Regional Differences in Hepatitis C Treatment with Peginterferon and Ribavirin in Japan in Both Genotype 1 and Genotype 2: A Retrospective Cohort Study

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There has been no report on the genotype-dependent regional, especially prefectural, differences in hepatitis C treatment in Japan. We conducted a retrospective cohort study using the nationwide database. The registration period of the database was from December 2009 to April 2013. Individuals with chronic hepatitis C were identified from the database. The sustained virologic response (SVR) rates in each prefecture were calculated stratified by genotype. Confounding variables were identified using stepwise logistic regression analysis. The range of the point estimate of the adjusted odds ratio explained prefectural differences in treatment outcomes. During the registration period, 36 prefectures registered cases to the database. A total of 16349 cases were registered and 11653 cases were included in the analysis. The mean age was 57.9±10.5 years; 7950 (68.2%) had hepatitis C virus (HCV) genotype 1 and 3703 (31.8%) had HCV genotype 2. The range in SVR rates was 30.0 to 63.0% for genotype 1 and 55.0 to 100.0% for genotype 2. In the multivariate analysis, the ranges of the adjusted odds ratio of each prefecture were 0.658 to 2.125 for genotype 1 and 0.364 to 2.630 for genotype 2. Our results suggest that regional, particularly prefectural, differences in chronic hepatitis C treatment with peg-interferon (IFN) and ribavirin (RBV) exist in Japan and that these regional differences may similarly exist both in HCV genotypes 1 and 2. Additional studies using these methods, considering medical situations in each prefecture and new treatments regimens, could greatly contribute to improving and standardizing chronic hepatitis C treatment.

Key words hepatitis C; interferon; ribavirin; regional difference; nationwide database

Hepatitis C virus (HCV) infections affect 130 to 150 million individuals worldwide, and >300000 individuals die from liver diseases related to HCV infection every year. After acute infection, approximately 55 to 85% of individuals develop chronic infections. At least 15% of chronic infections lead to cirrhosis, which is a life threatening condition. Therefore, standardized efficacious treatment of chronic hepatitis C is important to reduce the number of deaths from liver disease related to HCV infection.

There are several treatment approaches for chronic hepatitis C: i) peginterferon-α (peg-IFN) and ribavirin (RBV); ii) peg-IFN with direct-acting antivirals; and iii) all-oral IFN-free regimens. Most recent strategies using all-oral interferon free regimens are expected to cure more than 90% of individuals with hepatitis C infection, but the cost of these regimens are exceptionally high and only limited number of individuals can select this option. Compared with these strategies, the sustained virologic response (SVR) of the treatment with peg-IFN and RBV is relatively low. The response is only ca. 50% in the case of genotype 1, which is difficult to treat. This virologic response rate indicates the importance of the standardized treatment performance and outcome. Knowledge of regional differences in treatment outcome is essential to standardize treatment performance and outcome. Masaki et al. reported regional differences in hepatitis C treatments in Japan, but the study did not focus on prefectural differences.

A prefecture is the unit of Japan’s local government that sets local medical plans to promote the best local medical practices. Investigations of treatment outcome differences at the level of prefectures are preferable to reveal the most realistic situation.

We conducted a retrospective cohort study on the genotype-dependent regional differences in hepatitis C treatment with peg-IFN and RBV using the nationwide Japanese interferon database. We compared treatment outcomes among genotypes, as the effect of peg-IFN and RBV depends on the genetic background of the virus.

MATERIALS AND METHODS

Study Design Masaki et al. published a detailed explanation of the nationwide Japanese interferon database used in this study. Briefly, the database was based on information from a nationwide retrospective cohort study that has been ongoing since December 2009. The study was authorized by the Basic Act on Hepatitis Measures (Act No. 97; December 4, 2009), and all 47 prefectural governments in Japan were invited to participate. The prefectures participated in this study sent the standardized case report form to the Hepatitis Information Center of the National Center for Global Health and Medicine in Japan (Chiba, Japan). The standardized case report form used in this study included the following information: demographic features of the individuals (sex, date of birth, age, IFN treatment history), clinical and/or histologic diagnosis, scheduled treatment data, IFN treatment regimen (type of IFN, with or without RBV), laboratory test results (serum HCV RNA level, HCV serotype and/or genotype, aspartate aminotransferase level, alanine aminotransferase

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[ALT] level, platelet count), adverse events, treatment outcomes (SVR), and completion of treatment. Serum HCV RNA level was measured by real-time polymerase chain reaction quantitative (q) PCR (COBAS AmpliPrep/COBAS TaqMan HCV test; Roche Molecular Systems, Pleasanton, CA, U.S.A.). The viral load was categorized as follows: High, ≥100 KIU/mL (COBAS AmpliPrep) or ≥5.0 Log IU/mL (COBAS TaqMan); Low, <100 KIU/mL (COBAS AmpliPrep) or <5.0 Log IU/mL (COBAS TaqMan). The viral response after the peg-IFN and RBV treatment was determined 24 weeks after discontinuing the treatment; the treatment outcome can be defined not only when treatment is completed, but also when it is withdrawn. The treatment outcome of this study was given as SVR, and it was defined as a reduction in serum HCV RNA to less than detectable levels 24 weeks after discontinuation of treatment.

