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**Treatment strategies for chronic hepatitis C prior to and following liver transplantation**

**Perumpail** RB *et al.* HCV therapy in the setting of liver transplantation

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**Abstract**

Hepatitis C virus (HCV)-related liver disease is the leading indication for liver transplantation (LT) worldwide. However, HCV is an independent predictor of lower survival following LT, and recurrence of HCV post-LT is virtually universal. The historic standard of care during the interferon era of HCV therapy was expectant management-initiation of antiviral therapy in the setting of documented disease progression following LT. With the advent of new direct acting antiviral (DAA) therapies for HCV, the paradigm of expectant treatment for recurrent HCV infection post-LT is shifting. The safety, tolerability, and efficacy of DAAs, even among the sickest patients with advanced liver disease, enables treatment of HCV in the pre-transplant setting among LT waitlist registrants. Finally, emerging data are supportive of preemptive therapy with DAAs in liver transplant recipients as the preferred approach. Expectant management of HCV following LT can rarely be justified in the modern era of HCV therapy.

**Key words:** Hepatitis C virus; Liver transplantation; Direct acting antivirals; Sustained virologic response

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**Core tip:** The historic standard of care during the interferon era of hepatitis C virus (HCV) therapy was expectant management-initiation of antiviral therapy in the setting of documented disease progression following liver transplantation. With the advent of new direct acting antiviral (DAA) therapies for HCV, the paradigm of expectant treatment for recurrent HCV infection post-liver transplantation (LT) is shifting. The safety, tolerability, and efficacy of DAAs, even among the sickest patients with advanced liver disease, enables treatment of HCV in the pre-transplant setting among LT waitlist registrants. Emerging data support preemptive therapy with DAAs in liver transplant recipients as the preferred approach.

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**INTRODUCTION**

Hepatitis C virus (HCV) infection afflicts an estimated 180 million people worldwide, or nearly 3% of the global population[1,2]. HCV results in 8000 to 13000 deaths annually in the United States[3].To date, HCV remains the leading indication for liver transplantation (LT) in developed nations and represents 33% of patients currently on the LT waitlist[3,4].

**NATURAL HISTORY OF HCV INFECTION BEFORE LT**

Among 70% to 75% of patients, acute HCV infection is asymptomatic. The remaining minority of patients develops systemic symptoms, including weakness, malaise, anorexia, and, rarely, jaundice. Eighty-five percent of patients with acute HCV infection do not clear the infection without treatment and instead develop chronic infection[5]. Progression to cirrhosis or hepatocellular carcinoma occurs in between 15% to 40% of patients with chronic HCV[1]. Accelerated development of cirrhosis and end-stage liver disease ensue under certain conditions. Rate of progression to cirrhosis is impacted by age at exposure - higher risk with HCV exposure at advanced age; route of transmission - blood transfusion portends greater risk than injection drug use; duration of infection; HCV genotype; and coexisting illnesses, including human immunodeficiency virus infection, hepatitis B virus (HBV) infection, and alcoholic liver disease[6-10].

**TREATMENT OF HCV INFECTION BEFORE LT**

Although 5-year survival among patients with compensated cirrhosis due HCV ranges from 84% to 91%, there is a 20% risk of decompensation and a 10% risk of HCC[11,12].Attainment of sustained virologic response (SVR) is associated with lower rates of hepatic decompensation, HCC, and all-cause mortality[13]. Indeed, an international multicenter study demonstrated that patients with chronic HCV who achieve SVR have long-term survival comparable to that of the general population[14,15]. Moreover, recent data reveal improved long-term survival following LT among patients in whom HCV was eradicated prior to LT[16]. As a third of LT in the United States are performed for HCV-related liver disease[4] and HCV-positive recipients have worse outcomes following LT[17], attaining pre-transplant SVR may yield significant improvements in patient outcomes. In the interferon era, HCV therapy was instituted with caution in patients with advanced liver disease due to the potential risk of hepatic decompensation. Now, with the advent of safe, well-tolerated, and efficacious direct acting antivirals (DAAs), a paradigm shift toward pre-transplant treatment of HCV is warranted. The shortage of donor livers in the United States, which results in substantial liver transplant waitlist mortality and dropout[18], underscores the importance of treating HCV prior to LT. The significance of this shift is even greater in regions where the availability of LT is limited to only very sick patients[19]. Treatment of HCV pre-transplant stands not only to improve post-LT outcomes but also reduce the overall societal need for LT. Viral suppression in HBV has been shown to lead to regression of fibrosis[20,21]. Likewise, emerging data now reveals histological regression of fibrosis among patients with HCV who have achieved SVR[4]. As such, long-term virologic suppression of HCV may lead to disease reversal.

**LT FOR HCV**

LT is optimal therapy for decompensated cirrhosis due to chronic HCV, but HCV reinfection poses challenging management issues that may arise either early or late after transplantation[22,23].

