

Comment: Humoral and T-cell Immunities to SARS-CoV-2 Vaccines: Safety, Efficacy, and Challenges in Autoimmune Neurology

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With the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA (mRNA) vaccinations, we have been witnessing a new era in vaccinology because these vaccines do not contain viral proteins but mRNA or viral vectors that instruct the cells to make viral-specific protective antibodies. To effectively fight SARS-CoV-2 infection, however, these vaccines need to induce both humoral and cell-mediated immune responses, with antibodies that block viral replication and viral-specific T cells that kill viral-infected cells and generate antibody-producing plasma cells and long-lived memory cells.^{1,2} The need for such vaccine-induced coordinated immunities has generated concerns in autoimmune neurology questioning whether (1) the existing autoimmune disease affects the vaccines' efficacy, (2) the underlying autoimmunity predisposes patients to SARS-CoV-2 mRNA-triggered disease exacerbations, and (3) the immunomodulating or immunosuppressive therapies they receive prevent the generation of sufficient antibodies or T-cell responses to ensure vaccine effectiveness. These issues have been especially concerning to patients with multiple sclerosis (MS) treated with immunomodulating drugs; B-cell-depleting agents such as rituximab, ocrelizumab, and ofatumumab; or with molecules altering cell trafficking and lymphocyte DNA synthesis, such as fingolimod and cladribine. Similar concerns are also raised in patients with myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy, and autoimmune myopathies who commonly receive steroids and immunosuppressants, such as mycophenolate, azathioprine, cyclosporine, or tacrolimus. These issues have now been addressed in 2 important new studies, one in MS³ and the other in MG⁴ evaluating the generation of anti-region-binding domain (RBD) neutralizing antibodies and spike (S)-specific T-cell responses after 2 SARS-CoV-2 vaccinations.

In the first large study of patients with MS, the median anti-RBD antibody titer after 2 mRNA vaccinations was lower in patients treated with ocrelizumab, fingolimod, and cladribine compared with immunized healthy people while serum neutralizing activity was only seen in a few fingolimod-treated patients.³ On the other hand, the interferon (IFN)- γ -producing T-cell-specific response, although reduced, was detected in most of the patients and correlated with lymphocyte counts and anti-RBD antibody titers. Importantly, the ocrelizumab-treated patients mounted a spike-specific T-cell response comparable with patients with MS treated with IFN- β or cladribine, which probably explains why the anti-CD20-treated patients exhibit low frequency of vaccine failures.³

The second study in this issue by Professor Isabel Illa's collaborative team,⁴ addressed the same questions in 100 prospectively studied patients with MG assessing IgG antibodies against nucleocapsid protein and the IFN- γ -producing T-cell response after 2 mRNA vaccinations in conjunction with clinical and safety correlations. They showed that patients with MG (1) did not clinically worsen, although a few patients with preexisting, poor disease control, unrelated to vaccines had transient worsening; (2) experienced less adverse events probably because of receiving corticosteroids; and (3) achieved high rates of humoral and cellular immune responses. The combined therapy of prednisone and another immunosuppressant correlated with lower seroconversion and T-cell response ratio with 6 times higher risk of not developing antibodies against spike protein and 3 times more risk of not achieving cellular response, compared with healthy controls. These lower response rates however were deemed sufficient to offer adequate protection because none of these patients became infected 6 months after the second dose in a "hot-spot" high-infection period.

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Both studies are important and novel but with some inevitable limitations because the science on coronavirus disease 2019 (COVID-19) vaccinology and autoimmunity is rapidly evolving. Because in both MS and MG patients the humoral and cellular immunities were reduced, it is important to know the immunity strength at serial time points, especially after B-cell-depleting therapies, to determine the need and proper timing of boosting doses. T-cell responses were only based on IFN- γ measurements, but information on more T-helper-related cytokines connected to activated CD4 and CD8⁺ cells in correlation with RBD antibody titers is needed. Although robust T-cell responses have been associated with mild/asymptomatic COVID-19 infection even in the absence of antibodies,^{1,2} it is untested whether the vaccine-induced spike-specific T cells provide sufficient protection in a setting of the noted impaired humoral immunity. Importantly, the vaccine protection should be further defined if is only against severe viral illness, protecting the patients with preexisting autoimmune neurologic diseases from further worsening or also against mild illness. This is concerning because mild illness is associated with high titers of COVID-19-specific neutralizing antibodies⁵ which were found reduced in both MG and MS vaccinated patients receiving immunotherapies.^{3,4} It is important therefore to know whether even a breakthrough mild COVID-19 disease, as we are observing today in fully vaccinated healthy people, will not substantially affect these patients' underlying neuroautoimmunity. In addition, the vaccine-evoked immunities need to be reexamined after the third and fourth boosters to assess whether the emerging variants can escape immunity in patients with MG, MS, and neuromyelitis optica spectrum disorder that now receive anti-B-cell and anticomplement therapeutics. We are certain that these questions are already being pursued by the authors of both studies. Unfortunately, these investigations will move forward without the expertise of Professor Isabel Illa who died a few weeks ago.

During her career as a clinician-scientist, Isabel was interested in a wide range of topics leading to many publications that included studies on HIV-associated inflammatory myopathies,⁶ a controlled trial on high-dose IV immunoglobulin as treatment for dermatomyositis,⁷ her contribution to the discovery of the dysferlin gene,⁸ and the clinical phenotypes of the dysferlinopathies.⁹ Her studies on MG are multiple, ranging from the demonstration of a higher than expected incidence in the older patients¹⁰ to showing that myasthenia associated to muscle-specific kinase antibodies is highly responsive to rituximab.¹¹ More recently, she led a team of young neuroscientists to make outstanding discoveries that now define the "autoimmune nodopathies,"¹²⁻¹⁴ a field she was proud of creating and one of her many legacies.

Isabel had a passion for teaching and education and was the first woman to be elected President of the Spanish Society of Neurology. The present work on vaccinations that Isabel prospectively designed with her team is inspiring.⁴ Although it does not provide all the answers, it offers a reassuring and calming message to patients with MG that mRNA vaccines

are safe and effective and should be used. This message will be part of her enduring legacy and highlights her dedication to improving patients' lives. Both of us have lost a dear friend and the autoimmune neuromuscular community a great scientist.

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