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COVID-19 vaccination in patients with Multiple Sclerosis: A Practical guide for Neurologists

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is more common in patients with multiple sclerosis because of receiving immunosuppressive or immunomodulating disease-modifying therapies (DMTs). On the other hand, some of these drugs may interact on COVID-19 vaccines. In this commentary, first we introduce some available COVID-19 vaccines and then discuss the effect of different DMTs on immune responses after vaccination. We have not found a connection between vaccination and MS relapses, so we suggest that the benefit from the vaccine outweighs any potential risks in these patients.

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Abbreviations

COVID-19, Coronavirus disease 2019; DMTs, Disease modifying treatments; MS, Multiple sclerosis; SARS-CoV-2, Severe acute respiratory syndrome coronavirus type-2; CNS, Central nervous system; WHO, World health organization; MRI, Magnetic resonance imaging; UK, United Kingdom; IFN, Interferon; GA, Glatiramer acetate; TFNM, Teriflunomide; DMF, Dimethyl fumarate; SP1RM, Sphingosine-1-phosphate receptor modulators; CDC, Centers for disease control and prevention.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), has quickly become a global pandemic (1).

The scientific community has been motivated to find impressive therapeutic options and vaccines to control the running COVID-19 pandemic. One of the most cost-effective procedures for immunizing people and preventing potentially severe and life-threatening infectious diseases is vaccination (2).

COVID-19 in patients with Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, and neurodegenerative disease of the central nervous system (CNS). The underlying cause of MS is uncertain, but it is a complex disorder; many genes increase disease susceptibility in addition to several environmental factors such as vitamin D, ultraviolet B light (UVB) exposure, Epstein-Bar virus (EBV) infection, obesity and smoking (3).

There is no cure for multiple sclerosis and available treatments can only improve patients' overall quality of life and minimize their long-term disability by preventing relapses and severe acute MS attacks. Recently many new disease-modifying drugs (DMDs) have become available that target the underlying immunologic etiology of the disease. Hence, most MS patients require immunosuppressive or immunomodulating disease-modifying therapies (DMTs) to alleviate their symptoms (4).

According to the confirmation of the Centers for Disease Control and Prevention, patients receiving immunotherapies and those with disabilities are possible high-risk groups for COVID-19 (5).

Receiving DMTs may expose patients to a higher risk for widespread viral and respiratory infections and infection-related threats. More significantly, some DMTs may interact on SARS-CoV-2 vaccines. Thus, realizing the effect of each DMT on the immune system, its related infection risks, and its potential impact on vaccination is mandatory for the management of MS patients safely during the COVID-19 pandemic (6).

Available vaccines

There are some COVID-19 vaccines available now.

Two vaccines by companies, Pfizer/BioNTech and Moderna, are approved and use the messenger RNA model. The other vaccine, produced by the AstraZeneca Company and the University of Oxford, is a viral vector-based vaccine (2). Also, a single dose adenoviral-based Johnson & Johnson/Janssen vaccine has been approved in the Netherlands (7). Some other COVID-19 vaccines, such as Sputnik V and Sinopharm and Sinotech, are used in some countries; however, only the Sinopharm vaccine has been approved by the world health organization (WHO) (8). Medicago Covifenz and Novavax Nuvaxovid are also approved in Canada (9).

All of these vaccines are expected to elicit an immune response to SARS-CoV-2; but they work by different mechanisms.

The mRNA vaccines generate the antigens using a laboratory-made genetic code of the virus to create an immune response, and thus they do not contain live particles (10).

Viral vector vaccines create immunity using a replication-deficient adenovirus. The AstraZeneca vaccine is based on a chimpanzee adenovirus, which does not lead to human disease (11), as the Johnson and Johnson vaccine is based on a human adenoviral vector. Since MS patients under immunosuppressive treatment are generally advised to avoid the live virus vaccines, it is important to inform them that this kind of vaccine is not live anyway.

The safety of vaccination in MS patients has been discussed for decades. There have been some reports of clinical onset and relapses of MS after vaccination (12, 13).

