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Characteristics of natural immunity to SARS-CoV-2 over time in wait-listed dialysis patients and recent kidney transplant recipients

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Studies in nontransplant populations [1–7] have demonstrated waning natural immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) over time; however, the immune response in kidney transplant recipients, while known to be attenuated, is less well described [8–10]. The impact of immunosuppression, specifically induction immunotherapy, in patients with end-stage kidney disease (ESKD) has not been studied. Compared with vaccination, kidney transplant patients with a history of coronavirus disease 2019 (COVID-19) illness have much higher titers of antireceptor binding domain (RBD) antibody levels and neutralizing antibodies [11]. In this article, we describe the changes observed in the antibodies to the RBD and to neutralizing antibodies in dialysis patients with COVID-19 illness with and without exposure to induction immunosuppression.

Between 28 May 2020 and 7 December 2020, 72 patients were tested for SARS-CoV-2 antibodies before and after kidney transplantation. Vaccination was not yet available and therefore positive antibody testing reflected previous infection with SARS-CoV-2. A total of 25 of 72 patients tested were antibody positive at the time of transplant and 17 patients (68%) had persistent evidence of antibodies after induction immunosuppression. All eight patients who had a positive test prior to transplant and converted to a negative test posttransplant denied a history of COVID-19-like illness and therefore were all considered to be asymptomatic for COVID-19. Conversely, of the 17 who had persistently positive tests, only 7 (41%) were asymptomatic infections. Patients with symptomatic COVID-19 illness pretransplant were significantly more likely to have a persistently positive test posttransplant ($P = .01$). Of those who tested positive before transplantation, 10 patients had at least one pretransplant and one posttransplant stored sample available for further analysis. For comparison, during the same period, eight paired sera samples taken 2 months apart from four wait-listed dialysis patients with SARS-CoV-2 antibodies were analyzed. All samples were tested using the following assays: measurement of the immunoglobulin G (IgG) index value and IgM index value using the SARS-CoV-2 Pylon 3D analyzer (ET Healthcare, Palo Alto, CA, USA) as previously described [12], SARS-CoV-2 total RBD assay to measure the overall binding between SARS-CoV-2 antibodies and the RBD of the virus spike (S) protein, SARS-CoV-2 antibody avidity assay that measures the rate of SARS-CoV-2 specific antibody dissociation from RBD, which is inversely correlated with the antibody avidity, and SARS-CoV-2 surrogate neutralizing antibody (SNAb) assay, which is a competitive binding assay that measures the percentage of RBD-angiotensin-converting enzyme 2 (ACE2) binding and inversely correlates with the SNAb binding inhibition (neutralizing activity). Figure 1 demonstrates the comparisons between the sequential testing of transplant ($n = 10$) and dialysis patients ($n = 4$). Panel A demonstrates the measurement of IgG over time; panel B shows the total RBD antibody assay, demonstrating the binding between SARS-CoV-2 antibodies and the RBD of the virus S protein; panel C demonstrates the avidity over time and panel D demonstrates the neutralizing antibody over time. In panel C, the dissociation measured is inversely correlated to antibody avidity (the decrease over time shown demonstrates an increase in avidity over time) and in panel D, the percentage of RBD-ACE2 binding is inversely correlated with neutralizing activity (the increase shown over time in the transplant recipients signifies a decrease in neutralizing activity over time). For all assays there was no difference in baseline measurements between pretransplant values and

