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 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 been marked 1–6 in the sketch (see text for details). They are broadly grouped in two main categories: (A) pre-transplant 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 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

Feasibility and Effectiveness

There are several studies that have showed that it is feasible to treat patients with cirrhosis of liver, with better results than were possible in interferon era.^{33–36} Many of these trials included patients awaiting LT,^{31,37} and those with decompensated cirrhosis of liver.^{31,38,39} There are several controlled trials with interesting acronyms such as ALLY-1, SOLAR-1, SOLAR-2, SATURN and CORAL-1, which have shown that it is now feasible to treat patients with decompensated cirrhosis (Table 1).^{31–53}

In addition, there have been several real world data studies which have given similar conclusions.^{47–53} Earlier experience had shown that pegylated interferon (Peg-IFN) and ribavirin (RBV) based treatment regimen failed to achieve desired aims due to poor tolerability and limited efficacy in this unique patient population. Firstly, SVR rates hovered around 25% even when using a low accelerating dose Interferon regimen,⁵⁴ and not all patients could be offered treatment. Only those with CTP score less than 7 could be offered therapy, as patients with more severe liver disease would lead to serious adverse events such as bacterial infections, cytopenias, and worsening decompensation. The tolerability of DAA based regimens is definitely better with exception of those who have impaired renal function.⁵⁵

Most of the studies shown in Table 1 have shown good results. What is not shown in the table is that there is also an improvement in liver function and reversal of decompensation to some extent as more and more patients become aviremic. Afdhal (2015)⁵⁶ was first to show that 48 weeks' treatment with sofosbuvir (SOF) + RBV in decompensated cirrhosis patients resulted in SVR12 rate of 72% and led to significant improvement in ascites, encephalopathy, CTP, and model for end-stage liver disease (MELD) scores in the majority. Most of his patients however were those with early disease (CTP stages A and B) and there were no CTP C patients in this trial.

SOLAR-1 and SOLAR-2 trials^{36,41} carried out in US and Europe, respectively have assessed the efficacy of ledipasvir (LDV) + SOF in genotype (GT)-1 or 4 related decompensated HCV cirrhosis patients given prior to LT. In the SOLAR-1 trial, 108 patients with HCV-related decompensated cirrhosis (59 CTP-B, 49 CTP-C) were randomized to receive 12 or 24 weeks of SOF/LDV/RBV. SVR12 was achieved in 86–89% and efficacy of treatment was similar in CTP B and C patients irrespective of the duration of therapy. MELD as well as CTP scores were shown to improve in the majority of the patients, while bilirubin and albumin levels improved significantly in CTP B but not in CTP C patients. Several patients showed better control of ascites and improvement in grade of hepatic encephalopathy. There was also a report of a patient who was delisted from transplant list. MELD score in most of these patients was less than 20. SOLAR-2 study also included 108 patients with decompensated cirrhosis

awaiting liver transplant. Here again, the results were similar with SVR12 rates were 87% in the 12-week treatment group and 89% in the 24-week treatment group.

More recent open-label ALLY-1 study⁴² also studied compensated and decompensated cirrhosis patients and reported good results in the 60 decompensated cirrhosis patients (GT-1, 2, 3 and 4 had SVR rates: 82%, 80%, 83%, and 100%, respectively) when treated with a combination of SOF, daclatasvir (DCV) and RBV for 12 weeks. SVR12 rates were higher in patients with CTP class A or B (93%) versus class C (56%). As in most trials studying decompensated cirrhotics, the initial dose of RBV was 600 mg/day, and this was gradually escalated up to 1000 mg/day based on creatinine clearance values, as well as the hemoglobin values.

Astral-4⁴³ study included 267 patients of decompensated cirrhosis with mixed GT 1–4. Overall rates of sustained virologic response were 83% among patients who received 12 weeks of SOF-velpatasvir (VLP), 94% among those who received 12 weeks of SOF-VEL + RBV, and 86% among those who received 24 weeks of SOF-VEL.

