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EDITORIAL

SARS-CoV-2 vaccination in heart transplantation: What we do and do not know

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Vaccination is a key component in our armamentarium against coronavirus disease 2019 (COVID-19) and, in particular, for preventing severe illness and death from this infection. Unfortunately, but not surprisingly, solid organ transplant recipients (SOTR) mount a less robust antibody response, and to a lesser degree, cellular response to vaccines.[1] It is therefore not surprising that heart transplant (HT) recipients experience lower rates of seroconversion following COVID-19 vaccination. In general, detectable antibodies against the receptor-binding domain of the spike protein of the SARS-CoV-2 virus are demonstrated in 10% to 57% and cellular response in 10% to 70% of HT recipients following 2 doses of mRNA vaccines.[2-6] Increased intensity of immunosuppression, use of antimetabolites such as mycophenolate, and agents that inhibit B-cell response are associated with reduced immunogenicity. Other factors include older age, use of belatacept, lower total lymphocyte count, lower estimated glomerular filtration, and hypogammaglobulinemia.[4,6,7] Despite suboptimal seroconversion rates, vaccination was associated with reduced risk of death from COVID-19 in a National United Kingdom registry [8] as well as 80% reduced risk of symptomatic disease in a single center cohort, when compared to unvaccinated SOTR.[9]

Third dose mRNA vaccination in SOTR is associated with an increase in detectable humoral response ranging from 55% to 67.9%.[7,10-12] However, specific HT data in this setting has been sparse as previous studies included only 28 HT patients and HT-specific results were not reported.[10-12] Additionally, safety of third doses in HT recipients is not clear. A case of biopsy-proven acute antibody mediated rejection in a HT recipient was reported and occurred 7 days following a third vaccine dose.[12] Myocarditis is a rare complication and estimated to occur in 12.6 cases per million doses of second-dose mRNA vaccine among individuals between 12 and 39 years of age with a male predominance. Most confirmed vaccine-related myocarditis cases are mild, occur within 7 days of vaccination, and associated with complete resolution.[13] Vaccine-related myocarditis in HT recipients has not been described.

The study by Peled et al. is the first to systematically assess the safety and immunogenicity of a third dose mRNA vaccine administered approximately 6 months following the second in HT recipients. The authors report an acceptable safety profile in 96 adult HT patients with no reported serious adverse events or episodes of rejection within a month of follow-up from the third dose. At 18 days following the third vaccine dose, detectable antibody response increased from 23% to 67%; SARS-CoV-2 neutralization titers also increased significantly. In this study, mycophenolate use, poor kidney function, and elevated C-reactive protein levels were independently associated with a reduced likelihood of generating an immune response. A subset of 15 patients underwent assessment of specific T-cell response, which was present in 80% after the third dose. In this study, as in others, cellular responses were evident in the absence of measurable antibodies, suggesting benefit, even when there did not appear to be an antibody response.[4]

As we start administering third dose mRNA vaccines to SOTR and other patient populations, much of the world that received non-mRNA vaccines is left behind. Current data from Europe demonstrates superior immunogenicity (both humoral and cellular responses) with a heterologous prime/boost strategy for the ChAdOx1 vaccine (Oxford-AstraZeneca) followed by mRNA vaccines BNT162b2

Abbreviations: HT, Heart Transplant; SOTR, solid organ transplant recipient

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(Pfizer) and/ or mRNA1273 (Moderna) compared to homologous strategy of two doses of ChAdOx1 [14-16] in otherwise healthy patients; one study noted superiority of this regimen to two doses of mRNA vaccine as well though not seen in others.[15] Similarly, heterologous boosting with mRNA vaccine after vector priming led to significantly increased antibody and Cd4 T-cell response in SOTR in a recent study.[17] Specific data on which approach to boosting SOTR who received non-mRNA vaccines are minimal and use of booster doses in these patients is ideally performed as part of a research study to inform best practices. Developing these data is essential to allow boosting with the optimal strategy for all patients who may need additional doses of vaccine.

Vaccines reduce the risk of infection, generally through production of humoral responses, and reduced risk of severe disease (hospitalization and death) through generation of cellular immune responses. Seroprotective levels of antibodies have yet to be defined for SARS-CoV-2 vaccine in the general population and SOTRs and neutralizing antibody titers are not routinely available to providers clinically. Importantly, the limited data we have suggests that even with a third dose, SOTRs may produce very low neutralizing titers against the more recent variants.[18] The clinical impact of 2 and 3 doses of vaccination in SOTR on symptomatic COVID-19, hospitalizations, and related deaths is not well described and should be investigated especially in the setting of current surges related to the delta variant and probably additional variants as they occur. Clinical effectiveness, ongoing monitoring for rare serious adverse events, and immunogenicity data can all help develop risk benefit assessment for individual patients regarding additional vaccination doses.

Further, since a large number of patients are not fully protected with even a third dose, other COVID-19 preventive strategies need to be investigated in SOTR such as the use of monoclonal antibodies as primary prophylaxis in vaccine nonresponders and use of other vaccine candidates, including higher dose and adjuvant vaccines. In the meantime, ongoing masking, social distancing, less risky social choices, and vaccination of household members are recommended while the pandemic is ongoing. It is likely that eventually SARS-CoV-2 will become endemic with ongoing intermittent surges related to new variants. This may in turn, require periodic booster vaccines aimed at inducing a response to these new variants, as currently done with annual influenza vaccinations.

To summarize, COVID-19 vaccination is generally safe and well tolerated in SOTR, including HT recipients. Additional vaccine doses are now recommended for SOTRs in some countries who have received mRNA SARS-CoV-2 vaccines due to less effective humoral and cellular responses following the original dosing strategies. We believe that while we work on optimizing immunogenicity in vaccinated SOTR, we also need to devote time and energy in outreach efforts to increased vaccination rates overall as well as alternative strategies to effectively protect our patients from COVID-19. While significant attention has been paid to boosters for our SOTRs, large numbers of our patients remain unvaccinated.

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