In December 2019, COVID-19, caused by infection with SARS-CoV-2, was discovered and since, has rapidly spread around the world. To date, 56.3 million documented cases have been reported in the US with 825,000 deaths and a death rate of approximately 1.54%, based on data from the Centers for Disease Control and Prevention (CDC). Many people with multiple sclerosis (MS) take disease-modifying therapies (DMTs) that suppress or alter their immune systems, which could impart higher risk for worse COVID-19 outcomes.

COVID-19 Outcome Risk Factors in MS

An evaluation of electronic health records (EHRs) from 39 large US health systems identified over 150,000 patients with MS, including more than 30,000 who were taking a DMT at the time of analysis, November 30, 2020. The incidence of COVID-19 at that point in time was 0.5% for people with MS. Among those using DMTs, polymerase chain reaction (PCR)-confirmed COVID-19 rate was 1.13% (344/30,478). At the time, the mortality rate of COVID-19 in the general US population was approximately 3.1%, whereas the overall, unadjusted COVID-19 mortality rate among those with MS in the EHR records analyzed was between 3% and 4.5%.

The COViMS registry was created early in the pandemic as a North American database collecting information from patients with demyelinating diseases of the central nervous system (CNS), primarily MS, with confirmed/suspected SARS-CoV-2 infection. Data in the COViMS registry is reported voluntarily by healthcare professionals. Data collected from COViMS as of December 31, 2021, showed 85 deaths among 3,660 people with MS and COVID-19, a 2.32% mortality rate. Approximately 90% of the reported cases had positive laboratory confirmation of COVID-19. Based on COViMS data through December 23, 2021, risk factors for increased COVID-19 severity among people with MS were similar to those for the general North American population. In COViMS, male sex, older age and increased disability were all associated with increased risk of severe COVID-19 requiring admission to an intensive care unit (ICU) and/or ventilator support, as well as death from COVID-19. Notably, people with MS who were nonambulatory had a mortality rate of 14%, a 25 times higher rate than in ambulatory people with MS after adjustment for other risk factors (P<.001). Black North American persons with MS had a 50% increased odds of hospitalization alone and more than twice the increased risk of ICU admission and/or ventilation, but did not have a statistically significant increased risk of death compared with white individuals in the COViMS registry. Individuals with progressive MS in the COViMS registry were more likely to have a worse clinical course of COVID-19 than seen with relapsing-remitting MS. These COViMS data were in line with other observational studies, which also found higher age and ambulation impairment were significant predictors of hospitalization due to COVID-19.

DMTs and COVID-19 Risks and Outcomes

Significant concern continues regarding the effects of certain DMTs for MS on susceptibility to and outcomes of COVID-19. The EHR database study already described also analyzed 30,478 people with MS using DMTs and found hospitalization risk of 21.5% (74/344) due to COVID-19. Deaths due to COVID-19 were 4.2% (32/761) in the overall population with MS in this study and 3.5% (12/344) in those using DMTs. With adjustments for age, sex, body mass index (BMI), the social construct of race, and comorbidities, the odds of developing COVID-19 were higher for those taking antiCD20 therapies vs fumarates (odds ratio[OR], 3.25; 95% CI 2.31-4.64; P<.0001) and when compared to the aggregate of all DMTs (P<.0001). Interestingly, the COVID-19 incidence in those with prescriptions for interferon β or glatiramer acetate was less than for all other DMTs (0.61% vs 1.27% and 0.51% vs 1.31%, respectively, P<.0001 for each).

COViMS North American registry data have also provided insights into effects of specific DMTs, with approximately 85% of entries reporting DMT use. Approximately 30% were taking ocrelizumab, whereas use of sphingosine-1-phosphate receptor
(S1PR) modulators, natalizumab, fumarates, or rituximab (off-label) comprised about 9.5%, 10.6%, 11.3%, and 4.7%, respectively. In earlier published analyses of these data, those using rituximab had a 4.5-times increase in the odds of hospitalization compared with those using no DMT. Those using ocrelizumab had 1.63-times increase in the odds of hospitalization for COVID-19. Findings from COViMS were in accord with data from other international registries, including early results from an Italian MS registry and a later analysis of combined Italian and French registry data. Each analysis found worse clinical outcomes with the use of antiCD20 agents and with longer duration of antiCD20 exposure. In the early Italian cohort, recent use of methylprednisolone was also associated with worse outcomes (OR 5.2, \( P = .001 \)), a finding that was reproduced by the later analyses of the combined Italian and French registries (OR = 2.7, \( P < .001 \)). In COViMS, glucocorticoid use in the prior 2 months was associated with twofold increased risk of hospitalization and fourfold increased risk of death. Notably, in the North American, Italian, and French registries, interferon \( \beta \) and glatiramer acetate treatments were consistently associated with a lower incidence of developing severe COVID-19 in comparison to other DMTs, suggesting a potential protective effect. This association persisted after adjustment for age, sex, race, BMI, and other comorbidities.

