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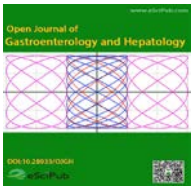

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Effectiveness and safety of glecaprevir and pibrentasvir for hemodialysis patients with hepatitis C virus infection at a single center

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ABSTRACT

Background/Aims: Glecaprevir/pibrentasvir (GLE/PIB) is a pan-genotypic regimen for the treatment of hepatitis B virus (HCV) infection. GLE and PIB are direct acting antiviral (DAA) agents that can be used for patients with chronic renal failure who are on hemodialysis (HD) and those with HCV genotype 2 infections. Here, we report the usefulness and safety of GLE/PIB in 13 hemodialysis (HD) patients with HCV infection.

Material and Methods: The subjects comprised patients with genotype 1 and 2 (six each) and one unknown genotype patient in whom GLE/PIB therapy was introduced by December 2018. The mean age was 69.2 (59-78) years (seven men and six women). The mean HCV RNA amount prior to treatment initiation was 4.81 (2.1-6.5). The administration periods were 8 and 12 weeks (n = 9 and 4, respectively).

Results: Twelve patients received all the doses orally while an increase in total bilirubin (T-BIL) caused administration to be discontinued in one patient. HCV RNA at week 4 after treatment initiation became undetectable in 11 (91.6%) of the 12 patients. All patients achieved rapid viral response (RVR). Concerning adverse effects, although itching occurred in three (25%) patients, the symptom improved following administration of oral medication and the treatment was able to be continued.

Conclusion: The results suggest that GLE/PIB can also be safely administered to HD patients. However, the usefulness and safety need to be further studied by examining more cases.

Keywords: hepatitis C, hemodialysis,

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Introduction

The treatment of chronic hepatitis C (HCV) with interferon (INF) started in 1992 and the complete response rate was low. However, with the concomitant use of oral medications, which started in 2016, the complete response rate has increased to over 90%. Various medications for genotype 1-infected patients on hemodialysis (HD) have emerged and the complete response rate has remarkably improved, whereas there are no medications for genotype 2-infected patients on HD. Glecaprevir/ pibrentasvir (GLE/PIB) is a pan-genotypic regimen for the treatment of HCV infection. GLE and PIB are direct-acting antiviral (DAA) agents that can be used for patients with chronic renal failure who are on HD and in genotype2-infected patients. Here, we report the usefulness and safety of this regimen for hemodialysis (HD) patients.

Materials and Methods

Patient characteristics

The subjects included in this study were 13 patients in whom GLE/PIB therapy was introduced by December 2018, consisting of six patients each with genotype 1 and 2 infection and one with unknown genotype infection. The mean age was 69.2 (59-78) years (seven men and six women). The mean HCV RNA amount was 4.81 (2.1-6.5) and the administration periods were 8 and 12 weeks (n = 9 and 4, respectively, Table 1).

No patient had a medical history of hepatocellular carcinoma (HCC) in the present study and this was the first viral therapy for all the patients. We explained the objectives and methods in writing to subjects and obtained informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki following the ethical guidelines for medical research involving human subjects (The Ministry of Education, Science, Sports and Culture and The Ministry of Health, Labor and Welfare, revised in 2014) and received approval from the ethics committee to perform the present study.

Results

Twelve patients received all the doses orally while elevation of the total bilirubin (T-Bil) value to 5.0 mg/dL in one patient on day 4 of administration, led to treatment discontinuation at the request of the patient and the patient's family. The T-Bil value improved to the normal level after discontinuation. HCV RNA at week 4 after treatment initiation became undetectable in 11 (91.6%) of the 12 patients. It was also undetectable by week 8 in 11 patients and the sustained virologic response rate (SVR) was 100% by week 12 after treatment completion (Fig 1).

Although itching occurred in two (33%) patients, the symptom improved following oral administration of medication and the study treatment was continued.

