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TOPIC HIGHLIGHT

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Hepatitis C-related liver cirrhosis - strategies for the prevention of hepatic decompensation, hepatocarcinogenesis, and mortality

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Abstract

Liver cirrhosis (LC) is a critical stage of chronic liver disease, including that caused by hepatitis C virus (HCV). In the absence of antiviral therapy, 67%-91% of patients with HCV-related LC patients die of liver-related causes, including hepatocellular carcinoma (HCC) and liver failure. Among the therapeutic strategies used to prevent liver-related complications in these patients is standard therapy with pegylated interferon and ribavirin, which induces a sustained virological response (SVR) in 25% of HCV genotype 1-infected patients and in 69% of patients infected with genotypes 2 and 3. SVR in patients with HCV-related LC has been associated with reduced rates of hepatic decompensation, HCC, and mortality. More recently developed direct-acting antiviral agents have shown excellent antiviral efficacy, with preliminary data demonstrating that an interferon-free regimen that includes these direct-acting antiviral agents achieved SVR in more than 50% of patients with HCV genotype 1 LC. Branched-chain amino acid supplementation, improvement of insulin resistance, and the use of β-blockers for portal hypertension may also reduce liver-related complications. Here, we review advances in antiviral and adjunctive therapies for improved outcomes in patients with HCV-associated LC.

Key words: Hepatitis C virus; Liver cirrhosis; Hepatic decompensation; Hepatocellular carcinoma; Mortality; Prevention; Interferon; Direct-acting antiviral agents

Core tip: Liver cirrhosis (LC) is the critical stage of hepatitis C virus (HCV)-related chronic liver disease. Many studies of HCV-related LC patients have indicated that sustained virological response (SVR) after interferon therapy is highly associated with reductions in hepatic decompensation, hepatocellular carcinoma incidence, and mortality. Furthermore, direct-acting antiviral agents have shown excellent antiviral efficacy. Preliminary data have indicated that an interferon-free regimen achieved SVR for more than 50% of patients with LC due to HCV genotype 1. Branched-chain amino acid supplementation, improvement of insulin resistance, and the use of β-blockers for portal hypertension may also contribute to a reduction in liver-related complications.

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INTRODUCTION

Hepatitis C virus (HCV) infection is one of the most

Table 1 Comparison of natural histories among patients with hepatitis B virus-related, hepatitis C virus-related, nonalcoholic steatohepatitis-related, and alcoholic compensated liver cirrhosis

Natural history	HCV	HBV	Alcoholic	NASH	Ref.
Hepatic decompensation	5.6%	3.2%			[5]
	5.6%		4.4%		[7]
	6.0%			4.5%	[11]
Hepatocarcinogenesis	2.0%	1.8%			[5]
	8.3%	3.3%			[6]
	4.7%		0.6%		[7]
	6.1%			2.3%	[12]
Mortality	3.2%	2.8%			[5]
	6.3%	3.6%			[6]
	5.1%		4.3%		[7]
	2.0%			0.4%	[11]
	5.2%			5.0%	[12]

All figures are expressed as average annual percentage rates. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Nonalcoholic steatohepatitis; LC: Liver cirrhosis.

serious global health problems. The incidence of HCV infection is increasing, with over 185 million people infected worldwide[1]. Moreover, approximately 370000 HCV-infected individuals die of liver-related causes each year[2]. HCV-related liver disease can progress in an insidious manner over several decades. The advanced forms of the disease are liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Approximately 20%-30% of subjects chronically infected with HCV are estimated to develop LC 15-25 years later[3]. A recent systematic review found that, in HCV-infected patients with compensated LC, 2.8%-11.7% develop hepatic decompensation, 1.8%-8.3% develop HCC, and 2.7%-6.7% die or undergo liver transplantation each year[4]. In the absence of antiviral therapy, 67%-91% of patients with HCV-related LC die due to liver-related causes, including HCC or hepatic failure[5-7]. Hence, LC is a critical stage in HCV-related chronic liver disease, as is LC due to other causes, including hepatitis B virus (HBV)[8], alcohol abuse[9], and nonalcoholic steatohepatitis (NASH)[10]. Here, we review advances in therapeutic strategies to prevent hepatic decompensation, hepatocarcinogenesis, and mortality in patients with HCV-related LC.

