Disease-Modifying Therapies During the COVID-19 Outbreak: A Narrative Review of the International and National Recommendations

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Running head: DMTs During COVID-19 Outbreak

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Practice Points

- There are no clinical trials or observational studies guiding treatment decisions for MS in the current COVID-19 pandemic. Recommendations are from expert opinions. Therefore, treatment should be tailored to an individual after a detailed discussion of risks and benefits.
- Disease-modifying therapies (DMTs) that do not decrease lymphocyte counts are the preferred options for starting the treatment during the COVID-19 outbreak.
- Patients who are currently taking a DMT should continue the treatment. Extended interval dosing for cell-depleting therapies and natalizumab may be considered.
- In patients with active COVID-19 infection, a clinician may consider holding all injectable and oral DMTs, as well as delaying cell-depleting DMTs.

Abstract

Background: Managing multiple sclerosis (MS) during the novel coronavirus (COVID-19) pandemic is a challenge due to the lack of evidence from clinical studies. Disease-modifying therapies (DMTs) may affect the immune response and subsequently alter the risk of COVID-19 infections.

Methods: A literature search was conducted on MEDLINE, Embase, and Cochrane databases. A focused Google search was also performed. The recommendations regarding the use of DMTs during the COVID-19 outbreak from national or international MS/neurology societies were identified and reviewed.

Results: The review included 16 recommendations from international and national MS organizations. All recommendations are based on expert opinions. The recommendations regarding DMT initiation and management during this outbreak were summarized. Moreover, the experts' views about the risk of COVID-19 infection with each DMT were discussed as well.

Conclusions: There is significant agreement among most experts' recommendations from a variety of sources based on collective clinical experience. However, the recommendations will likely evolve as sufficient clinical data are limited. Several ongoing registries will help to provide the information for future recommendations.

Introduction

The novel coronavirus disease (COVID-19) is a current global challenge. In December 2019, clusters of patients with pneumonia of unknown etiology were reported in Wuhan, Hubei Province, China. By analyzing samples from the patients, a novel *betacoronavirus* was discovered by the China Novel Coronavirus Investigating and Research Team.[1] Subsequently, the novel coronavirus became an outbreak in many regions across the globe. On March 11, the World Health Organization declared the COVID-19 outbreak a global pandemic.[2]

Multiple sclerosis (MS) is the most prevalent chronic immune-mediated disorder of the central nervous system (CNS), affecting more than 2 million people worldwide.[3] In the past few decades, a number of disease-modifying therapies (DMTs) with variable mechanisms of action were developed for the treatment of MS. The resultant modulation and suppression of the immune system by these DMTs may alter the risk of infection in MS patients. Currently, there is no consensus guiding clinicians to manage DMTs during this pandemic.

This article includes a narrative review of the international and national recommendations regarding DMT management during this pandemic. Furthermore, this review discusses the immunopathogenesis of coronavirus and the effects of DMTs on the immune system.

Methods

Literature Search Strategy

Two investigators (S.T. and M.A.) independently searched for publication articles indexed in MEDLINE, Embase, and Cochrane databases from inception to April 14, 2020. A focused Google search was also completed in the same day. The search strategy included the terms for MS and coronavirus. The search strategy is available as Table S1. References of the included articles and the relevant links were also manually reviewed for additional eligible articles. Non-English articles were reviewed by an M.D. who is a native speaker or an expert in that language.

Selection Criteria and Data Extraction

The inclusion criteria for the narrative review included the recommendations regarding the use of DMTs during the COVID-19 outbreak from national or international MS/neurology societies. Data extraction was independently performed by S.T. and M.A. A standardized data collection form was used to extract the following information: the name of MS societies, recommendations for starting and managing DMTs during the COVID-19 outbreak, risk of COVID-19 infection of each DMT, and management of DMTs in active COVID-19 patients. Any discrepancies found in the data record forms were resolved by referring to the original articles.

