Regular Article

Safety Profile of Telaprevir-Based Triple Therapy in Elderly Patients: A Real-World Retrospective Cohort Study

Maiko Akutagawa,[a] Kazuki Ide,[a,b,c] Yohei Kawasaki,*[,a,b] Mie Yamanaka,[a] Ryo Iketani,[a] Hiroshi Yamada,[a] and Naohiko Masaki[d]

[a] *Department of Drug Evaluation & Informatics, Graduate School of Pharmaceutical Sciences, University of Shizuoka; Shizuoka 422–8526, Japan:* [b] *Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University; Kyoto 606–8501, Japan:* [c] *Center for the Promotion of Interdisciplinary Education and Research, Kyoto University; Kyoto 606–8501, Japan: and* [d] *Laboratory Testing Department, National Center for Global Health and Medicine; Tokyo 162–8655, Japan.*
Received April 29, 2017; accepted June 2, 2017; advance publication released online June 9, 2017

To compare the rate of treatment discontinuation due to adverse events for telaprevir-based triple (T/PR) and pegylated interferon-alfa-2b and ribavirin (PR) therapy for the treatment of hepatitis C virus (HCV) infection in patients over the age of 65 years, in Japan. Retrospective analysis of the health data of patients over the age of 65 years treated for a HCV infection genotype 1 using T/PR or PR therapy, from 38 prefectures in Japan. The primary outcome was the rate of treatment discontinuation due to adverse events for T/PR and PR. The secondary outcome was to evaluate the prevalence and type of adverse events during the treatment period that resulted in treatment discontinuation for both therapies. For comparison, the T/PR and PR populations were matched using the propensity score method, and adjusted odds ratios (ORs) for treatment discontinuation calculated by multivariate logistic regression analysis. The study group included 1330 patients, 328 in the T/PR group and 1002 in the PR group. The rate of treatment discontinuation due to adverse events in the matched population was lower for T/PR (19.82%) than PR (35.98%) therapy, (adjusted OR, 0.418; 95% confidence interval, 0.292–0.599; $p<0.01$). Malaise was the principal cause of treatment discontinuation in both groups (T/PR, 30.77%, and PR, 42.37%). Using real-world health data of elderly individuals in Japan, we identified a lower rate of treatment discontinuation for T/PR than PR. Our outcomes provide information for a segment of the population that is generally excluded for clinical trials.

Key words elder patient; hepatitis C; safety profile; telaprevir; real-world data

Hepatitis C virus (HCV) infection is one of the most serious diseases worldwide, with 70% of individuals infected with HCV developing a chronic infection status[1] and 22% developing liver cirrhosis within 20 years of HCV infection,[2] with progression to liver cancer in some cases. Considering that liver cancer is the second highest cause of mortality in the world,[3] providing anti-viral treatment to individuals infected with HCV would be important to prevent the development of these secondary HCV-related comorbidities.[4]

The effectiveness of anti-viral treatment for HCV infection has improved recently with the approval of direct-acting anti-viral agents (DAAs), used as an alternative to or in combination with pegylated interferon-alfa-2b and ribavirin (PR) therapy. Telaprevir is one such DAA that has been used in combination with PR therapy for the treatment of HCV genotype 1 infection. Telaprevir-based triple therapy (T/PR) has been shown to be effective in achieving a sustained virologic response (SVR) in 60–70% of HCV cases, compared to a 40–50% SVR with PR therapy.[5,6] Moreover, a 90% SVR has been reported in clinical trials using DAA interferon-free therapy.[7–9] In practice, HCV treatment is selected based on a patient's individual clinical background.[10]

T/PR therapy, however, is associated with a high risk of adverse events, with a discontinuation rate of >10% for T/PR therapy due to adverse events, compared to <10% for PR therapy.[11,12] However, in clinical practice, it is important to note that the characteristics of a real-world population are likely to be different from those of a clinical trial group.[13] As an example, a real-world study reported a lower discontinuation rate for T/PR than for PR therapy.[14] Of clinical relevance is the evaluation of HCV therapy in elderly individuals in whom the risk for HCV is specifically higher than in younger adults[15] and yet, this segment of the population is generally excluded from clinical trials. This issue is of relevance in Japan, where the proportion of elderly in the general population is significantly higher than in Europe and the United States.[16] Therefore, our aim was to compare the rate of treatment discontinuation due to adverse events for T/PR and PR for the treatment of HCV infection among elderly patients, over the age of 65 years, in Japan. This study is of clinical relevance to establish real-world evidence of the effectiveness of HCV therapy in elderly individuals.

