Potential Liver Transplant Recipients with Hepatitis C: Should They Be Treated Before or After Transplantation?

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Treatment of hepatitis C virus (HCV) with newer directly acting antivirals (DAAs) and lead to sustained viral response (SVR) in majority of patients and SVR has been documented to be associated with reversal of liver cirrhosis. The improved SVR rates and safety profiles of DAAs have led to the treatment of patients with decompensated cirrhosis awaiting liver transplantation (LT). Several clinical trials of DAAs in decompensated HCV patients have recently demonstrated SVR rates above 80%, which have been associated with significant improvements, in the Child–Pugh–Turcotte scores/or model for end-stage liver disease scores in a proportion of patients. Moreover, it has been shown that HCV RNA becomes negative after 2–4 weeks of treatment, and those who are transplanted after becoming HCV RNA negative will be have very low the risk of HCV recurrence after transplantation. Some of the patients may have reached the "point of no return" and may proceed to worsening of decomposition over time. To avoid the risk of worsening, there is an additional option of treating these patients after LT should they develop recurrent HCV infection. Currently there are no guidelines as to select patients who would benefit from treatment prior to LT as opposed to those who will be better off being treated after the transplant surgery. The article discusses a possible approach for such selection. (J Clin Exp Hepatol 2017;7:42–54)

Hepatitis C is a common cause of chronic liver disease globally, and its global prevalence has been estimated to be over 2%.[1–5] India, with one-fifth of world's population, is a major contributor to this global burden. Prevalence in India has been estimated to be between 0.5% and 1.5% of general population.[6] There are several hotspots in India such as Moga district in Punjab, where prevalence as high as 21% has been recorded in some areas. Similarly, some tribal populations in India have very high prevalence.[7–9] Hepatitis C virus (HCV) is possibly one of the commonest causes of liver cirrhosis (~28%) and hepatocellular carcinoma (~26%).[10] The burden of HCV is immense in low- and middle-income countries from South Asia (which includes India), East Asia, North Africa, the Middle East, and Southeast Asia, and contributes more than 80% of the global HCV burden.[11,12] India's 12–18 million HCV infected cases account for a major portion of global HCV due to her enormous population. When historical data from India was populated in a previously validated HCV disease burden model, it was estimated, with the current standard of care, advanced liver disease and liver-related mortality would rise further, despite decreasing prevalence. Recently a report from North India suggested that most patients with HCV infection in India present rather late in the natural history for treatment.[13] Of the 777 patients studied, cirrhosis was the presentation in 56% and 7% had presented with hepatocellular carcinoma. Of patients who had cirrhosis (including those with HCC), 36% were Child–Turcotte–Pugh (CTP) stage A; 51% were CTP stage B and 14% were CTP stage C. Since the study was done during the interferon era, the authors had lamented that they could offer treatment only to about 45% of those who were diagnosed to have HCV infection. Has the situation changed after introduction of directly acting antiviral drugs (DAAs), which permit interferon free regimens during last two years?

HCV related cirrhosis is the commonest etiology among those who are candidates for liver transplantation (LT).[14,15] In a study published from India, 372 liver transplant recipients were analyzed and it was noted that 31% of them had hepatitis C as etiology while additional 1.6% had co-infection of hepatitis B and C.[16] Data from our center

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Abbreviations: CTP: Child–Turcotte–Pugh staging; CSA: cyclosporine A; DAA: directly acting antivirals; DCV: daclatasvir; DDLT: deceased donor liver transplant; DSB: dasabuvir; EBV: elbasvir; FCH: fibrosing cholestatic hepatitis; GT: genotype; GRZ: grazoprevir; HCV: hepatitis C virus; IU: international units; LDLT: living donor liver transplant; LDV: ledipasvir; LT: liver transplantation; MELD: model for end-stage liver disease RNA; OMB: ombitasvir; Peg-IFN: pegylated interferon alfa; PTV: paritaprevir; RBV: ribavirin; rt: ritonavir; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained virological response, (SVR 12 signifies SVR at 12 weeks); TAC: tacrolimus; VLP: velpatasvir
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(January–August 2016) showed that HCV related disease was the commonest indication of LT (45%) during 2016.[17] Both these reports are from transplant centers and indicates that all such patients are offered LT without consideration for medical treatment for HCV. With interferon free regimens gradually replacing older toxic regimens[18,19] over last few years, what will be the ideal time to treat patients with decompensated cirrhosis-before or after transplantations? This question is relevant because of two main facts. Firstly, recurrent infections in graft after LTs are nearly universal.[20–22] At our center recurrence rate has been found to be about 85%. Secondly, recurrent hepatitis C after LT often follows a more sinister course.[23,24] Liver cirrhosis has been reported in 20–40% of the patients within 3–5 years, leading to significant graft loss and even death. In addition, fibrosing cholestatic hepatitis (FCH) has been recorded leading to graft loss in <1 year in 2–5%. Avoiding these complications should be a priority if it is possible. Treatment for HCV infection can be offered at many stages in these patients and they are summarized in Figure 1. Pretransplant treatment (marked as A in Figure 1) can be offered to patients who are considered for being listed for deceased donor liver transplantation (DDLT) (marked as 1 in Figure 1), those awaiting DDLT (marked as 2 in Figure 1), those who report to living donor liver transplantation (LDLT) centers (marked as 3 in Figure 1) and those who are found ineligible for transplantation or can not afford LDLT (marked as 4 in Figure 1). This group of patients will hope that the treatment would lead to improvement so that transplantation can be avoided. Post-transplant treatment (B in Figure 1) can be offered to patients who have received either DDLT (5 in Figure 1) or LDLT (6 in Figure 1). There will be different factors that will need to be considered in setting of LDLT as compared to that of DDLT.