Results

The literature review process is shown in Figure S1. The review included 16 recommendations from international and national MS organizations including the Multiple Sclerosis International Federation (MSIF),[4] the European Academy of Neurology (EAN),[5] the European Multiple Sclerosis Platform (ESMP),[6] Multiple Sclerosis Australia (MSA),[7] the Francophone Society of Multiple Sclerosis (SFSEP),[8] the Multiple Sclerosis Society of Ireland (MSS-Ireland),[9] the Italian Multiple Sclerosis Association (AISM),[10] the Multiple Sclerosis Society of New Zealand (MSNZ),[11] Multiple Sclerosis Spain,[12] the Swiss Multiple Sclerosis Society (Swiss MSS),[13] the Association of British Neurologists (ABN),[14] the Multiple Sclerosis Society of the United Kingdom (MSS-UK),[15] and the National Multiple Sclerosis Society (NMSS) of the United States. MSIF and ESMP recommendations are the same. Several national societies, including the Brazilian Multiple Sclerosis Association,[16] the Japanese Society of Neuroimmunology,[17] and Stichting MS Research[18] have translated the MSIF recommendations to their languages. All recommendations are based on expert opinions. The summary of the recommendations is shown in Table 1.

Starting Disease-Modifying Therapies

The NMSS recommends starting a DMT in patients with a recent diagnosis with MS. MS providers and patients should discuss the risk of infection, including COVID-19, weighing against MS activity, age, other medical conditions, and other potential factors that could impact DMT.[19] The risk of COVID-19 in the specific region should be taken into consideration when choosing a DMT.[4,6]

The DMTs not associated with significant lymphopenias such as interferons (IFNs), glatiramer acetate, and natalizumab are the preferred choices.[4,6,7] The NMSS warned to consider specific risk and benefit before starting natalizumab and fingolimod as they potentially lead to an increase in disability after discontinuation.[19] During the pandemic, MSIF and ESMP recommend careful consideration before starting teriflunomide, dimethyl fumarate, fingolimod, and siponimod.[4,6] The ABN considers teriflunomide and dimethyl fumarate as the safe option to start as well.[14] MSS-UK recommends considering alternative DMT in patients who plan to start fingolimod.[15]

Cell-depleting DMTs, including alemtuzumab, anti-CD20 monoclonal antibodies, and cladribine, are not considered the favorable options given the prolonged effect on lymphopenia.[4,6] EAN advises considering delayed initiation of these DMTs until the peak of the pandemic is over in the region, except when the benefit of therapy outweighs the risk of severe COVID-19 infection.[5] According to the ABN recommendation, alemtuzumab and cladribine should not be started during the pandemic. Although the persistently higher risk of infection is anticipated during the virus outbreak, ocrelizumab may be an option if a high-efficacy DMT is indicated and a patient is not eligible for natalizumab.[14]

Continuation of Disease-Modifying Therapies

All MS patients without an active infection should continue with their current DMT, especially IFNs, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, and natalizumab.[4-11,13-15,19] Although the ABN considers natalizumab as a safe option, considering

extended interval dosing may be appropriate.[14] Most of the MS organizations recommend considering delay dosing for cell-depleting therapies based on individual risk of relapse and infection.[4-10,13-15] For infusion therapies, EAN advises considering home infusion rather than at an infusion center depending on the regional COVID-19 incidence.[5] Additionally, the EAN, MSA, and MSNZ recommend continuing intermittent immunotherapies (i.e., plasma exchange and intravenous immunoglobulin) with an appropriate preventive measure of COVID-19 infection.[5,7,11]

MSNZ advises keeping blood monitoring for DMTs up to date in patients taking teriflunomide, dimethyl fumarate, fingolimod, siponimod, and natalizumab. If lymphopenia occurs, frequent monitoring may be needed.[11] Because of increasing pressures on health care services and the elevated risk of infection in patients visiting clinics or hospitals, blood monitoring may need to be abbreviated in some situations. ABN has proposed for minimal blood monitoring during this outbreak. However, patients must remain vigilant to recognize any signs or symptoms of adverse events to medications.[14]

