Direct antiviral agent treatment of decompensated hepatitis C virus-induced liver cirrhosis

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Abstract

Recently, direct antiviral agents (DAAs) have been increasingly used for the treatment of chronic hepatitis C virus (HCV) infections, replacing interferon-based regimens that have severe adverse effects and low tolerability. The constant supply of new DAAs makes shorter treatment periods with enhanced safety possible. The efficacy of DAAs for treatment of compensated liver cirrhosis (LC) is not less than that for treatment of non-cirrhotic conditions. These clinical advantages have been useful in pre- and post-liver transplantation (LT) settings. Moreover, DAAs can be used to treat decompensated HCV-induced LC in elderly patients or those with severe complications otherwise having poor prognosis. Although encouraging clinical data are beginning to appear, the actual efficacy of DAAs for suppressing disease progression, allowing delisting for LT and, most importantly, improving prognosis of patients with decompensated HCV-LC remains unknown. Case-control studies to examine the short- or long-term effects of DAAs for treatment of decompensated HCV-LC are urgently need.

Key words: Decompensated liver cirrhosis; Prognosis; Direct antiviral agent; Hepatitis C virus; Comorbidity; Nucleic acid analogue

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Core tip: Decompensated liver cirrhosis (LC) due to hepatitis C virus (HCV) infection is a severe disease with poor prognosis. Because interferon-included regimens are contraindicated at this stage, liver transplantation has been the only way to cure the disease. However, recent development of direct antiviral agents (DAAs) is offering a hope for this difficult situation. Promising antiviral effects of DAAs for LC have been observed, suggesting
they might be useful for treatment of decompensated HCV-LC. To explore this possibility, large case-control studies are needed.

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INTRODUCTION

Hepatitis C virus (HCV) - induced decompensated liver cirrhosis (LC) is a life-threatening illness with an average 5-year survival rate of 50%[1,2]. Although liver transplantation (LT) has been the only curative therapy for these patients, the recently-developed direct antiviral agents (DAAs) are now helping patients cope with these difficult situations. Because DAAs have far fewer adverse effects and are better tolerated than interferon (IFN), they can be used to treat the elderly or patients with comorbidities, such as leuko- or thrombocytopenia. It is well-known that IFN-based therapies provide lower sustained viral response (SVR) rates as the disease progresses and fibrosis levels increase. However, this may not be the case for DAA treatments, because the presence of compensated cirrhosis reportedly has not hampered the therapeutic outcomes[3,4]. Because these patients have the higher risk of mortality and hepatocellular carcinoma (HCC), the benefits of eradicating the virus, may be greater than doing so in those having less-advanced disease.

There have been only a few reports of the effects of DAA therapy in patients with decompensated HCV-induced LC (HCV-LC). The effects and safety of DAAs for treatment of severe liver diseases in both pre- and post-LT patients have been demonstrated[5,6]. After LT, reinfection of the grafted liver frequently occurs if HCV is not eradicated, and subsequently one third of liver transplant recipients with HCV infection either died, experienced allograft loss, or developed cirrhosis by the fifth post-operative year[7]. Thus, the primary endpoint of DAA therapy in the setting of LT is to clear the virus before transplantation and prevent reinfection of grafted livers. Importantly, findings obtained from studying this situation can be extended to therapy for elderly patients and those having comorbidities-patients having no indications for LT in the real-world settings.

On the other hand, there have been numerous clinical experiences of use of oral nucleoside analogues (NAs) for HBV-induced compensated or decompensated LC, and clinical benefits for both in short- and long-term prognosis have been established[8]. In this review, we summarize the data on use of DAAs for treatment of advanced HCV-LC and comorbidities, referencing the past experience with use of NAs for these HBV patients.

DECOMPENSED HCV-LC: NATURAL HISTORY AND TREATMENT

Chronic hepatitis C infection is one of the leading causes of chronic liver diseases and the most common indication for LT. Because of its indolent clinical course, patients occasionally suffer from advanced disease before diagnosis is made. In its natural history, cirrhosis develops in 4%-24% of patients during 20 years of chronic infection[9]. The annual occurrence rate of HCC is about 2%-4% of patients with cirrhosis, and it is reported to be around 7% in Japanese patients[8,10]. Signs of decompensation include ascites, jaundice, encephalopathy and variceal bleedings. The 5-year survival rate for decompensated HCV-LC is about 50%; the condition is a good indication for LT[11,2]. However, implementation rates of LT vary among the countries depending on the accessibility of donor livers. In a country like Japan, where chronic insufficiency of donor livers is the usual situation, most of patients with decompensated HCV-LC cannot benefit from LT. Above all, most of these patients are elderly and have several clinical complications, and are generally not considered suitable candidate for LT.