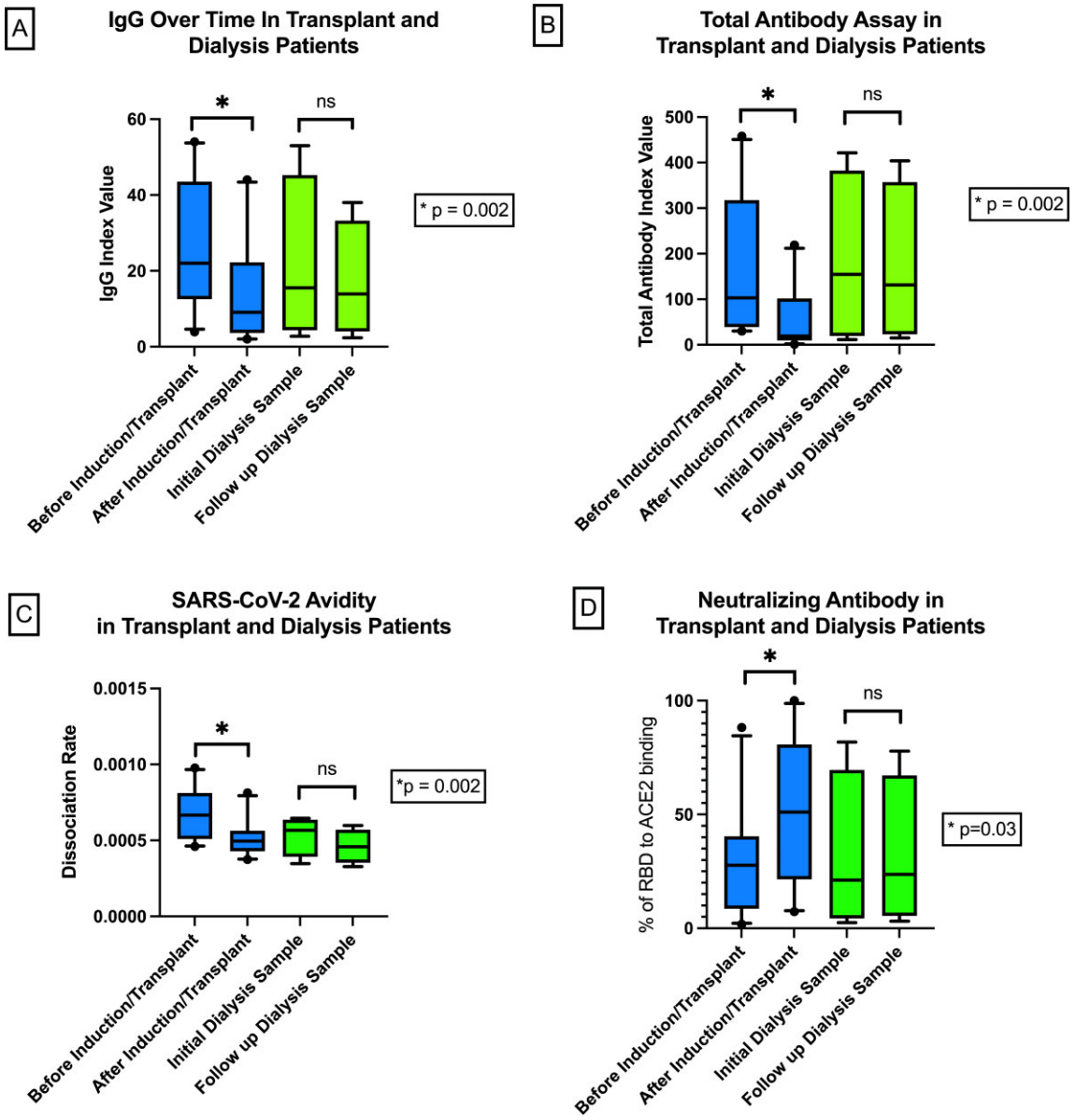

FIGURE 1: SARS-CoV-2 antibody response over time in transplant and dialysis patients. (**A**) Box and whisker plots showing the 10th, 25th, 50th (median), 75th and 90th percentiles for IgG in transplant and dialysis patients over time. A positive value is an index value (IV) >1. (**B**) Box and whisker plots showing the 10th, 25th, 50th (median), 75th and 90th percentiles for the total RBD antibody assay (TAb) that measures the overall binding between SARS-CoV-2 antibodies and the RBD of the virus S protein. A positive value is an IV >1. (**C**) Box and whisker plots showing the 10th, 25th, 50th (median), 75th and 90th percentiles of the avidity assay that measures the rate of SARS-CoV-2 specific antibody dissociation from RBD, which is inversely correlated with the antibody avidity. The *y*-axis represents the relative dissociation rate (dR), which is calculated by fitting the first-order rate equation to the dissociation profile: ln(Signal_t/Signal_0) = ln[(bound)]/(total)] = –dRt. The dissociation measured is inversely correlated to antibody avidity (i.e. the decrease over time shown demonstrates an increase in avidity over time). (**D**) Box and whisker plots showing the 10th, 25th, 50th (median), 75th and 90th percentiles of the SNAb that is based on the SARS-CoV-2 antibody-mediated inhibition of the interaction between the ACE2 receptor protein and the RBD. The *y*-axis represents the percentage of RBD–ACE2 binding and is measured as %B/B0 = [sample relative fluorescence unit (RFU)/negative blank (RFU)]*100%, which is inversely correlated with antibody neutralizing activity (therefore the increase shown over time in the transplant recipients signifies a decrease in neutralizing activity over time). The mean time from pretransplant sample to posttransplant sample was 84 days, while the mean time from initial dialysis sample to follow-up dialysis sample was 60 days. The difference in time between the initial and follow-up samples in the transplant and dialysis cohorts was not significant ($P = .34$).