Risk of COVID-19 Infection in Patients with Disease-Modifying Therapy

At this moment, there is no clinical study to determine the risk of coronavirus infection in MS patients. The NMSS, MSS-UK, ABN, MSS-Ireland, and Swiss MSS have provided opinions regarding the risk of COVID-19 infection. IFNs[7,13-15,19], glatiramer acetate[7,9,13,15,19] and natalizumab[9,13,19] are not considered to significantly elevate the risk. There is a significant concern of increased COVID-19 infection risk with alemtuzumab, anti-CD20 monoclonal

antibodies, and cladribine.[9,13-15,19] Some concerns are raised with fingolimod[5,9,13-15,19] and siponimod[5,15,19] as well. While MSS-UK and MS-Ireland do not consider an increased risk in patients with teriflunomide and dimethyl fumarate, the NMSS and Swiss MSS have a concern that these DMTs may elevate the risk. The expert opinions regarding the risk of COVID-19 infection and DMTs are summarized in Table 2.

Management of Disease-Modifying Therapies During Active COVID-19 Infection

EAN, AISM, and ABN recommend holding all injectable and oral DMTs, as well as delaying cell-depleting DMTs.[5,10,14] However, physicians may consider continuing IFN because of the potential anti-viral effect.[10] For patients on fingolimod and natalizumab, there is a concern about rebound disease activity after discontinuation. Physicians must individualize the treatment plans based on the clinical situation.

Hematopoietic Stem Cell Therapy

Hematopoietic stem cell therapy (HSCT) includes intense chemotherapy; therefore, it severely impairs the immune response for an extended interval. All experts recommend considering postponing the procedure.[4,6,7,9,14,15] Furthermore, the patients who underwent recent HSCT should extend the isolation period.[4,6,7]

Discussion

At this moment, there are no data from observational studies or clinical trials guiding health providers to manage DMTs for MS during the current COVID-19 pandemic. All recommendations from international and national MS societies are based on expert opinions. There was no major disagreement among experts' views. However, the recommendations from each organization may change as the situation evolves. We encourage practitioners to visit the websites provided in Table S2 for the latest information.

It is also important to understand the effect of this COVID-19 on the immune system to understand these latest recommendations. There are currently seven known strains that infect humans (HCoVs) – 229E, OC43, HKU1, and NL63 are community-acquired strains and cause the common cold, while the 2003 severe acute respiratory syndrome CoV (SARS-CoV) and the 2012 Middle East respiratory syndrome (MERS-CoV) caused severe respiratory illnesses.[20-22] The newest HCoV, COVID-19 (also known as SARS-CoV-2 and 2019nCoV, and previously named Wuhan coronavirus), is the cause of the current pandemic.

The majority of the cases developed lymphopenia. Severe cases requiring intensive care unit had high levels of proinflammatory cytokines, such as interleukins 2, 7, and 10, as well as granulocyte-colony stimulating factor, and tumor necrosis factor α.[23] A recent cohort has shown that neutrophilia, lymphopenia as well as decreased CD3 and CD4 counts are associated with higher risks of the development of ARDS.[24]

Further pathogenesis has been challenging to determine because of the novelty of this virus; however, COVID-19 is from the same lineage as SARS-CoV and shares 82% of their genetic material, and indeed, the pathogenesis is quite similar between the two viruses.[25,26] It is, therefore, fair to deduce further information about COVID-19 based on what we know from

SARS-CoV. It is known that SARS-CoV has at least seven IFN antagonists.[27] In an animal study, rapid SARS-CoV replication induced a delayed IFN α and β response, which is an essential response to viral infection.[28] A study from 128 SARS-CoV convalescent samples demonstrated the importance of adaptive immunity, especially CD8+ T cell response. Moreover, most of the SARS-CoV convalescent possessed a strong neutralizing antibody produced by B-cells.[29]

