Immune response to SARS-CoV-2 infection and vaccination in patients receiving kidney replacement therapy

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In this issue of *Kidney International*, the initial experience regarding the immunogenicity of prior coronavirus disease 2019 (COVID-19) infection and the response to the COVID-19 vaccines among patients on maintenance dialysis and kidney transplant recipients is summarized. Preliminary data suggest that there is durability of immune response after COVID-19 infection. Although immune response to the first dose of vaccine is less in infection-naïve patients than healthy individuals in both groups, after the second vaccine dose a significant portion of patients receiving maintenance dialysis develop robust antibody titers, whereas kidney transplant recipients show a less-strong immune response.

Patients with end-stage kidney disease (ESKD) receiving maintenance dialysis or who have had a kidney transplant are at increased risk for morbidity and mortality after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with the general population.[1] Efforts are underway to vaccinate as many individuals as possible throughout the world to get the pandemic under control.[2] Although the nephrology community has called for ESKD patients to have priority for vaccination as a vulnerable population, there has been an underlying concern that these patients may not mount a good response to vaccination or even after a previous infection with SARS-CoV-2. In this issue of *Kidney International*, we present the initial experience of nephrologists from around the world regarding the immunogenicity of prior coronavirus disease 2019 (COVID-19) infection and the response to the COVID-19 vaccines among patients with ESKD receiving kidney replacement therapy (Table 1[3–14]).

What do the studies show?

In a study of 356 patients receiving maintenance hemodialysis (MHD), Clark *et al.* screened for nucleocapsid protein (anti–nucleocapsid protein) and receptor-binding domain (RBD; anti-RBD) antibodies at time 0 (baseline) and at month 6 to assess durability and functionality of the immune response to SARS-CoV-2 infection.[3] They also screened for SARS-CoV-2–specific T-cell responses in those who became seronegative at 6 months. Their results showed that in 136 patients who were antibody-positive at baseline, up to 85% of patients maintained serologic evidence of immune responses at 6 months. In 8 of 11 patients who became seronegative at 6 months, there was evidence of robust cellular immunity measured by T-cell response to SARS-CoV-2 structural proteins, suggesting that >95% of patients receiving MHD maintained serologic or cellular evidence of immune responses at 6 months. Prior seropositivity seemed to be protective against subsequent SARS-CoV-2 infection. These results are consistent with the report by Forbes *et al.*, who suggested in a study of 122 patients receiving MHD, there is robust and sustained antibody response after confirmed COVID-19 infection with no suggestion that immunosuppression weakens this response.[4] They also reported that seroconversion rates increase over time, suggesting a longer than usual immune response adaptation in patients receiving MHD compared with healthy controls. Of note, in a small cohort of 14 pediatric patients receiving MHD, Canas *et al.* reported a seroconversion rate of 38% at 13 weeks, which may reflect a time-dependent early response because other data suggest a longer time interval to full immunization.[6]

In a separate smaller but more thoroughly examined cohort, Anft *et al.* performed an observational case-control study comparing the frequencies and functionality of SARS-CoV-2 reactive T cells as well as antibody titers in 14 COVID-19 convalescent hemodialysis patients compared with 14 age- and sex-matched healthy controls.[5] They showed that not only were spike-specific antibody titers comparable in both groups, frequencies of SARS-CoV-2–reactive $CD4^+$ and $CD8^+$ T cells, producing the effector cytokines granzyme B, interleukin-2, tumor necrosis factor, and interferon-γ, were similar or for certain cytokines even significantly higher in patients receiving MHD. These data are

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Table 1 | Characteristics of studies examining immune response to COVID-19 infection and the response to the COVID-19 vaccines among patients with ESKD receiving kidney replacement therapy

Author	Patient population	Infection vs. vaccine	Sample size	Follow-up	Outcome	Result
Clark et al.[3]	MHD	Infection	136	6 mo	Anti-NP Anti-RBD	85% Seropositive; 70% T-cell response in seronegative patients
Forbes et al.[4]	MHD	Infection	122	184 d	Anti-NP	100% Seropositive Increasing Ab over time
Anft et al.[5]	MHD and control	Infection	14 and 14	Not provided	T-cell response	Robust response in MHD
Canas et al.[6]	MHD/ pediatric patients	Infection	14	13 wk	Anti-S IgG	38% Seropositive
Torreggiani et al.[7]	MHD	Vaccine/ Pfizer	101	3 wk after first vaccination	Anti-S IgG	35% Seropositive
Billany et al.[8]	MHD	Vaccine/ Pfizer + AZ	94	28 d after first dose	Anti-S IgG	80% Seropositive
Attias et al.[9]	MHD	Vaccine/ Pfizer	69	Weekly until 3 wk after second dose	Anti-S IgG	80% Seropositive previous infection better response after first dose
Simon et al.[10]	MHD and control	Vaccine/ Pfizer	81 and 80	3 wk after second vaccine	Anti-NP	Low titers in MHD (171 vs. 478)
Berar Yanar et al.[11]	MHD, PD, and control	Vaccine/ Pfizer	127, 33, and 132	21–35 d after the second dose	Anti-S IgG	Low titers in dialysis patients, 6 de novo infections in dialysis patients
Boyarsky et al.[12]	Kidney Tx	Vaccine/ both mRNA vaccines	436	20 d	Anti-S IgG	17% Seropositive
Benotmane et al.[13]	Kidney Tx	Vaccine/ mRNA 1273	242	28 d	Anti-S IgG	11% Seropositive

