Special Report

JSH Guidelines for the Management of Hepatitis C Virus Infection: A 2016 update for genotype 1 and 2

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PREAMBLE

THE JAPAN SOCIETY of Hepatology and Drafting Committee for Hepatitis Management Guidelines produced the first clinical practice guidelines for the management of hepatitis C virus (HCV) infection in 2012, followed by frequent updates. As English versions, we published JSH guidelines in 2013,1 and a 2014 update for genotype 1 in 2014.2 Thereafter several interferon-free regimens with direct acting antivirals (DAAs) have been launched in the clinical setting both for genotype 1 and 2 and treatment recommendations have been greatly changed with these progresses.

In this year 2016, the Drafting Committee for Hepatitis Management Guidelines launched a 2016 update for genotype 1 and 2. These JSH guidelines are intended to assist physicians and other healthcare providers to assist their decision making in the clinical process. The Committee definitely hope these guideline help patients infected with HCV, their families and other interested individuals to overcome HCV infection and improve the outcome and quality of life with assistance of physicians and other healthcare providers.

In these updated version, we focused on newly-available IFN-free DAAs and the current treatment recommendations. Please refer to the previous versions1,2 when IFN, ribavirin, and other IFN-based DAAs (telaprevir, simeprevir) are of interest.
INTRODUCTION

The goal of hepatitis C therapy

Hepatitis C virus (HCV) was discovered by Choo et al. in the United States of America in 1989, and it has become clear that at least 90% of patients who were diagnosed as non-A, non-B hepatitis and at least half of all patients who were diagnosed as alcoholic liver diseases have liver damages caused by HCV. It is estimated that 170 million persons around the world and between 1.5 and 2 million persons in Japan are HCV carriers. When healthy persons are infected with HCV, around 30% have an acute course and then recover, and in around 70% the HCV infection persists and progresses to chronic hepatitis. If the infection becomes chronic, the incidence of spontaneous clearance of the virus is extremely low – 0.2% annually – and hepatic fibrosis results from inflammation caused by the infection, and the disease progresses to cirrhosis and/or hepatocellular carcinoma.

The goal of hepatitis C therapy is to improve the long-term prognosis for chronic liver disease caused by persistent HCV infection – specifically, to prevent hepatocarcinogenesis and death associated with liver disease. To reach this goal, antiviral therapies are administered to achieve HCV clearance. Hepatocarcinogenesis is not completely prevented even in patients achieving HCV RNA clearance through IFN therapy. It is not at present clear whether or not the clearance of HCV through the use of IFN-free DAAs will afford the same level of hepatocarcinogenesis prevention efficacy as IFN therapy. Follow-up for hepatocarcinogenesis needs to be performed to improve the long-term prognosis even after HCV clearance has been achieved through the use of antiviral therapy. Patients who are elderly and have advanced fibrosis and are therefore at high risk for carcinogenesis need to be monitored particularly carefully.

History of antiviral therapy for hepatitis C

IFN therapy started to be used for hepatitis C in the clinical setting in the West in 1991 and in Japan in 1992 following confirmation by Hoofnagle et al. in 1986 that the administration of human recombinant IFN-alfa in non-A, non-B hepatitis resulted in the normalization of transaminases. IFN monotherapy gave way to the use of IFN in combination with ribavirin (RBV), and Pegylated IFN (Peg-IFN) and RBV combination therapy ended up becoming the standard antiviral therapy, and resulted in an increase in the percentage of patients achieving an SVR. However, among HCV genotype 1 and high viral load patients, who are difficult to treat, the percentage achieving SVR on this same therapy is 40% to 50%, and about half of these patients do not achieve HCV clearance. In recent years, a number of novel antiviral drugs have been developed with the aim of improving treatment efficacy or reducing the adverse reactions, and in November 2011, it became possible to use telaprevir, a first-generation protease inhibitor, in the clinical setting in genotype 1 and high viral load patients. Telaprevir + Peg-IFN + RBV combination therapy results in a higher SVR rate – 70% – in treatment-naïve patients. This therapy therefore affords better antiviral efficacy, but adverse events including the progression of severe anemia, the emergence of serious skin erosions, and decreased renal function have been observed. Then, in November 2013, insurance coverage was approved for the use of simeprevir, a second-generation protease inhibitor, in genotype 1 and high viral load patients. A Japanese clinical study of simeprevir + Peg-IFN + RBV combination therapy, the percentage of treatment-naïve patients achieving SVR rose to about 90%, and the adverse reactions were nearly identical to those seen in the placebo group.

Recommendations:

- The goal of hepatitis C therapy is to improve the long-term prognosis for chronic liver disease caused by persistent HCV infection – specifically, to prevent hepatocarcinogenesis and death associated with liver disease. To reach this goal, antiviral therapies are administered to achieve HCV clearance.
- Hepatocarcinogenesis is not completely prevented even in patients achieving HCV RNA clearance through IFN therapy.
- It is not at present clear whether or not the clearance of HCV through the use of IFN-free DAAs will afford the same level of hepatocarcinogenesis prevention efficacy as IFN therapy.
- Follow-up for hepatocarcinogenesis needs to be performed to improve the long-term prognosis even after HCV clearance has been achieved through the use of antiviral therapy. Patients who are elderly and have advanced fibrosis and are therefore at high risk for carcinogenesis need to be monitored particularly carefully.

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Then, in July 2014, IFN-free DAA combination therapy with a protease inhibitor (asunaprevir) and an NS5A inhibitor (daclatasvir) was approved, and it became possible to treat IFN-ineligible and non-responded patients, who had been difficult to treat with conventional antiviral therapies; the SVR rate in Japanese clinical studies was 80% to 90%. Furthermore, in a Japanese clinical study of combination therapy with an NS5B inhibitor (sofosbuvir) and an NS5A inhibitor (ledipasvir), which are second-generation IFN-free DAAs, the SVR rate was 90%, and none of the patients in the sofosbuvir plus ledipasvir combination therapy group discontinued from the study because of adverse reactions and no serious adverse reactions occurred. Furthermore, in September 2015, combination therapy with a protease inhibitor (paritaprevir), NS5A inhibitor (ombitasvir) and ritonavir, which has no antiviral effect but is added for anticipating booster effect (increasing plasma concentration and prolongation of half-life of paritaprevir) was approved, and the SVR rate in Japanese clinical trials was excellent as well, more than 95%. In genotype 2 patients, although the SVR rate on Peg-IFN + RBV combination therapy had normally been about 80%, in September 2014 is became possible to use telaprevir + Peg-IFN + RBV combination therapy in patients for whom Peg-IFN plus RBV combination therapy is not particularly effective. Then, in March 2015, the use of the IFN-free combination therapy sofosbuvir plus RBV was approved for use in genotype 2 patients as well; the SVR rate in Japanese clinical studies was 97%.

Eligibility for antiviral therapy for hepatitis C

Generally, the liver diseases of patients with persistent HCV infections progress gradually, accompanied by ALT increases, and the risk of carcinogenesis increases along with the progression of fibrosis. Conversely, carcinogenesis from a normal liver with no inflammation or fibrosis is almost never seen. Therefore, although all HCV infected patients, except for decompensated cirrhosis patients, are eligible for antiviral therapy, patients with increased ALT levels that are indicative of liver inflammation (ALT > 30 U/l) and patients with decreased platelet counts that are indicative of liver fibrosis (platelet count < 150,000/μl) are good candidates for antiviral therapy for HCV. In addition, patients with poor prognoses because of concurrent illnesses other than liver diseases should not be targeted for antiviral therapy. It needs to be kept in mind when determining the suitability of antiviral therapy that patients with ALT < 30 U/l and platelet count ≥ 150,000/μl are at low risk of hepatocarcinogenesis. However, it should also be kept in mind that in the elderly, the risk of carcinogenesis is not low, even in elderly patients with ALT < 30 U/l and platelet count ≥ 150,000/μl.

The basic approach to treating hepatitis C

In analyses of hepatocarcinogenesis in hepatitis C, although the definition of who is an elderly person is not uniform, with the cutoff sometimes being 55 years, or 60 years, or 65 years, even among elderly persons the risk of carcinogenesis increases as age increases. In this guideline, elderly persons are defined as persons with “age ≥ 66 years” based on, for example, the fact that the incidence of hepatocarcinogenesis increases after age 65. In addition, although advanced fibrosis is defined as “hepatic fibrosis ≥ F2 or platelet count < 150,000/μl,” it is necessary to keep in mind that the risk of carcinogenesis is particularly high in those patients with “hepatic fibrosis ≥ F3 or platelet count ≥ 120,000/μl.”

In patients at high risk for carcinogenesis (patients who are both elderly and have advanced fibrosis), antiviral therapy should be initiated as soon as possible, provided the treatment is judged to be tolerable, and patients who are either elderly or have advanced fibrosis should also be started on antiviral therapy early on. However, in patients who are neither elderly nor have advanced fibrosis, who
are at low risk for carcinogenesis, the suitability of antiviral therapy should be determined taking into account therapeutic efficacy and adverse reactions as well as the risk of carcinogenesis.

In addition, in both groups, it is at present difficult to achieve viral clearance with antiviral therapy, and liver supporting therapies with ursodeoxycholic acid and glycyrrhizin should be administered in patients with abnormal ALT levels (< 30 U/l). Moreover, the long-term use of low doses of Peg-IFN to bring inflammation under control is another option. If such therapies fail to afford adequate efficacy, and iron overload is suspected, then switching to phlebotomy therapy or adding phlebotomy therapy as a concomitant therapy should be considered. The goal of these therapies is to maintain the ALT level at no higher than 30 U/l and to keep the ALT level as low as possible. Strict ALT control is particularly necessary in patients at high risk for carcinogenesis. Furthermore, low-dose Peg-IFN therapy should be discontinued if an improvement in ALT levels (≤10 ng/ml) is not achieved within 6 months.27,28

**Recommendations:**
- In patients at high risk for carcinogenesis (patients who are both elderly and have advanced fibrosis), antiviral therapy should be initiated as soon as possible, provided the treatment is judged to be tolerable.
- In patients who are at low risk for carcinogenesis (patients who are neither elderly nor have advanced fibrosis), the suitability of antiviral therapy should be determined taking into account therapeutic efficacy and adverse reactions as well as the risk of carcinogenesis.
- If viral clearance cannot be achieved, liver supporting therapies should be administered with the aim of preventing the progression of hepatic lesions and carcinogenesis. The long-term use of low doses of Peg-IFN to bring the hepatitis under control is another option. If such therapies fail to afford adequate efficacy, and iron overload is suspected, then switching to phlebotomy therapy or adding phlebotomy therapy as a concomitant therapy should be considered.

**The need for follow-up after SVR has been achieved**

SVR is defined as a negative result for HCV RNA at 24 weeks after the end of antiviral therapy. Patients who achieve SVR following IFN therapy normally remain HCV RNA negative, and the percentage of subjects achieving SVR on IFN + RBV combination therapy who remain negative has been reported to be between 99% and 100% (mean course observation period of 5.6 years; range: 1 year to 8.3 years).29,30 In studies conducted before the year 2000, however, the percentage of patients remaining HCV RNA negative was reported to be somewhat lower: 96% to 98%.31–35 This is attributed to the fact that, in these studies, IFN monotherapy was the principal therapy administered, and to the fact that at that time HCV RNA detection sensitivity was low, and false positive results were obtained when assessing SVR.

When SVR is achieved through IFN therapy, the patients remain negative for HCV RNA, and the risk of carcinogenesis developing from hepatitis C is significantly decreased.7–9,12,36 However, liver cancer has been reported during course observation even in patients who have achieved SVR. There are many reports in Japan of hepatocarcinogenesis following achievement of SVR,9–16 with the reported incidence of carcinogenesis ranging from 0.9% to 4.2% over a mean observation period of 3.3 years to 8.0 years. Reported risk factors for carcinogenesis include advanced age, male sex, advanced fibrosis, alcohol use, fatty liver, and insulin resistance. The time from SVR achievement to carcinogenesis is most often less than 10 years, although there have been scattered reports of carcinogenesis occurring after more than 10 years. Therefore, although no definitive conclusions have been reached about what hepatocarcinogenesis screening period is required following the achievement of SVR through IFN therapy, it appears that screening for liver cancer should be continued for 5 to 10 years after achievement of SVR.

In addition, at present there is little evidence regarding whether or not a level of hepatocarcinogenesis prevention efficacy equivalent to that obtained with IFN-induced SVR is obtained when SVR is achieved with the IFN-free DAA therapies that are not being introduced to the clinical setting. Therefore, once HCV clearance is achieved through DAA therapy, patients need to be screened more closely for hepatocarcinogenesis. Careful follow-up is particularly recommended for patients at high risk of hepatocarcinogenesis (patients who are both elderly and have advanced fibrosis).

**Recommendations:**
- Reported risk factors for carcinogenesis after IFN-induced SVR include advanced age, male sex, advanced fibrosis, alcohol use, fatty liver, and insulin resistance, and the presence of these risk factors necessitates continued screening for hepatic cancer, even after marked efficacy is obtained.
- At present there is little evidence regarding whether or not a level of hepatocarcinogenesis prevention efficacy equivalent to that obtained with IFN-induced SVR is obtained.
when SVR is achieved with IFN-free DAA therapies, and patients receiving these therapies will therefore need to be screened more closely for hepatocarcinogenesis. Careful follow-up is particularly recommended for patients at high risk of hepatocarcinogenesis (patients who are both elderly and have advanced fibrosis).

IFN-FREE DIRECT ACTING ANTIVIRALS (DAAS)

The positive stranded RNA genome of the hepatitis C virus has approximately 9,600 base pairs; the non-structural region that is not incorporated into the viral particles comprises NS2 through NS5B proteins. The current targets of DAAs are the NS3/4A, NS5A, and NS5B proteins, which have, respectively, protease activity, virus genome replication complex formation, and RNA-dependent RNA polymerase activity. As of now, December 2015, five NS3/4A protease inhibitors (telaprevir, simeprevir, asunaprevir, vaniprevir, and paritaprevir), two NS5A replication complex inhibitors (daclatasvir, ledipasvir and ombitasvir), and one NS5B inhibitor (sofosbuvir) have been approved and are used in daily practice (Fig. 1). Among them, combinations of NS3/4A and NS5A (daclatasvir/asunaprevir and paritaprevir/ombitasvir) and NS5A and NS5B (sofosbuvir/ledipasvir) are currently used as interferon-free DAA regimens.

Daclatasvir, asunaprevir

Daclatasvir

Daclatasvir was the first NS5A inhibitor that was developed and approved for use in the clinical setting (Fig. 1). The HCV nonstructural protein region NS5A is a region that codes for a phosphorylation protein comprising 447 amino acid residues. This region contains an IFN sensitivity determining region (ISDR; aa2209-2248) that correlates to the efficacy of IFN therapy and an IFN/RBV resistance-determining region (IRRDR; aa2334-2379) that correlates to the efficacy of IFN + RBV therapy. Although the functions of NS5A have not been thoroughly elucidated, NS5A is believed to play an important role in virus RNA replication; specifically, it is inferred that the NS5A protein and the core protein interact in HCV particle formation. NS5A inhibitors are low-molecular-weight inhibitors that are expected to have significant virus replication inhibition efficacy. Daclatasvir is a first-in-class, picomolar, highly selective NS5A replication complex inhibitor that exhibits effects in various genotypes. It has been reported, on the basis of investigation of its antiviral efficacy in HCV infected patients, that the HCV RNA load is markedly decreased by the oral administration of daclatasvir 10 mg and above. The adult dose is 60 mg as oral daclatasvir once a day.