METHODS

Study Design A retrospective analysis of patient health data from a nationwide Japanese interferon database, was conducted, including representative data across 38 prefectures in Japan. The original data was collected by The Hepatitis Information Center of the National Center for Global Health and Medicine (Chiba, Japan), between December 2009 to August 2015.[17] The following information is included in the database: sex, date of birth, age, start/end date of treatment, treatment experience, histologic diagnosis, type(s) of treatment, HCV serotype or/and genotype, serum HCV RNA level, SVR rate, adverse events, and laboratory test results (levels of

* To whom correspondence should be addressed. e-mail: kawasaki.yohei.2r@kyoto-u.ac.jp

© 2017 The Pharmaceutical Society of Japan

alanine aminotransferase (ALT) and aspartate aminotransferase (AST), 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 SVR, used to quantify treatment outcome, was calculated from serum levels of HCV RNA obtained at 24 weeks post-cessation of treatment. SVR was deemed to be attained when the serum level of HCV RNA was below the detectable level.

Study Population Our study population of interest consisted of elderly patients, over the age of 65 years, with HCV infection, genotype 1, treated with T/PR or PR therapy. The exclusion criteria were as follows: HCV genotype other than 1; HBV infection only; diagnosis of liver cirrhosis; treatment other than T/PR or PR; treatment duration exceeding the recommended length, namely 24 weeks for T/PR and 48 weeks for PR; treatment discontinuation for reasons other than adverse events; and missing data required for analysis.

Study Outcomes The primary outcome was the rate of treatment discontinuation, due to adverse events, for T/PR and PR therapy. The secondary outcome was to evaluate the type of and prevalence of adverse events during the standard treatment period (24 weeks for T/PR and 48 weeks for PR) that resulted in treatment discontinuation in both groups.

Statistical Analysis Continuous variables are presented as the mean±standard deviation (S.D.), and categorical variables as a count and percentage (%). For evaluation of the study outcomes, we performed matching of the T/PR and PR populations using the propensity score matching (PSM) method, which controls for selection bias in a non-randomized study design.[18,19] The propensity score (PS) was computed separately for the T/PR and PR groups using multivariate logistic regression analysis, controlling for the following covariate: sex (male *versus* female), HCV viral load (high [≥5.0 log IU/mL or ≥100 K IU/mL] *versus* low [<5.0 log IU/mL or <100 K IU/mL]), platelet count ($<15\times10^4/\mu$L *versus* $\geq15\times10^4/\mu$L) and treatment experience (initial *versus* re-treatment). The PS was calculated using the following formula:

$$\log\left(\frac{p_i}{1-p_i}\right)=\beta_0+\beta_1\chi_{1i}+\beta_2\chi_{2i}+\beta_3\chi_{3i}+\beta_4\chi_{4i}$$

p_i, probability of being assigned T/PR therapy; χ_{1i}, sex; χ_{2i}, HCV viral load; χ_{3i}, platelet count; and χ_{4i}, treatment experience.

