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MENACTRIMS practice guideline for COVID-19 vaccination in patients with multiple sclerosis

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SUMMARY

Patients with multiple sclerosis (MS) should be vaccinated against COVID-19.

All COVID-19 vaccines are effective and do not appear to carry any additional risk for patients with MS. Patients with MS should get a COVID-19 vaccine as soon as it becomes available. The risks of COVID-19 disease outweigh any potential risks from the vaccine.

Even if vaccinated, patients with MS should continue to practice standard and recommended precautions against COVID-19, such as wearing a face mask, social distancing and washing hands.

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.

COVID-19 Vaccines are safe to use in patients with MS treated with disease-modifying therapies (DMTs).

The effectiveness of vaccination may be affected by few of the DMTs but yet some protection is still provided.

For certain DMTs we may consider coordinating the timing of the vaccine with the timing of the DMT dose to increase vaccine efficacy.

1. Introduction

Multiple sclerosis (MS) is an autoimmune, demyelinating, neurodegenerative disease of the central nervous system (CNS) that might cause significant and irreversible disability (Compston and Coles, 2008). Patients with MS are at increased risk for acquiring infections and disease-modifying therapies (DMTs), which suppress or modulate the immune system, have been associated with increased risk of infections (Castelo-Branco et al., 2020; Persson et al., 2020; Epstein et al., 2018). For this reason, vaccination as the most efficient measure to prevent infections is imperative in this population. This is particularly pertinent in the era of emerging novel vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), causative agent of the COVID-19 disease pandemic.

Several COVID-19 vaccines with various mechanisms of action and diverse immunogenic properties are currently available worldwide, authorized to varying degrees by the Food and Drug Administration (FDA), European Medicine Agency (EMA) and World Health Organization (WHO) under emergency use authorizations (EUAs), with many others in development (World Health Organization, 2021). As the COVID-19 vaccine repertoire is becoming complex, questions regarding potential interactions between the novel vaccines against COVID-19 and different DMTs are arising among MS patients and clinicians.

Immunological studies have shown that the coordinated interactions between T and B lymphocytes of the adaptive immune system are essential to the successful generation of immunological memory and production of neutralizing antibodies following recognition of vaccine antigens by innate immune cells (Siegrist, 2013; Luckheeram et al.,

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2012; Bonilla and Oettgen, 2010; Tay et al., 2021; Lubbers et al., 2017; Siegrist and Lambert, 2016; Whitmire et al., 2009). CD4⁺T cells facilitate CD8⁺T cell and B cell activation, while B cells drive and sustain T cell memory. Previous studies of conventional vaccines in MS patients have highlighted how each DMT or class of DMTs might impact the efficacy of a COVID-19 vaccine (Lebrun and Vukusic, 2019; Riva et al., 2021; Coyle et al., 2021; Ciotti et al., 2020). DMTs such as interferons, glatiramer acetate, dimethyl fumarate, teriflunomide, and natalizumab may not impair the immune response to vaccination, whereas, DMTs that rely on sequestration or depletion of T cells, B cells or both such as shingosine-1-phosphate (S1P) receptor modulators, cladribine, alemtuzumab and anti-CD20 therapies may reduce vaccine efficacy.

Although robust data to support evidence-based recommendations on COVID-19 vaccinations is not yet available, this practice guideline aim is to offer guidance on vaccinating MS patients during the COVID-19 pandemic based on previous vaccine studies, mechanism of action of each DMT, currently available COVID-19 vaccine studies, and expert opinion.

2. Methodology

A group of regional experts selected by MENACTRIMS (Middle East North Africa Committee for Treatment and Research in Multiple Sclerosis) held two consecutive meetings and several subsequent discussions to review all available evidence regarding COVID-19 vaccines in MS patients. The aim was to develop practical recommendations that would support clinical practice in the region. After reviewing all of the evidence, preliminary recommendations were developed by a subcommittee. Using the Delphi methodology through online meetings, the final version of this guideline was developed.

3. Types of vaccines

There are several COVID-19 vaccines currently in use in different countries under EUAs, with many more currently under trial. There are currently four different types of COVID-19 vaccine in use or in development that work in different ways (Table 1).

4. MS and COVID-19 vaccination

- Patients with MS should be vaccinated against COVID-19.
- Available studies show that COVID-19 vaccines are safe, effective and unlikely to trigger an MS relapse. Vaccines can cause fever which

Table 1
Types of COVID-19 vaccines.