Asunaprevir

Asunaprevir, on the other hand, is similar to telaprevir and simeprevir in that it is a protease inhibitor that targets the NS3-4A region (Fig. 1). The HCV nonstructural protein 3-4A (NS3-4A) is a noncovalent bond complex that comprises NS3 and the cofactor thereof, NS4A. NS3 is a 70 kDa multifunctional protein with a serine protease region in the N-terminal one-third of the protein (amino acids [aa]1-180). The serine protease is a proteolytic enzyme that cleaves the NS3-5 protein. Protease inhibitors, by directly inhibiting this serine protease, inhibit the production of the virus proteins needed for virus genome replication and viral particle formation, and thus strongly inhibit virus replication. Asunaprevir, which is a second-generation protease inhibitor, possesses strong antiviral effects against genotype 1a, 1b, and 4 HCV because it possesses a mechanism of action such as that described above. The adult dose is 100 mg as oral asunaprevir twice a day.

Daclatasvir/asunaprevir combination therapy

In Japan, clinical trials of daclatasvir + asunaprevir combination therapy have been conducted in IFN-ineligible or intolerant patients and in IFN-non responders, and based on the results of these studies, in July 2014 daclatasvir + asunaprevir combination therapy received health insurance coverage for use in IFN-ineligible/intolerant or non-responded patients. Another clinical trial was then conducted in treatment-naïve and relapsed patients, and based on the results of this trial the limitations on health insurance coverage for this therapy were completely lifted in March 2015, and daclatasvir + asunaprevir combination therapy is now covered by health insurance for use in all genotype 1 chronic hepatitis/compensated cirrhosis patients. This therapy is an IFN-free antiviral therapy, which makes it possible to avoid the various adverse reactions that are experienced with IFN, but which also has problematic adverse reactions of its own including elevation of liver enzymes as well as producing drug-resistance associated variants (RAVs), and which therefore needs to be administered by a physician with sufficient knowledge of and experience with the treatment of viral liver disease who has confirmed that the patient is a suitable candidate for said therapy.

Results overseas

Similar to other DAAs, asunaprevir and daclatasvir are used together in a two-drug combination therapy because they are insufficiently effective alone. Lok et al. has reported the results of a comparison conducted in the United States in 21 genotype 1 patients who were null responders to Peg-IFN + RBV combination therapy in

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which 11 patients received daclatasvir + asunaprevir combination therapy (group A) and 10 patients received Peg-IFN + RBV in addition to daclatasvir and asunaprevir (group B). The treatment period was 24 weeks for both groups. In group A, 4 of the 11 patients achieved SVR. By genotype, the SVR rate in genotype 1a patients was 22.2% (2 of 9 patients), and all two genotype 1b patients achieved SVR. In group B, however, 9 of the 10 patients achieved SVR. These results show that daclatasvir + asunaprevir combination therapy is more effective in genotype 1b patients than in genotype 1a patients.

**Results of Japanese clinical studies**

*IFN-ineligible and intolerant, or non-responded patients.* In Japan, a phase 3 study of daclatasvir + asunaprevir combination therapy was conducted in IFN-ineligible or intolerant patients, and non-responded patients. Table 1 shows the backgrounds of the patients enrolled. There were 87 non-responders and 135 IFN-intolerant or ineligible patients. The median ages in these two groups were 60 years and 64 years, respectively, the sex ratios (males/females) were 39/48 and 39/97, respectively, the IL28B genotype (rs12979860) ratios (CC/CT, TT) were 16/71 and 94/41, and the median HCV RNA loads (Log IU/mL) were 6.8 and 6.6. Twenty-two patients with Child-Pugh Grade A compensated cirrhosis were included in this study. However, no studies have been performed in patients with decompensated cirrhosis.

Looking at the antiviral efficacy in the study population overall, the HCV RNA virological response rate after treatment initiation was 75.2% (RVR) at week 4, 91.0% (cEVR) at week 12, and 92.3% at week 24 or at the end of treatment (EOT). The percentage of patients with HCV RNA below the limit of quantitation after EOT was 88.7% at week 4 (SVR) and 85.1% at week 12 after EOT (SVR12); the SVR24 rate in the study population overall was 84.7% (188 of 222 patients). The SVR24 rates in non-responders and IFN (+RBV)-intolerant/ineligible patients were, respectively, 80.5% (70 of 87 patients) and 87.4% (118 of 135 patients), and 90.9% (20 of 22 patients) in the compensated cirrhosis patients (Fig. 2). Efficacy was therefore confirmed in compensated cirrhosis as well.

Looking at the results of treatment by background factor, by IL28B genotype, which has a substantial effect on the therapeutic efficacy of IFN, the SVR24 rates in the TT and

**Table 1** Japanese Phase 3 Study of Daclatasvir + Asunaprevir (IFN-ineligible/intolerant or Refractory Patients) – Patient Backgrounds

<table>
<thead>
<tr>
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<th>IFN-ineligible/intolerant patients</th>
<th>IFN-non-responders</th>
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<tbody>
<tr>
<td>n</td>
<td>135</td>
<td>87</td>
</tr>
<tr>
<td>Median age [range]</td>
<td>64 [24–75]</td>
<td>60 [40–74]</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>38/97</td>
<td>39/48</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>IL28B polymorphism (rs12979860)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>94</td>
<td>16</td>
</tr>
<tr>
<td>CT</td>
<td>40</td>
<td>66</td>
</tr>
<tr>
<td>TT</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Median HCV-RNA [SD]</td>
<td>6.6 (0.58)</td>
<td>6.8 (0.47)</td>
</tr>
<tr>
<td>PegIFN-ineligible</td>
<td>100</td>
<td>N/A</td>
</tr>
<tr>
<td>PegIFN-intolerant</td>
<td>35</td>
<td>N/A</td>
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</tbody>
</table>
TG/GG groups were, respectively, 84.8% and 84.3%, so there was no difference in therapeutic efficacy between these two groups. In addition, therapeutic efficacy remained the same for the other background factors as well, such as age, sex, and HCV RNA load at initiation (Fig. 3).

The number of patients who experienced relapse after EOT was 6 (7.9%) in the non-responders group and 11 (8.5%) in the IFN (+ RBV)-intolerant/ineligible group. The number of patients who experienced viral breakthrough during treatment was 10 (11.5%) in the non-responders and 4 (3.0%) in the IFN (+ RBV)-intolerant/ineligible group, and the numbers of patients in these groups who were HCV RNA positive at EOT were, respectively, 1 and 2.

**Recommendations:**

- **Daclatasvir + asunaprevir combination therapy should be administered by physicians with sufficient knowledge of and experience with the treatment of viral liver disease who have determined that the patient is eligible for daclatasvir + asunaprevir combination therapy.**
- In a Japanese phase 3 study of daclatasvir + asunaprevir combination therapy that was conducted in IFN non-responders and IFN (+ RBV)-intolerant/ineligible patients, the SVR24 rate in the study population overall was 84.7%. The SVR24 rates in non-responders and IFN (+ RBV)-intolerant/ineligible patients were, respectively, 80.5% and 87.4%.
- No differences were found in therapeutic efficacy by background factor (e.g., IL28B genotype, age, sex, HCV RNA load at initiation).
- In overseas clinical studies, therapeutic efficacy was attenuated in genotype 1a patients, and the SVR rate was 22.2%.

**Treatment-naïve patients and relapsed patients.** A phase 3 study of daclatasvir + asunaprevir combination therapy was conducted in treatment-naïve and relapsed patients. This study was conducted based on a protocol that called for comparing daclatasvir + asunaprevir combination therapy to telaprevir + Peg-IFN + RBV combination therapy in treatment-naïve patients, and for using only daclatasvir + asunaprevir combination therapy in relapsed patients. The backgrounds of the patients enrolled are shown in Table 2; there were 119 treatment-naïve patients and 22 relapsed patients. Because the treatment-naïve patients were studied based on a comparison versus telaprevir + Peg-IFN + RBV combination therapy, these patients were relatively young, with a median age of 57 years; none were over 70 years of age. In addition, patients with compensated cirrhosis (Fibrotest score F4) accounted for only 6 (5.0%) of the patients.

The results of treatment in this study were generally good: the SVR12 rate in the treatment-naïve patients was 89.1% (compared to 62.2% in the telaprevir therapy controls) and 95.5% in the relapsed patients (Fig. 4). As in the clinical study in non-responders and IFN-ineligible/intolerant patients, no significant differences were found in the treatment results by sex, age, HCV RNA load at treatment initiation, or IL28B polymorphism.

**Adverse reactions**

In a phase 3 study in IFN-ineligible/intolerant and non-responders, serious adverse events occurred in 13 patients (5.9%). The most common adverse events included nasopharyngitis and headache. The most common laboratory abnormality was elevations of AST/ALT. The study was performed using a protocol that specified that liver chemistries be performed every 2 weeks until 12 weeks after treatment initiation, and then every 4 weeks thereafter, and that treatment should be discontinued immediately if
Grade 4 elevation of ALT was found. Grade 3/4 elevation of ALT or AST (Grade 3: ≥ 5X and ≤ 10X ULN; Grade 4: > 10X ULN) occurred in 7.2% of patients (16 patients) and 5.4% of patients (12 patients), respectively. Ten patients (4.5%) discontinued study treatment. The median time to onset of ALT elevation was 10 weeks after treatment initiation, the shortest time to onset was 4 weeks, and the longest was 23 weeks; no fixed pattern was found. However, in most of the patients who experienced Grade 4 ALT elevation, the time it took from when the ALT started to increase until it reached Grade 4 was less than 28 days, with the shortest time being 5 days. All of the patients who discontinued from study treatment exhibited improvement in their ALT levels, and 8 of the 10 patients who discontinued achieved SVR. In addition, although no significant differences were found in safety between compensated cirrhosis patients and other patients, decompensated cirrhosis patients were not enrolled in clinical studies, and the safety in such patients has therefore not been confirmed. Therefore, daclatasvir + asunaprevir combination therapy should not be administered to decompensated cirrhosis patients.

Recommendations:

- In a Japanese phase 3 study of daclatasvir + asunaprevir combination therapy in IFN-ineligible/intolerant or non-responders patients, Grade 3/4 AST or ALT elevation occurred in, respectively, 7.2% of patients (16 patients) and 5.4% of patients (12 patients), and 10 patients (4.5%) discontinued from study treatment.
- No set pattern was found to the time of onset of ALT elevation.
- Liver enzymes were monitored every 2 weeks until 12 weeks after treatment initiation and every 4 weeks thereafter, and treatment was discontinued in the event of Grade 4 ALT elevation; the ALT values of all of the patients improved.
- No clinical studies have been conducted in decompensated cirrhosis patients, and safety has not been confirmed in such patients. Therefore, daclatasvir + asunaprevir combination therapy should not be administered to decompensated cirrhosis patients.

Drug interactions

Daclatasvir is a CYP3A4 substrate, and asunaprevir is a CYP3A and OATP1B1 and 2B1 substrate. In addition, daclatasvir has an inhibitor effect on P-glycoprotein, OATP1B1, 1B3, and BCRP, and asunaprevir has an inhibitory effect on CYP2D6, OATP1B1, 1B3, 2B1, and P-glycoprotein, and acts to induce CYP3A4. Because the concomitant use with daclatasvir and asunaprevir of the CYP3A4 inducers or inhibitors, OATP inhibitors, or CYP2D6 substrates with a narrow therapeutic range could result in decreases or increases of the blood levels of daclatasvir, asunaprevir, or the coadministered drugs, the concomitant use of these drugs is contraindicated. Drugs that when coadministered could either affect daclatasvir or asunaprevir or be affected by said coadministration should be coadministered with care.41,43 The package insert of any

![Figure 4](https://example.com)
Drug that is going to be coadministered must be checked thoroughly before initiating coadministration.

**Drug resistant associated variants (RAVs)**

The following are known polymorphisms (RAVs) that significantly reduce the therapeutic efficacy of DAAs: for asunaprevir, which is a protease inhibitor, the NS3-4A position 168 amino acid variants D168A/E/V; and, for daclatasvir, the NS5A region position 31 and 91 amino acid variants L31M/V and Y93H. Because HCV is a virus that has tremendous diversity in its base sequences, there are patients who have these RAVs prior to DAA treatment. In a Japanese phase 3 study of daclatasvir + asunaprevir in IFN-ineligible/intolerant patients and IFN-non-responders patients, out of 214 patients in whom an exploration of HCV RAVs was performed before treatment initiation using a direct sequencing method, 30 patients (14.0%) had Y93H and 8 patients (3.7%) had L31M/V before treatment initiation. Fig. 5a and b show the treatment results by the presence or absence of NS5A RAVs before treatment.

In the IFN (+ RBV)-ineligible/intolerant groups, 102 of the 107 patients who did not have Y93H RAVs before treatment achieved SVR. Therefore, when the population was limited to those patients without RAVs, the SVR rate was a good 95.3%. However, out of the 21 patients who had Y93H RAV, only 10 (47.6%) achieved SVR (Fig. 5a). In the IFN-non-responders group, the SVR rate in patients without Y93H before treatment initiation was 85.7% (66 of 77 patients), compared to a rate of 33.3% (3 of 9 patients) in patients with Y93H before treatment initiation. Of the 80 patients without L31M/V, 68 (85.0%) achieved SVR. In patients with L31M/V, of which there were admittedly few, of the 6 patients with such RAVs, only 1 (16.7%) achieved SVR (Fig. 5b). In addition, in an overseas phase 3 study (HALLMARK-DUAL), 48 patients (8%) had Y93 RAVs before treatment initiation, and the SVR rate in these patients was 38% (18 of 48), and 27 patients (5%) had L31 RAVs before treatment initiation, and the SVR rate in these patients was 41% (11 of 27 patients).

In a phase 3 study in treatment-naïve and relapsed patients, as well, the treatment results are clearly significantly worsened by the presence before treatment of NS5A RAVs. Out of 129 patients for whom NS5A RAVs were measured by a direct sequencing method, 18 (14.0%) had Y93H and 6 (4.7%) had L31M/V, and 23 (17.8%) had either one or both kinds of RAVs. Of the 106 patients who did not have any RAV, 104 (98.1%) achieved SVR12. This is in contrast to the rate of 47.8% (11 of 23 patients) in patients with either one or both kinds of RAVs (Fig. 6).

Furthermore, in daclatasvir/asunaprevir combination therapy null responders, the emergence of viruses that are resistant to both drugs has been reported. Specifically, when RAVs were measured after breakthrough or relapse in patients who only had NS5A Y93 or L31 RAV before therapy, RAVs were found to have emerged not only in the NS5A region, but also at NS3 D168. In the overseas phase 3 HALLMARK-DUAL study, L31 RAVs emerged in 63%, Y93 RAVs emerged in 58%, and NS3 D168 RAVs emerged in 92% of null responders, and NS5A and NS3 RAVs emerged in 77% of null responders. Of these NS5A and NS3 RAVs, the NS5A RAVs were found to persist for at least 1 year.

In an in vitro test system, virus variants carrying multiple NS5A RAVs that had both Y93H and L31M/V were more resistant to NS5A inhibitors than viruses carrying only Y93H or L31M/V, and the emergence of a strain carrying...
L31V-Q54H-Y93H RAV that was a strain with a high level of resistance and high replication capability was also reported (Table 3). In patients with no history of treatment with NS5A inhibitors, it is expected that Y93H and L31M/V will be simultaneously detected in no more than 1% of patients (direct sequencing method), and that multiple NS5A RAVs will be extremely rare. However, in daclatasvir/asunaprevir combination therapy null responders, Y93H and L31M/V are detected simultaneously very frequently, and multiple NS5A RAVs thus appear to be present in a high proportion of such patients.47 Because there are currently no established therapies that are effective against such viruses carrying multiple drug resistance variants, it is of the utmost importance to prevent the emergence of such viruses.

