Review Article

Timing of Hepatitis C Virus Treatment in Liver Transplant Candidates in the Era of Direct-acting Antiviral Agents

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Abstract

Chronic hepatitis C virus (HCV) infection remains the leading indication for liver transplantation (LT) in the United States. While most patients with chronic HCV infection remain asymptomatic, up to one-third develop progressive liver disease resulting in cirrhosis. LT is often the only curative treatment once significant hepatic decompensation develops. However, antiviral therapy for HCV infection has advanced markedly in the past 5 years with the discovery and approval of direct-acting antiviral agents. These new regimens are well tolerated, of short duration and highly effective, unlike the traditional treatment with pegylated-interferon and ribavirin. As achieving sustained virological response becomes increasingly attainable for a majority of HCV-infected patients, concerns have been raised regarding the optimal timing of treatment for HCV infection in the setting of end-stage liver disease and during the peri-transplant period. On one hand, HCV treatment may improve hepatic function and negate the need for LT in some, which is crucial given the scarcity of donor organs and mortality on the waiting list in certain regions. On the other hand, HCV treatment may result in lowering the priority for LT without improving quality of life, thereby delaying potentially curative LT surgery. This review evaluates the evidence supporting the use of direct-acting antiviral agents in the period before and following LT.

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Introduction

Chronic hepatitis C virus (HCV) infection remains one of the most common causes of liver disease in the United States. It is estimated that 1.0–1.5% of the United States' population, or 2.7 to 3.5 million persons, have chronic HCV infection and that more than 15,000 persons will die of HCV-related complications each year.[1–3] End-stage liver disease due to HCV is currently the leading indication for liver transplantation (LT) in the US, accounting for over 30% of all transplants annually.[4,5] However, treatment for chronic HCV infection has revolutionized in the past 5 years with the approval of second-generation direct-acting antiviral (DAA) agents.

These newer DAA-based regimens are highly effective, resulting in sustained virological response (SVR) in greater than 90% of patients. Data continue to demonstrate that SVR significantly reduces the risk of progressive liver disease, hepatic decompensation, hepatocellular carcinoma (HCC), liver-related mortality and all-cause mortality.[6] However, the timing of treatment in HCV-infected patients awaiting LT remains controversial. The treatment of HCV followed by SVR in patients with cirrhosis may improve the model for end-stage liver disease (MELD) score, thereby lowering the likelihood of LT, without improving the poor quality of life associated with complications of end-stage liver disease; a situation termed 'MELD purgatory'.[7,8]

This reviews aimed to aggregate and evaluate current data on the treatment of chronic HCV infection in the peri-transplant period and determine the validity of 'MELD purgatory'.

Natural history of HCV infection

Acute hepatitis develops in 20% of patients within 2 weeks of exposure to HCV. Symptoms during acute infection are often unnoticed, but some may experience jaundice, malaise, nausea and anorexia. Approximately 55–85% of patients are unable to spontaneously clear the virus and will develop chronic infection. Chronic HCV infection is a slowly progressive disease that leads to the development of cirrhosis in 10–40% of patients over 20–30 years.[9] The progression can be accelerated in specific populations, including the elderly, patients co-infected with human immunodeficiency virus[10] and LT recipients.[11]

The vast majority of patients with chronic HCV infection are asymptomatic, although fatigue is a common complaint. Once cirrhosis has developed, there is a 1–5% annual risk of HCC and 3–6% annual risk of hepatic decompensation with several host and viral factors influencing these rates.[12] Chronic HCV infection is currently the leading cause of HCC among patients with cirrhosis, accounting for 55% of

Keywords: Hepatitis C virus; Direct-acting antiviral therapy; Liver transplantation.
Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; FCH, fibrosing cholestatic hepatitis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LT, liver transplantation; MELD, model for end-stage liver disease; SVR, sustained virological response.
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all HCC.[13] In patients who develop hepatic decompensation, the risk of death within 1 year is approximately 15–20%, and LT generally remains the only life-saving option.[14]

HCV infection in liver transplant recipients

LT serves as a curative management option for HCV-infected patients with severe hepatic decompensation with or without HCC. However, in chronically infected HCV-seropositive patients at the time of LT, recurrence of HCV infection in the graft is universal, with up to one-third of patients progressing from graft dysfunction to cirrhosis within 5 years of LT.[15] Few published cases describe spontaneous clearance of HCV infection following LT without a clearly defined mechanism.[16] Nonetheless, such cases are rare. In a study evaluating 149 patients with recurrent post-transplant HCV infection, 12% experienced no evidence of chronic hepatitis on liver biopsy while 70% developed mild chronic hepatitis within 6 months.[17]

