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SARS-CoV-2 vaccine strategies in kidney transplant recipients

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Conventional vaccine strategies against SARS-CoV-2 can be insufficient to generate immunological responses to vaccine or provide protection from COVID-19 in kidney transplant recipients (KTRs). In this group, vulnerability to infection remains high.[1] In contrast to the general population, in which there is good evidence for booster doses of mRNA vaccine leading to enhanced immunological responses and protection from infection, a significant proportion of KTRs do not benefit from third or even fourth vaccine doses.[2] In KTRs, and other patients who are immunosuppressed, investigation of modified vaccination strategies is needed to potentially enhance protection of this vulnerable group.

In *The Lancet Infectious Diseases* Marcia M L Kho and colleagues report an open-label randomised study of three alternative approaches to enhance vaccine responses: heterologous vaccine administration, double-dose vaccination, or temporary withdrawal of mycophenolate mofetil.[3] There is a good rationale for each of these strategies. In phase 1 studies of both mRNA-1273 and BNT162b2, higher doses of vaccine elicited greater immunological responses.[4,5] There is also evidence for this approach from other vaccine platforms such as hepatitis B. Previous evidence for heterologous vaccine strategies is more variable. Although some retrospective studies suggest that it might be of benefit, a previous randomised trial has shown no difference to homologous vaccination.[6,7] Finally, several large cohorts of KTRs have shown that the use of mycophenolate mofetil is associated with particularly weak vaccine responses, and one study in KTRs who were non-responders to three doses of vaccine reported high seroconversion rates with mycophenolate mofetil withdrawal for 5 weeks around the time of the fourth dose.[8,9]

In the current study, KTRs who had failed to seroconvert at 14–56 days after the second or third dose of an mRNA-based COVID-19 vaccine were invited to participate in one of two cohorts. Patients receiving any combination of immunosuppressive drugs were included in cohort 1, which randomly assigned patients 1:1:1 to single dose mRNA-1273, two doses of mRNA-1273 (administered simultaneously), or to single dose Ad26.COV2-S. Only patients receiving triple immunosuppression (calcineurin inhibitor, mycophenolate mofetil, and steroids) were randomly assigned in cohort 2, to either mycophenolate mofetil withdrawal for 1 week either side of vaccination, or to mycophenolate mofetil continuation. All participants in this cohort received a single dose of mRNA-1273. The authors found no difference between any of the vaccination strategies studied. In cohort 1, seropositivity rates at 28 days following booster vaccination were 68%, 69%, and 63% for single dose mRNA-1273, double dose mRNA-1273, and single dose Ad26.COV2-S, respectively. In cohort 2, seropositivity rates were 67% in the mycophenolate mofetil continuation group, and 80% in the mycophenolate mofetil withdrawal group. Interestingly, despite testing seronegative at the time of initial screening, by the time of vaccine administration, over 20% of patients were now seropositive (47/230 in cohort 1 and 28/103 in cohort 2; although a different test was used than for screening). A small number of participants developed a significant antibody titre, raising the possibility of undetected intervening natural infection, however the majority had low titres suggesting that they might have had delayed seroconversion at more than 56 days postvaccination. Nonetheless, excluding these patients from analysis had no effect on the study results, although seroconversion rates were proportionally lower overall. Similar results, with no difference between alternative vaccine strategies, were seen for both T cell responses, as measured by IFN-γ ELISpot, and (in a subset of patients) for neutralisation of ancestral, delta, and omicron strains, measured by plaque reduction neutralisation tests.

The results of this study identify that, despite a range of alternative vaccine strategies, up to a third of KTRs remain seronegative following third or fourth vaccine doses, and up to half have no detectable T cell responses. In those who do respond, serological responses are often weak; the highest median titre observed in any group in this study was 156 BAU/mL. Given the heterogeneity of immune responses that now exists in this group of patients, owing to a combination of natural infection, different vaccine platforms, underlying diseases, and immunosuppression use, we would suggest that serological screening would be of benefit to identify

those most at risk. In those who have not responded, an alternative approach to repeated doses of booster vaccination is likely to be required. In light of the results from Kho and colleagues, modulation of the immunosuppression regimen remains an unproven strategy. The risk of rejection, even if small, might also be unacceptable to patients; cohort 2 in this study was significantly smaller than prespecified due to difficulties with recruitment, largely due to patient anxiety related to withdrawal of mycophenolate mofetil. Alternative vaccine platforms, in development, such as those inducing mucosal immunity, those which make use of nanoparticle technology to display multiple copies of spike immunogens, or vaccines incorporating conserved epitopes beyond the spike region could be of benefit in the future.[10] However, as long as it remains effective against the currently circulating variants, pre-exposure prophylaxis, which uses neutralising monoclonal antibodies, might be the best option in vulnerable KTRs with absent or impaired immune responses.[11]

We declare no competing interests.

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