INVITED EDITORIAL

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LEADING TOPIC

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Immune response to COVID-19 vaccines in patients with multiple sclerosis treated with disease-modifying therapies

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Scientific reports indicate that multiple sclerosis (MS) does not constitute a factor increasing the probability of contracting COVID-19, and neither does it increase the risk of the disease's severe course or death compared to the general population [1, 2]. There is also no convincing evidence that vaccination increases the risk of the development of MS or a relapse. It is believed that it is safe to vaccinate people with MS, and it would be wrong not to vaccinate solely because of having been diagnosed with MS [3, 4]. Vaccination, along with following the principles of prevention, is the best strategy in the era of COVID-19. An increasing number of studies have shown that when determining the indications for vaccination, as well as when determining the optimal moment to implement, the type of applied treatment modifying the course of the disease (DMT) should be taken into consideration. It has been shown that in people with MS (pwMS), some DMTs, especially the anti-CD20 monoclonal antibodies and sphingosine-1--phosphate receptor modulator (S1PRM), may have an impact on both post-infection and post-vaccination immune response to COVID-19 [5–9].

In this issue of *Neurologia i Neurochirurgia Polska,* the topic of immune response after vaccination and following COVID-19 infection in pwMS is addressed by Kulikowska et al. [10].

The authors of that study analysed the presence of antibodies against the spike (S) and nucleocapsid protein (N) of the SARS-CoV-2 virus in patients with relapsing-remitting multiple sclerosis treated with DMT. The analysis included both after infection and vaccinated individuals. The study included a population of Polish MS patients treated mainly with dimethyl fumarate (DMF), interferon beta (IFN-β), and glatiramer acetate (GA). A minor part of the study group consisted of patients taking fingolimod (FG) and cladribine (CLAD), while there were no patients treated with anti-CD20 monoclonal antibodies (ocrelizumab, OXR, rituximab, RTX, ofatumumab, and OFA). The main conclusion from the study was that pwMS treated with dimethyl fumarate, beta interferon, and glatiramer acetate can successfully produce antibodies against SARS--CoV-2, both after infection and after vaccination.

These results are consistent with the reports of other authors who state that these DMTs do not interfere with developing humoral immunity against SARS-CoV2 after vaccination or being infected with COVID-19 in people with MS [6–8].

However, most authors emphasise the impact of anti--CD20 and S1PRM on developing post-vaccination immunity [6–9].

On the basis of a prospective, multicentre cohort study with pwMS, in which SARS-CoV-2 vaccination with mRNA vaccines (BNT162b2, Pfizer/BioNTech or mRNA-1273, Moderna) has been carried out, Sormani et al. showed that treatment with anti-CD20 and fingolimod led to a reduced post-vaccination humoral response [11]. In the course of multivariate analysis, antibody concentration levels achieved by patients treated with ocrelizumab (a 201-fold decrease), fingolimod (26-fold decrease), and rituximab (20-fold decrease) were significantly lower compared to untreated subjects [11].

The aim of this study was to assess humoral response after mRNA vaccination in pwMS treated with high-efficiency DMTs [12]. Protective humoral response at the level of 100% was observed in untreated pwMS patients, 100% in patients treated with cladribine, 22.7% with ocrelizumab, and 3.8% with fingolimod. SARS-CoV-2 IgG antibody titres were high in untreated pwMS and those treated with cladribine. Only 22.7% of patients treated with ocrelizumab developed a humoral IgG response regardless of normal absolute lymphocyte count. The majority of patients treated with fingolimod had very low lymphocyte counts and did not develop SARS--COV-2 antibodies [12].

In a different study, Cohen et al. assessed the percentage of patients with reactive IgG anti-SARS-CoV-2 antibodies

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depending on the type of DMT used [13]. In pwSM who received an mRNA vaccine, Cohen et al. found that post-vaccination IgG rates were 40% for anti-CD20, 41% for sphingosine-1-phosphate receptor modulators (S1PRM), and 100% for all other DMTs. The authors concluded that anti-CD20 and S1PRM therapies reduce IgG response to SARS-CoV-2 vaccination. In terms of other DMTs, the IgG response is maintained [13].

48 studies involving 6,860 MS patients have been included in a recently published meta-analysis [14]. PwMS with anti-CD20 and S1PRM treatments had an attenuated serological response after full vaccination compared to those without DMTs. Additionally, pwMS vaccinated within the six months since their last anti-CD20 therapy were at significantly higher risk of blunted response compared to those receiving anti-CD20 therapy more than six months prior to vaccination. The authors found no significant associations between other treatments (including IFN-β, GA, DMF, TERI, NTZ, CLAD, and ALE) and humoral response to SARS-CoV-2 vaccines in pwMS. As for T-cell response, no significant difference was found between pwMS on anti-CD20 and those without DMTs after vaccination, while S1PRM was marginally associated with impaired cellular response [14].

Recently published research results concerning a new drug, ofatumumab, which is also a monoclonal anti-CD20 antibody, have provided interesting data.

Data presented at the 2022 AAN Annual Meeting from the ALITHIOS and KYRIOS trials suggests that ofatumumab is safe with up to four years of treatment, and does not prevent the cellular and humoral immune response to mRNA vaccines [15].

Further data from the ongoing KYRIOS open-label, prospective study showed that pwMS on ofatumamab are able to produce an immune response to the COVID-19 mRNA vaccine [16, 17]. All participants in KYRIOS who were vaccinated during treatment developed an immune response as soon as the first week after their initial vaccination, and the response in those who received a booster shot during treatment was similar to those who received a booster before treatment [16–18].

Even though treatment with small doses of ofatumumab results in B-cell depletion and is associated with an impaired humoral response to SARS-CoV-2 vaccination, the T-cell response is maintained.

The research results presented above show that the majority of DMTs used in pwMS allow complete post-vaccination immunity to be obtained through the use of mRNA vaccines. Serological monitoring after SARS-CoV-2 vaccination may be indicated in patients treated with anti-CD20 (ocrelizumab) and S1PRM antibodies. In these cases, it seems beneficial to use a booster dose and determine the optimal interval between the last anti-CD20 therapy and vaccination [19].

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