Abstract

The COVID-19 pandemic has resulted in challenges for the practice of neurology. One major concern is how to best manage patients with multiple sclerosis (MS) who are on disease-modifying therapies (DMTs). DMTs frequently have immunosuppressive properties that both increase the risk for COVID-19 and potentially reduce the immunologic response to vaccination in a group already vulnerable to infection due to neurologic deficits. Here, we review early data on COVID-19 outcomes in patients with MS and discuss what is known about vaccine effectiveness in those on anti-CD20 and sphingosine-1-phosphate receptor agents, which are proposed to have attenuating effects based on their mechanisms of action. In addition, we provide recommendations to best use novel COVID-19 vaccines in this population and highlight what information may better inform vaccine strategies in the future.

COVID-19 is a major public health challenge that has resulted in over 2 million deaths worldwide, in addition to extensive economic and social harms. Vaccination for the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has emerged as a critical mechanism to prevent COVID-19. In this context, there are unique considerations for patients with multiple sclerosis (MS), particularly those patients who are on immunosuppressive disease-modifying therapies (DMT) that may heighten risk for infection, worsen clinical outcomes from infection, and limit responsiveness to vaccines. Here, we discuss considerations for COVID-19 vaccination in patients with MS on DMT, as well as recommendations for vaccination planning in this vulnerable population.

Discussion

Patients with MS are at heightened risk of infections, particularly urinary and pulmonary infections. Furthermore, patients with MS are at heightened risk for severe infections (defined by hospitalization) than patients with other autoimmune conditions, which may reflect the contributions of neurologic deficits from MS (e.g., bladder dysfunction and dysphagia). Immunomodulatory DMTs, such as glatiramer acetate and interferons, do little to increase the risk beyond this baseline, as seen in their respective clinical trials and real world experience. However, immunosuppressive DMTs (particularly anti-CD20s) exacerbate the risk of infection. In the subpopulation treated with anti-CD20 DMT, male sex and time on rituximab increase the infection risk, but higher disability is a key factor. Although knowledge is evolving, these risks appear to extend to COVID-19. Risk for severe COVID-19 in the MuSC-
hypogammaglobulinemia, in addition to most patients with iatrogenic B-cell depletion, can recover from COVID-19 infection, indicating that although B cells may be important in the response to infection, they are not strictly necessary for recovery.\textsuperscript{5,6,12}

There is activation of virus-specific CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells in response to BNT162b1, indicating that at least with mRNA-based vaccines, the protective response may be multifacotorial.\textsuperscript{13}

The potential for B cell–depleting therapies to attenuate vaccine response is a concern due to their direct effect on humoral immunity and the role of B cells in antigen presentation. This is concordant with concerns about serologic conversion following COVID-19 infection. We are aware of 9 cases of patients with MS who were on anti-CD20 DMT with documented COVID-19 by PCR, but negative serologic testing.\textsuperscript{14-17} That said, the portion of patients, if any, who do seroconvert from infection is not known, and how any degree of baseline hypogammaglobulinemia affects this process is similarly uncertain. Broadly, the recent VELOCE trial demonstrated reduced levels of vaccine (tetanus toxoid, pneumococcal 13, and influenza) responsiveness and protection, as well as impaired humoral response to stimulatory antigen keyhole limpet hemocyanin, in patients with MS on ocrelizumab.\textsuperscript{18} There are no specific data on vaccine responsiveness in patients with MS on rituximab or-ofatumumab; the literature from rheumatoid arthritis suggests that rituximab decreases responsiveness similarly.\textsuperscript{19}

The other class of medications concerning for impairing vaccine responsiveness is sphingosine-1-phosphate receptor modulators, which suppress lymphocyte egress from lymph nodes. In a placebo-controlled trial, patients on fingolimod were significantly less likely to respond to influenza and tetanus toxoid vaccines, although the majority still did mount an appropriate response.\textsuperscript{20} An additional study evaluating response to influenza vaccination in patients on fingolimod demonstrated reduced response rates when compared with patients not on DMT, in addition to those on glatiramer acetate or interferon beta (neither of which was different from control).\textsuperscript{21} Like B cell–depleting therapies, fingolimod may prevent seroconversion.\textsuperscript{22} There are limited data on siponimod with 1 placebo-controlled study demonstrating reduced responsiveness to vaccination and no published data on ozanimod.\textsuperscript{23}

**Conclusions**

Widely available and effective vaccination for COVID-19 is an exciting prospect. Although the first FDA-authorized vaccines were given December 2020, the logistics of administration remain challenging. Widespread vaccination may not occur until late 2021. This poses critical questions for patients on or considering initiation of DMT.

