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From Heresy to Standard of Care: A Virologic Journey

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In this month's issue, Bohorquez and colleagues⁽¹⁾ review their experience with transplanting hepatitis C virus (HCV)+ donor livers into HCV- recipients. In a retrospective analysis, the authors report from June 2018 to December 2019, following verification of direct-acting antiviral (DAA) access, the absence of critical drug-drug interactions, and informed consent, allocated HCV Nucleic Acid Amplification Testing (NAT+) organs were routinely offered to all patients on the waiting list for liver transplantation irrespective of recipient HCV status. After excluding 47/339 HCV- recipients for HCV viremia, refusal to receive HCV+ organs, or inability to receive DAA following transplantation, 61 HCV- recipients received an HCV NAT+ liver and 231 HCV- recipients received an HCV NAT- liver. Median time from transplant to the start of DAA treatment was 66.9 days, and all patients who completed DAA treatment achieved a sustained virological response (SVR). At 1 year, both patient and graft survival were similar between groups. The authors conclude that this practice should now be considered the standard of care.

What exactly is standard of care? Standard of care is typically defined as the level and type of care that

a reasonably competent and skilled health care professional, with a similar background and in the same medical community, would provide to a patient under specific circumstances. It can also be defined as “. . . not a guideline or list of options: instead, it is a duty determined by a given set of circumstances that present in a particular patient, with a specific condition, at a definite time and place.”⁽²⁾ In other words, standard of care defined as such is sensitive to person, time, and place. Most medical therapies trace their beginnings to attempts to help reduce the burden of disease using the tools at hand while weighing the risks and benefits of the treatments. Early on, clinicians experienced with hepatitis C in liver transplantation recognized the deleterious effects of the virus, and the transplant community certainly did not endorse potential transmission of the virus during transplantation at that time. So what has been our journey from a place where hepatitis C was a relative contraindication to transplant to the place where this may now be considered the standard of care to transmit the virus in the process of transplantation?

Studies regarding liver transplantation for hepatitis C and the use of HCV+ donor organs date back to the early 1990s. Despite findings of near 100% persistent virus and recurrent hepatitis and fibrosis following transplantation, the 5-year reported graft and patient survivals were reported as similar when compared with patients who were HCV-.^(3,4) HCV+ donor organs when used in HCV+ recipients resulted in similar graft and patient survivals compared with HCV- donor organs.⁽⁵⁾ At the time, prior to 1994, donor organs met or exceeded the number of liver transplantation registrants, allowing ample consideration and selection of donor organs for the pool of patients awaiting liver transplantation.⁽⁶⁾ During those early years, treatment for HCV was limited to interferon and ribavirin, which were both poorly tolerated and resulted in suboptimal SVR rates in transplant recipients.⁽⁷⁾ Therefore, when taking into account person, time, and place and given the limitations of available treatment, the standard of care was to transplant HCV+ recipients with or without the use of HCV+ organs and with or without available antiviral therapy,

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; SVR, sustained virological response.

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but the use of HCV+ organs were restricted to HCV+ recipients.

In the years that followed, increasing numbers of HCV+ transplanted patients coupled with longer follow-up led to a realization that beyond 5 years, graft and patient survivals were in fact inferior to those patients who were HCV-. In a landmark article using the United Network for Organ Sharing database, Forman et al. found that liver transplantation in HCV+ recipients was associated with an increased rate of both death and allograft failure compared with transplantation in HCV- recipients.⁽⁸⁾ Numerous studies followed that outlined the various factors likely contributing to poorer outcomes. Given the documented increased risk of reduced graft and patient survivals, consensus statements at that time focused on optimizing interferon treatment to control infection in HCV+ recipients while reinforcing the restricted use of HCV+ livers in HCV+ recipients.^(9,10) Despite these recommendations and the growing number of potential HCV+ recipients, the discard rate of HCV+ organs remained high.⁽¹¹⁾

Long-term graft and patient survival data at the time began to enforce the idea that if SVR could be achieved with antiviral therapy, overall patient and graft survival rates from transplantation could be improved.⁽¹²⁾ With the introduction of DAAs, the challenge at that time was the need for continued use of interferon in combination with DAAs, which restricted the overall potential benefit of treatment given the limited tolerance seen with interferon. However, as treatment advanced with the introduction of second-generation DAAs eliminating the need for interferon, increasing numbers of HCV+ transplant recipients could now be eligible for treatment. In 2015, data from the SOLAR trials demonstrated that early posttransplant treatment for HCV in liver transplantation recipients was both well tolerated and resulted in 96% to 98% efficacy using second-generation DAAs alone with or without ribavirin.⁽¹³⁾ This was a major leap forward in our ability to control the virus and improve transplant outcomes for HCV recipients. Simultaneous with the availability of well-tolerated and highly efficacious treatment for HCV in liver recipients was the rising number of HCV+ donor organs, resulting from premature deaths as a result of the advancing opioid crisis.⁽¹⁴⁾ This was paralleled by a decline of potential HCV+ recipients in need of transplant because of improved clinical outcomes with treatment prior to liver failure. Other factors at play included the growing disparity between liver

transplantation listings and available donor organs.⁽¹⁵⁾ The pressure to expand the organ pool demanded that the transplant community investigate ways to now use every possible available organ, including those that were HCV+.

In 2017, a proof of concept for expanding the potential donor pool by using HCV+ organs in HCV- recipients came from the THINKER trial, showing that the use of HCV+ kidneys could result in excellent graft function and SVR in HCV- recipients receiving DAA therapy.⁽¹⁶⁾ These data sparked numerous case reports and trials using HCV+ organs in HCV- liver, kidney, heart, and lung recipients. All of the reports and trials supported good early graft and patient outcomes, excellent medication tolerance, and high SVR.⁽¹⁷⁻²⁰⁾ In their review of clinical practice for liver transplantation from 2008 to 2018, Cotter et al. used the Scientific Registry of Transplant Recipients database to show a corresponding increase in the use of HCV livers in HCV- recipients from 7 in 2008 to 107 in 2018.⁽²¹⁾ Their findings confirmed the results from the numerous investigations as noted previously, which showed graft and patient outcomes using HCV+ organs as similar when compared with HCV- organs in HCV- recipients.

As Bohorquez et al. suggest in this month's issue, do we now consider the use of HCV+ organs as the standard of care in HCV- recipients? The American Society of Transplantation Consensus document in 2017 concluded that there was a "need for well-designed clinical trials with conclusive finding to justify payer coverage of DAA medications." Furthermore, the authors concluded that the use of HCV+ organs in HCV- recipients should be conducted under institutional review board-approved protocols and studies. Since that time, there have been numerous studies supporting both the safety and positive outcomes of this policy as outlined previously. In 2019, there were 12,111 candidates waiting for liver transplantation, 8896 liver transplantations performed, and 1200 waitlist deaths.⁽¹⁵⁾ The cumulative experience and data confirm that HCV+ donor organs can be used safely with adequate treatment and high SVR using current DAA treatment. The combination of significant risk of waitlist death in patients not receiving donor organs should push us further to consider that now is the time to consider using HCV+ organs as the standard of care for all potential recipients with rigorous informed consent and assurance of access to DAA therapy. The journey from heresy to standard of care has been made through the rigorous investigations by hundreds of

authors who have defined the safety and the efficacy of using HCV+ organs in HCV- recipients. I believe the “standard of care” balancing the risks and potential benefits of HCV+ organs in transplant recipients has now been met.

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