OUTCOMES IN PATIENTS WITH HCV-RELATED LC AND THOSE WITH LC DUE TO OTHER CAUSES

The outcomes of patients with LC due to HCV differ somewhat from the outcomes of patients with LC due to other causes. Table 1 summarizes the outcomes of patients with LC due to HBV, HCV, alcohol, and NASH. A study of a large Asian population compared outcomes in patients with HCV- and HBV-related compensated LC, none of whom had received any antiviral therapy. HCC (8.3% per year *vs* 3.3% per year, $P < 0.001$) and mortality (6.3% per year *vs* 3.6% per year, $P < 0.001$) rates were significantly higher in patients with HCV- than HBV-related LC[6]. In contrast, a study in a Caucasian population found that 5-year HCC (10% *vs* 9%, $P = 0.66$) and mortality (16% *vs* 14%, $P = 0.89$) rates were similar in untreated patients with HCV- and HBV-related LC, although the 5-year rate of hepatic decompensation was significantly higher in the former than in the latter group (28% *vs* 16%, $P = 0.0094$)[5]. In a study that compared outcomes in untreated Asian patients with HCV- and alcohol-related LC, the rates of hepatic decompensation (5.6% per year *vs* 4.4% per year, $P = 0.77$) and mortality (5.1% per year *vs* 4.3% per year, $P = 0.76$) did not differ significantly, although the HCC rate was significantly higher in the former group than in the latter group (4.7% per year *vs* 0.6% per year, $P = 0.0003$)[7]. Furthermore, a recent analysis of a Caucasian population found that the 10-year rates of hepatic decompensation (60% *vs* 45%, $P < 0.007$) and death (20% *vs* 4%, $P < 0.004$) were significantly higher in patients with HCV- than in patients with NASH-related compensated LC. Analysis of the entire cohort also revealed that HCC rates during the entire follow-period were significantly higher in the former group (17% *vs* 7%, $P < 0.01$)[11]. However, in Asian patients, the 5-year HCC (30.5% *vs* 11.3% at 5 years, $P = 0.185$) and mortality (26.2% *vs* 24.8% at 5 years, $P = 0.393$) rates were similar in patients with HCV- and NASH-related LC[12].

Altogether, these studies indicate that the rates of hepatic decompensation, HCC occurrence, and death in patients with LC due to HCV are similar to or higher than the rates in patients with LC due to other causes.

RISK FACTORS FOR HEPATIC DECOMPENSATION, HEPATOCARCINOGENESIS, AND MORTALITY

Knowledge of the prognostic factors in patients with HCV-related LC is essential for patient management.

Hepatic decompensation

Hepatic decompensation is generally defined as the development of ascites, jaundice, variceal bleeding, and/or

Table 2 Antiviral therapies for hepatitis C virus-related liver cirrhosis

Antiviral therapy	Number of treated patients	SVR rate	Decompensation[1]	HCC[1]	Mortality[1]	Severe AE rate[2]	Ref.
IFN-based therapy aiming at SVR							
IFN monotherapy	271	15.1% for genotype 1; 47.2% for others		0.65 (0.31)	0.54 (0.05)		[32]
IFN + RBV	132	30.3% for genotype 1b; 80.0% for others		(0.28)		12.1%	[33]
Pegylated IFN + RBV	57	24.2% for genotype 1; 70.8% for others				10.5%	[26]
	87	20.5% for genotype 1/4; 72.1% for genotype 2/3				25.0%	[28]
	568	24.4% for genotype 1; 54.9% for others				29.6%	[36]
Pegylated IFN + RBV + boceprevir	39 (all genotype 1)	59.0%					[79]
Pegylated IFN + RBV + telaprevir	21 (all genotype 1)	61.9%					[24]
Pegylated IFN + RBV + simeprevir	83 (all genotype 1)	70%-73% for relapsers; 15%-82% for partial responders; 31%-46% for null responders					[82]
Pegylated IFN + RBV + mericitabine	21 (genotype 1/4)	38.1%					[83]
IFN-based therapy after treatment for HCC							
IFN monotherapy	76 (pure HCV, 42)			0.30[3]		0%	[74]
Pegylated IFN maintenance therapy	427			0.45			[57]
	311 (portal hypertension, 39)		0.25[4]			17%	[56]
Faldaprevir + deleobuvir + RBV	34 (all genotype 1)	57% in patients treated thrice daily; 54% in patients treated twice daily					[85]