Vaccine Type	MOA/effect	Examples
mRNA vaccines (Jackson et al., 2020; Polack et al., 2020)	◦ Have the genetic code for the coronavirus 'spike' protein made as an "mRNA" and delivered in lipid nanoparticles	Pfizer-BioNTech (Comirnaty) Moderna (Spikevax)
Non-replicating viral vector vaccines (Sadoff et al., 2021; Folegatti et al., 2020; Logunov et al., 2021)	◦ Have the spike protein genes in a nonreplicating viral vector (commonly from an adenovirus).	AstraZeneca/Oxford (Vaxzevria) Gamaleya Research Institute (Sputnik V) Johnson and Johnson (Janssen COVID-19 vaccine)
Inactivated virus vaccines (Wang et al., 2020)	◦ Use an inactivated form of the whole coronavirus.	Sinovac (CoronaVac) Sinopharm (Sinopharm CNBG)
Protein vaccines (Keech et al., 2020)	Contains the full-length spike glycoprotein of the virus plus an adjuvant delivered on the surface of synthetic lipid nanoparticles.	Novavax (NVX-CoV2373)

in turn may exacerbate MS symptoms. Patients with MS should get a COVID-19 vaccine as soon as it becomes available. The risks of COVID-19 disease outweigh any potential risks from the vaccine.

There is no theoretical reason or evidence from clinical trials to indicate that any of the currently available vaccines can pose any particular risk to patients with MS (Louapre et al., 2020; Sormani et al., 2021; Salter et al., 2021).

- Progressive MS, older age, higher level of disability and comorbidities (e.g., diabetes, high blood pressure, obesity, heart and lung disease, pregnancy), increase the risk for hospitalization due to COVID-19²⁴⁻²⁶. Patients with MS in these high-risk groups are especially encouraged to get vaccinated as soon as vaccines becomes available.
- Most of the COVID-19 vaccines require two doses. Following full vaccination (both doses), it may take at least 2 weeks for the vaccination to achieve full effect.
- If a patient had COVID-19 and recovered, he/she should also get the vaccine, because prior infection does not appear to protect from future COVID-19 infection indefinitely. However, recent studies (Callegaro et al., 2021; Malek et al., 2021; Amit et al., 2021; Pawlowski et al., 2021) have shown that a single dose of the mRNA vaccines might provide adequate immunity in previously infected patients.
- Even if vaccinated, patients with MS should continue to take precautions against COVID-19, such as wearing a face mask, social distancing and washing hands.
- We do not know how long a person is protected from COVID-19 after being vaccinated, although clinical trial data (Hansen et al., 2021) indicate that protection is high for at least 6–7 months. Repeated doses of the COVID-19 vaccines may be required in the future, similar to the flu vaccine, especially in case of emergence of new variants.
- Patients with MS should avoid receiving live attenuated vaccines.

5. COVID-19 vaccines use in patients with MS treated with DMTs

- COVID-19 Vaccines are safe to use in patients with MS treated with DMTs.
- The Astra-Zeneca and Johnson & Johnson (J&J) COVID-19 vaccines have recently been associated with thrombotic events, mostly venous sinus thrombosis, and mainly in young females. The J & J vaccine has also been recently associated with Guillain-Barre Syndrome. Such events, however, are rare and benefits of the vaccine still outweigh its risks. It does not appear that there is any additional risk for patients with MS.
- Some DMTs (Ciotti et al., 2020; Baker et al., 2020) may make the vaccine less effective but it might still provide some protection.
- It is important to note that most studies evaluating the effect of DMTs on vaccine efficacy, have measured serum antibodies. However T-cell mediated immunity might still be able to provide protection against infection with COVID-19 even if antibody response to the vaccine is reduced.
- For certain DMTs we may consider coordinating the timing of the vaccine with the timing of the DMT dose to increase vaccine efficacy (Table 2).
- The decision of when to give the COVID-19 vaccine and whether to delay the DMT dose should include a risk/benefit evaluation balancing the risk of COVID-19, (see the risk factors for severe COVID-19 infection above) including the current state of the pandemic in the area, vs the current state of the patient's MS. Another factor to be taken into consideration in certain countries is the availability of vaccines for a limited period of time depending on the patient risk category.
- If the risk of MS worsening outweighs the risk of COVID-19, then DMT schedule should not be altered and the vaccine should be given when it is available to the patient. On the other hand, if the patient's

Table 2
Timing of COVID-19 vaccine in patients treated with DMTs.

