Therapy with Direct-Acting Antiviral Agents for Hepatitis C-Related Liver Cirrhosis

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Chronic hepatitis C virus (HCV) infection may eventually lead to liver cirrhosis (LC), a condition associated with a high risk of liver failure and hepatocellular carcinoma. Although interferon (IFN)-based therapy has made substantial contributions to the management of HCV-infected patients, this therapy has limitations for LC patients in terms of eligibility, tolerability, relatively low and high rates of sustained virological response (SVR), and serious adverse events. Therapy with newly developed direct-acting antiviral agents (DAAs) can overcome these limitations in IFN-based therapy. Recent phase 3 trials have demonstrated that DAA therapy achieved high SVR rates (more than 90% for genotype 1; 80% to 90% for genotype 2; 60% to 70% for genotype 3) for compensated LC patients, with high tolerability and relatively low rates of serious adverse events. Furthermore, trials have suggested that DAA therapy can be used for the treatment of decompensated LC patients as well as pretransplant and post-transplant LC patients. In this article, we review the current status of DAA therapy for HCV-related LC patients.

IFN-BASED THERAPY FOR LC PATIENTS

Since boceprevir and telaprevir, first-wave, first-generation nonstructural protein 3/4A (NS3/4A) protease inhibitors, emerged in 2011 as DAAs, triple therapy with pegylated IFN, ribavirin (RBV), and DAA has become the standard IFN-based therapy for chronic HCV genotype 1 infection. Phase 3 trials of triple therapy with pegylated IFN, RBV, and boceprevir or telaprevir found that 59% to 88% of HCV genotype 1-infected patients achieved a sustained virological response at 24-week follow-up (SVR24).4-7 SVR24 rates in compensated LC patients were 35% to 77% for the boceprevir regimen and 62% for the telaprevir regimen. Overall, 9% to 12% and 7% to 15% of patients had serious adverse events and discontinued the therapy, respectively. Most recently, another triple therapy with pegylated IFN, RBV, and simeprevir, a second-wave, first-generation NS3/4A protease inhibitor, has been applied in patients with HCV genotype 1 infection. In the phase 3 QUEST-18 and QUEST-29 trials, in which the triple therapy was provided to treatment-naive patients with HCV genotype 1 infection, SVR12 rates were 80% and 81%, respectively. As for compensated LC patients, the SVR12 rate was 58% in QUEST-1 and...
65% in QUEST-2. In another phase 3 study with the simeprevir-containing regimen, the Protease Inhibitor TMC435 in Patients Who Have Previously Relapsed on IFN/RBV (PROMISE) study, patients with HCV genotype 1 infection who relapsed after previous IFN-based therapy received the triple therapy with pegylated IFN, RBV, and simeprevir; 79.2% of the patients achieved SVR12. The regimen was successful in achieving SVR12 for 74.4% of compensated LC patients. A large-scale randomized controlled trial of 763 patients with HCV genotype 1 infection with or without LC, the Retreatment of Null and Partial Responders with TMC435 (ATTAIN) study, showed that the efficacy of simeprevir with pegylated IFN and RBV was not inferior to that of telaprevir with pegylated IFN and RBV and that the rate of serious adverse events was lower in the former than in the latter (2% vs 9%). However, even with this simeprevir-containing regimen, grade 3/4 adverse events occurred in 23% of patients.

DAAAs other than protease inhibitors have been incorporated into IFN-based therapy. Triple therapy with pegylated IFN, RBV, and sofosbuvir, the first approved HCV NS5B nucleotide polymerase inhibitor with potent antiviral activity against all HCV genotypes, is another treatment option for chronic HCV infection. In a phase 3 trial of the triple therapy for previously untreated patients with HCV genotype 1, 4, 5, and 6 (mostly genotype 1) infection, the NEUTRINO trial, 90% of patients achieved SVR12. The SVR rate was slightly different between non-LC patients and LC patients (92% vs 80%). Multivariate analysis revealed the presence of LC as an independent factor associated with a reduced response.

The above phase 3 studies included results from small percentages (6% to 27%) of LC patients. The recent large-scale cohort Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (CUPIC) study was aimed to clarify the efficacy and safety of triple therapy with pegylated IFN, RBV, and boceprevir or telaprevir in 511 patients with HCV genotype 1 and compensated LC patients. Most of the trials were performed in the United States and Europe, where HCV genotypes 1, 2, and 3 are prevalent (e.g., the prevalence rates of genotypes 1, 2, and 3 in the United States are reported to be 80.1%, 11.1%, and 7.4%, respectively). Overall, DAA therapy for LC patients had an excellent tolerability with a low rate of serious adverse events and achieved a high SVR rate with a low rate of treatment failure due to resistant variants.

1. DAAs for LC patients with HCV genotype 1 infection

1) Daclatasvir and asunaprevir

Daclatasvir is the first approved first-generation NS5A inhibitor with potent pan-genotypic antiviral activity against HCV. Asunaprevir is a second-wave first-generation NS3/4A inhibitor with potent antiviral activity against HCV 1, 4, 5, and 6 genotypes. A phase 2a study from the United States of combination therapy with daclatasvir and asunaprevir for HCV genotype 1 infection showed for the first time that an IFN-free, DAA-only regimen could achieve SVR in a high percentage of HCV-infected patients. This study suggested that the SVR rate tended to be lower in patients with HCV genotype 1a than in those with genotype 1b infection.

Phase 3 trials of combination therapy with daclatasvir and asunaprevir resulted in high SVR rates for patients with HCV genotype 1 infection. In a trial in Japan, 222 patients with HCV genotype 1b infection (9.9% compensated LC) received 24 weeks of this combination therapy. SVR24 was achieved in 87.4% of patients ineligible for or intolerant to previous IFN-based therapy and in 80.5% of nonresponders to previous IFN-based therapy. The SVR24 rate was similar between non-LC and LC patients (84.0% and 90.0%). Serious adverse events occurred in 5.9% of the whole cohort. In total, 12.6% of patients discontinued the combination therapy, mainly due to adverse events, including elevated serum aminotransferase levels or lack of efficacy. In another study in 18 countries, including in North and South America, Europe, and Asia, the HALLMARK-DUAL study, 747 patients with HCV genotype 1b were assigned to a high risk of treatment-associated serious adverse events. Furthermore, LC patients often have severe cytopenia, and this condition is not eligible for IFN-based therapy. More efficacious and less harmful antiviral therapy for HCV-infected patients, particularly LC patients, has therefore been desired.