Discussion

HD patients with chronic renal failure are at numerous risks for exposure to HCV such as during administration of blood products, invasive dialysis operation, and frequent hospital visit. The number of deaths of HD patients related to liver disease is 5.89-fold higher in those infected

Table 1. Patient characteristics

Sex ratio (men/women)	7/6
Age (years)	69.2 (59-78)
White blood cells	9861(2700-6800)
Hemoglobin	10.7 (9.3-14.2)
Platelets	13.9 (8.9-20.7)
AST	20 (11-41)
ALT	14 (6-33)
Serum albumin	3.62 (2.8-4.1)
FIB-4 index(<3.25/3.25≧)	2/11
Wisreria floribunda agglutinin＋Mac-2-binding protein (C.O.I)	2.26 (0.53-6.38)
Alpha-fetoprotein(ng/mL)	2.85 (1.17-5.52)
HCV RNA (log IU/mL)	4.81(2.1-6.5)
Serotype(1/2/non)	6/6/1
A history of treatment	None
Administration period	(8/12 week)9/4

AST, aspartate transaminase; ALT, alanine aminotransaminase; FIB-4, fibrosis index based on the four factors

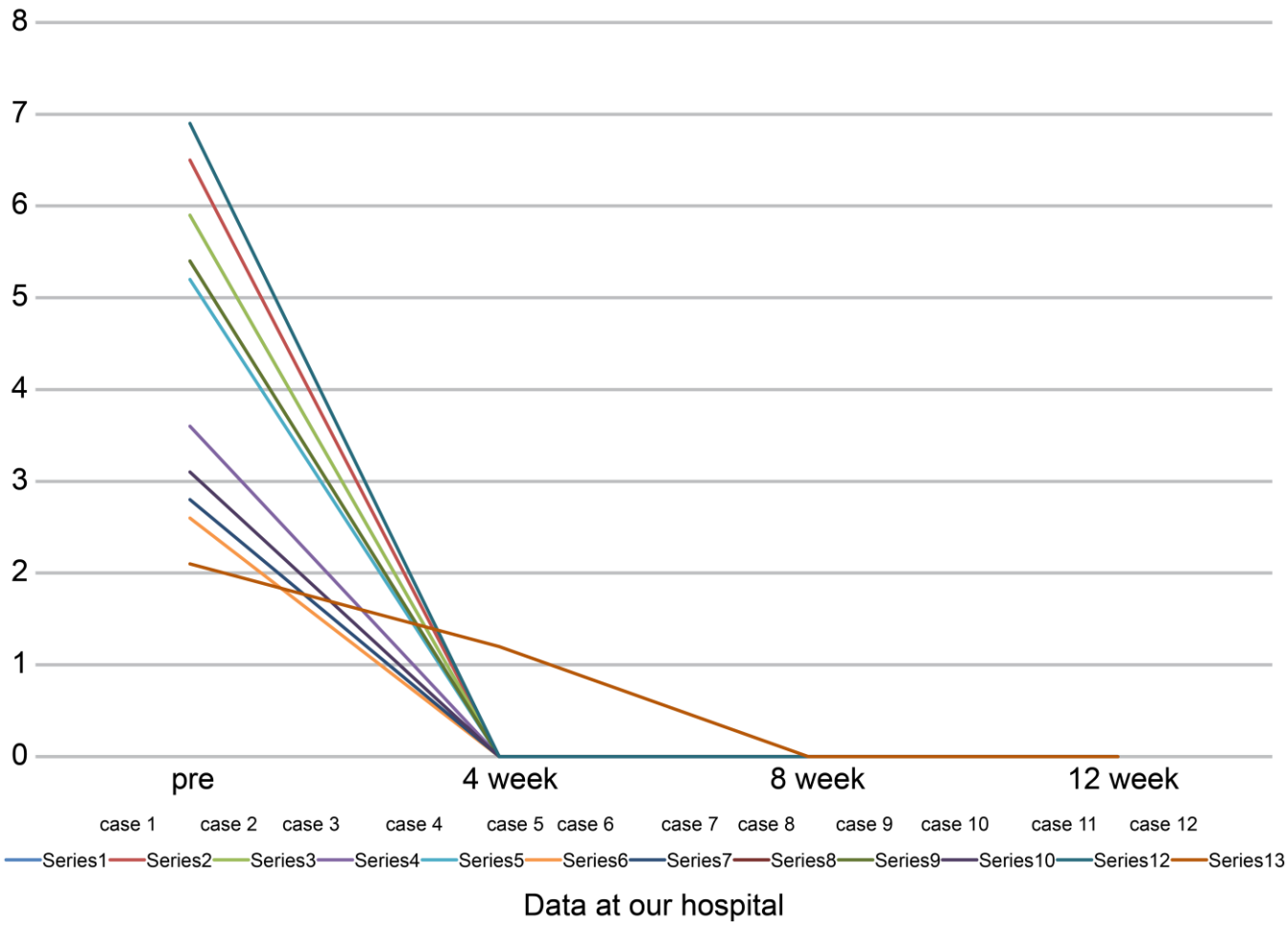