From the real world data, experience from NHS England Expanded Access Program^{48,57} showed somewhat similar results. In this study treatment was as per physician's choice and consisted of SOF in combination with either LDV or DCV with or without RBV and 467 patients with decompensated cirrhosis (CTP score 7 or more) were analyzed. SVR 12 could be achieved in 91% of GT-1 patients and in 69% of GT-3 patients. Addition of RBV to the regimen led to slight improvement in the SVR 12 rates. A multivariate analysis was done to determine baseline factors that could predict virologic failure and it showed GT-3, BMI > 30 kg/m², and detectable HCV RNA at week 2 of therapy were associated with poor response.

French early access program (EAP),⁴⁷ treated patients on transplant list with SOF and DCV, with or without RBV, for 12 or 24 weeks. SVR rate ranged from 95% to 100%. Extending treatment to 24 weeks and use of RBV were both significantly associated with higher SVR, whereas cirrhosis emerged as the main predictor for treatment failure. Similarly, a retrospective Australian Compassionate Use Program (TOSCAR Study)⁵⁸ used SOF + DCV (without RBV) for 24 weeks in 92 patients with decompensated cirrhosis (MELD ≥ 15). In this study, hepatic functions improvement with therapy was limited to those with baseline MELD scores <20. European compassionate use program showed similar findings.⁵⁹

Prevention of Post-Transplant Recurrence of Hepatitis C Virus

An earlier paper by Curry et al.³¹ had demonstrated that SOF + RBV given before LT resulted in good post-transplant virologic response (PTVR) and prevented HCV recurrence. In their study of 61 patients with HCV-cirrhosis and

Table 1 Some Important Studies on Treatment of HCV Infection in Decompensated Cirrhosis and in Recurrent HCV Infection After LT.

Study name	Patient population	Genotype (GT)	Numbers	Drugs used	SVR rates pre-transplant	SVR rates post-transplant
Curry et al. (2015) ³¹	Awaiting LT	72% GT-1	61	SOF + RBV	93% RNA negative by time of transplantation	70% of these had SVR after transplantation
SOLAR-1 (US) ³⁶	Decompensated cirrhosis	1 and 4	108	SOF + LDV + RBV	CTP stage B: 86% (12 week)/89% (24 week); CTP stage C: 86% (12 week), 90% (24 week)	96–98% (without cirrhosis or with compensated cirrhosis), 85–88% (moderate hepatic impairment), 60–75% (severe hepatic impairment), and all 6 patients with FCH
SOLAR-2 (Europe) ⁴¹	Decompensated cirrhosis	1 and 4	108	SOF + LDV + RBV	CTP stage B: 87% (12 week)/96% (24 week); CTP stage C: 85% (12 week), 78% (24 week)	CTP stage B: 95% (12 week)/100% (24 week); CTP stage C: 50% (12 week), 80% (24 week)
ALLY-1 ⁴²	Compensated/decompensated cirrhosis	GT-1 to 4	60/53	DCV + SOF + RBV	CTP stage A/B: 93%; CTP stage C: 56%	GT-1: 95%; GT-3: 91%
ASTRAL-4 ⁴³	Decompensated cirrhosis	All GTs	267	SOF + VLP with/without RBV	83% (12 weeks without RBV), 94% (12 weeks with RBV) and 86% (24 weeks without RBV)	–
SATURN ⁴⁴	Post-transplant recurrent HCV	All except 3	21 (METAVIR: F1-F2) and 14 (METAVIR: F3-F4)	SMV + DCV + RBV	–	90–93%
CORAL-1 ⁴⁵	Post-transplant recurrent HCV	GT-1 to 4	34	3D (PTV/rt + OMB + DSB) + RBV	–	97%
HCV-TARGET ⁴⁶	Decompensated cirrhosis	GT-1 to 4	170	SOF + LDV ± RBV	87.9	–
French ATU study ⁴⁷	Before and after transplantation	All except 3	147	DCV + SOF ± RBV	95–100%	–
UK EAP Study ⁴⁸	Decompensated cirrhosis	GT-1 and 3	467	By clinician's choice: SOF + LDV/DCV + RBV	GT-1: 60–86%; GT-3: 43–71%	–
EU CUP Trial ⁴⁹	Advanced liver disease/decompensated cirrhosis	GT-1 and 3	485/196	DCV + SOF ± RBV	CTP stage B/C: 85–88%	–
French CUP ⁵⁰	Compensated and decompensated cirrhosis	GT-3	196	DCV + SOF ± RBV for 12/24 weeks	CTP stage B/C: 33–71%	–
Spanish study ⁵¹	Decompensated cirrhosis	GT-1	739	SOF + SMV (45%), SOF + DCV (22%), and LDV/SOF (16%)	94%	–
Saxena et al. (2015) ³⁹	Compensated and decompensated cirrhosis	GT-1	160	SOF + SMV ± RBV	CTP stage B/C: 73%	–
Aqel et al. (2015) ⁵²	Compensated and decompensated cirrhosis	GT-1	119	SOF + SMV ± RBV	CTP stage B/C: 68%	–
Anand et al. (2017) ⁵³	Post-transplant recurrent HCV	GT-3 and 1	63	SOF + RBV for 24 weeks	–	93.7% (GT-1: 92.3%; GT-3: 95.9%)