**Recommendations:**

- There are NS3-4A D168A/E/V RAVs that confer resistance to asunaprevir, a protease inhibitor, and there are NS5A L31M/V and Y93H RAVs that confer resistance to daclatasvir, an NS5A inhibitor.
- In a Japanese phase 3 study in IFN-ineligible, intolerant, or non-responders patients, investigations using a direct sequencing method performed before treatment initiation found L31M/V in 3.7% of the study population and Y93H in 14.0% of the study population.
- In IFN (+ RBV)-ineligible or intolerant patients, the SVR rate was 95.3% in patients with no Y93H RAVs before treatment initiation and 47.6% in patients with Y93H before treatment initiation. In IFN-non-responders patients, however, the SVR rate was 85.7% in patients with no Y93H before treatment initiation, and the SVR rate was 85.0% in patients with no L31M/V before treatment initiation and 16.7% in patients with L31M/V before treatment initiation.
- In a phase 3 study in treatment-naive patients and relapsed patients, 98.1% of patients without any Y93/L31 RAV achieved SVR12; however, the SVR12 rate in patients with either one or both types of resistance RAVs was 47.8%.
- Viruses with multiple NS5A RAVs and viruses that are resistant to both drugs frequently emerge in daclatasvir/asunaprevir combination therapy null responders. Because there are currently no established therapies that are effective against such viruses carrying multiple drug resistance variants, it is of the utmost importance to prevent the emergence of such viruses.

**Sofosbuvir + RBV combination therapy**

RNA-dependent RNA polymerase, which is necessary for virus replication, is encoded by HCV NS5B. Antiviral drugs that act directly on NS5B polymerase are broadly classified into two groups, the first being nucleoside NS5B polymerase inhibitors, which are taken up into the virus genes during HCV RNA replication, and the second being non-nucleoside inhibitors that inhibit the enzyme activity of the NS5B polymerase proteins. Sofosbuvir is a non-nucleoside NS5B polymerase inhibitor that is converted in hepatocytes into the uridine triphosphate form that is the active metabolite, and is then taken up into the virus genome during HCV RNA replication, and acts as a chain terminator that stops the RNA elongation reaction. Sofosbuvir does not have any inhibitory effects on human DNA or RNA polymerase. Sofosbuvir possesses antiviral activity against multiple HCV genotypes: in vitro assays performed using replicons have found that the 50% effective concentration (the EC50) in genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a was, respectively, 0.04, 0.11, 0.05, 0.015, 0.05, 0.04, 0.015, and 0.014 μmol/L.

**Table 3** Resistance Profile of Daclatasvir to NS5A Region RAVs

<table>
<thead>
<tr>
<th>Replicon*</th>
<th>Replication Level (%) Average (SD)</th>
<th>EC50 (ng/mL) Average (SD)</th>
<th>Fold Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>100</td>
<td>0.0019 (0.0007)</td>
<td>1</td>
</tr>
<tr>
<td>L31M</td>
<td>99 (23)</td>
<td>0.0062 (0.0014)</td>
<td>3</td>
</tr>
<tr>
<td>L31V</td>
<td>158 (54)</td>
<td>0.053 (0.015)</td>
<td>28</td>
</tr>
<tr>
<td>Q54H</td>
<td>83 (18)</td>
<td>0.0024 (0.0003)</td>
<td>1</td>
</tr>
<tr>
<td>Q54N</td>
<td>83 (29)</td>
<td>0.0027 (0.0006)</td>
<td>1</td>
</tr>
<tr>
<td>Y93H</td>
<td>27 (16)</td>
<td>0.046 (0.018)</td>
<td>24</td>
</tr>
<tr>
<td>L31M-Y93H</td>
<td>70 (68)</td>
<td>13.5 (12.2)</td>
<td>7,105</td>
</tr>
<tr>
<td>L31V-Y93H</td>
<td>50 (38)</td>
<td>28.1 (24.7)</td>
<td>14,789</td>
</tr>
<tr>
<td>Q54H-Y93H</td>
<td>22 (7)</td>
<td>0.018 (0.005)</td>
<td>9</td>
</tr>
<tr>
<td>L31V-Q54H-Y93H</td>
<td>189 (25)</td>
<td>36.1 (7.7)</td>
<td>19,000</td>
</tr>
</tbody>
</table>

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Sofosbuvir has been approved in many other countries, including the United States and Europe. In Japan, a clinical study of sofosbuvir + RBV combination therapy was conducted in genotype 2 patients and, based on the results of this study, sofosbuvir + RBV combination therapy was approved in March 2015 for use in genotype 2 chronic hepatitis C/compensated cirrhosis patients. The dose and mode of administration is oral sofosbuvir 400 mg once a day in combination with RBV for 12 weeks. The use of sofosbuvir is contraindicated in patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m²) or renal failure requiring dialysis. For the RBV dose and the criteria for reducing the dose or discontinuing treatment because of adverse reactions, the RBV package insert is followed.

Results overseas (Table 4)

Treatment-naïve patients. In the ELECTRON study in treatment-naïve patients, the need for the concomitant use of either IFN or RBV in a therapy that includes sofosbuvir was evaluated. Genotype 2 patients were divided into five groups, a group that received sofosbuvir monotherapy for 12 weeks (10 patients, a group that received sofosbuvir + RBV for 12 weeks (10 patients), and groups that received Peg-IFN for 4, 8, or 12 weeks during treatment with sofosbuvir + RBV for 12 weeks (9, 10, and 11 patients, respectively). Although the SVR rate in the group that received sofosbuvir monotherapy for 12 weeks was 60%, the SVR rate in the group that received sofosbuvir + RBV was 100%, and the SVR rate was 100% in the group that received Peg-IFN in combination with sofosbuvir + RBV for 12 weeks, regardless of the duration of Peg-IFN coadministration. These results therefore showed that in genotype 2 patients, the concomitant use of RBV is necessary, and the concomitant use of Peg-IFN is not necessary.49

In the successively conducted FISSION study, a phase 3 randomized study that compared 24 weeks of Peg-IFN + RBV combination therapy to 12 weeks of sofosbuvir + RBV combination therapy in treatment-naïve genotype 2 patients, the SVR rate in the 67 genotype 2 patients who received Peg-IFN + RBV for 24 weeks was 78%, whereas the SVR rate in the 70 genotype 2 patients who received sofosbuvir + RBV for 12 weeks was 97%.50 In the POSITRON study, the SVR rate was 93% in the 109 genotype 2 patients overall, 94% in compensated cirrhosis patients, and 92% in non-cirrhotic patients.51 In the VALENCE study, which was conducted in 32 patients, the SVR rate was 97%.52 Therefore, in each of the aforementioned clinical studies, the SVR rate was at least 90% in patients receiving sofosbuvir + RBV combination therapy for 12 weeks.

Treatment-experienced patients. Looking at phase 3 studies in genotype 2 patients previously treated with Peg-IFN + RBV, in the FUSION study, a randomized study in which patients were retreated with sofosbuvir + RBV for either 12 weeks (36 patients) or 16 weeks (32 patients), the SVR rate was, respectively, 86% and 94%.51 The SVR rate in patients who received sofosbuvir + RBV combination therapy for 12 weeks was 60% in compensated cirrhosis patients and 96% in non-cirrhotic patients. The SVR rate in patients who received sofosbuvir + RBV combination therapy for 16 weeks was 78% in compensated cirrhosis patients and 100% in non-cirrhotic patients. The VALENCE study was a study of sofosbuvir + RBV combination therapy for 12 weeks in 41 patients; the SVR rate was 90% in non-responders to therapies including IFN.

Table 4 Results of Overseas Phase 3 Studies of Sofosbuvir + RBV Combination Therapy in Genotype 2 Patients

<table>
<thead>
<tr>
<th>Study population</th>
<th>Treatment</th>
<th>SVR12 (%)</th>
<th>Non-cirrhotic/cirrhosis</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISSION50</td>
<td>Treatment-naive</td>
<td>SOF+RBV, 12W (n = 70)</td>
<td>97</td>
<td>Non-cirrhotic (n = 92)</td>
</tr>
<tr>
<td></td>
<td>Peg-IFN+RBV, 24W (n = 67)</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POSITRON51</td>
<td>IFN-eligible or intolerant</td>
<td>SOF+RBV, 12W (n = 109)</td>
<td>93</td>
<td>Non-cirrhotic (n = 92)</td>
</tr>
<tr>
<td>patients or patients refusing IFN</td>
<td>placebo (n = 34)</td>
<td>0</td>
<td>Compensated cirrhosis (n = 17)</td>
<td>94</td>
</tr>
<tr>
<td>VALENCE52</td>
<td>Treatment-naive</td>
<td>SOF+RBV, 12W (n = 32)</td>
<td>97</td>
<td>Non-cirrhotic (n = 92)</td>
</tr>
<tr>
<td></td>
<td>placebo (n = 18)</td>
<td>0</td>
<td>Compensated cirrhosis (n = 17)</td>
<td>94</td>
</tr>
<tr>
<td>FUSION51</td>
<td>Non-responders to therapies</td>
<td>SOF+RBV, 12W (n = 41)</td>
<td>90</td>
<td>Non-cirrhotic (n = 92)</td>
</tr>
<tr>
<td>including IFN</td>
<td>placebo (n = 9)</td>
<td>94</td>
<td>Compensated cirrhosis (n = 10)</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>SOF+RBV, 12W (n = 36)</td>
<td>86</td>
<td>Compensated cirrhosis (n = 10)</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>SOF+RBV, 16W (n = 32)</td>
<td>94</td>
<td>Non-cirrhotic (n = 92)</td>
<td>92</td>
</tr>
</tbody>
</table>

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the study population overall and 78% in the 9 patients with cirrhosis.

**Results of the Japanese clinical study**

The target patient population of the phase 3 clinical study that was conducted in Japan was genotype 2 non-cirrhotic/compensated cirrhosis patients with age $\geq 20$ years, body weight $\geq 40$ kg, and HCV RNA $\geq 4.0$ log IU/mL. The inclusion criteria were: AST or ALT not more than 10 times the reference value, platelet count $\geq 50,000/\mu l$, albumin $\geq 3.0$ g/dl, and hemoglobin $\geq 11$ g/dl for females and $\geq 12$ g/dl for males. Of the 153 patients enrolled, 90 had been treatment-naïve and 63 had been previously treated. Of the treatment-naïve patients, 80% were IFN-eligible, 6% were IFN-ineligible, and 14% did not want to be treated with IFN. Of the previously treated patients, 24% were non-responders, 71% had experienced relapse or breakthrough, and 5% were IFN-intolerant. Genotype 2a patients accounted for 60% of the patients and genotype 2b patients accounted for 40%. The mean age was 57 years (range: 25–74 years), and the median eGFR was 85 ml/min (range: 51–209). Cirrhotic patients diagnosed based on a liver biopsy or Fibroscan ($>12.5$ kPa) accounted for 11% of the patients. The doses administered were as follows: sofosbuvir 400 mg once a day after breakfast, and RBV 600 mg, 800 mg, or 1000 mg, depending on body weight, twice a day after breakfast and supper, for 12 weeks.

The SVR12 rate was 97% in the study population overall, 98% in treatment-naïve patients, and 95% in previously treated patients. In non-cirrhotic patients, the SVR12 rate was 97% overall, 98% in treatment-naïve patients, and 96% in previously treated patients. In cirrhosis patients, the SVR12 rate was 94% overall (16 of 17 patients), 100% (8 of 8 patients) in treatment-naïve patients, and 89% (8 of 9 patients) in previously treated patients, all of which were extremely high rates (Fig. 7).

There was no decrease in the SVR12 rate because of any conventional factors for non-responders in IFN therapy. The SVR12 rate was 97% in major IL28B (rs12979860) CC patients, 94% in hetero/minor non-CC patients, 97% in patients with age $< 65$ years, 94% in patients with age $\geq 65$ years, 100% in patients with HCV RNA $< 5.0$ Log, and 96% in patients with HCV RNA $\geq 5.0$ Log (Fig. 8).

The percentage of patients who turned HCV RNA negative ($<25$ IU/ml) was 97% at 2 weeks after treatment initiation and 100% at 4 weeks; no patients became HCV RNA non-negative or experienced breakthrough during therapy. All five of the patients who did not achieve SVR12 (2 of whom were treatment-naïve patients and 3 of whom were previously treated patients) were relapsed patients. The relapse rate was 3% in the population overall, 2% in treatment-naïve patients, and 5% in previously treated patients. No patients experienced relapse after completing 12 weeks of therapy, and all of the patients who achieved SVR12 achieved SVR24.

**Recommendations:**

- The SVR rate for sofosbuvir + RBV 12-week combination therapy is high in genotype 2 non-cirrhotic/compensated cirrhosis patients; in the Japanese phase 3 study, it was between 95% and 98%.
- No differences in therapeutic efficacy were found by background factor (e.g., cirrhosis, IL28B genotype, age, HCV RNA load at treatment initiation).

**Adverse reactions**

Although adverse reactions occurred in 73% of the patients in the Japanese phase 3 clinical study, 84% of these were mild (Grade 1). The most common adverse reaction was nasopharyngitis, at 29%. Other common adverse reactions were anemia (12%), headache (10%), generalized malaise (7%), and skin itchiness (6%). No Grade 4 adverse reactions occurred. Grade 3 adverse reactions associated with the study drug were reported in 2 patients, anemia requiring hospital admission was reported in 1 patient, and transient hyperbilirubinemia associated with RBV was reported in another patient. The serious adverse reactions that were reported were the aforementioned patient who had to be hospitalized because of anemia and one patient who developed anaphylaxis because of a bee sting. No patients discontinued from the study because of adverse reactions. There were 20 patients whose RBV doses were reduced because of anemia and 1 patient whose treatment was suspended for 1 day.
because of nasopharyngitis. There were no differences in either the incidences or seriousness of the adverse events depending on the presence or absence of cirrhosis. Although the incidences of the adverse reactions when stratified by age were similar overall, the incidence of anemia was high in patients with age \( \geq 65 \) years, and the decrease in hemoglobin was \( /C_0 1.7 \) g/dl in patients with age \( \geq 65 \) years, compared to \( /C_0 1.0 \) g/dl in patients with age \( < 65 \) years. It is therefore necessary to adjust the RBV dose as appropriate depending on changes in the hemoglobin level.

In addition, because sofosbuvir is metabolized primarily by the kidneys, plasma exposure increases depending on the severity of renal dysfunction. Although dose adjustment is not necessary for patients with mild or moderate renal dysfunction receiving sofosbuvir 400 mg, because the blood levels of the final metabolite GS-331007 increase in patients with severe renal dysfunction and hemodialysis patients, in particular, the package insert contraindicates the use of sofosbuvir in patients with severe renal dysfunction (eGFR \( < 30 \) mL/min/1.73 m\(^2\)) or renal failure requiring dialysis.

Furthermore, because decompensated cirrhosis patients were not included in the target population for the Japanese clinical studies, as was the case for other DAA drug products, the safety of sofosbuvir in these patients has not been confirmed. Sofosbuvir should therefore not be administered to patients with decompensated cirrhosis.

**Recommendations:**

- In the Japanese phase 3 study, no Grade 4 adverse reactions occurred, and no patients discontinued from the study because of adverse reactions.

**Drug resistance**

When resistance was investigated by subculturing replicon-containing cells in the presence of sofosbuvir, NS5B S282T RAV were detected, regardless of HCV genotype. Furthermore, assays of replicons into which S282T had been introduced found that the presence of S282T increased the EC50 by between 2.4 and 18.1 times. Such *in vitro* assay results showed that NS5B S282T decrease sensitivity to sofosbuvir.

In a Japanese phase 3 clinical study, however, no S282T or known NS5B RAVs were detected as a result of deep sequencing analysis of relapsed patients who did not...
achieve SVR12, and no strains that were resistant to sofosbuvir were found in a phenotype analysis, either. In each of the overseas phase 3 clinical studies FISSION, POSITRON, and FUSION of sofosbuvir + RBV combination therapy for 12 weeks in genotype 2 patients, no S282T was detected in relapsed patients who did not achieve SVR12, and no resistant strains were found in a phenotype analysis, either.

**Recommendations:**

- In vitro assays have confirmed that NS5B S282T variant confer resistance to sofosbuvir.
- In an analysis of clinical samples, no S282T was detected in patients who did not achieve SVR in Japanese or overseas phase 3 studies, nor has resistance to sofosbuvir been found by phenotype analysis.

