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Development of Interferon-Free, Direct-Acting Antivirals Treatment for Japanese Patients with Chronic Hepatitis C Infection and Chronic Kidney Disease

Masanori Atsukawa[1], Chisa Kondo[1], Tadamichi Kawano[1], Tomomi Okubo[2], Taeang Arai[1], Ai Nakagawa-Iwashita[1], Norio Itokawa[1] and Katsuhiko Iwakiri[1]

[1]Division of Gastroenterology and Hepatology, Nippon Medical School, Tokyo, Japan
[2]Division of Gastroenterology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan

Chronic hepatitis C virus (HCV) infection can progress to liver cirrhosis and hepatocellular carcinoma. Interferon-based treatment was previously the only antiviral therapy for chronic hepatitis C infection; however, development of interferon-free, direct-acting antivirals, in 2014, markedly improved treatment efficacy and safety. Treatment indications were expanded to include elderly adults, patients with advanced liver fibrosis, and patients with chronic hepatitis C infection complicated by chronic kidney disease, for whom antiviral therapy had been difficult or contraindicated. The median age of patients with chronic HCV infection in Japan is 70 years, older than in other countries. Because diminished renal function is common in elderly adults, a safe and effective treatment for chronic hepatitis C complicated by chronic kidney disease has been expected in Japan. In addition, the HCV antibody-positive rate is higher in hemodialysis patients than in non-hemodialysis patients in Japan. Numerous studies have reported that direct-acting antivirals are safe and effective for hepatitis C patients on hemodialysis. This review summarizes treatments available in Japanese clinical practice for patients with chronic HCV infection complicated by chronic kidney disease, including hemodialysis patients.
 (J Nippon Med Sch 2021; 88: 163−170)

Introduction

A report published in 2017 noted that about 17 million people are infected with hepatitis C virus (HCV) worldwide and that 400,000 die annually from diseases associated with chronic hepatitis C, such as liver cirrhosis and hepatocellular carcinoma[1]. In Japan, 1.5 to 2 million people are estimated to be infected with HCV[2,3]. The objective of treatment for chronic hepatitis C is to eliminate the virus, prevent progression to liver cirrhosis and hepatocellular carcinoma, and improve prognosis and quality of life. HCV infection was recently reported to be associated with death related to multiple organs other than liver disease; thus, early treatment is recommended[4,5].

Although interferon-based therapy has been used as antiviral therapy for chronic HCV infection since the 1990s, the rate of sustained virologic response (SVR) after interferon-based treatment is only 40% to 80%, and the high frequency of adverse events reduces therapeutic effectiveness[6–10]. Factors determining the effectiveness of interferon-based therapy include HCV genotype and the presence of amino acid substitutions at position 70/91 of the HCV core region[11] and ISDR mutation of the NS5A region[12,13]. In addition, low vitamin D level was reported to diminish the therapeutic effects of interferon[10], and a single nucleotide polymorphism near the IL28B gene greatly diminished the effectiveness of interferon-based therapies as a host factor in patients with chronic hepatitis C[8,14].

To overcome these limitations of interferon-based therapy, interferon-free, direct-acting antivirals (DAAs) were

introduced in 2014 in Japan, before their introduction in Western countries. DAAs target the non-structure (NS) protein of the HCV RNA genome, specifically, NS3, NS5 A, and NS5B, which are not incorporated in the virion. Currently, a regimen that combines 2 or more NS3 protease inhibitors, an NS5A inhibitor, and an NS5B polymerase inhibitor or NS5B polymerase inhibitor and ribavirin, is approved for therapy. Daclatasvir/asunaprevir[15], ombitasvir/paritaprevir/ritonavir[16], elbasvir/grazoprevir[17], and pibrentasvir/glecaprevir[18] are combinations of an NS5A inhibitor and NS3 protease inhibitor, and sofosbuvir/ledipasvir[19] and sofosbuvir/velpatasvir±ribavirin[20] are combinations of an NS5B polymerase inhibitor and NS5A inhibitor. Daclatasvir/asunaprevir/beclabuvir[21], a combination of 3 drugs (an NS3 protease inhibitor, NS5A inhibitor, and NS5B polymerase inhibitor) is available in Japan, as is sofosbuvir/ribavirin, a combination of an NS 5B inhibitor and ribavirin[22]. The indications and recommendations for each regimen depend on HCV genotype and the presence of decompensated liver cirrhosis[23].