Age, HCV viral load and platelet count were classified according to the guidelines of The Japan Society of Hepatology,[4] these factors having previously been identified as contributing to the differential rate of treatment discontinuation for T/PR *versus* PR.[14] We also considered treatment experience as a covariate based on previously published guidelines[10] that recommend physicians consider treatment experience when deciding which therapy to provide to a patient. Model performance was assessed using the C-index, with a C-index of '1′ indicative of a perfect discrimination between the T/PR and PR groups, with an index >0.8 recommended to calculate a PS.[20] Patients in the two groups were matched 1 : 1, based on the PS, using the following previously published algorithms.[21] Briefly, we used the nearest neighbor, or greedy, matching method, which selects a PR therapy unit for each T/PR therapy unit based on the smallest distance in PS. We performed this method as follows. First, the maximum allowable difference in PS was 0.1 between matched units. Second, once the sample was selected for matching, we did not use the same sample (sampling without replacement). Last, we performed this method with randomized matching orders. The adjusted odds ratios (ORs) for treatment discontinuation, and the associated 95% and confidence intervals (95% CI), were calculated for the matched patient subpopulation, using multivariate logistic regression analysis. Therapy group and covariates used for the calculation of the PS were included as covariates in the logistic regression analysis. A conditional logistic regression analysis was used as a sensitivity analysis. All statistical analyses were conducted using SAS software, version 9.4 for Windows (SAS Institute Inc., Cary, NC, U.S.A.).

Ethical Considerations The original study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan (#738; October 1, 2009), and performed in accordance with the Declaration of Helsinki.

RESULTS

Characteristics of the Study Population A flow diagram of the study procedure is presented in Fig. 1. Of the 25989 patients registered in the database, 24659 were excluded after screening for the inclusion and exclusion criteria. Reasons for exclusion were as follows: genotype other than 1, 10242 patients; HBV infection only, 775 patients; liver cirrhosis, 1060 patients; treated with therapy other than T/PR or PR, 10780 patients; <65 years old, 18466 patients; treatment exceeding the standard duration, 3870 patients; treatment discontinuation for reasons other than adverse event, 1801 patients; missing data for analysis, 2236 patients. Note that duplicate cases were included in the number of excluded cases. After screening for exclusion, the data of 1330 patients were included in the analysis. The baseline demographics of the study population are presented in Table 1. Baseline characteristics were comparable for the T/PR and PR groups, with the exception of treatment experience ($p<0.01$). Specifically, only a few patients were treated with T/PR prior to 2011, as insurance coverage for Telaprevir has only been available since 2011.[22]

Propensity Score Matching Coefficients for the logistic regression for the computation of PS were as follows: $\hat{\beta}_0$: 1.373, $\hat{\beta}_1$: −0.001, $\hat{\beta}_2$: −0.436, $\hat{\beta}_3$: 0.042, $\hat{\beta}_4$: −0.785 (C-index, 0.686). Patients in the PR group were selected based on the T/PR group, with 328 patients selected from a possible 1002 patients who met the inclusion criteria in the PR group. Covariates, before and after matching, are presented in Table 2.

Logistic Regression Analysis Results of the main and sensitivity analysis are presented in Table 3. The rate of treatment discontinuation due to adverse events in the matched study population was lower for the T/PR (19.82%) than PR (35.98%) group (adjusted OR, 0.418; 95% CI, 0.292–0.599; $p<0.01$). The following covariate factors contributed to treatment discontinuation: sex (adjusted OR, 1.998; 95% CI, 1.403–2.847; $p<0.01$); HCV viral load (adjusted OR, 2.351; 95% CI, 0.661–8.365; $p=0.19$); platelet count (adjusted OR, 1.151; 95% CI, 0.809–1.637; $p=0.43$); and treatment experience (adjusted OR, 0.967; 95% CI, 0.675–1.386; $p=0.86$). The overall OR for the sensitivity analysis was 0.436 (95% CI, 0.302–0.629; $p<0.01$).

