

International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates

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(*Transplantation* 2017;101: 945–955)

Rapid advances in the therapeutic arena for patients with hepatitis C virus (HCV), particularly in the context of liver transplantation (LT), mandate updated guidance. In 2016, the International Liver Transplantation Society convened a working group to develop a new guideline focused on the use direct-acting antiviral (DAA) therapy. A set of predetermined Patient Intervention Comparison Outcome questions were developed delineating issues facing transplant physicians in their daily practice (Table S1, SDC, <http://links.lww.com/TP/B416>).

The 8 questions of interest were: (i) treatment of patients with compensated cirrhosis and hepatocellular carcinoma (HCC), (ii) treatment of patients with decompensated cirrhosis without and (iii) with HCC, (iv) management of HCV in the context of an anti-HCV-positive donor, (v) treatment of posttransplant severe cholestatic hepatitis, (vi) treatment of recurrent HCV infection, (vii) treatment of recurrent HCV cirrhosis, and (viii) treatment of HCV pre- and post-LT in human immunodeficiency virus (HIV)-HCV coinfecting patients. These

Received 12 December 2016. Revision received 26 January 2017.

Accepted 6 February 2017.

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The authors declare no funding or conflicts of interest.

N.A.T. is a consulting/advisory board for Merck, Gilead. Grants: BMS, Gilead, AbbVie. G.W.M., Advisory boards/speaker fees: Gilead Sciences, AbbVie. K.A., Grants: BMS, Gilead, Roche. Advisory Boards: AbbVie, Achillion, BMS, Gilead, Intercept, Merck,

Novartis. E.G., Speakers bureau or advisory board for AbbVie, Allos Pharmaceuticals, Gilead Sciences, Janssen, Merck, Novartis, Novira. K.B., Consulting: E.G., Gilead, AbbVie, Merck, BMS, Bayer; Grant: Gilead, AbbVie. M.B. Grant: Gilead, Advisory boards: Gilead, AbbVie, MSD, BMS. M.P.C. Grants: Gilead. Consulting: Gilead, BMS, AbbVie, Trio Health Analytics. J.F., Grant: Novartis. M.G.P., Advisory Board/Speakers bureau: AbbVie, Alexion, BMS, Gilead, MSD. D.S. Consultancy for Astellas, BMS, Gilead, LFB, MSD, Novartis, Roche, Biotest, AbbVie, Intercept. S.F., speaker's bureau for Gilead Sciences, MSD, AbbVie, Bristol-Myers Squibb, Novartis. S.I.S., Advisory boards/speaker fees: Gilead Sciences, AbbVie, MSD, Bristol-Myers Squibb. A.G., Advisory boards/speaker fees: Gilead Sciences, AbbVie, MSD, Bristol-Myers Squibb, Novartis., P.Y.K., Advisory Committees or Review Panels: AbbVie, Abbott, BMS, Gilead, Janssen, Merck; Grant/Research Support: AbbVie, BMS, Gilead, Janssen, Merck. P.B., Gilead, Alfa Wassermann. M.C., Gilead, Merck, Janssen, Bristol Myers, Novartis, AbbVie.

N.T. participated in the conception, study design, acquisition and interpretation of results, drafting and revision of article. G.M.C. conception, study design, acquisition and interpretation of results, drafting and editing of article. M.C. study design, acquisition and interpretation of results, drafting and editing of article. S.F. study design, acquisition and interpretation of results, drafting and editing of article. J.F. study design, acquisition and interpretation of results, drafting and editing of article. K.A. study design, acquisition and interpretation of results, editing of article. L.L. study design, acquisition and interpretation of results, editing of article. S.S. study design, acquisition and interpretation of results, editing of article. K.B. study design, interpretation of results, editing of article. A.G. study design, acquisition and interpretation of results, editing of article. P.K. study design, acquisition and interpretation of results, editing of article. P.B. study design, interpretation of results, editing of article. D.S. study design, acquisition and interpretation of results, drafting and editing of article. M.P. conception, study design, acquisition and interpretation of results, drafting and editing of article. M.B. conception, study design, acquisition and interpretation of results, drafting and editing of article.

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Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

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ISSN: 0041-1337/17/10105-0945

DOI: 10.1097/TP.0000000000001708

questions were addressed via a critical review of the literature and working group consensus.

The guidelines are presented using the Grading of Recommendations Assessment Development and Evaluation approach.¹ This method includes consideration of the quality of evidence, benefits and harms, values and preferences, resource use, and cost-effectiveness. Quality of the evidence was rated as very low, low, moderate, or high. The strength of the recommendation was rated as strong or conditional (weak) and reflects confidence that adherence to guidance will result in more good than harm. The consensus findings and recommendations on treatment of HCV in the pre-LT setting including patients with HIV-HCV coinfection and management of anti-HCV-positive donors are presented here. The reader is referred to the ILTS Consensus Statement on HCV management in Liver Transplant Recipients for the findings and recommendations on treatment of HCV in the post-transplant setting.² This updated guidance is intended for healthcare professionals caring for patients on the waiting list or post-LT and should assist policy makers in optimizing the care of LT candidates and recipients.

Advances in HCV therapy will continue with the goal of providing safe and effective treatment for all infected persons. These guidelines reflect the currently approved therapies but with recognition that the specific drugs recommended may change as new drugs are approved, including therapies to treat patients who fail a first-line DAA combination.

