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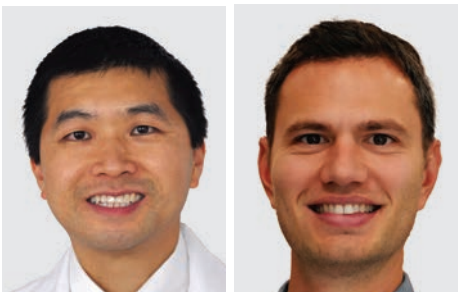
Editorial

The Third Dose Is the Charm: Effective Cellular and Humoral Immune Responses to Third COVID-19 Vaccine Doses in Immunosuppressed Nonresponders



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Pathogens drive an effective immune response by stimulating the innate immune system, leading to activation of host T and B cells.[1] Subsequent pathogen exposure leads to a more robust response through memory T and B cells. Vaccines attempt to mimic the host-pathogen response to provide long-lasting cellular and humoral protection without the sequelae of disease.[2,3] Patients with autoimmune diseases or solid organ transplant recipients receive immunosuppressive medications that limit productive immune responses following vaccination. Indeed, multiple case series show that the humoral response is blunted following the 2-dose SARS-CoV-2 mRNA primary vaccine series while taking mycophenolate, rituximab, or methotrexate (MTX).[4-7] In this issue of *The Journal of Rheumatology*, Isnardi and colleagues evaluate the cellular and humoral responses after a third SARS-CoV-2 vaccine dose in patients with rheumatoid arthritis (RA) who did not develop detectable anti-SARS-CoV-2 antibodies following completion of the primary SARS-CoV-2 vaccine series.[8]

Isnardi et al[8] enrolled 21 patients who met 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology criteria for RA from 2 sites in Argentina and who did not develop any detectable levels of SARS-CoV-2 antibodies after 2 doses of the SARS-CoV-2 vaccine. Blood was collected 21 to 40 days after the third vaccine dose to measure anti-SARS-CoV-2 antibodies with neutralizing activity, and T cell activity was quantified using an interferon-γ ELISA-based assay with the SARS-CoV-2 receptor binding domain from the spike protein.

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The cohort was immunosuppressed, with 29% of patients taking glucocorticoids, 81% taking conventional disease-modifying antirheumatic drugs, and 85% taking biologics (6 patients treated with abatacept [ABA] and 4 patients treated with rituximab [RTX]). The time between last RTX infusion and the third vaccine dose was between 11.4 and 14.0 months. Most patients in the cohort did not receive an mRNA-based SARS-CoV-2 primary vaccine series. More than 90% of the cohort received either the Gam-COVID-Vac (adeno virus vector), ChAdOx1 nCoV-19 (adeno virus vector), or BBIBP-CorV (inactivated virus). For the third dose, all patients received the BNT162b2 vaccine, except 1 patient who received ChAdOx1 nCoV-19, with a median time of 180 days between completion of the primary series and the third vaccine dose.

After the third vaccine dose, the majority of patients (91%) developed detectable antibodies against SARS-CoV-2. Overall, ABA and RTX were associated with lower titers of neutralizing antibodies. There were 2 patients who did not develop detectable SARS-CoV-2 spike antibodies following the third vaccine dose and both had received the inactivated SARS-CoV-2 vaccine as the primary vaccination regimen and were taking MTX and ABA or RTX. With regard to T cell responses, a third vaccine dose increased T cell responses from 41% to 71%. ABA use was also associated with a decreased T cell response, and in 2 patients this was associated with the absence of a quantifiable neutralizing antibody titer. As one might expect, patients who received RTX and did not have a humoral response were able to develop a detectable T cell response.

Isnardi and colleagues[8] showed that a third dose of the SARS-CoV-2 mRNA vaccine can stimulate a robust immune response in previous primary series vaccine nonresponders. It is unknown whether any immunosuppressive medications were held prior to receiving any of the vaccine doses as currently recommended.[9] ABA decreases T cell activation and priming by blocking CD28-CD80/CD86, which also decreases B cell

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activation due to the lack of T cell help. In this study,[8] ABA use was associated with decreased T and B cell responses. On the other hand, RTX targets B cells without a direct effect on T cells. As expected, RTX use was associated with decreased neutralizing antibodies titers without an appreciable effect on T cell responses. Two (10%) patients did not develop any detectable level of anti-SARS-CoV-2 antibodies even after a third vaccine dose, and both patients received BBIBP-CorV, which is the inactivated SARS-CoV-2 vaccine. Inactivated viral vaccines have limited immunogenicity and often require adjuvants and multiple primary and booster doses for effective immune responses.[2] It would be useful to have increased numbers of patients and to stratify patients based on the type of primary vaccine series to understand if this patient cohort is truly nonresponsive or the result of receiving ineffective vaccines, particularly when compared to the mRNA vaccines. Additionally, long-term follow-up is necessary to determine whether humoral and cellular protection wanes sooner in patients receiving immunosuppression.

For SARS-CoV-2, the Centers for Disease Control and Prevention (CDC) currently recommends 3 doses of the mRNA vaccine as part of the primary series, with a follow-up booster dose in immunosuppressed patients. Current ACR guidelines recommend holding ABA, belimumab, cyclophosphamide, and other conventional or targeted synthetic immunomodulatory or immunosuppressive medications for 1 to 2 weeks and RTX for several months prior to each injection with the SARS-CoV-2 vaccine, when possible.[9] Data from Isnari and colleagues[8] support the CDC recommendation that the primary SARS-CoV-2 vaccination series should include 3 rather than 2 doses in immunocompromised patients. Further studies on the effect of immune suppression on host-pathogen responses are needed to develop more efficacious vaccines, vaccination strategies, and vaccine response monitoring for our immunosuppressed patient population.

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