Prior to the approval and introduction of DAA agents, LT for HCV-positive patients was associated with lower outcomes, with increased rate of death (hazard ratio [HR]: 1.23, 95% confidence interval [CI]: 1.12–1.35) and allograft failure (HR: 1.30, 95% CI: 1.21–1.39) compared to LT for other indications.[18] The inferior graft and survival rates were largely due to accelerated graft fibrosis from recurrent HCV infection along with ineffective and intolerable interferon-based therapies. In the era of DAA-based therapy, it is expected that outcomes for HCV-positive LT recipients will be similar, if not better than LT recipients for other indications.[19,20]

Treatment of HCV prior to liver transplantation

Achieving SVR after HCV treatment has repeatedly demonstrated lower rates of cirrhosis, hepatic decompensation, HCC, liver-related mortality and all-cause mortality.[6] Prior to DAA agents, pegylated-interferon and ribavirin were the cornerstone of HCV treatment, but their use was limited due to lower clinical efficacy, poor tolerance due to adverse effects and inability to treat patients with hepatic decompensation.[21] Treatment of chronic HCV infection with DAA agents has significantly improved outcomes in HCV-related liver disease due to high SVR rates, improved adherence and relatively liberal use in patients with decompensated cirrhosis.[10] These qualities naturally fuel a desire to treat all patients with chronic HCV infection; however, the timing of treatment is an important factor to consider.

In 2015, the landmark SOLAR-1 trial reported encouraging results in patients treated with sofosbuvir, ledipasvir and ribavirin for 12–24 weeks, with an overall SVR-12 rate of 86–89% in a non-transplant cohort who are decompensated (Child-Turcotte-Pugh class B [CTP-B] and Child-Turcotte-Pugh class C [CTP-C]).[19] In post-transplant patients without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh class A [CTP-A]), 96–98% achieved SVR compared to 85–88% in patients with moderate hepatic impairment (Child-Turcotte-Pugh class B [CTP-B]) and 60–75% (n = 9) in patients with severe hepatic impairment (Child-Turcotte-Pugh class C [CTP-C]) with 12–24 weeks of sofosbuvir/ledipasvir plus ribavirin. Seven patients underwent re-transplantation, with four receiving the LT prior to completing HCV treatment; SVR was noted in six of these patients during the post-transplant phase.[18] This suggests that HCV treatment in the pre-transplant phase with DAA agents can successfully prevent recurrent HCV infection in LT recipients.

Second generation DAA agents are also more effective than prior therapies in special sub-populations of HCV-infected patients previously termed difficult-to-treat. SVR rates with DAA agents in the geriatric population are comparable to younger populations.[22] ASTRAL-1, an international multicenter trial, noted the high efficacy of sofosbuvir and velpatasvir treatment in patients that failed prior HCV treatment and African Americans.[23] Companion trials, ASTRAL-2 and ASTRAL-3, subsequently showed comparable SVR results in patients with HCV genotypes 2 and 3, which previously had lower SVR rates.[24] These studies suggest that DAA agents can improve outcomes for a broad range of patients, including populations who were less likely to achieve SVR with interferon-based therapies.

Additionally, DAA agents have demonstrated efficacy and tolerability in patients with moderate to severe hepatic decompensation. A recent pooled analysis from all major clinical trials with DAA-based regimens used in CTP-B/C patients for all HCV genotypes found an overall SVR rate of 83.5%. Furthermore, treatment with DAA agents led to stabilization or improvement in hepatic function in up to 60% of decompensated patients, while 17% had no change and 23% had a worsening in MELD score.[25] An analysis of safety data from the SOLAR studies demonstrated that the combination of sofosbuvir and ledipasvir with ribavirin in decompensated patients was safe and well-tolerated, with expectant rates of severe adverse events (28–30%) and death (5%).[26] Importantly, enrollment of patients with MELD score > 20 and CTP-C disease in these trials was often limited, so these estimates may not be applicable to patients with higher MELD scores or severe liver decompensation.

Table 1. Advantages and disadvantages of HCV treatment in liver transplant candidates before liver transplantation

Advantages	Disadvantages
Liver function and MELD score may improve	MELD may improve but with ongoing poor health (i.e., 'MELD purgatory')
Liver transplant may no longer be necessary	Possibly eliminates the option of a curative treatment for liver disease
Societal benefit given scarcity of organs and limited donor pool	May limit access to hepatitis C virus-positive donors, thereby prolonging time on liver transplant waitlist and risk of death or dropout
Prevent post-transplant recurrence of hepatitis C virus infection	If HCV treatment fails, risk of resistance to NS5A inhibitors and compromised sustained virological response rates when re-treating post-liver transplantation
Cost effective strategy if liver transplantation can be obviated	

Abbreviation: MELD, model for end-stage liver disease.