**Sofosbuvir+ledipasvir combination tablets**

DAAs that target NS3/4A, NS5A, and NS5B have been developed, and many clinical studies of IFN-free DAA combination therapies are being conducted. In this environment, NS5A inhibitors are key drugs that are included in all of these regimens. NS5A is a phosphoprotein made up of 447 amino acids that does not possess enzymatic activity but that is necessary for HCV replication and particle formation, and NS5A inhibitors inhibit HCV replication 10 to 1000 times more strongly than NS3 inhibitors. Ledipasvir, an NS5A inhibitor, inhibits HCV replication at picomolar concentrations: the EC50 is 31 picomoles in genotype 1a patients and 4 picomoles in genotype 1b patients. The sofosbuvir + ledipasvir combination drug has received marketing approval in many other countries, including the United States and Europe, and an approval application was filed in Japan as well, based on the results of a clinical study conducted in genotype 1 patients in Japan, and approval was received in July 2015 for use in genotype 1 non-cirrhotic C/compensated cirrhosis patients. The dose and mode of administration is as follows: sofosbuvir 400 mg and ledipasvir 90 mg fixed-dose combination drug administered orally once a day for 12 weeks. RBV is not coadministered. The use of this combination drug is contraindicated in patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2) or renal failure requiring dialysis.

**Overseas results (Table 5)**

In the ION studies, phase 3 clinical studies that were conducted overseas, the need for RBV coadministration and the optimal treatment period were investigated using a fixed-dose combination drug containing sofosbuvir 400 mg and ledipasvir 90 mg.

The ION-1 study was study in which 865 treatment-naïve patients were randomized into 4 groups that received the sofosbuvir + ledipasvir combination drug for 12 or 24 weeks and that did or did not receive RBV concomitantly. The SVR rate was 99% in the group that received sofosbuvir + ledipasvir for 12 weeks without concomitant RBV, 97% in the group that received sofosbuvir + ledipasvir for 12 weeks with concomitant RBV, 98% in the group that received sofosbuvir + ledipasvir for 24 weeks without concomitant RBV, and 99% in the group that received sofosbuvir + ledipasvir for 24 weeks with concomitant RBV. The ION-3 study was a study in which 647 non-cirrhotic, treatment-naïve patients were randomized into a total of 3 groups: a group that received the sofosbuvir + ledipasvir combination drug for 8 weeks with concomitant RBV, a group that received the sofosbuvir + ledipasvir combination drug for 8 weeks without concomitant RBV, and a group that received the sofosbuvir + ledipasvir combination drug for 12 weeks.

### Table 5 Results of Overseas Phase 3 Clinical Studies of Sofosbuvir + Ledipasvir Combination Therapy in Genotype 1 Patients

<table>
<thead>
<tr>
<th>Study population</th>
<th>Treatment</th>
<th>Cirrhosis (%)</th>
<th>SVR12(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1 Treatment-naïve</td>
<td>SOF/LDV, 12W (n = 214)</td>
<td>16</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV+RBV, 12W (n = 217)</td>
<td>15</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV, 24W (n = 217)</td>
<td>15</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV+RBV, 24W (n = 217)</td>
<td>17</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV, 12W (n = 109)</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV+RBV, 12W (n = 111)</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV, 24W (n = 109)</td>
<td>20</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV+RBV, 24W (n = 111)</td>
<td>20</td>
<td>99</td>
</tr>
<tr>
<td>ION-2 Patients non-responders to or with relapse after treatments that included IFN</td>
<td>SOF/LDV, 8W (n = 215)</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV+RBV, 8W (n = 216)</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>SOF/LDV, 12W (n = 216)</td>
<td>0</td>
<td>95</td>
</tr>
</tbody>
</table>

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without concomitant RBV.\textsuperscript{57} The SVR rate was 94% in the group that received sofosbuvir + ledipasvir for 8 weeks without concomitant RBV, 93% in the group that received sofosbuvir + ledipasvir for 8 weeks with concomitant RBV, and 95% in the group that received sofosbuvir + ledipasvir for 12 weeks without concomitant RBV. The ION-2 study was a study in which 440 patients who had been previously treated with Peg-IFN + RBV combination therapy were randomized to 4 groups that received the sofosbuvir + ledipasvir combination drug for 12 or 24 weeks and that did or did not receive RBV concomitantly.\textsuperscript{58} Compensated cirrhosis patients accounted for 20% of the study population. The SVR rate was 94% in the group that received sofosbuvir + ledipasvir for 12 weeks without concomitant RBV, 99% in the group that received sofosbuvir + ledipasvir for 24 weeks without concomitant RBV, and 99% in the group that received sofosbuvir + ledipasvir for 24 weeks with concomitant RBV. The SVR rate was 98% in patients without cirrhosis but 92% in patients with cirrhosis, and among patients with cirrhosis, the SVR rates in the groups that were treated for 24 weeks (99% without concomitant RBV and 99% with concomitant RBV) were higher than those in the groups that were treated for 12 weeks (86% without concomitant RBV and 82% with concomitant RBV).

Japanese clinical study results (Fig. 9)

The phase 3 clinical study in Japan was conducted in genotype 1 HCV infected patients, both non-cirrhotic and cirrhotic, with age $\geq 20$ years, body weight $\geq 40$ kg, and HCV RNA $\geq 5.0$ log IU/ml.\textsuperscript{59} Of the 341 patients in the study, 166 were treatment-naïve and 175 were treatment-experienced, including 40 patients who had been treated previously with protease inhibitors. Genotype 1a and 1b patients accounted for, respectively, 3% and 97% of the study population. The mean age was 59 years, and 22% of the patients had cirrhosis diagnosed by liver biopsy or Fibroscan ($>12.5$ kPa). The patients were randomized into two groups, one of which received a fixed-dose oral combination drug containing sofosbuvir 400 mg and ledipasvir 90 mg once a day for 12 weeks without concomitant RBV, and the other of which received concomitant RBV twice a day after breakfast and supper at a dose of 600 mg, 800 mg, or 1000 mg, depending on body weight.

The SVR12 rate was 99% in the study population overall, 100% in patients who did not receive concomitant RBV, and 98% in patients who received concomitant RBV.\textsuperscript{59} In treatment-naïve patients, the SVR rate was 100% in patients who did not receive concomitant RBV and 96% in patients who did. In treatment-experienced patients, the SVR rate was 100% in patients who did not receive concomitant RBV and also 100% in patients who did. In patients with compensated cirrhosis, as well, the SVR rate was 100% in patients who did not receive concomitant RBV and 97% in patients who did. In IL28B (rs12979860) hetero/minor non-CC patients, as well, the SVR rate was 100% in patients who did not receive concomitant RBV and 98% in patients who did. All of the 40 patients who had been previously received treatments that included protease inhibitors achieved SVR. The only patients who did not achieve SVR were 2 patients who discontinued from the study in the early stages of treatment and 1 patient who relapsed after the end of treatment. The patient who relapsed was a treatment-naïve 55 year-old female without cirrhosis who was assigned to the group that received concomitant RBV and who had good treatment adherence, but in whom HCV RNA reappeared at 4 weeks after the end of treatment. This patient had an NS5A Y93H RAVs both before treatment initiation and at relapse.

On the basis of the results of this clinical study, treatment for 12 weeks with the sofosbuvir + ledipasvir combination drug without concomitant RBV was approved for genotype 1 HCV infected patients, both non-cirrhotic and cirrhotic.

**Recommendations:**

- The SVR rates for therapy for 12 weeks with the sofosbuvir + ledipasvir combination drug in genotype 1 non-cirrhotic/compensated cirrhosis patients are excellent, and were 100% in the Japanese phase 3 study.
No differences in therapeutic efficacy have been found by background factor (e.g., cirrhosis, IL28B genotype, age, HCV RNA load at treatment initiation).

Adverse reactions
In the Japanese phase 3 clinical study, the 2 patients who discontinued from the study because of adverse reactions were both in the group that received concomitant RBV; one discontinued because of a rash, and the other died because of cardiac arrest. The patient who died had cirrhosis, concurrent illnesses (sarcoidosis, diabetes, pulmonary fibrosis), a history of splenectomy, and also had a viral gastrointestinal infection at the time of adverse event onset. Serious adverse reactions occurred in 2 patients, both in the group that received concomitant RBV; one was the aforementioned patient who died because of cardiac arrest, and the other was a patient who developed acute myocardial infarction.

In the group that did not receive concomitant RBV, 65% of the patients experienced adverse reactions. The most common adverse reaction was nasopharyngitis (29%). Other common adverse reactions were headache (7%), generalized malaise (5%), and skin itchiness (4%).

Recommendations:
- In the Japanese phase 3 study, 1.2% of patients in the group that received concomitant RBV, including the patient who died, discontinued from the study because of adverse reactions, and 1.2% experienced serious adverse reactions. However, none of the subjects who received the sofosbuvir + ledipasvir combination drug for 12 weeks without receiving concomitant RBV discontinued from the study because of adverse reactions, nor did any of these patients experience serious adverse reactions.
- No clinical studies have been conducted in patients with decompensated cirrhosis, and the safety of the sofosbuvir + ledipasvir combination drug has not been confirmed in such patients. Therefore, the sofosbuvir + ledipasvir combination drug should not be administered to patients with decompensated cirrhosis.

Drug interactions
Because sofosbuvir and ledipasvir are transporter (P-glycoprotein, BCRP) substrates, plasma levels of sofosbuvir and ledipasvir may decrease if they are used in combination with drugs that induce P-glycoprotein in the intestinal tract. Therefore, the use of rifampicin, carbamazepine, phenytoin, and St. John’s Wort, which have strong P-glycoprotein inducing effects, in combination with sofosbuvir and ledipasvir is contraindicated, and rifabutin and phenobarbital are drugs that should be coadministered with care. In addition, when gastric pH increases, the solubility of ledipasvir decreases, and the plasma concentration therefore decreases. Caution should therefore be exercised when using the following drugs in combination with ledipasvir: antacids such as aluminum hydroxide and magnesium hydroxide; H2 receptor antagonists, and proton pump inhibitors. Caution should also be exercised when using the following drugs in combination with ledipasvir, because their blood concentrations are increased by ledipasvir’s inhibitory effects on P-glycoprotein and BCRP: digoxin, lovastatin, and tenofovir.50

Overseas, postmarketing, 9 cases have been reported of the concomitant use with sofosbuvir of not only DAAs but also amiodarone resulting in bradycardia; 3 of these patients had received the sofosbuvir + ledipasvir combination drug, 5 had received sofosbuvir + daclatasvir, and 1 had received sofosbuvir + simprevir. Of these 9 patients, 7 had been concomitantly receiving beta blockers; 6 of these patients experienced the onset of bradycardia within 24 hours after treatment initiation, and the remaining 3 experienced the onset of bradycardia between 2 and 12 days after treatment initiation. One of these patients died because of cardiac arrest, and 3 needed to have pacemakers implanted. Although the details of the interactions of the sofosbuvir + ledipasvir combination drug and amiodarone, as well as the mechanism of bradycardia onset, are unknown, the coadministration of amiodarone with the sofosbuvir + ledipasvir combination drug cannot be recommended.

Recommendations:
- The concomitant use of rifampicin, carbamazepine, phenytoin, and St. John’s Wort, which act to induce P-glycoprotein, is contraindicated, and caution should be exercised when coadministering rifabutin and phenobarbital.
- Caution should be exercised when coadministering amiodarone, H2 receptor antagonists, or proton pump inhibitors because the coadministration of these drugs decreases the plasma concentration of ledipasvir.
- Caution should be exercised when coadministering digoxin, lovastatin, or tenofovir because the plasma concentrations of these drugs are increased because of ledipasvir’s inhibitory effects on P-glycoprotein and BCRP.
- Cases have been reported of bradycardia being caused by the use of amiodarone in combination with the sofosbuvir + ledipasvir combination drug. The use of the sofosbuvir + ledipasvir combination drug therefore cannot be recommended in patients receiving amiodarone.
Drug resistance
When RAVs were investigated by subculturing replicon-containing cells in the presence of ledipasvir, NS5B Y93H variants were detected. Furthermore, assays of replicons into which Y93H variants had been introduced found that the presence of Y93H variants increased the EC50 by 3310 times. Such in vitro assay results showed that NS5B Y93H decrease sensitivity to ledipasvir. In replicons into which other NS5A variants had been introduced, moreover, L31M and P32L increased the EC50 by between 10 and 50 times, and P58D increased the EC50 by between 100 and 1000 times. These NS5A variant replicons were sensitive to sofosbuvir. In addition, the S282T replicons that exhibited resistance to sofosbuvir were sensitive to ledipasvir.

In clinical investigations, in a Japanese phase 3 clinical study, although deep sequencing analysis with a detection sensitivity of 1% found NS5A RAVs before treatment initiation in 76 patients (22%), the only patients who did not achieve SVR12 was a patient who had a Y93H before treatment initiation (the SVR12 rate was 99%). Although deep sequencing analysis of the one patient who did not achieve SVR12 found a Y93H both before treatment and at 4 weeks after the end of treatment, no other NS5A RAVs or NS5B S282T were detected. Furthermore, the study population did not include any patients who had been previously treated with NS5A inhibitors, and it is necessary to keep in mind, regarding the aforementioned therapeutic efficacy of sofosbuvir+ledipasvir in patients with NS5A RAVs before treatment initiation, that this efficacy was found in patients who had NS5A RAVs before treatment initiation, and not in patients with treatment-induced RAVs. Specifically, the therapeutic efficacy of sofosbuvir+ledipasvir in daclatasvir+asunaprevir combination therapy non-responders with multiple induced NS5A RAVs is at present not known.

Recommendations:
• In vitro assays have confirmed that NS5A Y93H variants confer resistance to ledipasvir.
• In a Japanese phase 3 clinical study, a high proportion of patients without a history of NS5A inhibitor treatment achieved SVR, even when they had Y93H variants before treatment initiation.
• At present, the therapeutic efficacy of sofosbuvir+ledipasvir in daclatasvir+asunaprevir combination therapy non-responders with multiple induced NS5A RAVs is not known.

Ombitasvir+Paritaprevir+Ritonavir combination tablets
Ombitasvir is a H5SA inhibitor. In the HCV replicon cells ombitasvir inhibits replication of HCV replicons derived from HCV genotype 1a and 1b, and the EC50 was 14.1 pmol/L. 5.0 pmol/L, respectively. Paritaprevir is a NS3/4A protease inhibitor, which plays a role in processing of proteins coded by HCV genome. Paritaprevir inhibits replication of HCV replicon derived from genotype 1a and 1b in the HCV replicon cells, and the EC50 was 1.0 nmol/L and 0.21 nmol/L, respectively. Paritaprevir is mainly metabolized by cytochrome P450 sa4 (CYP3A4). With concomitant use of ombitasvir and paritaprevir, antiviral effect was additively or synergistically increased at every concentration tested in the HCV genotype 1 replicon cells.

Ritonavir was developed as an anti-HIV agent belonged to protease inhibitors. With its strong inhibitory effect of CYP3A4, ritonavir inhibit metabolism of other protease inhibitors, resulting in increase of plasma concentration and prolongation of half-life (boosting effect). Ritonavir has no anti-HCV effect in replicon cells and no effect on anti-HCV activity of paritaprevir. However, ritonavir is concomitally used with taking advantage of this booster effect and for increasing exposure of paritaprevir.