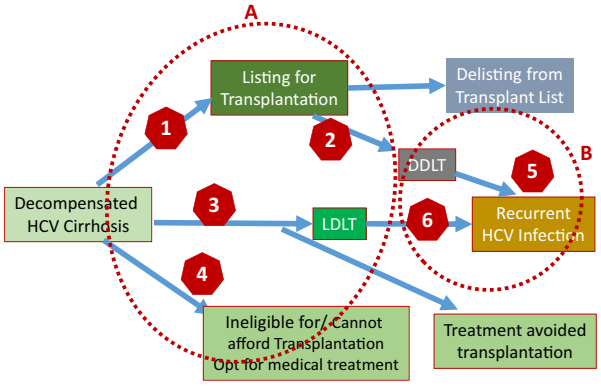

Figure 1 Options for timing of treatment. Decompensated patients with HCV cirrhosis will either be listed for DDLT, or will reach a center where LDLT is available, or opt for conservative treatment. Majority of those who undergo transplantation will develop graft reinfection. Possible timing of medical treatment for HCV infection has be marked 1–6 in the sketch (see text for details). They are broadly grouped in two main categories: (A) pretransplant setting or (B) post-transplant settings.

TREATMENT BEFORE TRANSPLANTATION

Historical data clearly shows that if patients achieve sustained viral response (SVR), they benefit. An elegant study involving five large tertiary care Hospitals in Canada and Europe, wherein 530 patients with chronic hepatitis C with advanced fibrosis/cirrhosis were treated between 1990 and 2003 and followed up to 2011 had shown interesting results.[25] There were 192 patients (36%) who achieved SVR; in time-dependent multivariate Cox regression analysis, SVR was associated with reduced risk of all-cause mortality (hazard ratio [HR], 0.26) and reduced risk of liver-related mortality or transplantation (HR, 0.06). The 10-year cumulative incidence rate of liver-related mortality or transplantation was 1.9% with SVR and 27.4% without SVR (*P* 0.001). There were 7 patients with SVR and 76 without SVR who developed HCC (10-year cumulative incidence rate, 5.1% vs 21.8%; *P* 0.001), and 4 patients with SVR and 111 without SVR experienced liver failure (10-year cumulative incidence rate, 2.1%, vs 29.9%; *P* 0.001). They had concluded that among patients with chronic HCV infection and advanced hepatic fibrosis, sustained virological response to interferon-based treatment was associated with lower all-cause mortality. There have also been reports of SVR leading to reversal of liver cirrhosis.[26] The problem with this form of treatment was that only 36% patients had achieved SVR. All patients in this study were not decompensated, but they were in another study that showed similar results and an SVR after antiviral therapy is a positive prognostic factor.[27] Yet another more recent study showed similar results and concluded that approximate threefold reduction in all-cause mortality is seen in patients with HCV who are treated and achieve SVR compared to those without SVR.[28] Even regression of cirrhosis was demonstrated in some cases.[29]

The improved SVR rates and safety profiles of all oral DAA has led to the treatment of patients with decompensated cirrhosis awaiting LT.[30] Moreover, it has been shown that HCV RNA becomes negative after 2–4 weeks of treatment, and those who are transplanted after becoming HCV RNA negative will be have very low the risk of HCV recurrence after transplantation.[31] This treatment is generally well tolerated and there is no difference in the incidence of hospitalization, sepsis and death between treated and untreated cohorts. We have, however, yet to prove that benefits noted in interferon era can be reproduced in DAA era with better results.

The treatment of hepatitis C in decompensated cirrhotic population is primarily aimed at eradicating the circulating HCV (make the patient aviremic) and expect (a) consequent stabilization or improvement in liver function; (b) reduction in portal hypertension (c) prevent sequelae such as HCC; (d) if possible, reverse decompensation and (e) avoid LT. It goes without saying that above should be achieved safely without any added risk.[32]