Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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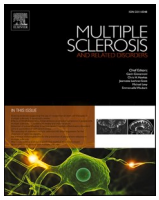

Editors welcome

B cell therapy and the use of RNA-based COVID-19 vaccines

As an increasing number of people access vaccines to coronavirus disease (COVID-19), those with multiple sclerosis (MS), neuromyelitis optica (NMO), and other individuals receiving immunosuppressive medications are concerned about the safety and efficacy of these vaccines. B cell depletion with anti-CD20 drugs such as rituximab, ocrelizumab, or the more recently approved, ofatumamab (Hauser et al., 2020), are of particular interest because prior studies have suggested that there is decreased vaccine-induced protection in the setting of CD20 blockade (Day et al., 2020; Killestein et al., 2020; Westra et al., 2014). While there is as of yet no published data about COVID-19 vaccine efficacy in any immunosuppressed populations, there are cogent arguments on both sides of the debate surrounding whether CD20 blocking immunotherapy may have an impact on the efficacy of new RNA-based COVID-19 vaccines.

Vaccine-induced protection relies on both humoral (antibody-mediated, predominantly B-cell) and cellular (predominantly T-cell mediated) mechanisms of immunogenicity (Zrzavy et al., 2019; Clem, 2011). Sustained cellular immunity that surveils and protects against predominantly intracellular pathogens, such as viruses, relies on CD8+ T cells, which are activated in response to foreign antigens presented by infected cells. Humoral immunity, meanwhile, protects predominantly against extracellular pathogens, which bind to circulating antibodies or B cells via antigen-specific B cell receptors (Clem, 2011). The CD20 receptor is expressed on the surface of maturing B lymphocytes, so therapeutic monoclonal antibodies against CD20 deplete these circulating B cells, and specifically impair the maturation of new memory B cells and antibody-producing plasma cells which give rise to humoral immunity (Day et al., 2020; Westra et al., 2014; Ineichen et al., 2020; Myhr et al., 2019).

Several previous studies of vaccine responses in patients receiving anti-CD20 therapies have been done with rituximab and ocrelizumab. In a prospective controlled study of vaccination in rituximab-treated patients with rheumatoid arthritis, predominantly B cell-dependent vaccination responses (to pneumococcal vaccine and the neoantigen keyhole limpet hemocyanin (KLH)) were decreased, while more T-cell dependent responses, as measured by the response to tetanus toxoid vaccine and the delayed-type hypersensitivity response, were preserved in both groups (Bingham et al., 2010). The recently completed 'Study to Evaluate the Effects of Ocrelizumab on Immune Responses in Participants With Relapsing Forms of Multiple Sclerosis' (VELOCE) was a clinical trial conducted to specifically assess humoral responses to various (non-COVID-19) inactivated vaccines in ocrelizumab-treated patients with multiple sclerosis (Hughes et al., 2021). The study demonstrated attenuated humoral responses, as measured by antibody titers, to tetanus-toxoid containing vaccine, Pneumovax vaccine, KLH, and influenza vaccine in patients who had received ocrelizumab. However, cellular immunity responses to the vaccines were not studied (Bar-Or et al., 2020). The outcome measures in the trial were antibody titers, and anti-CD20 medications are known to mechanistically block formation of new memory B cells and lower antibody production. Vaccine efficacy, however, is not exclusively antibody-mediated, and no study has looked directly at infection rates after vaccination, as this would not be feasible in the setting of extremely low baseline rates of most vaccine-preventable disease. So, the ultimate question of whether patients on CD20-depleting medications receive less real-world protection from vaccines remains unaddressed.