I. TREATMENT OF PATIENTS WITH HCV RELATED COMPENSATED CIRRHOSIS AND HCC

Background

HCV-related HCC is a leading indication for LT worldwide. In the United States, there has been a 163% increase in waitlist registrations for this indication between 1999 and 2006.³ Successful eradication of HCV with interferon-based regimens before the development of HCC has been associated with a reduction in the relative risk of subsequent HCC development in all patients and in those who have advanced fibrosis and cirrhosis.⁴⁻⁶ The advent of potent, well-tolerated DAA therapies for HCV has seen significantly improved sustained virologic response (SVR) rates over those seen with interferon-based therapies in all cohorts of patients including those previously labeled as “difficult to cure.” SVR can be achieved in 95% to 97% of patients without cirrhosis or with compensated Child-Turcotte-Pugh (CTP) A cirrhosis and 85% to 95% in patients with more advanced cirrhosis (CTP B or C) including those awaiting LT.⁷⁻¹¹ Treatment of HCV in the pretransplant period has been associated with a reduction in risk of post-LT recurrence.^{12,13}

Recommendation 1.1

We suggest that waitlisted HCV-infected patients with compensated cirrhosis and HCC be treated with antiviral therapy.

Quality of evidence: Low

Strength of recommendation: Conditional

Technical Remarks

1. The decision to treat a waitlisted patient with HCC should be individualized. Potential benefits and harms of antiviral therapy to be considered in the patient-provider shared decision making are shown in Table 1. The prevention of recurrent HCV post-LT is the primary benefit of pre-LT therapy for HCC patients with compensated cirrhosis.
2. Additional center-specific factors to consider when carefully weighing the benefits and potential harms of antiviral therapy include:
 - Anticipated time to LT
 - Access to living donor LT
 - Availability of anti-HCV-positive donors
 - Waitlist drop-off rates for HCC progression
 - Access to and costs of antiviral therapy
3. The combination of an NS5B inhibitor, sofosbuvir, and ribavirin is a safe and well-tolerated option for waitlisted patients with HCC without renal insufficiency (creatinine clearance [CrCl] ≥ 30 mL/min).¹⁴ However, this regimen has been surpassed by others approved for compensated cirrhosis.¹⁵⁻¹⁷ Although these regimens have not been studied with the intent of preventing HCV recurrence post-LT, the high rates of SVR pre-LT support their use in waitlisted patients. Notably, regimens including a protease inhibitor (PI) are appropriate choices for patients with CTP-A cirrhosis and HCC but not recommended for those with CTP-B or C cirrhosis.
4. If treatment is undertaken, allowing sufficient time to complete treatment is recommended. If LT occurs before completion of a planned HCV regimen, continued treatment of HCV through and after LT can be considered to complete the intended course. However, the decision to continue treatment post-LT depends upon the likelihood of post-LT virologic response without additional antiviral therapy, presence of post-LT renal function (sofosbuvir-containing regimens not recommended if CrCl < 30 mL/min), severity of liver dysfunction (may limit use of PIs) and drug-drug interactions with immunosuppressive medications.
5. Treatment with sofosbuvir and ribavirin for a duration that achieved an undetectable HCV RNA for at least 30 days pre-LT yielded the highest rate of being HCV-free post-LT (termed post-transplant virologic response [pTVR]). If LT occurs before completion of planned HCV regimen or before a period of > 30 days of undetectable HCV RNA, continuation of HCV treatment after LT to complete the intended course should be strongly considered.
6. There is a recent controversy as to whether DAA antiviral therapy exacerbates and promotes HCC recurrence and/or development. Until this is resolved, the strength of the recommendation is conditional.

Evidence and Rationale

There is 1 published open-label study of sofosbuvir and ribavirin in the treatment of patients with HCV cirrhosis within Milan criteria and HCC listed for LT.¹⁴ A total of 61 patients were enrolled and 44 patients (73%) had CTP-A compensated liver cirrhosis. The overall intent to treat pTVR was 49% (30/61) and CTP score 7 to 8 had no effect on SVR. The pTVR for patients with undetectable HCV RNA at the time of LT was 70%, for those patients who had undetectable HCV RNA longer than 30 days before LT was 95% and for patients who had undetectable HCV RNA longer than 90 days before LT, the pTVR was 100%. Multivariable analysis showed that the number of consecutive days with undetectable HCV RNA was the only predictor of pTVR. Of note, only patients with

TABLE 1.**Antiviral therapy in patients with compensated cirrhosis with HCC**

Potential benefits	Potential harm
▪ High SVR rates can be achieved ▪ Reduce posttransplant recurrence rate if SVR achieved before transplant ▪ May reduce risk of decompensation and death on the waiting list ▪ May increase likelihood of tolerating locoregional therapy for HCC ▪ May improve QOL while on waiting list	▪ If treatment failure, viral resistance is likely and may limit retreatment options in short-term ▪ If ribavirin-inclusive DAA regimen, tolerability may be reduced ▪ May disadvantage patients from receiving HCV-positive grafts ▪ Potential increase in HCC activity after SVR ▪ Treatment to prevent recurrence is a lower priority as effective therapies are available posttransplant

HCC who were within Milan criteria at the time of screening were included. The median duration of exposure to study medication was 21 weeks with a range of 2.3 to 52.3 weeks. In a separate study from France of patients with HCV cirrhosis on the waiting list, with and without HCC (64% CTP class A), treated with a variety of sofosbuvir-containing DAA regimens for 12 to 24 weeks, 82% achieved SVR¹⁸ (Coilly personal communication).

There has been recent concern that treatment of HCV with DAAs in patients with successfully treated HCC may result in the unintended consequence of aggressive HCC recurrence. Reig and colleagues¹⁹ reported an HCC recurrence rate of 27.6% after median 6 months follow-up in 58 patients who had been treated with hepatic resection ($n = 7$) and local ablation ($n = 9$). All patients had confirmed complete radiological response by the validated European Association for the Study of the Liver criteria before DAA therapy. In a second study by Conti and colleagues,²⁰ 344 patients with HCV cirrhosis who received DAA therapy were followed up for 24 weeks after completing treatment for development or recurrence of HCC. SVR was achieved in 91% of patients. Eight of 17 patients had prior surgical resection, and the remaining 9 patients received locoregional single-modality or multimodality treatment for HCC. HCC recurred in 28.81% of patients with prior HCC and 3.16% of patients without a prior history of HCC. Both studies suggested that HCC recurrence in DAA-treated patients was higher than that historically observed in patients who had not received DAA therapies, though neither study included a matched control group. Another preliminary report found no increase in the incidence of de novo HCC but a higher frequency of multifocal or infiltrative HCC at presentation compared with historical controls.²¹ Conversely, a recent article from the Agence Nationale de Recherches sur le Sida et les hépatites virales collaborative study group analyzed 3 prospective cohorts of patients with HCV infection and failed to show any evidence that DAA therapy increased the risk of recurrence of HCC.²² Given the low quality of the evidence, this factor may be considered in the individualized assessment of treatment benefit versus harm but is insufficient to withhold antiviral therapy in waitlisted patients with HCC. There are no available results on waitlist mortality, HCC progression, and posttransplant HCC recurrence and survival.