The median age of chronic hepatitis C patients in Japan is 70 years, which is older than in other countries. Long-term chronic inflammation promotes liver fibrosis in many patients. Moreover, renal function is frequently diminished in elderly adults. The rate of chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) in adults 70 years or older is approximately 27% among men and 31% among women. Moreover, the HCV antibody-positive rate is about 5% in hemodialysis patients, higher than in the general population, and 60% of hemodialysis patients are believed to have chronic HCV infection[24].

Unfortunately, because the intermediate metabolites of sofosbuvir and ribavirin are metabolized by the kidney, they are contraindicated for patients with severe renal impairment in Japan. Therefore, indicated regimens for patients with CKD, including hemodialysis patients, are limited to daclatasvir/asunaprevir, ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, and pibrentasvir/glecaprevir[23].

This report reviews the safety and effectiveness of DAA combination therapy for chronic HCV infection complicated by CKD in Japanese clinical practice.

Interferon-Based Treatment

Because ribavirin is contraindicated for patients with CKD, interferon monotherapy was the only option for such patients until DAAs became available. A multicenter study (REACH study) in Japan reported that interferon monotherapy was not effective for hemodialysis patients. The SVR rate was approximately 30% in genotype 1 patients, who are considered interferon-resistant, and the rate of treatment cessation attributable to adverse events was high[25].

Resistance-associated substitutions (RASs) were noted early on when DAAs were used alone during drug development; thus, several treatment regimens that combine DAAs with interferon and ribavirin were developed. Telaprevir was approved in 2011 as a first-generation DAA, and simeprevir was approved in 2013 as a second-generation DAA. Both were used in a triple-drug regimen requiring concomitant use of pegylated-interferon (PEG-IFN) and ribavirin. The SVR rate of 75% to 80%, even for patients with chronic HCV genotype 1 infection that responded poorly to interferon-based treatment, was a marked improvement over the SVR rate achieved by conventional PEG-IFN/ribavirin combination therapy. However, these regimens are not indicated for patients with chronic HCV infection complicated by CKD.

Daclatasvir/Asunaprevir

After the era of PEG-IFN/DAA combination therapy, a treatment regimen using interferon-free DAAs-daclatasvir/asunaprevir combination therapy-was approved in 2014 in Japan. This regimen enabled treatment of patients for whom antiviral therapy was contraindicated because of ineligibility for interferon-based therapy and nonresponse to interferon. To our knowledge, there have been 12 reported clinical cases complicated by CKD in clinical practice in Japan. Treatment effectiveness for these cases is shown in **Table 1**[26–37]. The SVR rate was 75% to 100% in hemodialysis patients, which indicates high effectiveness, and tolerance was favorable[26–30,36,37]. In addition, the SVR rate was high, 83.6% to 100%, in patients with stage 3/4 CKD not requiring hemodialysis[35].

However, the presence of RASs, especially against daclatasvir, was a notable limitation of this regimen. Iio et al. reported that treatment outcomes were worse in patients with a history of previous treatment with simeprevir and in those with NS5A resistant-associated variant Y 93H on the first treatment[38]. Furthermore, transaminase elevation is a frequently reported adverse event[39]. Although daclatasvir/asunaprevir combination therapy has proven highly effective in Japan, this regimen, as of 2020, is not recommended as a first-line treatment, regardless of the presence of CKD, after the development of regimens with high efficacy against RASs, described below[23].

Table 1   Real-world outcomes of daclatasvir and asunaprevir therapy for hepatitis C patients with chronic kidney disease in Japan

HCV genotype	Sample size	SVR rate (%)	Number of hemodialysis patients [SVR rate (%)]	Authors Reference number
GT1	28	100	28 (100)	Toyoda H et al. (26)
GT1	21	95.5	21 (95.5)	Suda G et al. (27)
GT1	18	100	18 (100)	Kawakami Y et al. (28)
GT1	4	75	4 (75)	Sato K et al. (29)
GT1	10	100	10 (100)	Miyazaki R et al. (30)
GT1	21	95.2	0 (-)	Nakamura Y et al. (31)
GT1	29	93.1	0 (-)	Morisawa N et al. (32)
GT1	24	100	0 (-)	Suda G et al. (33)
GT1	90	94.4	0 (-)	Ishigami M et al. (34)
GT1	55	83.6	0 (-)	Kondo C et al. (35)
GT1	23	91.3	23 (91.3)	Otsuka T et al. (36)
GT1	67	95.5	67 (95.5)	Fujii H et al. (37)