Immunization of MS patients

Although there is no robust evidence that vaccines increase the risk of relapse in MS, some specialists are still concerned that vaccination may worsen disease activity in MS patients with recent relapses. The vaccination is not usually urgent in patients with MS, and the risk of infectious diseases would not be significantly increased by a delay of a few weeks. Thus immunization of MS patients experiencing a recent relapse or significant MRI activity is better to be postponed for at least 4 weeks until the disease activity is no longer present (14).

The impact of individual DMTs on immune responses to available vaccines has been investigated in recent years and can help us to predict expected responses to the SARS-CoV-2 vaccine (15). In addition, some results of immune responses after CVOID-19 vaccinations have been published in recent months.

It is important to consider that the efficacy of routine vaccines has been shown to be lower in clinical high-risk groups. Influenza vaccination coverage for the UK population aged over 65 years is more than 70%; however, this rate in individuals aged less than 65 years in clinical high-risk groups remains suboptimal and is only 50.3% in people with neurological conditions (16). This might persuade us to be cautious about the level of protective immunity of the COVID-19 vaccine in patients with MS.

Effect of DMTs on immune responses after vaccination

In patients treated with beta-interferon, the immune responses have been preserved to multiple vaccine types. Thus, the response to COVID-19 vaccines is expected to be maintained at the normal rate in MS patients under interferon beta treatment. On the other hand, patients receiving subcutaneous IFN β-1a for treatment of relapsing MS have somewhat low rates of serious disease or severe consequences with COVID-19 (17).

In patients treated with Glatiramer acetate (GA), a reduced response to influenza vaccination compared with healthy control or interferon beta was shown. This may make the response to the COVID-19 vaccine doubtful, but it is not probably so concerning regarding the mechanism of action of GA in patients with MS (18). Recently it has been approved that glatiramer acetate does not impact vaccine efficacy (19).

Since Teriflunomide (TFNM) was associated with a modest negative effect on the response to influenza and rabies vaccines, it may interact with the COVID-19 vaccine. However, considering the low grade of lymphopenia in patients under TFNM treatment, this is probably not so remarkable in MS patients under treatment with this first-line DMT.

A single study did not show a negative effect of dimethyl Fumarate (DMF) on T-cell and humoral responses. However, patients who have higher grades of lymphopenia with DMF may have reduced response to the COVID-19 vaccine as expected (20).

Sphingosine-1-phosphate receptor modulators (SP1RM) receptor modulators (Fingolimod and Siponimod, Ozanimod and recently approved one Ponesimod) reduce the immune response to the influenza vaccine. So, the response to the COVID-19 vaccine is expected to be reduced (18, 21, 22).

SP1RM treatments avoid lymphocytes migrating the lymph nodes. These drugs offer an underwhelming vaccination response in relation to both humoral (41–51.4) and cellular responses (11.0%–14.0%) (23).

Humoral vaccine responses were remarkably impaired by B cell depleting anti-CD20 monoclonal antibody therapies. These therapies are probably one of the most widely used MS DMTs that may interfere markedly with reducing the immune response to vaccines. Interestingly, the pre-existing humoral immunity to vaccines is not affected in patients who are currently initiated on B cell therapies because the plasma cells are not affected. This makes the timing of vaccination of particular importance in MS patients who want to initiate or continue B cell therapies (15).

Sormani et al. observed a SARS-CoV-2 serological response after COVID-19 in only 44.6% of the patients on anti-CD20 therapies compared with 78.7% of the rest of patients. Similar seroconversion rates are seen after vaccination (40.0%–50.0%). In these patients, seroconversion is highly predicted by B-cell count and time passed since the last infusion.

Despite the lessening of seroconversion, it remains a robust T-cell response after both infection (66.7%) and vaccination (86.4%–92%). Therefore, in anti-CD20-treated patients, optimizing the moment of vaccine administration could potentially lead to an increased vaccine response (24).