How would this prior data apply to the new mRNA-based vaccines, however? Both the approved Moderna vaccine and the BioNTech/Pfizer vaccine are lipid-nanoparticle formulated (LNP), nucleoside-modified RNA vaccines encoding the SARS-COV-2 spike (S) glycoprotein. There is no in-vivo data thus far about the efficacy of these vaccines in immunosuppressed patients or those receiving B cell depleting therapy. A case report has recently been published of a patient on ocrelizumab who received the Pfizer mRNA COVID-19 vaccine, and failed to seroconvert 27 days after his second vaccine dose (Khayat-Khoei et al., 2021). However, lack of antibody production may not equal lack of efficacy and preliminary studies suggest that mRNA vaccines utilize both humoral and cellular immunity mechanisms. A phase I/II study of an mRNA vaccine candidate, BNT162b1, produced by Moderna and closely related to their COVID vaccine, demonstrated a robust cellular immune response, as evidenced by skewed T-helper type 1 (Th1) response, interferon- γ production by CD8+ and CD4+ T cells, and expansion of these memory T cells. While B cells would be expected to help in the T cell activation, they may not be necessary to achieve a response. Thus one may postulate that the mRNA vaccines could be effective in persons using B cell depleting drugs, due to the preserved T cell response.

While B cell depleting drugs remove 95–100% of B cells from the circulation and probably reach bone marrow and lymph nodes as well, total body depletion of B cells in other tissues is not likely (Thurlings et al., 2008). Different B cell depleting drugs have differing degrees of penetration into tissues, and B cells from various compartments may be recruited to sites of inflammation (Kunkel and Butcher, 2003). Therefore, a rituximab-treated person who received a COVID vaccine may yet achieve a partial humoral response.

Further prospective clinical studies examining the relative contributions of humoral and cellular immunity to the protective response against the SARS-COV-2 vaccine will be necessary to guide management decisions in patients receiving anti-CD20 therapy. It is fair to speculate that mRNA vaccines may stimulate reduced humoral responses in this population compared to the general population, however the bottom

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line impact on efficacy is unknown. Patients and providers alike wonder whether they should defer or delay treatment with anti-CD20 therapy, delay vaccination to coincide with the end of their anti-CD20 therapy cycle, or conversely aim to be vaccinated as soon as possible without modification to their immunosuppressive therapy. Given the ongoing substantial risk of COVID-19, as well as the supposition that the vaccine will be safe and at least partially effective in patients on anti-CD20 therapy, we would argue against systematically delaying vaccination or delaying anti-CD20 therapy. When addressing the question of deferring or delaying immunosuppressive therapy, we weigh a known risk of exacerbated neurologic disease against an unknown theoretical benefit of modifying treatment plans on COVID-19 vaccine efficacy. Overall, for the time being, the decision will need to be personalized based on the assessed risk of delaying anti-CD20 treatment, so that patients with benign or low risk neurologic disease may reasonably choose to delay therapy based on the theoretical concerns of vaccine efficacy, whereas those for whom delaying anti-CD20 therapy is more of a risk may continue without modification. There is also not strong evidence for switching from anti-CD20 therapy to alternative disease-modifying therapies, as there is a risk that other T-cell targeting or nonspecific therapies may also impact vaccine efficacy via decreased cellular immunity responses. Questions also remain regarding whether additional booster doses of the vaccines would be helpful in this population, and if so, what the timing and dosage of these would be. In addition, further studies on vaccine efficacy in this population should carefully evaluate efficacy in relation to the timing of anti-CD20 therapy, as there have been suggestions that timing vaccine administration to the end of the CD20 therapy cycle would improve efficacy by maximizing the number of available B cells that can be recruited.

The persistent high prevalence of COVID-19 provides a unique opportunity to study infection rates after mRNA vaccination in patients using B cell depleting drugs. Whereas previous studies of vaccination efficacy have necessarily utilized biomarkers of immunogenicity, and particularly humoral immunity, to predict protection from infection, the current pandemic allows us directly study the effect of anti-CD20 therapy on vaccine efficacy by measuring infection rates. There are currently more questions than answers regarding COVID-19 vaccines in immunosuppressed patients, however deferring or stopping anti-CD20 therapy in order to optimize COVID-19 vaccine efficacy may yet prove to be unnecessary.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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