Treatment of HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors

With the large disparity between patients in need of organ transplantation and available donor organs, some transplant programs are turning to use of organs from HCV-viremic donors. In the past, organs from HCV-viremic donors were primarily used in recipients with chronic hepatitis C or discarded. With the advent of safe and effective HCV DAA regimens, however, organs from HCV-viremic donors may be considered for use in recipients without HCV infection. Use of these organs increases the pool of available organs, patient access to transplantation (Sageshima, 2018), and potentially reduces waitlist time (Bhamidimarri, 2017); (Scalea, 2015) and related mortality (Sawinski, 2019); (Shelton, 2018); (Kucirka, 2012).

All organ donors undergo HCV-antibody and HCV nucleic acid testing (NAT). Nonhepatic donors who are HCV antibody positive but HCV RNA negative likely pose a negligible risk of HCV transmission to the recipient, although more data are needed to confirm this. However, among increased risk donors (as defined by the US Public Health Service [PHS] guidelines) who had a recent HCV exposure, HCV RNA may not yet be detectable and transplant recipients from these donors should be monitored for HCV in addition to HBV and HIV per the increased risk donor testing protocols (Levitsky, 2017); (Seem, 2013b). Emerging data indicate that transplant recipients who receive a liver from an HCV-antibody-positive/HCV-RNA-negative donor should be monitored more closely after transplantation given the potential risk for HCV transmission (Bari, 2018). Donors who are HCV RNA positive (with or without anti-HCV) pose the highest risk for HCV transmission to transplant recipients. Because of the significant risk for HCV infection when transplanting an organ from an HCV-viremic donor into an HCV-uninfected recipient, rigorous informed consent and post-transplantation, HCV-related follow-up processes are recommended.

Recommendations When Considering Use of HCV-Viremic Donor Organs in HCV-Uninfected Recipients

RECOMMENDED	RATING
Informed consent should include the following elements: • Risk of transmission from an HCV-viremic donor (and with a PHS-defined increased risk donor, the potential risks for other viral infections) • Risk of liver disease if HCV treatment is not available or treatment is unsuccessful • Benefits, specifically reduced waiting time and possibly lower waiting list mortality • Unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure is attained) • Risk of graft failure • Risk of HCV transmission to partner	I, C
Transplant programs should have a programmatic strategy to: • Document informed consent • Assure access to HCV treatment and retreatment(s), as necessary • Ensure long-term follow-up of recipients (beyond SVR12)	I, C

Recent data indicate increasing acceptance of organs from HCV-viremic donors among HCV-uninfected recipients (Cotter, 2019); (Potluri, 2019); (Bowring, 2018). Although no published data are available regarding the long-term (beyond 1 to 2 years) consequences to HCV-negative recipients transplanted with organs from HCV-viremic donors who are

treated post-transplant with DAAs, limited short-term data from liver, kidney, heart, and lung transplant programs are encouraging.

Liver Transplantation

Among 10 HCV-negative liver transplant recipients of organs from HCV-viremic donors, 100% achieved SVR12 with 12 to 24 weeks of various DAA regimens (Kwong, 2019); the median time from transplantation to treatment initiation was 43 days (interquartile range [IQR] 20-59 days). Noteworthy was the high rate of acute cellular or antibody-mediated rejection (30%) during or after DAA therapy in this study. A retrospective study of deceased donor liver transplantations in the US from January 2008 through January 2018 demonstrated that 2-year graft survival was similar, regardless of HCV status concordance or discordance between the allograft donor and recipient (Cotter, 2019). Unlike with other organs, shorter durations of HCV therapy should not be used in recipients of livers from HCV-viremic donors because of the large reservoir of HCV in the transplanted organ.

Transplantation of Other Organs

In the THINKER trial, 10 HCV-uninfected kidney transplant recipients received allografts from genotype 1 HCV-viremic donors and were treated with 12 weeks of elbasvir/grazoprevir; 100% achieved SVR (Goldberg, 2017). In a 1-year follow-up study that included 10 additional participants (n=20) who received 12 to 16 weeks of elbasvir/grazoprevir (± ribavirin), all achieved SVR12. Kidney function in those who received kidneys from HCV-infected donors was comparable to matched controls who received allografts from HCV-uninfected donors (Reese, 2018). A separate open-label trial similarly demonstrated 100% SVR12 with 12 weeks of elbasvir/grazoprevir (± sofosbuvir) therapy initiated immediately prior to transplantation in 10 HCV-uninfected kidney transplant recipients of allografts from HCV-viremic donors (Durand, 2018). Notably, organ recipients in this study received the first dose of elbasvir/grazoprevir on call to the operating room. Of the 10 patients treated, only 3 had detectable HCV viremia compared to 100% in the THINKER trial, which utilized the same regimen but initiated therapy on day 3 after transplantation. Other regimens (including glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, and sofosbuvir/velpatasvir) have been studied in HCV discordant kidney donors and transplant recipients and demonstrated high SVR12 rates and no treatment-related toxicities (Franco, 2019); (Friebus-Kardash, 2019).