**DONOR LIVER ALLOCATION FOR LT**

In 2002, the Model for End-Stage Liver Disease (MELD) score shown to predict LT waitlist mortality was implemented as an allocation criterion for donor livers[24]. The goal is to improve survival and quality of life among patients with end-stage liver disease. LT has proven to be effective at achieving these goals. The benefits of LT are most established for patients with MELD scores of at least 15 or higher[25]. The MELD score necessary to receive a donor liver varies widely by United Network for Organ Sharing (UNOS) region. While patients with MELD scores in the mid-20s receive offers in some regions, MELD scores in the high-30s are commonly needed in other regions. Because offers are allocated to patients with higher MELD scores, concern has emerged about the possibility of a so-called “MELD purgatory” with pre-transplant treatment of HCV. Concern exists that certain patients may have delayed progression of liver disease after achieving SVR without substantial reversal or improvement in quality of life[26]. Proponents of this view contend that post-LT treatment of HCV would alleviate this concern. We should be cognizant of the fact that up to 3000 potential liver transplant candidates are removed from the waitlist annually in the United States – half develop contraindications for LT while the wait for a potential donor and the other half die from complications of end-stage liver disease[27]. Therefore, necessitating changes in allocation policies to reduce waitlist mortality[28]. Therefore, deferring antiviral therapy from pre- to post-LT phase may not be safe. Morbidity and mortality associated with LT are low, but should be ignored with emerging DAA data supporting instituting treatment in the pre-transplant phase. Furthermore, most experts agree that fibrosing cholestatic hepatitis and compensated recurrent HCV infection following LT demonstrates relatively lower efficacy with DAA therapy[29,30]. The concerns regarding the use of HCV-positive allografts have been alleviated with more recent data suggesting that transplant outcomes for recipients who accept HCV-positive donor allografts may be comparable with those who receive HCV-negative allografts[31]. Emerging treatments to eradicate HCV have further improved the course of HCV-positive individuals, with improved efficacy and reduced side-effects. HCV-positive donors constitute 4.8% of HCV-positive LT recipients[32]. The use HCV-positive donor in HCV-negative recipients with the availability of DAAs needs to be studied further. Lastly, if LT is imminent in a Child-Turcotte-Pugh class C patient with MELD score > 35 or hepatocellular carcinoma patient with exception MELD points - it may be pragmatic to wait and institute antiviral therapy following LT[33].

**NATURAL HISTORY OF HCV INFECTION FOLLOWING LT**

Studies demonstrate worse outcomes post-LT among patients with recurrent HCV infection compared to patients transplanted for other causes of cirrhosis[23,34]. The natural history of HCV infection in liver transplant recipients is typically accelerated, partially due to concomitant administration of post-LT immunosuppression. Up to 20% of HCV-infected patients develop cirrhosis by 5 year following LT[23]. Recurrent disease ranges from asymptomatic mild hepatitis to severe chronic hepatitis and cirrhosis. Reinfection with HCV post-LT is virtually universal, occurring in over 95% of cases[22].

**PREEMPTIVE TREATMENT OF HCV FOLLOWING TRANSPLANTATION**

Historically, preemptive use of antiviral therapy post-LT was not advisable because of the increased rate of acute allograft rejection associated with interferon therapy[35]. However, with the emergence of safe and efficacious DAAs, the previous concern of interferon-related immunomodulation with allograft rejection and poor tolerance due to anti-HCV therapy following LT is abating. None of the new DAAs have yet been approved by the United States Food and Drug Administration for use among patients following LT, but the powerful body of emerging literature suggests that approval may be expected in the near future[29,30]. Preemptive treatment of HCV in the post-LT setting may alleviate the need for re-transplantation.

**EXPECTANT TREATMENT OF HCV FOLLOWING TRANSPLANTATION**

Despite being the previous standard of care in the interferon era, expectant management of HCV does not seem to have a role for the vast majority of patients in the era of DAAs. Delaying HCV therapy post-LT is not advisable due to the rapid progression of HCV-related liver damage and promising data regarding the use of DAAs.

**CONCLUSION**

Advances in peri-transplant management of liver transplant recipients in the setting of chronic hepatitis C have resulted in long-term post-transplant survival rates approaching 90%[36]. Nevertheless, survival following LT remains lower among patients with HCV compared to those undergoing LT for liver disease related to other etiologies[17]. Attaining SVR pre-transplant reduces all-cause mortality, may decrease the need for LT, and may improve survival following LT[14,15]. The improvements in the efficacy of antiviral therapy against HCV infection with DAAs argue against the interferon-era paradigm of expectant use of antiviral therapy following LT. The decision between treating patients pre-transplant or preemptively in the early post-transplant setting should be individualized for each patient in the context of the regional waitlist trends and exception policies for LT. Despite advancements in LT, there remains a shortage of donor livers to meet the demands for LT in the United States Treatment of patients on the LT waiting list may ultimately decrease the number of patients needing LT and help address the imbalance in supply and demand.

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