Editorial Commentary

Liberalizing transplantation of HCV positive donor organs into HCV negative recipients

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In the United States, the demand for solid organ transplantation exceeds the availability of donor organs. As of April 14, 2020, an estimated 103,170 kidney, 12,960 liver, 3,682 heart, 1,283 lung transplant candidates are waiting transplantation with only 5,676 kidney, 2,198 liver, 874 heart, and 670 lung transplants being done thus far (1). Historically, HCV seropositive donor organs had been discarded due to concerns of transmission to recipients, poor graft function and increased mortality (2). This has resulted in prolonged wait times on transplant lists for all organs, including heart, lung, liver, and kidneys. However, with the recent surge in opioid overdose related deaths came a large pool of young, otherwise healthy, but HCV seropositive donors (3,4). This, coupled with the advent of curative direct acting antiviral (DAA) agents in the treatment of HCV, has opened up the potential of transplanting HCV donor organs into HCV negative recipients (D+R–). Adoption of this strategy has not only limited organ wastage, but also decreased the amount of time patients wait for organ availability (5-9). Although this sounds straightforward, controversy exists in determining if patients should undergo pre-emptive/prophylactic treatment as opposed to reactive treatment, as well as in determining duration of treatment.

Accumulating data is pushing the transplant community toward a shift in paradigm. In July 2019, The Lancet published a provocative article titled, "Pre-emptive pangenotypic DAA therapy in donor HCV-positive to recipient HCV-negative heart transplantation: an open-label study." The study included 25 HCV positive donor hearts, 20 of which were viremic. Recipients of HCV viremic hearts were given pre-emptive glecaprevir/pibrentasvir (GP), with one dose given immediately prior to transplantation, and with subsequent once daily dosing for 8 weeks. In the 5 non-viremic HCV Ab positive organs, a reactive treatment strategy was adopted, with treatment only initiated if patient developed viremia, a phenomenon that did not occur during the span of the study. GP was selected due to fewer drug-drug interactions with amiodarone. The study, although relatively small, non-blinded, and with relatively short follow up of one year, determined that patients receiving an HCV positive donor heart received that organ more quickly, and that *pre-emptive* administration of GP led to rapid HCV suppression and prevention of chronic HCV without compromising allograft function (10). Historically, HCV positive solid organ transplant recipients were not treated post-transplant for fears of interferon induced organ rejection. Thus, solid organ recipients with HCV may have been treated pre-transplant or even considered ineligible for transplant due to active infection. To think that centers are now willing to infect recipients to facilitate transplant is truly monumental.

The risk of HCV transmission in D+R– solid organ transplantation will depend on both the donor viral load and the organ being transplanted. Thus, the post-transplant strategy may vary based on risk. Organs which are HCV Ab positive with a negative viral load have a very low risk of potential transmission to the recipient, even in liver transplantation (11-13). There may be a slightly higher transmission risk in HCV Ab positive, RNA negative "high risk donors" as identified by the US Public Health Service, and according to AASLD guidelines. Recipients of "high

risk donor" organs should be monitored post transplantation for possible transmission (14-16). The highest risk of transmission is in Ab+, NAT+ donors, which can result in nearly 100% transmission in liver transplants, however was less so with other organs such as heart and kidney (17). A recent study by Kapila et al. of viremic donor organs (NAT+) transplanted into aviremic recipients showed that 95% kidney transplants, 100% of liver transplants, and 100% of heart transplants became viremic, however with use of DAA, all but one of 77 patients achieved sustained virologic response (SVR) (17).

The treatment of HCV after transplantation has proven safe and effective (16). Until recently, most post-transplant HCV was a result of transplanting an organ either HCV positive or negative into an HCV positive recipient. Even in this scenario, post-transplant protocols varied without consensus on when to initiate therapy, though most agree that early treatment is preferred.

Transplantation of a seropositive organ into a seronegative recipient has had relatively recent historical precedence. It has been trialed extensively in kidney and liver transplants, and more recently in lung and cardiac transplantations (2,7,8,10,18,19). Extending viremic HCV positive transplant to HCV negative recipients has viral induced risk including fibrosing cholestatic HCV (FCH) and extra-hepatic manifestations of HCV such as membranoproliferative glomerulonephritis (MPGN). Initiating DAA therapy also has well defined risk including drug interactions and potential toxicity. While studies have shown that the risks of transmission are low, there can be a risk of DAA related graft rejection and loss, although the long term adverse effects are yet to be understood (20-23).

Given that transmission may not be 100%, many early protocols deferred therapy until after post-transplant viremia was documented and the patient was considered appropriate for treatment. Unfortunately, there were rare but sometimes lethal consequences of delaying treatment.

Shortening duration of therapy from the standard 8–12 weeks is a potential strategy to limit treatment associated side effects. This has been effective is small trials of non-liver solid organ transplant, with Feld *et al.* presenting a preliminary data from of 25 D+R– patients given pre-emptive GP and the HCV entry blocker ezetimibe, followed by 7 post-operative daily doses (24).

In 2020, AASLD published updated guidance which supported either pre-emptive/prophylactic or reactive, pan-genotypic DAA treatment regimen for HCV negative recipients of an HCV viremic donor organ. Initiation of this can be done in two different strategies: prophylactic treatment at the time of transplant, or reactive treatment if the recipient develops HCV viremia (16). Some recent data, including that from Bethea *et al.*, suggest that a prophylactic strategy reduces the risk of intra and extra hepatic complications and may even allow for a shorter course of therapy, with treatment regimens as short as one week being studied at present (10,19,25-27). Effective pan-genotypic treatment regimens include an 8-week course of GP, a 12-week course of sofosbuvir/velpatasvir (16). Drug choice should be carefully considered, especially in the setting of potential drug-drug interactions, most particularly with regards to concomitant calcineurin inhibitor use.

Although accumulating evidence is pushing the transplant community to consider HCV D+R– standard of care, more data is essential to identify which patients are most appropriate to receive HCV positive allografts and the ideal post-transplant treatment strategies (pre-emptive vs. prophylactic DAA administration), coupled with study into determining adequate duration of therapy to minimize "overtreatment." In addition to identifying an ideal duration of therapy, long term follow-up of recipients of HCV positive donor organs will provide beneficial information regarding complications and allograft function.

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