Note: CTP: Child–Turcotte–Pugh; CUP: compassionate use program; DCV: daclatasvir; DSB: dasabuvir; EAP: early access program; FCH: fibrosing cholestatic hepatitis; GT: genotype; LDV: ledipasvir; LT: liver transplantation; PTV/rt + OMB: paritaprevir/ritonavir + ombitasvir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained virological response; VLP: Velpatasvir.

HCC, (mostly GT-1 or 4), patients were treated with SOF + RBV for varying periods up to 48 weeks before LT. Most (75%) of the patients were CTP grade A and in all cases MELD score was <15. HCV RNA had become undetectable at the time of transplantation in 90% and remained undetectable at 12 weeks after LT (PTVR 12) in 70% of all cases suggesting an absence of hepatitis C recurrence. HCV recurrence was inversely related to period for which HCV RNA had remained undetectable before LT. There was nearly universal (95%) chance of achieving PTVR12 in patients in whom HCV RNA had been undetectable for over 30 days before the transplantation.

Improvement in Portal Hypertension

Evidence for the improvement of portal hypertension is not yet robust. There are two trials that have addressed this issue. First study⁵⁶ had enrolled 50 patients with baseline hepatic venous pressure gradient (HVPG) >6 mm of Hg and were treated with SOF + RBV for 48 weeks. 66% of the patients had HVPG levels more than 12 mmHg at baseline. The study showed that 24% of these patients had a fall in HVPG to the extent exceeding 20%, and in half of them the HVPG had dropped to a value of <12 mmHg. The second study⁶⁰ enrolled 56 patients with cirrhosis in whom HVPG was measured before starting treatment with SOF + RBV or DCV and simeprevir (SMV) for 12–24 weeks. Majority (73%) of these patients had a baseline HVPG >10 mm of Hg. However, post-treatment indirect markers of HVPG levels were reported; and reported an improvement in liver stiffness and platelet counts as surrogate markers for improvement in portal pressure. There have been report of regression of advanced F4 fibrosis (including histological cirrhosis) HCV infection after achievement of SVR. However, it is unclear if cirrhosis with distortion of microvasculature and marked portal hypertension can reverse.⁶¹

Delisting from Transplant List

DAA treatment can lead to improvement in decompensated HCV cirrhosis to an extent that one is delisted from transplant list but it is not clear if he can improve to an extent that he may not need transplantation at all. Data on delisting from the LT list are scarce but accumulating.⁶² Initial report was from France that described a patient with MELD score 16, refractory ascites, encephalopathy who was listed for transplantation in October 2013. Patient was treated with SOF + RBV in December 2013 and was given for 24 weeks. Follow-up till September 2014 showed that her MELD score had dropped to 12 and she was delisted from transplantation. In another subsequent study⁶³ wherein 103 consecutive listed patients without hepatocellular carcinoma were treated with different DAA combinations in 11 European centers between February 2014 and February 2015. The cumulative incidence of inactivated and delisted patients was respectively 15.5% and 0% at 24 weeks, 27.6% and 10.3% at 48 weeks, 33.3% and 19.2%

