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Correspondence to: Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies

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In a recent article by Achiron *et al.* entitled "Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies,"[1] the authors measured SARS-CoV-2 IgG response using anti-spike protein-based serology in a group of multiple sclerosis (MS) patients on three different types of disease modifying therapies (DMTs), including cladribine ($n=23$), ocrelizumab ($n=44$), and fingolimod ($n=26$). Given the current COVID-19 pandemic and development of novel vaccines against SARS-CoV-2, there is growing need to understand the effectiveness, immune response, and long-term safety of these vaccines in immunocompromised patients, including MS patients on DMTs. While there is strong need to characterize the immune response in mRNA-COVID-19 vaccines in MS patients on highly efficacious DMTs, this particular article draws several concerning and potentially inaccurate conclusions based on the data provided in the manuscript.

The conclusion drawn to recommend against the mRNA COVID-19 vaccine in MS patients on fingolimod and postponing ocrelizumab treatment in MS patient is not supported based on the data presented in this article and has the potential for severe impacts on an already vulnerable population already documented to have worse outcomes with COVID-19.

The reported mRNA COVID vaccine studies have noted increases in antibody, neutralizing antibodies (NAb), and T-cell responses in healthy controls following vaccination.[2,3] However, it is unclear which aspect or aspects, or a combination of the immune responses are responsible for immunity to the virus. Additionally, the degree or quantification of these immune responses that correlate to clinical effectiveness of vaccination is not yet known.[4]

One major issue in the study presented by Achiron *et al.* is that it disregards the potential importance of T-cell response. While the authors do recognize the limitation of not capturing T-cell response, as indicated in the discussion, the conclusion grossly overstates their findings and the recommendation to forgo vaccination in the setting of fingolimod use and postponing ocrelizumab for 9 months (which has the potential to have detrimental effects in regards to their MS). Because ocrelizumab depletes B cells, it might be expected that antibodies and NAb levels following the SARS-CoV-2 vaccine may be decreased as compared with MS patients not on a DMT or compared with healthy controls. This was shown for other vaccines in the VELOCE study, where patients mounted an attenuated but protective response to tetanus toxoid vaccine and variably attenuated responses to different strains of *Streptococcus pneumonia* and influenza vaccines.[5] However, this study did not evaluate the cellular immune responses to these vaccines. Theoretically, T-cell responses should not be affected significantly in patients treated with ocrelizumab. Prior studies have shown only a

modest decrease in blood cytotoxic T cells (CD8), but not in cluster of differentiation 4 (CD4) levels in patients on ocrelizumab,[6] and ocrelizumab did not appear to affect the ability of T cells to elicit a functional cytokine response to stimulation.[7] Additionally, recent data presented from New York University in COVID-19 infected, unvaccinated patients with MS demonstrated persistent humoral and T-cell immune memory to SARS-CoV-2 up to 10 months following infection, even in B-cell-depleted patients with MS.[8] These findings suggest that ocrelizumab-treated patients are able to fight off COVID-19 infection despite depressed antibody responses.

Furthermore, not only is it problematic to draw this conclusion from the SARS-CoV-2 IgG response alone, the anti-SARS-CoV-2 enzyme-linked immunosorbent assay (ELISA) used (Euroimmun) in this study has a reported sensitivity of approximately 90%. Several other commercially available assays (Abbott, Liaison, Roche, Siemens, Oxford) have shown in a head-to-head assessment to achieve sensitivity and specificity of at least 98%,[9] thus making the assay used in this particular study suboptimal.

In summary, clinicians and patients need to know whether administering an mRNA vaccine to MS patients who are receiving DMTs are potentially capable of immune response compatible with immunity to COVID-19. While this study reports the detection of SARS-CoV-2 IgG, albeit interesting data regarding the humoral response to the vaccine, it is inaccurate to declare this confers either the absence or presence of a protective immune response.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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