REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 1, pages: 90–100
DOI: 10.5603/PJNNS.a2023.0004

ISSN: 0028-3843, e-ISSN: 1897-4260

LEADING TOPIC

Leading Topic Editor: Alina Kułakowska, MD, PhD, Department of Neurology, Medical University of Bialystok, Bialystok, Poland

Navigating the landscape of COVID-19 for Multiple Sclerosis patients and clinicians

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ABSTRACT

The purpose of this literature review was to summarise relevant findings regarding the clinical management of multiple sclerosis (MS) in the COVID-19 pandemic, with the focus on patient risks, and the implications of disease-modifying treatment, both on COVID-19 severity and on the response to the SARS-CoV-2 vaccinations. Although MS per se does not seem to put patients at risk for more severe COVID-19, alongside the risk factors known to apply to the general population, progressive disease course, higher disability status, and B-cell depleting therapies may all negatively affect infection severity. The question of COVID-19 sequelae in patients with MS (pwMS) remains unresolved, challenging researchers to further explore this area. The safety profile of COVID-19 vaccinations in pwMS is similar to that of the general population. The efficacy of the vaccination might be affected by B-cell depletion, as well as by S1PR-modulating medications that attenuate humoral responses to the COVID-19 vaccination. Future research should focus on gathering evidence regarding the clinical course of MS following COVID-19 infection and vaccination in larger studies, as well as on establishing the safest and most efficient schedule of COVID-19 vaccination in pwMS on cell-depleting therapies.

Key words: multiple sclerosis, COVID-19, SARS-CoV-2, COVID-19 vaccination, disease-modifying therapy

(*Neurol Neurochir Pol 2023; 57 (1): 90–100*)

Introduction

Since patients with multiple sclerosis (MS) are a group considered to be vulnerable to hospitalisation and death from lower respiratory tract infections [1–4], one of the most pressing matters regarding the outbreak of the Coronavirus disease (COVID-19) pandemic, caused by the SARS-CoV-2 virus infection, was determining the influence of the underlying neurological condition on susceptibility to COVID-19.

Another issue was the impact of disease-modifying therapies (DMTs) on this susceptibility, and answering the question as to whether or not patients' treatment could be continued while they were infected with COVID-19. And when vaccinations were eventually approved, it became crucial to establish their safety in the MS population and their efficacy, especially in patients treated with immune therapies.

The neurological world adapted fairly quickly to the pandemic reality, releasing subsequent versions of recommendations with regards to DMT initiation in the pandemic, DMT continuation in the case of COVID-19 infection [5, 6], COVID-19 vaccinations [7–9], and even telemedicine [10] in the context of the MS population.

In this review, we have aimed to answer the key questions that MS patients and their clinicians may ask in the context of SARS-CoV-2 infection, thus facilitating a complex navigation through the landscape of the pandemic.

Are MS patients at risk of severe COVID-19, and how does the infection influence their subsequent MS course?

COVID-19 morbidity and mortality in the MS population

Although early reports on the outcomes of COVID-19 in patients with MS (pwMS) yielded mostly reassuring results [11–14, 16, 17, 21], a French study of 347 pwMS found that 21%

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Received: 21.12.2022; Accepted: 09.01.2023; Early publication date: 02.02.2023

of them had a more severe course of the infection, and 3.5% had a fatal outcome [15]. Comparing outcomes among hospitalised patients, fatality rates were higher in pwMS than in the general population for most age groups, suggesting that MS was associated with increased mortality. A systematic review of studies comprising 4,310 pwMS and COVID-19 revealed that 837 of them were hospitalised and 130 died, representing 20.7% and 3.0% of the sample, respectively [20]. Although the mortality rate in this review was not increased, the authors suggested that this result could be a function of demographic characteristics of pwMS, who tend to be on average younger and more female than the average population, and thus less susceptible to severe infection. Indeed, a study exploring COVID-19 general mortality risk factors in a cohort of 1,931 MS patients revealed that those at high risk comprised less than 1% of the sample [21].

In a retrospective study comparing patients with and without a concurrent MS diagnosis, the authors described lower rates of ICU admission, use of ventilation, and in-hospital mortality in pwMS [19]. After an age group-stratified analysis, the positive effect of comorbid MS on admissions to ICU and ventilation use, although attenuated, remained significant, but no difference between MS and non-MS patients was found in terms of in-hospital mortality.