at 60 weeks. Thirty-four patients who were inactivated showed a median improvement of 3.4 points for MELD (delta MELD, $P < 0.0001$) and 2 points for CTP score (delta-CP, $P < 0.0001$). A multivariate competing risk model as predictors of inactivation showed three significant variables which were baseline MELD classes (MELD 16–20: HR = 0.120; $P = 0.0005$, MELD >20: HR = 0.042; $P < 0.0001$), delta MELD (HR = 1.349; $P < 0.0001$) and delta albumin (HR = 0.307; $P = 0.0069$) both assessed after 12 weeks of DAA therapy. The authors of this study concluded that all oral DAAs were able to reverse liver dysfunction and favored the inactivation and delisting of about one patient out-of-three and one patient out-of-five in 60 weeks, respectively. Patients with lower MELD scores had higher chances to be delisted. The longer term benefits of therapy still needed to be ascertained. Curry's recent editorial⁶⁴ stating that 'DAA for decompensated cirrhosis: Efficacy and safety are now established' was accompanied by a very tantalizing graphic on the cover of journal issue which depicted a very sick patient getting up and walking away, possibly from transplant list!

Safety/Adverse Effects

Safety of DAAs in treatment of decompensated cirrhosis has been a matter of concern, but to a lesser extent as compared to interferon based regimens. Worsening of hepatic decompensation remains a major risk and we do not as yet have reliable pre-treatment predictors to identify such patients. Overall, one can expect serious adverse events requiring hospitalization and hepatic decompensation events in about 20% patients, discontinuation of treatment in about 10% cases and deaths on treatment in 0–4% cases. Some studies have reported unusually high mortality. For example Irish EAP study [by Irish Hepatitis C Outcomes and Research Network (ICORN)] mentioned 6% mortality in CTP stage B cases and 16% mortality in CTP stage C cases among 101 patients who were treated with SOF, LDV and RBV.⁶⁵

Thirteen patients in the SOLAR-1 trial³⁶ (6 in the pre-LT cohort) and 17 in SOLAR-2⁴¹ (5 in pre-LT cohort) died, primarily due to worsening of hepatic decompensation, sepsis, and multi-organ dysfunction syndrome (MODS). In addition, the SOLAR-1 and 2 trials, the most common grade 3/4 adverse effects seen in the decompensated patients were an increase in serum bilirubin and a decrease in lymphocyte count. In the SOLAR-1 trial, anemia was noted in 39% who dropped their hemoglobin values to less than 10 g/dl; in 13%, it dropped to below 8.5 g/dl. Blood transfusion or erythropoietin was used in 15% of the cases in this trial.

In the NHS EAP study,⁴⁸ 6% of the patients discontinued treatment due to adverse effects, while seven patients died. Adverse outcomes were more common in patients with a higher baseline MELD score, low serum albumin (<3.5 g/dl), higher age (>65 years), and low serum sodium values (<135 mEq/L). In fact it was suggested that patient with age above 65 years and/or serum albumin values less

than 3.5 g/dl one may expect more harm than benefit. In this study, anemia with hemoglobin value of <8 g/dl was seen in 5% of the cases. Acute kidney injury, (defined by an increase in serum creatinine by 1.5 times from baseline value) was seen in 3% cases. Two cases of significant hepatotoxicity related to treatment with SOF and NS5A inhibitors as part of the English early access program were recently reported.⁶⁶

Even in ASTRAL-4 cohort⁴³ serious adverse events occurred in 19% of patients who received 12 weeks of SOF + VLP, 16% of those who received 12 weeks of SOF + VLP plus RBV, and 18% of those who received 24 weeks of SOF + VLP. The most common adverse events were fatigue (29%), nausea (23%), and headache (22%) in all patients and anemia (31%) in the patients receiving RBV. In addition to these adverse effects, there are also reports of DAA induced hepatotoxicity. According to the core safety information for SOF, LDV and DCV no dose adjustment is required in those with hepatic impairment (irrespective of CTP score).^{67,68} However, few patients with decompensated cirrhosis have had treatment with DAAs, so the exact pharmacokinetics in this population have not been characterized.