IFN-BASED TREATMENT FOR ADVANCED HCV-INDUCED LIVER DISEASES

Currently IFN-based regimen for the patients with chronic HCV having genotype 1 (GT1) mainly consists of pegylated-interferon (PEG-IFN), ribavirin (RBV) and a protease inhibitor (PI). Xu et al[11] reported that SVR rates of PEG-IFN plus RBV therapy for patients with decompensated HCV-LC were 19.7% for GT1 and 42.9% for GT2, resulting in significant suppression of disease progression, compared to control patients. Thus IFN-based regimens might improve the prognosis of the patients with advanced type C liver diseases when treatment is safe and compliance is good. However, in the era of DAAs which have both strong anti-viral effect and sufficient tolerability, IFN-based regimens may no longer be prioritized for patients with advanced type C liver diseases; and rather, may be relatively contraindicated because of severe complications and low probability of attaining SVR[12].

RECENT PROGRESS OF DAA TREATMENTS

NS3/4A protease inhibitors (PIs) such as telaprevir, simeprevir, vaniprevir have been approved in Japan for treatment of GT1b, in combination with PEG-IFN plus RBV. These regimens have greatly improved therapeutic efficacy; SVR rates have been reported to be more than 70% for telaprevir or simeprevir plus PEG-IFN and RBV regimens[13,14]. However, the recent replacement, which was approved in 2014, of the IFN-based regimen, which had severe adverse effects and poor tolerability, by the
The current status of DAA treatment for compensated HCV-LC

Most IFN-free DAA trails up to now have enrolled only a modest population (10%-20%) of cirrhotics with well-compensated diseases\[^{15,20,25,26}\]. SVR rates for cirrhotics in these studies were comparable to those of non-cirrhotic patients, in contrast to the result of IFN-based regimens, for which, as fibrosis of liver progresses, the rate of SVR decreases and the incidence of adverse effects increases. A recently-published phase III trial (Turquoise-\(II\)) with ABT-450/r-ombitasvir and dasabuvir plus RBV-based regimens, was performed exclusively in patients with GT1 HCV-LC\[^{16}\]. This study included 380 patients with cirrhosis in Child-Pugh class A5 to A6, randomly assigned to receive either 12 or 24 wk of treatments. Patients achieved SVR12 of 91.8% and 95.9% in the 12-wk and 24-wk treatment arm, respectively. In addition, differences in rates of SVR12 between patients with mild to moderate fibrosis (F0 to F2) vs F3 to F4 were not statistically significant\[^{27}\]. These outstanding SVR rates accompanied by a high safety and tolerability profile in cirrhotics allow IFN-free DAA regimens to be much more available to even compensated cirrhosis patients.

DAA treatment for decompensated HCV-LC

DAA treatments for patients with severe liver diseases before and after LT have been reported\[^{7,28}\]. The primary endpoint of treatment in the liver-transplant setting is to eradicate the virus to prevent reinfection by HCV of the grafted liver tissue. SOF-based DAA regimens have been playing a central role in these settings. A total of 61 patients, mainly with compensated LC (≤ CTP (Child-Turcotte-Pugh) 7, or < MELD (Model of End-Stage Liver Disease) 22) and HCC, on the waiting list for LT, had received up to 48 wk of SOF plus RBV treatment, and 30% of 43 (70%) whose HCV RNA levels were less than 25 IU/mL at transplantation obtained post-transplantation virologic response at 12 wk. Safety profiles were excellent\[^{26}\]. In addition, combination treatment of SOF + RBV (± Peg-IFN) were tested in 104 patients who had early severe recurrence (52), LC (52) after LT\[^{7}\]. SVR 12 was obtained in 35 of 48 (73%) with early severe recurrence. Importantly, 59 of 103 (57%) reported clinical improvement. These studies showed that SOF-based, IFN-free regimens provided high rates of SVR with a good safety profile in difficult peri-LT settings.

Clinical and epidemiological features of HCV-infected patients vary among the countries. In Japan, candidates for DAA treatment are mainly the elderly or those with complications. Presently, published results in patients with decompensated cirrhosis in real-world settings consist mostly of preliminary conference reports. Afdhal et al\[^{29}\] reported on 48 wk of SOF plus RBV treatment for a total of 50 patients with GT1-4 HCV-LC (60% of them were CPT7-10 and 20% ≥ MELD 14) and 89% of rapid viral response (RVR) 4 and 97% RVR 8 were obtained. SVR 4 was obtained in 16/18 (89%) GT1 and CTP Class B patients after 12 wk of SOF/LDV treatment\[^{30}\]. A total of 108 patients with CTP Class B or C cirrhosis with GT1 and 4 were treated with SOF/LDV and RBV, and SVR was achieved in 87% of those given the 12-wk treatment and 89% in the 24-wk treatment\[^{31}\]. It is remarkable that these SVR rates are comparable to those for compensated LC or even non-cirrhotic patients. Although the numbers were still small and the results were preliminary, these studies suggest that such treatments may extend the life expectancy of patients who would otherwise be considered end-stage without the use of DAA.

