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RESEARCH LETTER

Seroresponse to Third Doses of SARS-CoV-2 Vaccine Among Patients Receiving Maintenance Dialysis

To the Editor:

Beginning August 13, 2021, third doses of SARS-CoV-2 mRNA vaccine were recommended for patients with immunocompromise,[1] possibly but not definitively including patients undergoing dialysis,[2] who have increased risk for poor outcomes from COVID-19.[3] In this study, we examined the seroresponse to an additional dose of vaccine in this vulnerable population.

Dialysis Clinic, Inc (DCI) is a national not-for-profit provider caring for approximately 15,000 patients at 260 outpatient dialysis clinics in 29 states. As previously described, beginning in January 2021, DCI physicians had the option of activating a SARS-CoV-2 vaccine protocol, in which anti-spike IgG antibodies were measured monthly with routine labwork.[4] The chemiluminescent assay ADVIA Centaur XP/XPT COV2G, which measures IgG antibodies against the receptor-binding domain of the S1 subunit of SARS-CoV-2 spike antigen, had received emergency use authorization (EUA) in July 2020.[5,6] This semi-quantitative assay reports a calibrator-established Index Value between 0 and 20 or of ≥20; per manufacturer specifications, titer ≥1 represents detectable antibodies, likely signifying seroresponse.[5] This study includes all adult patients who received an additional SARS-CoV-2 vaccine dose after completion of an initial series, and who had at least 1 anti-spike IgG level checked both between the initial series and the additional dose and at least 14 days after the additional dose. Among patients who developed COVID-19 at any time after completing an initial series, titers measured after developing COVID-19 were excluded from analysis. Demographic and clinical data, vaccination dates, antibody titers, and COVID-19 diagnosis history were obtained from the DCI electronic health record.

For each patient, 3 titers of interest were identified: (1) the maximum level reached at least 14 days after completion of the initial vaccine regimen but before the additional vaccine dose (labeled "Max Pre"); (2) the last titer measured prior to the additional vaccine dose ("Last Pre"); and (3) the first titer measured after the additional vaccine dose ("First Post"). In analyses, Index Value strata of ≥20, 7-<20, and <7 were used. The threshold of 20 reflects the semi-quantitative nature of the assay; the threshold of 7 represents a hypothesized level of protection from severe disease.[7]

This study was approved for exemption by the WCG IRB (Work Order 1-1456342-1); given the IRB exemption, no consent procedures were implemented. Statistical analyses were performed using R v4.0.2.

Of 399 patients who received an additional vaccine dose, just 4 received Ad26.COV2.S/Janssen as the initial vaccine regimen and so were excluded from further analysis (Fig S1). Of the remaining 395 patients, 294 (74%) received a homologous vaccine regimen (Fig S2). No patient received a reduced ("booster") dose of mRNA-1273/Moderna vaccine. Baseline characteristics are shown in Table S1.

Among the 395 third dose recipients, 336 (85%) had Max Pre titer ≥7 and 203 (51%) had Last Pre titer ≥7 (the latter measured a median 16 [IQR, 12-28] days before the third dose) (Fig 1A). Overall, 383 (97%) patients had First Post titer ≥7, measured a median 33 [IQR, 21-40] days after the third dose. Among the 59 patients with Max Pre titer <7, First Post titer was ≥7 in 49 (83%). Of the 192 patients with Last Pre titer <7, First Post titer was ≥7 in 180 (94%). Analyses were repeated for subgroups by COVID-19 history (Fig 1B and C) and by vaccine type (Table S2); results were not notably different, though a limited number of patients had a history of COVID-19. Analyses with an additional Index Value stratum of <1 are in Table S3.

Among maintenance dialysis patients, a third dose of SARS-CoV-2 mRNA vaccine is associated with a high prevalence of seroresponse. Previous studies have shown that although patients receiving maintenance dialysis are able to mount a robust initial immune response, this seroresponse wanes over time.[8] Studies of the BNT162b2/Pfizer vaccine in France showed that a third dose administered shortly after a second dose was associated with increased seroresponse.[9–13] The current study includes a larger cohort with representation of both mRNA-1273/Moderna and BNT162b2/Pfizer vaccine recipients. The data further demonstrate robust seroresponse with titers ≥7 in 97% of recipients of a third vaccine dose, including 94% of those whose titer after the initial vaccine regimen had waned to <7.