Japanese clinical study results (Fig. 10)
In Fig. 10, the phase 2 clinical study in Japan conducted in genotype 1b HCV infected patients are shown. Inclusion criteria were Japanese HCV genotype 1b patients, with age 18 to 75 years, and 1) null or partial responder to previous Peg-IFN + RBV therapy, 2) more than 10,000 IU/mL of plasma HCV-RNA levels at screening, 3) non-cirrhotic, 4) without HIV or HBV coinfection, and 5) no etiology of liver diseases other than HCV infection. The patients were randomized into 4 groups, 1) ombitasvir 25 mg + paritaprevir 100 mg + ritonavir 100 mg for 12 weeks, 2) ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg for 12 weeks, 3) ombitasvir 25 mg + paritaprevir 100 mg + ritonavir 100 mg for 24 weeks, and 4) ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg for 24 weeks. The SVR 24 rate was 100% (18/18), 88.9% (16/18), 100% (19/19) and 100% (18/18), respectively, yielding excellent efficacy (Fig. 10). On the basis of the results of this clinical study, the phase 3 clinical trial was performed with ombitasvir 25 mg + paritaprevir 150 mg + ritonavir 100 mg for 12 weeks of treatment period.

The phase 3 clinical trial in Japan (GIFT-1 study) enrolled HCV genotype 1b infected Japanese non-cirrhotic
and cirrhotic patients, with HCV RNA ≥ 10,000 IU/ml, and age 18 to 75 years. In non-cirrhotic patients (n = 321) double-blinded study was done, consisting of ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg for 12 weeks (actual drug group; n = 215) and placebo for 12 weeks followed by actual drugs for 12 weeks (n = 106). On the other hand, open-label study was performed in patients with compensated cirrhosis (n = 42), with 6 or less of Child-Pugh score, with administration of actual drugs for 12 weeks. The SVR 12 rate in non-cirrhotic patients was 94.9% (294/215) in the actual drug group and 98.1% (104/106) in placebo-actual drug group, respectively, and 90.5% (38/42) in cirrhotic patients (Fig. 11). Age, sex, HCV-RNA load at baseline, IL28B polymorphisms, and a history of previously treatment with IFN were not associated with therapeutic efficacy.

**Recommendations:**

- The SVR rates for therapy for 12 weeks with the ombitasvir + paritaprevir + ritonavir combination in genotype 1b, non-cirrhotic/compensated cirrhosis patients are 91 - 98% in the Japanese phase 3 study.
- No differences in therapeutic efficacy have been found by background factor (e.g., cirrhosis, IL28B polymorphisms, age, HCV-RNA load at baseline and a history of previously treatment with IFN).

**Adverse reactions**

In the Japanese phase 3 clinical study, adverse reactions were observed in 30.7% (66/215) in actual drug group and 14.2% (15/106) in placebo-actual drug group, respectively, in non-cirrhotic patients and 40.5% (17/42) in cirrhotic patients with actual drugs. These adverse effects included periphery edema (n = 15, 4.1%), headache (n = 12, 3.3%), and nausea (n = 10, 2.8%). Although frequency was low, liver injuries such as elevation of ALT (0.3%) or bilirubin (0.3%) were observed. No mortality associated with adverse reactions was reported.

Three serious adverse events which were considered to be associated with the drug were reported: hypotension, anuria and pulmonary edema. The case with hypotension was a male in 70’s, taking nifedipine 40 mg daily. On the second day of administration of ombitasvir + paritaprevir + ritonavir combination tablet hypotension and edema developed, and the patients was admitted to the hospital. Since blood pressure recovered and edema was subsided immediately after stopping the combination tablet, it was possible that exposure of calcium channel blocker might be increased due to CYP3A4 inhibitory effect of ritonavir. In cases with annuria, oliguria and edema developed on the second day of administration of the combination tablet as well, while fever and cough with dyspnea developed on the 25th and the 29th day after commencement of the combination therapy, respectively, and a diagnosis of pulmonary edema was made. Although hypotension was not confirmed to develop in the latter two cases, both patients were taking calcium channel blockers. In the phase 3 clinical study, adverse events associated with edema was found in 24 cases overall, and calcium channel blockers were concomitantly used in 22 cases (92%) among them. By contrast, the incidence of adverse events associated with edema was 0.7% (2/279) in patients without taking calcium channel blockers and 26.2% (22/84) in those who were taking them.

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According to the package insert of ombitasvir + paritaprevir + ritonavir combination tablet, azelnidipine that is regarded to be contraindicated in the package insert of ritonavir tablet is also contraindicated, and caution should be exercised when using other calcium channel blockers.63 Taken together, it is not recommended to concomitantly use ombitasvir + paritaprevir + ritonavir combination tablet with calcium channel blockers. When it cannot be avoided to concomitantly use, dosage of calcium channel blockers should be reduced.

In addition, because decompensated cirrhosis patients were not included in the target population for the Japanese clinical studies, as was the case for other DAA drug products, and the safety in these patients has not been confirmed, ombitasvir + paritaprevir + ritonavir combination tablet should therefore not be administered to decompensated cirrhosis patients. In particular, in the West, severe liver injuries including hepatic failure occasionally developed due to administration of Viekira Pak (ombitasvir + paritaprevir + ritonavir + dasabuvir) to patients with advanced cirrhosis at baseline, and FDA decided the use of Viekira Pak for patients with Child-Pugh grade B or C as contraindicated. Along with this decision, the administration of ombitasvir + paritaprevir + ritonavir for patients with Child-Pugh grade B or C is contraindicated in Japan as well.

**Recommendations:**
- In the Japanese phase 3 study, adverse events associated with edema developed in 26.2% of those who were taking calcium channel blockers, and serious adverse effects including hypotension, anuria and pulmonary edema occurred in some patients.
- It is not recommended to concomitantly use ombitasvir + paritaprevir + ritonavir combination tablet with calcium channel blockers. When it cannot be avoided to concomitantly use, dosage of calcium channel blockers should be reduced.
- No clinical studies have been conducted in patients with decompensated cirrhosis, and the safety has not been confirmed in such patients. Therefore, ombitasvir + paritaprevir + ritonavir combination tablet should not be administered to patients with decompensated cirrhosis.
- The administration for patients with Child-Pugh grade B or C is contraindicated as well, even if compensated.

**Drug interactions**
Ombitasvir is oxidatively metabolized through amid hydrolysis and is a substrate of P-glycoprotein. Paritaprevir is a substrate and inhibitor of P-gp, BCRP, and OATP1B1/1B3. Ritonavir is mainly metabolized by CYP3A4/5, and is a substrate and inhibitor of P-gp. Also ritonavir has an inhibitory effect for CYP3A4 and BCRP. As a result, concomitant use of ombitasvir + paritaprevir + ritonavir and drugs which use CYP3A, P-gp, BCRP and OATP1B1/1B3 as substrates may increase plasma concentration of these drugs and therefore dose adjustment as well as careful observation is needed.

Calcium channel blockers are substrate of CYP3A4 and plasma concentration of calcium channel blockers may be increased due to inhibitory effect for CYP3A4 of ritonavir with concomitant use with ombitasvir + paritaprevir + ritonavir combination tablet. According to the package insert of ombitasvir + paritaprevir + ritonavir combination tablet, the AUC of amlodipine 5 mg single dosage is increased by 2.572 times (90% confidential interval: 2.312-2.862) with concomitant use with this combination tablet.63 Therefore, as described above, dosage of calcium channel blockers should be reduced when it cannot be avoided to concomitantly use both of them.

**Drug resistance**
According to the experiments testing resistant variants against paritaprevir using replicon cells, NS3 D168A/V variant increased the EC50 by 29-159 times compared to wild type.64 Moreover, the combination of Y56H and D168A/V also increased the EC50 by 700 – 2,472 times. Similarly, investigation of resistant variants against ombitasvir demonstrated that NS5A L31F/V increased the EC50 by 8 – 10 times, and Y93H increased the EC50 by 77 times.65 Presence of L28M, R30Q, L31M or L31V in addition to Y93H increased the EC50 by 142 – 12,328 times.

The therapeutic efficacy of 12 weeks administration of ombitasvir + paritaprevir + ritonavir combination tablet was decreased when NS5A Y93 RAVs are present at
baseline. The SVR12 rate was 99.9% (301/304) in cases without NS5A Y93 RAVs at baseline, while was decreased to 83.0% (39/47) with Y93 RAVs (Fig. 12). Therefore, before commencement of ombitasvir + paritaprevir + ritonavir combination therapy, Y93 RAVs should be tested and it should be confirmed that no Y93 RAVs are present. On the other hand, presence of NS3 D168 RAVs and NS5A L31 RAVs were not associated with therapeutic efficacy, and other NS3 RAVs and NS5A RAVs had no effect on therapeutic efficacy as well.

In Table 6, results of virological analyses before and after treatment are shown in treatment failure 11 cases (viral breakthrough or relapse) in the Japanese phase 3 study. While NS3 RAVs were not detected before treatment, D168 RAV was noted in 10 cases after treatment failure, and multiple D168 and Y56 RAVs were found in 5 patients out of 10. As for NS5A RAVs, while Y93 RAV was detected in 8 patients and not in 3 before treatment, single or multiple Y93 RAVs were detected in 10 out of 11 patients, and single L31 RAV was found in 1 patient, after treatment failure. In addition, as described above, replicon assays have demonstrated that multiple D168A/V and Y56H variants in the NS3 region and multiple Y93H and L28M, R30Q, L31M, P58S in the NS5A region exhibit higher resistance compared to single D168 RAV or Y93H RAV.

**Recommendations:**

- The therapeutic efficacy of 12 weeks administration of ombitasvir + paritaprevir + ritonavir combination tablet was decreased when NS5A Y93 RAVs are present at baseline. Viruses with multiple NS3 and NS5A RAVS resistant to both drugs frequently emerge in treatment failure with ombitasvir + paritaprevir + ritonavir combination therapy.
- To avoid emergence of these viruses with multiple RAVs resistant to both drugs it is recommended to test NS5A RAVs and to confirm there is no Y93 variants.

**TREATMENT STRATEGY FOR NON-CIRRHOTIC PATIENTS**

**Genotype 1**

**Basic treatment approach**

At present, genotype 1 patients can receive the following therapies in normal clinical practice: IFN-based antiviral therapy (Peg-IFN ± RBV ± a protease inhibitor [simeprevir, vaniprevir, telaprevir]), or IFN-free antiviral therapy (daclatasvir + asunaprevir combination therapy, sofosbuvir + ledipasvir combination therapy, or ombitasvir + paritaprevir + ritonavir combination therapy). If an antiviral therapy is not going to be administered, a liver supporting therapy (SNMC, UDCA) or low-dose Peg-IFN (IFN) therapy can be administered if the patient’s ALT levels are abnormal. In addition, the treatment of a genotype 1 and 2 mixed infection should conform to the treatment provided for a genotype 1 infection.

Furthermore, previously treated patients who received Peg-IFN monotherapy without RBV as their previous treatments are handled in these guidelines as treatment-naïve patients, and not as treatment-experienced patients, because the result of the previous therapy is not a predictive factor for efficacy.

**IFN-based antiviral therapy.** In 2004, the use of Peg-IFN + RBV combination therapy became possible in Japan. Although the coadministration of RBV with Peg-IFN increased the therapeutic efficacy, the number of adverse reactions, such as anemia, also increased. Subsequently, therapy started being optimized for individual patients, centered about a response-guided approach in which the treatment period is changed to match the response to the therapy. In 2011, it became possible to use a three-drug combination therapy consisting of the telaprevir (a first-generation protease inhibitor, and the first DAA in Japan), Peg-IFN, and RBV. The coadministration of telaprevir with Peg-IFN + RBV allows the treatment period to be shortened from 48 weeks (72 weeks) to 24 weeks, and although there are problems with adverse reactions, therapeutic efficacy is clearly improved. Then, in November 2013, simeprevir, a second-generation protease inhibitor, became covered by national health
insurance for use in genotype 1 patients. Although simeprevir + Peg-IFN + RBV combination therapy has the same treatment period (24 weeks) as telaprevir + Peg-IFN + RBV combination therapy, it is an oral therapy that is administered once a day, the SVR rate in clinical studies conducted in treatment-naïve patients in Japan (the DRAGON study, the CONCERTO-1 study, and the CONCERTO-4 study) was high (between 80% and 90%), and this therapy was nearly identical in terms of adverse reactions to the Peg-IFN + RBV therapy administered to the placebo group. Furthermore, in September 2014, vaniprevir, another second-generation protease inhibitor, also became covered by national health insurance for use in genotype 1 patients. The SVR rate in clinical studies of vaniprevir + Peg-IFN + RBV combination therapy was a high 83.7%, and the adverse reactions were nearly identical to those that occurred with the Peg-IFN + RBV combination therapy that was administered to the placebo group. Thus, at present the treatments of first choice are simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy.

IFN-free antiviral therapy. In July 2014, the first IFN-free DAA combination therapy – daclatasvir + asunaprevir combination therapy – became covered by national health insurance. Although daclatasvir + asunaprevir combination therapy was initially covered only for IFN-ineligible/intolerant patients and IFN-non-responders patients, in March 2015 coverage was expanded to include treatment-naïve patients and relapsed patients. Daclatasvir + asunaprevir combination therapy can now therefore be used in all genotype 1 non-cirrhotic and compensated cirrhosis patients. The SVR rate in clinical studies of daclatasvir + asunaprevir combination therapy in treatment-naïve patients in Japan was 89.1%, and the SVR rate in IFN-ineligible/intolerant patients who cannot use IFN was also high, at 87.4%. However, when a response is not achieved with DAA combination therapy, multidrug resistant variantss are frequently acquired. Therefore, when considering daclatasvir + asunaprevir combination therapy, it is important before initiating therapy to confirm that the patient has no HCV NS5A region (Y93/L31) polymorphisms (variants) that are associated with daclatasvir resistance. In fact, in the phase 3 study in IFN-ineligible/intolerant or non-responders, although the response rate for daclatasvir + asunaprevir combination therapy was 85% (188 of 222 patients) in the study population overall, the response rate for patients with Y93H RAVs (which patients accounted for 14% of the study population) was 43% (13 of 30 patients), which was lower than the response rate for patients without such RAVs, which was 91% (168 of 184 patients). Although L31M/V

Table 6  Change of RAVs before and after treatment in virological failure cases. (Japanese Phase 3 Clinical Study)

<table>
<thead>
<tr>
<th>Case</th>
<th>The cause of failure</th>
<th>NS3</th>
<th>NS5A</th>
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<tbody>
<tr>
<td>1</td>
<td>viral breakthrough</td>
<td>baseline</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>relapse</td>
<td>baseline</td>
<td>Y56H+D168V</td>
</tr>
<tr>
<td>3</td>
<td>relapse</td>
<td>baseline</td>
<td>Y56H+D168V</td>
</tr>
<tr>
<td>4</td>
<td>relapse</td>
<td>baseline</td>
<td>D168D/V</td>
</tr>
<tr>
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<td>relapse</td>
<td>baseline</td>
<td>D168V</td>
</tr>
<tr>
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<td>7</td>
<td>viral breakthrough</td>
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<td>none</td>
</tr>
<tr>
<td>8</td>
<td>relapse</td>
<td>baseline</td>
<td>Y56H, D168V</td>
</tr>
<tr>
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<td>baseline</td>
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<td>11</td>
<td>relapse</td>
<td>baseline</td>
<td>D168V</td>
</tr>
</tbody>
</table>

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were not common (incidence: 3.7%), the response rate was 25% (2 of 8 patients) in patients with such RAVs, which was lower than the response rate of 87% (179 of 206 patients) in patients without such RAVs (Fig. 5a, b).

Multi-drug resistant variants acquired by failure in daclatasvir + asunaprevir combination therapy have been reported to persist for 1 year or more after treatment. Therefore, although this is not presently covered by insurance, testing of Y93/L31 RAVs should be performed before initiating daclatasvir + asunaprevir therapy, and if any RAVs are found, then as a rule daclatasvir + asunaprevir combination therapy should not be considered to be a treatment option. Although variants associated with asunaprevir resistance are in the HCV NS3 region (D168), the same as is the case for simeprevir, because such variants account for less than 1% of genotype 1 HCV, there is little significance to performing such measurements before initiating therapy in treatment-naïve patients with DAAIs. It has been reported that viruses carrying D168 variants induced in daclatasvir + asunaprevir therapy non-responders gradually decrease after the end of treatment, and after about 1 year they fall to not more than the limit of detection sensitivity (direct sequencing method) in most patients. In addition, because, as described below, viruses carrying D168 variants may be present in simeprevir + Peg-IFN + RBV or vaniprevir + Peg-IFN + RBV combination therapy non-responders, as a rule daclatasvir + asunaprevir combination therapy should not be initiated in such patients (see section 4-2-2-1. Retreatment of patients previously treated with protease inhibitors).