DMTs for MS generally involve some form of immunomodulation, immune-cell sequestration, or immunosuppression. Therefore, DMTs may alter the risk of COVID-19 infection and the disease course during this pandemic. Several DMTs, especially cell-depleting DMTs, can cause lymphopenia, which is associated with adverse outcomes in COVID-19 infection.[24]

IFN-β, the oldest MS DMT, now exists in several formulations including IFN-β1a, IFN-β1b, and peginterferon-β1a. IFN-β is believed to downregulate proinflammatory cytokine production as well as decrease T-cell activation and migration.[30] Although lymphopenia is common, the events are mild and transient.[31] Data from clinical trials and more than 20 years of real-life experience have not revealed an increased prevalence of specific infections except for local infection at the injection site.[30] In a physiologic state, IFN α and β signaling pathways play a role in the defense against viral infection. Moreover, an *in vitro* study demonstrated a capacity of cytopathic effect inhibition of IFN-β1b in SARS-CoV infected cells.[32] Experts' opinions from all national MS and neurology societies do not believe that IFNs will increase the risk of COVID-19 infection.[9,13-15,19] Furthermore, IFN-β, in combination with lopinavir/ritonavir and

ribavirin, is currently in a clinical trial for the treatment of COVID-19 (ClinicalTrials.gov Identifier NCT04276688).

The proposed mechanism of glatiramer acetate is promoting the development of regulatory T-helper 2 cells, which decrease the inflammatory response.[33] Leukopenia is uncommon in patients with glatiramer acetate. When it occurs, it is generally mild.[34] Not surprisingly, current expert opinions agree that glatiramer acetate should not significantly elevate the risk of COVID-19 infection.[9,13,15,19]

Teriflunomide is an oral DMT. The proposed mechanism of action is selectively and reversibly inhibition of dihydroorotate dehydrogenase, a key enzyme in the *de novo* pyrimidine synthesis. Therefore, it leads to a reduction in the proliferation of activated T and B lymphocytes without causing cell death.[35] In phase 3, randomized controlled trial, reversible neutropenia, and lymphopenia were observed in the teriflunomide group, and all patients are asymptomatic. There was no significant difference in the incidences of respiratory tract infection between treatment and placebo group.[36]. However, some minor differences exist among some experts' in the field regarding the risk of COVID-19 infection in patients taking teriflunomide.[9,13,15,19]

The precise mechanism of action of dimethyl fumarate is unclear. It is believed to activate nuclear factor erythroid-derived 2-related factor 2, a transcription factor. Dimethyl fumarate decreases absolute lymphocyte counts and altered the proportion of lymphocyte subsets toward an anti-inflammatory state. Reduction of CD8+ T-lymphocytes was more marked than that of other lymphocyte subsets in MS patients treated with dimethyl fumarate.[37] An integrated analysis of phase 2b/3/long-term extension studies showed that the mean total lymphocyte count decreased by 30% during the first year of dimethyl fumarate therapy and subsequently

stabilized.[38] However, the incidences of infection among treatment groups and placebo were not significantly different; even when stratified by total lymphocyte counts or T-cell subset frequency.[37,39] Similar to teriflunomide, only minor differences exist between experts regarding the risk of COVID-19 infection in patients taking dimethyl fumarate.[9,13,15,19]

Fingolimod and siponimod bind to sphingosine-1 phosphate receptors (S1PR) on T-cells preventing lymphocyte egression from the lymph nodes into the circulation, leading to sequestration of T-cells in lymph nodes. After one month of fingolimod, circulating lymphocyte count were reduced significantly.[40] A subsequent study demonstrated the redistribution of lymphocyte subset – increased natural killer cells and decreased CD4+ T-lymphocytes.[41] An integrated analysis of long-term data from phase2/3 studies did not show a significant difference in the incidences of infections between the fingolimod and the placebo group.[42] In a phase 3 study, 1% of patients treated with siponimod developed lymphopenia. The adverse events related to infection were similar between the siponimod and placebo group except for herpes zoster reactivation (2% in siponimod, and 1% in placebo).[43] However, experts from national MS societies have raised a concern that fingolimod[9,13-15,19] and siponimod[15,19] may elevate the risk of COVID-19 infection. On the other hand, there is an ongoing Phase 2 clinical trial evaluating fingolimod for the prevention of ARDS in COVID-19 infection (ClinicalTrials.gov Identifier NCT04280588).