Future Research

Given the more rapid decline in HCV RNA achieved with current DAA combinations, additional studies to determine the minimum duration of pretransplant HCV RNA undetectability

necessary to achieve pTVR would be beneficial. Further studies are needed to better define if treatment of HCV in patients with compensated liver cirrhosis and HCC is beneficial in terms of preventing drop-off from the waiting list due to liver decompensation or HCC progression or alternatively if treatment is detrimental by increasing the risk of HCC recurrence while awaiting LT.

Cost effectiveness studies suggest that pretransplant eradication of HCV is more cost-effective than waiting until after transplant except in cases where the patient's need for transplant is not modifiable, as for patients with HCC.²³ In patients with HCC as indication for LT, another cost-effectiveness study focused on the impact of anti-HCV-positive donor availability. The post-LT treatment strategy was cost-saving compared with the pretransplant DAA treatment strategy except possibly in the setting of low HCV-positive donor liver availability.²⁴

II. TREATMENT OF PATIENTS WITH DECOMPENSATED CIRRHOSIS (WITHOUT HCC)

Background

The spectrum of patients with decompensated cirrhosis on the waiting list is broad, making recommendations regarding antiviral treatment more challenging. Added to this is the variable time from listing to LT across different transplant programs, which in turn, influences model of end-stage liver disease (MELD) at LT and mortality rates on the waiting list.

The primary goal of treating patients with decompensated HCV cirrhosis is eradication of HCV to improve liver synthetic function and/or reduce portal hypertensive complications (Table 2). The clinical improvements after SVR, in turn, should improve patient survival on the waiting list and in some cases, may also allow avoidance of LT. The secondary goal is to prevent HCV recurrence after LT.

There are potential harms of treating patients on the waiting list for decompensated cirrhosis (Table 2). Achievement of SVR may not prevent disease progression or liver-related mortality in the sickest patients. This is referred to as the "point of no return" and may be due to limited regeneration potential related to severe hepatic insufficiency and portal hypertension. A related but different concern is that achievement of SVR will improve MELD and clinical symptoms of decompensation, but not to the point of being able to avoid a LT, yet potentially reducing access to LT because of the lower MELD or CTP score. Finally, SVR rates are modestly reduced in those with CP-B or C cirrhosis and treatment failure is usually associated

TABLE 2.
Antiviral therapy in patients with decompensated cirrhosis

Potential benefits	Potential harm
▪ Acceptable SVR rates can be achieved, especially for those with CTP B cirrhosis ▪ Reduce posttransplant recurrence rate if SVR achieved before transplant ▪ Reduce cirrhosis progression and mortality on the waiting list ▪ Improve MELD and clinical status ▪ Increase eligibility for bridging therapy for HCC ▪ Improve QOL while on waiting list	▪ Lower SVR rates in decompensated group compared with posttransplant ▪ Lowering of MELD resulting in reduced priority for LT ▪ Potentially greater risk of drug toxicity with decompensated liver disease ▪ May disadvantage patients from receiving HCV-positive grafts ▪ Potential increase in HCC activity after SVR ▪ Treatment to prevent recurrence is a lower priority as effective therapies are available posttransplant

with emergence of viral resistance substitutions (RASs) that may reduce posttransplant treatment options.

Recommendation 2.1

We suggest that HCV-infected patients with decompensated cirrhosis with CTP Class B and/or MELD less than 20 on the waiting list for liver transplantation, who are without refractory portal hypertensive symptoms or other conditions requiring more immediate transplantation, should be treated with antiviral therapy.

Quality/Certainly of Evidence: Moderate
Strength of Recommendation: Conditional

Recommendation 2.2

We suggest that HCV-infected patients with advanced decompensated cirrhosis (MELD 30) or those who are expected to undergo liver transplantation within 3 months should not undergo antiviral therapy.

Quality/Certainly of Evidence: Very low
Strength of Recommendation: Conditional

Recommendation 2.3

We suggest that HCV-infected patients with decompensated cirrhosis with intermediate MELD scores and/or low MELD scores but refractory portal hypertensive complications who are on the waiting list be offered treatment with antiviral therapy selectively.

Quality/Certainly of Evidence: Low
Strength of Recommendation: Conditional

making are shown in Table 2. Reversal of decompensation with the potential to avoid LT or prevention of waitlist mortality are the primary benefits of antiviral therapy in patients with decompensated cirrhosis.

