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Antibodies, boosters and optimizing SARS-CoV-2 vaccine for transplantation: A call for more research

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Abbreviations:
COVID-19: Coronavirus Disease-2019
FDA: Food and Drug Administration
SOT: Solid Organ Transplant

Abstract: Despite emerging data suggesting reduced antibody responses among SOT recipients following SARS-CoV-2 vaccine, critical unanswered questions remain. The clinical implications of the reduced humoral response need to be assessed through prospective studies. Studies are likewise needed to inform which vaccine dosing strategies result in improved immunity and if such approaches maximize protection against severe infection in the vulnerable transplant population.

As additional information has emerged on the clinical and immunologic efficacy of SARS-CoV-2 vaccine responses in immunocompromised patients, it has become clear that further data are needed to inform best clinical practices. While some have advocated for wider use of routine serologic assessment and booster doses based on existing data, questions remain about the utility and safety of such approaches.

As outlined by a recent advisory from the FDA (https://www.fda.gov/medical-devices/safety-communications/antibody-testing-not-currently-recommended-assess-immunity-after-covid-19-vaccination-fda-safety), current emergency use authorized serologic assays were developed as a diagnostic tool and not to assess humoral vaccine responses. Assays differ based on target, assessment of neutralizing antibodies, and ability to provide quantitative titers and none have had protective thresholds defined. Such assays are only a surrogate marker for immunity, as they do not measure the full spectrum of comprehensive and specific immunologic responses to the vaccine. As a result, patients and providers may be misled to think a positive result is definitive proof of protection or a negative result as a vaccine failure – both of which

can be dangerous. For example, cellular immune responses are not routinely measured but have been documented even among seronegative vaccinated patients; these responses may provide protection against severe disease.(1) Further, SOT recipients who have positive results frequently have titers that are significantly lower compared to healthy vaccinated patients and which may be less effective against novel variants.(2) Lastly, since seroprotective titers have not been established, interpretation of the results is extremely challenging. A recently completed study that looked at the response to a booster (third) dose of an mRNA based, for all transplant patients, did not use serology to inform the decision to give the third dose and yet benefit was seen in all seropositive and many seronegative patients.(3) More data are needed before post-vaccine serologic testing of solid organ transplant (SOT) recipients can be recommended as part of standard of care. Further, the data from this French study suggest that having post-second dose data is likely not needed as it is unlikely to affect further management.

The currently authorized vaccines were assessed based on prevention of clinical COVID-19 and we should be looking carefully at both the risk and severity of breakthrough infection in SOT recipients. From available data, immunocompetent vaccinated individuals rarely developed breakthrough infections and these infections were infrequently severe and/or fatal infections.(4) While rates of breakthrough infection after completing vaccine are higher in SOT recipients than in the general population, they remain rare (0.65%) and are, like breakthrough infections in immunocompetent, rarely severe.(5, 6) While the number of patients remain low, there were no breakthrough infections in 131 patients who received a third dose, despite the fact that 38% remaining seronegative after 3 doses.(3, 7) Without evidence of poor clinical outcomes in vaccinated SOT patients, it is unclear if a rush to “improve” vaccine responses is necessary. In fact, available data indicate a need for a more thoughtful scientific approach.

Early data on a third dose of vaccine has recently been published from two groups.(3, 7) While there has been a lot of interest in these studies, they must be interpreted

cautiously. The American study is based on preliminary findings on 30 randomly identified patients and includes a diversity of initial and booster dose vaccines, utilized two different assays for determining serologic responses and focuses on seroconversion instead of seroprotection. One assay has a range of results of 0 to >250 units/mL and the other 0 to >12 arbitrary units, making it difficult to compare antibody titers between patients; neither assay has not had seroprotective thresholds defined. Comparing data from healthy and SOT patients, the majority of patients with a seropositive response after the booster dose may not have achieved sufficient titers to protect against infection; based on these data, it suggests that only 10% of patients who received the third dose achieved a response that might correlate with estimates of seroprotection in the general population. The French study is a larger cohort (101 patients). This study was more homogeneous as all patients received 3 doses of BNT162b2 (Pfizer-BioNTech) mRNA vaccine in a fixed schedule, with the third dose being given 61±1 days after the second dose. Testing in all patients was done retrospectively using the same SARS-CoV-2 Spike IgG (Beijing Wantai Biological Pharmacy Enterprise); this assay is not designed to assess virus neutralization and has not had seroprotective thresholds defined. Of the 131 patients in both studies, of which only 129 had complete data at the second and third dose, all of the 46 patients with positive antibodies after the second dose had consistently higher antibody titers after the third dose. Of the 83 who were seronegative after the second dose, only 34 (41%) seroconverted; it is unclear how many of these has achieved seroprotective responses as protective thresholds are not established. There were no breakthrough infections in any of the subjects in either study; however, additional time are needed to validate these findings.