Fig 1　Changes in quantity of virus after treatment

Table 2. Pretreatment blood test results (63-year-old woman)

Peripheral blood	
WBC	5500/μL
RBC	386×10^4/μL
Hb	13.2 g/dL
Plt	15.8×10^4/μL
M2BPGi	2.27
P-3-P	49.4 ng/mL
Type IV C.7S	5.3 ng/mL
AFP	2.4 ng/mL
Fib 4-index	1.68
Age	63
AST	14
ALT	11
PLT	15.8
Blood chemistry	
AST	14 IU/L
ALT	11 IU/L
LDH	207 IU/L
ALP	275 IU/L
γ-GTP	19 U/L
TP	5.7 g/dL
Alb	3.6 g/dL
BUN	46 mg/dL
Cr	7.77 mg/dL
GFR	5
Viral marker	
HBs-Ag	negative
HCV group	2
HCV-RNA	7.2

with HCV than uninfected patients and been shown to be caused by the development of cirrhosis and liver cancer (1). The study of INF therapy for HD patients by Kikuchi et al. (2) showed an SVR of 39% (22/56) in the REACH Study of PEG-INFα2a, in which the SVR was not high enough and the subjects were limited to young patients and those with less complications (2). Then, the administration of INF-free oral medications commenced in 2016 and was indicated for HD patients with genotype 1 HCV infections.