Adverse Events Leading to Treatment Discontinuation

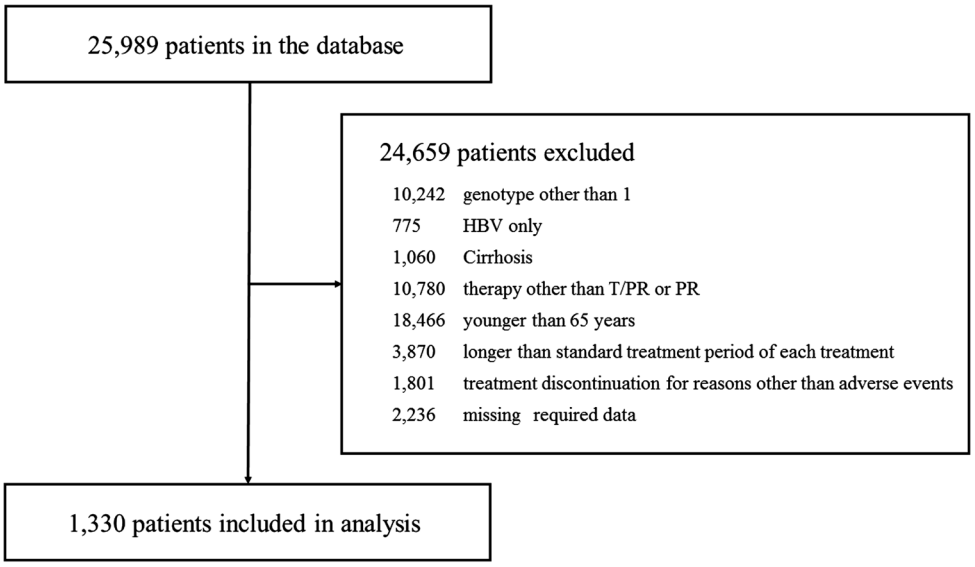

Fig. 1. Flow Diagram of the Study

Table 1. Baseline Demographics of Study Population

	T/PR (N=328)	PR (N=1002)
Age (years), mean±S.D.	68.31±3.02	68.84±3.24
Sex, N (%)		
Male	175 (53.35)	518 (51.70)
Female	153 (46.65)	484 (48.30)
Treatment duration (weeks), mean±S.D.	19.85±7.01	36.52±15.16
AST (IU/L), mean±S.D.	53.14±34.68	57.97±36.50
ALT (IU/L), mean±S.D.	57.09±44.94	64.31±50.22
Platelet count ($\times 10^4/\mu$L), mean±S.D.	15.63±4.79	15.41±4.89
Platelet count ($\times 104/\mu$L), N (%)		
≥15	163 (49.70)	478 (47.70)
<15	165 (50.30)	524 (52.30)
HCV viral load, N (%)		
Low, <5.0 log IU/mL or <100 K IU/mL	10 (3.05)	58 (5.79)
High, ≥5.0 log IU/mL or ≥100 K IU/mL	318 (96.95)	944 (94.21)
Treatment experience, N (%)		
Initial	132 (40.24)	762 (76.05)
Re-treatment	196 (59.76)	240 (23.95)

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; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; S.D., standard deviation.

The number of adverse events leading to treatment discontinuation are presented in Table 4. For patients with ≥2 adverse events, each adverse event was counted. Malaise was the most frequent cause of treatment discontinuation: 30.77%, T/PR therapy, and 42.37%, PR therapy. Other adverse events leading to T/PR discontinuation included exanthema, dizziness and kidney dysfunction.

DISCUSSION

We investigated the rate of discontinuation of T/PR therapy due to adverse events, compared to the rate for PR therapy, in elderly patients. Our results for patients ≥65-years-old were comparable to a previous study that included patients ≥16-years-old from the same database.[14] Moreover, previously published real-world evaluation of treatment discontinuation rates in Japan reported no difference in the rate for patients >60-years-old than for younger patients, for both dual and triple therapy.[16] Similarly, the rate of treatment discontinuation in our study for patients over the age of 65 years was consistent with previously reported rates in the general population. Considering the above information, it is likely that careful management and monitoring of adverse events among patients on T/PR therapy was effective in avoiding discontinuation. In fact, T/PR therapy is only provided in medical institutions with a certified hepatologist and a consulting certified dermatologist for consultation.[23]