GT1: Genotype 1, SVR: sustained virologic response

Table 2   Real-world outcomes of ombitasvir/paritaprevir/ritonavir combination therapy for hepatitis C patients with chronic kidney disease in Japan

HCV genotype	Sample size	SVR rate (%)	Number of hemodialysis patients [SVR rate (%)]	Authors Reference number
GT1	54	98.1	0 (-)	Arai T et al. (43)
GT1	10	80.0	10 (80.0)	Morisawa N et al. (44)
GT1	31	96.8	31 (96.8)	Atsukawa M et al. (45)
GT1 and 2	4	75	4 (75)	Sato k et al. (46)

GT1: Genotype 1, SVR: sustained virologic response

Sofosbuvir/Ledipasvir

In 2015, a second-generation interferon-free DAA regimen, sofosbuvir/ledipasvir, was approved[19]. A Japanese phase 3 clinical trial investigated patients with chronic HCV genotype 1 infection, and the SVR rate was 100%. For genotype 2, a phase 3 study trial that included sofosbuvir/ribavirin combination therapy as a control confirmed the noninferiority of sofosbuvir/ledipasvir to sofosbuvir/ribavirin, which resulted in approval[40]. However, these regimens are contraindicated for patients with severe renal impairment in Japan because intermediate metabolites of sofosbuvir and ribavirin are metabolized in the kidney. However, Okubo et al. reported that sofosbuvir/ledipasvir was safe and effective for genotype 1 patients with stage 1-3 CKD[41]. The SVR rate was 94.7% in stage 3 CKD patients, and no progression of renal impairment was noted during treatment.

Sofosbuvir/Ribavirin

In a Japanese phase 3 study of 153 genotype 2 chronic hepatitis C patients with a median eGFR of 85 mL/min/1.73 m^2 (range, 51-209) the overall SVR rate was 97%[22].

We previously reported treatment outcomes for 270 patients with genotype 2 chronic hepatitis C; the SVR rate was 97%[42]. However, sofosbuvir is contraindicated for patients with an eGFR lower than 30 mL/min/1.73 m^2, and ribavirin cannot be given to patients with a creatinine clearance lower than 50 mL/min. The therapy was administered to patients with an eGFR of 32 mL/min/1.73 m^2 or higher in the study. In Japan this regimen remains contraindicated for patients with severe renal impairment, as is sofosbuvir/ledipasvir.

Ombitasvir/Paritaprevir/Ritonavir ± Ribavirin

In 2015, a combination tablet containing ombitasvir, paritaprevir, and ritonavir with a booster effect on these drugs was approved for genotype 1 patients[16]. Because these 3 drugs are mainly metabolized in the liver, they are theoretically administrable to patients with CKD, including those on hemodialysis. To our knowledge, 4 reports have described the use of ombitasvir/paritaprevir/ritonavir in Japanese clinical practice for chronic HCV genotype 1 infection complicated by CKD[43–46]. Data on the effectiveness of this regimen are shown in **Table 2**.

Table 3   Real-world outcomes of elbasvir and grazoprevir therapy for hepatitis C patients with chronic kidney disease in Japan

HCV genotype	Sample size	SVR rate (%)	Number of hemodialysis patients [SVR rate (%)]	Authors Reference number
GT1	109	97.2	20 (100)	Atsukawa M et al. (50)
GT1	23	96.7	23 (96.7)	Suda G et al. (51)
GT1	105	98.1	20 (95)	Ogawa E et al. (52)

GT1: Genotype 1, SVR: sustained virologic response

The limitations of this regimen include a slight reduction in effectiveness for patients with RASs of the NS5A region (as observed with daclatasvir), a reduction in SVR rate in patients with advanced liver fibrosis[47], and the fact that many drugs require caution, or are contraindicated, when used concomitantly with ritonavir, which resulted in the discontinuation of this regimen in Japan. A regimen including ribavirin for genotype 2 was also approved, and efficacy in non-CKD patients was high[48], but it cannot be administered to patients with severe renal impairment.

