Association of the Low-density Lipoprotein Cholesterol/High-density Lipoprotein Cholesterol Ratio with Glecaprevir-pibrentasvir Treatment

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Abstract:
Objective The change in serum lipid levels by direct-acting antiviral (DAA) treatment for chronic hepatitis C varies depending on the type of DAA. How the lipid level changes induced by glecaprevir-pibrentasvir (G/P) treatment contribute to the clinical outcome remains unclear. We conducted a prospective observational study to evaluate the effectiveness of G/P treatment and the lipid level changes.

Methods The primary endpoint was a sustained virologic response at 12 weeks (SVR12). The total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels and LDL-C/HDL-C (L/H) ratio were measured every two weeks.

Patients This study included 101 patients. Seventeen cases of liver cirrhosis and nine cases of DAA retreatment were registered. The G/P treatment period was 8 weeks in 74 cases and 12 weeks in 27 cases.

Results SVR12 was evaluated in 96 patients. The rate of achievement of SVR12 in the evaluable cases was 100%. We found significantly elevated TC and LDL-C levels over the observation period compared to baseline. The serum levels of HDL-C did not change during treatment but were significantly increased after treatment compared to baseline. The L/H ratio was significantly increased two weeks after the start of treatment but returned to the baseline after treatment.

Conclusion The primary endpoint of the SVR12 achievement rate was 100%. G/P treatment changed the serum lipid levels. Specifically, the TC and LDL-C levels increased during and after treatment, and the HDL-C levels increased after treatment. G/P treatment may be associated with a reduced thrombotic risk. Therefore, validation in large trials is recommended.

Key words: chronic hepatitis C, interferon-free direct-acting antiviral treatment, cholesterol

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**Introduction**

The global prevalence of viremic hepatitis C virus (HCV) was estimated to be 1.0% in 2015, corresponding to 71.1 million viremic infections. HCV still infects many people and is one of the most important diseases in the world (1).

In recent years, HCV treatment has dramatically changed due to the emergence of direct-acting antivirals (DAAs). Glecaprevir and pibrentasvir (G/P) treatment has high anti-HCV activity and has yielded excellent results with regard to achieving a sustained virologic response (SVR) and high tolerance in clinical trials (2-4). Based on these results, G/P treatment was approved for DAA-naïve patients and those with a history of DAA failure with hepatitis C in September 2017 in Japan. Clinical trials involving G/P treatment for Japanese patients (CERTAIN-1 and CERTAIN-2 trials) have reported SVR rates of 99%-100% in DAA-naïve patients with HCV genotype 1 and 2 with or without compensated cirrhosis (8-week treatment without cirrhosis and 12-week treatment for compensated cirrhosis) (5-7).

However, HCV utilizes the lipid metabolism system and efficiently increases the number of hepatocytes. Scavenger receptor class B type 1 and low-density lipoprotein receptor, which are receptors for high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), are involved in HCV entry (8). Patients with HCV infection reportedly show lower total cholesterol (TC) levels than the general population without HCV infection (9). However, how this lipid level fluctuation affects patients with HCV infection remains unclear. Furthermore, the differences in the effects of DAA treatment are unknown. While many reports on lipid level changes after DAA treatment have been published, the lipid level changes vary depending on the type of drug and thus remain difficult to grasp (10-24).

In this study, we performed a prospective observational study of the treatment efficacy and lipid level fluctuations following G/P treatment.

**Methods**

**Patients**

Between January 2018 and February 2019, patients with chronic hepatitis and liver cirrhosis who underwent G/P treatment were enrolled.

**Therapeutic protocols**

G/P treatment was administered for either 8 or 12 weeks. The diagnosis of cirrhosis was determined by the attending physician based on the clinical and imaging findings. Cases of compensated cirrhosis, DAA retreatment, and genotype 3 were treated for 12 weeks, and other cases were treated for 8 weeks. According to the package insert for G/P treatment, concomitant use with atorvastatin is contraindicated. Therefore, patients being treated with atorvastatin were switched to another dyslipidemia drug. The attending doctor was allowed to choose all dyslipidemic drugs, except for atorvastatin. Patients on atorvastatin therapy were switched to other agents at least two weeks before G/P treatment; patients were excluded if they started or changed their medication for lipid level abnormalities between the start of G/P treatment and 24 weeks after treatment.