Alemtuzumab reduces the response to vaccines, at least to the same degree and may even more than B cell therapies due to additive effects on T cell lineage. Similarly, the immune response to vaccines that have already been mounted due to previous vaccinations is preserved, making the timing of treatment as a determining feature in vaccine efficacy (18).

MS patients under treatment with Natalizumab were shown to have an adequate response to vaccination because the drug does not actually cause systemic immunosuppression. This has made Natalizumab as a superior monoclonal antibody in highly active or aggressive MS patients during the COVID-19 era, not only because of the lower risk of severe COVID but also because of the impact on vaccine efficacy.

There is not enough data on vaccine responses in patients with MS taking Cladribine and high-dose corticosteroids. Particularly, most of these studies have focused on humoral responses, with few considering cellular immune responses to vaccination (15, 18).

Although, in a study by Livnat Brill et al., healthy controls (n=30) and MS patients treated with Cladribine (n=32) had a 100% positive serology response against the SARS-CoV-2 spike protein following the second vaccine dose (25).

According to German COVID-19 vaccination guidelines for patients with MS, vaccination should be done 3 to 4 weeks before starting Cladribine and 3 to 4 weeks after the first drug cycle or 6 weeks after the second cycle. However, the vaccine immunogenicity may be lower at lesser intervals. It is assumed that the lymphopenic effects of Cladribine have no significant effect on vaccine immunogenicity (6).

The COVID-19 vaccine can be given at any time in MS patients who are stable on DMTs, but the timing of vaccination may be an important consideration in patients on B cell therapies and Alemtuzumab to have the most efficacy. Ideally, the vaccine should be initiated before starting immunoblotting DMTs (at least two weeks). However, in patients currently receiving B cell-depleting DMTs, the vaccine efficacy would probably be better if administered at the end of the fifth month after the last dose of Rituximab/Ocrelizumab or after when CD20 lymphocytes are going to be repopulated. If so, the dose of B cell therapy should be given at least 2 weeks after the last dose of the vaccine. Considering the possible extended interval dosing of B cell therapies for stable patients with MS, this strategy can provide both the MS and vaccine needs. This is the same strategy that is probably helpful with Alemtuzumab (6, 15).

There is still an agreement between experts about the vaccination of patients with B cell-depleting therapies. Despite the reduced response to the vaccine, these patients should still be able to grow an antibody response to it. The vaccine will still prime T cells and could theoretically enhance memory T cells in coronavirus exposures (15, 26).

The current vaccines all require two doses (except than Johnson and Johnson vaccine) and it takes time for your body to build up a strong immune response. For the Pfizer/BioNTech vaccine, you need to have a second dose 21 days after your first dose and then wait a further 7 days until you are protected (27). People are considered fully vaccinated for COVID-19 ≥2 weeks after they have received the second dose in a 2-dose series or ≥2 weeks after they have received a single-dose vaccine (Johnson and Johnson [J&J]/Janssen) (28).

We should advise the MS patients that certain DMTs may interfere with achieving a protective immune response to the vaccine and that serological verification of a response may be essential after vaccination.

In this sense, Uhr L and Mateen FJ evaluated vaccine willingness in 701 pwMS with an online survey. About 76.6% of those were COVID-19 vaccine willing, a higher rate than the general population (69%) (29). Furthermore, we assessed COVID-19 vaccine willingness and acceptability in 892 MS patients, from which 68% of the participants expressed willingness to be vaccinated (30).

No vaccine gives 100% protection from illness, so patients should still take care to avoid infection, particularly if they are clinically extremely vulnerable. Researchers are not yet sure whether people who have been vaccinated are still able to carry and transmit COVID-19, even if they are themselves protected. To protect others, all should adhere to the Centers for Disease Control and Prevention (CDC) and local health guidelines (28, 31).

Summary of recommendations could be viewed in the table 1.