[1]The relative risk reduction of clinical events is expressed as a hazard ratio: total cases (SVR cases); [2]Severe AE rate is expressed as the rate of IFN discontinuation due to adverse events; [3]HCC recurrence in adherent patients with pure HCV; [4]Hepatic decompensation in patients with portal hypertension. HCV: Hepatitis C virus; SVR: Sustained virological response; HCC: Hepatocellular carcinoma; AE: Adverse event; IFN: Interferon; RBV: Ribavirin; DAA: Direct-acting antiviral agent.

hepatic encephalopathy. Factors predictive of hepatic decompensation include low serum albumin levels[5,7,13], elevated serum bilirubin levels[14,15], low platelet counts[5,15], and the presence of esophageal varices[14,15].

Hepatocarcinogenesis

Older age[5,15-17], male sex[7,14-17], low serum albumin levels[5,15], low platelet counts[16,17], elevated serum α-fetoprotein levels[7,14,15,17,18], and the absence of interferon (IFN) therapy[18,19] have been found to be independent risk factors for hepatocarcinogenesis.

Mortality

Low serum albumin levels[5-7,13,14,19], older age[5,15], male sex[5,15], and elevated serum α-fetoprotein levels[6,15] have been found to be independent risk factors for patient mortality.

THERAPIES TO PREVENT HEPATIC DECOMPENSATION, HEPATOCARCINOGENESIS, AND MORTALITY

Various treatments are used to prevent liver-related complications in patients with HCV-related LC. These methods may be classified as either antiviral or adjunctive therapy. We describe their efficacies and limitations.

Antiviral therapy

Table 2 lists antiviral therapies for HCV-related LC.

IFN-based therapy: Early small randomized controlled studies that examined the efficacy of IFN therapy in patients with HCV-related LC yielded conflicting results[18,20,21]. However, accumulated data have shown favorable outcomes in patients receiving IFN therapy, particularly in patients who achieve a sustained virological response (SVR).

IFN therapy targeting an SVR: HCV-related liver disease may be cured by methods that eradicate HCV. IFN-based regimens have been established as definitive and curative treatments for patients with chronic hepatitis C without LC. SVR has proven to be the best surrogate marker for HCV eradication by IFN[22]. IFN therapy targeting an SVR is more challenging in HCV patients with than without LC because of the relatively low response rates and high rates of severe adverse events in patients with LC. Studies in treatment-naïve HCV patients, most of whom had chronic hepatitis without LC, demonstrated that the standard combination therapy with pegylated IFN and ribavirin or triple therapy with pegylated IFN, ribavirin, and a nonstructural protein 3/4A (NS3/4A) protease inhibitor (boceprevir or telaprevir) achieved SVR in 63%-75%[23,24] of patients with HCV genotype 1 and in 79%-93%[25] of patients with genotypes 2 and

3. In contrast, a study of treatment-naïve HCV patients with compensated LC found that combination therapy with pegylated IFN and ribavirin achieved SVR in 25% of genotype 1-infected patients and in 69% of patients with genotypes 2 and 3[26]. Similar results have been reported in other studies that included patients infected with genotypes 1, 2, 3, and 4 and advanced fibrosis/LC[27-30]. Severe adverse events were reported for 14.5% of patients with HCV-related LC who received IFN-based treatments, leading to the discontinuation of therapy[31].