A large cohort study of clinician-submitted data from over 30 countries in Europe, North America, and South America reporting on 2,340 people with MS with 1,683 confirmed COVID-19 cases also found the same associations that remained after adjustment for age, sex, MS phenotype and Expanded Disability Status Scale (EDSS) scores. As shown in the Figure, compared with dimethyl fumarate, rituximab use had 2.43 increased adjusted odds of hospitalization, 3.93 times increased adjusted odds of ICU admission, and 4 times increased odds of requiring ventilation support. Use of ocrelizumab showed 1.56 increased adjusted odds of hospitalization and 2.30 times increased in the odds of ICU admission, but no increase for artificial ventilation was observed. Characteristics of these individuals were assessed in an effort to determine if these associations were due to disease characteristics of those using these treatments vs use of other DMTs. Worse clinical outcomes associated with rituximab and ocrelizumab were attributable to the DMTs and not a function of other known risk factors of those taking these DMTs.

All registry data discussed are subject to several limitations of voluntary registry data, including lack of denominators, ascertainment bias, and a likely lag in time from COVID-19 occurrence until data entry. Moreover, the behaviors of the participant populations cannot be controlled for and may change.
over time. Improvements in COVID-19 treatment and introduction of vaccines have likely changed outcomes. Virus variants have also appeared over time and in different geographies.

**Effects of COVID-19 and Vaccination Against COVID-19 on MS**

Although anecdotal reports of MS exacerbation with COVID-19 exist, no clear association has yet been shown. In a retrospective cohort study of 474 people with MS from February 1, 2020 to December 31, 2020, 63.3% of whom had confirmed COVID-19 infection, 49 (10.3%) had exacerbation of existing neurologic symptoms (“pseudoexacerbation”) whereas only 2 (0.4%) had true MS disease activity (relapse). Both of these individuals developed new-onset sensory myelitis at weeks 1 and 3 after resolution of viral symptoms.

MS is not intrinsically an immunosuppressive condition, but people with MS are at increased risk of infections. Before the COVID-19 pandemic, people with MS had higher rates of any infection compared with the general population and twice the rate of hospitalizations for infection, most commonly urinary tract or kidney infections. Additionally, several of the DMTs used to treat MS can suppress or modulate the immune system. The National MS Society of the United States and other groups (eg, the American Academy of Neurology) have published expert consensus recommendations that people with MS should follow all local vaccine standards, delaying vaccination only in the case of an active relapse and only until after clinical resolution of that relapse.

In the US, 3 COVID-19 vaccines have been authorized by the Food and Drug Administration (FDA). Data specific to people with MS about safety of these vaccines are limited. An observational study in 555 individuals with MS who received the BNT162b2 (Biontech-Pfizer) vaccine found no increased risk of relapse activity over a median 20 to 38 days after the first and second vaccine doses. Rates of acute relapse (2.1% and 1.6% following the first and second doses) were similar to the rate of acute relapse during the same time period in prior years. Approximately 2% of patients after the first dose and 4.8% after the second dose had worsening of prior MS symptoms or a “pseudoexacerbation” that usually lasted 1 to 2 days.

**Effect of DMTs on Vaccination Efficacy**

Several prepandemic studies have examined the effect of DMTs on vaccination response, showing adequate response in people using interferon β or fumarates. Variably modest reductions in vaccine response have been seen in people using glatiramer acetate, teriflunomide, and natalizumab, depending on the vaccine type. Alemtuzumab had no clear effect on vaccine response, although timing of vaccination relative to alemtuzumab dosing is likely important. Studies of vaccine response in people with MS taking oral cladribine are few, but thus far have shown little to no negative effects. In contrast, S1PR modulators and antiCD20 monoclonal antibodies have each shown greatly reduced humoral responses to some vaccines, likely reflecting the importance of B-cell adaptive immunity for optimal vaccination response.

