EDITORIAL

Reading the "T" Leaves of COVID-19 Vaccine Responses in Multiple Sclerosis

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The view of the multiple sclerosis (MS) therapeutic landscape became clouded by the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Previous strategies for explaining MS medication options to patients were challenged by the lack of knowledge about how MS therapies might affect acute coronavirus disease 2019 (COVID-19) infections. With the unprecedented capabilities of research laboratories and the worldwide biotechnology industry, we were able to offer COVID-19 vaccines to people who had a high risk of COVID-19 infection in just over a year from the emergence of the virus. There was still a brume over the therapeutic landscape, however, due to the uncertainty about vaccine efficacy in patients treated with lymphocyte-depleting and -sequestering medications. Early concerns focused on B-cell–depleting therapies (e.g., rituximab, ocrelizumab). Individuals with MS treated with ocrelizumab had previously demonstrated attenuated antibody responses to common vaccines.[1] While it was appreciated that T-cell response to COVID-19 vaccines was going to be important, the ability to measure T-cell immune responses lagged behind antibody measurements in most clinical centers.

The relevance of measuring T-cell responses to the mRNA COVID-19 vaccines is highlighted by Tortorella et al.[2] in this issue of *Neurology*®. The authors demonstrated in a cohort of 108 vaccinated patients with MS that, contrary to early predictions, a lymphocyte-sequestering agent (fingolimod) was associated with both reduced humoral and T-cell responses to the mRNA COVID-19 vaccines. The encouraging overall message of the article is that most patients with MS on diverse types of medications have a detectable response to the vaccines and should pursue full courses of vaccination. It is interesting to note that all MS medications evaluated (ocrelizumab, fingolimod, interferon beta, and cladribine) conferred reduced (although detectable) T-cell responses to the spike protein compared to responses from 186 health care worker controls. Because there were no patients off treatment in the analysis, it is unclear whether the MS disease state itself contributed to this difference in all case groups vs healthy controls in this study. As expected, antibody responses were reduced in those participants on ocrelizumab, but these patients had adequate T-cell responses.

Prior work by Achiron et al.[3] in a cohort of 125 patients with MS had shown reduced vaccine antibody responses in ocrelizumab- and fingolimod-treated patients but had left unanswered the question of T-cell responses. Tortorella et al. report that the majority of patients with MS on ocrelizumab (92%), cladribine (70%), and interferon beta (89%) have detectable T-cell responses to the mRNA vaccines, but only 14% of fingolimod-treated patients had detectable T-cell responses.

Apostolidis and colleagues[4] were the first to address cellular immunity after SARS-CoV2 mRNA vaccination in a small group of anti–B-cell (ocrelizumab)–treated patients with MS. In-depth analyses confirmed that spike-specific and receptor-binding domain (RBD)–specific antibody and memory B-cell responses were decreased and related to timing of the last infusion and the degree of B-cell depletion. However, all patients had antigen-specific CD4 and CD8 T-cell responses after vaccination. Patients without anti-RBD immunoglobulin G showed weaker circulating follicular helper T-cell responses and more robust CD8 T-cell responses.

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Brill and colleagues[5] confirmed normal SARS-CoV-2–specific T-cell responses in anti-CD20–treated patients with MS who also had decreased humoral responses after full vaccination. Recently, Tallantyre and colleagues[6] also addressed vaccine responses in anti-CD20– and fingolimod-treated patients, showing lower seroconversion after vaccinations for both groups. T-cell responses to SARS-CoV2 were tested in a preliminary analysis of patients who had a negative humoral response after complete vaccination. A measurable T-cell response was observed in fewer than half of the 16 patients, including 1 of 6 patients using fingolimod and 4 of 8 on B-cell–depleting therapies.

Beyond the inclusion of both humoral and cellular responses in patients on different types of disease-modifying therapy, additional strengths of the current article included quantifying both the RBD and neutralizing antibodies as measures of the vaccine humoral response.[2] For cellular responses, the authors examined both CD4+ and CD8+ cells and confirmed that each has a role in viral response in human participants as in in vitro studies. Samples were taken at a uniform time point of 2 to 4 weeks after the vaccine cycle, and vaccine timing in relation to pulsed therapies (ocrelizumab, cladribine) was prescribed as per the recommendations of the Italian and European neurologic societies.

While Tortorella et al. report important observations, the cross-sectional study was modestly powered, and the drugs studied were representative of different medication classes but still limited to only 4 agents. Important questions remain unanswered about the clinical consequences of the relative humoral and T-cell vaccine responses across MS medications. In addition, it is unclear how to define a cutoff level for antibodies or cellular immunity that would provide sufficient protection against infection or a more severe COVID-19 course in anti-CD20– or S1P receptor modulator–treated patients with MS. In addition, the cross-sectional natures of the vaccine response studies to date do not address critical questions about the best timing of vaccines and effects of boosters or third doses to maximize humoral and cellular responses. Nonetheless, it is a critical advance to be able to read the "T" leaves of the cellular response to COVID-19 mRNA vaccines in the MS population and to use these data in the planning of the next steps in vaccination strategies for sustained protection against the SARS-CoV-2 virus over time.

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