In a pooled analysis of studies comprising 5,634 patients [22], crude death rates in pwMS and the general population did not differ substantially, but a 24% increased risk of death was found in pwMS after age-standardisation.

The ever growing data on COVID-19 in pwMS often throws up contradictory evidence, which can cause confusion. However, most authors agree that the course of COVID-19 in pwMS is mostly favourable i.e. asymptomatic or mild. Importantly, although multiple sclerosis patients are on average younger, and more frequently women, than the general population, it is worth acknowledging that discrepancies in analysed samples' demographics between different studies do affect the results. Preliminary studies included relatively small samples and from countries that had been differently affected by COVID-19, especially during the first wave, with diverse safety measures taken by the various governments affecting COVID-19 prevalence and causing inconsistent results. Moreover, there is a profound heterogeneity in the outcome measuring scales used for statistical analysis across the studies on COVID-19, as well as in the varying hospital admission criteria, COVID-19 diagnostic tools, and even COVID-19 definition, with some researchers considering both suspected and confirmed cases, while others have been taking into account only PCR-confirmed SARS-CoV-2 infections. All these factors contribute to a major difficulty in attempting outcome comparisons.

The number of possible variables and factors impacting the course of COVID-19 in pwMS made it crucial to evaluate specific risk factors accounting for morbidity and mortality in this population, shifting the focus to the adoption of a more personalised approach.

Risk factors for severe COVID-19 in MS patients

Rapidly conducted research around novel coronavirus disease enabled the prompt identification of risk factors associated with COVID-19 severity in the general population, as well as in pwMS [23]. The assessment of demographic and clinical characteristics conducted by Louapre et al. provided the first insights into MS-related factors associated with unfavourable disease course [15]. The authors identified older age, male sex, obesity, and disability (in the form of a higher EDSS score) as independent risk factors for increasing COVID-19 severity. Similar findings were reported by Sormani et al. [24], who found older age, male sex, higher EDSS, as well as methylprednisolone use within one month before infection, to be predictors of worse outcomes in both univariate and multivariate analyses. Other variables associated with the risk of severe SARS-CoV-2 infection identified in this study were: progressive MS course, longer disease duration, comorbidities, increased BMI, and treatment with an anti-CD20 drug.

The COViMS Registry associated older age, male sex, obesity, ambulatory disability, cardiovascular comorbidities, and recent corticosteroid treatment with higher risks of hospitalisation and mortality [25]. Black race and rituximab exposure were associated with an increased risk for hospitalisation, but not for death [25]. The association with hospitalisation persisted for ocrelizumab exposure, although only to a slight extent. An analysis of pooled updated cohorts of SARS-CoV2 cases in MS patients from Italy and France confirmed this finding, indicating that both anti-CD20 agents significantly increase the risk for severe disease course, although the influence of rituximab was of a greater magnitude [26]. Consistently, recently updated results of the MS Global Data Sharing Initiative, comprising 5,648 patients, have reinforced previous reports in what is the largest sample to date [27].

Unexpectedly, not being on DMT therapy has been associated with an increased risk of severe COVID-19 in pwMS, as most of the studies have proved that patients on DMTs have more favourable outcomes of SARS-CoV-2 infection [28, 29]. However, this finding was successfully explained by other factors putting pwMS without DMT at risk, since they are usually affected by progressive disease course and/or higher disability, precluding them from receiving most DMTs, or are older than the typical MS population [27].

Recovery from COVID-19 in MS patients

Current research provides quite consistent data regarding COVID-19 symptoms and infection course in MS patients, suggesting that most pwMS develop a relatively mild infection, with symptoms similar to those observed in the general population [30–32].

The link between viral infections and multiple sclerosis exacerbations has been researched extensively, meaning that a proper exploration of the risk of COVID-19-triggered worsening and relapses is of great importance. Neurological manifestations of SARS-CoV-2 infection have suggested a possible neurotropism of the novel infectious agent, which could potentially increase the risk of future neurodegeneration, especially in those considered vulnerable due to the underlying chronic neurological conditions [33–35].

