Hepatitis C and liver transplantation in direct acting antiviral era

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Abstract: Chronic hepatitis C virus (HCV) infection remains a principle causative factor for cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation world-wide. The inevitable HCV recurrence of the engrafted liver was associated with the worst post-liver transplant survival outcome as compared to other etiologies in the interferon era. The inception of direct acting antiviral agents (DAAs) has changed the paradigm of HCV management in the liver transplant setting. These highly effective agents can cure HCV infection even in advanced cirrhosis with adequate safety. The future appears promising for HCV with expected decline in hepatic decompensation and incidence of HCC, but a significant proportion of patient with cirrhosis will remain at risk for HCC despite HCV cure. Use of DAAs has not affected the global transplant activity due persistent gap between the donors and the potential recipients. Curing HCV may improve the liver transplant outcome by controlling the co-morbidities like diabetes and chronic kidney disease in patients transplanted for HCV.

Keywords: Direct acting antivirals (DAAs); liver transplantation; hepatitis C virus (HCV); efficacy; hepatitis C recurrence

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Introduction

The emergence of direct acting antivirals (DAAs) has revolutionized the paradigm for the treatment of hepatitis C virus (HCV) in the current era. HCV related liver cirrhosis and hepatocellular cancer has historically been the most common indication for liver transplant world-wide since last two decades (1). Similarly, recurrent infection of the allograft following liver transplantation was inevitable and associated with considerable morbidity and mortality due to accelerated fibrosis in the presence of immunosuppressive therapy leading to cirrhosis in 30% of patients by 5 years of liver transplantation (2).

Currently, the highly potent and effective new DAAs can now cure HCV infection in virtually all cases safely, regardless of the disease severity. Therefore, a large proportion of patients have, within a short time period, received treatment including those with advanced fibrosis with an associated anticipation of an eventual decline in the HCV burden on liver transplantation. Unfortunately, one hepaticologic epidemic follows another and more recently, both in North America and Europe non-alcoholic steatohepatitis has evolved as a leading cause of end stage liver disease and hepatocellular cancer and surpassed HCV infection among patients listed for liver transplant (3,4). Although, viral hepatitis related cirrhosis and hepatocellular carcinoma (HCC) still remain a major indication for liver transplantation in Asia there is an epidemiological world-wide trend of obesity and fatty liver disease such that liver transplantation will always remain relevant (5). This review will focus HCV infection with the context of DAAs on liver transplantation.

HCV infection in liver transplant recipients

The current approach to minimize the risk of allograft re-infection and graft loss is either to achieve a sustained
virological response (SVR) prior to liver transplant or on-treatment aviremia at the time of transplant. However, these strategies were inconceivable only until few years ago, due to poor efficacy and tolerability of interferon based therapy with SVR of around 30% especially for those with advanced disease on liver transplant wait list (6). In 2011, the first generation protease inhibitors (telaprevir and boceprevir) were approved and triple therapy became the standard of treatment for HCV genotype 1 infection and raised the viral eradication rate up to 70% (7) in advanced liver disease and 60% in liver transplant recipients but at the cost of significant side effects, drug-drug interactions, and even mortality (8-10). These agents are no longer recommended after the recent approval of new highly active interferon-free HCV agents.

With the second wave DAAs, the horizon of HCV treatment was completely revolutionized with all-oral regimens associated with higher efficacy, shorter therapy, and excellent safety profile. These excellent results were consistent both in clinical trials and real-world cohorts treating cirrhotic patients as well as in post liver transplant HCV recurrence.

The initial experience with sofosbuvir and ribavirin in a phase 2 study of waitlist patients appeared effective, with the majority maintaining viral clearance after 12 weeks post-liver transplantation (11). A SVR rate of 86–89% was achieved in SOLAR-1 trial involving NS5A inhibitor ledipasvir in combination with sofosbuvir and ribavirin for patients with genotype 1 and 4 HCV cirrhosis with severe hepatic impairment (12). Moreover, SOLAR-2 and ALLY-1 studies, involving ledipasvir or daclatasvir with sofosbuvir and ribavirin in patients with advanced liver disease pre liver transplantation and HCV recurrence post transplantation demonstrated high SVR rates in Child class A and B but a suboptimal response was seen in Child class C (SVR, 56%) (13,14). Treatment of decompensated cirrhosis remained challenging even in the DAA era with the SVR rarely reaching 90% or above but newer combinations therapy can improve this outcome. The sofosbuvir and velpatasvir combination in decompensated cirrhotic genotype 1 patients attained a SVR in 88% when treated for 12 weeks, 96% when ribavirin was added and 92% for extended treatment of 24 weeks (15). Therefore, a ribavirin-based regimen is likely to improve SVR rates provided that the patients can tolerate ribavirin, and if not, treatment prolongation to 24 weeks appears promising.