DAA treatment for comorbidities

IFN-based regimens are contraindicated for depressed patients and cautions should be exercised in their use for those with psychiatric disorders. The presence of leucocytopenia and thrombocytopenia may severely impair compliance with IFN-based therapies\[^{32}\]. DAA can be administered safely in these situations and also to elderly patients with cardiovascular complications and diabetes. However, caution should be used in patients with anemia, renal insufficiency and cardiopulmonary complications if the regimen contains RBV.

Because SOF also has renal toxicity, caution is necessary in those with renal dysfunction. However, the newly-developed DAAs grazoprevir and elbasvir...
are metabolized by the liver and easily administered to patients with renal dysfunction without adjustment of dose\textsuperscript{24}. In general, unlike IFN, DAAs can be administered to patients with autoimmune disorders unless RBV, which might affect the immune status, is included in the regimen\textsuperscript{33}. Human Immunodeficiency Virus (HIV)/HCV co-infected patients have the same cure rates, of over 90\%, with IFN-free DAA combinations. Therefore, guidelines no longer separate mono- and co-infected patients. The only special consideration in HIV/HCV co-infected subjects is the need to check for drug-drug interactions between anti-HIV and -HCV agents\textsuperscript{34}.

**EXPECTATIONS AND CONCERNS OF DAA TREATMENT FOR DECOMPENSATED HCV-LC**

Past clinical experiences from the results of NA treatment of patients with advanced HBV liver diseases may provide useful information when predicting the short- and long-term effects of DAA therapy for decompensated HCV-LC, a practice that is still in the beginning stages. Jang et al\textsuperscript{35} reported the long-term effect of the NAs in patients with decompensated HBV-LC. They followed 284 untreated patients and 423 treated with NAs for more than 7 years and found that transplant-free survival was significantly improved in those treated with NAs (59.7\% vs 46.0\%). CTP and MELD scores improved significantly as a consequence of continuous suppression of HBV. They found that the degree of improvement was greater in those with higher CTP or MELD scores and early commencement of therapy was more important in the improvement of prognosis.

There are some similarities and differences between the following two situations: That is, NAs for HBV and DAAs for HCV. Anti-viral effects of DAAs against HCV might possibly surpass that of NAs against HBV, given that DAAs eliminate HCV RNA from serum in a very short period. Safety profiles may be comparable to NAs. Most importantly, DAAs may induce virus-free state if SVR is accomplished with only short duration of treatment, whereas the NAs for HBV cannot eliminate covalently closed circular DNA in liver and even long-term treatment may not eradicate the virus. Thus, DAA treatment for decompensated HCV-LC might elicit a similar clinical impact as NAs for decompensated HBV-LC with only a short-term treatment. Actually, preliminary report showed that DAAs for decompensated LC improved MELD scores in 60\% to 79\% patients only 4 wk after treatment finalization\textsuperscript{31}. For these reasons, DAA treatments would be indicated positively for those with decompensated LC-HCV in real world-settings\textsuperscript{36}.

Despite of these encouraging situations and that a standardized mortality rate analysis reported a lower liver-related mortality among HCV-cirrhotics with SVR by IFN treatment\textsuperscript{27}, to our knowledge there are currently no data on disease progression, delisting from LT, and improvement of life expectancy after the achievement of SVR for decompensated LC-HCV. It is well-known that the level of liver fibrosis can be decreased with the eradication of virus\textsuperscript{38}. However, it is uncertain whether the severe fibrosis observed in decompensated HCV-LC could be reversed to some extent. Although successful treatment outcomes in HCV induced cirrhosis resulted in the significant prevention of HCC\textsuperscript{39}, it is not yet clear whether DAA treatment for decompensated HCV-LC lowers the incidence of HCC. Actually, despite clinical improvement, the occurrence of HCC was not significantly suppressed by NA treatment for decompensated HBV-LC\textsuperscript{40}. However, given the difference of pathogenesis between HBV and HCV, in that one virus integrates into the genome and the other does not, the two infections might not always respond in a similar fashion.

There are also several issues to be considered when commencing the treatment of DAA for decompensated HCV-LC. Early mortality due to aggravation of liver function during therapy might occur as was observed during treatment with lamivudine for decompensated HBV-LC\textsuperscript{40}. Patients with advanced cirrhosis still have a high risk for hospitalization after the initiation of DAA treatment\textsuperscript{36}. In addition, decompensated cirrhosis patients are more prone to develop drug-induced side-effects when compared to patients with compensated cirrhosis. For example, simprevir is contraindicated to Child C LC, asunaprevir to Child B-C and ABT-450/r to Child B\textsuperscript{41}. Especially patients on SOF regimens should also be monitored for renal dysfunction\textsuperscript{41}.

Currently it is possible to perform a large scale case-control study to clarify short- or long-term effects of DAA treatment for decompensated HCV-LC patients in real-world settings. Until these results are available, treatment of decompensated HCV-LC patients should be individualized on a case-by-case basis, giving due consideration to viral factors like genotype and clinical background factors including age, severity of liver diseases and presence of comorbidities.

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