**Demographic data and laboratory tests**

Demographic data, sex, and age at the initiation of therapy were collected. Aspartate 2-oxoglutarate aminotransferase (AST), alanine 2-oxoglutarate aminotransferase (ALT), TC, LDL-C, HDL-C, and TG levels were examined every two weeks. Blood tests were performed on an empty stomach. HCV RNA was measured every 4 weeks during G/P treatment and at weeks 4, 12, and 24 after treatment.

**Endpoint**

The primary endpoint was the achievement of an SVR rate at week 12 (SVR12) after the end of G/P treatment (EOT). The secondary endpoints were the SVR rate at week 24 (SVR24), breakthrough rate, relapse rate, safety, treatment failure factors, and changes in lipid levels (TC, LDL-C, HDL-C, and TG) during and after G/P treatment. SVR12 and SVR24 were assessed in the intention-to-treat (ITT) population and the modified ITT (mITT) population excluding patients lost to follow-up after EOT.

**Ethical standards**

Written informed consent was obtained from each patient, and the study protocol was approved by the Institutional Review Board of Sapporo Medical University (Sapporo, Japan) in accordance with the Declaration of Helsinki (approval nos. 292-161). The research plan was registered as UMIN 000034794.

**Statistical analyses**

All statistical analyses were performed using the JMP software program, version 14 (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed as the mean ± standard deviation. Tukey-Kramer’s method was used to compare data between patients given 8- and 12-week administrations. Longitudinal changes in the same group were compared using a paired Student’s t-test. A two-tailed probability (P) value of <0.05 was considered statistically significant.

**Results**

**Patient characteristics**

The registration flowchart is shown in Fig. 1. During the enrollment period, 101 patients were enrolled in the study. Patients who were treated for eight weeks despite retreatment and those who were started for dyslipidemia in the DAA treatment period were excluded from this study. There
Figure 1. The registration flowchart.

Table 1. Demographics and Clinical Characteristics at Baseline of 101 Patients with Chronic Hepatitis C.

| Characteristic                  | Total (n=99) | 8 w (n=72) | 12 w (n=27) | p value† |
|--------------------------------|-------------|-----------|-------------|---------|
| Male/female                    | 46/53       | 35/37     | 11/16       | 0.48    |
| Age (range), years             | 66 (27–101) | 66 (27–101)| 66 (43–85)  | 0.54    |
| History of DAA failure (%)     | 8 (8)       | 0         | 8 (29.6)    |         |
| Cirrhosis (%)                  | 21 (21)     | 0         | 21 (77.8)   |         |
| HCV Serogroup 1/2/3            | 54/44/1     | 41/31/0   | 14/12/1     | 0.24    |
| AST, IU/L (IQR)                | 43.5 (29–73)| 40 (26.8–70.5)| 58 (29–79)| 0.20    |
| ALT, IU/L (IQR)                | 43 (23–72.8)| 41 (22.7–70)| 59 (22–74)  | 0.77    |
| PLT×10^3 μL (IQR)              | 16.6 (12.4–20.7)| 17.1 (13.9–21.9)| 11.7 (9.2–18.1)| 0.0002 |
| T-bil, mg/dL (IQR)             | 0.6 (0.5–0.8)| 0.6 (0.45–0.8)| 0.7 (0.5–1.09)| 0.12    |
| Alb, g/dL (IQR)                | 4 (3.8–4.3)| 4 (3.9–4.2)| 3.9 (3.5–4.3) | 0.26    |
| HCV RNA, log_{10} IU/mL (IQR)  | 6.2 (5.7–6.7)| 6.3 (5.7–6.7)| 6.1 (5.6–6.7)| 0.71    |
| TC, mg/dL (IQR)                | 161.5 (136–184)| 163.8 (140–188)| 152 (135–171)| 0.0497  |
| LDL-C, mg/dL (IQR)             | 89 (70–109)| 91.5 (70.8–116.8)| 73 (60.5–95)| 0.0096  |
| HDL-C, mg/dL (IQR)             | 49 (38–58.5)| 49.5 (38–58) | 48 (38.5–64.3) | 0.53    |
| TG, mg/dL (IQR)                | 101 (76.5–145)| 104.5 (74–146)| 88 (77.5–129)| 0.45    |
| LDL/HDL ratio (IQR)            | 1.84 (1.34–2.32)| 1.88 (1.54–2.44)| 1.6 (0.96–2.20)| 0.035   |