Hepatocellular Carcinoma (HCC)

There have been increasing reports of development of HCC after viral clearance with DAA.⁶⁹⁻⁷⁵ For example, a recent Italian study has analyzed 344 consecutive cirrhotic patients, without HCC, who were treated with DAA, and followed for 24 weeks. Fifty-nine of these patients had previous HCC, while DAA therapy induced sustained virological response in 91% of patients. During 24-week follow-up, HCC was detected in 26 patients, which is much higher than expected rate of about 1-3%.⁷⁶ Of 59 patients with previous HCC, 17 (29%) developed recurrence of tumor. And, 285 patients without previous HCC 9 (3.16%) had developed de novo HCC. CTP stage B, more severe liver fibrosis, lower platelet count, and previous HCC were significantly associated with HCC development. At multivariate analysis, CTP stage (OR: 4.18) and history of HCC (OR: 12.0) were independently associated with HCC development. Among the 59 patients with previous HCC, younger age and more severe liver fibrosis were significantly associated with HCC recurrence, both at univariate and at multivariate analysis. The authors concluded that in patients with HCV-related cirrhosis, DAA-induced resolution of HCV infection does not seem to reduce occurrence of HCC. Patients previously treated for HCC have still a high risk of tumor recurrence, in the short term. This is different from result shown with Interferon based regimens, which have been mentioned above.²⁵ Limitations of these studies must be understood before accepting their results to condemn DAAs. Firstly all these have been observational studies and no randomized trials are available. Secondly, the HCC rates are variable in the studies published from Europe. Similar report from other

countries are lacking so far and new data from HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network; see hcvtarget.org)⁷⁷ may throw more light on this subject.

TREATMENT AFTER LIVER TRANSPLANTATION

Recurrent HCV infection is common after LT for HCV related cirrhosis and may be seen in over 80% such cases.^{20,78} It can lead to graft loss due to rapid development of cirrhosis in 20-40% patients or less often due to FCH in 2-5%. It is also a recognized cause of mortality in these patients.⁷⁹ Achievement of SVR with treatment could improve outcome significantly in these patients,⁸⁰ but use of interferon containing regimens was associated with significant morbidity.⁸¹ Therefore it was considered a difficult to treat group a few years back. Availability of DAAs has changed all that. Many of these drugs can now be safely given concomitantly with immunosuppressive agents (see Table 2)⁸² and have shown excellent response rates with interferon free regimens.

Thus, it is now possible to treat these patients in post-liver-transplant period.^{41,42,83} Successful therapy has been shown to have a positive impact on both graft and patient survival.⁸¹ Newer DAAs have simplified treatment of HCV of patients in peri-transplant period. Curry et al.'s report³¹ has already been referred to above, which showed that SOF + RBV given before liver transplant resulted in excellent PTVR and prevented HCV recurrence.

Feasibility of Treating Post-Transplant Recurrence of Hepatitis C Virus Infection

The key to use of DAAs in post-liver-transplant period lies in the risk of drug interactions with immunosuppressive agents, antimicrobials and other drugs that are required to be used in post-transplant period. SOF is rapidly absorbed and undergoes extensive first-pass hepatic metabolism. The predominant circulating metabolite, GS-331007, is formed by dephosphorylation of nucleotide metabolites, and accounts for approximately 78% of total systemic exposure and is principally excreted in urine.⁶⁸ RBV has extensive volume of distribution and is eliminated mainly through the kidneys.⁸⁵ There is increased risk of anemia in patients with cirrhosis due to associated hypersplenism, reduced output of erythropoietin, poorer bone marrow response, nutritional deficiencies and occult gastrointestinal blood loss. It is therefore, advisable to start with lower doses and gradually adjusted to weight based doses depending on hemoglobin and creatinine response.⁸⁶ All other DAAs are metabolized by the liver and thus their metabolism. A combination of SOF and DCV does not appear to change significantly in patients with moderate or severe liver impairment and therefore can be used in

Table 2 Precautions in Use of Directly Acting Antivirals Against HCV in Patients with Decompensated Cirrhosis and in Post-Transplant Situations When Patients Are on Immunosuppressive Agents.

Drugs	Decompensated cirrhosis: drug can be used in CTP stage class	Post-transplant use with calcineurin inhibitors
SOF	A, B and C	No dose adjustment required for tacrolimus or cyclosporine
LDV + SOF	A, B and C	No dose adjustment required for tacrolimus or cyclosporine
DCV	A, B and C	No dose adjustment required for tacrolimus or cyclosporine
RBV	A, B and C	No dose adjustment required for tacrolimus or cyclosporine
SMV	A only	SMV dose changes are not required with tacrolimus and mTOR inhibitors; use of SMV with cyclosporine is not recommended
PTV/rt + OMB	A only	Tacrolimus dose needs be adjusted to 0.5 mg once weekly or 0.2 mg every 3 days; cyclosporine dose needs to be reduced to 20% of the daily dose
VLP	A or B	Information inadequate
GRZ + EBV	A only	Tacrolimus dose needs to be reduced (AUC of tacrolimus 40% higher when used with GRZ + EBV); Use along with cyclosporine is not recommended

Modified from Ref. 82.