Nevertheless, real-world data regarding a link between COVID-19 and MS course is limited, and the results are contradictory. In a sample of 404 patients, Garjani et al. [36] observed MS exacerbations in 57% of patients who contracted SARS-CoV-2. Among those patients, 20% reported developing new symptoms and 51% experienced worsening of preexisting ones. The authors also found that DMT treatment reduced the risk of developing new MS symptoms. In a relatively small sample of 111 patients, Conway et al. observed neurological deterioration in 36.9% of pwMS following a SARS-CoV-2 infection, with a correlation between COVID-19 severity and the frequency of neurological complications, mostly pseudo-relapses and worsening of preexisting symptoms [37]. Those results were in line with the general population studies, where infection severity and hospitalisation for COVID-19 were associated with a higher risk of neurological symptoms post-COVID-19 [38]. In contrast to previous findings, an Austrian matched-control study comprising 211 MS patients with COVID-19 and 211 MS controls revealed that neither relapse nor disability worsening risk was increased in the MS and COVID-19 group [39]. Similarly, in a relatively small retrospective study, pwMS who contracted SARS-CoV-2 presented a lower incidence of disease exacerbation and an unaltered relapse risk following the infection [40].

An important insight into relapse risk was presented in a study of Chinese pwMS, where a significant increase in relapse rate during the pandemic was observed, but only in those patients who experienced treatment discontinuation, dose reduction, or were not receiving any MS therapy [41].

Long COVID in patients with multiple sclerosis

'Long COVID' is defined as symptoms that continue or develop after acute COVID-19 and includes both ongoing symptomatic COVID-19 (4-12 weeks) and post-COVID-19 syndrome [42].

Post-COVID-19 syndrome develops during or after COVID-19, and lasts for more than 12 weeks. The symptoms include dyspnoea, cough, fatigue, cognitive impairment, sleep disturbances, headache, loss of smell and/or taste, gastrointestinal problems, joint/muscle pain, and psychiatric symptoms, and cannot be explained by an alternative diagnosis [42].

The prevalence of prolonged COVID-19 symptoms was assessed by Garjani et al. [43] in non-hospitalised pwMS. They concluded that 30% of the sample experienced residual COVID-19 symptoms for at least four weeks and in 12% of patients these persisted for at least 12 weeks. These results exceeded those seen in the general population. Moreover, among MS patients, preexisting severe disability and, as described for the general population, female sex and higher anxiety/depression levels, predisposed to COVID-19 sequelae.

Bsteh et al. [39] found that residual fatigue, dyspnoea, and hyposmia persisted for 3–6 months in a small proportion of patients before resolving, mostly within 12 months.

Another study reported that nearly 45% of pwMS with COVID-19 reported residual symptoms after the initial infection, of whom 20% had symptoms lasting more than 12 weeks. The most commonly reported were: fatigue and cognition complaints including concentration, attention, memory domains, and headache [44].

COVID-19 sequelae in pwMS have been under-researched with limited data, and guidelines for management tailored to this population are yet to emerge.

How do different disease-modifying therapies (DMTs) influence COVID-19 severity in MS patients?

Disease-modifying therapies are used for controlling disease activity in multiple sclerosis, mainly by reducing the rate of relapses and radiological activity [45]. Their mode of action is through altering the immune system either by immunomodulation or immunosuppression, and thus the emergence of a novel, dangerous infectious agent posed an important threat to DMT safety during the pandemic outbreak; however, thanks to their antiviral properties, some DMTs have been evaluated for their effectiveness in COVID-19 [46, 47].

Beta-interferons, type I interferons originally known for their antiviral effects, have been used in MS as a first-line, moderate-efficacy therapy, and have proved particularly useful for pregnant or breastfeeding pwMS [48]. From the beginning of the pandemic, beta-interferons were designated as a safe medication to continue and to start during the pandemic [49–53]. Emerging research provided evidence that beta-interferons did not increase the risk of severe SARS-CoV-2 infection, and most patients on this therapy were recovering safely from COVID-19 [54]. Some studies suggested that beta-interferons might even provide some level of protection, lowering the odds of developing infection when compared to other therapies [55]. Prosperini et al. [56] concluded that beta-interferons exerted a favourable effect on mortality, even after adjusting for age and progressive disease course in a multivariable meta-regression.

This hypothesis has recently been challenged by the results of a large study on a cohort of 5,568 patients with COVID-19 and MS, which showed there was no difference in hospitalisation rate, ICU admission percentage, or death risk between beta-interferons and pooled other DMTs [57], although the authors reveal that in comparison to those treated with other DMTs, patients treated with beta-interferons were slightly older and more frequently diagnosed with progressive MS, both of which predispose to a poor COVID-19 outcome.