In June 2015, sofosbuvir + ledipasvir combination therapy, which is a second-generation IFN-free DAA combination therapy, became covered by insurance. In a phase 3 study in Japan, treatment-naïve and previously treated genotype 1 HCV-infected patients (including 166 untreated patients, 175 treated patients, and 76 compensated cirrhosis patients) were randomly assigned to a group that received sofosbuvir + ledipasvir for 12 weeks or a group that received sofosbuvir + ledipasvir + RBV for 12 weeks. The response rates in these groups were, respectively, 100% (83 of 83 patients) and 96% (80 of 83 patients) in treatment-naïve patients and 100% (88 of 88 patients) and 100% (87 of 87 patients) in previously treated patients. Because all of the adverse reactions were insignificant, sofosbuvir + ledipasvir combination therapy is the treatment of first choice for genotype 1 patients. However, because sofosbuvir is metabolized primarily in the kidneys, its use is contraindicated in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m²) and patients with renal failure requiring dialysis. In addition, as is the case for daclatasvir + asunaprevir combination therapy, because the safety of sofosbuvir + ledipasvir combination therapy in decompensated cirrhosis patients has not been confirmed, sofosbuvir + ledipasvir combination therapy should not be administered to such patients. Furthermore, because it has been reported that in the case of a genotype 1 and 2 mixed infection, the response rate among genotype 2 patients to sofosbuvir + ledipasvir combination therapy was 96% (25 of 26 patients), the use in such patients of the sofosbuvir + ledipasvir combination therapy that is used in genotype 1 patients is recommended.

Furthermore, in September 2015, new IFN-free regimen, ombitasvir + paritaprevir + ritonavir combination therapy was approved. In Japanese phase 3 clinical trial, patients with genotype 1b, non-cirrhotic as well as cirrhotic patients (Child-Pugh grade 6 or less) were enrolled. In non-cirrhotic patients (n = 321) double-blinded study was done, consisting of ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg for 12 weeks (actual drug group; n = 215) and placebo for 12 weeks followed by actual drugs for 12 weeks (n = 106). On the other hand, open-label study was performed in patients with compensated cirrhosis (n = 42), with 6 or less of Child-Pugh score, with administration of actual drugs for 12 weeks. The SVR 12 rate in non-cirrhotic patients was 94.9% (294/215) in the actual drug group and 98.1% (104/106) in placebo-actual drug group, respectively, and 90.5% (38/42) in cirrhotic patients (Fig. 11). On the basis of the results of this clinical study, ombitasvir + paritaprevir + ritonavir combination therapy, along with sofosbuvir + ledipasvir combination therapy, is regarded as the therapy of first choice for genotype 1b, non-cirrhotic patients.

On the other hand, there are four points that should be particularly noted when initiating ombitasvir + paritaprevir + ritonavir combination therapy. First, the efficacy of this regimen for genotype 1a has not been confirmed. In oversea clinical studies, the SVR12 rate of ombitasvir (25 mg) + paritaprevir (200 mg) + ritonavir (100 mg) for patients with genotype 1a, untreated, non-cirrhotic patients was 62.5% (5/8). Second, the therapeutic efficacy was decreased when NS5A RAVs are present, as daclatasvir + asunaprevir combination therapy. In Japanese phase 3 trial, the SVR12 rate was 99.0% in patients without NS5A RAVs and 83.0% in patients with NS5A RAVs. This clinical trial also indicated that L31 RAVs that were known to be associated with the efficacy of daclatasvir + asunaprevir combination therapy had little effect on that of ombitasvir + paritaprevir + ritonavir combination. Third, ritonavir dispensed for expecting booster effect as increasing plasma concentration and prolongation of half life of paritaprevir has strong CYP3A4 inhibitory effect and thus may increase plasma concentration of calcium channel blockers if
coadministered. In the phase 3 trial, serious adverse effects were reported in a patient who developed hypotension and edema on the second day of administration of ombitasvir + paritaprevir + ritonavir combination tablet and was needed to be admitted, and other serious events, anuria as well as pulmonary edema, were also reported in different patients. All these three cases were taking calcium channel blockers. Lastly, in the West, severe liver injuries including hepatic failure occasionally developed due to administration of Viekira Pak (ombitasvir + paritaprevir + ritonavir + dasabuvir) to patients with advanced cirrhosis at baseline, and the administration of ombitasvir + paritaprevir + ritonavir for patients with Child-Pugh grade B or C is contraindicated in Japan as well.

Therefore, since excellent results are anticipated with ombitasvir + paritaprevir + ritonavir combination therapy if NS5A RAVs are tested and it is confirmed that no NS5A Y93 RAV are present before initiating treatment, this combination is recommended as the first-line therapy for genotype 1b with sofosbuvir + ledipasvir combination therapy.

**Recommendations:**

- The therapy of first choice in genotype 1 patients is sofosbuvir + ledipasvir combination therapy (in cases without severe renal impairment), or ombitasvir + paritaprevir + ritonavir combination therapy (in cases without NS5A Y93 RAVs).
- Daclatasvir + asunaprevir combination therapy is also an option if no Y93/L31 RAVs are present.
- Simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy are IFN-based therapies that are options in genotype 1 patients.
- If antiviral therapy is not going to be administered, and the patient's ALT levels are abnormal, then liver-supporting therapies (SNMC, UDCA) and/or low-dose Peg-IFN (IFN) therapy should be administered.
- The treatments that are administered to genotype 1 patients should be administered for genotype 1 + 2 mixed infections.

**Selection of antiviral therapy in treatment-naïve patients (Fig. 13)**

In treatment-naïve genotype 1 patients, sofosbuvir + ledipasvir combination therapy in cases without renal impairment, or ombitasvir + paritaprevir + ritonavir combination therapy in cases with no NS5A Y93 RAVs is the therapy of first choice. In addition, daclatasvir + asunaprevir combination therapy is another option in patients with no Y93/L31 RAVs. Although simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy are IFN-based therapy options in genotype 1, high viral load patients, it has been found that the SVR rate differs depending on the presence or absence of IL28B SNP polymorphisms. Specifically, in a Japanese phase 3 study of simeprevir + Peg-IFN + RBV combination therapy in treatment-naïve patients (the CONCERTO-1 study), the response rate by IL28B polymorphism was 94% in major allele (TT) patients and 71% in minor allele (TG/GG) patients, and the response rate for vaniprevir + Peg-IFN + RBV combination therapy was 92% in major allele (CC) patients and 68% in minor allele (CT/TT) patients. Therefore, in genotype 1, high viral load patients, simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy is recommended for patients with the IL28B major allele.

Furthermore, although sofosbuvir + ledipasvir combination therapy, ombitasvir + paritaprevir + ritonavir combination therapy and daclatasvir + asunaprevir combination therapy are all covered by health insurance for genotype 1, low viral load patients, neither simeprevir + Peg-IFN + RBV nor vaniprevir + Peg-IFN + RBV is covered by health insurance; the only IFN-based therapy that can be used in such patients is Peg-IFN monotherapy.

**Recommendations:**

- In treatment-naïve genotype 1 patients, sofosbuvir + ledipasvir combination therapy in cases without renal impairment, or ombitasvir + paritaprevir + ritonavir combination therapy in cases with no NS5A Y93 RAVs is the treatment of first choice, regardless of viral load.
- Daclatasvir + asunaprevir combination therapy is the treatment of first choice in patients without Y93/L31 RAVs.
- Simeprevir/vaniprevir + Peg-IFN + RBV is the treatment of first choice in treatment-naïve genotype 1, high viral load patients, and both of these therapies are recommended in patients with the IL28B major allele.
- PegIFN monotherapy is the only IFN-based therapy that can be used in genotype 1, low viral load patients.

**Predicted therapeutic efficacy of retreatment**

Response to therapy at the time of the initial therapy is the best indicator for the efficacy of retreatment with IFN-based therapy in IFN/Peg-IFN + RBV combination therapy non-responders. The response to the previous therapy in IFN/Peg-IFN + RBV combination therapy non-responders may be broadly divided into “relapse” (HCV RNA negative at one point during treatment, but reemergence after the end of treatment) and “non-response” (no HCV RNA negative results during treatment).
Furthermore, “non-response” may be divided into “null response” (indicating virtually no response, as evidenced by a decrease in the HCV RNA load $< 2$ log at 12 weeks after treatment initiation) and “partial response” (did not turn HCV RNA negative during therapy, but had a decrease in HCV RNA $\geq 2$ log at 12 weeks after treatment initiation).70 Furthermore, in previously treated patients who did not receive RBV – that is, in retreatment with RBV combination therapy of patients previously treated with IFN or Peg-IFN monotherapy – because the response to the previous treatment is not a strong predictive factor for efficacy, as a rule, retreatment is administered in accordance with the guidelines for treating treatment-naïve patients. Even if the details of the patient’s previous treatment are unknown, treatment should be administered in accordance with the guidelines for treating treatment-naïve patients.

In Peg-IFN + RBV combination therapy non-responders, a condition for retreatment with the same therapy is that the patient’s response to the previous therapy was not a “null response.” In patients who received the standard therapy for 48 weeks as their previous therapy, extending the duration of treatment to 72 weeks resulted in an improvement in therapeutic efficacy.67 In addition, the REALIZE study that was conducted in the West showed that, in retreatment with telaprevir + Peg-IFN + RBV combination therapy, as well, the efficacy of the previous treatment was an extremely important predictive factor for therapeutic efficacy.74 This was a clinical study of the administration for 48 weeks of telaprevir + Peg-IFN + RBV combination therapy to genotype 1a non-cirrhotic C patients previously treated with Peg-IFN + RBV combination therapy, and it was reported that when the efficacy of the previous therapy was the same, then the SVR rates in IL28B SNP (rs12980275) major allele (CC) and minor allele (CT or TT) patients were nearly identical.76 In a phase 3 study in Japan in patients previously treated with simeprevir + Peg-IFN + RBV combination therapy, the SVR rate was 90% (44 of 49 patients) in relapsers and 51% (27 of 53 patients) in non-responders. Furthermore, in the CONCERTO-4 study in which Peg-IFN alfa-2b was used, as well, the SVR rate was 97% (28 of 29 patients) in relapsers and 38% (10 of 26 patients) in non-responders, results that were virtually identical to the results that had been obtained for simeprevir 3-drug combination therapy in which Peg-IFN alfa-2a had been used (the CONCERTO-2/3 study). Thus, in simeprevir + Peg-IFN + RBV combination therapy, as well, the efficacy of the previous treatment is currently...
the most important factor contributing to SVR. In addition, in a Japanese phase 3 study of vaniprevir + Peg-IFN + RBV combination therapy, although a simple comparison is not possible because the vaniprevir treatment periods were different for relapers (12 weeks) and non-responders (24 weeks), the SVR rates in these two groups were, respectively, 92.0% (23 of 25 patients) and 61.9% (26 of 42 patients).

On the other hand, there is no relationship between the efficacy of retreatment with IFN-free DAA combination therapy and treatment response to IFN monotherapy or IFN + RBV combination therapy. In a phase 3 study in Japan of daclatasvir + asunaprevir combination therapy, the SVR24 rate was 80.5% (70 of 87 patients) even in patients who were non-responders to their previous therapies. Furthermore, in a Japanese phase 3 study of sofosbuvir + ledipasvir ± RBV combination therapy, the SVR24 rate in previously treated patients was 100% (88 of 88 patients) in patients without concomitant RBV and 100% (87 of 87 patients) in patients with concomitant RBV. In addition, in a Japanese phase 3 study of omibitasvir + paritaprevir + ritonavir combination therapy, the SVR12 rate in previously treated patients was 96.1% (73/76) in actual drug group, and 97.4% (37/38) in placebo followed by actual drug group.

Recommendations:

- **Response to the previous treatment** is the best indicator of the efficacy of retreatment with IFN-based therapy in Peg-IFN + RBV combination therapy non-responders.
- **There is no relationship between response to previous treatment with IFN monotherapy or IFN + RBV combination therapy and the efficacy of retreatment with IFN-free DAA combination therapy.** The SVR rate with sofosbuvir + ledipasvir combination therapy in a clinical study in previously treated patients was 100%.

Selection of antiviral therapy in treatment-experienced patients (Fig. 13)

The same treatment plan that is used for treatment-naïve patients should be used in treatment-experienced patients. Specifically, in genotype 1 patients being re-treated, sofosbuvir + ledipasvir in cases without severe renal impairment, or omibitasvir + paritaprevir + ritonavir in cases without Y93 RAVs is the therapy of first choice.

When omibitasvir + paritaprevir + ritonavir combination therapy is selected, every effort should be made to measure HCV NS5A Y93 before initiating therapy, and should not be an option if these RAVs are present. Similarly, L31 as well as Y93 variants in NS5A region should be measured before initiating daclatasvir + asunaprevir combination therapy. Daclatasvir + asunaprevir combination therapy is also an option for patients without Y93/L31 RAVs. Although HCV NS3 region (D168) polymorphisms (variants) that are associated with resistance to asunaprevir exhibit cross-resistance to simeprevir and/or vaniprevir, because patients not previously treated with protease inhibitors account for less than 1% of genotype 1 HCV patients, this is of little clinical significance. However, because viruses carrying D168 variants may persist in simeprevir + Peg-IFN + RBV or vaniprevir + Peg-IFN + RBV combination therapy non-responders, daclatasvir + asunaprevir combination therapy as well as omibitasvir + paritaprevir + ritonavir combination therapy are not recommended for such patients; instead, such patients should receive sofosbuvir + ledipasvir combination therapy.

Although simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy are IFN-based treatment options, as described above, the SVR rates that are achieved with these therapies differ widely depending on the patient’s response to previous treatment: the SVR rate is 50% to 60% in non-responders patients, but much higher, around 90%, in relapsed patients. Simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy is therefore recommended for relapsed patients.

Retreatment of patients not previously treated with DAAs. Relapsed/non-responders patients. For sofosbuvir + ledipasvir combination therapy, omibitasvir + paritaprevir + ritonavir combination therapy, and daclatasvir + asunaprevir combination therapy, which are IFN-free therapies, the efficacy of the previous treatment is not related to the response rate. Therefore, as with treatment-naïve patients, sofosbuvir + ledipasvir combination therapy in cases without severe renal impairment, or omibitasvir + paritaprevir + ritonavir combination therapy in cases without Y93 RAVs is the treatment of first choice. Daclatasvir + asunaprevir combination therapy is also an option for patients without Y93/L31 RAVs. If Y93/L31 RAVs are present, then neither daclatasvir + asunaprevir combination therapy nor omibitasvir + paritaprevir + ritonavir combination therapy is not recommended, as the response rate for the former and the latter is no more than around 40% and 80% in such patients, respectively.

In simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy, which are IFN-based therapies, the efficacy of the previous therapy is a predictive factor for therapeutic efficacy. Specifically, in relapsed patients, simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy
have high response rates of around 90%, are therefore an option, but in non-responders patients, simeprevir + Peg-IFN + RBV combination therapy has a response rate of 40% to 50%, and vaniprevir + Peg-IFN + RBV combination therapy has a response rate of around 60%. Simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy are therefore not recommended in non-responders patients. In addition, it should be kept in mind that if a response is not obtained with simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy, then there is a considerable risk of inducing NS3-resistant viruses.

Furthermore, because simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV therapy is very likely to afford patients non-responders to Peg-IFN monotherapy without RBV a good level of therapeutic efficacy similar to that achieved in treatment-naïve patients, if an IFN-based therapy is going to be administered, then simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy should be administered.