Note: AUC: area under curve (as in receiver operating characteristic analysis); CTP: Child–Pugh–Turcotte stage; DCV: daclatasvir; EBV: elbasvir; GT: genotype; GRZ: grazoprevir; LDV: ledipasvir; mTOR: mechanistic target of rapamycin; PTV/rt + OMB: paritaprevir/ritonavir + ombitasvir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; VLP: velpatasvir.

patients with decompensated cirrhosis without the need of dose adjustment.^{87,88} Paritaprevir (PTV)/ritonavir (rt)/ombitasvir (OMB) + dasabuvir (DSB) fixed dose combination with RBV appears to be safe in patients in cirrhosis, but should be avoided in decompensated patients due to the risk of developing further hepatic impairment. SMV as well as fixed-dose combination of grazoprevir (GRZ)/elbasvir (EBV) is not recommended in CTP stage B and C cirrhosis.^{89,90}

When earlier generation DAAs such as boceprevir and telaprevir were used, there was genuine concern for drug interactions with immunosuppressive agents used after LT.⁹¹ With currently used DAAs such as SOF, LDV and DCV, there is no need to adjust the dose of tacrolimus (TAC) or cyclosporine A (CSA) when given simultaneously.^{88,92} However, same rule does not apply to all DAAs. SMV when given along with calcineurin inhibitors does not significantly affect the levels of the latter, but results in a rise in plasma concentrations of SMV (approximately 200% with TAC and 600% with CSA), therefore this combination is not recommended.⁹⁰ When GRZ/EBV are used with TAC, the combination leads to approximately 40% increase in TAC levels, necessitating frequent monitoring of TAC levels. When used along with CSA, GRZ/EBV levels may rise up to 15 times and hence this combination is also not recommended to be used.⁹³ Wherever rt boost is required in DAA regimens, the dose of calcineurin inhibitors will need to be adjusted as per levels, as rt is a strong CYP3A inhibitor.

Safety and Efficacy

There is ample data now to show that newer DAAs are safe as well as effective when used after liver LT. The important

paper on the subject have already been summarized in Table 1 above and will be briefly mentioned here.

Initial report by Charlton et al.³⁶ showed that SOF + RBV combination therapy for 24 weeks is an effective and well-tolerated interferon-free regimen for post-transplantation HCV infection. In their study of 40 post-liver-transplant HCV infected patients, SVR was found to be 70%. A few other studies have also shown the beneficial effect of this regimen in post-liver-transplant patients.^{81,94} CORAL-1 trial studied OMB/PTV + DSB in post-transplant recurrent HCV (GT-1) infection and showed 97% SVR rates.⁹² Another UCLA study using SOF + SMV also showed 93% SVR rates in patients treated for recurrent HCV infection after liver transplantation and confirmed the efficacy of DAAs in this setting.⁹⁵

Safety as well as efficacy of DAA was also clearly demonstrated in the post-liver-transplant limb of SOLAR trials.^{36,41} Predominantly GT-1 patients were treated with SOF + LDV + RBV. In the SOLAR-1 study, for 12 or 24 weeks, SVR12 was achieved in 95% patients with F0-3 fibrosis and 98% with CTP stage-A cirrhosis. FCH is an uncommon complication of post-liver-transplant HCV recurrence and may lead to death if untreated. SOLAR-1 (6 cases) and SOLAR-2 trials (5 cases), showed that FCH patients can also be successfully treated as well as any other HCV patients. These studies also did not record any drug-to-drug interaction with any of the immunosuppressive agents in these trial.

A study by Fontana et al.⁹⁶ demonstrated safety and efficacy of DCV + SOF in post-liver-transplant patients. A total of 97 cases after LT were treated with DCV + SOF (77 patients) and DCV + SMV (18 patients), and SOF + DCV + SMV (2 patients). RBV was also added for 35% of the patients. Most patients had HCV GT-1 infection. The

SVR12 rate was 87% overall while it was higher with DCV + SOF than with DCV + SMV (91% vs 72%; $P = 0.047$).