Glatiramer acetate (GA), a molecule resembling myelin basic protein (MBP), is a first-line immunomodulatory medication that has been associated with a low risk for COVID-19 severity [50–53]. Current research concludes that this medication does not increase morbidity or mortality of COVID-19, as fatality rates in glatiramer acetate-treated pwMS remained among the lowest [15, 55]. GA was recently evaluated in comparison to a no-DMT group among pwMS suffering from COVID-19, which revealed that untreated patients were 5% more likely to be hospitalised and 1% more likely to die, although these results should be interpreted with caution because the outcomes in untreated patients were generally considered to be a function of confounding factors [27].

Teriflunomide is a selective dihydroorotate dehydrogenase inhibitor interfering with DNA synthesis, targeting especially lymphocytes and thus potentially causing slight lymphopenia [58–60]. However, teriflunomide has not been associated with significant immunosuppression and phase III clinical trials did not indicate an increased risk for infections [59]. This data, in combination with potential antiviral priorities owing to pyrimidine synthesis blockage, resulted in teriflunomide being categorised as a low-risk medication in the context of COVID-19 severity, with treatment continuation generally recommended in pwMS [50–53]. The outcomes of preliminary case reports as well as studies conducted on relatively small samples further reinforced this recommendation [15, 61, 62]. In a pooled cohort of 5,634 patients, teriflunomide was associated with lower lethality in both univariate and multivariate models [56].

Dimethyl fumarate is another first-line medication with immunomodulatory properties, modifying lymphocyte subsets proportions, as well as reducing pro-inflammatory cytokine production [63]. In some patients, dimethyl fumarate has been proven to cause lymphopenia with a small proportion of patients developing grade 3 lymphopenia (ALC 200–499/μL) [64]. While this fact may be of concern, the research data so far does not indicate an elevated risk of severe COVID-19 in dimethyl fumarate-treated pwMS [24, 55]. Conversely, the authors of the North American Registry of Patients With Multiple Sclerosis study found decreased odds of ICU admission and/or ventilation in patients on dimethyl fumarate [25]. Importantly, the latest reports from the Global Data Sharing Initiative found no association between this medication and increased severity of SARS-CoV-2 infection, and no increase in the probability of hospitalisation, ICU admission/artificial ventilation, or death compared to GA [27].

Sphingozine 1-phosphate receptor (S1PR) modulators act as DMTs in MS by preventing lymphocyte excretion. Decreasing the amount of peripheral, circulating immune cells, S1PR--modulators reduce the autoimmune reaction within the CNS [65, 66]. Through their mode of action, S1PR-modulators induce lymphopenia, which can render patients potentially prone to infections. However, common viral infections do not seem to severely affect S1PR-treated patients [67]. There are now four S1PR-modulators approved for treating MS — fingolimod, siponimod, ozanimod, and ponesimod [68]. With fingolimod being the first S1PR-modulator registered in MS, most of the available literature focuses on its influence on COVID-19 severity. Current research does not find an increased risk for severe COVID-19 in fingolimod-treated pwMS [69]. In a review of fingolimod-treated patients from Novartis database safety and clinical trials, the outcomes of COVID-19 were similar to those observed in the standard population [70]. This same study evaluated the risks for siponimod patients as well, concluding that even though pwMS treated with siponimod tend to be older and with a higher disability (as siponimod is registered for secondary progressive disease), they do not seem to be vulnerable to severe COVID-19. However, because of the spontaneous nature of case reporting, incomplete data accumulation, and the low number of siponimod-treated patients, caution should be exercised when interpreting these results.

Natalizumab is a second-line highly effective medication for MS. A monoclonal antibody, binding alpha-4-beta-1-integrin on immune cells, natalizumab reduces immunosurveillance of the CNS, blocking adhesion to the endothelium and limiting migration across the blood-brain barrier [71, 72]. Although patients receiving natalizumab are not considered high risk for common infections, reduced viral clearance from CNS with a combination of SARS-CoV-2 neurotrophic properties initially raised concerns of possible encephalitis [73]. Current research does not find evidence of natalizumab increasing severity rates in COVID-19 pwMS [24, 25, 27]. Consistent with these results, a recently published systematic review found that natalizumab was associated with a decreased risk of severe COVID-19 compared to no DMT [74].