Disease-Modifying Therapy (DMT)	Wait Prior To Initiating Treatment	Wait After Last Dose Given
Interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate, natalizumab	Do not delay	Do not delay
Fingolimod, siponimod, ozanimod	2–4 weeks	Do not delay
Alemtuzumab	4 weeks	6 months
Cladribine	2–4 weeks	Do not delay
Ocrelizumab, rituximab	2–4 weeks	Limited data available (until B cell recovery ≈7–9 months)
Ofatumumab	2–4 weeks	Do not delay

MS is stable, and vaccine availability is flexible, consider the following adjustments in DMT administration to enhance the effectiveness of the vaccine:

i Interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate, natalizumab

For patients about to start one of these DMTs, there is no need to delay treatment for vaccination. For patients already taking one of these DMTs, no adjustments to DMT administration are needed (Ciotti et al., 2020).

ii Fingolimod, siponimod, ozanimod

For patients about to start fingolimod, siponimod or ozanimod, it is recommended to obtain full vaccination 2–4 weeks before starting treatment (Kappos et al., 2015). For patients already taking fingolimod, siponimod or ozanimod, treatment should continue as prescribed and patients can get vaccinated as soon as the vaccine is available. However, recent data has shown that patients on fingolimod have a significantly decreased humoral response to COVID-19 vaccines (Achiron et al., 2021).

iii Alemtuzumab

For patients about to start alemtuzumab, it is recommended to obtain full vaccination

4 weeks before starting treatment. For patients already taking alemtuzumab, consider starting the vaccine injections at least 6 months after the last alemtuzumab dose (McCarthy et al., 2013). When possible, resume alemtuzumab at least 4 weeks after full vaccination. It is acceptable to delay the second cycle of alemtuzumab for up to 2 months to obtain full vaccination.

iv Cladribine

For patients about to start cladribine, it is recommended to obtain full vaccination 2–4 weeks before starting treatment. Recent data showed that the efficacy of COVID-19 vaccines in patients on cladribine was similar to healthy controls when vaccination was initiated 4.4 months after the last dose of cladribine, even in patients with Grade III lymphopenia (Achiron et al., 2021). Other studies have also shown that patients on cladribine with Grade I or II lymphopenia mount adequate antibody response to influenza vaccines (Roy and Boschert, 2021; Wu et al., 2021). However, the number of patients in those studies was small. For patients already taking cladribine, consider giving the vaccine whenever available since timing does not seem to affect vaccine efficacy. For patients due for their second course, administer cladribine 2–4 weeks after full vaccination. It is acceptable to delay the second cycle of cladribine for up to 2 months to obtain full vaccination.

v Ocrelizumab, rituximab

For patients about to start ocrelizumab or rituximab, it is recommended to obtain full vaccination 2–4 weeks before starting treatment. Recent data showed a significantly decreased response to COVID-19 and other types of vaccines in patients on

ocrelizumab (Achiron et al., 2021; Bar-Or et al., 2020). In patients on rituximab, the ability to respond to the influenza vaccine was significantly decreased but appeared to be related to the degree of B cell recovery at the time of vaccination, which starts by 7–9 months following the last dose (Eisenberg et al., 2013). For patients already taking ocrelizumab or rituximab consider delaying the next dose, allowing for early B cell recovery by monitoring the CD-19 count, if the patient's disease status and vaccine availability permit. When possible, resume ocrelizumab or rituximab at least 3–4 weeks after the last vaccine injection. This suggested scheduling is not always possible and a case by case approach is advisable.

6. Conclusion

COVID-19 vaccination is recommended for all MS patients, and currently available vaccines are safe and effective. Attenuated but potentially partially protective vaccine response is expected in MS patients taking S1P modulators and B cell-depleting therapies. Other DMTs are not expected to significantly impact efficacy of COVID-19 vaccines. Coordinating vaccine timing with dosing regimens for some therapies may optimize vaccine efficacy.

CRediT authorship contribution statement

Bassem I Yamout: Conceptualization, Writing – original draft, Writing – review & editing. **Magd Zakaria:** . **Jihad Inshasi:** . **Mohammad Al-Jumah:** . **Maya Zeineddine:** Conceptualization, Writing – original draft, Writing – review & editing. **Maurice Dahdaleh:** . **Saeed Bohlega:** . **Riadh Gouider:** . **Raed Alroughani:** .

Declaration of Competing Interest

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Authors' Contributions

All authors participated as members of the panel of experts in the meetings that led to the development of the manuscript. All authors actively contributed to the discussion and the consensus reached. Bassem Yamout and Maya Zeineddine drafted the initial version of the manuscript and all authors discussed and reviewed the final version of the manuscript. All authors read and approved the final manuscript.

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