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MINIREVIEWS

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

Ryan B Perumpail, Thomas A Hahambis, Avin Aggarwal, Zobair M Younossi, Aijaz Ahmed

Ryan B Perumpail, Avin Aggarwal, Aijaz Ahmed, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Palo Alto, CA 94304, United States

Thomas A Hahambis, Gilead Sciences, Foster City, CA 94404, United States

Zobair M Younossi, Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA 22042, United States

Zobair M Younossi, Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA 22042, United States

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Correspondence to: Ryan B Perumpail, MD, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 750 Welch Road, Suite 210, Palo Alto, CA 94304, United States. rperumpail@gmail.com
Telephone: +1-650-4986091
Fax: +1-650-4985692

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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

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 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 years 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.

REFERENCES

1 **Wray CM**, Davis AM. Screening for hepatitis C. *JAMA* 2015; **313**: 1855-1856 [PMID: 25965235 DOI: 10.1001/jama.2015.2833]

2 **Chung RT**, Baumert TF. Curing chronic hepatitis C--the arc of a medical triumph. *N Engl J Med* 2014; **370**: 1576-1578 [PMID: 24720678 DOI: 10.1056/NEJMp1400986]

3 **Moyer VA**. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; **159**: 349-357 [PMID: 23798026 DOI: 10.7326/0003-4819-159-5-201309030-00672]

4 **Dhanasekaran R**, Sanchez W, Mounajjed T, Wiesner RH, Watt KD, Charlton MR. Impact of fibrosis progression on clinical outcome in patients treated for post- transplant hepatitis C recurrence. *Liver Int* 2015; **35**: 2433-2441 [PMID: 26058570 DOI: 10.1111/liv.12890]

5 **Tong MJ**, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med* 1995; **332**:

1463-1466 [PMID: 7739682 DOI: 10.1056/NEJM199506013322202]
6 **Brechot C**, Nalpas B, Feitelson MA. Interactions between alcohol and hepatitis viruses in the liver. *Clin Lab Med* 1996; **16**: 273-287 [PMID: 8792072]
7 **Gordon SC**, Bayati N, Silverman AL. Clinical outcome of hepatitis C as a function of mode of transmission. *Hepatology* 1998; **28**: 562-567 [PMID: 9696025 DOI: 10.1002/hep.510280238]
8 **Marrone A**, Sallie R. Genetic heterogeneity of hepatitis C virus. The clinical significance of genotypes and quasispecies behavior. *Clin Lab Med* 1996; **16**: 429-449 [PMID: 8792081]
9 **Poynard T**, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**: 825-832 [PMID: 9121257 DOI: 10.1016/S0140-6736(96)07642-8]
10 **Simmonds P**. Variability of hepatitis C virus. *Hepatology* 1995; **21**: 570-583 [PMID: 7531173 DOI: 10.1002/hep.1840210243]
11 **Fattovich G**, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; **112**: 463-472 [PMID: 9024300 DOI: 10.1053/gast.1997.v112.pm9024300]
12 **Serfaty L**, Aumaître H, Chazouillères O, Bonnand AM, Rosmorduc O, Poupon RE, Poupon R. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; **27**: 1435-1440 [PMID: 9581703 DOI: 10.1002/hep.510270535]
13 **Veldt BJ**, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, Manns MP, Hansen BE, Schalm SW, Janssen HL. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007; **147**: 677-684 [PMID: 18025443 DOI: 10.7326/0003-4819-147-10-200711200-00003]
14 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]
15 **van der Meer AJ**, Wedemeyer H, Feld JJ, Dufour JF, Zeuzem S, Hansen BE, Janssen HL. Life expectancy in patients with chronic HCV infection and cirrhosis compared with a general population. *JAMA* 2014; **312**: 1927-1928 [PMID: 25387192 DOI: 10.1001/jama.2014.12627]
16 **Fortune BE**, Martinez-Camacho A, Kreidler S, Gralla J, Everson GT. Post-transplant survival is improved for hepatitis C recipients who are RNA negative at time of liver transplantation. *Transpl Int* 2015; **28**: 980-989 [PMID: 25818896 DOI: 10.1111/tri.12568]
17 **Forman LM**, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002; **122**: 889-896 [PMID: 11910340 DOI: 10.1053/gast.2002.32418]
18 **Charpentier KP**, Mavanur A. Removing patients from the liver transplant wait list: A survey of US liver transplant programs. *Liver Transpl* 2008; **14**: 303-307 [PMID: 18306339 DOI: 10.1002/lt.21353]
19 **Gentry SE**, Massie AB, Cheek SW, Lentine KL, Chow EH, Wickliffe CE, Dzebashvili N, Salvalaggio PR, Schnitzler MA, Axelrod DA, Segev DL. Addressing geographic disparities in liver transplantation through redistricting. *Am J Transplant* 2013; **13**: 2052-2058 [PMID: 23837931 DOI: 10.1111/ajt.12301]
20 **Chang TT**, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, Safadi R, Lee SS, Halota W, Goodman Z, Chi YC, Zhang H, Hindes R, Iloeje U, Beebe S, Kreter B. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; **52**: 886-893 [PMID: 20683932 DOI: 10.1002/hep.23785]
21 **Marcellin P**, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Aguilar Schall R, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; **381**: 468-475 [PMID: 23234725 DOI: 10.1016/S0140-6736(12)61425-1]
22 **Ferrell LD**, Wright TL, Roberts J, Ascher N, Lake J. Hepatitis C viral infection in liver transplant recipients. *Hepatology* 1992; **16**: 865-876 [PMID: 1383115 DOI: 10.1002/hep.1840160403]
23 **Gane EJ**, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, Maertens G, Williams R. Long-term outcome of hepatitis C infection after liver transplantation. *N Engl J Med* 1996; **334**: 815-820 [PMID: 8596547 DOI: 10.1056/NEJM199603283341302]
24 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]
25 **Åberg F**, Nordin A, Mäkisalo H, Isoniemi H. Who is too healthy and who is too sick for liver transplantation: external validation of prognostic scores and survival-benefit estimation. *Scand J Gastroenterol* 2015; **50**: 1144-1151 [PMID: 25865580 DOI: 10.3109/00365521.2015.1028992]
26 **Bonacci M**, Londoño MC, Esforzado N, Forns X, Sotoca JM, Campistol JM. Antiviral treatment with sofosbuvir and simeprevir in a kidney transplant recipient with HCV-decompensated cirrhosis: viral eradication and removal from the liver transplant waiting list. *Transpl Int* 2015; **28**: 1345-1349 [PMID: 26073850 DOI: 10.1111/tri.12622]
27 **Massie AB**, Caffo B, Gentry SE, Hall EC, Axelrod DA, Lentine KL, Schnitzler MA, Gheorghian A, Salvalaggio PR, Segev DL. MELD Exceptions and Rates of Waiting List Outcomes. *Am J Transplant* 2011; **11**: 2362-2371 [PMID: 21920019 DOI: 10.1111/j.1600-6143.2011.03735.x]
28 **Massie AB**, Chow EK, Wickliffe CE, Luo X, Gentry SE, Mulligan DC, Segev DL. Early changes in liver distribution following implementation of Share 35. *Am J Transplant* 2015; **15**: 659-667 [PMID: 25693474 DOI: 10.1111/ajt.13099]
29 **Forns X**, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, Brandt-Sarif T, Chang P, Kivett V, Castells L, Prieto M, Fontana RJ, Baumert TF, Coilly A, Londoño MC, Habersetzer F. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology* 2015; **61**: 1485-1494 [PMID: 25557906 DOI: 10.1002/hep.27681]
30 **Charlton M**, Gane E, Manns MP, Brown RS, Curry MP, Kwo PY, Fontana RJ, Gilroy R, Teperman L, Muir AJ, McHutchison JG, Symonds WT, Brainard D, Kirby B, Dvory-Sobol H, Denning J, Arterburn S, Samuel D, Forns X, Terrault NA. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology* 2015; **148**: 108-117 [PMID: 25304641 DOI: 10.1053/j.gastro.2014.10.001]
31 **Patwardhan VR**, Curry MP. Reappraisal of the hepatitis C virus-positive donor in solid organ transplantation. *Curr Opin Organ Transplant* 2015; **20**: 267-275 [PMID: 25944236 DOI: 10.1097/MOT.0000000000000191]
32 **Northup PG**, Argo CK, Nguyen DT, McBride MA, Kumer SC, Schmitt TM, Pruett TL. Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: a US National Transplant Registry analysis. *Transpl Int* 2010; **23**: 1038-1044 [PMID: 20444239 DOI: 10.1111/j.1432-2277.2010.01092.x]
33 **Charlton M**, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungpapong S, Korenblat KM, Muir AJ, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology* 2015; **149**: 649-659

[PMID: 25985734 DOI: 10.1053/j.gastro.2015.05.010]

34 **Maor-Kendler Y**, Batts KP, Burgart LJ, Wiesner RH, Krom RA, Rosen CB, Charlton MR. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. *Transplantation* 2000; **70**: 292-297 [PMID: 10933151 DOI: 10.1097/00007890-200007270-00009]

35 **Sperl J**, Petrasek J, Spicak J, Viklicky O. Acute rejection of non-functional allograft in kidney transplant recipients with hepatitis C treated with peginterferon-alpha 2a. *J Hepatol* 2008; **49**: 461-462; author reply 462-463 [PMID: 18644649 DOI: 10.1016/j.jhep.2008.06.002]

36 **Ghobrial RM**, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, Markmann JF, Drazan KE, Holt C, Imagawa D, Goldstein LI, Martin P, Busuttil RW. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. *Ann Surg* 1999; **229**: 824-831; discussion 831-833 [PMID: 10363896 DOI: 10.1097/00000658-199906000-00009]

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