DAA THERAPY FOR LC PATIENTS

Recent studies have shown that IFN-free, oral DAA therapy can overcome the drawbacks of IFN-based therapy in the treatment of HCV-related LC patients. Tables 1 and 2 show an overview of clinical trials for DAA therapy for such patients. Because treatment regimens with DAAs vary according to HCV genotypes, we describe the results of DAA therapy for each HCV genotype infection. Table 3 summarizes the results regarding LC patients. Most of the trials were performed in the United States and Europe, where HCV genotypes 1, 2, and 3 are prevalent (e.g., the prevalence rates of genotypes 1, 2, and 3 in the United States are reported to be 80.1%, 11.1%, and 7.4%, respectively). Overall, DAA therapy for LC patients had an excellent tolerability with a low rate of serious adverse events and achieved a high SVR rate with a low rate of treatment failure due to resistant variants.

1. DAAs for LC patients with HCV genotype 1 infection
### Table 1. Overview of Studies on Direct-Acting Antiviral Agent Therapy for Liver Cirrhosis Patients with Hepatitis C Virus Genotype 1

| DAA regimens according to HCV genotypes | RBV Duration, wk | No. | Proportion of LC patients, % | SVR12 rate in all patients, % | SVR12 rate in LC patients, % | SVR12 rate in patients with resistant variants at baseline, % | Overall serious adverse events, % | Overall discontinuation, % | Reference |
|----------------------------------------|-----------------|-----|-----------------------------|-----------------------------|-----------------------------|-------------------------------------------------|--------------------------------|-----------------------------|------------|
| Daclatasvir (60 mg) and asunaprevir (100 mg) | | | | | | | | | | |
| Phase 3 NCT01497834 for genotype 1b | Without | 24 | 222 (compensated) | 9.9 | 84.7* | 90.9* | 40.5* (NS5A); 60.0* (NS3/4A) | 5.9 | 12.6 | [19] |
| Phase 3 HALLMARK-DUAL for genotype 1b | Without | 24 | 645 (compensated) | 32.1 | 84.3 | 83.5 | 38.7 (NS5A and/or NS3/4A) | 6.1 | 1.6 | [20] |
| Daclatasvir (30 mg), asunaprevir (200 mg), and beclabuvir (75 mg) | | | | | | | | | | |
| UNITY-2 for genotypes 1a (74%) and 1b (26%) | With/without | 12 | 202 (compensated) | 100 | 90.2 (without RBV); 96.0 (with RBV) | 90.2 (without RBV); 96.0 (with RBV) | 92.9 (NS5A) | 2.0–7.0 | 0–4.0 | [22] |
| Sofosbuvir (400 mg) and ledipasvir (90 mg) | | | | | | | | | | |
| Phase 3 ION-1 for treatment-naïve, genotypes 1a (67%) and 1b (32%) | With/without | 12/24 | 865 (compensated) | 15.7 | 99.5 (without RBV, 12 wk); 100 (with RBV, 12 wk) | 98.7 (NS5A) | 96.4 (NS5A) | 1.9 (12 wk); 5.8 (24 wk) | 0 (12 wk); 2.3 (24 wk) | [27] |
| Phase 3 ION-2 for treatment-experienced, genotypes 1a (79%) and 1b (21%) | With/without | 12/24 | 440 (compensated) | 20.0 | 93.6 (without RBV, 12 wk); 96.4 (with RBV, 12 wk) | 86.4 (without RBV, 12 wk); 81.8 (with RBV, 12 wk) | 88.7 (NS5A) | 0 (12 wk); 4.1 (24 wk) | 0 (12 wk); 0 (24 wk) | [28] |
| Phase 3 NCT01975675 for genotype 1b (97%) | With/without | 12 | 341 (compensated) | 22.3 | 100 (without RBV); 98.2 (with RBV) | 100 (without RBV); 97.1 (with RBV) | 98.7 (NS5A) | 1.5 (non-LC, 1.1; LC, 2.6) | 0.6 (non-LC, 0.4; LC, 1.3) | [29] |
| Phase 2 SIRIUS for genotypes 1a (63%) and 1b (35%) | With/without | 12/24 | 155 (compensated) | 100 | 96.1 (without RBV, 12 wk); 97.4 (with RBV, 24 wk) | 96.1 (without RBV, 12 wk); 97.4 (with RBV, 24 wk) | 91.7 (NS5A) | 7.7 | 9.6 | [30] |
| Phase 2 SOLAR-1 for genotypes 1a (71%) and 1b (29%) | With | 12/24 | 337 (compensated/decompensated) | 65.3 | 90.5 (12 wk); 92.6 (24 wk) | 92.9 (NS5A) | 92.9 (NS5A) | 2.2 (non-LC, 16.2; LC, 26.8) | 3.8 (non-LC, 1.8; LC, 5.0) | [31] |
| DAA regimens according to HCV genotypes | RBV Duration, wk | No. | Proportion of LC patients, % | SVR12 rate in all patients, % | SVR12 rate in LC patients, % | SVR12 rate in patients with resistant variants at baseline, % | Overall serious adverse events, % | Overall discontinuation, % | Reference |
|----------------------------------------|-----------------|-----|----------------------------|-----------------------------|-----------------------------|------------------------------------------------------|---------------------------|------------------|-----------|
| **Phase 2 SOLAR-2 for genotypes 1a (49%), 1b (40%), and 1c (11)%** | With 12/24 | 328 | 69.4 (compensated/decompensated) | Overall: 90.5 (12 wk); 93.2 (24 wk) | Genotype 1: non-LC and CP class A: 96.0 (12 wk); 98.3 (24 wk) | Genotype 1: CP class B and C: 87.7 (12 wk); 88.5 (24 wk) | 21.0 (non-LC and CP class A LC, 143; CP class B and C LC, 28.1) | 1.8 (non-LC and CP class A LC, 0.6; CP class B and C LC, 3.1) | [32] |
| **Sofosbuvir (400 mg) and simeprevir (150 mg)** | With/without 12/24 | 167 | 24.6 (compensated) | 85.7 (without RBV, 12 wk); 90.9 (with RBV, 12 wk) | 100 (without RBV, 24 wk); 92.3 (with RBV, 24 wk) | 87.9 (NS3/4A) | 0 (12 wk); 4.7 (24 wk) | 0 (12 wk); 4.7 (24 wk) | [33] |
| **Grazoprevir (100 mg) and elbasvir (50 mg)** | With/without 12/18 | 253 | 67.2 (compensated) | 95.3 (without RBV, 12 wk); 90.5 (with RBV, 12 wk) | 97.7 (with RBV, 18 wk) | 92.4 (NS3/4A); 8.24 (NS5A) | 4.0 (12 wk); 1.6 (18 wk) | 0.8 (12 wk); 0.8 (24 wk) | [37] |
| **Phase 2 C-WORTHY for genotypes 1a (64%) and 1b (34%)** | With/without 12/18 | 253 | 67.2 (compensated) | 95.3 (without RBV, 12 wk); 90.5 (with RBV, 12 wk) | 97.7 (with RBV, 18 wk) | 92.4 (NS3/4A); 8.24 (NS5A) | 4.0 (12 wk); 1.6 (18 wk) | 0.8 (12 wk); 0.8 (24 wk) | [37] |
| **Grazoprevir (100 mg) and elbasvir (50 mg)** | With 12/18 | 253 | 67.2 (compensated) | 95.3 (without RBV, 12 wk); 90.5 (with RBV, 12 wk) | 97.7 (with RBV, 18 wk) | 92.4 (NS3/4A); 8.24 (NS5A) | 4.0 (12 wk); 1.6 (18 wk) | 0.8 (12 wk); 0.8 (24 wk) | [37] |
| **Phase 2 C-SALVAGE for genotypes 1a (38%) and 1b (62%)** | With 12/18 | 253 | 67.2 (compensated) | 95.3 (without RBV, 12 wk); 90.5 (with RBV, 12 wk) | 97.7 (with RBV, 18 wk) | 92.4 (NS3/4A); 8.24 (NS5A) | 4.0 (12 wk); 1.6 (18 wk) | 0.8 (12 wk); 0.8 (24 wk) | [37] |
| **C-EDGE Treatment-Naïve for genotypes 1a (50%), 1b (41%), and others (9%)** | Without 12/18 | 421 | 21.9 (compensated) | 94.6 (genotype 1: 94.8) | 97.1 | 96.4 (NS3/4A); 75.7 (NS5A) | 29 (non-LC, 3.0; LC, 2.2) | 0 (12 LC; 0.6; LC, 2.2) | [27] |
| **Phase 2 C-SALT for genotypes 1a (90%) and 1b (10%)** | Without 12/18 | 308 | 75.0 (decompensated) | 92.5 | 90.0 | 100 (NS3/4A); 87.5 (NS5A) | 10.0 (non-LC, 0; LC, 13.3) | 0 | [40] |
| **Paritaprevir (150 mg)/ritonavir (100 mg), ombitasvir (25 mg), and dasabuvir (250 mg)** | With 12/24 | 380 | 100 (compensated) | 91.8 (12 wk); 95.9 (24 wk) | 91.8 (12 wk); 95.9 (24 wk) | 6.2 (12 wk); 4.7 (24 wk) | 1.9 (12 wk); 2.3 (24 wk) | 1.9 (12 wk); 2.3 (24 wk) | [45] |