Nevertheless, IFN-based therapy that aims to achieve SVR can provide significant benefits for patients with HCV-related LC. The achievement of SVR is highly associated with reductions in clinical events, including hepatic decompensation, HCC, and mortality. A prospective study of patients with HCV-related LC revealed that those who achieved SVR in response to IFN-α monotherapy had lower risks for HCC (HR = 0.31) and death (HR = 0.05) than untreated patients[32]. Furthermore, clinical trials and cohort studies showed that combination therapy with IFN and ribavirin resulted in significant benefits in patients with HCV-related LC. For example, patients who achieved SVR with the combination of IFN-α2b and ribavirin had a significantly lower cumulative 4-year rate of HCC than patients who did not achieve SVR (8% *vs* 28%, $P = 0.018$)[33]. In a randomized controlled study in which most LC patients were infected with HCV genotype 1b, the SVR rate tended to be higher in patients treated with pegylated IFN-α2b and ribavirin than in those treated with pegylated IFN-α2b alone (21.6% *vs* 9.8%, $P = 0.06$), and the rates of liver-related events, including hepatic decompensation and HCC occurrence, were significantly lower in patients who did than did not achieve SVR ($P = 0.03$)[34]. A recent study analyzing the relationship between response to combination treatment with pegylated IFN and ribavirin and outcomes in HCV patients, more than half of whom had LC, reported that non-achievement of SVR was an independent risk factor for HCC (HR = 3.06), liver-related complications (HR = 4.73), and liver-related mortality (HR = 3.71)[35]. Moreover, a retrospective study involving a large number of patients with HCV-related LC who received pegylated IFN and ribavirin showed that the 5-year event-free survival (91% *vs* 59%, $P < 0.001$) and overall survival (98% *vs* 86%, $P = 0.005$) rates were significantly higher in patients who did than did not achieve SVR[36]. Meta-analyses have revealed that SVR after IFN therapy significantly reduced the rate of HCC in HCV patients with and without LC[37-39].

Some data have suggested that SVR after IFN therapy can cause reversal of liver fibrosis. In studies that compared the histological findings of liver biopsy specimens between pre- and post-IFN therapy, 44%-66% of HCV-related LC patients who achieved SVR had regression of LC[40-42]. In support of these results, SVR was reported to prevent or delay the *de novo* onset of esophageal varices in patients with compensated HCV-related LC[43].

LC patients generally have reduced daily activity levels owing to impaired physical and neurocognitive functions[44-46]. As with LC due to other causes, neurocognitive impairment in patients with HCV-related LC has thus far been considered as a sign of hepatic encephalopathy due to liver disease progression. However, recent evidence has suggested that HCV infection per se also can impair neurocognitive function, regardless of the presence or absence of LC. In a recent study that supports the hypothesis that HCV may directly induce neurocognitive impairment, investigators not only detected HCV RNA in brain tissue of individuals infected with HCV but also noted that brain microvascular endothelia and brain endothelial cells expressed all of the major HCV entry receptors[47]. Furthermore, results from a recent study that investigated the effects of combination treatment with pegylated IFN and ribavirin on neurocognitive function in HCV patients revealed that patients who achieved SVR had improved cerebral metabolism and neurocognitive function[48]. Thus, SVR may contribute to the improvement of neurocognitive function in HCV patients, including LC patients, and may lead to increased daily activity levels.

Although HCV patients who achieve SVR as a result of IFN-based therapy have the most favorable outcomes, there is evidence that a subset of patients without SVR may achieve equivalent outcomes. An elevated serum α-fetoprotein level has been shown to be an independent risk factor for HCC in patients with HCV-related LC[7,14,15,17,18]. Thus, therapies that reduce serum α-fetoprotein levels may prevent hepatocarcinogenesis in these patients. A recent study involving a large cohort of Japanese patients with chronic HCV infection, including patients with LC, who were treated with IFN, found that the cumulative rate of HCC was significantly lower in patients with post-treatment serum α-fetoprotein levels below 6.0 ng/mL, even if these patients did not achieve SVR[49]. Conversely, the rate of HCC was significantly higher in patients with post-treatment serum α-fetoprotein levels ⩾ 10 ng/mL, even if they achieved SVR. Little is known about the relationship between post-IFN serum α-fetoprotein levels and HCC in patients with HCV-related LC, which suggests a need for future studies to assess this relationship.

Thus, in conclusion, IFN-based therapy that aims to achieve SVR presents definite advantages for patients with HCV-related LC, although many of these patients may experience severe adverse events during therapy. A recent large retrospective analysis of LC patients with HCV genotype 1 who underwent IFN therapy determined that SVR was associated with reduced all-cause mortality (HR = 0.15) and clinical disease progression (HR = 0.16)[50]. This analysis also estimated that the number needed to treat to prevent clinical endpoints in those patients has markedly declined in relation to the improvement of antiviral therapy over five years, *i.e.*, from 302 at 2% SVR (IFN monotherapy) to 13 at 35% SVR (pegylated

IFN and ribavirin). Nonetheless, long-term surveillance is essential because even patients who achieve SVR have a long-term risk of hepatocarcinogenesis[51].