While HCV treatment of all patients prior to LT is desirable, it may not be beneficial for patients if transplantation cannot be obviated.[27] This may be true for LT candidates with HCC or severely decompensated liver disease when LT surgery is the only curative option.[28] HCV treatment prior to LT in this cohort may reduce the available donor pool, as HCV-positive donors may no longer be considered an option. Such allografts are increasingly available in the current opioid epidemic, often from first-time and naive opiate users who are otherwise healthy. The proportion of HCV-positive donors in the local regional donor pool is an important factor to consider prior to treatment.[29] In a single-center retrospective review of all deceased-donor transplants, Ofosu *et al.*[30] observed that 40% of their HCV-seropositive recipients ultimately received transplants from HCV-positive donors. This number is likely to vary by region but should be considered when pursuing HCV treatment in a LT candidate. Treatment of such patients in a region with a high prevalence of HCV-positive donors may result in extending LT waiting time, thereby increasing the risk of waitlist dropout while awaiting a suitable donor. In the future, policies may change with universal acceptance and uniform distribution of HCV-positive donors for patients with and without HCV infection awaiting LT.

Patients treated for HCV prior to LT may still accept an HCV-positive donor but would need to be re-treated post-transplantation, incurring additional healthcare costs. A recent analysis of the cost effectiveness in treating patients before or after LT indicated that treatment is likely to be cost effective in patients whose risk of LT can be successfully modified with treatment. Treatment in such patients would improve MELD scores and risk of hepatic complications, which subsequently reduces the risk of repeated hospitalizations, death and possibly LT. In patients whose risk of LT cannot be modified, such as for patients with HCC or severe liver dysfunction, HCV treatment prior to LT would not be cost effective.[31] Advantages and disadvantages of this treatment strategy are summarized in Table 1.

Treatment of HCV following liver transplantation

Achievement of SVR in the post-LT setting is associated with significantly reduced morbidity and mortality in LT recipients.[32] The standard of care for post-transplant HCV treatment prior to DAA agents was pegylated-interferon and ribavirin, which was suboptimal at best. A systematic review of 19 studies evaluating 611 post-transplant HCV-infected patients treated with interferon-based therapy demonstrated SVR rate of 30.2% (8–50%). This was due to the poor adverse effects profile often leading to dose reduction and discontinuation of treatment (73% and 27.6%, respectively).[33] However, post-transplant HCV treatment with DAA agents has shown improved SVR rates due to improved efficacy and tolerability.

A recent retrospective study noted that treatment with a combination of sofosbuvir and simeprevir achieved SVR in 88% of LT recipients. In the more difficult-to-treat cohort with advanced fibrosis (defined as stage 3 or 4 on liver biopsy), only 64% achieved SVR.[34,35] In another study from Canada, 120 LT recipients with recurrent HCV infection were treated with sofosbuvir-based regimens and 85% achieved SVR; of the 53 patients with advanced fibrosis, 81% achieved SVR.[36] Treatment with sofosbuvir is also highly effective in the post-transplant period in patients with fibrosing cholestatic hepatitis (FCH), a more aggressive form of HCV recurrence associated with worse outcomes. In a recent study evaluating five patients that developed FCH, all were treated with sofosbuvir and simeprevir for 24 weeks and were noted to have undetectable levels of HCV RNA by the end of treatment.[37]

These recent studies demonstrating safety and efficacy of DAA agents in the post-transplant setting, especially in