DAA, direct-acting antiviral agent; HCV, hepatitis C virus; RBV, ribavirin; LC, liver cirrhosis; SVR, sustained virological response; CP, Child-Pugh.

*SVR24; Group 1, CP class B without previous transplantation; group 2, CP class C without previous transplantation; group 4, CP class A with previous transplantation; group 5, CP class B with previous transplantation; group 6, CP C with previous transplantation; Preliminary results are shown; Fifty milligrams of grazoprevir and 100 mg of elbasvir for LC patients.
### Table 2. Overview of Studies on Direct-Acting Antiviral Agent Therapy for Liver Cirrhosis Patients with Hepatitis C Virus Genotype 2, 3, or 4

| Genotypes 2 and 3 | DAA regimens according to HCV genotypes | RBV | Duration, wk | No. | Proportion of LC patients, % | SVR12 rate in all patients, % | SVR12 rate in LC patients, % | SVR12 rate in patients with resistant variants at baseline, % | Overall serious adverse events, % | Overall discontinuation, % | Reference |
|-------------------|------------------------------------------|-----|--------------|-----|-----------------------------|-----------------------------|-----------------------------|---------------------------------|-----------------------------|-----------------------------|-----------|
| Genotypes 2 and 3 | Sofosbuvir (400 mg) and RBV              |     |              |     |                             |                             |                             |                                 |                             |                             |           |
| Phase 3 POSITION for genotypes 2 (53%) and 3 (47%) | With 12 | 207 | 15.0 (compensated) | 77.8 (genotype 2: 92.7; genotype 3: 6.1) | 6.13 (genotype 2: 94.1; genotype 3: 21.4) | No resistant variants (NS5B) | 5.3 (non-LC, 5.1; LC, 6.5) | 1.9 (non-LC, 1.1; LC, 6.5) | [48] |
| Phase 3 FUSION for genotypes 2 (34%) and 3 (63%) | With 12/16 | 201 | 33.8 (compensated) | Genotype 2: 86.1 (12 wk); 93.8 (16 wk); Genotype 3: 29.7 (12 wk); 61.9 (16 wk) | Genotype 2: 60.0 (12 wk); 77.8 (16 wk); Genotype 3: 19.2 (12 wk); 60.9 (16 wk) | No resistant variants (NS5B) | 4.0 (non-LC, 1.5; LC, 8.8) | 0.5 (non-LC, 0.8; LC, 0) | [48] |
| Phase 3 FIISSION for genotypes 2 (27%) and 3 (71%) | With 12 | 256 | 19.5 (compensated) | 67.2 (genotype 2: 97.1; genotype 3: 5.5) | 46.9 | No resistant variants (NS5B) | 2.7 (non-LC, 2.4; LC, 4.0) | 1.2 (non-LC, 1.0; LC, 2.0) | [13] |
| VALENCE for genotypes 2 (22%) and 3 (78%) | With 12/24 | 419 | 21.5 (compensated) | Genotype 2: 93.2 (12 wk); Genotype 3: 27.3 (12 wk); 85.2 (24 wk) | Genotype 2: 81.8 (12 wk); Genotype 3: 68.3 (24 wk) | No resistant variants (NS5B) | 0 (12 wk); 4.0 (24 wk) | 1.2 (12 wk); 0.4 (24 wk) | [49] |

Genotype 4

| Genotypes 4 | Sofosbuvir (400 mg) and RBV |     |              |     |                             |                             |                             |                                 |                             |                             |           |
|--------------|-----------------------------|-----|--------------|-----|-----------------------------|-----------------------------|                             |                                 |                             |                             |           |
| Phase 2 trial for genotype 4 (Egyptian) | With 12/24 | 60 | 23.3 (compensated) | 67.8 (12 wk); 93.1 (24 wk) | 42.9 (12 wk); 100 (24 wk) | No resistant variants (NS5B) | 3.2 (12 wk); 10.3 (24 wk) | 0 (12 wk); 0 (24 wk) | [51] |
| Phase 2 SOLAR-2 for genotypes 1a (49%), 1b (40%), and 4 (11%)* | With 12/24 | 328 | 69.4 (compensated/ decompensated) | Genotype 4: 77.8 (12 wk); 92.9 (24 wk) | Genotype 4: non-LC and CP class A: 90.9 (12 wk); 100 (24 wk) | Genotype 4: CP class B and C: 97.1 (12 wk); 85.7 (24 wk) | 21.0 (non-LC and CP class A: 14.3; CP class B and C: 18.1) | 1.8 (non-LC and CP class A: 0.6; CP class A: 3.1) | [32] |

DAA, direct-acting antiviral agent; HCV, hepatitis C virus; RBV, ribavirin; LC, liver cirrhosis; SVR, sustained virological response; CP, Child-Pugh.