Maintenance therapy with pegylated IFN: Despite recent advances in IFN-based therapy, the overall SVR rate in patients with HCV-related LC has been reported to be only approximately 30%[52]. Long-term, low-dose pegylated IFN maintenance therapy was therefore advised for patients who do not achieve SVR. An early randomized trial of maintenance pegylated IFN-α2a in patients with HCV-related compensated LC did not demonstrate significantly enhanced complication-free 12- and 24-mo survival rates, which were 98% and 72.3%, respectively, in treated patients and 90% and 70.7%, respectively, in untreated patients (P = 0.59)[53]. Three independent mega-trials were conducted subsequently to evaluate the efficacy of maintenance pegylated IFN in HCV patients with advanced hepatitis or LC who had failed to achieve SVR with IFN therapy: the Colchicine Versus PegIntron Long-term Therapy (COPILOT) trial[54]; the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial[55]; and the Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC)[56]. The COPILOT trial, which included HCV patients with Ishak stages 3-6 who were randomized to treatment with pegylated IFN-α2b or colchicine identified no significant between-group differences in rates of liver-related complications and mortality/liver transplantation, although complications of portal hypertension, mainly variceal bleeding, occurred more frequently in the colchicine group than in the pegylated IFN-α2b group[54]. In the HALT-C trial, approximately 40% of HCV patients had LC, while the remaining patients had advanced chronic hepatitis; all the patients were randomly assigned to either the pegylated IFN-α2a group or the control group. The rates of clinical events, including hepatic decompensation, HCC occurrence, and mortality, were similar in the pegylated IFN-α2a and control groups (34.1% *vs* 33.8%, P = 0.90)[55]. After a long-term follow-up (median, 6.1 years), the rate of HCC in patients with LC, but not those with fibrosis, was significantly lower in the treatment group than in the control group (7.8% *vs* 24.2% at 7 years, P = 0.009, HR = 0.45)[57]. In the EPIC^3 trial, all participants had compensated HCV-related LC and were randomly assigned to pegylated IFN-α2b or a control group. The overall rates of clinical events (9% *vs* 11%, P = 0.14) and HCC were similar in both groups. However, among patients with portal hypertension, the clinical event rate was significantly lower in the pegylated IFN-α2b group than in the control group (10% *vs* 33%, P = 0.016), primarily because of differences in the rates of ascites and variceal bleeding[56].

In summary, these megatrials did not show any overall benefits of maintenance pegylated IFN therapy in patients with HCV-related LC. However, these trial results suggested that certain subsets of patients might benefit from treatment.

Combination of statins with IFN-based therapy: The HCV life cycle is unique in that its replication is highly associated with host lipid metabolisms: HCV circulates as lipo-viro particles that contain HCV core protein, cholesterol, triglyceride, and apolipoproteins B and E[58]. HCV-associated cholesterol plays a key role in virion maturation and infectivity[59]. HCV replicates by a mechanism in which the HCV NS5A protein binds to a host geranylgeranylated cellular protein, FBL2[60]. Statins inhibit the synthesis of cholesterol and geranylgeranylated proteins, suggesting that statins may inhibit HCV replication. Notably, although statin monotherapy was reported to have no or little antiviral effect in HCV patients[61-63], the addition of statin to IFN-based therapy may enhance the efficacy of the latter[64-66]. In a retrospective study involving a large number of patients, multivariate analysis revealed that the addition of statin to pegylated IFN and ribavirin was an independent factor that contributed to a higher SVR rate[67]. A recent meta-analysis of randomized controlled trials found that statin supplementation increased SVR (OR = 2.02) without additional adverse events observed in HCV patients treated with IFN-based therapy[66]. Thus, statin supplementation may be a promising method to enhance the efficacy of standard IFN-based therapy, particularly for patients with HCV genotype 1 and/or contraindications to protease inhibitors[66]. Further studies are needed to establish the efficacy of these combinations in patients with LC.

