Optimum timing of treatment for hepatitis C infection relative to liver transplantation

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The approval of direct-acting antiviral agents that may be given orally in an interferon-free regimen has greatly changed the landscape of treatment for hepatitis C virus (HCV) infection, especially for patients with the most severe disease, who have decompensated cirrhosis, or who are waiting for or have undergone liver transplantation. Treatment with interferon proved to be ineffective and poorly tolerated because of high risks of infection and transplant rejection. The availability of new drugs poses new questions about the optimum time to give treatment to prevent HCV recurrence, taking into account efficacy, tolerance, and drug–drug interactions. Treatment is acceptable before and after transplantation, but the two strategies have subtle differences. In this Review, we present the available data on the treatment of HCV infection before and after transplantation, and discuss new challenges for practice.

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Introduction

Infection with hepatitis C virus (HCV) is one of the main causes of end-stage liver disease and indications for liver transplantation worldwide.[1] If patients have detectable HCV RNA in serum at the time of transplantation, HCV infection always recurs on the graft and leads to the return of end-stage liver disease, graft loss, and death without the possibility of retransplantation.[2,3] After treatment with pegylated interferon and ribavirin and in patients cured before needing liver transplantation, in historical cohorts survival at 5 years was 75% and at 10 years was 68%.[3] The outlook is poor if cirrhosis is diagnosed on the liver graft in transplant recipients, with a rate of decompensation of around 40% at 1 year.[4] Use of pegylated interferon to treat patients on the waiting list yields a sustained virological response (SVR) in 20% after transplantation, but this strategy is contraindicated in patients with decompensated cirrhosis because of the high risk of severe infection.[5,6] Treatment of recurrent HCV after liver transplantation results in SVR in 20–30% of patients with genotype 1 and 40–50% of those with genotype 2 or 3 infection.[5]

First-generation protease inhibitors were the first direct-acting antivirals available to treat recurrent HCV infection. In combination with pegylated interferon and ribavirin, protease inhibitors improved SVR in people infected with HCV genotype 1. In the CUPIC study,[7] 53–70% of patients with cirrhosis and previous relapse achieved SVR at 12 weeks after the end of treatment (SVR12). After transplantation, SVR12 was seen in 38 (47%) of 81 recipients who developed severe on-graft recurrence.[8,9] However, this improvement in efficacy was limited by a poorer safety profile than with pegylated interferon and ribavirin, especially for cytopenia leading to an increase of 20% in the frequency of anaemia, and potent drug–drug interactions. The approval of direct-acting antivirals, combined in all-oral interferon-free regimens, has substantially changed the landscape of treatment for patients with decompensated cirrhosis, who are awaiting or have undergone transplantation. In patients undergoing transplantation, therapy based on pegylated interferon has been completely replaced with direct-acting antiviral regimens. Powerful and well tolerated therapeutic options are provided by the NS5B inhibitors sofosbuvir and dasabuvir, the NS5A inhibitors ledipasvir, daclatasvir, and ombitasvir, and the protease inhibitors simeprevir and paritaprevir. However, physicians still have to choose the best strategy for timing of treatment—that is, before or after transplantation. Although both options are acceptable, subtle differences in efficacy, tolerance, advantages, and limitations should be considered.

Efficacy before and after transplantation

Treatment after transplantation

Direct-acting antivirals show good efficacy in the treatment of HCV in liver transplant recipients. In an open-label study, 40 patients with recurrent HCV infections of all genotypes were treated with combined sofosbuvir and ribavirin for 24 weeks after liver transplantation.[10] SVR12 was achieved in 28 (70%) patients, and all cases of virological failure were caused by relapse. Although, this strategy is suboptimum, it showed that an all-oral interferon-free regimen could be used in liver transplant recipients and achieve results similar to those in patients who did not require transplantation. In a phase 2 study,[11] the combination of paritaprevir, ritonavir, ombitasvir, and dasabuvir plus ribavirin for 24 weeks was given to 34 liver transplant recipients with HCV genotype 1 infection and mild to moderate fibrosis on grafts; 33 (97%) patients achieved SVR12.

In the ALLY-1 phase 3 study,[12] 53 liver transplant recipients were given sofosbuvir and daclatasvir plus ribavirin. 16 (30%) of these patients had cirrhosis on the graft, and SVR12 was achieved in 50 (94%) patients. In the SOLAR studies,[13,14] 227 liver transplant recipients received sofosbuvir and ledipasvir plus ribavirin for 12 or 24 weeks. SVR12 was achieved in 96% with 12 weeks of treatment and 98% with 24 weeks of treatment.