*Preliminary results are shown.
| Genotype 1 | DAA regimens according to HCV genotypes | Main results for LC patients | Reference |
|-----------|-----------------------------------------|-----------------------------|----------|
| Genotype 1 | A regimen for genotype 1b-infected patients. For compensated LC patients, SVR12/24 rates were 83.5%–90.9%. In case of the presence of NS3/4A- or NS5A-resistant variants, SVR rates were low [37.8%–50.0% for all patients, including LC patients]. The elevation of serum aminotransferase was an adverse event. | [19,20] |
| Daclatasvir (60 mg) and asunaprevir (100 mg) | A regimen for compensated LC patients with HCV genotype 1a or 1b infection. In the UNITY-2 study, SVR12 rates were 90.2%–96.0%. Even for patients with NS5A-resistant variants, the SVR12 rate was high (92.9%). | [22] |
| Daclatasvir (30 mg), asunaprevir (200 mg), and beclabuvir (75 mg) | A regimen for both genotype 1a- and 1b-infected patients. For compensated LC patients, SVR12 rates were 81.8%–100%. In the SIRIUS trial focusing on compensated LC, SVR12 rates were 96.1%–97.4%; even for patients with NS5A-resistant variants, the SVR12 rate was high (91.7%). This regimen can be applied to decompensated LC patients, including candidates for liver transplantation. In the SOLAR-1 and SOLAR-2 trials, SVR12 rates were 96.0%–96.2% for compensated LC patients and 60.0%–88.9% for decompensated LC patients. Notably, a majority of decompensated LC patients had decreased CP scores. | [27-32] |
| Sofosbuvir (400 mg) and ledipasvir (90 mg) | A regimen for compensated LC patients with HCV genotype 1a or 1b infection. In the TURQUOISE-II trial, SVR12 rates were 91.8%–95.9%. HCV genotype 1a and previous null response were negative predictors of SVR12. | [45] |
| Sofosbuvir (400 mg) and simeprevir (150 mg) | A regimen for both genotype 1a- and 1b-infected patients. For compensated LC patients, SVR12 rates were 85.7%–100%. Even for patients with NS3/4A-resistant variants, the SVR12 rate was high (91.7%). | [33] |
| Grazoprevir (100 mg) and elbasvir (50 mg) | A regimen for both genotype 1a- and 1b-infected patients. For compensated LC patients, SVR12 rates were 90.9%–97.7%. This regimen can be applied to decompensated LC patients. In the C-SALT study, the SVR12 rate was 90.0% for CP class B LC patients. Approximately two-thirds of the class B LC patients had a decreased CP score. Overall, SVR12 rates were 91.2%–100% for patients with NS3/4A-resistant variants and 75.0%–87.5% for those with NS5A-resistant variants. | [37,40] |
| Paritaprevir (150 mg)/ritonavir (100 mg), ombitasvir (25 mg), and dasabuvir (250 mg) | A regimen for compensated LC patients with HCV genotype 1a or 1b infection. In the TURQUOISE-II trial, SVR12 rates were 91.8%–95.9%. HCV genotype 1a and previous null response were negative predictors of SVR12. | [45] |
| Genotype 2 and 3 | A regimen for both genotype 2- and 3-infected patients. For patients with compensated LC and genotype 2 infection, SVR12 rates were 60.0%–94.1% with the 12-week regimen and 77.8% with the 16-week regimen. By contrast, for patients with compensated LC and genotype 3 infection, SVR12 rates were 19.2%–21.4% with the 12-week regimen and 60.9%–68.3% with the 16- or 24-week regimen, suggesting that extension of the antiviral therapy duration could improve the DAA efficacy for this genotype infection. No NS5B-resistant variants emerged. | [13,48,49] |
| Genotype 4 | A regimen for Egyptian patients with compensated LC. SVR12 rates were 42.9% with the 12-week regimen and 100% with the 24-week regimen. No NS5B-resistant variants emerged. | [51] |
| Sofosbuvir (400 mg) and RBV | For Egyptian patients with compensated LC, SVR12 rates were 42.9% with the 12-week regimen and 100% with the 24-week regimen. No NS5B-resistant variants emerged. | [51] |
| Sofosbuvir (400 mg) and ledipasvir (90 mg) | In the SOLAR-2 trial, 1% of the patients had HCV genotype 4 infection. For non-LC and compensated LC patients, SVR12 rates were 90.9% with the 12-week regimen and 100% with the 24-week regimen; for decompensated LC patients, SVR12 rates were 57.1% with the 12-week regimen and 85.7% in the 24-week regimen. | [32] |

DAA, direct-acting antiviral agent; HCV, hepatitis C virus; LC, liver cirrhosis; SVR, sustained virological response; CP, Child-Pugh; RBV, ribavirin.
to the following therapy: 24 weeks of combination therapy with daclatasvir and asunaprevir for 645 patients (205 treatment-naive patients, 205 nonresponders to previous pegylated IFN and RBV, and 235 patients ineligible for or intolerant to previous IFN-based therapy; 32% compensated LC); or 12 weeks of matching placebo (followed by 24 weeks of this combination therapy) for 102 treatment-naive patients. This combination therapy resulted in SVR12 in 90% of treatment-naive patients, in 82% of nonresponders, and in 82% of ineligible or intolerant patients. When SVR12 rates were compared between non-LC and LC patients, the rates were 89% and 91% in treatment-naive patients, 80% and 87% in nonresponders, and 84% and 79% in ineligible or intolerant patients. Multivariate analysis revealed that the presence of LC did not affect SVR12 rates. However, the SVR rates tended to be lower in patients with low platelet counts between \(50 \times 10^3\)/L and \(90 \times 10^3\)/L (71%) than in patients without thrombocytopenia (86%). Overall, serious adverse events occurred in 6% of patients. A total of 1.6% of patients discontinued the therapy mainly because of elevated serum aminotransferase levels. No differences in the rates of elevated serum aminotransferase levels greater than five times the upper limit of normal were found between non-LC and LC patients.

