COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society

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ABSTRACT

A working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society has developed a statement with regard to the currently available mRNA vaccines (Pfizer-BioNTech and Moderna) preventing novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) infection, which causes Coronavirus disease 2019 (COVID-19), in patients with multiple sclerosis (MS).

This statement has been based on the literature available as of 15 January, 2021. The guidance will be updated as new data emerges. All data regarding the above-mentioned vaccines comes from clinical trials which have been reviewed, published and approved by the regulatory authorities [1, 2]. In the current manuscript, whenever a SARS-CoV-2 vaccine is discussed, it refers to mRNA vaccines only.

Key words: multiple sclerosis, COVID-19, vaccines, SARS-CoV-2, guidelines

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Vaccines against SARS-CoV-2 have not been used in MS patients, but are expected to be safe

Vaccines against SARS-CoV-2 have not been used in patients with autoimmune diseases, including MS. Therefore, clinical reasoning in this context should be based on the experience from other vaccines' use in MS and from the knowledge of immunology, vaccinology and virology [3–5]. Currently in Poland there are two COVID-19 vaccines available: Pfizer-BioNTech and Moderna. Both of these are messenger RNA (mRNA) vaccines [1, 2]. As such, they are not able to induce COVID-19 infection, but instead induce mRNA-based synthesis of a viral protein (and not an active SARS-CoV-2), which results in an immune response that determines the patient's future immunity against SARS-CoV-2. The vaccine is administered in a two-dose regimen, given 21 days apart for Pfizer-BioNTech and 28 days apart for Moderna [1, 2]. So far, mRNA vaccines have been approved and used in oncology and for Ebola and Zika immunisation. It may be anticipated that the rules and safety of COVID-19 vaccines should be similar to those for seasonal influenza inactivated vaccines [6]. In the case of mRNA-based vaccines, there is no associated risk of developing an active infection. However, some of the disease modifying therapies (DMTs) used for MS could hamper the immune response necessary for developing immunity against

SARS-CoV-2 [7–10]. As with any other vaccine, in MS patients each decision needs to be taken individually after a thorough consideration of the potential risks and benefits [11–16].

The following rules are suggested for MS patients with regard to vaccines preventing SARS-CoV-2 infection:

All MS patients should adhere strictly to the World Health Organisation (WHO) guidelines for reducing the risk of SARS-CoV-2 infection [17]. They should follow the vaccination rules that apply in their country of residence and that are described in the summary of the product characteristics [18–19].

Multiple Sclerosis patients who are not using DMTs should be offered a prompt vaccination against SARS-CoV-2 infection, especially if they are soon to be started on fingolimod, alemtuzumab, ocrelizumab and oral cladribine therapy.

Vaccinations preventing SARS-CoV-2 infection in MS patients treated with DMTs

Multiple Sclerosis patients treated with beta-interferons, glatiramer acetate, teriflunomide, dimethyl fumarate or natalizumab

Based on the available data, no safety or efficacy issues are likely to emerge in these patients. A SARS-CoV-2 vaccine could be administered at any point during the above-mentioned DMTs regimen. In the case of dimethyl fumarate, given the relatively high frequency of lymphopenia associated with therapy [20], the absolute lymphocytes count (ALC) should be checked before the vaccination. If lymphopenia is found, there is a risk of inadequate response to the vaccine, which may prevent the development of immunity against SARS-CoV-2.

Multiple Sclerosis patients treated with fingolimod, ocrelizumab, alemtuzumab or oral cladribine

Patients treated with the above-mentioned DMTs should be informed that there is a risk of inadequate response to the vaccine, which results from their modes of action [21]. Choosing the most appropriate moment for vaccination in the therapy regimen may optimise its efficacy. Moreover, in this group of patients it is advised that their families, caregivers and all close contacts are vaccinated to decrease the risk of spreading infection to patients.

Fingolimod-treated MS patients

At present there is insufficient data to advise fingolimod-treated patients to stop treatment in order to optimise vaccination efficacy. There is a risk of rebound associated with fingolimod withdrawal [22]. Also, if fingolimod is to be interrupted for more than two weeks, the same hospital-based monitoring as for treatment initiation is recommended [23].

Therefore, patients can be vaccinated at any point during fingolimod therapy. However, in patients with extremely low ALCs the potential benefit of the vaccine should be individually assessed, as it may not result in immunity against SARS-CoV-2. It seems that the same rules should be applied to patients treated with other sphingosine-1-phosphate receptor modulators including ozanimod and siponimod.

Ocrelizumab-treated MS patients

In patients yet to be started on ocrelizumab therapy, vaccination should be planned so that the two-dose regimen is completed at least 4–6 weeks before treatment initiation.