In recent open-label ALLY-1 study,⁴² 53 liver transplant recipients with recurrent HCV infection were treated with a combination of DCV + SOF + RBV. SVR12 was achieved in 50 out of 53 patients (94%). Even though CSA can increase DCV exposure with a 40% increase in AUC_{0–24}, this is not of much clinical consequence. Thus, the standard immunosuppression need not be changed when co-administered with DAAs. CORAL-1 trial results also confirm these findings.

Pre-Emptive or Reactive Treatment?

Now that DAAs have been found to be safe and effective for treatment of post-liver-transplant HCV recurrence, one question still remains unanswered. Should such patients be treated pre-emptively,^{97,98} even before the clinical or even molecular recurrence of HCV infection has been diagnosed? Or should one wait for a few months and start treatment only when recurrence has been diagnosed? Arguments in favor of pre-emptive treatment are: firstly, it has been found to be safe, unlike previously used interferon based treatment. Secondly, it is well tolerated, highly effective, increases graft survival and improves long-term survival. Thirdly, it can prevent development of fibrosis in the graft and can mitigate small risk of developing FCH. And lastly, the risk of drug–drug interactions is minimal to non-existent. Main argument for reactive treatment would be to avoid unnecessary drugs at a time when patient is recovering from a major surgery. Currently most hepatologists wait for about three months before checking HCV-RNA levels in patients who are doing well. This allows initial upheavals of transplant surgery to stabilize and also allows time for steroid dose to be brought down. Once a diagnosis of recurrence has been made, treatment can safely be instituted. The fact remains that patients with high viral load, GT 1 infection, females, older donor age, being treated for cytomegalovirus or for acute rejection, have a high risk for rapidly progressive recurrent hepatitis C.⁹⁹ Therefore it must be accepted that the most appropriate time for starting DAA treatment in post-transplant period has not yet been settled and additional innovative approaches may help us in arriving at such decision.

For example one report¹⁰⁰ has described the role of the expression of HLA variants and the interleukin 28B (IL28B) C/C GT (rs12979860) in the prediction of the outcome of LT in HCV-recipients after studying 449 patients with a median follow-up of 10 years. They showed that the graft survival in HLA-DRB1*11-positive recipients was significantly longer. Graft survival was much better if IL28B GT of both recipient and donor was C/C. On basis of this information, one may suggest that patients lacking both these markers should undergo antiviral therapy as soon as possible after transplantation whereas others

probably can wait until their clinical course has completely stabilized and recurrence has been detected.¹⁰¹

PROS AND CONS

How should one decide to treat a patient with decompensated cirrhosis of liver due to HCV infection—before or after transplantation? Pre-transplant treatment offers several theoretical advantages. Firstly, it offers a chance that native liver functions may improve to the extent that it may obviate the need for transplantation. It will save an organ and enhance the organ pool in DDLT setting. Secondly, it will prevent post-transplant recurrence of HCV infection in those who do not improve significantly. And finally, it may be the only option available in situations where LT is unavailable, contraindicated or out of reach. In the latter situation it may prevent emotional dilemmas as described elsewhere.¹⁰²

But there is a flip side too. Firstly, one must consider a definite risk of worsening of liver disease on DAA's as has been outlined above. Deaths have been recorded due to worsening liver decompensation in all the trials. Such worsening becomes more probable at higher MELD score. Secondly, SVR may preclude the patient from receiving anti-HCV-positive graft in DDLT setting and delay his chances of getting early transplantation. Thirdly, improvement in MELD may temporarily eliminate the opportunity to have curative treatment, i.e. LT. One may improve decompensation to some extent and be delisted from transplantation waiting list and thereby be condemned to live a poor quality of life. Such a patient may be placed in a situation where one's productivity or creativity is seriously hampered due to poor quality of health repeated hospitalizations. While the patient may have clinically improved he continues to be at risk of progressive liver disease and more important, the risk of developing hepatocellular carcinoma. There is some data to suggest that latter complication may even be more common after DAA treatment even if HCV infection has been eliminated. And final point is that those who failed therapy in decompensated stage, may have developed resistance associated variants and this exposure to NS5A inhibitors may compromise the patient's chances of developing SVR when he/she is retreated after LT.