2. Additional center-specific factors to consider when carefully weighing the benefits and potential harms of antiviral therapy include:
- Anticipated time to LT
 - Access to living donor LT
 - Availability of anti-HCV-positive donors
 - Waiting list mortality rates
 - Access to and costs of antiviral therapy
3. The MELD cutoffs that are cited are intended as guides rather than rules to determine who should be treatment. The entire clinical presentation, including severity of portal hypertensive complications, symptoms affecting quality of life (QOL), comorbidities and MELD should be considered when deciding whether to treat with DAA therapy.
4. The “Point of No Return” (ie, when antiviral therapy yields no clinical improvements) is unknown but baseline MELD and severity of portal hypertension may be important determinants of likelihood of improvement.
- The magnitude of improvement in liver function from baseline (Δ MELD score, CTP score) is usually small at 12 weeks posttreatment and may not be clinically significant. In the sickest patients, SVR may not prevent liver-related death before clinical improvement has occurred.
 - Clinical improvement and decreases in MELD and CTP scores are greatest for those with higher baseline MELD scores. However, higher MELD score patients require a greater delta MELD or CTP to achieve actual clinical benefits.
 - Improvements in portal hypertension are more frequent in patients with subclinical (hepatic venous pressure gradient [HVPG] <10 mm Hg) or mild-moderate portal hypertension (<15 mm Hg).
 - Clinical improvement may continue with longer follow-up post-SVR and be associated with reduction in morbidity and mortality.
5. Due to safety concerns with PIs, any regimen that includes this drug class is contraindicated in patients with decompensated cirrhosis.
6. Based on safety, tolerability and efficacy, the combination of NSSB inhibitor, sofosbuvir, plus hepatitis C virus nonstructural protein 5A (NS5A) inhibitor (daclatasvir, ledipasvir, or velpatasvir) is recommended for patients with decompensated disease (Table 3).
7. Ribavirin appears to reduce the risk of relapse in decompensated patients and should be strongly considered for inclusion in antiviral combinations. However, RBV-induced

Technical Remarks

1. The decision to treat a waitlisted patient with HCC should be individualized. Potential benefits and harms of antiviral therapy to be considered in the patient-provider shared decision

TABLE 3.**Recommended regimens for treatment of decompensated HCV cirrhosis**

HCV GT	Regimen	Duration, wk	Quality/certainty of evidence	Strength of recommendation
	First line			
1, 4	Ledipasvir-sofosbuvir + ribavirin 400-800 mg daily ^{9,25}	12	High	Strong
1, 4	Ledipasvir-Sofosbuvir ^{a9,25}	24	Very Low	Moderate
1-6	Sofosbuvir-velpatasvir + ribavirin 400-800 mg daily ¹¹	12	Moderate (CTP B only)	Strong
1-6	Sofosbuvir-velpatasvir ^{a11}	24	Moderate (CTP B only)	Strong
1-6	Sofosbuvir + daclatasvir + ribavirin 400-800 mg daily ¹⁰	12	Moderate	Strong
1-6	Sofosbuvir + daclatasvir ^{a26,27}	24	Low	Weak
	Second Line			
1-6	Sofosbuvir + ribavirin, 400-800 mg daily ¹⁴	24	Low	Weak

^a For ribavirin-intolerant patients.

hemolysis is enhanced in renal impairment, which is common in end-stage liver disease. Hence, the recommended starting dose is 600 mg daily and the dose should be adjusted according to baseline CrCl and hemoglobin. Frequent monitoring of hemoglobin is recommended. The maximum dose recommended is 1000 mg (<75 kg) to 1200 mg (≥75 kg).

8. Duration of therapy is 12 to 24 weeks, depending on genotype, use of ribavirin and presence of other negative prognostic factors. All patients with genotype 3 and those ineligible for ribavirin should be treated for 24 weeks. Those with non-3 genotypes with baseline RASs, prior treatment failure, older age and low platelet count may be considered for 24 weeks therapy even when ribavirin is used.
9. Sofosbuvir-based therapy is not currently recommended in patients with CrCl less than 30 mL/min due to concerns about cumulative toxicity from sofosbuvir and the major metabolite GS-331007. Until additional safety data in decompensated patients with CrCl less than 30 mL/min are available, antiviral therapy is best deferred until post-LT when improved renal status can be expected.
10. There are no accepted criteria for delisting patients for clinical improvement after SVR. One real-world study found baseline MELD less than 20 and on-treatment ΔMELD greater than 4 and Δalbumin greater than 0.5 g/dL predicted subsequent inactivation and delisting. These predictors need to be validated.

Evidence and Rationale

SVR rates decrease with worsening liver function, with rates of 90% or greater in those with CTP class A cirrhosis, 80% to 90% in patients with CTP Class B cirrhosis, and only 60% to 80% in those with CTP class C cirrhosis.²⁶⁻²⁹ This decrease in SVR reflects increased rates of nonvirologic failure (death from disease progression) and virologic failure. Virologic failure to sofosbuvir-ledipasvir, sofosbuvir-velpatasvir, and daclatasvir-sofosbuvir is associated with emergence of NS5A RASs, which persist long term and which may limit retreatment options in the posttransplant period. Although there are next-generation regimens in clinical development (glecaprevir/pibrentasvir; sofosbuvir/velpatasvir/voxilaprevir) which may provide effective retreatment for DAA failures, both regimens contain an NS3 PI and therefore cannot be used in patients with hepatic decompensation.

The exact MELD cutoff adopted for this “Point of No Return” may vary between centers reflecting waiting times, but individual factors which influence likelihood of SVR may also be important, such as HCV genotype and prior DAA experience. Viral eradication could actually reduce access to LT for some patients if SVR is associated with a small