Natalizumab reduced the migration of leukocytes from the blood to CNS by disrupting the interaction between α4 integrins and vascular cell adhesion molecule 1. As a result, circulating T and B-lymphocytes are increased.[44] In phase 3 clinical trial, the overall incidences of infection had no difference between treatment and placebo groups. Serious infections,

including severe pneumonia and urosepsis, were reported in 3.2% of patients with natalizumab and 2.6% in placebo.[45] However, experts agree that natalizumab should not significantly increase the risk of COVID-19 infection.[9,13,19] Furthermore, the ABN views natalizumab as a safe option for high-efficacy therapy for COVID-19 pandemic.[14]

Ocrelizumab and rituximab are monoclonal antibodies that deplete CD20+ B-lymphocytes. Ocrelizumab has been approved by the US Food and Drug Administration for both relapsing-remitting and primary progressive MS. On the other hand, rituximab is currently used off-label in various immune-mediated neurologic disorders, including MS. The median time to B-lymphocyte replenishment for ocrelizumab is 72 weeks.[46] In rituximab, B-lymphocyte repopulation has a considerable intraindividual variation with the lowest and the average intervals being 3.6 and 8.3 months, respectively.[47] Because of the prolonged B-lymphocyte depletion, all expert panels are concerned about the increased risk of infection in both ocrelizumab[9,13-15,19] and rituximab[15,19] during this outbreak.

Alemtuzumab depletes circulating CD52+ lymphocytes and has reprogramming effects on tolerogenic networks of the immune system. CD8+ T-lymphocytes and B-lymphocytes restorations take approximately 3 and 6 months, respectively. Repopulation of CD4+ may take up to 1-2 years.[48] A pooled analysis of 6-year data from 3 randomized trials showed that the overall infection risk with alemtuzumab decreases over time. However, lymphocyte count after alemtuzumab cannot predict the risk.[49] Like B-cell depleting therapies, experts agree that alemtuzumab possesses a concern for increased risk of COVID-19 infection because of its immunosuppressive effect during the first months post infusion.[9,13-15,19]

Cladribine is a deoxyadenosine analogue prodrug. After it is taken up by cells, it is phosphorylated to an active form, which causes DNA strand breakage leading to cell death. Cladribine reduces total lymphocyte counts. The depletion of B-lymphocytes is markedly more than T-lymphocytes. After discontinuation, 75% of patients have normal lymphocyte counts at week 144.[50] Thus, there is a concern of increased infection risk, at least during periods of lymphopenia, in this pandemic with cladribine.[9,13-15,19]

At this moment, there are several ongoing registries collecting the data of COVID-19 infection in MS patients such as COViMS-19 (https://www.covims.org/) in North America and MuSC-19 (https://musc-19.dibris.unige.it/) in Italy. Additionally, data from the registry for all COVID-19 patients, such as LEOSS (https://leoss.net/), will allow the researchers to compare COVID-19 infection rates between MS patients and other populations. We encourage clinicians to share data with these registries as these databases will be invaluable resources for the development of further recommendations.

Conclusion

Despite a lack of clinical studies, several international and national MS societies have provided expert opinions regarding DMT management during the current COVID-19 outbreak. There was no major disagreement among expert views. Notably, several DMTs can cause lymphopenia, and a recent cohort study showed that lymphopenia is a risk factor for ARDS in COVID-19 infection. The understanding of the immunopathogenesis of coronavirus infection, as well as the DMTs mechanism of action and their effects on the immune system, will assist in

clinical decision making. Data from the current ongoing registries will provide evidence for future recommendations.