IFN therapy after curative treatment of HCC: Frequent recurrence following curative treatment, such as surgical resection and radiofrequency ablation, is a major issue in the treatment of HCV-related HCC[68,69]. Because IFN reduces the incidence of HCC in HCV patients, clinical trials have addressed whether IFN-based therapy might reduce the recurrence of HCV-related HCC after curative therapy. Earlier randomized controlled trials with small numbers of HCV patients suggested that IFN-α or IFN-β monotherapy might prevent HCC recurrence after curative treatment of HCC[70-73]. In contrast, a randomized controlled study of HCV-related LC patients with HCC reported that adjuvant IFN-α monotherapy after surgical resection failed to reduce overall HCC recurrence, although it reduced late HCC recurrence[74]. Two retrospective studies with small numbers of patients suggested that pegylated IFN-based therapy after curative treatment may increase survival rates for patients with HCV-related HCC and that SVR after IFN therapy may contribute to prolonged patient survival[75,76]. Furthermore, a recent study involving a large number of patients with HCV-related HCC showed that adjuvant therapy with pegylated IFN-α (either 2a or 2b) and ribavirin significantly decreased the rate of HCC recurrence after surgical resection (HR = 0.64)[77].

Taken together, these results indicate that standard pegylated IFN-based therapy may prevent HCC recurrence and mortality after curative treatment of HCC.

Studies that focus on patients with HCV-related LC and HCC are warranted to confirm its efficacy. In particular, the relationship between SVR after therapy and the rate of HCC recurrence should be clarified.

Direct-acting antiviral agents: IFN-based therapy has limitations, including its relatively low efficacy in patients infected with HCV genotype 1 and its capacity to cause severe adverse events, particularly in patients with HCV-related LC[26,31]. Hence, more effective, less toxic antiviral agents are urgently needed to manage HCV patients. In recent years, direct-acting antiviral agents (DAAs), including NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors, have been developed, and their efficacy and safety have been tested in many clinical trials[78]. Boceprevir and telaprevir are first-generation NS3/4A protease inhibitors and have been used combined with pegylated IFN and ribavirin in the antiviral therapy for HCV patients. Recent randomized controlled trials have demonstrated that triple therapy with pegylated IFN, ribavirin, and boceprevir or telaprevir resulted in a higher SVR rate than the combination of pegylated IFN and ribavirin in HCV genotype 1 patients with advanced fibrosis or LC (40%-68% *vs* 10%-39%, respectively)[24,79,80]. A large population-based study verified the high efficacy of the triple therapy wherein an SVR rate of 42.7% was reported in HCV genotype 1 patients with LC[81]. Furthermore, several clinical trials with other DAAs for HCV-related LC patients suggested promising results. In a phase 2b trial, previously treated patients with HCV genotype 1, including those with LC, were treated with pegylated IFN, ribavirin, and simeprevir (a NS3/4A protease inhibitor) or pegylated IFN and ribavirin. The SVR rate at 24 wk was generally higher in the triple than in the combination therapy group. Among LC patients, the SVR rates were 70%-73% in relapsed patients, 15%-82% in partial responders, and 31%-46% in null responders[82]. In another phase 2 trial of previously untreated patients with HCV genotype 1 or 4, including patients with LC, the SVR rates in response to triple therapy with pegylated IFN, ribavirin, and mericitabine (a nucleoside analog NS5B polymerase inhibitor) and to combination therapy with pegylated IFN and ribavirin in patients with LC were 38.1% and 21.7%, respectively[83]. The phase 2b Safety and Antiviral Effect of Oral Combinations without Interferon in Patients Diagnosed with Hepatitis C (SOUND-C2) trial tested the efficacy and safety of faldaprevir (a NS3/4A protease inhibitor), deleobuvir (a non-nucleoside NS5B polymerase inhibitor), and ribavirin in previously untreated HCV genotype 1 patients[84]. This trial was the first to report results from patients with HCV-related LC who were treated with an IFN-free regimen. Interim analysis revealed that SVR rates were 57% in patients treated three times daily and 54% in patients treated twice daily[85]. Moreover, fewer than 10% of the latter group discontinued treatment due to adverse events.