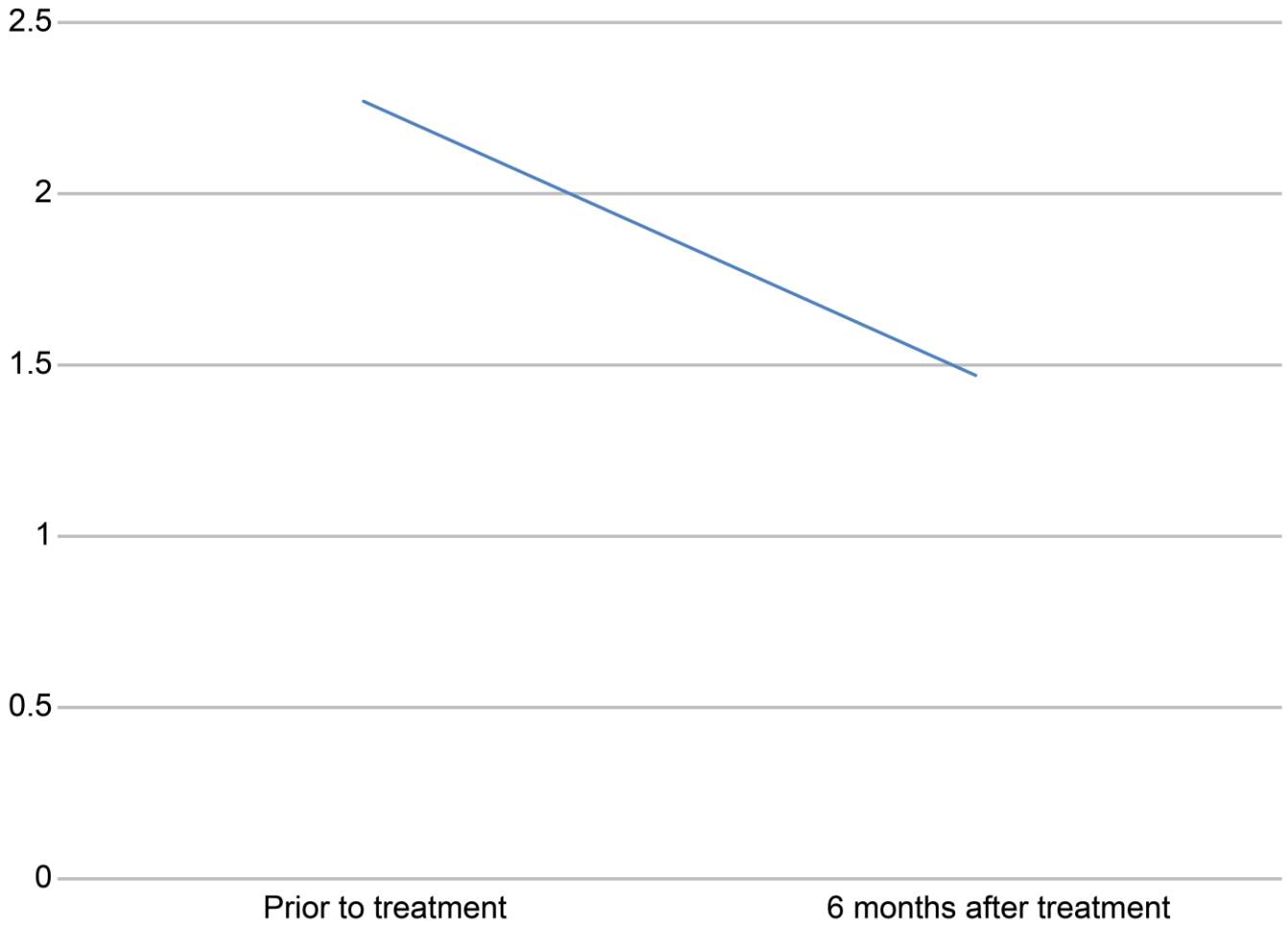

Fig 2 Changes in Mac-2-binding protein glycosylation isomers (M2BPGi) level before and after treatment

Toyoda et al. (3) and Suda et al. (4) reported that the SVR12 reached 100% (28/28) and 95.5% (20/21), respectively in HD patients. However, oral medications were not indicated for genotype 2 patients. Although the subsequently launched ombitasvir/ paritaprevir/ ritonavir combination was also indicated for HD patients, these agents were contraindicated for concomitant use with many medications and were not indicated for genotype 2 patients (5). The SVR was reported to be 99% following the use of grazoprevir and elbasuvir, which were also not indicated for genotype 2 patients (6). A pan-genotypic regimen of GLE/PIB, which is indicated for

genotype 2 HD patients is considered useful for the treatment of HD patients with complicated HCV infection (7-9).

We successfully administered the regimen for each indicated period to all six genotype 2 patients at our hospital. However, the period of oral administration needed to be set to 8 or 12 weeks in the present study. Based on the guidelines for HD indicate, it is difficult to compare the aspartate aminotransferase/ alanine aminotransferase (AST/ALT) values of HD patients with those of normal individuals. However, even when the liver function is normal, liver fibrosis is shown to be advanced. Presently, markers of liver fibrosis such as Mac-2-binding protein glycosylation isomers (M2BPGi) (10) and autotaxin have emerged. The fibrosis index based on the four factors (FIB4 -INDX), age (years) × AST (U/L)/platelets (109/L) × ALT (U/L) (11) is a serum marker of fibrosis. This is one of the markers of fibrosis based on age, AST, ALT, and platelets.