With regard to adverse events leading to treatment discontinuation, anemia was identified as a common and serious adverse event associated with ribavirin therapy,[4] as well as being the most common cause of discontinuation of PR therapy.[24,25] Furthermore, older age and T/PR therapy were identified as factors increasing the risk of anemia.[5,26] A meta-analysis study of randomized clinical trials reported a relative risk of anemia for T/PR *versus* dual therapy of 1.39.[27] In our study group, the prevalence of anemia as a cause of treatment discontinuation was low, with no significant difference between the T/PR (15.38%) and PR (14.41%) groups. Taken together, the findings from the various studies indicate that physicians should adjust the T/PR treatment program as needed to avoid the development of anemia to lower the rate of discontinuation. As an example, previous studies have indicated that lower drug doses can decrease the incidence rate of anemia with T/PR, while maintaining an effective.[28–30] In our study, the SVR of the matched population was 75.91% for T/PR therapy and 39.02% for PR therapy; these rates were comparable to previously reported clinical results.[5,6] Dosage effects were not considered in our analysis as information regarding treatment dose was not readily understandable in the database.

The limitations of our study should be considered. First, the sample size was relatively small. Therefore, our findings will need to be verified using an updated database of HCV treatment, which will increase the sample size. Second, other

Table 2. Baseline Demographics of before and after Matching

	After PSM		Before PSM
	T/PR (N=328)	PR (N=328)	PR (N=1002)
Age (years), mean±S.D.	68.31±3.02	68.70±3.14	68.84±3.24
Sex, N (%)			
Male	175 (53.35)	188 (57.32)	518 (51.70)
Female	153 (46.65)	140 (42.68)	484 (48.30)
Treatment duration (weeks), mean±S.D.	19.85±7.01	36.66±14.99	36.52±15.16
AST (IU/L), mean±S.D.	53.14±34.68	55.54±31.72	57.97±36.50
ALT (IU/L), mean±S.D.	57.09±44.94	64.48±50.22	64.31±50.22
Platelet count ($\times 10^4/\mu$L), mean±S.D.	15.63±4.79	15.27±4.41	15.41±4.89
Platelet count ($\times$104/μL), N (%)			
≥15	163 (49.70)	163 (49.70)	478 (47.70)
<15	165 (50.30)	165 (50.30)	524 (52.30)
HCV viral load, N (%)			
Low, <5.0 log IU/mL or <100 K IU/mL	10 (3.05)	10 (3.05)	58 (5.79)
High, ≥5.0 log IU/mL or ≥100 K IU/mL	318 (96.95)	318 (96.95)	944 (94.21)
Treatment experience, N (%)			
Initial	132 (40.24)	132 (40.24)	762 (76.05)
Re-treatment	196 (59.76)	196 (59.76)	240 (23.95)

PSM, propensity score matching; 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; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; S.D., standard deviation.

Table 3. Logistic Regression Analysis for the Study Outcomes

	Multivariate logistic regression		Conditional logistic regression	
Covariate	Adjusted OR for covariate (95% CI)	p-Value	Adjusted OR for covariate (95% CI)	p-Value
Therapy group (T/PR *vs.* PR)	0.418 (0.292–0.599)	<0.01	0.436 (0.302–0.629)	<0.01
Sex (Female *vs.* Male)	1.998 (1.403–2.847)	<0.01		
HCV viral load (High *vs.* Low)	2.351 (0.661–8.365)	0.19		
Platelet count ($<15\times10^4/\mu$L *vs.* $\geq15\times10^4/\mu$L)	1.151 (0.809–1.637)	0.43		
Treatment experience (Initial *vs.* Re-treatment)	0.967 (0.675–1.386)	0.86		

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; HCV, hepatitis C virus.

