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SARS-CoV-2 Vaccine in Dialysis Patients: Time for a Boost?

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Patients with kidney failure with replacement therapy (ie, dialysis or transplant) appear to be particularly vulnerable to coronavirus disease 2019 (COVID-19) and may have increased mortality.[1] Advancing age, comorbid

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medical conditions, and use of shared dialysis centers in this population likely contribute to the risk. The development of highly effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been one of the most promising advances of the pandemic; however, patients on kidney replacement therapy (KRT) and/or receiving immunosuppressive therapy were largely excluded from phase 1-3 clinical trials. Patients with advanced chronic kidney disease have decreased immune response to other commonly administered vaccinations, such as those against hepatitis B virus and influenza, demonstrating lower rates of antibody seroconversion and reduced durability.[2] Small observational studies to date suggest that patients on KRT have a lower rate of seroconversion in response to SARS-CoV-2 vaccination compared to healthy controls, although it remains unclear how this translates into vaccine efficacy.[3] With the spread of the Delta variant, increased breakthrough cases have occurred in both immunocompetent and immunocompromised individuals, highlighting the importance of preventative strategies for all.

Third or booster doses of SARS-CoV-2 vaccine have become policy in many countries and have been studied in both observational cohort studies and randomized trials with the goal of improving humoral and cellular response in patients with incomplete protection after 2 doses or to enhance antibody titers in patients with waning immunity. Given historical reduced response to other vaccines, the French National Authority for Health recommended a third booster vaccine at least 4 weeks after the second dose for all dialysis patients after April 2021. In this issue of *AJKD*, a single-center observational cohort study of 69 dialysis patients (38 hemodialysis and 31 peritoneal dialysis) who received 3 doses of BNT162b2 messenger RNA vaccine against SARS-CoV-2 presents data on humoral responses to the third dose of vaccine.[4] The study collected blood from patients at 2 time points, after the second dose but prior to the third dose and at least 3 weeks after the third dose. The authors used a commercial Roche Elecsys assay that detects total antibody against SARS-CoV-2 spike protein S1, which was originally developed as a qualitative assay to detect prior exposure to SARS-CoV-2. Based on interpretation of a single study, patients with a level between 0.8 and 50 AU/mL were considered weak responders; other studies have used other thresholds. After 2 doses, the median anti-spike titer was 284 AU/mL, with no response detected in 4% (3 patients) and weak responses in 17% (12 patients). After the third dose, median anti-spike immunoglobulin levels increased to 7,554 AU/mL. Only one-third of nonresponders after 2 doses responded to the third dose, although all but 1 low responder had an increase in antibody titer above the 50 AU/mL level. While clinical follow-up was limited to a median of 30 days after the third dose, there were no breakthrough infections after the third dose.

The debate about need for a third or booster dose is ongoing and these data add to the discussion. There are emerging data demonstrating that some populations, including the elderly, have declining antibody titers over time.[5] Studies are emerging suggesting that there is an increase in breakthrough infections, particularly with regard to the Delta variant. While hospitalizations and deaths rarely occur in fully vaccinated patients, even with Delta, there remains a significant benefit among those who have been vaccinated even when breakthrough infections occur.[6] A randomized, placebo-controlled study in solid organ transplant recipients clearly demonstrated an increase in humoral and cellular response in the majority of recipients of a third dose of mRNA vaccine, although 45% did not have antibody titers above a prespecified threshold after the third dose.[7] Much like the current study, boosting was seen in those with prior response, although a third dose did not result in seropositivity in many who were seronegative after the second dose.

One of the main challenges at this time is identifying immune correlates of protection, and specifically what SARS-CoV-2 antibody levels—especially for those receiving KRT—are needed to be considered protective. Furthermore, B- and T-cell memory plays an important role and contributes to some degree of protection.[8] In addition, there is strong evidence of the role of neutralizing serum antibodies for protection against COVID-19.[8] However, quantitative SARS-CoV-2 neutralizing antibody assays are not widely available, and thresholds of total or functional antibodies required for COVID-19 seroprotection are currently being defined. In general, neutralizing antibody levels tend to correlate with total antibody quantity, but it is hypothesized that even small amounts of neutralizing antibody after a single dose of SARS-CoV-2 mRNA vaccine may be protective.[9] Also, the durability of protection may wane over time with declining neutralizing antibody levels and ongoing SARS-CoV-2 antigenic variation.[10]

Unfortunately, as noted earlier, the phase 1-3 studies for SARS-CoV-2 excluded the majority of individuals with

an immunocompromising condition; thus we rely on small cohort studies such as these to extrapolate and interpret immunogenicity data for these vulnerable populations.

So in the end, is a third dose of SARS-CoV-2 vaccine required in patients on dialysis? To answer this, several questions remain to be answered. The most important is what is the seroprotective threshold and how well does the booster move patients to protective levels. This study did not directly measure neutralizing titers against the Delta variant, and understanding that will be critical to inform which patients benefit from a booster dose. Additionally, the current study did not measure cellular immune responses, which are critical for impacting disease severity in breakthrough infections. In most populations, while serology is a good marker for presence of cellular response, many seronegative patients have detectable cellular responses.[11] In the end, the goal is to both minimize frequency of SARS-CoV-2 infections and minimize the clinical impact of any breakthrough infections. Even among the general population, despite the fact that breakthrough infections are exceedingly rare, initial data on breakthrough infections showed that 10% result in hospitalization and 2% die of the infection.[12] Owing to the significant reduction in risk of infection, the absolute risk reduction of hospitalization and deaths is significant. Further, many of those breakthrough infections are among patients who are more likely to have poor response to vaccines and the median age of fatal cases was 82 years old. While preliminary immune correlates have been defined, thresholds need to be established to best inform defining seroprotection.[13] Studies will have to also look at the utility of booster doses in preventing both infection and severe disease, including hospitalization and death. In addition, studies of approaches other than booster doses, including alternative vaccine strategies and prophylactic monoclonal antibodies, are needed, since many patients fail to respond even with a third dose.

In the United States, dialysis patients are among those who are authorized to receive a booster dose after 6 months of their initial Pfizer vaccine series. Ongoing data collection and research should inform the clinical impact of these booster doses on breakthrough and severe cases of COVID-19.

Article Information

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