Regarding COVID-19 vaccines, an Israeli study of 125 participants with MS and 47 healthy participants who received the BNT162b2 vaccine measured SARS-CoV-2 spike protein IgG responses about 1 month after the second vaccine dose. In healthy subjects, people with MS not using DMTs (n=32), and people with MS using cladribine (n=23), respectively, humoral immunity of 97.9%, 100%, and 100% was observed. In contrast, only 3.8% of people with MS using fingolimod (n=26) and only 22.7% people with MS treated with ocrelizumab (n=44) developed an IgG response to the spike protein. In this study, no clear relation between vaccine response and time since last prior ocrelizumab infusion was noted.

A prospective study from a US center enrolled 53 participants, including 42 with MS. Participants provided blood samples before and 3 weeks after their second dose of either the BNT162b2 or mRNA-1273 (Moderna) vaccinations. After vaccination, 100% of persons in all groups other than those taking B-cell depleting monoclonal antibodies developed antibodies to SARS-CoV-2. Of the 20 people with MS taking ocrelizumab in this study, those with lower serum IgM levels, lower B-cell numbers, or a shorter interval from the last B-cell depleting infusion to vaccination were less likely to show a positive humoral response to vaccination. No difference in total duration of B-cell depleting therapy was observed between vaccine responders and nonresponders.

A small study examined cellular and humoral vaccine responses in 20 people with MS treated with antiCD20 B-cell depleting therapy and found reduced memory B-cell response in addition to reduction of antibody responses to SARS-CoV2 spike protein and spike-protein receptor binding domain. The magnitude of antigen-specific memory B-cell response correlated with the extent of B-cell reconstitution at time of vaccination. T-cell responses were observed in all 20 participants but were somewhat reduced. Follicular T-helper cells were particularly reduced by B-cell depleting therapy.

In a study of B- and T-cell responses in 101 people with MS after vaccination, serum IgG responses to the SARS-CoV-2 spike protein and T-cell responses using an assay for interferon γ production in response to spike protein peptides were analyzed. Most participants received BNT162b2 or mRNA-1273 mRNA vaccines and 7 received adenovirus vectored vaccine (Johnson & Johnson). Responses were analyzed in relation to use of various DMTs and showed humoral responses to be present in 56.4% of the 39 participants treated with an antiCD20 agent vs 93.6% of the 63 participants using no or other DMTs. T-cell responses tested in a subset of 88 participants were detected in 86%, including 97% of the 33 being treated with antiCD20 therapies. The study noted a higher like-
lithology of a positive humoral response to vaccination following a longer time interval from last infusion of antiCD20 therapy.18

A prospective study from Italy of COVID-19 vaccination in 108 patients with MS being treated with various DMTs and 78 health care workers (HCW), measured humoral responses to vaccination by antireceptor binding domain (antiRBD) and neutralizing antibodies. T-cell responses were evaluated by interferon γ responses to SARS-CoV-2 spike peptides. In accord with other studies, the proportion who had an anti-RBD response was reduced in those taking ocrelizumab (40%; n=25). Different from prior studies, 85.7% of people with MS taking fingolimod (n=35) had antiRBD humoral responses. T-cell responses to the spike protein occurred in 100% of the HCW.19 Only 14.3% (5/35) of participants being treated with fingolimod had T-cell responses, in comparison to 92% (23/25) of those being treated with ocrelizumab, 89% (25/28) of those taking interferon β, and 70% (14/20) of those using oral cladribine. Individuals treated with cladribine or fingolimod had significantly lower response rates compared with HCWs (P<.0001). T-cell-specific responses to spike protein peptides were significantly, although weakly, correlated with lymphocyte count and antiRBD antibody titers (r=0.554, P<.0001 and r=0.255, P=.0078, respectively). In a subset of 69 HCW and 24 people with MS who were taking fingolimod, all HCW had detectable neutralizing antibodies to SARS-CoV-2 infected cells, and these responses positively correlated with antiRBD titers (r=0.754, P<.001). However, only 16.6% (4/24) of those taking fingolimod showed neutralizing activity, and when present, it was at low titer with a significant correlation between the neutralizing antibody and antiRBD antibody titers (r=0.591, P=.0024).19