Table 4. The Number of Adverse Events Leading Treatment Discontinuation

	T/PR (N=328)	PR (N=328)
Treatment discontinuation	65/328 (19.82)	118/328 (35.98)
Anemia	10/65 (15.38)	17/118 (14.41)
Anorexia	15/65 (23.08)	32/118 (27.12)
Interstitial pneumonia	1/65 (1.54)	5/118 (4.24)
Malaise	20/65 (30.77)	50/118 (42.37)
Psychoneurosis	9/65 (13.85)	25/118 (21.19)
Retinopathy	3/65 (4.62)	7/118 (5.93)
Thrombocytopenia	1/65 (1.54)	8/118 (6.78)
Other reason	41/65 (63.08)	47/118 (39.83)

If patients had two or more adverse events, we counted each adverse event. T/PR, telaprevir+pegylated interferon-alfa-2b+rivabirin; PR, pegylated interferon-alfa-2b+rivabirin.

treatment-related factors that could influence treatment adherence were not available in the current database and should be included in future real-world studies.

In conclusion, using real-world health data for elderly individuals treated for HCV infection in Japan, we identified a lower rate of treatment discontinuation. Our outcomes provide information for a segment of the population that is generally excluded for clinical trials, and can help inform physicians on safe and effective HCV treatment in elderly patients.

Acknowledgments This work was supported by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan (Research on Hepatitis: 2009–2014) and a Grant-in-Aid from the National Center for Global Health and Medicine (27A1301) to NM. The authors wish to thank Ms. Mikako Kajio and Ms. Asako Horihara for their technical assistance during data analysis. We would also like to acknowledge the great contributions of the 38 prefectural members and all the medical staff engaged in the long-term interferon treatment and data collection.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) Lavanchy D. The global burden of hepatitis C. *Liver Int.*, **29** (Suppl. 1), 74–81 (2009).