but clinically meaningless improvement in liver function that does not improve the patient's long-term QOL or transplant-free survival. Therefore, SVR, in this scenario, may not improve the patient's morbidity or mortality enough to justify removal from the waiting list. If the patient is listed at a center within an organ sharing network where liver allocation is determined by MELD, then SVR may reduce the patient's waiting list priority (so-called MELD limbo or purgatory). In the ASTRAL-4, study, improvements in CTP score was observed in 47% of patients, but these were greater than 1 point in only 14% of patients.¹¹ Similarly, although improvements in MELD scores were observed in 54% of patients, these were greater than 2 points in only 16% of the patients. It is likely that the small clinical improvements in liver synthetic function observed during treatment would increase with longer follow-up post-SVR. In the SOLAR-1 study, changes in MELD and CTP from baseline were determined at the end of treatment,⁹ whereas in the identical SOLAR-2 study,²⁵ these were determined at 24 weeks posttreatment. MELD scores improved in 67% of SOLAR-1 and 73% SOLAR-2 patients, and CTP scores improved in 67% of SOLAR-1 and 77% of SOLAR-2 patients.^{9,25} In the UK Expanded Access Program, extended follow-up to 15 months posttreatment was associated with continued improvement in liver synthetic function and rates of hepatic decompensation, sepsis, and adverse events were significantly lower beyond 6 months compared with during the first 6 months post-SVR.^{26,28} In a recent European report, changes in MELD scores in patients with MELD scores greater than 15 did not result in removal from liver transplant waiting lists unless the delta MELD was greater than 4.³⁰ In a recent Markov-like simulation model comparing long-term survival in treating U.S. patients on the waiting list without HCC with MELD scores 10 to 40 with DAAs, pretransplant DAA therapy increased life expectancy and QALYs compared with post-LT treatment, if the MELD was 27 or less and with the threshold for treatment varying between 22 and 27 depending on region (median MELD at LT).³¹ Another cost-effectiveness study of patients with decompensated cirrhosis found antiviral therapy before LT to be more cost-effective than delaying therapy until after LT.³²

Although sustained viral suppression may lead to rapid resolution of necroinflammation and liver regeneration, regression of liver fibrosis is a much slower process. Therefore, reduction in portal hypertension may be delayed despite recovery of liver synthetic function. In a long-term study of

treatment with sofosbuvir and ribavirin in patients (64% CTP B and 36% CTP A) with portal hypertension, significant reductions in portal pressure were only observed at 96 weeks posttreatment.²⁹ A European study found that 60% of patients with CTP score A cirrhosis had a decline in HVPg with SVR, with 23% achieving HVPg measurements less than 10 mm Hg, whereas less consistent reductions were seen in patients with CTP-B cirrhosis.³³ Therefore, although many patients will exhibit slow continued improvements in their MELD score after SVR, significant morbidity from complications of severe portal hypertension may persist.

The safety and tolerability of DAA therapies decreases with worsening liver function. Because NS3A PIs and non-nucleotide NS5B polymerase inhibitors undergo primarily hepatic metabolism, drug exposure is markedly increased in patients with hepatic impairment which will increase the risk of dose-limiting toxicity especially hepatotoxicity with NS3A PIs. PIs are contraindicated in patients with CTP-B/C cirrhosis. The safest DAA combination in decompensated patients is therefore a nucleotide NS5B inhibitor (renal clearance) plus an NS5A inhibitor (biliary clearance not metabolized). This includes ledipasvir-sofosbuvir, daclatasvir plus sofosbuvir, and sofosbuvir-velpatasvir. However, renal dysfunction is common in patients with end-stage liver disease awaiting LT. Sofosbuvir is not currently recommended in patients with CrCl less than 30 mL/min due to concerns about cumulative toxicity from sofosbuvir and its major metabolite GS-331007. In an ongoing Phase II study (NCT01958281) in patients with CKD Stage 4/5 (CrCl <30 mL/min), a reduced sofosbuvir dose of 200 mg/d resulted in suboptimal SVR rates presumably reflecting lower intrahepatocyte triphosphate formation. Increasing the sofosbuvir dose to the standard 400 mg/d, increased SVR rates to those achieved in patients with normal renal function, without any evidence of sofosbuvir-related toxicity. However, current labeling restrictions remain unchanged. Real-world studies, including TARGET-HCV report higher rates of anemia, renal-associated adverse events and worsening estimated glomerular filtration rate in patients with CrCl less than 35 or 45 mL/min than in patients with higher CrCl values.^{34,35} Because these studies were uncontrolled, whether these adverse side effects reflect use of ribavirin, the natural decline in renal function in those with preexisting renal disease or sofosbuvir-associated toxicity cannot be discerned.

Future Directions

There are 2 key issues. First, defining the “Point of No Return,” where the benefits of antiviral therapy do not yield clinical improvements or potential to be removed from the list due to improvements, remains a critical issue for the transplant community. Second is defining the group at risk of MELD purgatory, where antiviral therapy reduces MELD but does not yield sufficient clinical improvements and makes access to LT more difficult. It is unlikely that randomized controlled trials will ever be undertaken to address these issues. Large observational studies and modelling may provide insights. Future research should include evaluation of biomarkers of liver recovery or nonrecovery. Furthermore, understanding the factors responsible for the lower SVR rates in patients with decompensated disease (CTP score B/C) continues to be an unresolved question.

III. MANAGEMENT OF WAITLISTED PATIENT WITH DECOMPENSATED CIRRHOSIS AND HCC

Background

Although there is a large body of data on the treatment of patients with decompensated cirrhosis, and to a lesser extent compensated cirrhosis with HCC, there is a paucity of data regarding patients with both decompensation and HCC. The pragmatic approach is to adopt the treatment strategy for patients with decompensated cirrhosis without HCC, with a few key differences. For non-HCC decompensated patients, antiviral treatment may sufficiently improve the liver function to a point, whereby LT may no longer be necessary. However, for decompensated patients with HCC, LT will likely be required even with improvement in liver function. Additionally, the potential MELD purgatory that may occur with decompensated HCV without HCC becomes less of an issue for HCC patients who are eligible for LT through MELD exception points.

Recommendation 3.1:

We suggest that HCV-infected patients with decompensated cirrhosis and HCC, who are not expected to undergo liver transplantation within a short time (3-6 months), be treated with antiviral therapy.

Quality/Certainty of Evidence: Very Low

Strength of Recommendation: Conditional

Recommendation 3.2:

We suggest that HCV-infected patients with decompensated cirrhosis and HCC, who are expected to undergo liver transplantation within a short time (3-6 months), should not be treated with antiviral therapy.