Cladribine in tablets, a purine analogue, is a cell-depleting drug used in highly active relapsing-remitting MS (RRMS). Administered as two short treatment courses one year apart, cladribine induces lymphocyte apoptosis, causing the nadir shortly after the start of each cycle followed by gradual lymphocyte recovery, and is considered an immune reconstitution therapy (IRT) [75]. Although its beneficial effects on MS course persist over the long term, it causes transient lymphopenia, which theoretically could increase the risk of infections. Thus cladribine was marked as an intermediate/high-risk therapy during the COVID-19 pandemic [51–53]. Scant evidence exists regarding the safety of cladribine and COVID-19. One of the early studies assessing the prevalence of COVID-19 among DMT-treated pwMS concluded that IRT was associated with an increased risk of infection compared to beta-interferons and GA, although it is worth noting that no elevated risk for infection severity was detected and that the influence of cladribine was studied in a combination with another IRT, namely alemtuzumab [76]. Importantly, the Global Data Sharing Initiative found no association between increased risk for severe COVID-19 and cladribine exposure, although the number of patients on cladribine was relatively low [27]. In a group of cladribine-treated MS patients from

the Merck KGaA Global Patient Safety Database, 160 with confirmed and 101 with suspected COVID-19, the majority of the sample presented with a mild infection and only one patient (0.4%) had a fatal outcome, further indicating that cladribine-treated pwMS are not at a greater risk for severe SARS-CoV-2 infection [77]. A recently published systematic review of 5,138 MS patients with COVID-19 found a low hospitalisation rate (9.36%) and no fatal outcomes reported among 107 cladribine-treated pwMS, providing reassuring results [78]. To the best of our knowledge, no evidence exists of a greater risk for COVID-19 in cladribine-treated patients.

Alemtuzumab is an anti-CD52 monoclonal antibody that acts similarly to cladribine as immune reconstitution therapy providing long-term effects in RRMS through immune depletion and subsequent slow repopulation, although the reduction of lymphocyte counts can be prolonged and result in severe lymphopenia, causing susceptibility to infections [79]. Indeed, in phase III trials, alemtuzumab did significantly increase the risk of mild to moderate infections [80]. How this translates to the COVID-19 pandemic is of great importance, yet very little data is available on alemtuzumab use in relation to SARS-CoV-2 infection. As mentioned before, one study found an increased risk of contracting COVID-19 in patients on IRT compared to injectables [76]. Conversely, Biogen Safety Database results did not indicate a significant increase in the incidence of COVID-19 in patients on alemtuzumab, although the voluntary nature of pharmacovigilance data collection limits the significance of this finding [55]. While the first studies only included isolated cases of alemtuzumab patients, precluding the drawing of meaningful conclusions, reassuring results were obtained from the international sample of 2,340 patients, including 31 on alemtuzumab, where no increased risk for hospitalisation, ICU admission, and death was found in COVID-19 pwMS on this medication [81]. These results have been now replicated in the updated Global Data Sharing Initiative study, although the number of cases remains relatively low [27].

Anti-CD20 treatment is based on B-cell depletion and is considered a highly effective therapy for multiple sclerosis. Ocrelizumab is a humanised monoclonal antibody selectively depleting CD20+ B-cells used intravenously every six months for both RRMS and early primary progressive MS. Ofatumumab is a fully human anti-CD20 antibody that is administered subcutaneously on a monthly basis, and was most recently approved for the treatment of RRMS. Another anti-CD20 agent, rituximab, has not been approved for MS, but in some countries it has been used as an off-label medication for MS [82–84]. In an early Italian study, anti-CD20 was among the risk factors for severe COVID-19 in a multivariate model. The authors further evaluated the association between time since the last anti-CD20 infusion and total therapy duration, indicating there was a trend between anti-CD20 therapy duration and COVID-19 severity [24], while some researchers have suggested extending the interval of anti-CD20 dosing to reduce the risk of severe COVID-19 [85–87]. A pooled analysis by Sormani et al. confirmed that anti-CD20-treated patients have a higher risk of severe COVID-19. When separating the two most commonly used B-cell depleters, rituximab had a greater effect, although the influence of ocrelizumab remained significant [26]. Similar results were obtained from various studies and confirmed in a systematic review [22, 81, 88–91]. Although unfavourable results in anti-CD20-treated patients could be attributable to the fact that these patients typically have a higher degree of disability and a more progressive disease course, tested in multivariate models, ocrelizumab and rituximab persist as risk factors [26, 27]. Consistently, Global Data Sharing Initiative outcomes seem to confirm that rituximab and, to a lesser extent, ocrelizumab, independently increase COVID-19 severity [27]. The difference in the effect between those two anti-CD20 agents has been investigated, with some studies concluding that the discrepancy might exist due to a longer total treatment time and higher cumulative dose in rituximab-treated patients, since ocrelizumab has only recently become available, although the results are inconclusive [92–95].

