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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.,...
Table 1

| 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) |
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: Writing – review & editing.
Mohammad Al-Jumah: Maya Zeineddine: Conceptualization, Writing – original draft, Writing – review & editing.
Maurice Dahdaleh: Saeed Bohlega: Riadh Gouider: Raed Alroughani: Writing – review & editing.

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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References

Compton, A., Coles, A., 2008. Multiple sclerosis. Lancet 372 (9648), 1502–1517.
Castelo-Branco, A., Chiesa, F., Conte, S., Bengtsson, C., Lee, S., Minton, N., et al., 2020. Infections in patients with multiple sclerosis: a national cohort study in Sweden. Mult. Scler. Relat. Disord. 45, 102420.
Persson, R., Lee, S., Uliczka Yood, M., Wagner Usn, M.C., Minton, N., Niemczyk, S., et al., 2020. Infections in patients diagnosed with multiple sclerosis: a multi-database study. Mult. Scler. Relat. Disord. 41, 101982.

Epstein, D.J., Dunn, J., Deresinski, S., 2018. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect. Dis. 5 (6), sfy174.

World Health Organization, 2021. Draft Landscape and Tracker of COVID-19 Candidate Vaccines. WHO. https://www.who.int/publications/m/item/draftlandscape-of-covid-19-candidate-vaccines. Accessed Jun 5, 2021.

Siegrist, C.A., Plotkin, S.A., Orenstein, W.A., Offit, P.A., 2013. Vaccine immunology. editors Vaccines, 6th ed. Saunders, Philadelphia, pp. 14–32.

Luckeheen, R.V., Zhou, R., Verma, A.D., Xia, B., 2012. CD4+T cell: differentiation and functions. Clin. Dev. Immunol. 2012, 925135.

Bonilla, F.A., Oettgen, H.C., 2010. Adaptive immunity. J. Allergy Clin. Immunol. 125 (2), 523–540. Suppl 2.

Tay, R.E., Richardson, E.K., Toh, H.C., 2021. Revisiting the role of CD4 T cells in cancer immunotherapy—new insights into old paradigms. Cancer Gene Ther. 28 (1–2), 5–17.

Lubbers, R., van Essen, M.F., van Kooten, C., Trouw, L.A., 2017. Production of complement components by cells of the immune system. Clin. Exp. Immunol. 188 (2), 183–194.

Siegrist, C.A., Lambert, P.H., Bloom, R.R., Lambert, P.H., 2016. Chapter 2

Ciotti, J., Valtcheva, M., Cross, A., 2020. Effects of MS disease-modifying therapies on complement components by cells of the immune system. Clin. Exp. Immunol. 188 (2), 183–194.

Whitmire, J.K., Axano, M.S., Kaech, S.M., Sarkar, S., Hannum, L., Luning Prak, E.T., et al., 2013. Analysis of influenza and varicella zoster virus vaccine antibody responses in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther. Adv. Immunol. 1204–1319.

Baker, D., Roberts, C., Pryce, G., Kang, A., Marta, M., Reyes, S., et al., 2020. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Ther. Adv. Neurol. Disord. 14, 1–8.

McCarty, C.L., Tuohy, D., Compston, D.A.S., Kumararatne, D.S., Coles, A.J., Jones, J.L., 2018. Immune competence after alemtuzumab treatment of multiple sclerosis. Neurology 81 (10), 872–876.

Simental, M., Barry, A., Doherty, M., Falloon, I., et al., 2020. Analysis of influenza and varicella zoster virus vaccine antibody titers in patients with relapsing multiple sclerosis treated with cladribine tablets. Poster presented at ACTRIMS, 25 February 2021, Virtual Congress.

Eisenberg, R., Jawad, A., Boyer, J., Maurer, K., McDonald, K., Luning Prak, E.T., et al., 2013. Vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin. Exp. Immunol. 202 (2), 149–161.

Lubbers, R., van Essen, M.F., van Kooten, C., Trouw, L.A., 2017. Production of complement components by cells of the immune system. Clin. Exp. Immunol. 188 (2), 183–194.

Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., et al., 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N. Engl. J. Med. 383 (20), 1920–1931.

Dzharullaeva, A.S., et al., 2021. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report. N. Engl. J. Med. 383 (19), 1824–1835.

Logunov, D.Y., Dolzhikova, I.V., Shchelbyakov, D.V., Tukhvatullin, A.I., Zubiakov, O.V., Zharkovaeva, A.S., et al., 2021. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 397, 671–681.

Logunov, D.Y., Dolzhikova, I.V., Shchelbyakov, D.V., Tukhvatullin, A.I., Zubiakov, O.V., Zharkovaeva, A.S., et al., 2021. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 397, 671–681.