dialysis cohorts. Wilcoxon signed-rank tests for assays comparing before transplant and after transplant measurements demonstrated a significant decline in IgG over time total RBD assay over time, and neutralizing antibody over time, while a significant increase in avidity over time was found. There was no significant difference over time in any of the four assays for the dialysis cohort, although the trends seen mirror what is described in the general population. When comparing the changes seen in IgG in dialysis patients and transplant patients over time, there was a 53% reduction of

IgG in transplant patients as compared with a 14% reduction of IgG in dialysis patients ($P < .01$). We also found that there was a 75% reduction in total antibody binding for transplant patients as compared with a 1.5% increase for dialysis patients ($P < .01$). There was no significant difference between the percentage changes seen in transplant and dialysis patients for the avidity of the antibody (19% decrease in transplant patients as compared with a 6% decrease in dialysis patients; $P = .08$) or the neutralizing capabilities of the antibody (119% increase in transplant patients as compared with a 16.5% increase in dialysis patients; $P = .43$).

Our data demonstrate that when compared with wait-listed dialysis patients during a similar period, patients who received induction therapy for kidney transplantation had a significantly greater decline in antibody levels after the initiation of immunosuppression. Interestingly, our analysis of the quality of the immune response, specifically the avidity and neutralizing antibodies, demonstrated no significant change in the dialysis population, while the kidney transplant recipients demonstrated a significant increase in avidity and a decrease in neutralizing antibodies. Although there was no significant change in the avidity or neutralizing antibodies over time in dialysis patients, the overall trends seen mirror what is found in the general population [2–6]. These results suggest that total RBD antibody measurement may not be enough to understand the protective effects of natural immunity following COVID-19 illness or after SARS-CoV-2 vaccination. The observed increased antibody avidity over time is also consistent with the notion of continued evolution of the humoral immune response and supported by previous evidence that the memory B cell response continues to evolve and express antibodies with increased neutralizing potency and breadth [2, 13].

Our data also demonstrate the need for increased comprehensive surveillance, especially in patients undergoing transplantation. The American Society of Transplantation currently recommends COVID-19 vaccination in all solid organ transplant recipients with any available SARS-CoV-2 vaccine followed by a booster vaccination [14]. For patients with ESKD who plan to undergo transplantation, they should complete their immunization for SARS-CoV-2 at least 2 weeks prior to their transplant [14]. Yet many questions remain, including how to determine just what level of antibody is needed to provide protection and whether the lack of a measurable antibody response means that there is no true immunity or whether some protection is still conferred. Furthermore, there is no consensus on how soon after initial transplantation a booster should be administered. All patients in this study received antithymocyte globulin induction therapy. Recent analysis of immune response to vaccination in transplant recipients demonstrated that after two doses of a messenger RNA vaccine, patients on antimetabolite therapy and steroids were less likely to have a significant immune response, as were those in the first year after transplant [15]. Such studies reinforce the need for more data that examine the direct effects of high-dose immunosuppression and different maintenance immune therapies in organ transplant recipients. Whether a similar response would be observed with other induction and maintenance immunosuppression warrants further investigation. Additional data are needed that measures not just the quantitative IgG response, but also the quality and evolution of the immune response and associated clinical outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

CONFLICT OF INTEREST STATEMENT

None declared.

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