Quality/Certainty of Evidence: Very Low

Strength of Recommendation: Conditional

Technical Remarks

1. The decision to treat a waitlisted patient with HCC should be individualized. Potential benefits and harms of antiviral therapy to be considered in the patient-provider shared decision making are shown in Tables 1 and 2. The primary benefit of antiviral therapy is prevention of waitlist drop off due to worsening decompensation. The timeframe to complete antiviral therapy is typically 3 to 6 months, leading to the suggestion that patients with less than 3 months to LT have treatment deferred until post-LT.
2. Additional center-specific factors to consider when carefully weighing the benefits and potential harms of antiviral therapy include:
 - Anticipated time to LT
 - Access to living donor LT
 - Availability of anti-HCV-positive donors
 - Waiting list mortality rate
 - Access to and costs of antiviral therapy

3. The type of antiviral therapy, the use of ribavirin, and the duration of therapy should be the same as that recommended for patients with decompensated cirrhosis without HCC (Table 3).
4. Patients who undergo LT before completion of antiviral therapy should continue therapy after LT to complete the intended duration.
5. In centers where living donor LT and an eligible donor are available, antiviral treatment should be deferred into post-LT.

Evidence and Rationale

Only a few studies reported patients with both decompensation and HCC listed for transplantation. In each of these studies, patients with decompensated cirrhosis with HCC made up only a small proportion, with most patients having HCC and compensated cirrhosis or decompensated cirrhosis without HCC. In a phase 3 study of daclatasvir + sofosbuvir + ribavirin for 12 weeks, 6 of 60 patients had HCC with CTP B/C cirrhosis, of which 4 were transplanted, and 3 of these patients had a further 12 weeks antiviral treatment after LT.¹⁰ The SVR12 was 100% for these 6 patients. In a phase 2 study of sofosbuvir + ribavirin for 24 to 48 weeks, 17 of 61 patients had HCC with CTP B/C cirrhosis, with an intent-to-treat post-transplant virological response of 47%.¹⁴ In a cohort study using sofosbuvir-based regimen, 32 of 182 patients had CTP B/C cirrhosis and HCC, achieving a SVR12 of 76% and 81% for CTP B and C, respectively.¹⁸ Detailed analyses of these patients are not available because they represent a small subgroup of the study population, and were not subjected to separate analysis. Therefore, there are no available results on waitlist mortality, HCC progression, and posttransplant HCC recurrence and survival.

Future Directions

As antiviral therapy with achievement of SVR is likely to improve MELD, CTP and clinical status, the major unresolved issue is whether there is an increased potential risk of HCC recurrence and possible progression after achievement of SVR. An improved understanding of tumor biology in the setting of antiviral therapy and the identification of novel biomarkers to predict HCC recurrence would be of value. Any withholding treatment in specific subgroups with decompensated cirrhosis warrants special consideration, given their risk of worsening decompensation, waitlist mortality, or removal for being too sick.

IV. MANAGEMENT OF LIVER TRANSPLANT CANDIDATES INFECTED WITH HCV AND HIV

Background

HIV/HCV coinfecting patients with cirrhosis have lower survival after the first episode of decompensation than HCV monoinfected patients. In addition, HCC occurs at an earlier age in HIV/HCV coinfecting patients and has a more aggressive course than in HCV monoinfected patients. There is no clear explanation for this more severe course since this has been observed in patients with well-controlled HIV infection and restored cellular immune function. The control of HIV infection by highly active antiretroviral therapy (ART) and the recognition of liver disease as a major cause of death in HIV/HCV infected patients prompted several centers, in the early 2000s, to undertake LT in HIV/HCV infected patients with end-stage liver disease with and without HCC.³⁶⁻³⁹ LT was generally restricted to patients with controlled HIV

infection on ART or predicted to be controllable with ART, CD4 count over 100/mm³, and no AIDS-defining events although some preventable opportunistic infections are included.⁴⁰ It has been shown that MELD score is an important predictor of mortality in HIV/HCV coinfecting patients and the risk of death sharply increases with a MELD score of 15 and higher.⁴¹ However, no specific exception status exists for HIV/HCV coinfecting patients on the waiting list and the access to LT is based on the same rules than in monoinfected HCV patients.

Recommendation 4.1

We recommend that patients with HIV/HCV coinfection be offered liver transplantation for complications of HCC and/or decompensation.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Strong

Technical Remarks

1. HCV-HIV coinfecting patients should be referred for LT early, after the first episode of hepatic decompensation or if MELD is 15 or greater even in the absence of decompensating events

Recommendation 4.2

We recommend that patients with HIV/HCV coinfection on the waiting list for liver transplantation be treated with HCV antiviral therapy.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Strong

Technical Remarks

1. Due to safety concerns with PIs, any regimen that includes this drug class is contraindicated in patients with decompensated cirrhosis.
2. Change of ART may be necessary to avoid drug interactions with HCV antivirals. Advice from an HIV expert is strongly recommended.
3. Combination of sofosbuvir plus an NS5A inhibitor (ledipasvir, daclatasvir, velpatasvir) is a safe and well-tolerated option for patients with decompensated cirrhosis.^{15,16}
4. Ribavirin appears to reduce the risk of relapse in patients with decompensated cirrhosis and should be strongly considered for inclusion in antiviral combinations. The recommended starting dose of ribavirin should be 600 mg daily and adjusted to tolerability.
5. Duration of therapy is 12 to 24 weeks depending on genotype, use of ribavirin, and presence of other negative response factors. Negative response factors include baseline RASs, prior treatment failure, albumin below 3.5 g/dL, and low platelet count.