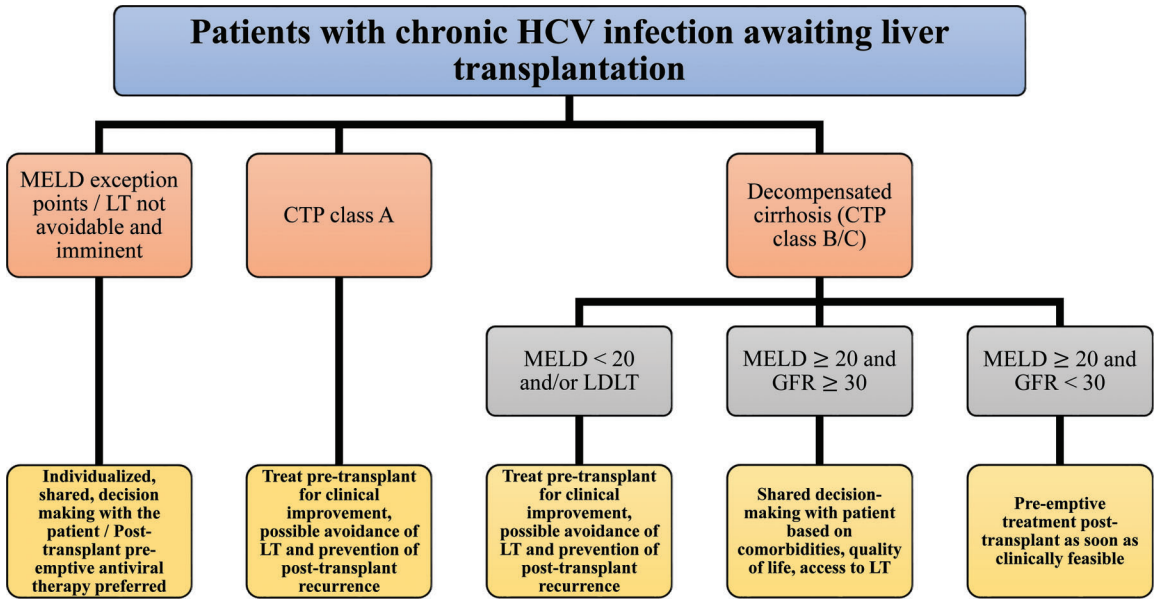

Fig. 1. Algorithm for treatment of HCV-infected liver transplant candidates.

Abbreviations: MELD, model for end-stage liver disease; LT, liver transplantation; CTP, Child-Turcotte-Pugh; LDLT, living donor liver transplantation; GFR, glomerular filtration rate.

patients with advanced fibrosis and FCH, are encouraging. Although larger prospective trials are required to establish specific therapy recommendations, timely pre-emptive treatment in patients unable to achieve SVR prior to LT appears to be a prudent approach and may reduce the burden of graft failure and re-transplantation.

MELD purgatory – fact or fiction

Despite the efficacy of DAA agents and significant clinical benefits of SVR, there remain concerns that HCV treatment for some patients on the LT waiting list may be ill-served in the current organ allocation system due to the possibility of 'MELD purgatory'. This refers to a limbo situation in which the LT candidate's MELD score may decrease but without an improvement in quality of life. In such patients there is a realistic risk of not receiving adequate priority on the LT waitlist, and perhaps HCV treatment following LT would be more appropriate.

Ideally, a prediction model could help identify which patients with hepatic decompensation are likely to experience clinical and biochemical improvement in hepatic function following HCV treatment and can be safely removed from the LT waitlist. Recent European studies evaluated the change in waitlist status of patients treated for HCV and found that patients listed with MELD $\geq$ 18 were less likely to attain significant biochemical or clinical improvement and remained active on the waitlist following treatment. These studies concluded that if transplantation is imminent, post-transplant treatment may be a better option for such patients.[38,39]

In the United States, algorithms for HCV treatment in waitlisted patients have been proposed in an effort to avoid 'MELD purgatory' and optimize survival.[40] Authors recommend pre-transplant HCV treatment in patients with hepatic decompensation and MELD < 20, in patients scheduled for living donor LT, and in patients with MELD scores 20–27 based on regional trends in LT. Post-transplant treatment is recommended for patients with MELD > 27 and/or significant renal impairment (with glomerular filtration rate < 30).[40] We propose a modified algorithm, as summarized in Fig. 1, in an effort to avoid 'MELD purgatory'. For the time-being, it is clear that patients with lower MELD scores and mild hepatic impairment benefit from HCV treatment pre-transplant and carefully selected patients with moderate hepatic decompensation may benefit as well, with the exception of those anticipating imminent LT.

Conclusions

The introduction of DAA agents has dramatically altered the treatment landscape for the HCV-infected patient population. DAA agents are better tolerated, safe and more effective in achieving SVR across the board, as compared to prior therapies. Given the benefits of SVR on liver function and mortality, the question is not *if* all patients should be treated for HCV, but rather *when* an individual patient should be treated, such that overall survival is maximized while maintaining access to LT if liver-related complications fail to improve despite a decline in MELD score. Unfortunately, the answers to these questions are not straightforward. Initial data suggest that patients with mild hepatic impairment and select patients with moderate impairment may improve to a point where LT is no longer required. Ultimately, robust predictors of improvement in hepatic function and quality of life are needed to identify patients for HCV treatment in the context of LT.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Drafted the initial and final manuscript (GC), supervised the project (AA, AG), contributed to study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript (GC, MJT, BJP, AL, ERY, AA, AG).

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