2) Daclatasvir, asunaprevir, and beclabuvir

Beclabuvir is an NS5B nonnucleoside polymerase inhibitor with potent antiviral activity against HCV genotypes 1, 3, 4, 5, and 6. Most recently, the UNITY-2 study was conducted to assess the efficacy and safety of DAA combination therapy with daclatasvir, asunaprevir, and beclabuvir for patients with HCV genotype 1-related compensated LC (74% genotype 1a; 26% genotype 1b). The study cohort comprised 112 treatment-naive patients and 90 treatment-experienced patients who had previous treatment with IFN and/or host-targeted antiviral agents or with DAs other than NS3/4 or NS5A inhibitors or NS5B thumb-1 inhibitors. Each patient group was randomly assigned (1:1) to receive additional RBV or placebo. For the regimen with placebo, SVR12 was achieved in 93% of treatment-naive patients and 87% of treatment-experienced patients; for the regimen with RBV, SVR12 was achieved in 98% of treatment-naive patients and 93% of treatment-experienced patients. SVR12 rates were similar between genotype 1a- and 1b-infected patients. Overall, the rates of serious adverse events and discontinuation of therapy were 28% and 0%, respectively, in patients receiving placebo and 7% and 4%, respectively, in patients receiving RBV.

3) Sofosbuvir and ledipasvir

In an early phase 2 trial, combination therapy with sofosbuvir and RBV was performed as an IFN-free therapy for chronic HCV genotype 1 infection. The efficacy of the treatment regimen was unsatisfactory: 24 weeks of sofosbuvir and weight-based or low-dose RBV resulted in SVR24 rates of 68% and 48%, respectively. In more recent trials, combination therapy with sofosbuvir and ledipasvir, a first-generation NS5A inhibitor with potent antiviral activity against HCV genotype 1, showed strong antiviral efficacy against HCV genotype 1 infection. In phase 2 trials, in which more than 80% of patients were infected with HCV genotype 1a, this combination therapy (administration of a fixed-dose combination tablet once daily) achieved a high SVR rate for LC patients as well as non-LC patients. In one trial, 12 weeks of triple therapy with sofosbuvir, ledipasvir, and RBV and of combination therapy with sofosbuvir and ledipasvir resulted in SVR12 rates of 100% and 70%, respectively, for LC patients who were null responders to previous IFN therapy. Based on the high efficacy of the combination therapy in phase 2 trials, phase 3 trials were conducted. In the ION-1 trial in the United States and Europe, 12 weeks or 24 weeks of sofosbuvir and ledipasvir with or without RBV for 865 treatment-naive patients (67% genotype 1a and 32% genotype 1b; 16% compensated LC) resulted in SVR12 rates of 97% to 99%. The efficacy of this regimen was similar between HCV genotype 1a- and 1b-infected patients. As for LC patients, SVR12 rates were 97% to 100%. The presence of LC did not influence the achievement of SVR12. Although 3.8% of the whole cohort had serious adverse events, no patients discontinued the therapy. In contrast to IFN-based therapy, the safety profile of this combination therapy did not alter irrespective of thrombocytopenia and a low albumin level, often observed in LC patients. In the ION-2 trial in the United States, the same treatment protocol as used in ION-1 trial was applied to 440 HCV genotype 1-infected patients (79% genotype 1a and 21% genotype 1b; 20% compensated LC) who had not achieved SVR after pegylated IFN and RBV with or without a protease inhibitor. As a whole, SVR12 rates ranged from 94% to 99%. The therapeutic efficacy was similar between HCV genotype 1a- and 1b-infected patients. Regarding LC patients, SVR rates were lower in patients receiving 12 weeks of treatment than in those receiving 24 weeks of treatment (82% to 86% vs 100%, p=0.007). Although 4.1% of the patients receiving 24 weeks of treatment had serious adverse events, no patients discontinued the therapy.

In the ION-1 and ION-2 trials, most of the enrolled patients were white and black. A similar phase 3 trial of combination therapy with sofosbuvir and ledipasvir with or without RBV was conducted for 341 Japanese patients with HCV genotype 1 infection (97% genotype 1b; 22% compensated LC). The treatment efficacy was excellent: SVR12 was achieved in 100% of patients receiving 12 weeks of sofosbuvir and ledipasvir and in 98% of patients receiving 12 weeks of sofosbuvir, ledipasvir, and RBV. The efficacy for LC patients was as follows: among treatment-naive patients, combination therapy with or without RBV resulted in an SVR rate of 100% or 91.7%, respectively; and among patients who had an experience of previous IFN-based therapy, the therapy with or without RBV resulted in an
SVR rate of 100% for both. Treatment-emergent serious adverse events occurred in 1.1% of non-LC patients and 2.6% in LC patients. Discontinuation of the combination therapy was observed in 1.2% of patients receiving the therapy with RBV (1 in non-LC patients and 1 in LC patients).