Given ongoing high rates of COVID-19 and rapidly waning immunity after an initial vaccine series, additional or booster doses of SARS-CoV-2 vaccine provided to all maintenance dialysis patients likely will have substantial benefits. Adequate seroimmunity is thought to both reduce breakthrough infections and hospitalizations and reduce transmission by those who become infected;[14–16] all are crucial for patients receiving maintenance dialysis, who are at increased risk for poor outcomes. Nevertheless, a non-negligible proportion of patients still have low titers even after a third dose and may benefit from a fourth ("booster") dose, as has been given to kidney transplant recipients with poor seroresponse,[17] or from prophylaxis with tixagevimab plus cilgavimab (Evusheld).[18] Of note, a test-based approach to vaccine re-dosing is already used for hepatitis B vaccination among patients receiving dialysis.[19]

This study's limitations include lack of data on cellular immunity and possible selection bias, both in enrollment for antibody monitoring and for the administration of an additional vaccine dose. We did not correlate antibody levels to breakthrough infections. Durability of seroresponse to the third dose remains unknown. The assay is semi-quantitative and had EUA but not full approval at the time of this study. Importantly, a major strength is that this

A

All	First Post: ≥20	First Post: 7-<20	First Post: <7	Total
Max Pre: ≥20	298	1	1	300
Max Pre: 7-<20	32	3	1	36
Max Pre: <7	43	6	10	59
Last Pre: ≥20	160	0	0	160
Last Pre: 7-<20	43	0	0	43
Last Pre: <7	170	10	12	192
Total	373	10	12	395

B

No COVID-19 history	First Post: ≥20	First Post: 7-<20	First Post: <7	Total
Max Pre: ≥20	237	1	1	239
Max Pre: 7-<20	32	3	1	36
Max Pre: <7	41	6	10	57
Last Pre: ≥20	101	0	0	101
Last Pre: 7-<20	42	0	0	42
Last Pre: <7	167	10	12	189
Total	310	10	12	332

C

Any COVID-19 history	First Post: ≥20	First Post: 7-<20	First Post: <7	Total
Max Pre: ≥20	61	0	0	61
Max Pre: 7-<20	0	0	0	0
Max Pre: <7	2	0	0	2
Last Pre: ≥20	59	0	0	59
Last Pre: 7-<20	1	0	0	1
Last Pre: <7	3	0	0	3
Total	63	0	0	63

Figure 1. Max Pre and Last Pre titers compared to First Post titer for (A) all patients; (B) patients without history of COVID-19, defined by a negative baseline and no COVID-19 prior to the initial vaccine series; and (C) patients with history of COVID-19, defined by a positive baseline or COVID-19 prior to the initial vaccine series. Red cells indicate decrease in stratum after versus before third vaccine dose. Green cells indicate increase in stratum after versus before third vaccine dose. Positive baseline defined as anti-spike IgG titer >1 before or ≤10 days after first dose of vaccine (representing likely prior COVID-19, which may or may not have been diagnosed). Prior COVID-19 was defined as positive SARS-CoV-2 test before full immunity (at 14 days after completion of initial vaccine series).

study includes real-world results on seroresponse to additional doses of SARS-CoV-2 vaccine.

In conclusion, additional SARS-CoV-2 vaccine doses elicit robust seroresponse among patients receiving maintenance dialysis, including those whose seroresponse has lapsed, suggesting that additional vaccine doses may play a role in maximizing and sustaining protection of maintenance dialysis patients.

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Supplementary Material

Supplementary File (PDF)

Figures S1-S2; Tables S1-S3.

