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EDITORIAL

Long-awaited treatment for hepatitis C virus decompensated cirrhosis

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Organ fibrosis is pathologically progressive due to the abnormal accumulation of extracellular matrix occurring during the wound healing process of repeated injuries and necrosis associated with inflammation and tissue necrosis [1]. It also causes organ dysfunction, reportedly accounting approximately 30% of the cause of death in developed countries [2]. Therefore, development of therapeutic drugs against fibrosis is an urgent problem. Liver cirrhosis, also known as liver fibrosis, is caused by viral hepatitis such as hepatitis B virus (HBV) and hepatitis C virus (HCV) and fatty liver, which are recently increasing and alcohol consumption. HCV cirrhosis, accounting for the majority of domestic liver cirrhosis, progresses from compensated Child–Pugh (CP) classification A with comparatively hepatic reserve preservation to decompensated CP-B and CP-C. As the liver cirrhosis progresses, complications such as ascites, jaundice, and encephalopathy increasingly occurred due to decreased liver function and ruptured esophageal varices, because of portal hypertension, which affect the prognosis of patients with cirrhosis. In fact, the one-year CP-C survival rate is approximately 40% [3]. In addition, cirrhosis is the primary cause of liver cancer that ranked as the fifth cause of domestic death; therefore, therapeutic drugs should be developed.

With the breakthrough advent of direct-acting antivirals (DAAs) against HCV, most patients infected with HCV could be excluded [4]. With the development of this therapeutic agent, several reports have demonstrated that antiviral therapy for chronic hepatitis and compensated cirrhosis, which improves liver function and prevents the occurrence of liver cancer, becomes possible [5–7]. Reports from domestic clinical trials as well as overseas treatment results have indicated good sustained virologic response (SVR) 12 results after DAA administration [8–10]. Since DAAs had fewer side effects compared with the conventional treatment based on IFN, subjects who were contraindicated with IFN (those with thrombocytopenia, leukopenia, depression, and kidney disorder, among others) can now be treated, which will greatly decrease the number of patients infected with HCV. Under these circumstances, patients with decompensated cirrhosis who are contraindicated with DAA still remain in the treatment target group. In Europe and the United States, liver transplant has been established as the standard treatment option, but remains not very popular in Japan. In one reported case, a sofosbuvir + ledipasvir + ribavirin combination therapy for decompensated cirrhosis achieved SVR12 and improved liver function, but there are no therapeutic medicines approved in Japan at present [11]. Therefore, decompensated cirrhosis remains one of the unmet medical needs in Japan.

In a study published in this issue, Takehara et al. demonstrate that administration of sofosbuvir + velpatasvir ± ribavirin combination therapy against HCV decompensated cirrhosis is sufficiently safe and effective [12]. Regardless of ribavirin involvement, the SVR 12 is 92%, which is comparable to that of the previous reports from other Western countries [13]. This therapeutic agent seems effective for HCV genotype 1 or 2, which is common in Japan. Compared with ASTRAL-4, a previous trial on concomitant administration of sofosbuvir + velpatasvir ± ribavirin for decompensated cirrhosis, this study's subjects could tolerate, although they were older than the

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registered patients (aged 66 vs. 58 years). Although this study reports that cirrhosis worsened in the ribavirin combination group, these patients should be carefully monitored because of the increasing death cases.

One of the notable results of this report is that if patients with decompensated cirrhosis can achieve SVR 12, approximately 25% of them showed improvement from CP-B to CP-A even in a short period of time. This is an effect of improved protein synthesis ability, such as of albumin. These results can improve the prognosis of decompensated cirrhosis by eliminating the causative HCV despite progression to decompensated cirrhosis. Future studies should also be conducted to confirm this finding; however, we expect that these DAAs will have a similar effect as IFN treatment, and may also reduce the incidence of liver cancer.

Finally, we need to consider which type of patients with decompensated cirrhosis should be treated in the future. In Japan, where liver transplantation is not actively carried out, the purpose of extending the period until the transplantation is not applicable, and analyzing the cost-effectiveness based on treatment is required. In addition, using DAAs eliminates the causative factors of liver cirrhosis, which will only recover normally due to the liver's regenerative ability. It has been demonstrated that resolution of cirrhosis takes time after HCV eradication [14]; therefore, therapeutic drugs that dissolve fibrosis are desirable in the future.

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