Elbasvir/Grazoprevir

Elbasvir/grazoprevir combination therapy was approved in 2016 in Japan. A Japanese phase 3 study investigated 336 patients with chronic HCV genotype 1 infection; those with renal dysfunction and a creatinine clearance lower than 50 mL/min were excluded. The SVR rate was 96.5% in patients with chronic hepatitis C infection and 97.1% in patients with compensated liver cirrhosis[17]. A study of elbasvir/grazoprevir combination therapy, the C-SURFER study, enrolled stage 4/5 CKD (eGFR<30 mL/min/1.73 m²) patients and hemodialysis patients in Western countries. The SVR12 rate was 99.1% (115/116)[49]. We previously reported treatment outcomes for elbasvir/grazoprevir combination therapy in HCV genotype 1 patients with CKD in Japan[50]. Among 337 patients, 49 had stage 3a CKD and 23 had stage 3b, 14 had stage 4, and 23 had stage 5 CKD (including 20 dialysis patients). The SVR12 rate was favorable in all groups. The frequency of adverse events was 6.4% (7/109) for patients with stage 3 or worse CKD and 9.7% (22/228) in the non-CKD group (stage 2 or milder)-a nonsignificant difference. To our knowledge, 2 studies have reported treatment clinical outcomes for patients with CKD[51,52]. The treatment outcomes for elbasvir/grazoprevir combination therapy in CKD patients in all 3 of the relevant reports are shown in **Table 3**. The SVR rate in CKD patients, including hemodialysis patients, was 97.2% to 98.1%, indicating high effetiveness[50–52]. As of 2020, elbasvir/grazoprevir combination therapy is a first-line treatment for chronic HCV infection complicated by CKD but is indicated only for genotype 1[23].

Pibrentasvir/Glecaprevir

The CERTAIN-1 and CERTAIN-2 Japanese phase 3 studies reported outcomes for pibrentasvir/glecaprevir combination therapy[53–55]. The SVR rate for pibrentasvir/glecaprevir combination therapy was investigated in patients with severe renal dysfunction and in hemodialysis patients in the Japanese phase 3 study CERTAIN-1, but the number of patients was small. Thus, we performed a prospective multicenter study and reported treatment outcomes and safety for pibrentasvir/glecaprevir combination therapy in patients with CKD stage 4/5[56]. Among patients with chronic hepatitis C and compensated liver cirrhosis treated with pibrentasvir/glecaprevir combination therapy, SVR was assessed in 832 patients, including 32 CKD stage 4 and 109 stage 5 CKD patients (including 100 dialysis patients). Of these patients, 38 had genotype 1 HCV, 102 had genotype 2, and 1 had genotype 3. The SVR12 rate was 99.3% (140/141) in patients with stage 4/5 CKD, and 100% (32/32), 99.1% (108/109), and 99.0% (99/100) in those with stage 4 CKD, those with stage 5 CKD (including dialysis patients), and hemodialysis patients, respectively. To our knowledge, 3 other studies investigated chronic HCV infection complicated by CKD in Japan[57–59]. The details of these reports are shown in **Table 4**. Pibrentasvir/glecaprevir combination therapy required a minimum of 8 weeks and safety was high. Pruritus was reported as an adverse event in many CKD patients, but efficacy was high for all genotypes. This regimen is now the first choice for CKD-complicated chronic hepatitis C[23]. Furthermore, pibrentasvir/glecaprevir combination therapy was effective for re-treatment of patients who failed to achieve SVR after previous treatment with DAAs. In clinical practice, Suda et al. reported that pibrentasvir/glecaprevir combination therapy was effective for 2 hemodialysis patients who failed to achieve SVR after daclatasvir/asunaprevir combination therapy[59].

Table 4 Real-world outcomes of pibrentasvir/glecaprevir therapy for hepatitis C patients with chronic kidney disease in Japan

HCV genotype	Sample size	SVR rate (%)	Number of hemodialysis patients [SVR rate (%)]	Authors Reference number
GT1-3	141	99.3	100 (99.0)	Atsukawa M et al. (56)
GT1-2	24	100	24 (100)	Morishita A et al. (57)
GT2	27	96.3	27 (96.3)	Suda G et al. (58)
GT1-2	2	100	2 (100)	Suda G et al. (59)

GT1: Genotype 1, SVR: sustained virologic response

Sofosbuvir/Velpatasvir

All the DAA-combining regimens described above are indicated for chronic hepatitis and compensated liver cirrhosis; however, no regimen was available for decompensated liver cirrhosis in Japan. A phase 3 Japanese study of patients with decompensated liver cirrhosis reported an SVR rate of 92%[20]. In addition, hepatic functional reserve improved in some patients who achieved SVR, which resulted in Japanese approval of sofosbuvir/velpatasvir combination therapy for decompensated liver cirrhosis, in 2019. In clinical practice, we reported a high SVR rate in a Japanese multicenter study of 71 patients with decompensated liver cirrhosis. This rate was similar to that reported in the phase 3 study[60]. However, this regimen is not indicated for patients with severe renal impairment because it includes sofosbuvir; thus, no DAA treatment option exists for decompensated liver cirrhosis complicated by CKD.