For stable patients, continuing current DMT is recommended. Although there is concern that outcomes may be worse and that vaccination may be less effective while on some DMTs, stopping or switching DMT leads to
considerable logistical challenges and may lead to rebound disease activity (e.g., for fingolimod). As there are data that the therapeutic effects of rituximab can extend for months beyond the timing of humoral immune reconstitution, it may be possible to extend the dosing interval to create a window to administer the COVID-19 vaccine and allow for immunologic response. To maximize the immunologic response, it is suggested by the Canadian Network of MS Clinics (cnms.ca/Covid19VaccineGuidance) to wait 4 weeks after the 2nd mRNA vaccine dose for new or repeat infusion of anti-CD20 DMT. For patients already on anti-CD20 DMT, waiting 12 weeks (as in the VELOCE study) after infusion to start the vaccination process is recommended. It has also been proposed to delay vaccination until B-cell reconstitution or toward the end of an infusion cycle, but the risks of contracting COVID-19 need to be considered.

For patients who have not started DMT, considerations for DMT include the expected impact on vaccine efficacy and what other treatment options are available to control the patient’s MS. If possible, a DMT start could be delayed. The prescribing information for ocrelizumab recommends that if possible, to vaccinate with nonlive vaccines 2 weeks before initiation of treatment (Genentech 2017). As above, it is reasonable to extend this interval to 4 weeks following the second dose of a COVID-19 mRNA vaccine. In addition, a bridging strategy could be used by temporarily choosing another DMT. Natalizumab (expected to have minimal impact on COVID-19 vaccine efficacy) is an alternative and could be used in the short-term, even in patients who are JC virus positive. Glatiramer acetate, interferon beta, and dimethyl fumarate are predicted to have relatively minimal impact on COVID-19 vaccination responsiveness and may be more frequently used.

Further characterizing specific vaccine responses with antibody titers and T-cell responses in patients on specific DMTs, in addition to clinical outcome data, will be useful in guiding how to treat and vaccinate patients with MS during the COVID-19 pandemic and into the future. It is recommended that despite uncertainty about vaccination effectiveness, all patients with MS without other contraindications receive a COVID-19 vaccine and follow the AAN vaccine guidelines. Long-term, more knowledge is needed about the factors that increase infection rates and how to mitigate them when possible. A comprehensive strategy around choosing how and when (or not) to treat patients with DMTs as well as developing a vaccination strategy for COVID-19 and other preventable infections in patients with MS is worthy of further investigation.

Study Funding
No targeted funding reported.

Disclosure
A. Wolf reports no disclosures relevant to the manuscript. E. Alvarez has consulted with Actelion/Janssen, Alexion, Bayer, Biogen, Celgene/BMS, EMD Serono/Merck, Genentech/Roche, Genzyme, Novartis, Sanoﬁ, and TG Therapeutics and research support from Biogen, Genentech/Roche, Novartis, TG Therapeutics, Patient-Centered Outcomes Research Initiative, National Multiple Sclerosis Society, NIH, and Rocky Mountain MS Center. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

References

Appendix Authors

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Publication History
Received by Neurology: Clinical Practice January 25, 2021. Accepted in final form March 18, 2021.


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COVID-19 Vaccination in Patients With Multiple Sclerosis on Disease-Modifying Therapy
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*Neurol Clin Pract* 2021;11:358-361 Published Online before print April 14, 2021
DOI 10.1212/CPJ.0000000000001088

This information is current as of April 14, 2021