consistent with those of Clark et al., and strongly suggest patients receiving MHD can generate an efficient T-cell immune response to SARS-CoV-2 infection, albeit only shown in a small, selected cohort.

In addition to the assessment of native response to SARS-CoV-2 infection, several important early reports of immunogenicity to COVID-19 vaccination in patients receiving MHD are published in this issue of Kidney International. In a preliminary report, Torreggiani et al. showed that in 101 patients receiving MHD who received the first dose of BNT162b2 COVID-19 mRNA vaccine, only 35% developed detectable antibodies to spike protein.[7] On the other hand, Billany et al. reported somewhat different preliminary results, with robust antibody response (80%) 28 days after the first

vaccination dose against COVID-19 in a cohort of 95 prevalent patients receiving MHD in the United Kingdom.[8] Although these 2 reports present data after 1 dose of vaccine, Attias et al. examined anti–spike 1 IgG antibody levels in 69 patients receiving MHD as a measure of antibody response to 2 consecutive BNT162b2 vaccine administrations.[9] They reported antibody titers weekly up to 7 weeks after the first injection. Among the entire cohort, 13 (19%) patients either had a previous COVID-19 infection or positive serology at baseline. Anti–spike 1 levels were higher in these patients compared with patients who were seronegative at baseline. Although seropositivity was at 6% (3 of 56) at the time of the second dose in patients without prior history of disease or seropositivity, the overall seropositivity rate reached >80% in the entire

cohort at the end of the follow-up period, suggesting a delayed but robust humoral immune response to the full course of mRNA-based vaccination in patients receiving MHD. These findings are important in instances in which a required second dosing of the vaccination might be delayed. In a preliminary report in 81 patients receiving MHD and 80 individuals without kidney disease who received 2 consecutive BNT162b2 vaccine administrations, Simon et al. reported anti–spike antibody titers 21 days after the second dose.[10] Although seropositivity rates based on the manufacturer's cutoff level were not reported, they showed substantially lower antibody titers in patients receiving MHD versus individuals without kidney disease (median, 171 U/ml vs. 2500 U/ml, respectively). Finally, in a study from Israel, Berar Yanay et al.

Table 2 | A summary of methods for the assessment of immunogenicity against infection and vaccination

	Notes
Humoral response to structural proteins	
IgG/IgM against spike protein	ELISA: most commonly reported; correlate with infection severity; likely reflects subsequent response; unclear disease prevention and efficacy
IgG against receptor-binding domain	
IgG against membrane protein	
Neutralization assay	Most time-consuming
Pseudovirus	SARS-CoV-2 spiked lentivirus
Live virus	Readout usually reflects half maximal inhibitory concentration
Focus reduction neutralization assay	
Plaque reduction neutralization assay	
Cellular response	
ELISpot: either T or B cell	Activation of single cells by specific Ag (i.e., spike protein, membrane protein, or a panel of SARS-CoV-2–related peptides)
	Requires PBMCs
Cytokine response	IFN-γ, TNF, IL-2
Ag-specific T cells	CD4/CD8$^+$ cells
Memory B-cell responses	Flow cytometry using tetramer staining

Ag, antigen; ELISA, enzyme-linked immunosorbent assay; IFN-γ, interferon-γ; IL-2, interleukin-2; PBMC, peripheral blood mononuclear cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.

reported anti–spike antibody levels 21 to 35 days after the second dose of the BNT162b2 COVID-19 mRNA vaccine in 127 patients receiving hemodialysis, 33 patients receiving peritoneal dialysis, and a control group of 132 hospital employees.[11] Although the median anti–spike antibody levels were statistically significantly lower in the patients receiving dialysis compared with controls (116.5 [interquartile range {IQR}, 66–160] arbitrary unit [AU]/ml vs. 176.5 [IQR, 142–235] AU/ml, respectively), there was >90% seropositivity in the group of patients receiving dialysis. Of some concern, 6 (4%) patients receiving dialysis developed COVID-19 infection 7 days after the second vaccination, whereas there were no infections in the control group. Although the circumstances related to these infections need to be clarified before making conclusions, it is important to advise all patients receiving dialysis to adhere to strict infection control measures regardless of full vaccination. These data also bring up the potential consideration for additional booster dosing in certain dialysis patients based on their risk profile once that is fully established by further data.