2) Freeman AJ, Dore GJ, Kaw MG, Thorpe M, Von Overbeck J, Lloyd AR, Marinos G, Kaldor JM. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology*, **34**, 809–816 (2001).
3) "GLOBOCAN2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012".: ‹http://globocan.iarc.fr/Pages/fact_sheets_population.aspx›, cited 7 March, 2017.
4) "JSH Guidelines for the management of hepatitis C virus infection 5.3th edition".: ‹https://www.jsh.or.jp/files/uploads/HCV_GL_ver5.3_Mar08.pdf›, cited 17 March, 2017.
5) McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ, PROVE1 Study Team. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N. Engl. J. Med.*, **360**, 1827–1838 (2009).
6) Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, Hayashi N. Telaprevir with peginterferon and ribavirin for treatment naive patients chronically infected with HCV of genotype 1 in Japan. *J. Hepatol.*, **56**, 78–84 (2012).
7) Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N. Engl. J. Med.*, **368**, 34–44 (2013).
8) Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir and ledipasvir fixed—dose combination with and without ribavirin in treatment—naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open—label, randomised, phase 2 trial. *Lancet*, **383**, 515–523 (2014).
9) Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski J-P, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P, ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N. Engl. J. Med.*, **370**, 1889–1898 (2014).
10) "The Japan Society of Hepatology".: ‹https://www.jsh.or.jp/files/uploads/R1__4.pdf›, cited 17 March, 2017.
11) Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki J-P, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky J-M, Zeuzem S, PROVE2 Study Team. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N. Engl. J. Med.*, **360**, 1839–1850 (2009).
12) Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S, ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *New Engl. J. Med.*, **364**, 2405–2416 (2011).
13) Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, Maliakkal B, Alam I, Stewart TG, Vainorius M, Peter J, Nelson DR, Fried MW, Reddy KR. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. *J. Hepatol.*, **62**, 286–293 (2015).
14) Iketani R, Ide K, Yamada H, Kawasaki Y, Masaki N. The safety profile of telaprevir-based triple therapy in clinical practice: a retrospective cohort study. *Biol. Pharm. Bull.*, **40**, 687–692 (2017).
15) Miyamura T, Kanda T, Nakamoto S, Wu S, Jiang X, Arai M, Fujiwara K, Imazeki F, Yokosuka O. Roles of ITPA and IL28B genotypes in chronic hepatitis C patients treated with peginterferon plus ribavirin. *Viruses*, **4**, 1264–1278 (2012).
16) Furusyo N, Ogawa E, Nakamuta M, Kajiwara E, Nomura H, Dohmen K, Takahashi K, Satoh T, Azuma K, Kawano A, Tanabe Y, Kotoh K, Shimoda S, Hayashi J, Kyushu University Liver Disease Study (KULDS) Group. Telaprevir can be successfully and safely used to treat older patients with genotype 1b chronic hepatitis C. *J. Hepatol.*, **59**, 205–212 (2013).
17) Masaki N, Yamagiwa Y, Shimbo T, Murata K, Korenaga M, Kanto T, Mizokami M, prefectural members contributing to the Japanese Interferon Database. Regional disparities in interferon therapy for chronic hepatitis C in Japan: a nationwide retrospective cohort study. *BMC Public Health*, **15**, 566 (2015).
18) Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav. Res.*, **46**, 399–424 (2011).
19) Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*, **70**, 41–55 (1983).
20) Hoshino T, Okada K. Estimation of causal effect using propensity score methods in clinical medicine, epidemiology, pharmacoepidemiology and public health; a review. *J. Natl. Inst. Public Heal.*, **55**, 230–243 (2006).
21) Lanehart RE, De Gil PR, Kim ES, Bellara AP, Jeffrey D, Lee RS, Florida S. Propensity score analysis and assessment of propensity score approaches using SAS® procedures. *SAS Glob. Forum 2012*, 314–325.
22) "Package insert (TELAVIC® Tablets 250 mg)".: ‹http://database.japic.or.jp/pdf/newPINS/00059795.pdf›, cited 28 May, 2017.
23) "Ministry of Health, Labour and Welfare".: ‹http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/houkoku-h231128.pdf›.
24) Kawaguchi Y, Iwane S, Kumagai T, Yanagita K, Yasutake T, Ide Y, Otsuka T, Eguchi Y, Ozaki I, Akiyama T, Kawazoe S, Mizuta T. Efficacy and safety of telaprevir, pegylated interferon α-2b and ribavirin triple therapy in Japanese patients infected with hepatitis C virus genotype 1b. *Intern. Med.*, **54**, 2551–2560 (2015).
25) Rubin RA, Russo MW, Brown KA, Fontana RJ, Levitsky J, Vargas H, Yoshida EM, Brown RS Jr. Twice-daily telaprevir for posttransplant genotype 1 hepatitis C virus: a prospective safety, efficacy, and pharmacokinetics study. *Exp. Clin. Transplant.*, 2016, in press.
26) Zeuzem S, Demasi R, Baldini A, Coate B, Luo D, Mrus J, Witek J. Risk factors predictive of anemia development during telaprevir plus peginterferon/ribavirin therapy in treatmentexperienced patients. *J. Hepatol.*, **60**, 1112–1117 (2014).
27) Dang SS, Wang W, Wang X, Li Y, Li M, Jia XL, Wang Y, Liu E, Zhao S. Telaprevir for chronic hepatitis C with genotype 1 : a meta-analysis. *Hepatogastroenterology*, **59**, 461–468 (2012).
28) Tamori A, Kioka K, Sakaguchi H, Enomoto M, Hai H, Kawamura E, Hagihara A, Fujii H, Uchida-Kobayashi S, Iwai S, Morikawa H, Murakami Y, Kawasaki Y, Tsuruta D, Kawada N. Effects on anemia of drug adjustment in patients with chronic hepatitis C during telaprevir-combined therapy. *Ann. Hepatol.*, **14**, 28–35 (2015).
29) Romero-Gómez M, Berenguer M, Molina E, Calleja JL. Management of anemia induced by triple therapy in patients with chronic hepatitis C : Challenges, opportunities and recommendations. *J. Hepatol.*, **59**, 1323–1330 (2013).
30) Sezaki H, Suzuki F, Hosaka T, Akuta N, Fukushima T, Hara T, Kawamura Y, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kumada H. Effectiveness and safety of reduced-dose telaprevir-based triple therapy in chronic hepatitis C patients. *Hepatol. Res.*, **44**, E163–171 (2014).