This marker only uses blood test results measured at each examination in ordinary clinical settings to calculate values using the formula. A value ≥ 3.25 is known to indicate advanced liver fibrosis. The present study, which used this index showed no increase in the value in genotype 2 patients, whereas an increase was observed in two genotype 1 patients administered the regimen for 12 weeks and fibrosis was found. M2BPGi is a glycomarker that specifically detects a change in the sugar chain structure of M2BP caused by liver fibrosis. Since the value increases as liver fibrosis advances, this protein is useful as a marker that can predict the degree of advancement from chronic hepatitis to cirrhosis without performing a liver biopsy and, therefore, came to be covered by insurance in 2015. Our study showed that there was no change in M2BPGi before and after dialysis.

In the present study, the highest value was 6.38 (12). To develop a therapeutic strategy, liver fibrosis needs to be predicted using these markers and the administration period of oral medications should be set to 8 or 12 weeks. One case of a 63-year-old female patient with genotype 2 HCV infection is presented below (Table 2). Based on the high values of the fibrosis markers, M2BPGi (2.27), and P-3-P (49.4 ng/mL), we decided to administer the regimen for 12 weeks. In the present study, the virus was eliminated from this patient in 8 weeks, and it did not flare up subsequently. In addition, although the M2BPGi level was 2.27 before treatment, it decreased to 1.47 6 months after treatment (Fig 2).

The results suggested that this treatment strategy improved liver fibrosis. Concerning adverse effects, itching, which was observed in three patients, did not appear immediately after administration but it occurred after week 2 of administration. The itching did not occur at the same time as drug administration and both patients were treated with medications. These patients were managed with nalfurafine hydrochloride, which improved the symptoms and allowed continuation of oral administration (13). Adverse effects may not occur immediately

after administration as seen in these cases; thus, patients should always be examined at week 1 and 2 after administration to monitor the symptom to ensure the treatment is safely conducted.

In contrast, patients with no symptom can be followed during long-term administration at 1 or 2 weeks after initial administration. In the present study, one patient had an unknown genotype infection and exhibited viral elimination by week 12 of administration. The treatment for all patients in the present study was conducted at our hospital and the branch and patient information including blood test results were available in electronic medical records, which allowed prompt management. Moreover, the effectiveness and safety of the treatment has not been previously reported by a single facility.

Okubo et al. (14) conducted an epidemiological study of the incidence of HCV infection and the status of interventions in approximately 3,000 HD patients at 31 dialysis facilities. Their findings demonstrated that the HCV antibody-positive rate was 5.3%, which was clearly higher than that of non-HD patients, and 45.5% of patients received interventions with anti-viral therapy and, thus, interventions were not performed in many patients (14). Administration of the medications investigated in the present study allowed the safe completion of treatment in 12 weeks at the most, which would contribute to the prevention of cirrhosis and HCC caused by advancement of liver fibrosis. Thus, we encourage patients to be aware of these facts when visiting hepatologists.

Lastly, the results showed that these oral medications can be safely used without any serious adverse effects, providing benefits to genotype 2 patients. Following the launching of new oral medications for genotype 2, pan-genotype treatment does not seem to be widely prescribed. However, patients should be treated with these medications based on the benefits, and therefore, it is very important to determine the state of liver fibrosis and establish an appropriate administration period. Although the number of cases was small in the present study, we plan to examine additional cases to further study the safety and effectiveness.

Conclusion

Our findings indicate that GLE/PIB are safe and effective DAA medications for HD patients as well. Finally, the usefulness and safety of this regimen needs to be further studied by accumulating and examining more patient cases.

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