Patients with a functioning kidney transplant on immunosuppression are at increased risk for severe complications of COVID-19 infection. In this issue of *Kidney International,* Benotmane *et al.* assessed anti–SARS-CoV-2 antibody response against the spike protein 28 days after the first injection of the Moderna mRNA-1273 vaccine (100 μg) in 242 kidney transplant recipients (KTRs).[13] These KTRs had no history of prior COVID-19 infection and were negative for anti–SARS-CoV-2 antibodies. Only 26 (10.8%) KTRs had a positive serology 28 days after injection, with a median IgG titer of 224 AU/ml (IQR, 76–496 AU/ml) compared with a median IgG titer of <6.8 AU/ml in seronegative KTRs. These data are consistent with the report by Boyarsky *et al.*, who measured antibodies against the RBD of the SARS-CoV-2 spike protein in 436 patients who received solid organ transplants (219 received a kidney transplant).[12] At a median of 20 days (IQR, 17–24 days) after the first dose of mRNA vaccines, antibody (anti–spike 1 or anti-RBD) was detectable in 76 of 436 participants (17%; 95% confidence interval, 14%–21%). These data suggest a diminished humoral response to mRNA-based vaccination in patients who received a kidney transplant and highlight the need for the second vaccine

administration and vigilant continued surveillance. They also suggest a response comparable or slightly less than observed in patients receiving MHD after the first dose of an mRNA vaccine. Of concern, also published in this edition of *Kidney International* is the follow-up data of 205 patients who received a kidney transplant who had received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine from France.[14] At 28 days after the second dose, only 48% of KTRs responded, generating a titer of >50 with a median antibody titer of 803 (IQR, 142–4609). Patients who received their first transplant, had a longer duration from transplant, experienced better graft function, and experienced lower levels of overall immunosuppression mounted a stronger immune response. These important real-world observations indicate that vaccination of the most vulnerable in our renal community does not fully protect and therefore should not promote any complacency about protection provided by COVID-19 vaccines in immunocompromised patients.

What do these studies mean for patients with advanced kidney disease?

To interpret these early data, one should revisit the basic methods of assessment of immunogenicity to native infection and vaccination, which are good but not perfect correlates of acquired protection or vaccine efficacy. Table 2 provides a summary of methods for assessment of immunogenicity. This inclusive, although not exhaustive, list covers humoral and cellular response to infection and vaccines.[15] For the humoral response, the most used and reported method is antibody (IgM or IgG) titer. These could be total antibody levels or levels against specific structural proteins, such as spike or membrane proteins of SARS-CoV-2. The antibody response can be reported as positive or negative based on the manufacturer's criteria, actual titers, or relative titers as ratio to an internal control. Not surprisingly, the variations in reporting are not only confusing for the lay reader, but also make assessment of immune response more complex and less precise. Accordingly, a more standardized reporting was

recommended by the World Health Organization International Standards for Anti–SARS-CoV-2 Immunoglobulin Group.[16] Although there are some data to suggest that these methods do reflect adequate prevention from subsequent infection or vaccine efficacy, as shown in recent randomized clinical trials in healthy individuals, there are no adequately powered comparisons available in patients with kidney disease.

Measurement of neutralizing capability against live viruses or pseudoviruses is another well-established method to assess immunogenicity in humans. These tests are more reflective of the robustness of humoral immune response because they directly measure the capability to suppress virus growth. The readouts usually reflect half maximal inhibitory concentration of the antibodies obtained from individuals either previously infected or vaccinated. For example, Anderson et al. showed that the 100-μg dose of SARS-CoV-2 mRNA-1273 vaccine induced higher binding and neutralizing-antibody titers than the 25-μg dose, which supported the use of the 100-μg dose in the phase 3 vaccine trial that was proven to be highly effective in the study and the real world.[17] Furthermore, Edara et al. reported robust neutralizing activity of infection- and vaccine-elicited antibodies against four SARS-CoV-2 variants, including B.1.1.7.[18] It is notable that the vaccine-elicited response was stronger than one induced by previous or acute infection. Although antibody responses and in particular neutralizing antibody responses are important, recent studies have shown a persistence of RBD antibody from memory B cells despite a drop in measured antibody responses to RBD, suggesting that durable long-term immunity in the B-cell compartment can be generated.[19,20] There are yet no reports regarding the neutralizing capability against live viruses or pseudoviruses in patients with kidney disease.