The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine of Japan (No. 738; October 1, 2009), and was conducted in accordance with the Declaration of Helsinki. The STROBE checklist is available as Supplementary Material (see Checklist 1, Supplementary materials).

**Study Population** The registration period of this study was from December 2009 to April 2013, and individuals with chronic hepatitis C were identified. The exclusion criteria was as follows: i) genotype other than 1 or 2, ii) comorbid cirrhosis or hepatitis B infection, iii) treatment other than peg-IFN and RBV, iv) younger than 16 years of age, v) any missing data (age, sex, diagnosis, treatment, or other clinical data).

**Statistical Analysis** Continuous variables are expressed as the mean±standard deviation (S.D.), and categorical variables as number and percentage (%). The SVR rates in each prefecture were calculated stratified by genotypes (genotypes 1 and 2) and completion of the treatment. Confounding variables for the SVR were identified using stepwise logistic regression analysis with a significance level for selection and elimination set at 1500. Adjusted odds ratios and 95% confidence intervals (95%CI) were calculated in the multivariate logistic regression analysis. The fit of the logistic models was assessed with the Hosmer–Lemeshow test. The range of the adjusted odds ratio for each prefecture explains prefectural differences in hepatitis C treatment outcome and descriptively compares genotypes. In these multivariate analyses, the prefecture numbered “1” was used as a reference category.

All statistical procedures were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, U.S.A.).

**RESULTS**

**Case Registration and Clinical Characteristics** During the registration period, 36 prefectures sent case reports to the Hepatitis Information Center of the National Center for Global Health and Medicine. A total of 16349 cases were registered, and 4696 cases were excluded according to the following reasons: 56 were missing age and/or sex data; 4 were younger than 16 years of age; 19 had HCV genotype 3; 300 had hepatitis B virus infection; 569 had cirrhosis; 163 were missing diagnostic data; 2892 received treatment other than peg-IFN and RBV; and 735 were missing other clinical data. Several individuals had two or more reasons for exclusion. After excluding these individuals, a total of 11653 individuals were included in the analysis (Fig. 1). The number of cases in each prefecture used in this study ranged from 12 to 1384. Seven prefectures registered less than 100 cases. The total number of treatment-completed cases was 9822.

The clinical characteristics of individuals are reported in Table 1. The mean age was 57.9±10.5 years; 5896 (50.5%) were men and 5776 (49.5%) were women; 7950 (68.2%) had HCV genotype 1 and 3703 (31.8%) had HCV genotype 2; 2297 (28.9%) with genotype 1 and 744 (20.1%) with genotype 2 had treatment experience.

**SVR Rate in Each Prefecture** The SVR rates for each prefecture are shown in Table 2. The total SVR rate was 49.9% for genotype 1 and 81.3% for genotype 2. The range in SVR rates was 30.0 to 63.0% for genotype 1. This range was 39.0 to 56.7% in prefectures that registered at least 100 cases. The range in SVR rates for genotype 2 was 55.0 to 100.0%. This range was 70.0 to 87.6% in prefectures that registered at least 100 cases. The SVR rates of treatment-completed cases for each prefecture are shown in Table 3. SVR rates for genotype 1 ranged from 37.5 to 65.4%. This range was noted to be from 49.5 to 65.4% in prefectures that registered at least 100...
cases. SVR rates for genotype 2 ranged from 55.6 to 100.0%. This range was noted to be from 74.1 to 92.3% in prefectures that registered at least 100 cases.