Clinical trials evaluating the efficacy and safety of antiviral DAAs in HCV-infected patients have only recently begun. Although future studies are required, the high SVR rates reported in patients with HCV-related LC treated with DAA(s)-containing regimens suggest that these treatments may reduce or prevent liver-related complications and deaths.

Adjunctive therapy

Although antiviral therapy plays a central role in the prevention of hepatic decompensation, hepatocarcinogenesis, and mortality in patients with HCV-related LC, not all such patients may benefit from these treatments, whether due to poor response and/or severe adverse events. However, several adjunctive therapies may prevent liver-related complications in these patients.

Branched-chain amino acid supplementation: Analyses of factors that are prognostic of clinical outcomes in patients with HCV-related LC have suggested that low serum albumin levels are highly associated with hepatic decompensation and HCC[5,7,13], suggesting that agents that maintain or increase serum albumin concentrations may improve patient outcomes.

Protein-energy malnutrition is frequent in patients with LC and is characterized by low serum albumin concentrations and decreased skeletal muscle volume[86]. Moreover, serum concentrations of branched chain amino acids (BCAAs) are low in LC patients because large amounts of BCAAs must be consumed for ammonia detoxification[87] and energy generation[88]. Experimental and clinical studies have revealed that BCAA supplementation increases serum albumin concentrations and improves protein malnutrition[86]. Based on these findings, clinical trials were performed to determine whether long-term BCAA supplementation might improve event-free survival and overall survival in patients with LC. An early randomized clinical trial in patients with decompensated LC suggested that long-term BCAA supplementation is useful in preventing progressive hepatic failure[89]. Furthermore, a large randomized controlled trial, in which approximately two-thirds of the enrolled patients had HCV-related LC, found that long-term BCAA supplementation increased serum albumin concentrations and was significantly associated with decreases in hepatic failure and mortality[90]. Subgroup analysis showed that the benefits of BCAA treatment in patients with HCV-related LC were similar to those in the entire patient cohort.

BCAA supplementation may also prevent HCC occurrence. For example, although a phase 2 randomized controlled trial involving patients with compensated HCV-related LC found no significant difference in HCC occurrence between the BCAA and control groups, subgroup analysis demonstrated that the HCC rate tended to be lower in patients with serum albumin levels < 4.0 g/dL who were assigned to the BCAA group[91]. A recent retrospective study examined the usefulness of BCAA supplementation in preventing hepatocarcinogenesis. Following one-to-one matching of propensity scores,

the BCAA group had a significantly lower rate of HCC occurrence than the control group ($P = 0.032$)[92].

Collectively, long-term BCAA supplementation may be a promising method for improving event-free survival and overall survival in patients with HCV-related LC. However, to date, the data remain insufficient, particularly regarding whether BCAA supplementation can prevent hepatocarcinogenesis. Moreover, the timing of BCAA treatment to obtain maximum benefits in patients with HCV-related LC is unclear, although the results of a randomized controlled trial suggested that patients with molar ratios of BCAA to tyrosine (BTR) < 4 undergo BCAA treatment even if they have compensated LC[93]. Further prospective studies are needed to assess the efficacy of BCAA supplementation in the treatment of patients with HCV-related LC.

Improvement of insulin resistance: Insulin resistance (IR) is commonly observed in HCV patients, with prevalence rates ranging from 30% to 70%[94]. Virus- and host-related mechanisms have been associated with IR in HCV patients. Accumulated evidence has shown that HCV infection *per se* induces IR. The HCV core protein activates suppression of cytokine signaling 3, which causes proteasomal degradation of insulin receptor substrates 1 and 2 and inhibits the translocation of glucose transporter 4, thereby resulting in IR. In addition, increases in inflammatory cytokines, such as tumor necrosis factor α and interleukin 6, and decreases in adiponectin may directly cause IR[94,95]. Furthermore, the rates of overweight and obesity are increasing worldwide, with 39%-42% of HCV patients having body mass indices (BMIs) ⩾ 25 kg/m^2[96,97]. Overweight can cause IR, and many LC patients are overweight. A recent study that examined the nutritional state of Japanese patients with compensated HCV-related LC found that 72.4% of these patients had excess energy and protein intake[98].