If vaccination was not possible prior to treatment initiation, vaccine administration can still be considered if it is carefully planned.

From the immunological standpoint, the optimal time for vaccination in ocrelizumab-treated patients seems to be 4-6 months after the last ocrelizumab infusion, so that the two-dose regimen is completed at least 4–6 weeks before the next infusion [24, 25]. On an individual basis, when the potential benefits of the vaccination clearly outweigh the risk of an MS relapse, one should consider delaying the next ocrelizumab infusion, so that the vaccine is administered 5–6 months after the last ocrelizumab dose and completed 4–6 weeks before the next one. Immunophenotyping of B lymphocytes (including CD19/CD20 ratio assessment) and measuring the levels of immunoglobulins G (IgG), IgM and IgA could aid in the decision-making process.

These parameters are used to establish whether the patient's B-cells repertoire has repopulated since the last ocrelizumab infusion. However, it must be borne in mind that in patients who are being treated with ocrelizumab, vaccination may not result in immunity against SARS-CoV-2 [26].

In MS patients who for any reason have stopped ocrelizumab therapy, the vaccine should be administered at least six months after the last ocrelizumab infusion, or after laboratory confirmation that the B cells have repopulated.

Multiple Sclerosis patients treated with immune-reconstitution therapies (alemtuzumab, oral cladribine)

In these patients, vaccination could be considered at least six months following the last course of treatment [27]. One must bear in mind that vaccine efficacy could be reduced if the last course of therapy was administered 12-24 months prior to vaccination. In the case of MS patients who are set to receive the second yearly cycle of therapy with alemtuzumab or cladribine, it seems safe to postpone the treatment until the two-dose SARS-CoV-2 vaccine regimen has been completed and the appropriate time for developing immunity has passed (typically 4–6 weeks). The last dose of the vaccine should be administered at least six weeks before the therapy is given.

Vaccinations in patients treated with non-DMT immunosuppressive therapies (mitoxantrone, cyclophosphamide, azathioprine, methotrexate)

The vaccine is likely to be safe. However, post-vaccination immunity against SARS-CoV-2 may not develop.

Patients treated with high-dose corticosteroids (> 40 mg of prednisone or the equivalent for at least seven days, or > 20 mg prednisone, or the equivalent for at least 14 days including 3–5 days of intravenous methylprednisolone in a daily dose of 500 mg up to 1 g) for an MS relapse

In these patients, vaccination could be considered 4–6 weeks after corticosteroid treatment cessation, which should provide optimal conditions for the development of immunity against SARS-CoV-2. A shorter interval could result in vaccine inefficacy.

Patients with secondary or primary progressive MS (SPMS and PPMS)

These subjects are often in a high-risk group for developing severe COVID-19, given their more advanced age and greater disability than relapsing-remitting patients. Moreover, most SPMS and PPMS patients do not receive DMTs (unless their disease is in an early and active phase), that could decrease vaccination efficacy. Therefore, in this patient group, it seems clear that the benefits outweigh any potential risk associated with vaccine administration.

In summary, for each MS patient the decision associated with the SARS-CoV-2 mRNA vaccine should be made individually, based on the risk of infection, the type of DMT the patient is on, their current immune status, their general health, and the coexistence of any other diseases.

References

1. Polack FP, Thomas SJ, Kitchin N, et al. C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020; 383(27): 2603–2615, doi: 10.1056/NEJMoa2034577, indexed in Pubmed: 33301246.

2. Baden LR, El Sahly HM, Essink B, et al. COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020 [Epub ahead of print], doi: 10.1056/NEJMoa2035389, indexed in Pubmed: 33378609.

3. Farez MF, Correale J, Armstrong MJ, et al. Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2019; 93(13): 584–594, doi: 10.1212/WNL.0000000000008157, indexed in Pubmed: 31462584.

4. Lebrun C, Vukusic S. French Group for Recommendations in Multiple Sclerosis (France4MS) and the Société Francophone de la Sclérose En Plaques (SFSEP). Immunization and multiple sclerosis: Recommendations from the French multiple sclerosis society. Mult Scler Relat Disord. 2019; 31: 173–188, doi: 10.1016/j.msard.2019.04.004, indexed in Pubmed: 31159998.

5. Loebermann M, Winkelmann A, Hartung HP, et al. Vaccination against infection in patients with multiple sclerosis. Nat Rev Neurol. 2012; 8(3): 143–151, doi: 10.1038/nrneurol.2012.8, indexed in Pubmed: 22270022.

6. Riva A, Barcella V, Benatti SV, et al. Vaccinations in patients with multiple sclerosis: A Delphi consensus statement. Mult Scler. 2020 [Epub ahead of print]: 1352458520952310, doi: 10.1177/1352458520952310, indexed in Pubmed: 32940128.