**Multivariate Logistic Regression Analysis** The selected confounding variables and the adjusted odds ratio (OR) for these variables in each prefecture are shown in Fig. 2. In the stepwise logistic regression analysis, sex (1.496 [1.364, 1.641]; p < .001), age (adjusted OR [95% CI], 0.966 [0.961, 0.971]; p < .001), treatment experience (0.763 [0.688, 0.845]; p < .001), HCV viral load (0.302 [0.237, 0.384]; p < .001), and platelet count (1.570 [1.430, 1.724]; p < .001) were selected as confounding variables for genotype 1. Age (adjusted OR [95% CI], 0.954 [0.946, 0.963]; p < .001), treatment experience (0.478 [0.393, 0.581]; p < .001), HCV viral load (0.373 [0.261, 0.533]; p < .001), platelet count (1.298 [1.079, 1.562]; p = .0057), and ALT level (1.666 [1.381, 2.012]; p < .001) were selected as confounding variables for genotype 2. In the analysis for treatment-completed cases, sex (1.524 [1.369, 1.696]; p < .001), age (adjusted OR [95% CI], 0.965 [0.959, 0.971]; p < .001), treatment experience (0.717 [0.639, 0.805]; p < .001), hepatitis C viral load (0.315 [0.237, 0.418]; p < .001), platelet count (1.532 [1.376, 1.705]; p < .001), and ALT level (1.117 [0.977, 1.277]; p = .107) were selected as confounding variables for genotype 1, whereas age (adjusted OR [95% CI], 0.951 [0.941, 0.961]; p < .001), treatment experience (0.509 [0.408, 0.634]; p < .001), hepatitis C viral load (0.318 [0.205, 0.494]; p < .001), platelet count (1.171 [0.950, 1.443]; p = .139), and ALT level (1.884 [1.533, 2.316]; p < .001) were selected as confounding variables for genotype 2. The ranges of the point estimate of the adjusted odds ratio of each prefecture were 0.658 to 2.125 for genotype 1 and 0.364 to 2.630 for genotype 2. The ranges for the analysis of treatment-completed cases were 0.445 to 2.331 for genotype 1 and 0.301 to 2.921 for genotype 2. The Hosmer–Lemeshow test showed good fit of the models (model for genotype 1, p = .75; model for genotype 2, p = .15; model for treatment-completed cases of genotype 1, p = .074; model for treatment-completed cases of genotype 2, p = .49).
DISCUSSION

We conducted a retrospective cohort study on the genotype-dependent regional differences in hepatitis C treatment with peg-IFN and RBV using the Japanese interferon database. We focused on differences in treatment responses among viral genotypes.

Our results suggest that regional, particularly prefectural, differences in chronic hepatitis C treatment with peg-IFN and RBV exist in Japan. The difference in the SVR rate in prefectures that registered at least 100 cases for genotype 1 was 17.7% (treatment completed cases, 15.9%), and that for genotype 2 was 17.6% (treatment completed cases, 18.2%). The adjusted OR for genotype 1 ranged from 0.658 to 2.125 and that for genotype 2 ranged from 0.364 to 2.630. A difference of more than 15% among prefectures and approximately >1.5 ranges in the point estimates of adjusted OR indicated the clinical implications based on the regional difference. In addition, the regional differences may be similar in both genotypes 1 and 2. Peg-IFN and RBV is a common treatment approach for chronic hepatitis C, but this is the first report of the genotype-dependent prefectural differences of chronic hepatitis C treatment in Japan. The occurrence rate of each genotype in Japan was consistent with a previous report. Therefore, the influence of the distribution in the number of case reports registered from each prefecture on the results could relatively weak. Additional studies with large numbers of case reports evenly collected from all prefectures might demonstrate similar results.

An additional potential limitation is the lack of information regarding the medical environment of the prefectures and the difference between treatment locations. The standardized case report form used in this study did not include information related to the medical environment and details about treatment locations; therefore, we could not analyze or discuss the potential differences in medical environments and treatment locations. The standard treatment regimen of peg-IFN and RBV for chronic hepatitis C was established and the guidelines were provided by the Japan Society of Hepatology. Therefore, regional differences based on pharmaceutical factors could be small. The treatment differences, including in patient care, could not be evaluated in this study, but there may exist disparities in patient care. This information should be collected in future investigations. Additionally, the medical environment includes medical resources in each prefecture, which should also be considered. Accessibility to medical resources is important to consider when standardizing treatment. Spaulding et al. reported difficulties in HCV treatments in rural areas or prisons because of a shortage of primary care physicians and a lack of their training. Problems because of lack of access to specialty care have also been reported and actions for resolving this problem, such as the development of
patient-centered medical home (PCMH) model and the extension for community healthcare outcomes (ECHO) model, have been carried out, especially in the United States.\textsuperscript{16–18}

The unavailability of data on “death or drop out” and treatment using the combination of 3 agents including peg-IFN and RBV was also a possible limitation of this study. The data revealing “death or drop out” along with that on other medical environments and treatment locations might be useful to interpret the differences in treatment and patients. In addition, the current study did not include treatment using a combination of 3 agents including peg-IFN and RBV.\textsuperscript{19} If these data were available, we could have also discussed the regional differences between treatment regimens as well as temporal changes.

Future studies considering the medical environment and other factors of the prefectures and the individuals can provide the opportunity to discuss the causes of regional differences in hepatitis C treatment and solutions for the problem.

These results and this process should contribute to future research on all oral, interferon-free HCV treatment approaches. Hepatitis C treatment using this approach began in 2014 in Japan.\textsuperscript{20,21} Information related to this treatment that will be collected over the next few years can provide useful information on the latest hepatitis C treatments and their regional differences.

CONCLUSION

Our results suggest that there may exist regional, particularly prefectural, differences in chronic hepatitis C treatment with peg-IFN and RBV in Japan. These regional differences may similarly exist both in HCV genotypes 1 and 2.

Additional studies using these methods, considering medical situations in each prefecture and new treatments using IFN-free regimens, could greatly contribute to improving and standardizing chronic hepatitis C treatment.

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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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