The phase 3 trials described above showed the high efficacy and safety of combination therapy with sofosbuvir and ledipasvir for compensated LC patients as well as non-LC patients. Recently, phase 2 trials focusing on LC patients were conducted with this combination therapy. In the SIRIUS trial, 12 weeks of the combination therapy with RBV or 24 weeks of that without RBV was performed for 155 compensated LC patients with HCV genotype 1 infection (63% genotype 1a; 35% genotype 1b) who had been nonresponders to previous pegylated IFN-based therapy.30 SVR12 rates were 96% for the 12-week regimen and 97% for the 24-week regimen, respectively. Rates of serious adverse events were 5% for the 12-week regimen and 10% for the 24-week regimen. Only 1% of patients treated with the 12-week regimen discontinued therapy. Furthermore, in the SOLAR-1 trial in the United States, the combination of sofosbuvir and ledipasvir was used as the first DAA combination therapy for advanced liver disease, including decompensated LC.31 The patient cohort comprised 337 HCV-infected patients without (cohort A) or with (cohort B) previous liver transplantation (71% HCV genotype 1a; 28% genotype 1b; 1% genotype 4). Cohort A was divided into group 1 (Child-Pugh [CP] class B, n=59) and group 2 (CP class C [scores 10 to 12], n=49). Cohort B was divided into group 3 (non-LC, n=111), group 4 (CP class A, n=51), group 5 (CP class B, n=52), group 6 (CP class C, n=9), and group 7 (fibrosing cholestatic hepatitis, n=6). All patients received 12 weeks or 24 weeks of combination therapy with sofosbuvir and ledipasvir plus RBV; SVR12 rates were 87% and 89% in group 1, 86% and 87% in group 2, 96% and 98% in group 3, 96% and 96% in group 4, 85% and 88% in group 5, 60% and 75% in group 6, and 100% and 100% in group 7, respectively. The SVR rates were similar between 12-week and 24-week regimen groups. From the viewpoint of CP class, the SVR rates were similar between CP class B and C nontransplanted patients, while the rates decreased with the progression of CP class among posttransplanted patients. Notably, a majority of patients with CP class B or C had decreased CP class B and C LC patients without previous liver transplantation, 12 weeks or 24 weeks of combination therapy with grazoprevir and elbasvir plus RBV; SVR12 rates were 96% and 99% in group 1, 97% and 97% in group 2, 100% and 100% in group 3, 99% and 99% in group 4, 98% and 98% in group 5, 95% and 95% in group 6, and 100% and 100% in group 7, respectively. The rates were similar between 12-week and 24-week regimen groups. From the viewpoint of CP class, the SVR rates were similar between CP class B and C nontransplanted patients, while the rates decreased with the progression of CP class among posttransplanted patients. Notably, a majority of patients with CP class B or C had decreased CP scores at 4 weeks after the therapy. By contrast, rates of serious adverse events were totally 23% (non-LC, 16%; LC, 27%); the rates according to groups were 10% and 34% in group 1, 26% and 42% in group 2, 11% and 21% in group 3, 12% and 16% in group 4, 19% and 42% in group 5, 20% and 75% in group 6, and 25% and 50% in group 7, respectively. The rates were higher in the 24-week regimen groups than in 12-week regimen groups. Overall, 4% of patients discontinued the combination therapy because of adverse events (non-LC, 2%; LC, 5%). Three percent of patients died, mainly due to complications related to hepatic decompensation. In the SOLAR-2 trial conducted in Australia, New Zealand, Canada, and Europe, the same regimens as those in the SOLAR-1 trial were used for the antiviral therapy for 328 HCV-infected patients without or with previous liver transplantation (49% HCV genotype 1a; 40% genotype 1b; 11% genotype 4).32 Tentative results were recently reported; the results on HCV genotype 1-infected patients were as follows. Among non-LC and CP class A LC patients, the 12-week and 24-week regimens resulted in SVR12 rates of 96% and 98%, respectively. By contrast, among CP class B and C patients, the 12-week and 24-week regimens resulted in SVR12 rates of 88% and 89%, respectively. When SVR12 rates were compared between CP class B and C LC patients without previous liver transplantation, the 12-week and 24-week regimens resulted in SVR12 rates of 87% and 96%, respectively, in class B patients and of 85% and 73%, respectively, in class C patients. When compared between CP class B and C LC patients with previous liver transplantation, the 12-week and 24-week regimens resulted in SVR12 rates of 95% and 100%, respectively, in class B patients and of 50% and 75%, respectively, in class C patients. Serious adverse events and discontinuation of therapy were observed in 14% and 0.6%, respectively, of non-LC and CP class A LC patients and in 28% and 3.1%, respectively, of class B and C LC patients. In total, 3% of patients died.

4) Sofosbuvir and simeprevir

Another sofosbuvir-containing regimen was developed for HCV genotype 1 infection. In a phase 2 study from the United States, the Combination of Simeprevir and Sofosbuvir in HCV-infected Patients (COSMOS) study, combination therapy with 12 weeks or 24 weeks of sofosbuvir and simeprevir with or without RBV was provided to 167 patients with HCV genotype 1 infection (78% genotype 1a and 22% genotype 1b; 25% compensated LC).33 The patient cohort comprised previous nonresponders to pegylated IFN and RBV with METAVIR scores F0 to F2 (cohort 1) and previous nonresponders and treatment-naïve patients with METAVIR scores F3 to F4 (cohort 2). SVR12 was achieved in 90% of patients in cohort 1 and 94% in cohort 2. The HCV genotype 1 subtypes did not affect the therapeutic efficacy. The combination therapy led to SVR12 in 93% of LC patients (91% and 92% by 12 and 24 weeks, respectively, of sofosbuvir, simeprevir, and RBV; 86% and 100% by 12 and 24 weeks, respectively, of sofosbuvir and simeprevir). Overall, 2% of the patients, all in the patient group receiving 24 weeks of treatment, had serious adverse events, and 2% discontinued the combination therapy.

5) Grazoprevir and elbasvir

Grazoprevir34,35 and elbasvir36 are second-generation inhibitors for NS3/4A protease and NS5A, respectively, with potent broad antiviral activity against HCV. The phase 2 C-WORTHY trial was conducted to assess the efficacy and safety of 12 weeks or 18 weeks of combination therapy with grazoprevir and el-
basvir with or without RBV for 253 patients with HCV genotype 1 infection (64% genotype 1a; 34% genotype 1b). The study patients comprised those who had treatment-naïve compensated LC (n=123) or had been null responders (n=130, including 37% of compensated LC patients) to previous pegylated IFN and RBV. In treatment-naïve LC patients, SVR12 rates ranged from 90% to 97%. Notably, 97% of the patients treated with 12-week regimen without RBV achieved SVR12. Regarding null responders, SVR12 rates ranged from 91% to 100%. Furthermore, null responders with LC achieved SVR12 rates of 92% with the 12-week regimen and 100% with the 18-week regimen, respectively. The efficacy was similar between HCV genotype 1a- and 1b-infected patients. Overall, serious adverse events and therapy discontinuation due to adverse events were observed in 3% and 1% of the patients, respectively. The phase 2 C-SALVAGE study was performed for 79 HCV genotype 1-infected patients (38% genotype 1a and 62% genotype 1b; 43% compensated LC) who had not achieved SVR after 24 weeks of pegylated IFN and RBV plus boceprevir (n=28), telaprevir (n=8), or simeprevir (n=43). Although 83.5% of patients had a history of previous virologic failure, this combination therapy achieved an SVR12 rate of 96.2%; the rates were 95.5% and 100% in patients with and without previous virologic failure, respectively. The efficacy did not differ between HCV genotype 1a- and 1b-infected patients. SVR12 rates were 97.8% in non-LC patients and 94.1% in LC patients. Although serious adverse events occurred in 5.1% of patients, serious drug-related adverse events did not occur. Therapy discontinuation was observed in 1.3% of patients. Recently, in the randomized C-EDGE Treatment-Naïve trial, 421 treatment-naïve, HCV-infected patients, including white, black, and Asian patients (50% genotype 1a, 41% genotype 1b, 6% genotype 4, and 3% genotype 6; 22% compensated LC) received 12 weeks of grazoprevir and elbasvir in an immediate- or a deferred-treatment manner. Of 316 immediate-treatment patients (50% genotype 1a, 42% genotype 1b, 6% genotype 4, and 3% genotype 6; 22% compensated LC), 299 (95%) achieved SVR12. In subgroup analysis of immediate-treatment patients, 92% and 99% of genotype 1a- and genotype 1b-infected patients achieved SVR12. Furthermore, 94% and 97% of non-LC and LC patients achieved SVR12; the presence of LC did not affect SVR12. The rates of serious adverse events were 3% (non-LC, 3%; LC, 2%). The discontinuation of therapy due to adverse events was observed in 1% of patients (non-LC, 1%; LC, 2%).

