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EDITORIAL

Immunity to a third BNT162B2 COVID-19 vaccine after heart transplantation: Bridging the knowledge gap to end the pandemic for organ transplant recipients



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Numerous studies published over the past year and a half have established that solid organ transplant (SOT) recipients are at the highest risk for poor humoral immunity after coronavirus disease 2019 (COVID-19) vaccination.¹⁻⁴ Rates of breakthrough infection and mortality are also unacceptably high in this patient population.^{5,6} The inferior COVID-19 vaccine efficacy in SOT recipients is likely to persist despite the steadfast evolution of vaccine recommendations by the United States Centers for Disease Control (CDC), the most recent iteration of which advises that immunocompromised individuals like SOT recipients receive a total of 5 mRNA vaccine doses.⁷ However, some SOT recipients may never mount a humoral response to vaccines. For instance, in a study of kidney transplant recipients, those who were seronegative after a 3rd BNT162b2 (Pfizer–BioNTech) dose were unlikely to mount a humoral immune response to the 4th dose.⁸ Thus, many SOT recipients will remain vulnerable to COVID-19 due to the absence of any meaningful vaccine-induced protection. Immune escape stemming from the ever-changing landscape of novel variants will exacerbate this problem and extend it even to SOT recipients who do mount a humoral immune response to COVID-19 vaccines.

The current 5-dose mRNA vaccine recommendation stems not from clinical trial data or observational studies,

but rather from an urgent need to optimize protection of vulnerable and immunocompromised individuals in the face of a fatal pandemic. Indeed, our understanding of vaccine responses to anything beyond the original mRNA vaccine series remains poorly understood. An even deeper knowledge gap surrounds cellular immune responses and how they evolve over time. In this issue, Peled et al begin to bridge these knowledge gaps by reporting the results of a cohort of 103 adult orthotopic heart transplant recipients, in whom they assess the changes in the humoral and cellular immune responses within 6 months after administration of a third BNT162b2 vaccine dose.⁹

There are several noteworthy observations in this work that can hopefully help propel the field of COVID-19 prevention in SOT recipients forward. First, even after 3 doses of BNT162b2, only 58.3% (60/103) of heart transplant recipients demonstrated neutralizing antibodies, a sobering figure that underscores the importance of counseling SOT recipients about the importance of masking, adherence to up to date vaccine recommendations, and chemoprophylaxis if available. Even among those with a neutralizing antibody response, serum obtained after two BNT162b2 doses was unable to neutralize the ancestral Omicron variant (B.1.1.529), and neutralization activity against Delta (B.1.617.2) was approximately half that of wild type severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (B.1). Second, compared to 2 doses, 3 doses of BNT162b2 resulted in superior neutralization against all 3 variants at 3 weeks after the last vaccine dose. However, neutralizing activity was significantly higher for wild type virus compared to Delta, and was minimal for Omicron. Unfortunately, by 6 months after the third BNT162b2 dose, neutralizing activity had tapered off for all 3 variants, with neutralization against Omicron becoming nearly negligible, underscoring how vulnerable SOT recipients remain in the

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Omicron era. Third, by performing interferon gamma ELISPOT assays on a subset of samples, the authors found that T-cell responses not only significantly increased between doses but were also maintained for 6 months, an observation which stands in stark contrast to the waning antibody response. There was no correlation between neutralization and T-cell responses, which corroborates Peled et al's prior work demonstrating that there are certain heart transplant recipients who develop T-cell responses after vaccination in the absence of an antibody response.¹⁰ While these observations may suggest that some SOT recipients could remain protected against severe COVID-19 despite minimal neutralizing antibody responses, much remains unknown.

The authors did not capture immune responses to additional vaccine doses, nor did they report the characteristics of individuals with breakthrough infections. Nonetheless, with Peled et al's findings in mind, we must consider how to synthesize these data with those of other studies to: (1) lead to new evidence generation in the form of observational studies and clinical trials; and (2) change clinical practice. Three broad approaches may be considered. First, it is expected that SARS-CoV-2 vaccination schedules will transform over the coming years, with the possibility of periodic vaccines over our lifetimes.¹¹ As policies change and countries begin to adopt new recommendations into their national vaccination protocols, it is imperative that longitudinal cohorts such as these continue to be followed, in order to define the impact of 4th, 5th, and other vaccine doses on neutralization responses and T-cell reactivity against both historic and contemporary variants. Special attention should be given to T-cell reactivity, as—unlike humoral immune escape, which has been a major theme in the pandemic—Spike proteins from novel variants do not appear to escape T-cell-mediated immunity elicited by the wild-type S protein.¹² Whether this will hold true for future variants is uncertain.