Type of DMTs	Continuous dose in each month	Time after last treatment dose: Cyclic doses			
		0-4 months	4-6 months	6-12 months	>12 months
Dimethylfumarate	Full efficacy	-	-	-	-
IFN β	Full efficacy	-	-	-	-
Teriflunomide	Reduced but sufficient efficacy	-	-	-	-
Glatiramer acetate	Reduced but sufficient efficacy	-	-	-	-
Natalizumab	Reduced but sufficient efficacy	-	-	-	-
Fingolimod / Ozanimod / Siponimod / Ponesimod	reduced efficacy	-	-	-	-
Ocerlizumab / Rituximab / Ofatumomab	-	Reduced efficacy	Slightly reduced efficacy	-	-
Cladribine	-	Reduced efficacy but may be efficient	Reduced but sufficient efficacy	Full efficacy	Full efficacy
Alemtuzumab	-	Reduced efficacy	Slightly reduced efficacy	Full efficacy	Full efficacy
Mitoxantrone	Reduced efficacy	Reduced efficacy	Slightly reduced efficacy	Slightly reduced efficacy	Slightly reduced efficacy
AHST (Autologous hematopoietic stem cell)	Reduced efficacy	Reduced efficacy	Reduced efficacy	Slightly reduced efficacy	Slightly reduced efficacy

Table 1: Summary of recommendations on COVID-19 vaccination in MS patients treated with different disease- modifying therapies (DMTs) (22, 23, 25, 24)

The summary of guide in clinical practice

1. In searching the reported data, we have not yet found a connection between vaccination and MS relapses. Having a COVID-19 infection can trigger MS relapses, so clearly, the benefit from the vaccine outweighs any potential risks. Obviously, it is not advisable to take any vaccine during an active relapse, but vaccines are safe otherwise when given during remission (6).

2. It is assumed that there is not any concern for taking beta interferon (Rebif, Avonex, Plegridy, Betaferon or Extavia), Glatiramer acetate (Copaxone, glatopa and Brabio), Dimethyl fumarate (Tecfidera), Teriflunomide (Aubagio) or Natalizumab (Tysabri) during COVID-19 vaccination. No time consideration should be done in patients who are treated with these DMTs. Before starting these DMTs, a timly consideration of 2 weeks after vaccination might be acceptable (17-20).

3. For Ocrelizumab (Ocrevus), Fingolimod (Gilenya), Siponimod (Myzent), Ozanimod (Zeposia), Ponesimod (Ponvory), Alemtuzumab (Lemtrada) or Cladribine (Mavenclad) immune system may not make as strong a response to the vaccine. The MS Society Medical Advisors have recommended that those receiving Ocrevus or Gilenya should be aware of this but not alter their treatment plan. For those treated with Ocrevus or Rituximab, the recommendation is to wait 4 to 5 months after the last course or infusion. If the patient needs a second course of treatment, it is safe to delay it until after vaccination. However, because the risk of contracting severe COVID-19 is higher in these populations, we recommend not to postpone vaccination in whom time-consideration could not be possible. Again, before starting these DMTs, a time consideration of 2 weeks after vaccination might be acceptable (21, 22).

4. MS patients with active relapse may experience worsening relapse severity after vaccination, so immunization of these patients should be postponed until clinical resolution. It seems reasonable to postpone immunization for 4 weeks in the setting of an MS relapse. For patients treated with corticosteroid pulse therapy for acute relapse, we should postpone vaccination for 4 to 8 weeks (preferentially 8 weeks) (14).

5. MS patients should be informed that certain therapies may interfere with achieving a protective immune response to the vaccine and that serological verification of a response may be needed after vaccination. It depends on the platform type of vaccination and many other variables such as the type of DMTs or even comorbidities and type and sensitivity of serological diagnostic kits (29).

6. No vaccine gives 100% protection from illness, so patients should still take care to avoid infection, particularly if they are clinically extremely vulnerable. Researchers are not yet sure whether people who have been vaccinated are still able to carry and transmit COVID-19. Whether they are considered to be fully vaccinated to protect others, all should adhere to CDC recommendations and the local guidelines of their area (32).