Continuous variables are shown as medians (interquartile range) with analysis by Mann–Whitney’s test. Categorical variables are expressed as the number of patients (n) with frequencies (%), with analysis using the chi-squared test. †8 w vs. 12 w

were 72 patients receiving 8-week treatment and 27 receiving 12-week treatment. The patient characteristics are shown in Table 1. In the 12-week treatment group, 29.6% (8/27) of patients had a history of DAA treatment, and 77.8% (21/27) had cirrhosis. A liver biopsy was performed in 13 patients. Thirteen patients were on medical therapy for dyslipidemia. There was one patient who was taking atorvastatin before G/P treatment. Therefore, that patient’s treatment for dyslipidemia was changed from atorvastatin to ezetimibe two weeks before the start of G/P treatment. The other dyslipidemic patients were treated with rosuvastatin in eight cases, pravastatin in two cases, bezafibrate in one case, and ethyl icosapentate in one case. The 12-week treatment group had significantly lower platelet counts, TC and LDL-C levels, and L/H ratios than the 8-week treatment group (Table 1).

Treatment effectiveness and safety

Dropout cases were observed in two cases of SVR4, five cases of SVR12, and nine cases of SVR24. The primary endpoint, the SVR12 achievement rate, was 95% in the ITT population and 100% in the mITT population. The secon-
changes in serum lipid levels

Changes in lipid levels were also examined. Longitudinal changes in serum TC, LDL-C, HDL-C, and TG levels in patients treated for eight weeks are shown in Fig. 2. The serum TC levels increased significantly from baseline to four weeks after the start of G/P treatment. Thereafter, the increase persisted until the 24th week after the EOT. The serum LDL-C levels increased signficantly from baseline to two weeks after the start of G/P treatment. Thereafter, similar to TC, the increase persisted until the 24-week time point after the EOT. In contrast, the serum HDL-C levels did not increase significantly during G/P treatment but did increase significantly after treatment compared with baseline. There was no significant change in the serum TG levels throughout the observation period.

Longitudinal changes in the serum TC, LDL-C, HDL-C, and TG levels in patients treated for 12 weeks are shown in Fig. 3. The serum TC levels gradually increased after the start of treatment and significantly increased from baseline to 12 weeks after the start of G/P treatment. After treatment, the TC levels rapidly increased and remained elevated. The serum LDL-C levels increased throughout the observation period. The serum LDL-C levels were significantly increased two weeks after the start of treatment. In addition, the LDL-C levels increased after treatment, similar to the TC levels. The serum HDL-C levels and eight-week administration were not significantly different during treatment but increased significantly after treatment. There were no significant changes in the serum TG levels throughout the observation period.

No significant differences in serum TC, LDL-C, HDL-C, or TG levels were observed between patients with and without cirrhosis.

The comparison of changes in the serum L/H ratio between patients treated for 8 weeks and 12 weeks

The serum LDL-C levels increased in the early stage of G/P treatment, and the HDL-C levels increased in the late stage of treatment. Based on these results, we examined the changes in the L/H ratio (Fig. 4). The L/H ratio was significantly increased at two weeks after the start of treatment in both treatment groups. However, the ratio gradually decreased over time, eventually returning to the baseline.
increased after treatment, and the L/H ratio increased during previous studies (5-7). Of note, the LDL-C levels increased in the mITT population, which was similar to the finding in by G/P treatment was 95% in the ITT population and 100% in the CERTAIN-2 trial, a phase III, open-label, multicenter study that assessed the safety and efficacy of G/P treatment in Japanese patients with genotype 2 HCV infection, no virologic failures occurred, resulting in an SVR12 rate of 100% in the mITT population. According to the CERTAIN-1 trial, a phase III, open-label, multicenter study that assessed the safety and efficacy of G/P treatment in Japanese patients with genotype 1 HCV infection, no virologic failures occurred, resulting in an SVR12 rate of 100% in the mITT population (5). Furthermore, according to the CERTAIN-2 trial, a phase III, open-label, multicenter study that assessed the safety and efficacy of G/P treatment in Japanese patients with genotype 2 HCV infection, no virologic failures occurred, resulting in an SVR12 rate of 100% in the mITT population (5).

