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EDITORIAL

The future of SARS-CoV-2 vaccines in transplant recipients: To be determined

The increasing availability of SARS-CoV-2 vaccines has been heralded as the intervention that will finally stem the COVID-19 pandemic. However, it is unclear how immunosuppressed patients, including solid organ transplant recipients, will respond to vaccination. Given the smaller numbers of affected patients, compared with vaccine trials in the general population, the changing epidemiology of the pandemic with the emergence of concerning viral variants, and greater precautionary measure adherence, it may be difficult to determine efficacy in this population. Consequently, the assessment of immunogenicity, including measurement of antibodies to the spike receptor-binding domain and evaluation of cellular responses, provides important information to define the host response to this vaccine.

The first immunogenicity results following first doses of mRNA vaccines from a large and relatively diverse group of transplant recipients, identified via social media enrollment have been published.[1] The sharing of preliminary results focused solely on antibody measurements following a single-dose vaccine series is unusual and may be confusing to those looking for data to inform vaccine use in transplant recipients. This study used samples from standard venipuncture or novel home collection devices with two different commercial assays to detect SARS-CoV-2 spike antibody responses. After the first dose of the mRNA-based COVID-19 vaccine, the authors observed that less than 20% of patients had detectable antibodies, with the lowest response in those receiving anti-proliferative medications (e.g., mycophenolic acid) and older individuals; the impact of age has previously also been noted in non-immunosuppressed individuals.[2] They also noted a difference in responses to the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines, with less frequent antibody responses in patients receiving the BNT162b2 vaccine. No unanticipated safety concerns, including rejection, were identified with limited follow-up after the first dose.[3] These are interesting and not entirely surprising results, given that diminished antibody responses have been frequently described with other vaccines, including influenza vaccine.[4] Nevertheless, although no real-world control group was recruited, the immunogenicity as measured by antibody response to mRNA COVID-19 vaccines in transplant recipients seems to be poor, especially when compared with the general population. Similar results are now being reported from two other centers.[5,6] The authors of the original study are continuing to accrue greater numbers of patients and we look forward to follow-up results after the second vaccination.

Despite the preliminary nature of these early results, some members of the transplant community are advocating changes in patient management to improve vaccine responses, in particular the suspension of anti-proliferative agents in anticipation of vaccination. However, unproven alterations in immunosuppression may ultimately be more detrimental than beneficial if changes increase the risk of rejection or provide no meaningful improvement in vaccine responses. Additionally, some now advocate preferential use of the mRNA-1273 vaccine. It is important to recognize that the timing of the antibody testing was variable in the transplant study, something that might impact results. Moreover, antibody responses after single doses of the two different mRNA vaccines were not predictive of second dose responses in clinical trials in the general population, in whom efficacy and immunogenicity were equivalent following completion of the full vaccine series.[7,8] Some experts have also suggested that there may be benefits from double dose or additional booster vaccinations. These recommendations are also premature given gaps in our data and the limited supply of the vaccine. Full immunogenicity data, including both humoral and cellular responses, after two doses are required. Likewise, comparative data across all available vaccines, including mRNA, viral vector, and adjuvanted protein platforms, are needed. Lastly, but extremely important, efficacy data and clinical correlates of protection from infections, hospitalizations, and deaths need to be collected over time.

Transplant recipients have also expressed concern after dissemination of these preliminary data via lay press reports. Transplant centers are being inundated with calls from worried patients looking for confirmation of their vaccine responses. Given the absence of robust data to support the use of commercially available tests for measuring vaccine responses, it has been difficult to address their concerns. The data published to date do not give us the granular detail to develop recommendations from individual test results. Most assays are qualitative or at best semi-quantitative. Having a positive result may mislead a patient into thinking they are "safe" from infection when in fact titers are below protective titers. Conversely, negative testing may add to patient anxiety, despite contributions from untested factors, such as cellular immune responses. Since the thresholds for protection and the impact of cellular responses are just now being established in healthy individuals, it further confounds our understanding of how to apply results to transplant recipients.

What these data do suggest is that we likely need to consider these patients as different from the general population. Ideally, it may be preferable to initiate vaccinations in waitlisted patients to avoid the diminished responses related to immunosuppression, based on preliminary data that suggest better responses in patients with ESRD than in transplant recipients.[6] It is important to note, however, that we do not know what impact induction immunosuppression will have on protection posttransplant. Additionally, if a lower response to SARS-CoV-2 vaccines is confirmed, public health authorities and transplant providers will need to have different thresholds for when these patients may safely return to more normal activity. Until we have more data, we should advocate continued adherence to diligent mask use, hand hygiene, and social distancing.

It is important to recognize the role of private philanthropy in funding the impressive and rapid accumulation of data by the Hopkins transplant group. Federal funding dollars have largely ignored questions related to the impact of COVID-19 on a large and growing population of transplant recipients, despite the substantial impact on outcomes of the pandemic on this group of patients.[9] Carefully designed prospective and controlled studies are critical to the understanding of the impact of SARS-CoV-2 vaccination on the large numbers of immunosuppressed hosts, who may fuel future epidemics if they remain one of the primary groups of inadequately protected individuals when the pandemic declines in the general population. The success of this research platform can provide insight into approaches in future pandemics and foster the implementation of large, pragmatic, interventional trials to increase knowledge regarding improving the efficacy of vaccination in transplant recipients. Given that a wide range of immunosuppressive agents is increasingly used for an array of clinical conditions beyond transplant recipients, greater attention should be paid to their differential impact on response to the SARS-CoV-2 vaccine.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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