Use of direct-acting antivirals after liver transplantation has been assessed in several observational real-life cohorts. The HCV-TARGET study[15] included patients infected with HCV genotype 1 after liver transplantation. All patients received sofosbuvir and simeprevir, with or without ribavirin. Of 151 patients, 133 (88%) achieved

SVR12. Similarly, in another study, SVR12 was achieved in 111 (90%) of 123 liver transplant recipients treated with sofosbuvir and simeprevir, including 37 (30%) with advanced fibrosis on the liver graft.[16] The largest observational real-life cohort of transplant recipients is the ongoing French CO23 ANRS CUPILT study,[17] which has so far enrolled 699 patients and is assessing the combination of sofosbuvir and daclatasvir with or without ribavirin. Of 137 assessed, SVR12 has been achieved in 132 (96%), irrespective of HCV genotype, duration of treatment (12 *vs* 24 weeks), or use of ribavirin. Finally, in a study by Fontana and colleagues,[18] more patients achieved SVR12 with sofosbuvir and daclatasvir than with daclatasvir and simeprevir (70 [91%] of 77 *vs* 13 [72%] of 18, p=0·047).[18,19] This strategy, however, is not used in liver transplant patients.

The results of direct-acting antiviral treatment in liver transplant recipients are particularly striking in those who have the most severe form of recurrence, fibrosing cholestatic hepatitis,[20,21] which is characterised by rapid portal fibrosis, cholestasis, and deterioration of the liver. The estimated frequency of fibrosing cholestatic hepatitis is 2–10%.[22] Prognosis is very poor, with mortality of 50–90% at 2 years.[23,24] Retransplantation for this complication is controversial owing to the frequency of poor outcomes.[24] Sofosbuvir was assessed as a treatment for severe recurrence after liver transplantation in a compassionate use programme. Clinical improvement was seen in 59 (57%) of 103 patients (even with fibrosing cholestatic hepatitis) at the final follow-up visit 12 weeks after treatment ended. 23 (22%) had unchanged and three (3%) worsened clinical status, and 13 (13%) patients had died. In the CO23 ANRS CUPILT study,[21] four sofosbuvir-based regimens (sofosbuvir plus ribavirin, pegylated interferon alfa plus sofosbuvir and ribavirin, sofosbuvir plus daclatasvir, or sofosbuvir plus daclatasvir and ribavirin) were assessed in 23 patients with fibrosing cholestatic hepatitis. Survival without retransplantation until week 36 and rapid and substantial improvement in clinical status were seen in all patients. 22 (96%) patients had a complete clinical response at week 36, defined as survival without retransplantation, no jaundice (bilirubin concentration <34 µmol/L), no ascites, and no hepatic encephalopathy.

Most combinations of direct-acting antivirals lead to HCV clearance in more than 90% of people after liver transplantation, including with the use of one NS5B inhibitor and one NS5A inhibitor, with or without a second-generation protease inhibitor. Although no head-to-head study has shown that a specific strategy is significantly better than another, sofosbuvir-based regimens seem to show the greatest efficacy, which has led to this drug becoming the backbone of pharmaceutical treatment in liver transplant recipients. However, with sofosbuvir plus ribavirin and daclatasvir plus simeprevir, SVR12 does not reach 90%, and these regimens are, therefore, suboptimum.

Remaining issues are the optimum time to start treatment, the duration of treatment, and the usefulness of ribavirin. Patients should be treated without waiting for a severe recurrence of HCV infection on the graft and, in the absence of stronger evidence for a different approach, before the cirrhotic stage. Early treatment could increase the likelihood of SVR and prevent injuries to the graft that would be harmful to the long-term outcome.

The optimum timing of treatment has not been well studied. An interim analysis of the multicentre prospective SOFOLT study[25] aimed to show the feasibility of treating patients pre-emptively. 20 patients received sofosbuvir plus ribavirin on the same day as liver transplantation and for the following 24 weeks. All patients showed a response at the end of treatment; however, a potential limiting factor is that postoperative complications could delay the start of treatment.

The relevance of including ribavirin has been questioned due to findings in a real-life cohort assessed in an ancillary study of the CO23 ANRS CUPILT study,[26] where results were similar with and without ribavirin. 100 patients treated with ribavirin were matched for fibrosis stage, genotype, viral load, and duration of treatment with 100 patients treated without ribavirin. SVR12 was achieved in 93% of patients treated with ribavirin and 97% of patients treated without ribavirin (p=0·22). However, this study, included small numbers of patients with cirrhosis and infection with HCV genotype 3.

Finally, 12 weeks and 24 weeks of treatment have yielded excellent results separately, but the two treatment durations have not been directly compared. However, deciding treatment duration in liver transplant recipients similarly to that in non-transplant patients—ie, according to fibrosis stage and genotype—seems to be sensible.

Treatment before transplantation

Treating patients with HCV infection and cirrhosis is more challenging than treating those without cirrhosis. Although efficacy seems similar in patients with compensated cirrhosis and without cirrhosis, this factor remains an important predictor of treatment response. Most studies show poorer results in patients with decompensated cirrhosis, with SVR usually achieved in less than 90% of patients with Child-Pugh class C disease.

Few data are available for treatment in patients on the waiting list for liver transplantation or with decompensated cirrhosis. Efficacy of direct-acting antivirals was investigated in an open-label phase 2 study of patients waiting for liver transplantation. 61 patients with hepatocellular carcinoma and well compensated cirrhosis (Child-Pugh score ≤7 and Model for End-Stage Liver Disease [MELD] score <15) were treated with sofosbuvir and ribavirin. 30 (70%) of the 46 patients who underwent liver transplantation during the study achieved SVR12.[27]