A study of HCV-uninfected recipients who received a heart transplant from an HCV-viremic donor showed that using a 12-week course of elbasvir/grazoprevir initiated a few days after transplantation (once the recipient became viremic) resulted in SVR12 in 9 out the 10 evaluable patients (McLean, 2019). In another clinical trial of 44 HCV-uninfected lung (n=36) and heart transplant (n=8) recipients from HCV-viremic donors, sofosbuvir/velpatasvir was administered prophylactically/preemptively, starting within a few hours after transplantation, and continued for 4 weeks (compared to the standard 12-week course). Among the initial 35 patients with at least 6 months of follow-up after transplantation, 100% achieved SVR and had excellent graft function (Woolley, 2019). There was an increase in the proportion of the HCV-viremic lung cohort who had acute cellular rejection compared to the non-HCV lung cohort, although this finding was not statistically significant and longer-term follow-up is needed to assess for chronic rejection. In a study of 20 HCV-uninfected heart transplant recipients of allografts from HCV-viremic donors, patients were treated prophylactically/preemptively with glecaprevir/pibrentasvir beginning just prior to transplantation and continued for 8 weeks. All participants achieved SVR12, and patient and graft survival were 100% with a median follow-up of 10.7 months (Bethea, 2019). Another clinical trial evaluated 22 HCV-uninfected lung transplant recipients of allografts from HCV-viremic donors; the 20 patients who became viremic after transplantation were treated with 12 weeks of sofosbuvir/velpatasvir beginning 2 to 6 weeks after transplantation (median 21 days; IQR 16.76-24.75 days). All lungs from HCV-viremic donors were treated with ex-vivo lung perfusion ± ultraviolet C perfusate irradiation to reduce HCV RNA concentration and infectivity, likely contributing to a slower rise in HCV viral load among recipients. Although all 20 DAA-treated patients had undetectable HCV RNA at the end of treatment, 2 patients experienced post-treatment relapse. One patient experienced severe hepatitis with early signs of fibrosing cholestatic hepatitis [FCH] on liver biopsy, and both patients exhibited complex NS3A and NS5A RASs at relapse. Both relapsed patients were successfully retreated with 24 weeks of sofosbuvir/velpatasvir/voxilaprevir plus ribavirin and achieved SVR12 (Cypel, 2019).

While these early results are encouraging, the overall number of published cases is small and treatment approaches notably variable. Known reported risks include DAA treatment failure with emergence of complex RASs and possible

severe or rapidly progressive liver disease (fibrosing cholestatic hepatitis) (Cypel, 2019); (Kapila, 2019); (Molnar, 2019). Additionally, ethical and scientific issues remain, including avoidance of selection bias, optimal timing of DAA therapy, and long-term graft and patient outcomes. Due to the limited and heterogeneous experience and lack of longer-term safety data, strong consideration should be given to performing these transplantations under IRB-approval protocols as recommended by the American Society of Transplantation consensus panel (Levitsky, 2017).

Recommendations Regarding Timing of DAA Therapy

RECOMMENDED	RATING
Prophylactic/preemptive treatment[a] with a pangenotyic DAA regimen is recommended.	II, B
ALTERNATIVE	**RATING**
Treatment with a pangenotypic DAA regimen within the first week after transplantation, is a reasonable alternative. A genotype-specific regimen may be used if genotype information from the donor or recipient is available to guide therapy.	II, B

[a] Prior to HCV RNA results, typically day 0 to 1 post-transplant

Recommended and alternative[a] regimens listed by evidence level and alphabetically for:

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RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, C
ALTERNATIVE	**DURATION**	**RATING**
Genotype 1 and 4 only: Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[c] for elbasvir	12 weeks	I, C
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, C

[a] Other considerations in selection of the DAA regimen:

- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended and alternative[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Organs From HCV-Viremic Donors

[c] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Initiation of DAA therapy for HCV-negative recipients of an allograft from an HCV-viremic donor can occur prophylactically/preemptively (ie, perioperatively without confirmation of viremia in the recipient) or reactively after documentation of HCV viremia. The goal is to undertake DAA therapy as early as clinically possible to avoid the development of acute hepatitis and other complications of HCV infection. Emerging data suggest that initiating prophylactic/preemptive DAA therapy before viremia occurs may reduce the likelihood of complications, such as FCH (Bethea, 2019); (Cypel, 2019); (Kapila, 2019); (Woolley, 2019); (Durand, 2018). A prophylactic/preemptive treatment approach may also allow for a shorter duration of DAA therapy in nonliver transplant recipients of organs from HCV-viremic donors (Woolley, 2019), although this is not currently recommended outside of a clinical trial setting and has only been studied in the context of nonhepatic transplantation.

Selection of the DAA therapy for HCV-negative recipients of an allograft(s) from an HCV-viremic donor should follow the same principles as for those who develop recurrent HCV infection post liver transplantation (see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation). Importantly, since genotyping of HCV-viremic donors is not routinely performed, only pangenotypic regimens should be utilized if a prophylactic/preemptive treatment approach is used. If treatment is delayed until the recipient has quantifiable HCV RNA, the recipient's genotype can be used to guide DAA treatment selection if a pangenotypic regimen is not used. Selection of regimens that avoid the use of ribavirin (to reduce ribavirin-associated side effects) and regimens that do not require baseline RAS testing are preferred. Thus, although there are data supporting the safety and efficacy of elbasvir/grazoprevir among HCV-negative kidney and heart transplant recipients of allografts from HCV-viremic donors, the regimen is designated an alternative regimen due to the necessity for baseline RAS testing and its limited genotype coverage. Similarly, ledipasvir/sofosbuvir is designated as an alternative regimen due to lack of pangenotypic coverage.

Notably, organs from HCV-viremic donors may be used in transplant candidates with current or prior HCV infection (see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation).

Drug-Drug Interactions Between DAAs and Calcineurin Inhibitors

The interaction of DAA agents and calcineurin inhibitors is complex and unpredictable without formal studies of drug-drug interactions. A summary of interactions between calcineurin inhibitors and DAAs with recommended dosing is provided in the DAA Interactions With Calcineurin Inhibitors table.

Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a 2-fold increase in elbasvir AUC can be expected with cyclosporine coadministration. Therefore, this combination should be avoided. Since a 40% to 50% increase in tacrolimus level is predicted with coadministration of grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored. No clinically significant drug-drug interactions have been observed between sofosbuvir-inclusive regimens and tacrolimus.

Last update: December 11, 2019

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