

mRNA COVID-19 Vaccine for People with Kidney Failure Hope but Prudence Warranted

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In recent *CJASN* publications, we find the highly anticipated results of two studies that assess the seroresponse to the BNT162b2 mRNA vaccine (Pfizer/BioNTech) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among patients on hemodialysis. Because patients on dialysis were excluded in the vaccine trials, this is the first information we have about our patients' response to vaccine. Grupper *et al.* found detectable Spike-1 antibody 30 days after the second dose of the BNT162b2 vaccine in a high proportion of patients on dialysis, 96% (54 out of 56), which compares with 100% (80 out of 80) of healthy controls (1). Titers were, however, significantly lower in patients on dialysis. In multivariable analysis, the lowest quartile of serotiter was associated with advancing age and a lower prevaccination lymphocyte count.

In the other report, Speer and colleagues provide a more in-depth look at the humoral response to the same vaccine among 21 patients on dialysis and 46 controls, assessing titers to the Spike-1 antigen after each of the first and second doses, components of the Spike-1 antigen, crossreactivity to SARS-CoV-1 and community-dwelling coronaviruses, and neutralizing ability (2). They found that neutralizing antibody was present in 16% of patients on dialysis versus 62% in controls after the first dose, but by the second dose, proportions were 82% and 100%, respectively. Titers of neutralizing and Spike-1 antibody were significantly higher in healthy controls, which persisted in an age-matched cohort analysis. The seroresponses to components of the Spike-1 antigen and other coronaviruses varied by antigen and strain, but in general, were more robust in healthy controls. Titers were significantly lower with older age in healthy controls, whereas age was less strongly associated with titers among patients on dialysis, although patients aged <50 years were not represented.

Among the strengths of these studies, the antibody assays had high sensitivity and a low false-positive rate. The studies measured antibody to Spike-1, which contains the receptor binding domain, the primary target of neutralizing antibodies that inhibit viral replication *in vitro*. Speer *et al.* had conducted active surveillance for, and excluded, infection; accordingly, these results represent the seroresponse to vaccine. This study also assessed neutralizing ability, which is a

more accurate measure of vaccine-induced protection than serotiters. The limitations are that they did not assess cell-mediated immune responses, the seroresponse in patients who were previously infected, the durability of the immune response, or infection rates (2).

The main finding from these two studies is that a remarkably high proportion of our patients elicit an immune response to this vaccine, higher than has been found after hepatitis B vaccine or influenza vaccines. Although this is good news, serotiters are not clinical efficacy results. This vaccine conferred 95% protection against symptomatic SARS-CoV-2 infections in the clinical trial population (3). However, our patients elicited a less robust seroresponse than healthy controls. What are the implications? The seroresponse correlates with immune protection for many pathogens, and accumulating evidence suggests this holds true for SARS-CoV-2. *In vitro* studies find a strong correlation of Spike-1 antibody titer with neutralizing ability and with recruitment of innate immunity and T cell-specific SARS-CoV-2 responses. Studies that predate the vaccine suggest the presence of circulating antibody confers a high level of protection from reinfection. For example, in a study of health care workers who were classified as Spike-1 antibody positive ($n=1265$) or negative ($n=11,364$) at time 0, and followed with PCR testing every 2 weeks, the incidence of PCR positivity was 1.09 versus 0.13 per 100 patient-days for patients who were Spike-1 antibody negative versus antibody positive. This is a nearly 90% reduction in reinfection in patients who were antibody positive (4). A study currently in press assessed the correlation between vaccine efficacy (expressed as log risk ratio of incidence rates for infection in the vaccine to placebo groups) and the geometric mean of the peak antibody titer 7–28 days postvaccination for the seven vaccines with phase 3 trial results and serotiter data available at the time. Serotiters were indexed to convalescent sera to enable comparison across assays. Results showed a strong correlation between vaccine efficacy and titers of neutralizing antibody ($P=0.79$) and binding antibody (receptor binding domain or Spike-1) ($P=0.93$) (5).

There may be a threshold effect of the immune response, on the basis of the finding that neutralization, and innate cellular immune functions occurred only in individuals with receptor binding domain antibody

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titers above a threshold in one study. The minimum titer that defines the ability to generate a robust immune response, and whether a threshold phenomenon bears out, remains to be determined. Because the vaccine elicits a robust memory T cell response, it is also possible the absence of, or reduced, serotiters may not indicate a loss of protection (6).