The development of IR in HCV patients can cause serious problems, including the progression of fibrosis and enhanced hepatocarcinogenesis. The degrees of IR and hepatic fibrosis are closely related[96,99,100]. A recent study of patients with HCV-related compensated LC demonstrated that a high homeostasis model assessment (HOMA)-IR score could predict the presence of esophageal varices, a manifestation of portal hypertension induced by the progression of fibrosis[101]. IR is largely responsible for the development of type 2 diabetes. A recent meta-analysis found that type 2 diabetes is highly associated with the risk of HCC (summary relative risks, 2.01)[102]. A study in patients with HCV-related or alcoholic LC indicated that overweight and type 2 diabetes correlated significantly with an increased risk of HCC occurrence[103]. Furthermore, a multivariate analysis of results in patients with HCV found that type 2 diabetes was predictive of the development of HCC in Ishak 6 LC patients (HR = 3.28)[104].

IR-associated problems in HCV patients may be prevented or reduced by lifestyle modifications such as improvements in dietary habits, although the therapeutic effects of diet require confirmation. Little is known about the efficacy of medical treatments to improve IR. A large case-control study, in which nearly 40% of the enrolled patients with HCC or LC were infected with HCV, suggested that treatment with metformin, an insulin-sensitizing agent used to treat patients with type 2 diabetes, was associated with a reduced risk of HCC[105]. Moreover, multivariate analysis of the results of a recent prospective study of patients with HCV-related LC and type 2 diabetes found that metformin treatment was independently associated with decreases in HCC occurrence (HR = 0.19) and liver-related death/liver transplantation (HR = 0.22)[106].

Lifestyle modification and treatment with insulin-sensitizing agents may contribute to improved outcomes in patients with HCV-related LC. Extensive efforts should be made to assess the effectiveness of these therapeutic strategies.

β-blockers: LC-associated portal hypertension is the driving force behind hepatic decompensation, including variceal bleeding and the development of ascites. Nonselective β-blockers reduce portal venous pressure by reducing cardiac output *via* the blockage of β1 receptors, produce splanchnic vasoconstriction, and reduce portal flow *via* the blockage of β2 receptors[107]. Therefore, many studies have assessed the capacity of β-blockers to prevent hepatic decompensation. These agents were shown to prevent variceal bleeding in patients with LC, regardless of the LC etiology[108], although another study found that β-blockers did not prevent variceal formation[109]. Recent studies suggested that carvedilol is superior to propranolol in preventing variceal bleeding[110]. Moreover, a recent study that assessed the capacity of nadolol to prevent ascites in patients with compensated LC complicated with esophageal varices, 75% of whom were infected with HCV, found that a ⩾ 10% reduction in hepatic venous pressure gradient significantly reduced the risk of the development of ascites and other related complications, such as refractory ascites and hepatorenal syndrome[111].

Because studies have suggested that β-blockers have anticancer effects[112], a retrospective study examined whether propranolol treatment can prevent HCC occurrence in compensated patients with HCV-related LC. Multivariate analysis showed that propranolol treatment was associated with a decreased risk of HCC occurrence (HR = 0.25) and was the only factor independently predictive of HCC in patients with esophageal varices (HR = 0.16)[113]. These results encourage prospective studies to examine the potential of β-blockers to prevent hepatocarcinogenesis.

Thus, accumulated evidence supports the usefulness of β-blockers in preventing liver-related complications in LC patients, including those with HCV. However, from a practical standpoint, there are some limitations to β-blocker treatment. Approximately 50% of patients are nonresponders[111]. Although measurement of the

hepatic venous pressure gradient can best distinguish responders from nonresponders[107], this assessment cannot easily be performed in routine practice. Other limitations include contraindications to β-blockers and limited tolerability to these agents due to adverse effects, such as general fatigue and lightheadedness.

CONCLUSION

Substantial progress has been made in the development of treatment regimens to prevent liver-related complications and mortality in patients with HCV-related LC. However, treatment results are not completely satisfactory. The key to improved results is the development of more effective, less toxic antiviral agents that can achieve SVR. With regard to antiviral therapy for chronic HCV infection, we are transitioning from the "IFN" into the "DAA" era[114]. We anticipate that this new era, along with the DAAs being developed, will enhance outcomes in patients with HCV-related LC.

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