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References

1. Media Statement from CDC Director Rochelle P. Walensky, MD, MPH, on Signing the Advisory Committee on Immunization Practices' Recommendation for an Additional Dose of an MRNA COVID-19 Vaccine in Moderately to Severely Immunocompromised People. Centers for Disease Control and Prevention; 2021. Accessed August 30, 2021. https://www.cdc.gov/media/releases/2021/s0813-additional-mRNA-mrna-dose.html
2. Steiger S, Rossaint J, Zarbock A, Anders HJ. Secondary immunodeficiency related to kidney disease (SIDKD)-definition, unmet need, and mechanisms. *J Am Soc Nephrol*. 2022;33(2):259-278.
3. Hsu CM, Weiner DE, Aweh G, et al. COVID-19 among US dialysis patients: risk factors and outcomes from a national dialysis provider. *Am J Kidney Dis*. 2021;77(5):748-756.e1.
4. Hsu CM, Weiner DE, Aweh GN, et al. Seroresponse to SARS-CoV-2 vaccines among maintenance dialysis patients. *Am J Kidney Dis*. 2022;79(2):307-310.
5. Irsara C, Egger AE, Prokop W, et al. Clinical validation of the Siemens quantitative SARS-CoV-2 spike IgG assay (sCOVG) reveals improved sensitivity and a good correlation with virus neutralization titers. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2021;59(8):1453-1462. doi:10.1515/cclm-2021-0214
6. Florin L, Maelegheer K, Vandewal W, Bernard D, Robbrecht J. Performance evaluation of the Siemens SARS-CoV-2 total antibody and IgG antibody test. *Laboratory Medicine*. 2021;52(6):e147-e153. doi:10.1093/labmed/lmab027

7. Manley HJ, Aweh G, Hsu CM, et al. SARS-CoV-2 vaccine effectiveness and breakthrough infections in maintenance dialysis patients. medRxiv; 2021. doi:10.1101/2021.12.20.21268124
8. Hsu CM, Weiner DE, Manley HJ, et al. Seroresponse to SARS-CoV-2 vaccines among maintenance dialysis patients over 6 months. *Clin J Am Soc Nephrol*. 2022 Mar;17(3):403-413.
9. Longlune N, Nogier MB, Miedougé M, et al. High immunogenicity of a messenger RNA-based vaccine against SARS-CoV-2 in chronic dialysis patients. *Nephrol Dial Transplant*. 2021;36(9):1704-1709.
10. Ducloux D, Colladant M, Chabannes M, Yannaraki M, Courivaud C. Humoral response after 3 doses of the BNT162b2 mRNA COVID-19 vaccine in patients on hemodialysis. *Kidney Int*. 2021;100(3):702-704.
11. Dekervel M, Henry N, Torreggiani M, et al. Humoral response to a third injection of BNT162b2 vaccine in patients on maintenance haemodialysis. *Clin Kidney J*. 2021;14(11):2349-2355.
12. Bensouna I, Caudwell V, Kubab S, et al. SARS-CoV-2 antibody response after a third dose of the BNT162b2 vaccine in patients receiving maintenance hemodialysis or peritoneal dialysis. *Am J Kidney Dis*. 2022;79(2):185-192.e1.
13. Frantzen L, Thibeaut S, Moussi-Frances J, et al. COVID-19 vaccination in haemodialysis patients: good things come in threes…. *Nephrol Dial Transplant*. 2021;36(10):1947-1949.
14. Earle KA, Ambrosino DM, Fiore-Gartland A, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine*. 2021;39(32):4423-4428.
15. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of vaccination on household transmission of SARS-CoV-2 in England. *N Engl J Med*. 2021;385(8):759-760.
16. Prunas O, Warren JL, Crawford FW, et al. Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel. *Science*. 2022;375(6585):1151-1154.
17. Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. *Ann Intern Med*. 2022;175(3):455-456.
18. Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19. *JAMA*. 2022;327(4):384-385.
19. Chi C, Patel P, Pilishvili T, Moore M, Murphy T, Strikas R. Guidelines for Vaccinating Kidney Dialysis Patients and Patients with Chronic Kidney Disease. Centers for Disease Control and Prevention; 2012. Accessed August 30, 2021. https://www.cdc.gov/dialysis/pdfs/vaccinating_dialysis_patients_and_patients_dec2012.pdf