Considering, these new DAAs are highly effective and potent, great enthusiasm has been seen across the globe in treating HCV infection even with advanced liver disease with the anticipation of an overall reduction in liver cirrhosis related complications and subsequent decline in need for liver transplant, as well as to avoid HCV recurrence post liver transplantation. Studies have shown that majority of these patients do achieve clinical and biochemical improvement, but the difference is modest and may not reach the point where a liver transplant is avoidable. A short-term follow-up (6 months) data showed a mean improvement of MELD score of −0.86, which may not be very clinically significant (16). On the other hand a subset of patients continues to deteriorate despite of virologic clearance indicating that the cirrhosis was already too advanced to improve. Therefore, clinicians need to be cautious in treating patients with more severe disease, as HCV eradication is not always associated with clinical improvement and patients may still continue to decline.

There are no standardized criteria for patients to be removed from the wait list. Data from longer follow up is required to appropriately select patients benefiting most with DAAs in terms of clinical outcome and removal from the wait list. The best predictor of improvement still appears to be a baseline Child-Pugh class. Patients in whom the liver transplant remains indicated due to an anticipated inadequate clinical benefit of SVR may be ill served with the current organ allocation system. It may be more appropriate to treat such patients following liver transplantation.

**Treatment of HCV after transplantation**

Over the last 2 years, the use of interferon free DAAs has changed the outlook of HCV management in the post-transplant setting. These agents can eradicate HCV infection and normalize graft function in nearly all the patients and will ultimately be associated with improved graft and patient survival. The majority of the DAAs are approved in post liver transplant recipients however, concern remains regarding the potential for interaction between DAAs and immunosuppressive medications.

Sofosbuvir and ribavirin combination was the first all-oral regimen used in these patients with an SVR rate of 70%, despite the suboptimal response none of the patients were primary non-responder or with virologic breakthrough during treatment (17). The combination of paritaprevir, ritonavir, ombitasvir, and dasabuvir plus ribavirin for 24 weeks appeared to be extremely potent with the SVR of 97% in HCV genotype 1 patients with mild to moderate graft fibrosis (n=34). Similarly, the ALLY-1 phase 3 study (14)
with sofosbuvir, daclatasvir and ribavirin and SOLAR studies involving sofosbuvir, ledipasvir with ribavirin for 12 or 24 weeks reported a high SVR rate of 96–98% in the post-transplant population (12,18). The safety and efficacy of DAAs were also assessed in several observational and real-world cohorts. In the HCV-TARGET cohort, 151 genotype 1 post-liver transplant recipients received sofosbuvir and simeprevir with or without ribavirin and 88% of them achieved SVR12 (19). In another multicentre study from Canada that studied the efficacy of sofosbuvir based regimens in a difficult to treat cohort of 120 liver transplant recipients; 85% achieved SVR; of the 53 patient with advanced fibrosis 81% achieved SVR (20,21). The largest French observational real-life cohort (CO23 ANRS CUPILT) (22) of liver transplant recipients, with a current enrollment of 699 individuals, was published recently, with results from 137 patients treated with combination therapy of sofosbuvir and daclatasvir with or without ribavirin. High SVR12 rates (96%) were seen regardless of treatment duration (12 vs. 24 weeks), or ribavirin use.

Sofosbuvir based treatment was also assessed in transplant recipients with fibrosing cholestatic hepatitis, an aggressive form of HCV recurrence formerly associated with an extremely poor prognosis, in a compassionate use program. This treatment appeared highly effective with clinical and biochemical improvement in 57% of patients (16).

