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EDITORIAL

Humoral immune responses against SARS-CoV-2 in transplantation: Actionable biomarker or misplaced trust?

In addition to a remarkable ability to spread and mutate, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), causes disease across the general population with greatest impact on immunocompromised individuals with multiple comorbid conditions common in organ transplant recipients. Severe disease in immunocompromised populations may reflect, in part, the inability to mount effective immune responses following vaccination. Moreover, viral variant (Omicron BA.1 and BA.2) evasion and limitations in monoclonal antibodies and small molecule therapeutics necessitate selection of individuals who might benefit most from these agents. *These assessments are complicated by incomplete understanding of the thresholds for protective immunity and variability in the performance of clinical and research assays that evaluate SARS-CoV-2 immunity.* Clinically, immunity is measured largely by assays for antibody levels or virus neutralization with variability in assay performance and interpretation (e.g., cut-off values). Such assays examine immunity involved in blocking transmission (neutralization) and ignore T cell and innate immune function that are intimately linked to disease attenuation and that are more resilient to viral evolution.[1] Transmission blockade observed in epidemiologic studies is adversely affected by naturally waning neutralizing antibody immunity and viral variation, making enduring transmission blockade an unrealistic goal for viral vaccines.[2] Strategies to evaluate mechanistic immune correlates of persistent protection against severe disease will determine future vaccine design, deployment, and boosting strategies.

Randomized trials and observational studies have demonstrated excellent rates of seroconversion and clinical effectiveness for mRNA-based vaccines in the general population.[3] Immune responses in solid organ transplantation (SOT) recipients are less robust.[4-6] Individuals may develop severe COVID-19 infection despite vaccination. Interestingly, there appears to be discordance between cellular and humoral immune responses and between measured immune responses and protection against hospitalization and disease progression. For example, in a retrospective study of vaccinated SOT recipients (prior to the emergence of Omicron), disease requiring hospitalization was greater than in normal hosts but remained uncommon,[7] *pointing to a dominant protective role for vaccine-induced immune responses in addition to neutralization as a correlate of protection against severe disease*. Most studies have relied on measures of humoral immunity, including total anti–SARS-CoV-2 immunoglobulin (Ig)G titers or neutralizing antibodies targeting the spike (S) glycoprotein, to assess immunity. However, antibody levels have not been correlated to the risk for breakthrough infections; agammaglobulinemic patients did not demonstrate increased severity of disease early in the pandemic.[8] In one small SOT study, antibodies were detected in 35.3% of patients and cellular immunity in 64.7% suggesting that "assessment of antibodies is insufficient to identify COVID-19-vaccine responders" in SOT. In liver and heart recipients, 64% of patients developed SARS-CoV-2 IgM/IgG antibodies and 79% S-ELISpot positivity.[9] Ninety percent of recipients developed either humoral or cellular responses. In one series, 35.7% mounted a cellular immune response without detectable neutralizing activity.[10] T cell depletion in the non-human primate model of SARS-CoV-2 resulted in a loss of control of SARS-CoV-2[11]; pre-existing cross-reactive common-Coronavirus immunity has been linked to milder disease in the general population.[12,13] However, correlations between cellular immunity and infectious risk in SOT are lacking. Collectively, *these data suggest that quantification of binding and neutralizing antibodies alone represents an incomplete metric of immunity to SARS-CoV-2*. While S-specific antibody levels and neutralization may provide insights into transmission blocking activity, *it remains unclear whether antibody levels to the original SARS-CoV-2 Spike antigen (included in vaccines) provide actionable insights on protection against severity of disease*.

Boosting improves antibody quality in immune competent hosts via enhanced affinity maturation, providing antibodies that recognize a broader array of variants.[14] In immunocompromised hosts, incomplete responses to vaccination could produce *greater humoral immune responses in the absence of enhanced affinity maturation*. Such lower affinity antibodies may neutralize wildtype SARS-CoV-2 found in vaccines, but with lesser cross-reactivity to additional variants of concern (e.g., Omicron). Incomplete affinity maturation in SOT could relate to impaired T cell help, disrupted germinal center activity, or altered antigen presentation.[15] Thus, *in the absence of a complete understanding the affinity and breadth of neutralization of the antibody response, S-specific titers may not adequately characterize protection against SARS-CoV-2 variants*.

Clinical laboratories are overwhelmed with requests for diagnostic assays during COVID. In a viewpoint paper by Werbel and Segev, measurement of antibody levels is advocated as an adjunct to clinical management.[16] They recommend quantitative FDA emergency use authorized anti-S1/RBD assays after full vaccination to assess antibody responses. As they note, there are few data supporting Mab use in vaccinated seronegative SOT recipients (or poor responders). The key question is whether antibody levels in SOT recipients are actionable biomarkers or simply an available assay, reassuring to the physician or patient but failing to reflect immune function?

With the appearance of Omicron BA.2, emerging antiviral therapies must be provided to those least likely to mount an effective immune response. Based on which tests? And is this the best use of a limited resource? In the immunodominant spike (S) protein, 5106 different amino acid replacements or substitutions have been identified as well as multiple deletions.[17] As variants emerged, natural antibodies (from prior infection), therapeutic monoclonal antibodies (targeting prior strains), and some vaccine-elicited antibodies have become less effective in preventing disease progression.[18] More than 85% of tested neutralizing antibodies are escaped by Omicron[19]; nearly all are escaped by Omicron sublineage BA.2.[20] Thus, routine assays for SARS-CoV-2 antibody levels might erroneously suggest viral protection when none exists to emerging variants.

Antibody levels provide an imperfect foundation for decisions regarding disease prevention or treatment. Assays of neutralizing antibodies detect vaccine-specific antibodies but may not measure antibodies to contemporaneous variants of concern. Furthermore, maintenance of antibody levels sufficient to maintain lifelong protection against viral transmission is an unrealistic goal. Instead, we need to understand the precise functional correlates of immunity responsible for disease control. Emerging multiplexed antibody assays will interrogate antibody binding across variants and may provide information regarding the efficacy of vaccine-induced or monoclonal transmission blocking activity. As further vaccine variants emerge, new pan-variant vaccines will be required. Identification of the key correlates of immunity will provide SOT patients and clinicians the insights required to optimize clinical care in this and future pandemics.

DISCLOSURE

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