6. Sofosbuvir-based therapy is not currently recommended in patients with CrCl < 30 mL/min due to concerns about cumulative toxicity from sofosbuvir and the major metabolite GS-331007. Until additional safety data in decompensated patients with CrCl less than 30 mL/min are available, antiviral therapy is best deferred until post-LT when improved renal status can be expected.
7. For patients started on antiviral therapy pre-LT and who undergo LT, therapy should be continued post-LT to complete the planned total treatment course whenever possible to reduce the risk of relapse. The ability to continue treatment immediately post transplantation will be dependent on CrCl and drug-drug interactions between HCV antivirals, immunosuppressive drugs, and ART.²

Rationale and Evidence

Not all transplant programs offer LT to HIV-infected patients. In part, this may be due to the programmatic resources needed to support the management of coinfecting candidates and recipients. The lower survival of HCV-HIV coinfecting patients may be another potential barrier to providing LT to HCV-HIV patients. However, these outcomes reflect LT in the pre-DAA era, and the availability of safe and effective antiviral drugs for use in HCV-HIV coinfecting patients pre- and post-LT is anticipated to yield survival rates comparable to HCV-infected transplant patients without HIV.⁴²

Data on treatment in HCV-HIV coinfecting patients with liver cirrhosis and decompensation are sparse⁴³ and thus guidance for management of coinfecting patients on the waiting list are based on studies conducted in HCV monoinfected patients (recommendations 1.1, 2.1-2.3, 3.1-3.2). It must be borne in mind that the trajectory from first decompensation event to death is accelerated in coinfecting patients with cirrhosis, warranting a timely consideration of antiviral therapy.⁴⁴ As with HCV monoinfected patients on the waiting list, the potential benefits and harms must be carefully considered (Tables 1 and 2). The benefits of antiviral treatment before LT are the prevention of posttransplant recurrence of HCV infection, prevention of liver disease progression and decompensation on the waiting list and improvement of the QOL while awaiting LT. The potential harms are reduced access to LT by lowering the MELD score, decreased access to HCV-positive liver grafts, risk of drug-drug interactions or side effects causing worsening clinical status, and failure to achieve SVR predisposing to the emergence of RASs. Factors to consider in deciding whether to treat on the waiting list include access to LT (not all programs offer LT to HCV-HIV coinfecting patients), presence of HCC, baseline MELD score and severity of portal hypertensive complications, and anticipated waiting-time to LT. Additionally, the recently passed HIV Organ Policy Equity Act allows for the utilization of HIV-positive organs in HIV-positive recipients and this may be an important strategy to shorten waiting-time for patients in the United States.

Future Directions

Given the more rapid clinical decline among HIV-HCV coinfecting patients with decompensated cirrhosis, defining the "Point of No Return," where the benefits of antiviral therapy do not yield clinical improvements to allow avoidance of LT needs to be defined for the coinfecting population. Additionally, for coinfecting patients with HCC, whether

DAA therapy is a risk for HCC recurrence while awaiting LT warrants investigation.

V. MANAGEMENT OF RECIPIENTS OF ANTI-HCV-POSITIVE DONORS

Background

The utilization rate of HCV-positive grafts has increased over the past 20 years, most strikingly during the DAA era. In a recent United Network of Organ Sharing study of HCV-infected recipients, the proportion who received HCV-positive livers increased from 6.9% in 2010 to 16.9% in 2015 and the discard rate declined over this same period from 28% to 11%.⁴⁵ The dilemma of using HCV-positive grafts stands on the balance between risk of HCV transmission (depending on quality of the screening, level of viral replication and detection, HCV status of the recipient) and potential benefits for the recipient (higher chances of receiving a graft). The availability of DAA therapy positively modifies that benefit-harm balance. All donors are screened for anti-HCV status but only a proportion will have active viral replication.⁴⁶⁻⁴⁸ Availability of nucleic acid testing (NAT) varies regionally. All anti-HCV-positive donors should be considered infectious in the absence of NAT results. Rarely, HCV transmission has been reported in NAT-negative donors, related to very recent HCV infection.⁴⁹ The proportion of NAT-negative anti-HCV-positive donors may increase over time related to increased use of antiviral therapy among all HCV-infected persons.

Recommendation 5.1:

We recommend the use of anti-HCV-positive grafts in antiHCV-positive, HCV-RNA-positive recipients.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Strong

Recommendation 5.2:

We recommend against the use of grafts from donors with F2 fibrosis.

Quality/Certainty of Evidence: Moderate
Strength of Recommendation: Strong

Technical Remarks

1. If NAT is not available, the anti-HCV-positive donor should be considered infectious. Anti-HCV-positive, HCV RNA-negative donors are a low risk for transmission and their use can be unrestricted.
2. HCV RNA-positive donors are best used in anti-HCV-positive recipients, as post-LT outcomes are not negatively affected and in those recipients who are HCV RNA-positive, HCV treatment post-LT would be required independent of the donor.
3. The quality of the HCV-positive graft should be carefully evaluated. Older (>55 years of age) donors and donor livers with fibrosis stage of more than F1 (mild) are associated with lower graft survival and should be used in cases of extreme need. The specific age cutoff should be guided by the local donor epidemiology.

4. Fibrosis assessment can be difficult on frozen sections and lead to under-staging of fibrosis. Additional measures, such as the surgeon's assessment, should also be used.
5. Genotype is not essential in making decisions regarding the use of an HCV-positive liver. No genotype-related restriction should be applied.
6. Retesting of HCV genotype post-LT may be necessary to determine whether the donor or recipient virus is predominant. This will guide post-LT antiviral decisions.