In short, with the current landscape of highly potent DAAs, recurrent HCV infection leading to graft dysfunction should no longer be an indication for re-transplantation. Viral eradication after liver transplant has successful treatment response, comparable to those in a non-transplant setting.

Remainder issues of DAAs

The optimum time to initiate antiviral therapy post liver transplant, treatment duration and usefulness of ribavirin remain important issues. Although, data is lacking for the optimal timing for the treatment, it seems logical to consider early treatment, not only increase the likelihood of SVR in a less fibrotic transplanted liver but also to improve the long-term outcome of the graft (i.e., avoid graft cirrhosis). An interim analysis of the multicentre SOFLT study focused on the utility of pre-emptive antiviral therapy with sofosbuvir and ribavirin combination starting from the day of liver transplantation for 24 weeks (23). All the patients cleared the virus only after 4th week of liver transplantation, though longer follow up would determine the viral kinetics and sustained response.

Clinical trials have shown the impact of treatment duration on the virologic outcome although the two (12 and 24 weeks) treatment durations have not really been compared directly. Clinicians usually consider fibrosis stage, genotype and addition of ribavirin before deciding the treatment duration similarly to that in non-transplant setting.

The effectiveness of adding ribavirin with DAAs has been questioned repeatedly. A recent meta-analysis involving 994 patients demonstrated no difference between the SVR12 among ledipasvir plus sofosbuvir with ribavirin and ledipasvir plus sofosbuvir for recurrent HCV infection; SVR12: 95.1% and 94.9% respectively (24).

Moreover, despite obtaining HCV cure by DAAs, these agents have so far been unable to modify the natural history of HCC in patients with cirrhosis; rather some studies have shown higher risk of developing either new or recurrent HCC (25-27). Therefore, post-transplant perseverance with vigilant screening for HCC is mandatory even after achieving HCV viral eradication.

Impact of DAAs on co-morbidities in liver transplant recipients

Chronic kidney disease and type 2 diabetes mellitus are common complications of liver transplantation and both of these conditions are strongly linked with HCV infection in both transplanted and non-transplanted patients. A Canadian multicenter study group has demonstrated the beneficial effect of HCV eradication on the renal function in liver transplant recipients (28). Improvement in renal parameters after antiviral therapy was seen in 58% of patients more commonly in those who achieved SVR, compared to those who did not (81% vs. 19%, P<0.05). Moreover, an improvement of renal function was seen in a cohort of HCV infected patients with chronic kidney disease not specifically thought to be secondary to HCV, after viral eradication with DAAs (29,30).

Studies have demonstrated that SVR is not only associated with decline in HOMA-IR in patients (31) with diabetes but also decrease the development of new onset diabetes in chronic HCV patients after controlling the metabolic syndrome (32). Thus, it is reasonable to assume that with DAAs and subsequent HCV cure after liver transplantation the cumulative incidence of chronic kidney disease and diabetes will be decreased, this will help improve outcome after transplantation; though more long-term data are needed.
So far, DAAs have not influenced the transplant volume; as the gap between the available donors and the recipients is almost double. Organs from HCV antibody positive/NAT negative individuals have not been generally offered for donation to non HCV recipients due to risk of disease transmission. Given the availability of safe and highly effective antiviral therapies, use of such organs could be considered to expand the donor pool. A recent report demonstrated the yield of 4 weeks of sofosbuvir and ledipasvir in the immediate post-operative period with the SVR rate of 88% in a small cohort of viremic liver transplant recipients (33). This pre-emptive approach if adopted may increase the access to transplantation by utilizing the organs from donors with considerable risk of viral transmission.

In conclusion, DAAs have radically transformed the spectrum of HCV and will considerably reduce the need for liver transplantation in this subset of patients. The previously unmet efficacy and safety concerns are no longer of concern, as almost all of these agents are associated with the sustained virologic response of beyond 95%. Patients’ selection and timing of the antiviral treatment would still play a role in advanced liver disease. However, there is a need for developing a model that could predict what patients would benefit most from HCV treatment before liver transplantation, and presumably avoid a transplant altogether. In addition, the future use of DAAs may increase the possibility of utilizing HCV positive organs safely in non HCV recipients, thus filling a gap between the candidates and the number of available donors.

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Footnote
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References