As with sofosbuvir and ledipasvir, combination therapy with grazoprevir and elbasvir focused on decompensated LC patients was performed in the phase 2 C-SALT study. Thirty CP class B LC patients (90% genotype 1a; 10% genotype 1b) and 10 non-LC patients (60% genotype 1a; 40% genotype 1b) received 12 weeks of this combination therapy. SVR12 rates were 90% in LC patients and 100% in non-LC patients, respectively. Of the LC patients, except for one who died at 4 weeks after the combination therapy, 62% (18/29) had a decreased CP score. The rates of serious adverse events and therapy discontinuation were 0% and 0%, respectively, in non-LC patients and 13.3% and 0%, respectively, in LC patients.

6) Paritaprevir/ritonavir, ombitasvir, dasabuvir, and RBV
Paritaprevir is a second-wave first-generation NS3/4 inhibitor that is used in combination with ritonavir to increase the concentration of paritaprevir by inhibiting cytochrome P450-3A4. Ombitasvir is a second-generation NS5A inhibitor with potent pan-genotypic antiviral activity against HCV. Dasabuvir is an NS5B nonnucleoside polymerase inhibitor. In the phase 3, TURQUOISE-II trial, combination therapy with the three DAAs plus RBV was performed for 380 HCV genotype 1-infected, compensated LC patients (42% treatment-naïve patients, 58% nonresponders to previous pegylated IFN and RBV; 69% genotype 1a, 31% genotype 1b). SVR12 was achieved in 92% (191/208) of patients receiving the 12-week regimen and 96% (165/172) of patients receiving the 24-week regimen; no significant difference in SVR12 was found. In subgroup analysis, SVR12 rates for the 12-week and 24-week regimens were as follows: 89% and 94% in patients with genotype 1a infection; 99% and 100% in those with genotype 1b infection; 94% and 95% in treatment-naïve patients; 97% and 100% in previous relapers; 94% and 100% in previous partial responders; and 87% and 95% in previous null responders. Multivariate analysis revealed that HCV genotype 1a and previous null response were negative predictors of SVR12. Overall, the rates of serious adverse events and discontinuation of therapy were 6% and 2%, respectively.

2. DAAs for LC patients with HCV genotypes 2 and 3 infection
Studies have demonstrated that IFN-based therapy for these genotype infections has the ability of achieving high SVR rates. In a large-scale study of pegylated IFN and RBV for patients with HCV genotype 2 or 3 infection, SVR24 rates after the 24-week regimen were 75% and 66% in intention-to-treat analysis and 82% and 71% in per-protocol analysis. However, the presence of bridging fibrosis and LC was found to be a negative predictor for SVR24. Furthermore, as with patient with HCV genotype 1 infection, some patients with genotype 2 or 3 infection are ineligible for or intolerant to IFN-based therapy. IFN-free, DAA-containing therapy can be a promising treatment method for overcoming these problems.

1) Sofosbuvir and RBV
In a recent article, the results of two randomized phase 3 studies on combination therapy with sofosbuvir and RBV for HCV genotype 2 and 3 infection were reported. In the POSITRON trial, which included patients for whom therapy with pegylated IFN was not an option, 207 patients received 12 weeks of the combination therapy, and the remaining 71 received placebo. The combination therapy group comprised 109
(53%) patients with HCV genotype 2 infection and 98 (47%) patients with genotype 3 infection; 15% were compensated LC patients. SVR12 was achieved in 93% of genotype 2-infected patients (92% of non-LC patients; 94% of LC patients) and in 61% of genotype 3-infected patients (68% of non-LC patients; 21% of LC patients). In multivariate analysis, the HCV genotype but not the stage of liver disease was significantly associated with SVR12. Among the combination therapy group, the rates of serious adverse events and discontinuation of therapy were 5% (non-LC, 5%; LC, 7%) and 2% (non-LC, 1%; LC, 7%), respectively. In the FUSION study, 201 patients who had been nonresponders to previous IFN-based therapy (34% genotype 2 and 63% genotype 3; 34% compensated LC) received 12 weeks or 16 weeks of sofosbuvir and RBV. With the 12-week regimen, SVR12 rates were 86% in patients with genotype 2 infection (96% for non-LC patients; 60% for LC patients) and 30% in those with genotype 3 infection (37% for non-LC patients; 19% for LC patients). By contrast, with the 16-week regimen, SVR12 rates were 95% in those with genotype 2 infection (100% for non-LC patients; 78% for LC patients) and 62% in those with genotype 3 infection (63% for non-LC patients; 61% for LC patients). The presence of LC was a negative predictor of SVR12 among genotype 3-infected patients receiving the 24-week regimen. Multivariate analysis on genotype 3-infected patients revealed that the presence of LC is a negative predictor of SVR12. As a whole, the rates of serious adverse events and discontinuation of therapy were 0% and 1%, respectively, for the 12-week regimen and 4% and 0.4%, respectively, in the 24-week regimen.