Discussion

Although we reviewed some DAAs regimens and their efficacy for patients with chronic hepatitis C with CKD, the current Japan Society of Hepatology guidelines recommend a 12-week elbasvir/grazoprevir regimen for genotype 1, and an 8- or 12-week pibrentasvir/glecaprevir regimen for all genotypes as the first choice for chronic hepatitis C complicated by CKD[23]. As described above, evidence for the effectiveness and safety of DAA treatment in clinical practice is strong. Patients with CKD and hemodialysis patients were previously difficult to treat, and development of DAA combination therapy has enabled safe and effective treatment for this patient population. Active introduction of DAA treatment for these patients is expected soon.

Values of biomarkers such as serum aspartate aminotransferase, alanine transaminase, and alpha-fetoprotein are lower in hemodialysis patients than in patients not receiving dialysis. However, hepatocellular carcinoma developed in approximately 10% of patients during a 10-year observation period, even in those with normal transaminase levels[61]. Thus, active introduction of DAA treatment is recommended for chronic hepatitis C complicated by CKD, which is similar to the recommendation for non-CKD patients. However, in a 2016 study, Okubo et al. distributed a questionnaire survey to Japanese physicians specializing in hemodialysis and found that about half were unaware of progress in chronic hepatitis C treatment for patients with CKD[24]. They suggested that medical cooperation between hepatologists and non-hepatologists would be needed in order to improve awareness.

The main purpose of eliminating HCV from chronic hepatitis C patients is prevention of progression to liver cirrhosis and hepatocellular carcinoma. In addition, the effects of HCV elimination on multiple organs other than the liver in chronic hepatitis C patients has frequently been reported. In 2011, Arase et al. reported that the rate of progression to CKD was markedly reduced by HCV elimination by interferon-based therapy[62]. In addition, insulin resistance was improved by achieving SVR with DAA treatment in patients with chronic hepatitis C[63]. Moreover, 50% to 70% of cardiovascular events were inhibited by achieving SVR with DAA treatment[64]. It is now possible to inhibit development of liver disease events of liver cirrhosis and hepatocellular carcinoma, and to improve systemic extrahepatic lesions, which suggests that nearly all HCV-positive patients can be treated.

Although almost all chronic hepatitis C patients now achieve virological cure because of the development of DAA treatment, progression of liver fibrosis due to persistent HCV infection does not immediately improve after achieving SVR, and hepatocellular carcinoma develops after HCV elimination in some patients. A high alpha-fetoprotein level after DAA treatment, the presence of liver cirrhosis, and a high level of Wisteria floribunda agglutinin-positive Mac-2 binding protein were reported to be associated with development of hepatocellular carcinoma after achieving SVR by DAA treatment[65–67]. Ide et

al. conducted a prospective study of 2,552 patients who achieved SVR after DAA treatment. The cumulative rate of hepatocellular carcinoma development was 1.3% after 1 year, 2.9% after 2 years, and 4.9% after 3 years, and advanced age, male sex, high γ-glutamyl transferase level, and high FIB-4 index were independent factors associated with development of hepatocellular carcinoma after achieving SVR[68].

Hepatic carcinogenesis is suppressed in patients with chronic hepatitis C, including CKD patients, who achieved SVR by DAAs treatment, as in non-CKD patients. In addition, Mahmoud et al. reported that the postoperative results were improved by prioritizing HCV treatment when performing kidney transplantation in patients with end-stage renal disease and chronic hepatitis C[69]. Thus, in patients with chronic hepatitis C with CKD, elimination of HCV by DAAs treatment not only prevents deterioration of renal function, but also prevents hepatic carcinogenesis and improves the results of renal transplantation.

In patients at high risk for hepatocellular carcinoma development after SVR, strict surveillance for early detection of hepatocellular carcinoma and curative treatments such as radiofrequency ablation and low-invasive surgery are strongly recommended[70].

Conclusion

Antiviral therapy for chronic hepatitis C has markedly improved, and a virological cure is now possible for almost all patients, including those with CKD. Outcomes are substantially worse for patients with chronic hepatitis C with CKD than for those without CKD. Thus, DAA treatment should be actively introduced for patients with chronic hepatitis C complicated by CKD, including those receiving hemodialysis.

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