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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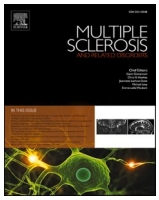

Editorial

COVID-19 vaccines and multiple sclerosis disease-modifying therapies

Much more evidence has emerged since our first editorial in April 2020 on the use of multiple sclerosis (MS) disease-modifying therapies (DMTs) during the pandemic (Giovannoni et al., 2020) and a further publication in MSARDs by Baker and colleagues on the biology underpinning the interaction between DMTs and SARs-CoV-2 (David Baker, Amor, et al., 2020). It is now clear that apart from anti-CD20 therapies (rituximab and ocrelizumab) MS DMTs do not appear to increase the risk of COVID-19 or severe COVID-19 (Maria Pia Sormani et al., 2021; Peeters et al., 2020; Salter et al., 2021). Importantly, people with MS (pwMS) treated with interferon-beta are less likely to get severe COVID-19 (Maria Pia Sormani et al., 2021), presumably due to its antiviral effects (Monk et al., 2021). The risks of COVID-19 associated with anti-CD20 therapy are relatively small with an approximate doubling of liability compared to people on other DMTs (Maria Pia Sormani et al., 2021; Peeters et al., 2020). The most important drivers of severe COVID-19 and death are age, disability and the presence of comorbidities (Maria P. Sormani et al., 2021; Louapre et al., 2020). Male sex and other social determinants of health such as deprivation and ethnicity also play an important role in outcomes from COVID-19 (Bhaskaran et al., 2021). When counselling individual patients about the doubling of the risk of getting severe COVID-19 when on an anti-CD20 therapy it should be stressed that a doubling of a low risk, particularly a low absolute risk, remains still a low absolute risk. People with MS could use one of the online risk calculators, for example the online QCovid® risk calculator developed by the University of Oxford (https://qcovid.org/) to assess their personal risk.

As we hopefully approach the final wave of the COVID-19 pandemic, some countries anticipate herd immunity towards the end of the summer in the northern hemisphere. The question of vaccine readiness in relation to DMTs (D. Baker et al., 2020; Reyes et al., 2021) and vaccine hesitancy concerning the long-term safety of the COVID-19 vaccines remain very topical (Reyes et al., 2021; Xiang et al., 2021; Moniz Dionísio et al., 2021).

A recent publication from Israel shows blunted antibody response to the Pfizer-BionTech mRNA-COVID-19 vaccine in ocrelizumab and fingolimod treated patients, compared to those treated with cladribine or no DMT (Achiron et al., 2021). The suboptimal ocrelizumab and fingolimod vaccine response results have been substantiated by a small French study (Bigaut et al., 2021) and in part refuted by an Italian real-life study that examined 32 patients with MS. In 10 out of 16 (62.5%) patients managed with fingolimod and 6 out of 16 (37.5%) treated with ocrelizumab there was a positive serological response after vaccination (Guerrieri et al., 2021). We suspect the discrepancy may relate to sensitivity of the assay used to detect the anti-SARS-CoV-2 spike protein antibodies.

These results are not surprising as there is good evidence that both anti-CD20 therapies (Cioc et al., 2008) and fingolimod (Han et al., 2004), a S1P modulator, disrupt germinal centre (GC) functioning in lymphoid tissue where naive B-cells are educated with the help of follicular T-helper cells. In the GCs, antibody gene rearrangement results in class switching, for example from IgM to one of the IgG subtypes, followed by affinity maturation and selection of high-affinity B-cell receptors or membrane-bound antibodies, prior to formation of memory B-cells and plasmablast clones that exit the GCs to produce high-affinity soluble IgG that can be detected in the peripheral blood (Lu and Craft, 2021).

It is important to stress that vaccine immunity is not all about antibody responses (B-cell mediated) and that T-cell responses are also important (Teijaro and Farber, 2021).