7. Although the efficacy of different COVID vaccines in neurological diseases has not been compared so far, we recommend mRNA model vaccines to patients with MS due to their higher immunogenicity (7).

8. In terms of COVID-19 vaccination in pregnant women, the World Health Organization (WHO) recently stated a message that the vaccine would be given only to those who have a higher risk of contracting the virus; and there is no exception to this role for pregnant MS patients (33). In addition, we should know that there is no report of increasing the risk of infection or the severity of COVID-19 in pregnant MS patients, so our suggestion in this group is to postpone vaccination after delivery. There is no data regarding COVID-19 vaccination during lactation. Besides, we should follow pamphlets or monographs of different vaccines according to the future global or local guidelines (34).

9. Given that there are no data about the results of COVID vaccination in patients under 18 years, we do not have any recommendations for pediatric MS patients at this moment. However, the clinical trials of mRNA-based vaccines in this age group (12-16 years) are ongoing (35).

10. Since disability in MS could be a risk factor for the severity of COVID-19 infection, we advise considdering the priority of vaccination for more disabled MS patients (36).

11. Regarding the reports of some adverse events in virus vector-based vaccines such as AstraZeneca and Johnson & Johnson/Janssen COVID-19 vaccination, including pathologic antibodies to platelet factor 4, which leads to thrombocytopenia and hemorrhagic phenotype, blood clots and also capillary leak syndrome (37, 38), we suggest until obtaining a more accurate data in a patient population who are prone to these events or in patients with autoimmune conditions like MS, consider a priority to any other COVID-19 vaccine platforms in these population. Furthermore, transverse myelitis, acute disseminated encephalomyelitis (ADEM), or MS relapses are being described after all types of SARS-CoV-2 vaccines (23).

12. The efficacy of vaccines should be tested after full vaccination of MS patients; i.e., the assessment of antibodies against COVID-19 coronavirus should be detected by different methods according to the platform of vaccines (21).

13. Since the production of antibodies against the coronavirus may be failed even after the full vaccination of MS patients, the possibility of a third or even fourth vaccine doses as the boosters should be considered in some MS patients those who treated with DMDs such as anti CD20 or Fingolimod (6).

14. Higher hospitalization rate has been reported in Rituximab-treated patients compared with the combination of all other DMTs (29.9% vs. 12.7%) (23).

15. Overall, most pwMS present an immunological response after SARS-CoV-2 infection (humoral response: 76.8%–83.4%; cellular response: 59.5%) or vaccination (humoral response: 74.4%–86.8%; cellular response: 62%–84.4%) regardless of their treatment. However, it is clear by now that anti-CD20 therapies and sphingosine-1 phosphate receptor modulator (SP1RM) therapies decrease these responses (23).

16. Although patients with MS do not seem to be at an increased risk of SARS-CoV-2 infection, factors such as older age, black race, comorbidities, higher disability or, a progressive form seem to increase the risk of severe COVID-19 in patients with MS (23). Patients with MS in these high-risk groups are especially encouraged to get vaccinated as soon as possible (39).

17. All COVID-19 vaccines are effective and do not appear to carry any additional risk for patients with MS.

18. Routine and frequent checking of COVID-19 antibodies or cellular immune responses after vaccination are not recommended. However, they could be used for the evaluation of immune status in some cases.

19. There is no evidence that patients with MS are at higher risk of complications from the mRNA, non-replicating viral vector, inactivated virus or, protein COVID-19 vaccines compared to the general population (39).

20. People who are in a condition or taking medications that weaken their immune system may not be protected even if they are fully vaccinated. Continuing to take all precautions recommended for unvaccinated people, including wearing a well-fitted mask, social distancing and washing hands, is mandatory for them until advised otherwise by their healthcare provider. Some people with moderately or severely compromised immune systems should receive an additional primary dose of the COVID-19 vaccine (39).

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Authors' contributions
SMN designing the study data; MM, EM, MG and MD data collection; MM preparing the first draft of the manuscript; SK editing and updating the manuscript; SMN and MV final revision and approval.

Ethics approval
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