Regarding ofatumumab and COVID-19 in MS patients, information is scarce. The largest available sample of pwMS and COVID-19 on ofatumumab was obtained from the ALTHIOS phase 3b extension study, where of 1,703 enrolled patients 245 reported COVID-19 [96]. Of those patients, 9.4% were hospitalised and 0.8% died, indicating that ofatumumab-treated pwMS mostly have a mild COVID-19 and lower risk for hospitalisation and death than the general MS population. Although these are promising outcomes, it should be emphasised that ALTHIOS is a study enrolling patients only up to 55 years old and without comorbid conditions, thereby excluding those most susceptible to severe infection. It should also be highlighted that a relatively short time of treatment with ofatumumab in reference to rituximab and ocrelizumab, and a lower cumulative dose, could result in a lower cumulative effect on immunity and prolonged cell depletion (Tab. 1).

COVID-19 vaccinations in MS patients — risks, benefits, and efficacy

Are patients with MS at risk of disease exacerbation following COVID-19 vaccination?

Since MS is an autoimmune disease, the question of the risks of disease deterioration after the COVID-19 vaccine emerges from the fact that similar immune reactions follow natural infection and vaccination, and that vaccination, by stimulating the immune system, could exacerbate the disease course in a similar way to what has been reported after infections in pwMS [97, 98]. Even though most studies do not find any significant association between vaccination and relapses in pwMS, with the one exception of the yellow fever vaccination, this area of research is of great interest and importance for both patients and their clinicians trying to apply a safe risk-benefit

Table 1. Safety of different disease-modifying therapies for Multiple Sclerosis with regards to COVID-19 severity and vaccine readiness

	Class/Drug	Mode of action	Efficacy	Class	In COVID-19
Very low infection risk, response to vaccine intact					
1.	Interferon beta	Immunomodulatory, pleiotropic immune effects	Moderate	Maintenance immunomodulatory	Safe to initiate and continue
2.	Glatiramer acetate	Immunomodulatory, pleiotropic immune effects	Moderate	Maintenance Immunomodulatory	Safe to initiate and continue
3.	Teriflunomide	Reduced *de novo* pyrimidine synthesis, antiproliferative	Moderate	Maintenance immunomodulatory	Safe to initiate and continue
Low infection risk, response to vaccine intact					
4.	Dimethyl fumarate	Pleiotropic, NRF2 activation, downregulation of NFk	Moderate	Maintenance immunomodulatory, potentially immunosuppressive when associated with lymphopenia	Safe to initiate and continue. However, caution should be exercised when managing patients with lymphopenia
5.	Natalizumab	Anti-VLA 4 selective adhesion molecule inhibitor	Very high	Maintenance immunosuppressive	Probably safe to initiate and continue. However, caution should be exercised in patients with active COVID-19 and recent infusion
Depending on the treatment phase: Low — to moderate infection risk, response to vaccine intact when lymphocyte count is > 500 /mm^3; Intermediate — to high infection risk, response to vaccine possibly blunted during depletion phase					
6.	Cladribine tablets	Immune depleting therapy	High/very high	IRT	Consider suspending
7.	Alemtuzumab	Immune depleting therapy	High/very high	IRT	Consider suspending
Low-to-moderate infection risk, response to vaccine blunted (humoral and cellular)					
8.	S1PR modulators (fingolimod, ozanimod, ponesimod, siponimod)	Selective S1P modulators prevent egress of lymphocytes from lymph nodes	High	Maintenance immunosuppressive	Probably safe to initiate and continue. Blunted response to COVID-19 vaccination
Intermediate/high infection risk, response to vaccine blunted (humoral)					
9.	Anti-CD20 (ocrelizumab, ofatumumab)	Anti-CD20, B-cell depleters	Very high	Maintenance immunosuppressive	Increased risk of severe COVID-19 for ocrelizumab and attenuated humoral response to COVID-19 vaccination in ocrelizumab-treated patients Consider planning vaccination according to treatment regimen — 4–6 months from last infusion and a minimum of 4–6 weeks before next infusion Data for ofatumumab is scarce