A Swiss study, that has yet to be peer-reviewed, evaluated 96 anti-CD20 treated patients and 29 immunocompetent controls. Anti-spike SARS-CoV-2 IgG antibodies were detected in 49% of patients after the second mRNA-COVID-19 vaccine dose, compared to 100% of controls. SARS-CoV2 specific interferon-γ release, a T-cell assay, was detected in 17% of patients and 86% of healthy controls (Moor et al., 2021). Only 5% of patients, but 86% of healthy controls showed positive results in both the antibody (B cell) and T cell assays. Importantly, the time elapsed since the last dose of an anti-CD20 therapy (>7.6 months), peripheral blood B-cell reconstitution (CD19+ cells >27/μl) and CD4+ lymphocyte count above 653/μl predicted an antibody vaccine response (Moor et al., 2021). In contrast, a US group of investigators confirmed that anti-CD20 therapy significantly reduced an anti-SARS-CoV-2 spike and receptor-binding domain (RBD) specific antibody and memory B cell responses in most patients. They also demonstrated that the effect was reduced with longer duration from the last infusion of anti-CD20 treatment and extent of B cell reconstitution (Apostolidis et al., 2021). In contrast, all patients treated with anti-CD20 therapies generated antigen-specific CD4+ and CD8+ T-cell responses following vaccination with mRNA vaccines (Apostolidis et al., 2021). In their group of patients, anti-CD20 therapy tended to skew the immune response away from so-called T-follicular helper cells and augmented the induction of antigen-specific CD8+ T cells (Apostolidis et al., 2021). These conflicting results are probably due to methodological issues. It is generally agreed that a reasonable IgG antibody response to a vaccine indicates a good CD4+ T cell response, particularly a T-follicular helper cell reaction, which is required to help educate and produce antigen-specific memory B-cells and plasmablasts in GCs (Lu and Craft, 2021). In the Swiss study above, 49% of anti-CD20 treated patients made an antibody response compared to 17% with the interferon-γ or T-cell assay. This suggests a problem with the sensitivity of their T-cell assay (Moor et al.,

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2021).

It is important to note that the majority of patients with MS on anti-CD20 therapy or a S1P-modulator make an unremarkable recovery from COVID-19. This implies that innate and T-cell responses which are critical in clearing SARS-CoV-2, are functional. In comparison, B-cell and antibody responses are not vital for eliminating the primary infection (Maria Pia Sormani et al., 2021) (Hughes et al., 2021), but are likely to play an important role in secondary immune responses, particularly sterilizing immunity, i.e. preventing repeat infection in people infected in the past or infection after vaccination (Sette and Crotty, 2021).

Putting all of this in context, it seems highly likely that patients with MS placed on anti-CD20 therapy or a S1P-modulator will have blunted, but not necessarily absent, antibody responses to the COVID-19 vaccines. These patients are likely to benefit from protective or at least partially protective T-cell responses to the vaccine, in keeping with what happens when they experience naturally occuring SARS-CoV-2 infection. This immunity is unlikely to be sterilizing, particularly because the new emerging SARS-CoV-2 varieties, e.g. the delta variant, are partially immune escape strains. Despite this, this immunity may be sufficient to prevent symptomatic infection, severe disease or death from COVID-19. The message should therefore remain the same; patients on anti-CD20 therapy or a S1P modulator (fingolimod, siponimod, ozanimod, ponesimod) should receive one of the licensed COVID-19 vaccines as soon as possible on the principle that during the pandemic some immunity, particularly T-cell immunity, is better than no immunity.

At this point in the pandemic we would not recommend withdrawal of anti-CD20 or S1P modulator therapy, to optimise vaccine responses. The risk of rebound disease activity from stopping and washing out a S1P modulator is particularly hazardous (Barry et al., 2019). Conversely, the longer duration of action of anti-CD20 therapies makes rebound disease activity after withdrawal less of an issue (David Baker, Pryce, et al., 2020). Despite this, we do not know whether this is necessary and if needed, what level of B-cell reconstitution is required to optimise vaccine responses. We anticipate through studies such as those highlighted by Pedotti and colleagues (Pedotti et al., 2021) in this journal, that we will find out if pwMS on these therapies, who are vaccinated against COVID-19, albeit suboptimally from a immunological perspective, have enough immunity to prevent COVID-19 in any shape or form.

We would like to conclude by addressing the recommendation for people with MS to have seasonal influenza vaccines, 5-year pneumococcal vaccines or travel vaccines as required and perhaps a seasonal/booster COVID-19 vaccine. At some point people with MS on anti-CD20 and S1P modulators, and potentially other emerging MS DMTs, such as the Bruton Tyrosine Kinase (BTK) inhibitors, must accept that they are immunocompromised and that this immunosuppression extends to blunted, but not necessarily absent, vaccine responses as well. Through accumulation of global data we will learn if and how optimization of vaccine responses may be achieved without compromising effective management of MS. It is vital that MS-treating clinicians balance the small absolute risks of suffering severe COVID-19 and potentially death and the blunted vaccine responses on anti-CD20 therapies and the blunted vaccine responses on S1P modulators against the risks of undertreating or not treating MS.

Declaration of Competing Interest

In the last 5 years, Gavin Giovannoni has received compensation for serving as a consultant or speaker for or has received research support from AbbVie, Aslan, Atara Bio, Biogen, BMS-Celgene, GlaxoSmithKline, GW Pharma, Janssens/Actelion, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck & Co, Merck KGaA/EMD Serono, Novartis, Sanofi-Genzyme, Roche/Genentech and Teva.

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