There are additional points that need to be considered in special social situations. In South Asia, for example, where states are unable to provide the facilities of LT, patients are dependent on LDLT being offered in private hospitals. It is not unusual for patients to borrow huge amount of money (or sell all their farming land to gather enough funds), travel to long distances with a live donor to get benefits of LDLT in a private hospital. If such a person is offered medical treatment, which will cost less but does not rule out the possibility of needing transplant mid way

Figure 2 Strategy for selecting timing of HCV treatment in decompensated cirrhosis of liver. Please see text for references supporting decisions. Note: MELD: model for end-stage liver disease; DAAs: directly acting antivirals; HCV: hepatitis C virus infection; LT: liver transplantation; estimated mortality <2% in 12 weeks, estimated chance of delisting 49%; # estimated mortality 3–10% in 12 weeks, estimated chance of delisting 18.4%; @ estimated mortality >19% in 12 weeks, estimated chance of delisting 15.2%.

or at the end of treatment, he may be pushed to financial ruin. Such people keep pushing for transplantation in the first place, and it may not be unreasonable to consider them for anti-HCV treatment after the transplantation.

PREFERRED STRATEGY FOR SUBCONTINENT

On basis of currently available data, the strategy suggested for treatment of HCV infection in the peri-transplant period is outlined in Figure 2. It has been shown that patient with age above 65 years and serum albumin values below 3.5 gm/dl are likely to be harmed more and benefited less.⁵⁷ Somewhat similar results have been shown by other studies.^{103,104} However, it must be understood that factors that determine improvement after DAA treatment in decompensated cirrhosis have not been fully elucidated. Analysis of data from European Liver and Intestine Association Study⁶³ suggests that patient with MELD scores less than 16 had high chance (25/51; 49%) of improving and being delisted from liver transplant list. On an average MELD score less than 16, as per historical data, has a 12-week mortality less than 2%.⁹⁹ Therefore, this group of patients are ideal for being offered DAA treatment prior to transplantation. In the same study, it has been shown that patients who had MELD scores over 20, had much lower (2/13; 15.4%) chance of being delisted from transplant list and 12-week mortality in this group of patients as per historical data may be over 10–19%. Thus this is a group where chances of being harmed are more than being

benefitted and they should be recommended treatment after the LT. The subgroup in between these extremes, i.e. those with MELD score from 16–20, have 18.4% (7/38) chance of improving to an extent that they will be delisted from transplant list⁶³ and in this group of patients expected mortality would be 3–9%. This is the group where the pros and cons need to be discussed with the patient and family and decision made regarding DAA treatment of transplantation. It may be recalled that even in other studies mentioned above,^{31,59} improvement is mainly seen among those who have MELD score 15 or less and hardly anyone with MELD score >20 has shown significant improvement. This may signify a point of no return for liver decompensation as far as therapy for HCV is concerned and they will be better off receiving LT first and being treated later, rather than accept the risk of further worsening or that of HCC recurrence.^{106–108}

CONCLUSIONS

Several currently available DAA regimens for patients with decompensated cirrhosis are associated with high SVR rates and some patients with MELD scores lower than 16 may even be delisted from transplant rosters. They are also safe in majority of patients with MELD scores less than 20. At the same time, SVR rates of patients treated for early HCV recurrence after LT has also been impressive. It should also be understood that even with successful therapy for HCV in cirrhosis, the risk of progressive liver disease and hepatocellular carcinoma is not eliminated.

SVR may prevent a patient from being eligible for anti-HCV-positive organs and delisting may preclude the patient from a curative treatment which can lead to good quality of life. While the medical science is working hard to identify predictors of good outcome in decompensated cirrhosis patients, the best approach at present appears to be to individualize treatment strategy in a given patient to suit his requirement, both medical and social. As a thumb rule, those MELD scores >20 should be advised to be treated after LT and those with MELD scores <16 can be considered for pre-transplant treatment. In any case the implications of such a decision and possible risks involved need to be explicitly discussed with the patient.

CONFLICTS OF INTEREST

The author has none to declare.

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