Modified from: https://practicalneurology.com/articles/2021-jan/ms-minute-the-covid-19-vaccine-vaccine-readiness-in-ms [Last accessed: 19.12.2022]

approach, especially during the pandemic [99, 100]. Most studies evaluating adverse events in pwMS after COVID-19 vaccination conclude that they are similar to those observed in the general population, mostly indicating pain at the injection site, fatigue, and flu-like symptoms [101–106]. A study of 1,661 pwMS vaccinated against COVID-19 showed that there was a slight increase in relapse rate at 90 days after the vaccination period, comparing the number of patients with at least one clinical relapse in this period to the number of patients with at least one clinical relapse in the previous 12 months [107]. Most relapses were mild, and the authors excluded relapses that occurred in patients with so-called 'unstable' disease, meaning patients with DMT change in each 90-day period; however, the study lacked an objective measure of disease activity such as MRI evidence. Studies with a shorter control time and smaller samples found no indication of an increased relapse rate in COVID-19-vaccinated patients [102, 107, 108]. Analysing a group of 2,346 German pwMS vaccinated against COVID-19, the authors found that the frequency of patient-reported relapses was 7.7% and that 14.8% of patients reported relapses within a year before the first vaccination. The authors also determined that: women compared to men, younger patients, those diagnosed with RRMS (as opposed to progressive forms), those not treated with DMTs, those with a lower disability level, and those who had their last relapse close to the date of their COVID-19 vaccination were all

prone to more often report relapses after vaccination [103]. Data on MS worsening after COVID-19 vaccination remains inconclusive, and more research is required.

How do different DMTs influence COVID-19 vaccination response?

Concern has been raised regarding DMTs immunomodulatory or immunosuppressive properties and vaccine efficacy. Previous studies evaluating the immune responses following infections in patients treated with DMTs found that although most DMTs did not seem to interfere with producing an effective response to infection, anti-CD20 therapies did decrease the odds of forming a humoral immune response [109–113]. These results now seem to be mirrored in the studies on the vaccine-induced immune response. Humoral response after COVID-19 vaccination has been extensively researched, and there exists strong evidence that anti-CD20 agents and S1PR-modulators impair humoral response to the COVID-19 vaccine in pwMS, causing lower seroconversion rates than in healthy controls and in other DMT-treated patients [114–121]. The level of seroconversion for anti-CD20- and S1PR-modulators-treated patients varies: 3.8% for ocrelizumab and 22.7% for fingolimod in a study by Achiron et al. [114], 52.6% for ocrelizumab and 63.6% for fingolimod in a study by Bsteh et al. [119], with one study [115] finding even 90.6%, 40.50%, and 61% seroconversion rates in fingolimod, ocrelizumab, and rituximab treated, respectively, in pwMS vaccinated with BNT162b2; and 100%, 61%, and 71% in those treated with fingolimod, ocrelizumab, and rituximab, respectively, and vaccinated with mRNA-1273.

While there is some uncertainty regarding other high-efficacy medications such as alemtuzumab and cladribine, with a few studies suggesting that patients treated with these therapies may produce lower titres of anti-S SARS-CoV-2 antibodies [118, 122], research articles, reviews and meta-analyses suggest that apart from anti-CD20 antibodies and S1PR-modulators the responses to COVID-19 vaccination do not differ from those in untreated pwMS.

This means that the majority of MS patients, including those treated with beta-interferons, glatiramer acetate, fumarates, teriflunomide, natalizumab, cladribine, and alemtuzumab, become seropositive after vaccination, similarly to healthy controls [123–131].

