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LETTER TO THE EDITOR

COVID-19 vaccination in immunocompromised patients

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Almost 1 year into the coronavirus disease 2019 (COVID-19) pandemic, and after more than 50 million cases and 1.35 million deaths globally, reports of the successful conclusion of phase III trials of two vaccines, BNT162b2 and mRNA1273, are most welcoming. Results from phase I/II for both these vaccines were highly encouraging with strongly elicited humoral as well as cellular responses, and no trial-limiting safety concerns [1, 2]. According to the preliminary data release, both vaccines have been reported to be almost 95% effective in preventing COVID-19 in their phase II/III trials [3, 4]. Further, the risk of severe illness from COVID-19 has been reported to be lowered by more than 90% after vaccination in both clinical trials [3, 4].

Both of these vaccines are mRNA-based vaccines, BNT162b2 encoding the receptor-binding domain of SARS-COV-2 spike protein and mRNA1273 encoding the S-2P antigen. Both were shown to elicit a strong humoral response by production of neutralizing antibodies, as well as a strong cellular response by inducing functional and pro-inflammatory CD4+ and CD8+ T cells and expression of Th1 cytokines [1, 2]. Immunocompromised patients including those with autoimmune disorders or on immunosuppressive medications were excluded from these vaccine trials. This population needs special attention, as infections are among the most common causes of mortality in them, although the data from the COVID-19 rheumatology registry so far has been reassuring and has not revealed an increased risk of COVID-19 complications in immunocompromised patients except those on moderate or high doses of corticosteroids [5, 6]. In addition to the unknown efficacy of the COVID-19 vaccine in these patients, there are several other unanswered questions about vaccinations in patients on immunosuppressive agents.

Suppression of humoral immunity by medications such as rituximab and methotrexate can suppress the production of neutralizing antibodies to neoantigens [7]. Rituximab and methotrexate have been shown to reduce humoral responses to seasonal influenza and pneumococcal vaccines [8]. While rituximab does so by direct suppression of CD20+ B cells, humoral suppression by methotrexate is thought to be mediated by interaction with the B cell activation factor (BAFF) and increasing immunosuppressive adenosine and regulatory B cells [9]. The immunogenicity of the seasonal influenza vaccine has been shown to be significantly improved by temporarily discontinuing methotrexate for 2 weeks post-vaccination without causing an increase in rheumatoid arthritis disease activity, while the immune response to neoantigen and polysaccharide-pneumococcal vaccines was significantly diminished in patients on treatment with rituximab [10, 11]. Thus, both rituximab and methotrexate have the potential to diminish response to vaccinations. There is no information available on whether this action transforms into clinical settings and impacts actual infection risk. However, the better serological response being a surrogate marker may theoretically indicate better protection against the infection. These findings have led to suggestions of holding methotrexate for 2 weeks after seasonal influenza vaccination and planning

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polysaccharide and primary immunizations before starting rituximab [10, 12].

With a vaccine for SARS-CoV2 on the horizon, patients on immunosuppressive medications will need special considerations. As previously mentioned, since this patient population was excluded from the vaccine trials, the efficacy of the vaccine in them still needs to be established. The effects of immunosuppressive medications, especially methotrexate and rituximab on a SARS-CoV2 vaccine response, are yet to be determined and will need evaluation especially given their effects on decreasing serological responses to other vaccines. Time is of the essence, and it may take several months before such information can be available. Planning the vaccination of the immunocompromised patients to ensure maximum possible seroprotection will be needed, and considerations can be given to hold methotrexate for 2 weeks after the vaccination, and scheduling rituximab a few weeks after the vaccination until further clinical trials can answer this question.

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Data availability All authors have full access to the manuscript and all the data in the study, and the corresponding author has the final responsibility for the decision to submit for publication.

Compliance with ethical standards

Disclosures None.

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