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EDITORIAL

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The challenge of evaluating of SARS-CoV-2 antibody responses among vaccinated transplant patients

INTRODUCTION

Data on the immunogenicity of the COVID-19 vaccines among SOT recipients are required to formalize COVID-19 vaccine recommendations for this immunocompromised population. Feingold et al. reported SARS-CoV-2 antibody responses following the use of COVID-19 mRNA vaccines among pediatric and young adult heart-transplant recipients.[1] In their study, among 28 recipients who had received COVID-19 vaccination, 17 (61%) had SARS-CoV-2 spike protein antibody responses after a 2-dose vaccination series. A subset received a third dose of an mRNA vaccine. They reported that four of seven (57%) patients who were seronegative after the second dose of vaccine developed antibody responses after the third dose. The findings may support recommendations from different jurisdictions that suggest a 3-dose primary mRNA COVID-19 vaccine series for moderately or severely immunocompromised persons 5 years of age and older, followed by a booster dose for those 12 years of age and older.[2]

The Feingold study provides an opportunity to highlight the importance of several key issues relating to the utility of antibody testing to assess vaccine responses among COVID-19 patients, as highlighted in this commentary.

CORRELATES OF PROTECTION

The full spectrum of immune correlates that define protection against SARS-CoV-2 infection and disease are yet to be determined. While many serologic tests that measure antibodies to spike protein are being used in different centres internationally, neutralizing antibody detection is still considered as the gold standard to evaluate immune protection, since neutralization tests more accurately correlate with the functional ability of the antibodies.[3] That said, studies have shown strong correlations between antibodies (both neutralizing and IgG binding) and protection in clinical efficacy trials. Given that up to 90% of the variability in efficacy of different vaccines could be explained by their antibody levels, it is reasonable to assume that post-immunization antibody levels can serve as a valid measure of short-term protection.[4,5]

The presence of detectable antibody is not the sole indicator of protection from SARS-CoV-2 infection. Other immune correlates, including mucosal immunity, cell-mediated adaptive immunity, and innate immunity, are believed to play important roles in immunity to SARS-CoV-2. The contributions of these components, singly or in combination, are unestablished as this relates to protection from SARS-CoV-2 infection and disease of varying severity.

PROTECTIVE ANTIBODY LEVELS

If antibody results correlate with protection, what antibody level is protective? Currently, longitudinal studies measuring antibody levels before and after the vaccination are ongoing to evaluate whether there is a certain threshold of antibody level for protection from SARS-CoV-2 infection. Most assays that have been approved for use under Emergency Use Authorization are typically not reported as quantitative. Results may be reported on a scale (e.g., as a signal to cut-off ratio, S/CO) but are not standardized to a reference value as a quantitative assay with a standardized clinical interpretation. The utility of WHO standard Binding Antibody Units has been proposed, and data are emerging on what antibody levels likely correlate with protection against different variants of SARS-CoV-2.[6]

INTERCHANGEABILITY OF SEROLOGIC ASSAYS AND TEST SENSITIVITY

Are different serologic assays interchangeable? With three different assays being used in the study by Feingold et al., variations in sensitivity, particularly over time, may lead to differences in results. Ideally, studies of this nature should involve the use of a single assay. If multiple assays are used, some form of cross-validation should be considered, where feasible. While the study by Feingold et al. reported no presumed cases of SARS-CoV-2 infection among their study participants, asymptomatic or mildly symptomatic patients are potentially more likely to have negative antibody responses.[7] This is accentuated by the immunocompromised state of participants.[8] Even if nucleocapsid antibody testing had been

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.

All authors meet the ICMJE authorship criteria.

undertaken to determine the occurrence of antibodies to the virus as opposed to the vaccine (as discussed below), it has been reported that there is the potential for a muted antibody response leading to the false assumption that no infection occurred. This is because when compared with adults, children may not develop a robust nucleocapsid antibody responses to infection.[9] The waning of antibody responses is another consideration. A study of kidney-transplant recipients revealed reduced titers of spike protein antibody after 6 months compared with 1 month after the third dose of mRNA vaccination.[10] In the above context, the performance characteristics of different assays relating to the above variables is worthy of consideration.

DETERMINING ANTIBODY RESPONSES TO VACCINE VERSUS INFECTION

As the authors have noted, differentiating SARS-CoV-2 infection from antibody response after vaccination is difficult among those who have positive spike protein antibodies. Nucleocapsid antibody testing is recommended to evaluate the evidence of prior infection among vaccinated populations.[7] Current vaccines only produce spike protein antibody responses, while both spike protein and nucleocapsid antibody responses are seen during SARS-CoV-2 infection. Because antibodies may cross-react, it has not been fully established whether antigens used by the antibody tests specifically detect only antibodies against those antigens but not other antigens, including those of seasonal coronaviruses.[7]

In summary, the study by Feingold et al. highlights to spike protein antibody responses among heart transplant recipients who received two or three doses of COVID-19 vaccination, adding serological evidence for the current recommendation of booster doses of COVID-19 vaccination for SOT recipients. The study also highlights the need for research on specific areas among SOT recipients, including but not limited to the degree of correlation of spike protein antibody levels with protection as well as the correlation between different antibody assays. Further study is required on the role of different components of the immune system on the prevention from infection and severe outcomes of COVID-19.

AUTHOR CONTRIBUTIONS

TK wrote the draft manuscript. AC and UA critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

KEYWORDS

Antibody, COVID-19, Immunogenicity, SARS-CoV-2, Solid organ transplant

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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