3. DAAs for LC patients with HCV genotype 4, 5, and 6 infection

HCV genotype 4, 5, and 6 infections are prevalent in Africa, the Middle East, and Asia. A recent review summarized the SVR rates of 48 weeks of pegylated IFN and RBV for patients with these genotypes of HCV as follows: 40% to 70% for patients with genotype 4, 60% to 70% for those with genotype 5, and 70% to 80% for those with genotype 6. These results suggest a limitation of IFN-based therapy for these HCV infection genotypes, especially for genotype 4 infection. Data on IFN-free, DAA-containing therapy for these HCV genotypes are currently scarce; however, a few trials of DAA-containing therapy for genotype 4 have provided promising results. In Egypt, the prevalence rate of HCV infection is the highest (estimated 15%) in the world, and over 90% of the patients are infected with HCV genotype 4. In a phase 2 trial, combination therapy with 12 weeks or 24 weeks of sofosbuvir and RBV was performed in 60 Egyptian patients (23% compensated LC). SVR12 was achieved in 68% of patients receiving the 12-week regimen and in 93% of those receiving the 24-week regimen. SVR12 rates of non-LC and LC patients were 75% and 43%, respectively, for the 12-week regimen and 91% and 100%, respectively, for the 24-week regimen. Overall, serious adverse events occurred in 3% for the 12-week regimen and 10% for the 24-week regimen. The SOLAR-2 trial included 37 HCV genotype 4-infected patients. The tentative results of these patients were as follows: among non-LC and CP class A LC patients, SVR12 rates were 91% for the 12-week regimen and 100% for the 24-week regimen; by
contrast, among CP class B and C patients, SVR12 rates were 57% for the 12-week regimen and 86% for the 24-week regimen.

4. DAA therapy for liver transplantation

One can expect that IFN-free, oral DAA therapy will result in decreasing cases of hepatic decompensation in HCV-infected patients, thereby reducing the need for future liver transplantation in such patients. However, at present, a considerable number of HCV-related LC patients are in a life-threatening condition and have no choice other than liver transplantation. A large-scale study examined the natural course of HCV-infected patients receiving liver transplantation and found the following results: among 502 recipients, 88 (18%) had LC due to HCV reinfection within 3.7 years; the rate of hepatic decompensation 1 year after LC was 30%; and once hepatic decompensation occurred, 1-year survival was 46%. Thus, HCV reinfection of the graft can cause poor outcomes in transplant recipients.

There are two approaches to address HCV infection when liver transplantation is considered: pretransplant or posttransplant antiviral therapy. Considering the magnitude of HCV reinfection on the outcomes of recipients, the eradication of HCV with pretransplant antiviral therapy is theoretically most preferable for the management of HCV-infected transplant candidates. Unfortunately, IFN-based therapy is applicable in only approximately 50% of transplant candidates, and tolerability of the therapy is poor. Furthermore, SVR rates after the therapy are unsatisfactory (22% to 30%). Recently, in a phase 2 study, up to 48 weeks of combination therapy with sofosbuvir and RBV was tried as DAA therapy for 61 HCV-infected transplant candidates. The HCV genotype was 1a in 24, 1b in 21, 2 in eight, 3a in seven, and 4a in one; the CP score was 5 in 26, 6 in 18, 7 in 14, and 8 in three. This trial suggested that pretransplant DAA therapy may be a promising therapeutic strategy. Of the 61 patients, 46 actually received liver transplantation. At the time of transplantation, 43 were negative for serum HCV RNA; 12 weeks after liver transplantation, 70% (30/43) achieved SVR, and 23% (10/43) had recurrent hepatitis, while 7% (3/43) died.

Of the 61 patients, 11 (18%) had serious adverse events, and two (3%) discontinued DAA therapy. Posttransplant antiviral therapy against HCV has been performed for recurrent hepatitis. Some studies have examined the efficacy of pegylated IFN and RBV for patients with recurrent hepatitis, of whom 16% to 33% developed LC. SVR rates were 32% to 40% for patients with HCV genotype 1 infection and 50% to 100% for patients with genotype 2 or 3 infection. More recently, therapy with pegylated IFN and RBV plus boceprevir or telaprevir was performed for patients with recurrent hepatitis due to HCV genotype 1 infection (24% genotype 1a and 76% genotype 1b; 16% LC). SVR12 rates were 71% for the boceprevir regimen and 20% for the telaprevir regimen.

However, discontinuation of the therapy was observed in many cases (28% for the boceprevir regimen and 58% for the telaprevir regimen) due to serious adverse events or virological breakthrough. As described above, in the SOLAR-1 and SOLAR-2 trials, DAA therapy with sofosbuvir and ledipasvir was tried for cases of HCV-related recurrent hepatitis after liver transplantation. The trials demonstrated that the combination therapy could achieve a high SVR rate in patients with recurrent hepatitis. Even in cases of CP class B and C LC, 24 weeks of sofosbuvir and ledipasvir plus RBV resulted in SVR12 rates of 75% to 89% in the SOLAR-1 trial and 88% in the SOLAR-2 trial. Moreover, the rates of discontinuation of therapy were low (See “Sofosbuvir and ledipasvir” section).

DAA therapy can be a promising therapeutic measure for the treatment of pretransplant and posttransplant HCV-related LC patients. Further studies are needed to establish criteria for the eligibility and tolerability of DAA therapy and its regimens for such patients.

CONCLUSIONS

Owing to DAAs, a new era of antiviral therapy for chronic HCV infection has begun. In the IFN era, HCV genotype 1 was the main refractory genotype. However, DAA therapy for this genotype infection can result in very high SVR rates (more than 90%) in compensated LC patients as well as in non-LC patients, with high tolerability and relatively low rates of serious adverse events. Some trials have provided evidence that DAA therapy can be used for the treatment of decompensated LC patients and pretransplant and posttransplant LC patients. SVR12 rates are reported to be 80% to 90% in CP class B and C LC patients with or without previous liver transplantation; pretransplant DAA therapy can achieve a relatively high rate (70%) of SVR after transplantation. Notably, in the trials, a majority of decompensated LC patients had improved liver function after DAA therapy. DAA therapy can also result in high SVR rates (80% to 90%) in genotype 2-infected LC patients. For the same DAA regimen, SVR rates are lower in patients with genotype 3 infection than in those with genotype 2 infection. Among genotype 3-infected patients, the presence of LC is a negative predictor of SVR. The extension of the antiviral therapy duration can improve the efficacy of DAA therapy for genotype 3 infection; SVR rates are reported to be 60% to 70% in this genotype-infected LC patients receiving the 24-week regimen. However, more efficacious DAA regimens should be established. Although data on DAA therapy for genotype 4, 5, and 6 infection are currently scarce, a few trials of DAA therapy for genotype 4 infection provide promising results.

DAA therapy provides a new way to manage HCV-related LC patients, who are at a high risk of serious conditions, including liver failure, variceal bleeding, and the occurrence of HCC. Future studies should be addressed to evaluate the impact of DAA therapy on patient outcomes. Further studies are also needed to
clarify how DAA therapy can contribute to improvement in the outcomes of HCV-related LC patients receiving liver transplantation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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