Preventive Treatment of COVID-19 for Immunosuppressed Individuals

On December 8, 2021, the FDA issued an emergency use authorization for combined treatment with 2 antiSARS-CoV-2 monoclonal antibodies to provide preexposure prophylaxis of severe COVID-19 in people at high risk of hospitalization. This antibody combination of tixagevimab and cilgavimab is given by intramuscular injection. Preventive treatment is intended for people with severe immunocompromise preventing optimal response to vaccination, including those with immunocompromise due to immunosuppressive medications, such as B-cell depleting treatments for MS. The protection from severe COVID-19 is expected to last for approximately 6 months. We recommend offering long-acting monoclonal antibodies targeting SARS-CoV-2 to eligible people with MS,20,21 although the initial supply of this preventive treatment has been limited.

Treatment of COVID-19 and Postexposure Treatment of High-Risk Individuals

Some treatments are available for individuals with high risk of hospitalization if they get COVID-19. Several available monoclonal antibodies that act on the spike protein RBD of SARS-CoV-2 have been created for use alone or in combination. These are approved for nonhospitalized individuals with mild-to-moderate COVID-19 at risk of progression to severe disease that would require hospitalization. These monoclonal antibody treatments have evolved with each new SARS-CoV-2 variant.22-24 Moreover, 2 oral anti-viral treatments for use within the first 5 days of symptom onset in individuals at high risk of severe COVID-19, molnupiravir tablets and the combination of nirmatrelvir plus ritonavir tablets, are each available under an FDA Emergency Use Authorization.25 We recommend checking the NIH COVID-19 website25 and the National MS Society website21 for the most current information about COVID-19 treatments and prevention.

Conclusions and Practice Opinions

Most studies have found a higher COVID-19 mortality rate in people with MS patients, around 3%, compared with the 1.5% seen in the general population. This increase may be explained by association with other factors including treatments for MS and disability due to MS. People with MS with ambulatory difficulties have a higher risk of worse outcomes with COVID-19 compared with those who are fully ambulatory. Similar to the general population, older age, male sex, obesity and other medical comorbidities also increase the risk of worse COVID-19 outcomes in people with MS. B-cell depleting therapies impart increased risk of a more severe COVID-19 course. Interferon β and glatiramer acetate may confer a lower risk of developing COVID-19 and severe COVID-19.

We recommend that everyone with MS be fully vaccinated and follow the most current recommendations for COVID-19 vaccine boosters, unless they have a compelling reason not to be vaccinated. Patients on S1PR modulators and antiCD20 antibody therapies should get the complete COVID-19 vaccine series recommended for patients who are immunocompromised and at risk of mounting suboptimal vaccine responses. So far, there has been no evidence that COVID-19 vaccines precipitate MS exacerbation, although a percentage of patients experience short-lived worsening of prior MS symptoms (“pseudo-exacerbations”) after vaccination.

Studies suggest that people with MS being treated with S1PR modulators and antiCD20 antibody therapies frequently have a lower humoral response to the COVID-19 vaccines. Some studies suggest that the longer the time since the last antiCD20 antibody infusion, the better the humoral response to vaccination, especially when there is evidence of some B-cell repopulation. We recommend consideration be given to waiting at least 12 weeks after prior antiCD20 infusion to get the COVID-19 vaccine to improve vaccine effectiveness. For individuals using S1PR modulators, it is generally advisable not to stop therapy to increase response
to vaccines due to risk of rebound MS activity. We recommend making these decisions on a case-by-case basis.

We advise our MS patients taking antiCD20 agents or S1PR modulators that they may have a suboptimal response to COVID-19 vaccination compared with the general population and should take extra precautions and get an additional dose of COVID-19 vaccine as per CDC recommendations. People with MS who are expected to have a poor response to vaccination are informed that they may be eligible for COVID-19 preventative treatment. For those who develop COVID-19 during active COVID-19 infection

**Abbreviation:** DMT, disease-modifying therapy; MS, multiple sclerosis.

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monoclonal-antibodies-pre-exposure


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