Evidence and Rationale

Most studies show a favorable outcome among anti-HCV-positive recipients who received anti-HCV-positive livers,^{46,48,50-60} leading to the recommendation that anti-HCV-positive donors be used preferentially in anti-HCV-positive recipients. The reported overall patient survival rates at 5 years range from 47% to 82% across studies, and are not significantly different from anti-HCV-positive recipients who receive anti-HCV-negative livers. However, specific risk factors for worse graft and patient outcome among anti-HCV-positive LT recipients who had an anti-HCV-positive donor included older donor age^{55,56} and presence of donor liver fibrosis.⁴⁶ HIV-HCV coinfecting transplant recipients receiving an organ from anti-HCV-positive donor had worse survival in 1 study.³⁶ Generally, either the donor or recipient strain dominates after grafting, with significantly longer disease-free survival reported in patients in whom the donor rather than recipient strain dominated after LT.^{47,48}

Recommendation 5.3:

We suggest a limited use of anti-HCV-positive grafts (HCV RNA-positive or unknown) in anti-HCV or HCV RNA negative recipients.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Evidence and Rationale

Three studies, with a total of 564 cases of anti-HCV-positive grafts in HCV-negative recipients, are available for review.^{46,52,53} Two studies found no difference in outcomes compared to recipients of anti-HCV-negative donors, but these studies were of low quality,^{46,53} leaving the study from Northup et al of United Network of Organ Sharing patients providing the highest quality data on this issue. In this study, a worst survival was seen in HCV recipient (R)-/donor (D)+ compared with all other groups (HCV R+/D+ and HCV R-/D-) but there were no data on the donor's HCV RNA and liver fibrosis status in this study.⁵² Historically, most anti-HCV-positive recipients were HCV RNA-positive at the time of LT but with the wider use of DAA therapy, a greater proportion of anti-HCV-positive LT candidates may be anti-HCV-positive but HCV RNA-negative. There are no studies of HCV-positive donors in HCV-negative recipients in the DAA era, though clinical trials are underway in kidney transplant recipients.

Given the donor shortage, the use of a potentially infectious organ may be considered in situations of high medical urgency and with full consent of the recipient and guarantee of access to antiviral therapy post-LT. Whether HCV uninfected patients receiving an anti-HCV-positive donor are a higher risk of early and severe disease is unknown, but in the absence of data, early therapy should be undertaken. Given the relevant ethical issue posed by grafting an HCV-positive organ in an HCV-negative recipient, a detailed informed consent process should be adopted.

Recommendation 5.4:

We recommend that liver transplant recipients of anti-HCV-positive grafts, with confirmed viremia after transplantation, be treated with antiviral therapy early.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Technical Remarks

1. Local legal, funding, and regulatory issues must be considered. Detailed informed consent should be obtained.
2. Anti-HCV-positive, HCV RNA-positive donors are at high risk of transmission and their use in HCV-negative recipients should be restricted to situations of high clinical need. Included are anti-HCV-positive recipients who are HCV-RNA-negative after antiviral therapy. If NAT is not available, the anti-HCV-positive donor should be considered infectious.
3. Given the potential for more rapid progression of recurrent HCV post-LT, donor graft quality should be carefully considered, that is, donor age and severity of fibrosis. Pending more experience with this scenario, younger donors with minimal or no fibrosis may be preferred.
4. The risk of future liver disease, or complications including HCC, in recipients of HCV-RNA-positive donors is currently unknown and the uncertain natural history should be discussed with the recipient as part of the consent process.

Technical Remarks

1. The source of post-LT infection may be from the recipient, donor or both, depending on the HCV RNA status of recipient and donor at the time of LT.
2. Documentation of post-LT viremia establishes the diagnosis of HCV infection. Quantifiable HCV RNA and genotyping can typically be obtained 2 to 4 weeks after LT. Determination of posttransplant genotype may be needed to guide antiviral therapy choices. If the donor or recipient has a history of prior HCV DAA treatment, consideration may also be given to testing for RASs pre-treatment.
3. The anti-hepatitis C therapy of choice for LT recipients who receive an anti-HCV-positive donor should be determined by the following:
 - Genotype
 - Available antiviral options
 - Prior treatment, if any, with NS5A-containing regimens
 - CTP score

- Patient's ability to tolerate ribavirin (baseline hemoglobin, CrCl)
 - Potential drug-drug interactions
 - Renal function
4. Pangenotypic DAA regimens may be useful in this setting, where mixed infections may be present but not identified by standard genotyping assays.
 5. Early antiviral therapy, starting weeks to a few months after transplantation, has the benefit of preventing hepatitis and fibrosis progression and thus is favored. Whether starting treatment immediately after transplantation (preemptive therapy) has an advantage over early therapy is unknown. Earlier treatment is strongly encouraged in HCV-negative patients who receive HCV RNA-positive donors. The patient's clinical status should be sufficiently stable to avoid interruption or early discontinuation of therapy.
 6. Current DAA regimens are predicted to be effective and have a positive effect on long-term outcomes, and it is important to be certain that the recipient will have access to these drugs post-LT.

Evidence and Rationale

HCV-infected recipients who receive an HCV RNA-positive donor may have donor or recipient strains persist post-LT. In a detailed study of 14 recipient positive -donor positive LT patients, the dominant viral strain post-LT was donor-derived in 8 patients and the recipient-derived in 6 patients.⁴⁸ Disease progression tended to be milder if the donor viral population was retained. Natural history studies reveal worse outcomes for HCV-negative recipients transplanted with HCV-positive donors.⁵² This may be related to a more aggressive HCV recurrence and/or the degree of fibrosis present in the transplanted graft. The best means to prevent acute and chronic and progressive complications is to achieve viral eradication early. For the HCV uninfected patient who receives an anti-HCV-positive and HCV RNA-positive graft, there may be a higher risk of early and severe disease, so starting treatment immediately or with a few days of liver transplantation (preemptive) may be considered, though data on the efficacy of this approach versus starting treatment a few weeks after LT are lacking.⁶¹

Future Directions

A key area of future research is the safety and efficacy of using anti-HCV-positive, NAT-positive donors in anti-HCV-negative recipients. Additionally, studies evaluating the optimal antiviral treatment strategy in this group are needed.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of panelists at the ILTS consensus meeting including: Michael Abecassis, Thomas Schiano, Helen Te, Gregory Everson, John Roberts, Roberta Fontana, Josh Levitsky, John Fung, Frederico Villamil, Maria Londano, in addition to the ILTS governing board, especially Elizabeth Pomfret, and organizational support from Lisa Pedicone.

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