Patients discontinuing IFN (+ RBV) therapy because of adverse reactions. In patients discontinuing IFN (+ RBV) therapy because of adverse reactions, although liver-supporting therapies have been used exclusively up until now, sofosbuvir + ledipasvir combination therapy, which is a DAA combination therapy that is both an IFN-free therapy and that does not involve the use of RBV can be used, and is recommended in cases without severe renal impairment. As with treatment-naïve patients, every effort should be made to measure HCV NS5A Y93 before initiating therapy, and ombitasvir + paritaprevir + ritonavir combination therapy can be used and is recommended in cases without Y93 RAVs. Although antiviral therapy with daclatasvir + asunaprevir is also an option, every effort should be made to perform Y93/L31 RAV measurements, as for treatment-naïve patients, and if such RAVs are present, then as a rule daclatasvir + asunaprevir therapy should not be administered.

Recommendations.

- **Sofosbuvir + ledipasvir combination therapy in cases without renal impairment, or ombitasvir + paritaprevir + ritonavir combination therapy in cases without Y93 RAVs is the treatment of first choice for genotype 1 retreatment patients.**

- **Daclatasvir + asunaprevir combination therapy is also an option for patients with no Y93/L31 RAVs.**

- **For relapsed patients, simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy is also an option. In non-responders patients, simeprevir + Peg-IFN + RBV combination therapy and vaniprevir + Peg-IFN + RBV combination therapy are not recommended.**

- **It should be kept in mind that there is a considerable risk of viruses with NS3 RAVs being induced when patients do not respond to simeprevir + Peg-IFN + RBV combination therapy or to vaniprevir + Peg-IFN + RBV combination therapy.**

- **Simeprevir + Peg-IFN + RBV combination therapy or vaniprevir + Peg-IFN + RBV combination therapy can also be used in patients non-responders to IFN (Peg-IFN) monotherapy.**

- **Sofosbuvir + ledipasvir combination therapy in cases without renal impairment, or ombitasvir + paritaprevir + ritonavir combination therapy in cases without Y93 RAV is recommended in patients who discontinue from IFN (+ RBV) therapy because of adverse reactions. Antiviral therapy with daclatasvir + asunaprevir can also be used in patients with no Y93/L31 RAVs.**

- **Antiviral therapy is not going to be administered, and the patient’s ALT levels are abnormal, then liver-supporting therapy (SNMC, UDCA) or low-dose Peg-IFN (IFN) therapy should be administered.**

Retreatment of patients previously treated with DAAs. Retreatment of patients previous treated with IFN-based therapies that included DAAs (Fig. 14). In Japan, patients eligible for such retreatment are genotype 1 patients who did not respond to three-drug combination therapy with simeprevir, vaniprevir, or telaprevir with Peg-IFN + RBV. Protease region RAVs appear to exist in each of these therapies. Therefore, when retreatting such patients, the use of sofosbuvir + ledipasvir combination therapy, which does not include a protease inhibitor, is recommended.

There is no evidence that D168 RAVs induced in simeprevir or vaniprevir combination therapy non-responders affect the therapeutic efficacy of daclatasvir + asunaprevir combination therapy or ombitasvir + paritaprevir + ritonavir combination therapy, and because the response rates to these therapies are expected to be low in patients with D168 variants, based on an investigation of patients in Japanese/overseas clinical studies who had not been previously treated with protease inhibitors, at present retreatment with daclatasvir + asunaprevir combination therapy or ombitasvir + paritaprevir + ritonavir combination therapy following simeprevir or vaniprevir combination is as a rule not recommended.

Similarly, because there is no evidence on the effects of D168 variants, retreatment with vaniprevir combination therapy following simeprevir combination therapy, or with simeprevir combination therapy following vaniprevir combination therapy, is as a rule not recommended.
Moreover, because there is at present no evidence, retreatment with antiviral therapy that includes a second-generation protease inhibitor (simeprevir + Peg-IFN + RBV combination therapy, vaniprevir combination therapy, daclatasvir + asunaprevir combination therapy, or ombitasvir + paritaprevir + ritonavir combination therapy) is not recommended in patients who do not respond to treatment with telaprevir + Peg-IFN + RBV combination therapy.

Recommendations:

- **Sofosbuvir + ledipasvir combination therapy** is recommended for the retreatment of patients non-responders to simeprevir, vaniprevir, or telaprevir + Peg-IFN + RBV three-drug combination therapy.
- **Viruses carrying D168 variants exhibit cross-resistance to simeprevir, vaniprevir, and asunaprevir, and paritaprevir.**
- Because simeprevir or vaniprevir combination therapy non-responders are highly likely to have viruses with D168 variants at the end of treatment, the use of daclatasvir + asunaprevir combination therapy or ombitasvir + paritaprevir + ritonavir combination therapy following simeprevir or vaniprevir combination therapy is as a rule not recommended.
- **As a rule, vaniprevir combination therapy after simeprevir combination therapy, or simeprevir combination therapy after vaniprevir combination therapy, is not recommended.**
- Moreover, because there is at present no evidence, retreatment with antiviral therapy that includes a second-generation protease inhibitor (simeprevir + Peg-IFN + RBV combination therapy, vaniprevir combination therapy, daclatasvir + asunaprevir combination therapy, or ombitasvir + paritaprevir + ritonavir combination therapy) is not recommended in patients who do not respond to treatment with telaprevir + Peg-IFN + RBV combination therapy.

Retreatment of patients treated with IFN-free DAA therapy (Fig. 15). In daclatasvir + asunaprevir therapy non-responders, because it is difficult to treat patients in whom Y93/L31 RAVs have already been induced, and because a comprehensive assessment of such patients is required, what therapies are indicated and what treatment plans should be followed for such patients should be decided by physicians with sufficient knowledge of and experience with the treatment of viral liver disease. Specifically, if IFN can be administered, then an IFN-based therapy for which the presence of RAVs does not pose a problem should be administered, and if IFN cannot be used, then a detailed drug resistance investigation should be conducted and an appropriate therapy selected based on the results thereof, to prevent the emergence of more complex RAVs.

If sofosbuvir + ledipasvir combination therapy is selected, RAVs including Y93/L31 should be measured in detail to at least confirm that there are not multiple L31/Y93 RAVs. The efficacy of sofosbuvir + ledipasvir combination therapy in patients with multiple L31/Y93 RAVs is as a rule not recommended.
RAVs induced by daclatasvir + asunaprevir combination therapy has not been confirmed, and there is no evidence on the efficacy of retreatment. What treatments are indicated and what treatment plans should be formulated for such patients should be decided keeping in mind the risk of carcinogenesis, the response rate achieved with sofosbuvir + ledipasvir combination therapy in patients with RAVs, and the risk of inducing more complicated multidrug resistant variants.

Recommendations:
- In daclatasvir + asunaprevir therapy non-responders, because it is difficult to treat patients in whom Y93/L31 RAVs have already been induced, and because a comprehensive assessment of such patients is required, what therapies are indicated and what treatment plans should be followed for such patients should be decided keeping in mind the risk of carcinogenesis, the response rate achieved with sofosbuvir + ledipasvir combination therapy in patients with RAVs, and the risk of inducing more complicated multidrug resistant variants.
- Specifically, if IFN can be administered, then an IFN-based therapy for which the presence of RAVs does not pose a problem should be administered, and if IFN cannot be used, then a detailed drug resistance investigation should be conducted and an appropriate therapy selected based on the results thereof, to prevent the emergence of more complex resistance variants.

Genotype 2 patients
Treatment-naïve patients (Fig. 16)
In March 2015, approval was granted for the use of RBV in combination with sofosbuvir, an NS5B polymerase nucleoside inhibitor, in genotype 2 patients. In a phase 3 clinical study in Japan, 90 treatment-naïve genotype 2 hepatitis C patients received sofosbuvir 400 mg/day in combination with RBV for 12 weeks. None of the patients discontinued from the study because of adverse reactions, and an SVR rate of 98% was achieved. This therapy is the treatment of first choice for treatment-naïve genotype 2 patients.

Furthermore, the IFN-based therapies that can be used are Peg-IFN + RBV combination therapy in high viral load patients, and Peg-IFN (IFN) monotherapy in low viral load patients. PegIFN monotherapy can be expected to result in cure in patients with HCV RNA < 1,000 KIU/ml (6.0 Log IU/ml). In particular, SVR can be achieved in at least 80% of patients who become HCV RNA negative in 4 to 8 weeks. Moreover, genotype 1/2 mixed infection patients should be treated similarly to genotype 1 patients.

Recommendations:
- Sofosbuvir + RBV combination therapy is the treatment of first choice for treatment-naïve genotype 2 patients.
PegIFN + RBV combination therapy is also an option for treatment-naïve genotype 2, high viral load patients, and Peg-IFN (IFN) monotherapy is also an option for treatment-naïve genotype 2, low viral load patients.

Genotype 1/2 mixed infection patients should be treated similarly to genotype 1 patients.

Retreatment (Fig. 14, Fig. 16)
As described above, in March 2015, sofosbuvir + RBV combination therapy was approved for use in genotype 2 patients. In a phase 3 clinical study in Japan, 63 previously treated genotype 2 hepatitis C patients were treated with sofosbuvir 400 mg/day plus RBV for 12 weeks, and the SVR rate was 95% (60 of 63 patients). From now on, sofosbuvir + RBV combination therapy is the treatment of first choice for previously treated genotype 2 patients. Sofosbuvir + RBV combination therapy is also recommended for patients previously treated with telaprevir + Peg-IFN alfa-2b + RBV combination therapy.

Telaprevir + Peg-IFN alfa-2b + RBV combination therapy can also be used in genotype 2 relapsed patients.

Treatment of patients with normal ALT levels
In an investigation of hepatocarcinogenesis in 809 HCV-infected, non-cirrhotic patients who received Peg-IFN + RBV combination therapy and had normal ALT levels at treatment initiation (M/F: 269/540 patients; mean age: 57 ± 11 years; genotype 1/2: 550/247 patients; mean observation period: 36.2 ± 16.5 months), the incidence of carcino genesis did not vary significantly depending on therapeutic efficacy in patients with platelets ≥ 150,000/μl (n = 586), and the incidence of carcino genesis was 1.5% even in non-responders patients. In patients with platelets-150,000/μl (n = 323), the 3-year cumulative incidence of carcino genesis was a high 10.1% in non-responders patients, but no carcino genesis occurred through 3 years in either responders or relapsed patients, and it was reported that carcino genesis was significantly inhibited by Peg-IFN + RBV combination therapy (P < 0.001). In addition, the efficacy of Peg-IFN + RBV combination therapy in patients with normal ALT levels is similar to that in patients with elevated ALT levels.

Therefore, antiviral therapy is indicated even for patients with ALT < 30 U/l if their platelet counts are below 150,000/μl, but patients with ALT < 30 U/l and platelet count ≥ 150,000/μl should be monitored without receiving antiviral therapy. However, these patients may experience elevated ALT levels while they are being monitored, and if they strongly desire to receive antiviral therapy, then they are eligible for said therapy. Furthermore, although Peg-IFN + RBV combination therapy is currently the main therapy for which data are available for patients with...
normal ALT levels, it appears that similar therapeutic efficacy can be expected with DAA + Peg-IFN + RBV combination therapy or an IFN-free DAA combination therapy.

Recommendation:
- Antiviral therapy can be administered to patients with normal ALT levels (ALT < 30 U/l) in the same manner as that used for patients with elevated ALT levels. Aggressive treatment is particularly desirable for patients with platelet counts < 150,000/μl.

TREATMENT STRATEGY FOR CIRRHOTIC PATIENTS

Antiviral therapy for compensated cirrhosis

A CONDITION IN WHICH hepatic reserve capacity is maintained and there are no symptoms of hepatic failure, such as jaundice, ascites, hepatic encephalopathy, or gastroesophageal varices hemorrhage, is referred to as “compensated cirrhosis,” and a condition that is accompanied by symptoms of hepatic failure is referred to as “decompensated cirrhosis.” Patients with cirrhosis who experience severe hepatic fibrosis progression are at high risk for hepatocarcinogenesis. In addition, even if hepatocarcinogenesis does not occur, if the condition progresses to hepatic failure, then the prognosis is poor. Therefore, the objective of treatment in cirrhosis is to prevent both hepatocarcinogenesis and hepatic failure, and there is consequently a considerable need for aggressive antiviral therapy in compensated cirrhosis. If viral clearance is obtained through antiviral therapy for compensated cirrhosis, then hepatocarcinogenesis and/or hepatic failure can be expected to be prevented. However, none of the DAAs telaprevir, simeprevir, or vaniprevir that have yielded improvements in therapeutic efficacy in recent years in noncirrhotic patients are covered by health insurance for use in cirrhosis, and to date the only antiviral therapy for cirrhosis is Peg-IFN + RBV combination therapy. In addition, because patients with advanced hepatic fibrosis are fundamentally resistant to IFN, and because pancytopenia associated with hypersplenism occurring concurrently with cirrhosis is an impediment to IFN therapy, HCV clearance through IFN-free DAA therapy even in patients with cirrhosis. Sofosbuvir + ledipasvir combination therapy or ombitasvir + paritaprevir + ritonavir combination therapy is the treatment of first choice for genotype 1 compensated cirrhosis patients. However, sofosbuvir + ledipasvir combination therapy is contraindicated in patients with severe renal impairment and dialysis patients. As for ombitasvir + paritaprevir + ritonavir combination therapy, the efficacy for genotype 1a is reduced. It is required to confirm absence of Y93 RAVs before treatment since the efficacy is reduced in cases with NS5A Y93 RAVs. Furthermore, the use of this regimen is contraindicated in patients with Child-Pugh grade B or C. Daclatasvir + asunaprevir combination therapy is an alternative in genotype 1b patients and after first confirming that there are no Y93/L31 mutations. However, the possibility that unexpected hepatic dysfunction could occur should be kept in mind when administering daclatasvir + asunaprevir combination therapy, and the use in patients with Child-Pugh grade B or C is contraindicated. Moreover, sofosbuvir + RBV combination therapy is recommended in genotype 2 compensated cirrhosis patients. An IFN-based therapy that includes telaprevir, simeprevir, or vaniprevir should not be used in cirrhosis patients.

Recommendations:
- In compensated cirrhosis type C, aggressive IFN-free DAA antiviral therapy should be administered to prevent hepatocarcinogenesis and hepatic failure.
- Cirrhosis patients should not receive IFN-based therapies that include telaprevir, simeprevir, or vaniprevir.

PegIFN + RBV combination therapy

In Japan, Peg-IFN alfa-2b or Peg-IFN alfa-2a + RBV combination therapy has been covered for use in compensated cirrhosis since 2011 regardless of viral load or genotype. In a Japanese clinical study in compensated cirrhosis, treatment for 48 weeks with Peg-IFN alfa-2b 1.0 μg/kg/week + RBV resulted in an SVR rate of 22% (15 of 69 patients) in genotype 1, high viral load patients and an SVR rate of 79% (26 of 33 patients) in other patients, which showed that this treatment is more effective in patients other than genotype 1 and high viral load patients. In addition, treatment for 48 weeks with two doses of Peg-IFN alfa-2a (90 μg and 180 μg) in combination with RBV yielded an SVR rate of 28% (17 of 61 patients) in the 90 μg group and 27% (17 of 63) in the 180 μg group. Therefore, no difference was found between the groups in the SVR rate. In the 90 μg group, the SVR rate was 21% (10 of 48 patients) in genotype 1 patients and 50% (6 of 12 patients) in
In a Japanese clinical study in compensated cirrhosis type C, Peg-IFN alfa-2a is 90 μg/week, and Peg-IFN alfa-2b is 1.0 μg/week. In compensated cirrhosis patients, the standard dose of Peg-IFN alfa-2b is 1.0 μg/kg/week, and the standard dose of Peg-IFN alfa-2a is 90 μg/week.