Second, it is imperative to amass data that define the elusive and complicated labyrinth referred to as the immune correlates of protection, both for standardization of reporting across studies, as well as patient counseling. To date, the United States Food and Drug Administration still recommends against routine measurement of SARS-CoV-2 antibodies to guide clinical care, given the lack of a uniform method of antibody unit reporting and no clear correlation between existing assays and protection.¹³ Practically, because neutralizing activity of SARS-CoV-2 antibodies is a moving target that is determined by the predominant variant of concern (as the current study has shown), it is all but impossible to give immunocompromised patients advice on how well-protected they are based on antibody levels. For instance, it has recently been shown that neutralizing antibody titers after vaccination with BNT162b2 were substantially lower against the Omicron subvariants BA.4 and BA.5 compared to BA.1, BA.2, and ancestral SARS-CoV-2.¹⁴ Furthermore, while a 4th mRNA vaccine dose resulted in an increase in antibody titers in SOT recipients, neutralization against Omicron was poor and did not increase after the fourth dose.¹⁵ Therefore, although antibody levels

correlate with neutralizing activity,⁴ a given antibody level (measured through a clinical assay) that may be considered "protective" against an ancestral variant is unlikely to be protective against other variants. Additionally, while the durability of T-cell responses may ameliorate the impact of breakthrough COVID-19 and even improve vaccine responses, it is known that neutralizing antibodies are still crucial for control of SARS-CoV-2.¹⁶ Thus, a more conservative approach would be to simply advise SOT recipients that existing COVID-19 vaccines are unable to adequately neutralize (and thus fully protect) against novel SARS-CoV-2 variants, thereby obviating the need to even measure antibody levels as part of clinical care. The only way to address this knowledge gap is by following prospective cohorts such as those in the study by Peled et al over time and correlate their episodes of breakthrough COVID-19 with antibody levels and T-cell responses, and variant type.

The third opportunity for improvement can only be achieved by determining whether adjusting immunosuppression can bolster vaccine responses. Although monoclonal antibody prophylaxis for immunocompromised patients is now available,¹⁷ focusing on mechanisms to amplify the endogenous immune response is also of paramount importance, due the durability of long-lasting memory B and T-cell responses. It is therefore essential to systematically study the strategy of temporary immunosuppression reduction around the time of vaccination, a practice which is already recommended among patients with rheumatological conditions.¹⁸ Early data from Europe have demonstrated that this approach is safe and effective among kidney transplant recipients who do not mount an antibody response to a 3rd mRNA vaccine dose, in whom a temporary, 5-week reduction or discontinuation of mycophenolic acid or azathioprine around the time of a 4th vaccine dose resulted in a substantial increase in the proportion of individuals with an antibody response, with minimal to no episodes of rejection.^{8,19} An ongoing, multicenter randomized trial is seeking to determine the safety and efficacy of immunosuppression reduction around the time of additional mRNA vaccination for kidney or liver transplant recipients who failed to mount an antibody response to prior vaccines (NCT05077254). Given the findings in the study by Peled et al, it would appear rational to perform similar trials in recipients of thoracic organ transplants.

Although much has been learned about the response to COVID-19 vaccines in SOT recipients since the spring of 2021, there is still work to be done to optimize COVID-19 prevention in these patients. In the future, it is hoped that landscape of vaccination after SOT will change from a "one size fits all" approach, to a paradigm whereby SOT recipients are given different vaccine doses or types, with or without modulation of their immunosuppression, based on individual risk factors for vaccine responses such as time from transplantation, type of transplant, age at vaccination, and others.^{1,4} Until then, we must continue to counsel our transplant patients that the pandemic is not yet over for immunocompromised individuals.

Disclosure statement

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