Finally, assessment of cellular response is also important in terms of long-term response to infection and vaccination. An important question has been raised in the lay public as well as scientific literature concerning whether durable immunity to SARS-CoV-2 infection can be achieved. That humans can retain a long-term immune response against SARS-CoV-2 has been studied by Le Bert et al., who demonstrated peripheral T-cell responses in patients previously infected with SARS-CoV-2 18 years after their original infection.[21] Reassuringly, spike-specific memory B cells were more abundant at 6 months than at 1 month after symptom onset in a recent study by Dan et al.[22] Because patients with ESKD and those on immunosuppressive therapies are known to have abnormalities in their innate and adaptive immune response, it is crucial to assess their cellular immunity after SARS-CoV-2 infection or vaccination. In that respect, the data by Anft et al. are promising but not conclusive.

What should be done going forward?
The early publications noted in this issue of Kidney International are noticeably instructive in terms of several strategies going forward. First and foremost, the data conclusively suggest that ESKD patients do mount an immune response to SARS-CoV-2 infection and vaccination; albeit it is not immediate, but increases over time. Based on published data to date, it is premature to conclude whether KTRs will behave similarly to patients receiving maintenance dialysis. Second, the data published to date do not inform as to whether the immune response in patients with ESKD is comparable to individuals without kidney disease. It should be kept in mind that patients with ESKD do have other comorbidities that could negatively influence their immune response, and it is premature to claim that advanced kidney disease per se has a major impact on immunogenicity to SARS-CoV-2 and its variants. For example, it is well-established that old age is associated with less immunogenicity against live viruses, although this may not be applicable to mRNA- or adjuvant-based vaccines. It is yet to be established whether comorbidities, such as diabetes, heart disease, hypertension, and obesity, individually or in combination

with advanced kidney disease and immunosuppression, lessen immunogenicity to SARS-CoV-2 infection and vaccination. Third, in new studies going forward is the need for comprehensive immunophenotyping of patients with kidney disease using state-of-the-art immune monitoring. Measuring all components, not just an antibody response, is critical to measuring the immune response. As antibody-dependent cell cytotoxicity is important, then it is important not just to measure total IgG to spike proteins, but to also measure IgG1 and IgG3 subtypes, as well as detailed responses in T- and B-cell compartments (ELISpot and tetramer staining). Accordingly, data to date in patients with ESKD should be considered preliminary.

Most important, the follow-up data on seroconversion following 2 doses of vaccine in KTRs from Benotmane et al. are concerning, as <50% of recipients developed a positive antibody titer. This study highlights further work on the frequency of vaccination that will be required in this population to achieve seropositivity, and whether this will translate into durable long-term immunity.

Finally, these data suggest that full vaccination protocols should be implemented in patients receiving MHD and KTRs. Preliminary data by Attias et al., Simon et al., Torreggiani et al., and Boyarsky et al. all highlight a limited humoral response after a single dose of vaccine. The adverse consequences of inadequate vaccination, such as infection by highly virulent variants, could be devastating in these individuals. These data also emphasize the importance of early vaccination of these patients in general and the important regulatory decisions for full vaccination in these patients. Although the recent decision by the Centers for Disease Control and Prevention to provide vaccines to large dialysis organizations for mass vaccination of patients receiving dialysis in the United States is commendable, it is unfortunately a delayed decision that might have had unintended consequences. We should learn from these experiences for future potential catastrophes to create a

more justifiable allocation system for vaccine distribution and administration. It is reasonable to create a priority list based on calculated risk whereby the vaccine distribution is centralized compared with the localized approach in the United States. For example, the laudable foresight by National Health Service in United Kingdom that required systematic research before mass vaccination of patients receiving MHD will likely provide invaluable data going forward.[23] In the meantime, these studies reinforce the need to continue good public health measures, such as hand hygiene, mask wearing, and social distancing, as practical means to help limit the spread of COVID-19 in our renal communities. In light of the reduced response in patients who received a kidney transplant, strategies that promote vaccination of close household contacts to provide so-called "ring vaccination" of those closest to transplant recipients seem a logical approach to reduce the chance of direct household spread, although studies showing vaccination reducing household transmission or shedding are still lacking.[24]

In summary, the investigators of these early studies are to be commended for their outstanding work. Although there is still more to be learned from these observations, it is enlightening to see the strong response to this devastating disease by the patients and clinicians.

DISCLOSURE

All the authors declared no competing interests.

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