Hepatitis C and liver transplantation in direct acting antiviral era

Nabiha Faisal

Department of Organ Transplantation and Hepatobiliary Sciences, King Abdul-Aziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia

Correspondence to: Nabiha Faisal, MD. Transplant Hepatologist, Department of Organ Transplantation and Hepatobiliary Sciences, King Abdul-Aziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia. Email: Nabiha.faisal@gmail.com.

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

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 hepatologic 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

Remaining 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.

Acknowledgements

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Eric M. Yoshida, Trana Hussaini) for the series "Liver Transplantation" published in *AME Medical Journal*. The article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.03.12). The series "Liver transplantation" was commissioned by the editorial office

without any funding or sponsorship. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: liver. Am J Transplant 2013;13 Suppl 1:73-102.

2. Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol 2013;58:1028-41.

3. Banini BA, Mota M, Behnke MM et al. Nonalcoholic Steatohepatitis Has Surpassed Hepatitis C as the Leading Etiology for Listing for Liver Transplant: Implications for NASH in Children and Young Adults. [Abstract #755]. Am J Gastroenterol 2016;111:S336-S400.

4. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547-55.

5. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol 2017;67:862-73.

6. Berenguer M. Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol 2008;49:274-87.

7. Hézode C, Dorival C, Zoulim F, et al. Safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in cirrhotic non responders. First results of the French early access program (ANRS CO20-CUPIC). J Hepatol 2012;56:S4.

8. Coilly A, Roche B, Botta-Fridlun D, et al. Efficacy and safety of protease inhibitors for several hepatitis C recurrence after liver transplantation: a first multicenter

experience. J Hepatol 2012;56:S21.

9. Pungpapong S, Aqel BA, Koning L, et al. Multicenter experience using telaprevir or boceprevir with peginterferon and ribavirin to treat hepatitis C genotype 1 after liver transplantation. Liver Transpl 2013;19:690-700.

10. Faisal N, Yoshida EM, Bilodeau M, et al. Protease inhibitor-based triple therapy is highly effective for hepatitis C recurrence after liver transplant: a multicenter experience. Ann Hepatol 2014;13:525-32.

11. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100-107.e1.

12. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology 2015;149:649-59.

13. Manns M, Forns X, Samuel D, et al. Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post liver transplantation patients with HCV infection: preliminary results of the prospective SOLAR 2 trial. J Hepatol 2015;62:S187-8.

14. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology 2016;63:1493-505.

15. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med 2015;373:2618-28.

16. Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224-31.

17. Charlton M, Gane E, Manns MP, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015;148:108-17.

18. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16:685-97.

19. Brown RS Jr, O'Leary JG, Reddy KR, et al. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: Real-world experience from the hepatitis C therapeutic registry and research network. Liver Transpl 2016;22:24-33.

20. Kwok RM, Ahn J, Schiano TD, et al. Sofosbuvir plus ledipasvir for recurrent hepatitis C in liver transplant recipients. Liver Transpl 2016;22:1536-1543.

21. Faisal N, Bilodeau M, Aljudaibi B, et al. Sofosbuvir-Based Antiviral Therapy Is Highly Effective In Recurrent Hepatitis C in Liver Transplant Recipients: Canadian Multicenter "Real-Life" Experience. Transplantation 2016;100:1059-65.

22. Coilly A, Fougerou-Leurent C, de Ledinghen V, et al. Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence - The ANRS CUPILT study. J Hepatol 2016;65:711-8.

23. Pasulo L, Di Benedetto C, Mazzarelli C, et al. Pre-emptive post-transplant HCV treatment with Ifn-free DAA: preliminary results from a pilot study. Transplantation 2016;48:e60.

24. Liao HT, Tan P, Huang JW, et al. Ledipasvir + Sofosbuvir for Liver Transplant Recipients With Recurrent Hepatitis C: A Systematic Review and Meta-analysis. Transplant Proc 2017;49:1855-1863.

25. Ravi S, Axley P, Jones D, et al. Unusually High Rates of Hepatocellular Carcinoma After Treatment With Direct-Acting Antiviral Therapy for Hepatitis C Related Cirrhosis. Gastroenterology 2017;152:911-2.

26. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719-726.

27. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727-733.

28. Faisal N, Renner EL, Bilodeau M, et al. Impact of sofosbuvir-based regimens on renal function in liver transplant recipients: Results of a multicentre study. Hepatology. 2015;62:84A.

29. Masetti C, De Leonardis F, Rossi P, et al. Treatment with direct-acting antiviral agents is associated with improvement of renal function in a cohort of hepatitis C virus infected patients with chronic kidney disease. J Hepatol 2017;66:S297.

30. Sise ME, Backman E, Ortiz GA, et al. Effect of Sofosbuvir-Based Hepatitis C Virus Therapy on Kidney Function in Patients with CKD. Clin J Am Soc Nephrol 2017;12:1615-23.

31. Chan CH, Hansen RD, Gilliver RS, et al. Sustained virological response following chronic hepatitis C treatment is associated with improvement in insulin resistance. Intern Med J 2013;43:656-62.

32. Pandya P, Pant C, Taylor R, et al. Impact of sustained virological response to chronic hepatitic C antiviral therapy on new onset diabetes mellitus type 2 after controlling for metabolic syndrome. J Investig Med 2017;65:765-71.

33. Levitsky J, Verna EC, O'Leary JG, et al. Perioperative Ledipasvir-Sofosbuvir for HCV in Liver-Transplant Recipients. N Engl J Med 2016;375:2106-8.