7. Ciotti JR, Valtcheva MV, Cross AH. Effects of MS disease-modifying therapies on responses to vaccinations: A review. Mult Scler Relat Disord. 2020; 45: 102439, doi: 10.1016/j.msard.2020.102439, indexed in Pubmed: 32769063.

8. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study. Neurology. 2020; 95(14): e1999–e2008, doi: 10.1212/WNL.0000000000010380, indexed in Pubmed: 32727835.

9. Pellegrino P, Carnovale C, Perrone V, et al. Efficacy of vaccination against influenza in patients with multiple sclerosis: The role of concomitant therapies. Vaccine. 2014; 32(37): 4730–4735, doi: 10.1016/j.vaccine.2014.06.068, indexed in Pubmed: 25000592.

10. Wiedermann U, Sitte H, Burgmann H, et al. Impfungen bei Immundefekten/Immunsuppression – Expertenstatement und Empfehlungen. Wiener klinische Wochenschrift. 2016; 128(S4): 337–376, doi: 10.1007/s00508-016-1033-6.

11. Zrzavy T, Kollaritsch H, Rommer PS, et al. Vaccination in Multiple Sclerosis: Friend or Foe? Front Immunol. 2019; 10: 1883, doi: 10.3389/fimmu.2019.01883, indexed in Pubmed: 31440255.

12. Reyes S, Ramsay M, Ladhani S, et al. Protecting people with multiple sclerosis through vaccination. Pract Neurol. 2020; 20(6): 435–445, doi: 10.1136/practneurol-2020-002527, indexed in Pubmed: 32632038.

13. Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. J Neurol. 2011; 258(7): 1197–1206, doi: 10.1007/s00415-011-5984-2, indexed in Pubmed: 21431896.

14. Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. J Neurol. 2017; 264(6): 1035–1050, doi: 10.1007/s00415-016-8263-4, indexed in Pubmed: 27604618.

15. Moiola L, Barcella V, Benatti S, et al. The risk of infection in patients with multiple sclerosis treated with disease-modifying therapies: A Delphi consensus statement. Mult Scler. 2020 [Epub ahead of print]: 1352458520952311, doi: 10.1177/1352458520952311, indexed in Pubmed: 32940121.

16. Waldman RA, Creed M, Sharp K, et al. Letter in Reply: Toward a COVID-19 Vaccine Strategy for Pemphigus Patients on Rituximab. J Am Acad Dermatol. 2020 [Epub ahead of print], doi: 10.1016/j.jaad.2020.10.075, indexed in Pubmed: 33130180.

17. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public (16 Jan 2021).

18. https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf (16 Jan 2021).

19. https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-product-information_en.pdf (16 Jan 2021).

20. Morales FS, Koralnik IJ, Gautam S, et al. Risk factors for lymphopenia in patients with relapsing-remitting multiple sclerosis treated with dimethyl fumarate. J Neurol. 2020; 267(1): 125–131, doi: 10.1007/s00415-019-09557-w, indexed in Pubmed: 31583427.

21. Zheng C, Kar I, Chen CK, et al. Multiple Sclerosis Disease-Modifying Therapy and the COVID-19 Pandemic: Implications on the Risk of Infection and Future Vaccination. CNS Drugs. 2020; 34(9): 879–896, doi: 10.1007/s40263-020-00756-y, indexed in Pubmed: 32780300.

22. Barry B, Erwin AA, Stevens J, et al. Fingolimod Rebound: A Review of the Clinical Experience and Management Considerations. Neurol Ther. 2019; 8(2): 241–250, doi: 10.1007/s40120-019-00160-9, indexed in Pubmed: 31677060.

23. https://www.ema.europa.eu/en/documents/product-information/gilenya-epar-product-information_en.pdf (16 Jan 2021).

24. https://www.ema.europa.eu/en/documents/product-information/ocrevus-epar-product-information_en.pdf (16 Jan 2021).

25. Safavi F, Nourbakhsh B, Azimi AR. B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. Mult Scler Relat Disord. 2020; 43: 102195, doi: 10.1016/j.msard.2020.102195, indexed in Pubmed: 32460086.

26. Mycko MP. B cell targeting therapies in MS patients during the SARS-CoV-2 pandemic - when immunosuppression meets infection? Neurol Neurochir Pol. 2020; 54(6): 490–501, doi: 10.5603/PJNNS.a2020.0083, indexed in Pubmed: 33073348.

27. McCarthy CL, Tuohy O, Compston DA, et al. Immune competence after alemtuzumab treatment of multiple sclerosis. Neurology. 2013; 81(10): 872–876, doi: 10.1212/WNL.0b013e3182a35215, indexed in Pubmed: 23925762.