reason," which included dermal disorders, increased uric acid levels, and kidney disorders. Some patients dropped out for more than one reason.

DISCUSSION

We conducted a retrospective cohort study in order to investigate the safety profile of telaprevir using a nationwide database. The results showed that the rate of dropout due to adverse events during the standard therapy duration was lower in the T/PR group than in the PR group. Adjustment for covariates did not alter this finding. Moreover, the dropout rate in the T/PR group was lower than that in the PR group in each of the individual time periods analyzed in the present study. Interestingly, a significant difference was identified during period 1, when telaprevir was administered to patients in the T/PR group.

These findings indicate that the addition of telaprevir to PR therapy contributed to treatment continuity. In contrast, it was previously reported that telaprevir was associated with an increasing incidence of adverse events including dermal disorders, severe anemia, and kidney disorders.[3,4] Additionally, a registered clinical trial found an increase in the dropout during telaprevir administration for the initial 12 weeks.[3] These findings appear to contradict each other. However, the present study focused on T/PR therapy during clinical practice, rather than in clinical trials. The differences between these two treatment environments may therefore have influenced the findings. A quarter of the T/PR group and a third of the PR group were aged over 65 years and would have been excluded from registered clinical trials. When this population is extracted and the dropout rate in each group recalculated, the dropout rate was 20.1% in the T/PR group and 32.7% in the PR group. Both values were higher than those reported for all patients in the present study, and equal to or higher than those in the registered trial excluding patients aged over 65 years.[3] Similar to the results of multivariate logistic regression analysis for the primary endpoint, being aged 65 years or older significantly increased dropout. However, the dropout rate in the T/PR group was more than 10% lower than that in the PR group. Since the safety of telaprevir has not been clarified in this age group, physicians may be more cautious during the treatment of elderly patients in order to maintain successful therapy. Although multivariate logistic regression analysis for the primary endpoint did not identify treatment experience as the covariate, the distribution of this factor differed between the T/PR and PR group. For a reason like age, physicians may be more cautious in treating re-treatment patients in order to avoid repeated treatment failure. This may have decreased the dropout rate in the T/PR group relative to that in the PR group.

The present study also identified the reasons for treatment dropout and the frequency at which these were expressed. Many possible reason categories were cited more frequently in the PR group, except for "any other reason." Since patients in the PR group received interferon and ribavirin for an additional 24 weeks, they probably dropped out due to the effects of interferon and ribavirin. However, several studies have reported that the addition of telaprevir to PR increased the incidence of more severe anemia.[3,4,13,16,17] Thus, although it was predicted that anemia-related dropout would be more frequent in the T/PR group, our findings did not support this. The rate of dropout due to anemia in the T/PR group was actually equal to, or slightly higher than, that of the PR group. This may reflect the range of treatment approaches used by physicians in clinical practice. For example, some studies have reported that dose adjustment provided an effective means of preventing dropout due to anemia.[18] During T/PR therapy, ribavirin dose reduction has been shown to reduce the risk for anemia without altering the SVR.[4,19] Similarly, telaprevir dose reduction from 2250 to 1500 mg reduced the risk of adverse events such as anemia while maintaining efficacy.[20,21] These previous studies and our findings suggested that the addition of telaprevir to PR provided various treatment approaches to physicians, especially hepatologists designated by the Japan Society of Hepatology, which were safer and more efficacious than PR therapy. Therefore, physician implementation or trialing of these approaches could greatly contribute to the decrease in T/PR therapy dropout. In Japan, the Ministry of Health, Labour and Welfare recommended that hepatologists consult with dermatologists when using telaprevir in order to appropriately manage patients, since severe dermal disorders leading to dropout were recognized in previous registered trials.[4,22,23] Because evidences related to appropriate use were constructed based on results of registered trials, dropout rates from T/PR therapy could be suppressed after the approval of telaprevir. Careful management by both hepatologists and dermatologists could influence treatment continuity during the therapy period, especially the initial 12 weeks when telaprevir was administered.

The lowest OR of dropout was recognized in period 2. In the clinical trial, the number of dropouts from T/PR therapy decreased after week 12 when patients finished telaprevir administration.[3] Additionally, patients generally finished PR administration at week 24. During period 2, most patients in the T/PR group were less likely to drop out due to telaprevir, and more finished the treatment due to treatment success. However, they may have continued treatment, which was essentially the same as PR therapy after week 24 because they were less likely to achieve SVR by T/PR therapy. Due to this, the difference in dropout rate between the T/PR and PR group

may be gradually diminished in periods 3 and 4.

There are several limitations to the present study. Firstly, although our study was conducted on a larger scale than registered trials conducted in Japan, the number of patients analyzed was insufficient to allow for extrapolation to the overall population.[4,23] It is estimated that 1.50–2.00 million people have HCV infection in Japan.[14] Within this group, at least 6900 people have received telaprevir.[24] Our study was conducted using the data derived from a maximum of 1674 patients receiving telaprevir. The population included in this study thus reflected less than 1% of the overall population and was likely to contain a certain bias. Secondly, analyses could only be conducted using the data available in the database consisting of standardized case report forms. This did not include the number of occurrences of adverse events, but rather, the number of occurrences of dropouts due to adverse events. Occurrences of adverse events in clinical practice may be more frequent in T/PR therapy than in PR therapy. We could not completely conclude that T/PR therapy was safer than PR therapy. The database also did not include information about medical institutions, complications, concomitant drugs, or drug doses. Because differences in standards judging therapy discontinuation between medical institutions or therapy group bias may influence dropout, potentially existing differences between medical institutions should be considered when interpreting the results of the present study. The incidence of interferon-related depression was reported to be greater in patients with chronic HCV infections in real world settings than in clinical trials, because these patients would normally be excluded from these trials.[11] Complications associated with previous treatments or hepatitis may also increase the risk of dropout. Additionally, as described above, previous studies have shown that the drug dose influenced the incidence of adverse events. Whether these factors influenced dropout in the present study therefore remains unclear. Finally, a reporting bias should be considered in the available data, which were recorded using a standardized report form.

In conclusion, the addition of telaprevir to PR appeared to reduce the incidence of treatment dropout due to adverse events in clinical practice in Japan. Hepatologists may greatly contribute to this positive effect on treatment continuity; however, it is not completely clear which therapy was safer, and how telaprevir produced its effects. Therefore, an additional study is required to investigate this using more detailed information.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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