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Humoral Response to SARS-CoV-2 in Hemodialysis Patients

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Patients with end-stage renal disease (ESRD) require maintenance dialysis while waiting for a kidney transplant or if not eligible for a transplant. Even with significant improvements in hemodialysis and peritoneal dialysis, there is still a high mortality rate. Infections are one of the major causes of death in renal patients requiring dialysis owing to an impaired innate and adaptive immune system induced by uremia.[1] The adaptive arm of the immune response reacts to specific antigens, generating immunologic memory; however, the T-cell functions that help to develop and control the immune response are compromised in the uremic milieu. Previous studies have revealed that hemodialysis patients experience a shift in the ratio of T-cell populations increasing the T helper type 1 cell population promoting an inflammatory immune response and a decrease in the T helper type 2 cell population.[2] This is specifically important for the cognate CD4+ T-cell help in the induction, differentiation, and maintenance of antigen-specific memory B-cells and antibody-secreting cells. Patients with ESRD do not necessarily have lower levels of serum immunoglobulins; however, there are data revealing the concentration of antigen-specific immunoglobulins is significantly lower in patients with ESRD requiring maintenance hemodialysis compared with healthy individuals.[3]

SARS-CoV-2, the causative agent of COVID-19, has been associated with a higher risk of hospital admission and mortality of patients with ESRD on maintenance dialysis compared with healthy individuals. As a result, there has been prioritization of chronic kidney disease patients, including patients with ESRD requiring maintenance dialysis, to receive the SARS-CoV-2 vaccine. These patients tend not to generate a potent immune response to established vaccines as previously found with the hepatitis B vaccine, which resulted in the modification of vaccine doses and scheduling to generate a more robust immune response.[4] There have been reports of the SARS-CoV-2 vaccination inducing the humoral immune response, including IgG-specific spike protein antibodies; however, the measured IgG levels were significantly lower in the maintenance hemodialysis patients compared with a healthy control group, 30 days after second vaccination.[5] Determining the longevity and functionality of the humoral immune response after infection or vaccination of patients with ESRD receiving maintenance hemodialysis is of great importance to understand the humoral and long-lasting immunity in this vulnerable population as approximately 65% of patients with kidney transplant lost the SARS-CoV-2–specific humoral immune response by 6 months after infection.[6] In this issue of the *Kidney International Reports*, there are 2 new studies, one investigated the longevity, Dudreuilh *et al.*,[7] and the second the functionality, Muir *et al.*,[8] of the humoral immune response after a confirmed SARS-CoV-2 infection in a patient population receiving maintenance hemodialysis.

In healthy controls, the presence of SARS-CoV-2 antibodies has been detected up to 8 months after infection, and Dudreuilh *et al.*[7] evaluated the persistence of these antibodies over time in maintenance dialysis patients. Analysis of 110 patients who had previously tested positive for SARS-CoV-2–specific IgG revealed that 94% of the patients who were either symptomatic or nonsymptomatic had detectable antibodies at 10 months postinfection. Nevertheless, the prevalence of SARS-CoV-2–specific antibodies detected in the serum of patients was slightly higher in patients who had symptomatic infection (96.8%)

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compared with patients who were asymptomatic (89.6%). These results are comparable with the observations found in healthy controls, including the suggested correlation of a more robust and longer lasting anti–SARS-CoV-2 IgG response with severity of disease. In this study, antibodies were measured by targeting the spike protein indicating the presence or absence of spike-specific IgG. This study did not evaluate the antibody response to other SARS-CoV-2 proteins and the titers of antibodies at each of the 2 time points. Furthermore, the neutralizing capacity of antibodies specific to SARS-CoV-2 was not evaluated, thus whether the presence of long-lasting antibodies can prevent infection was not determined. Evaluating whether the antibody functionality and titers decrease more rapidly over time in the maintenance hemodialysis patients compared with healthy individuals will have a significant impact on vaccine boost strategies in this patient population.

The analysis reported in the second study on SARS-CoV-2 humoral immune response in maintenance dialysis patients who were either symptomatic or asymptomatic for COVID-19 by Muir *et al*.[8] characterized the antibody titers and the presence of neutralizing antibodies. Similar to the previous reports, a more robust anti-nucleocapsid and anti-spike IgG immune response was found in maintenance hemodialysis patients who were symptomatic compared with the asymptomatic patients. The functional capacity of neutralizing antibodies was elevated in hemodialysis patients who were symptomatic compared with the asymptomatic group and correlated with the concentration of the anti-nucleocapsid and anti-spike IgG antibody response. The neutralizing antibodies, and the anti-spike and anti-nucleocapsid antibodies, were detected in patients who seroconverted up to 3 months from the baseline sampling. At 3 months, there was a decrease in the titers of antibodies compared with baseline samples, but the neutralizing capacity of the antibodies was still active. This is similar to the observations in healthy individuals and patients who are not at ESRD, in which neutralizing antibodies have been detected up to 6 months after SARS-CoV-2 infection.

Muir *et al*.[8] reported 2 cases in which the neutralizing antibodies were lost (below the threshold of detection),[8] but these patients received a transplant and were on maintenance immunosuppression (concurrent with the literature). The neutralizing effect of antibodies was evaluated using an attenuated HIV-1 virus pseudotyped with spike protein, instead of using the SARS-CoV-2 virus to determine if there are differences in the viral infectivity and replication using the neutralizing antibodies derived from patients on maintenance hemodialysis. Following this specific patient population for a longer period of time would be interesting to determine whether the presence of functionally neutralizing antibodies will be maintained up to and beyond 6 months from the initial baseline measurement and how the neutralizing activities compared with healthy individuals.

Both these studies revealed that patients on maintenance hemodialysis are capable of generating a functional and long-lived SARS-CoV-2–specific immune response. Nevertheless, a limitation of both these reports was the lack of analysis of the longevity and functional activity of the antibodies directed toward the reported emerging SARS-CoV-2 variants. Understanding the diversity and breadth of the SARS-CoV-2–specific immune response in this patient population is currently unknown, and this will have a significant impact on SARS-CoV-2 surveillance programs, including testing and virus sequencing, in the maintenance hemodialysis patient populations.

Patients on maintenance hemodialysis are particularly vulnerable to SARS-CoV-2 infection, and understanding the generated humoral immune response to either a SARS-CoV-2 infection or after vaccination is essential in protecting these patients. This may include SARS-CoV-2 surveillance of patients in dialysis units, if specific emerging variants are poorly recognized or not efficiently neutralized by pre-existing antibodies generated either from a previous infection or vaccination. The development of novel strategies to boost the immune response after vaccination and monitoring of the specific antiviral antibody levels will improve the management of patients requiring maintenance hemodialysis.

DISCLOSURE

The author declared no competing interests.

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