The American case series also raises concerns about safety as one heart transplant recipient (3.3% of studied patients) developed a biopsy-proven, antibody-mediated rejection 7 days after her third dose of vaccine; no specific details, including immunosuppression adjustments to optimize vaccine responses, are provided in the paper.(7) No patients in the French series experienced rejection.(3) By comparison, 1 patient (0.13%) developed acute rejection from a larger cases series of 741 patients

from a study of the safety of 2 doses of SARS-CoV-2 vaccine in SOT recipients.(8) If true, this could represent up to a 6-fold higher rate of rejection after a third dose, and potential unanticipated risk. Since the two studies included few heart recipients and there is emerging data that the mRNA vaccines can induce myocarditis, further data are likely needed, particularly in this unique population.(3, 7, 9)

Taken together, the limited data do not yet support routine testing for antibody titers after SARS-CoV-2 vaccination or a routine third dose in those with low or no antibody responses among SOT recipients. The risk of rejection or other safety concerns with a third dose remains undefined, particularly among heart transplant recipients. Despite benefit in many, a majority of seronegative patients after two doses do not seroconvert after the third. Additionally, there is no data on whether a booster dose impacts frequency of severe disease or death following breakthrough infections. The current data raise important questions regarding the degree of protection conferred by vaccines in immunosuppressed patients, and we urgently need further prospective studies to answer these questions. Further studies should help us to optimize our use of individualized testing for immunity, if clinically appropriate, and assure we promote more effective vaccine dosing strategies in this vulnerable population that maximize protection against severe infection.

Unfortunately, the extensive media attention about the poor antibody responses and the "impact" of booster dosing has generally ignored the fact that many remain seronegative after a third dose and does not link vaccine response with clinical efficacy. Further, the coverage fails, too, to highlight that the current EUA is limited to 2 doses of mRNA vaccine and that clinicians have less discretion about alternative approaches until FDA approval of the vaccine. Such media coverage and focus by many transplant professionals on seropositivity alone potentially sends conflicting messages to patients. It may be contributing to vaccine hesitancy among those who remain unvaccinated. This is especially important as existing data suggests, much like other vaccines, that SARS-CoV-2 vaccines provide clinical benefit by reducing severity of breakthrough infections.(10, 11) Since two mRNA vaccines in a transplant recipient are clearly better

than none, one wonders if transplant programs and professionals are putting as much focus and effort into ensuring all of their patients are vaccinated as they are to addressing questions about serology and third doses. To date, there have been few studies looking at SARS-CoV-2 vaccine use and drivers of hesitancy in SOT recipients. As with society in general, this remains a critical public health threat that warrants greater attention.

To move the field forward, we need specific clinical studies focused on vaccine efficacy in transplant population. Most urgently, we need a clearer understanding of breakthrough infections in transplant populations after completing SARS-CoV-2 vaccination. Collecting such data will require more than single site reports but instead data collaboration across a wide range of centers, transplant organizations and funding agencies. This is especially important as most of the available data comes from patients vaccinated with mRNA vaccines and there remain a paucity of data on patients vaccinated with viral vector-based vaccines. This data collection is best accomplished by a national registry of breakthrough infections to assess severity along with point-prevalence data on completed vaccine in transplant populations. Establishing such a registry could also be leveraged to study vaccine efficacy of other approved and recommended vaccines in the future and to be a tool for the community in future pandemics.

Second, we need studies to specifically address the best approach to protect our patients against SARS-CoV-2. While many have advocated for such studies much earlier in the pandemic, the studies still have not been funded or implemented. Ideally, these studies would leverage groups with a long track record of vaccine-related research. Such studies should investigate the optimal approach to generate humoral and cellular responses to vaccine and correlate these with protection from both infection and severe disease. While the current fixation on a booster dose will likely drive initial studies at this approach, broader studies are needed. Studies of primary vaccination and booster dose approaches should study a range of vaccines to determine if using the same vaccine, as was done with the French study, or mixed vaccines, as was done

by some in the American study, provides the greatest benefit. Other options, such as using yet to be authorized vaccines, including adjuvanted vaccines, should be considered as well. Most of our current booster dose data comes from patients who have received initial mRNA vaccines; how to optimize response for patients who previously received a single dose of viral-vectored vaccine needs to be defined in prospective studies. Current data suggest that there will still be suboptimal response even with optimized vaccine approaches, something that is not a surprise based on prior studies of vaccines in transplant patients over time.

Studies are needed to examine the impact of transplant or rejection treatment on previously vaccinated patients to determine if revaccination or other approaches are needed after these events that clearly impact the host-immune responses. Lastly, there is need to improve longitudinal funding for vaccine research in our immunocompromised patients. There is not a vaccine currently available today that does not have reduced humoral and clinical efficacy in this unique population. Studies are needed to understand the mechanisms driving the poor responses, development of predictive markers of reduced responses and approaches to optimize vaccine efficacy. Such studies will not only help us prevent the impact of pathogens we have vaccines for today, but will better prepare us for future pandemics. Linked to these important issues is the need to have a plan to study vaccine responses early in future pandemics.

In the meantime, transplant provider recommendations to patients should remain clear and to the point: to get all transplant recipients fully vaccinated, to vaccinate close contacts to provide ring protect of the immunocompromised patient, and to continue to encourage efforts to promote social distancing and masking where possible. While booster vaccines remain an option for patients, they should be offered in the context of clinical studies given the limitations of FDA authorization. Lastly, while there appears to be a link between certain immunosuppressive agents and poorer responses, the impact of temporarily modifying regimens is unstudied. As such, providers should not transiently reduce immunosuppression solely for the purposes of improving responses outside a clinical study.

As there is significant interest from patients in booster dosing, we would encourage providers to discuss that the risks and benefits are uncertain, available data suggests that the booster does not improve responses in many patients and that, in the absence of data, patients interested in booster doses should be discouraged from getting additional doses outside of a controlled research setting.

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