Discussion

This study demonstrated the effectiveness of G/P treatment and changes in serum lipid levels in patients with HCV infection. We found that the SVR12 achievement rate by G/P treatment was 95% in the ITT population and 100% in the mITT population, which was similar to the finding in previous studies (5-7). Of note, the LDL-C levels increased at an early stage during treatment, while the HDL-C levels increased after treatment, and the L/H ratio increased during treatment but returned to baseline after treatment.

In the present study, the SVR12 achievement rate was 100% in the mITT population. According to the CERTAIN-1 trial, a phase III, open-label, multicenter study that assessed the safety and efficacy of G/P treatment in Japanese patients with genotype 1 HCV infection, no virologic failures occurred, resulting in an SVR12 rate of 100% in the mITT population (5). Furthermore, according to the CERTAIN-2 trial, a phase III, open-label, multicenter study that assessed the safety and efficacy of G/P treatment in Japanese patients with genotype 2 HCV infection, no virologic failures occurred, resulting in an SVR12 rate of 100% in the mITT population (5).
The mechanism underlying the changes in lipid levels induced by DAA drugs remains unclear, but there are two possible explanations. One is the restoration of cholesterol synthesis along with an improved liver function after the disappearance of HCV. Notably, the difference in TC elevation at 6 months after GP treatment in the 12-week group was significantly greater than that in the 8-week group (P=0.04 paired t-test). The other is reduced liver inflammation associated with the elimination of the HCV protein. Extra-cellular HCV core protein transmits a signal through the receptor for the complement component C1q (gC1qR), resulting in the phosphorylation of Signal transducer and activator of transcription 3 (STAT3) in human monocytes, macrophages, and dendritic cells. Phosphorylation requires activation of the phosphoinositide 3-kinase/AKT pathway, as well as transcription, and translation. Furthermore, gC1qR-mediated STAT3 phosphorylation is dependent on the interleukin-6 autocrine pathway (25). HCV NS5A also activates STAT3 through cooperation with Janus kinase-1 (26).

Next, we focused on the changes in lipid levels induced by DAA drugs. The changes in lipid levels were different depending on the type of DAA and whether the changes were during or after treatment. All reports demonstrated a significant elevation of TC and LDL-C levels during DAA treatment that was sustained after treatment, while five reports showed a significant elevation of HDL-C levels during DAA treatment (13-15, 24), and four reports did not (10, 18, 21, 23). HDL-C levels were elevated during DAA treatment in studies with daclatasvir-asunaprevir and in genotypes 2, 3, and 4. However, there are no reports of drugs that did not induce changes in HDL-C levels during DAA treatment but increased the levels after treatment.
low risk of thrombosis is recommended.

There are two reports on changes in the L/H ratio after DAA treatment. El Sagheer et al. reported a significant increase in the L/H ratio at the end of simeprevir plus sofosbuvir treatment in comparison with pretreatment (14). Gitto et al. reported a significant increase in the L/H ratio at 24 weeks after 6 types of DAA treatment compared with pretreatment (16). In the present study, we found that the L/H ratio increased in the early stage after starting treatment and then returned to the baseline ratio. Compared with other DAAs, the change in the L/H ratio in HCV patients treated with G/P was transient. The reason for this change in the L/H ratio remains unclear, despite being characteristic of the drug. Therefore, G/P treatment can contribute to the reduction in the thrombotic risk, in contrast to other DAAs.

Several limitations associated with the present study warrant mention. First, the sample size was small. Second, we were unable to observe the long-term changes in the serum lipid levels. Therefore, we were unable to confirm whether or not the enrolled patients had thrombosis in the present study because the observation period was limited to 24 weeks after treatment. Third, we were unable to examine the relationship between the nutritional status and fatty liver because we did not measure the weight. Fourth, we were unable to check for interleukin 28B single nucleotide polymorphisms.

In conclusion, the SVR12 achievement rate with G/P treatment was 95% in the mITT population and 100% in the mITT population. G/P treatment for hepatitis C changes serum lipid levels. In particular, the TC and LDL-C levels increased during and after G/P treatment, and the HDL-C levels increased after treatment. G/P treatment may be a drug with a low thrombotic risk after HCV treatment. Further clinical trials with many patients are warranted.

The authors state that they have no Conflict of Interest (COI).

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