**Recommendations:**
- In compensated cirrhosis type C, the standard dose of Peg-IFN alfa-2b is 1.0 μg/kg/week, and the standard dose of Peg-IFN alfa-2a is 90 μg/week.
- In a Japanese clinical study in compensated cirrhosis type C, treatment for 48 weeks with Peg-IFN alfa-2b 1.0 μg/kg/week + RBV resulted in an SVR rate of 22% (15 of 69 patients) in genotype 1, high viral load patients; an SVR rate of 79% (26 of 33 patients) in other patients, which showed that this treatment is more effective in patients other than genotype 1, high viral load patients.
- In a Japanese clinical study in compensated cirrhosis type C, treatment for 48 weeks with Peg-IFN alfa-2a 90 μg in combination with RBV yielded an SVR rate 21% (10 of 48 patients) in genotype 1 patients and 50% (6 of 12 patients) in genotype 2 patients, which showed that this treatment is more effective in genotype 2 patients.

**Daclatasvir + asunaprevir combination therapy**
Daclatasvir is an NS5A inhibitor and asunaprevir is a protease inhibitor that targets the NS3-4A region. Daclatasvir is administered orally once a day at a dose of 60 mg, and asunaprevir is administered orally twice a day at a dose of 100 mg. A two-drug combination therapy is administered for 24 weeks. Dose reduction is unnecessary, even in compensated cirrhosis patients.

A Japanese phase 3 study of daclatasvir + asunaprevir in IFN-ineligible/intolerant or non-responders patients was conducted in 87 patients who were non-responders to previous therapy and 135 patients who were intolerant to or ineligible for IFN-based therapies. These patients included a total of 22 patients with compensated cirrhosis, 11 in the non-responders group and 11 in the IFN (+ RBV)-ineligible/intolerant group. The SVR rate in this group of 22 patients was 90.9% (20 of 22 patients). Thus, no significant differences were found between cirrhosis patients and non-cirrhotic patients, either in efficacy or safety, in the results of the Japanese phase 3 study.

However, the only patients targeted by this Japanese phase 3 study were compensated cirrhosis patients. Therefore, daclatasvir + asunaprevir combination therapy is not covered by health insurance for use in decompensated cirrhosis patients and the safety of daclatasvir + asunaprevir combination therapy has not been confirmed.

**Sofosbuvir + ledipasvir combination therapy**
In clinical studies in the West (ELECTRON, LONESTAR, ION-1, ION-2, ION-3, GS-US-334-0113, SIRIUS), 513 genotype 1 patients with compensated cirrhosis received sofosbuvir + ledipasvir ± RBV for either 12 or 24 weeks. In patients receiving sofosbuvir + ledipasvir for 12 weeks, the response was 96% in untreated cirrhosis patients, but was lower (90%) in IFN-experienced cirrhosis patients. In the SIRIUS study, 155 patients with compensated cirrhosis who were non-responders to Peg-IFN + RBV or protease inhibitor + Peg-IFN + RBV were randomized to either 12 weeks of treatment with sofosbuvir + ledipasvir + RBV combination therapy or 24 weeks of sofosbuvir + ledipasvir. The response rates in these two groups were, respectively, 96% and 97%. These results suggest that sofosbuvir + ledipasvir for 24 weeks is a treatment option for cirrhosis patients non-responded to previous therapy, and sofosbuvir + ledipasvir + RBV is a treatment option for patients for whom long-term therapy would be difficult.

In a phase 3 study in Japan in genotype 1 patients with compensated cirrhosis who received sofosbuvir + ledipasvir ± RBV for 12 weeks, the SVR rate in treatment-naïve patients was 100% (13 of 13 patients) in the sofosbuvir + ledipasvir group and 92% (11 of 12 patients) in the sofosbuvir + ledipasvir + RBV group, and the SVR rate in previously treated patients was 100% (28 of 28 patients) in the sofosbuvir + ledipasvir group and 100% (23 of 23 patients) in the sofosbuvir + ledipasvir + RBV group. In addition, none of the patients receiving sofosbuvir + ledipasvir combination therapy discontinued from the study because of adverse events. In light of these results, sofosbuvir + ledipasvir for 12 weeks is covered by health insurance in
Japan for both treatment-naïve and previously treated patients. Furthermore, sofosbuvir + ledipasvir combination therapy is not covered by health insurance for use in decompensated cirrhosis patients, in whom safety of this therapy has not been confirmed. Sofosbuvir + ledipasvir combination therapy should therefore not be used in decompensated cirrhosis patients.

**Recommendations:**

- In a Japanese phase 3 study, the SVR rate in genotype 1 compensated cirrhosis type C patients who received sofosbuvir + ledipasvir for 12 weeks was 100%.
- There are no significant differences in either efficacy or safety between compensated cirrhosis patients and non-cirrhotic patients.
- Sofosbuvir + ledipasvir combination therapy is not covered by health insurance for use in patients with decompensated cirrhosis, in whom the safety of this therapy has not been confirmed. Sofosbuvir + ledipasvir combination therapy should therefore not be used in patients with decompensated cirrhosis.

**Sofosbuvir + RBV combination therapy**

In the POSITRON study, an overseas phase 3 study, the SVR rate was 94% in treatment-naïve genotype 2 patients with compensated cirrhosis.\(^5^1\) In the FUSION study, which was conducted in genotype 2 patients previously treated with Peg-IFN + RBV, the SVR rate was 60% in compensated cirrhosis patients treated with sofosbuvir + RBV for 12 weeks.\(^5^1\) In the VALANCE study, the SVR rate was 78% in the 9 cirrhosis patients.\(^5^0\) In a Japanese phase 3 study, the SVR rate was 94% (16 of 17 patients) in the cirrhosis population overall, 100% (8 of 8 patients) in treatment-naïve patients, and 89% (8 of 9 patients) in previously treated patients. There were no differences in the incidences or degrees of seriousness of adverse reactions between patients with and without cirrhosis.\(^5^1\)

**Recommendations:**

- The SVR rate for 12 weeks of sofosbuvir + RBV combination therapy in genotype 2 compensated cirrhosis type C was 94% (16 of 17 patients) in the Japanese phase 3 study.
- No significant differences in efficacy or safety were found between patients with compensated cirrhosis and other patients.
- Sofosbuvir + RBV combination therapy is not covered by health insurance for use in decompensated cirrhosis patients, nor has its safety in these patients been confirmed.

**Ombitasvir + paritaprevir + ritonavir combination therapy**

**Selection of antiviral therapy in genotype 1 compensated cirrhosis patients (Fig. 17)**

Compensated cirrhosis patients have highly advanced fibrosis and are at extremely high risk of carcinogenesis and therefore require prompt antiviral treatment initiation. Because the therapeutic efficacy of Peg-IFN + RBV combination therapy, which is covered by health insurance for use in compensated cirrhosis, both for treatment-naïve and previously treated patients, is low, sofosbuvir + ledipasvir combination therapy or ombitasvir + paritaprevir + ritonavir combination therapy is the treatment of first choice for such patients. It should be kept in mind that sofosbuvir + ledipasvir combination therapy is contraindicated in patients with severe renal impairment and dialysis patients. As for ombitasvir + paritaprevir + ritonavir combination therapy, the efficacy for genotype 1a is reduced. It is required to confirm absence of Y93 RAVs before treatment. The use of this regimen is contraindicated in patients with Child-Pugh grade B or C. Although daclatasvir + asunaprevir combination therapy is also an option in genotype 1b patients, as is the case in non-cirrhotic, every effort should be made to perform Y93/L31 RAVs measurements before initiating treatment, and if any such RAVs are found, then daclatasvir + asunaprevir combination therapy should not be administered. The use in patients with Child-Pugh grade B or C is contraindicated.

If viral clearance is not achieved despite the administration of antiviral therapy, or if antiviral therapy is not indicated, and if the patient has an abnormal ALT level (> 30 U/l), then liver-supporting therapy or low-dose Peg-IFN (IFN) therapy should be administered. Low-dose IFN or Peg-IFN maintenance therapy in cirrhosis has been shown to be useful for preventing the progression of cirrhosis and for preventing hepatocarcinogenesis.\(^2^8,9^2,9^3\) However, efficacy is not achieved in all patients, and if efficacy is not achieved, treatment should be discontinued in accordance with the treatment discontinuation criteria.

**Recommendations:**

- In genotype 1 compensated cirrhosis, sofosbuvir + ledipasvir combination therapy or ombitasvir + paritaprevir + ritonavir combination therapy is recommended for both treatment-naïve and treatment-experienced patients.
- Sofosbuvir + ledipasvir combination therapy is contraindicated in patients with severe renal impairment and dialysis patients.
As for ombitasvir + paritaprevir + ritonavir combination therapy, the efficacy for genotype 1a is reduced. It is required to confirm absence of Y93 RAVs before treatment. The use of this regimen is contraindicated in patients with Child-Pugh grade B or C.

Although daclatasvir + asunaprevir combination therapy is an option in genotype 1b patients, as is the case for non-cirrhotic patients, every effort should be made to perform Y93/L31 RAVs measurements before initiating therapy, and if such mutations are found, then daclatasvir + asunaprevir combination therapy should not be administered.

If antiviral therapy cannot be administered, and if the patient’s ALT levels are abnormal, then liver-supporting therapy (SNMC, UDCA) should be administered. In addition, low-dose Peg-IFN (IFN) therapy for the purpose of hepatitis alleviation is also an option. However, if efficacy is not achieved, then treatment should be discontinued in accordance with the treatment discontinuation criteria.

Selection of antiviral therapy in genotype 2 compensated cirrhosis patients (Fig. 17)

Sofosbuvir + RBV combination therapy has also been approved for genotype 2 compensated cirrhosis in addition to Peg-IFN + RBV combination therapy. Daclatasvir + asunaprevir combination therapy is not covered by health insurance for use in such patients. Sofosbuvir + RBV combination therapy is the mainstay therapy for patients judged to be IFN-ineligible, both for treatment-naïve and previously treated patients. In patients judged to be IFN-eligible, moreover, Peg-IFN + RBV combination therapy has lower therapeutic efficacy, and also more adverse reactions, than sofosbuvir + RBV combination therapy, and sofosbuvir + RBV combination therapy is therefore the mainstay treatment for such patients. However, when selecting what therapy to use, it should be kept in mind that there is evidence for IFN-based therapies having a carcinogenesis prevention effect.

In all cases, if antiviral therapy fails to result in viral clearance, or if the patient cannot tolerate IFN therapy, and if the patient’s ALT level is abnormal, then liver-supporting therapy (SNMC, UDCA) should be administered. Low-dose Peg-IFN (IFN) therapy for hepatitis alleviation is also an option. However, if efficacy is not obtained, treatment should be discontinued in accordance with the treatment discontinuation criteria.

Recommendations

- In genotype 2 compensated cirrhosis patients, sofosbuvir + RBV combination therapy is the mainstay therapy for both treatment-naïve and previously treated patients.

- If antiviral therapy fails to result in viral clearance, or if antiviral therapy is not indicated, and if the patient’s ALT level is abnormal, then liver-supporting therapy (SNMC, UDCA) should be administered. Low-dose Peg-IFN (IFN) therapy for hepatitis alleviation is also an option. However, if efficacy is not obtained, treatment should be discontinued in accordance with the treatment discontinuation criteria.

Figure 17  Treatment Algorithm for Genotype 1/2, Compensated Cirrhotic Patients (Treatment-naïve and -experienced)*1.

*1: PegIFN + RBV combination therapy is also an option. *2: The use of SOF is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2 and patients with renal failure requiring dialysis. *3: The efficacy of OBV/PTV/r for genotype 1a has not been confirmed. The use for patients with Child-Pugh grade B is contraindicated. In general concomitant use of calcium channel blockers are not recommended. Dose adjustment may be required when drugs using CYP3A, P-gp, BCRP, OATP1B1/1B3 as substrate are coadministered. Every effort should be made to perform Y93 mutation measurements before initiating therapy to confirm the absence of such mutations. It should also be kept in mind that at present there are no established effective therapies for patients with multidrug resistant viruses induced in OBV/PTV/r non-responders. *4: DCV/ASV therapy is also an option in genotype 1b patients. However, every effort should be made to perform Y93/L31 mutation measurements before initiating therapy to confirm the absence of such mutations. It should also be kept in mind that at present there are no established effective therapies for patients with multidrug resistant viruses induced in DCV/ASV non-responders.

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Antiviral therapy for decompensated cirrhosis

Decompensated cirrhosis patients are at high risk for hepatic failure and death, and liver transplantation is the most effective therapy for patients for whom it is indicated. However, because around 30% of patients develop graft loss within 5 years following liver transplantation because of hepatitis C recurrence, overseas, IFN therapy is administered before transplantation to achieve HCV clearance or inhibition.94-95 In several clinical studies, Peg-IFN (+ RBV) therapy have been reported to be effective in genotype 2 patients, among others.92-94 However, in decompensated cirrhosis, the risk of the patient developing platelets decreased, anemia, infection, or hepatic decompensation during treatment is high, in many cases patients experience severe decreases in blood counts that result in treatment discontinuation. Serious concurrent infections associated with therapy have also been reported in Child-Pugh grade C patients, compared to grade A/B patients.31 Moreover, the safety of daclatasvir + asunaprevir combination therapy, sofosbuvir + ledipasvir combination therapy, ombitasvir + paritaprevir + ritonavir combination therapy and sofosbuvir + RBV combination therapy in decompensated cirrhosis patients has not been confirmed, and these therapies should therefore not be administered to such patients. Thus, at present there are no antiviral therapies that are recommended for use in decompensated cirrhosis patients.

Recommendations:
• IFN therapy affords little efficacy in decompensated cirrhosis type C. Child-Pugh grade C patients in particular poorly tolerate IFN therapy, and have been found to develop serious adverse reactions including decreased blood cell counts and infections.
• The safety of daclatasvir + asunaprevir combination therapy, sofosbuvir + ledipasvir combination therapy, ombitasvir + paritaprevir + ritonavir combination therapy and sofosbuvir + RBV combination therapy in decompensated cirrhosis patients has not been confirmed, and these therapies should therefore not be administered to such patients.

Treatment of patients with decreased platelet counts

The mainstay of antiviral therapy for patients with decreased platelet counts are IFN-free DAA therapies, which do not result in platelet count decreased adverse reactions. Specifically, sofosbuvir + ledipasvir combination therapy (in patients without severe renal impairment), ombitasvir + paritaprevir + ritonavir combination therapy (in patients without Y93 RAVs), and daclatasvir + asunaprevir combination therapy (in patients without Y93/L31 RAVs), are recommended in genotype 1 patients, and sofosbuvir + RBV combination therapy (in patients without severe renal impairment) is recommended in genotype 2 patients.

In patients with markedly decreased platelet counts associated with hypersplenism, it is difficult to initiate Peg-IFN or RBV combination therapy; IFN therapy is initiated after increasing the platelet count through splenectomy or partial splenic embolization (PSE).92-94 In Japan, Peg-IFN (+ RBV) therapy is initiated after splenectomy or PSE primarily in Child-Pugh A cirrhosis patients. Both methods result in an increase in the platelet count after treatment in most patients, and the results of studies have found that a high SVR rate has been achieved in genotype 2 patients. However, both with splenectomy and PSE, postoperative complications including overwhelming postsplenectomy infection (OPSI), portal vein thrombosis, and hepatic function abnormal have been reported.93-95 Overseas, the thrombopoietin receptor agonist eltrombopag has been developed as an oral agent that increases platelet counts,96 in Japan, however, this drug has not yet been introduced to the clinical setting.

Recommendations:
• In patients with decreased platelet counts, sofosbuvir + ledipasvir combination therapy (in patients without severe renal impairment), ombitasvir + paritaprevir + ritonavir combination therapy (in patients without Y93 RAVs), and daclatasvir + asunaprevir combination therapy (in patients without Y93/L31 RAVs), are recommended in genotype 1 patients, and sofosbuvir + RBV combination therapy (in patients without severe renal impairment) is recommended in genotype 2 patients.

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