Disease severity in general coincides with cell-mediated immune responses. The vaccine activates CD4⁺ and CD8⁺ T lymphocytes and induces robust production of IFN- γ , the latter impairs viral replication and augments the immune response. The infection rate was so low in the BNT162b2 trials that the ability to assess the effect of vaccine on disease severity was limited, but data from Israel have shown decreased disease severity in the context of mass vaccination. It is plausible that patients on dialysis may elicit weaker cellular responses. The extent to which cellular responses are augmented will be particularly important in modifying disease severity if the reduced seroresponse equates to less protection against infection.

Data from the mRNA vaccine trials suggest a robust antibody response is maintained for up to 3 months, but we have no data beyond this in the general population, and no data beyond 30 days in patients on dialysis (1). Recent studies of antibody waning after infection in patients on dialysis are encouraging and suggest a similar course as in the general population, with titers peaking at 30 days followed by a decline, and then a stabilization up to at least 6 months. For example, a recent study of 129 patients on dialysis after infection reported detectable antibody to receptor binding domain at 6 months after infection in 85%, and 97% had antibody to at least one of nucleocapsid or receptor binding domain, or T cell-specific responses (7). Confirming that prior infection confers a high level of protection in patients on dialysis, only two out of 129 patients that were binding antibody positive at baseline developed PCR positivity over 6 months. In both patients, the initial infections were asymptomatic or mild. It is not possible to compare serotiters elicited postvaccination in patients on dialysis (1,2) with serotiters elicited postinfection because the antibody assays have not been standardized. However, we know that in healthy controls, serotiters after the BNT162b2 vaccine are several times higher than convalescent sera, including sera from patients who are severely affected (8). It remains to be seen whether the seroresponse to vaccine in patients on dialysis is more robust, and the duration of antibody waning more prolonged than has been observed after infection in our patients.

Both of the studies that are the subject of this editorial show seroresponses to the BNT162b2 mRNA vaccine (1,2). We are not aware of any published or ongoing trial with the ChAdOx1 nCoV-19 vaccine from AstraZeneca or the Ad26.CoV2.S from Janssen; a study of vaccination in patients on dialysis is planned with the Russian vaccine, but is not recruiting yet. However, one might speculate that immune protection will be better with the SARS-CoV-2 mRNA vaccines because they elicit neutralizing antibody responses against vaccine-matched and emerging variants (9). Given the low response rate after the first BNT162b2 mRNA vaccine dose, we agree with Speer *et al.* (2) that we should not delay the injection of the second dose, as might be recommended for the general population.

Future studies are needed to enhance existing knowledge about the adequacy of response and its duration in patients on dialysis. At this point, it would be unethical to conduct placebo-controlled randomized trials. Vaccines and protocols can be compared on the basis of longitudinal assessment of antibody titers, cell-mediated responses, and, most importantly, the incidence and severity of infections. We need modeling studies to predict nonresponders and studies to assess strategies to augment the immune response in weak responders and nonresponders. Genotyping strains from patients who develop infection after vaccination are also critical.

The two *CJASN* studies (1,2) provide us with a positive message, because more than 80% of patients on dialysis generated a serological response after the second dose of the BNT162b2 vaccine. It is reasonable to speculate that patients with neutralizing antibodies are better protected than before vaccination. Given the extreme frailty of our patients from kidney failure and comorbidities, and their increased exposure risk with thrice weekly travel from home to the dialysis facility and frequent contact with staff and other patients within the dialysis facility, they should be prioritized for vaccination (10). A first objective will be to convince patients to accept vaccination, because this is not obvious to all of them. Patients' relatives and health care professionals should be vaccinated as well. Dialysis unit leaders may have to educate staff to accept vaccination, for their own protection and to reduce the risk of transmission to patients. The extent to which the vaccination offers protection and alters the severity of infection in patients on dialysis is unknown. Vaccine efficacy may change if evolving strains develop resistance. Measures of prevention, protection, screening, isolation, and cohorting are still needed until the pandemic is over, so at least for several more months.

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See related articles “Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis,” and “Early Humoral Responses of Hemodialysis Patients after COVID-19 Vaccination with BNT162b2,” on pages 1037–1042 and 1073–1082.