Some studies have evaluated factors associated with treatment protocols and antibody response, with Sormani et al. [115] finding a progressive trend between the time elapsed since the last infusion of rituximab and ocrelizumab and vaccination and antibody levels. Similar findings were reported by Pitzalis et al. [118], where the 6-month interval significantly increased antibody responses. Although Bsteh et al. [119] did not find an association between time from the last infusion and humoral response, their study concluded that B-cell depletion was a predictor of seronegativity. This has also been suggested in the study by Satyanarayan et al. [117], where a higher proportion of seroconverted patients were having circulating B cells (≥ 1 cell), although this kind of reconstitution was not always sufficient for the development of a humoral response. The same study also found shorter anti-CD20 therapy total time and prior COVID-19 increasing the odds of seroconversion. Similar results were obtained by Holryd et al. [116], who found a significant association between B-cell depletion and lower antibody titres and between time from the last anti-CD20 infusion and antibody titres. A study by Asplund Högelin et al. [132] found that B-cell levels are better predictors of seroconversion than time from the last infusion, and that seroconversion rates increase with decreasing rituximab concentration and higher B-cell counts.

Although humoral immunity is considered to be crucial to protection from breakthrough infections, cellular response contributes significantly to protection from severe COVID-19 [133, 134]. The T-cell response has also been studied in DMT-treated patients, with the latest research suggesting that cellular immunity after COVID-19 vaccination in pwMS on DMTs does not differ from that observed in healthy controls and untreated patients, apart from those treated S1PR-modulators, who seem to produce effective T-cell responses less often. Anti-CD20-treated patients have responses similar to, or even more robust than, untreated controls, which some authors suggest may be a compensation for weak antibody response [126–128, 135–139]. Because research on the effectiveness of maintained cellular response in anti-CD20-treated pwMS with negative seroconversion, as well as the influence of vaccination in fingolimod-treated patients on COVID-19, is still emerging, the data is as yet insufficient to draw meaningful conclusions. Even though there are now several types of COVID-19 vaccines available, most studies have evaluated the influence on immune responses and safety of mRNA vaccines in pwMS, and data regarding different types of vaccines is limited.

New SARS-CoV-2 variants and MS: early findings

The continuously changing properties of SARS-CoV-2 allow it to develop new variants, posing the triple threat of increased morbidity, mortality and vaccine inefficacy [140]. Thus, assessing the rate of breakthrough infections during new variant waves in vaccinated patients, as well as evaluating the safety and effectiveness of booster vaccines, is of great importance.

The reports on the third dose of the COVID-19 vaccine suggest that in pwMS the safety profile of the booster is similar to that of the first two doses [141–143]. Regarding the efficacy of the booster dose and anti-CD20 and S1PR-modulator treatment, currently there is no consensus, with some studies suggesting that the odds of developing humoral immunity after the booster in seronegative patients are low, although some patients seem to seroconvert after the booster [144–151]. In

seropositive patients on anti-CD20 and S1PR-modulators, the booster may upregulate antibody titres, providing better protection against COVID-19 [141, 143]. Preliminary findings from studies on breakthrough infections in patients on B-cell depleting therapies and fingolimod suggest that although there is an increase in risk for COVID-19, the infections are mostly mild to moderate, not requiring hospitalisation [146, 152]. The importance of vaccination for maintaining immunity against new variants was evaluated by Sormani et al. [153], showing that breakthrough infections in vaccinated patients during the Delta wave were mostly associated with low antibody titres after vaccination, and that the immunity that was waning over time was often insufficient during the Omicron wave, with a significant reduction of risk for Omicron infection in patients who received the booster dose.

Conclusions

Despite the rapid data accumulation and research development, and the fact that it has been three years since SARS-CoV-2's emergence, a good deal of uncertainty and controversy remains.

It seems that even if multiple sclerosis *per se* does not increase the risk of severe COVID-19, there are a lot of factors and patient characteristics, such as older age, male sex, progressive disease course, higher disability status, steroid and anti-CD20 treatment, that contribute to this risk and are worth acknowledging.

The implications of COVID-19 in pwMS are still unknown, with inconsistent evidence regarding relapses and disability worsening. COVID-19 vaccines seem safe in pwMS, but current research does not allow science to fully exclude the possibility of vaccination-induced disease exacerbation. Most pwMS develop immunity, although a proportion of patients treated with anti-CD20 and S1PR-modulators may have an impaired immune reaction to the vaccine and be at risk for breakthrough infection.

A personalised approach regarding risks and benefits in decision-making during the COVID-19 pandemic must remain important for clinicians taking care of multiple sclerosis patients.

Conflicts of interest: *None.*
Funding: *None.*

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