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References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382:727-733.
2. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Published 2020. Accessed March 19, 2020.
3. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18:459-480.
4. Multiple Sclerosis International Federation. The coronavirus and MS – global advice. https://www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/. Published 2020. Updated March 18, 2020. Accessed April 14, 2020.
5. Filippi M, Hochmeister S, Oreja-Guevara C. Immunotherapy for patients with neuroimmunological disorders during the COVID-19 pandemic. https://www.ean.org/fileadmin/user_upload/ean/ean/EANcore_COVID-19/recommendations___guidelines/Guidelines_for_neurological_disorders_immuntherapy_and_COVID19_final.pdf. Published 2020. Accessed April 14, 2020.
6. European Multiple Sclerosis Platform. Coronavirus disease (COVID-19) and MS. http://www.emsp.org/news-messages/coronavirus-disease-covid-19-and-multiple-sclerosis/. Published 2020. Accessed April 14, 2020, 2020.

7. Multiple Sclerosis Australia. COVID-19 information for people with MS. https://www.msaustralia.org.au/about-ms/covid-19-information-people-ms. Published 2020. Accessed April 14, 2020.

8. Conseil Médico-Scientifique (CMS), Comité Inter-Régional Médical de l'ARSEP (CIRMA) de la Fondation ARSEP, Centres de Ressource et de Compétence SEP (CRC-SEP), Conseil d'Administration de la Société Francophone de la SEP (SF-SEP), Ligue Française contre la SEP (LFSEP), Centre de Référence des Maladies Inflammatoires Rares du Cerveau Et de la Moelle (MIRCEM). General instructions to limit the risks of contagion by the COVID -19 virus in people with MS, NMO or other demyelinating pathologies at risk of severe infection. https://sfsep.org/conseils-a-propos-du-covid-19-pour-les-personnes-atteintes-de-sep/. Published 2020. Accessed April 14, 2020.

9. Multiple Sclerosis Society of Ireland. COVID-19 AND MS. https://www.ms-society.ie/covid-19-and-ms. Published 2020. Accessed April 14, 2020.

10. Associazione Italiana Sclerosi Multipla. Information on the management of the patient with MS during the epidemic of COVID-19 https://www.aism.it/sites/default/files/ComunicazioneGdSSINSM-Coronavirus.pdf. Published 2020. Accessed April 14, 2020.

11. Mason D, Boggild M, van der Walt HB, et al. [Updated] COVID-19 – Advice for Patients. https://www.msnz.org.nz/covid-19-advice-for-patients/. Published 2020. Accessed April 14, 2020.

12. Esclerosis Múltiple España. Recommendations on the coronavirus COVID-19 for people with Multiple Sclerosis. https://www.esclerosismultiple.com/el-coronavirus-y-la-esclerosis-multiple-lo-que-necesita-saber/. Published 2020. Accessed April 14, 2020.

13. Swiss Multiple Sclerosis Society. MS and COVID-19: Recommendations for Switzerland. https://www.multiplesklerose.ch/de/aktuelles/detail/ms-und-covid-19-empfehlungen-fuer-die-schweiz/#a_genauere-ausfuehrungen-zu-ms-medikamenten. Published 2020. Updated March 17, 2020. Accessed April 14, 2020, 2020.

14. Coles A, Lim M, Giovannoi G, Anderson P, Dorsey-Campbell R, Qualie M. ABN guidance on the use of disease-modifying therapies in multiple sclerosis in response to the threat of a coronavirus epidemic. https://cdn.ymaws.com/www.theabn.org/resource/collection/65C334C7-30FA-45DB-93AA-74B3A3A20293/02.04.20_ABN_Guidance_on_DMTs_for_MS_and_COVID19_VERSION_4_April_2nd.pdf. Published 2020. Accessed April 14, 2020.

15. Multiple Sclerosis Society. COVID-19 coronavirus and MS treatments. https://www.mssociety.org.uk/about-ms/treatments-and-therapies/disease-modifying-therapies/covid-19-coronavirus-and-ms. Published 2020. Accessed April 14, 2020.

16. Brazilian Multiple Sclerosis Association. COVID-19 global advice for people with MS. http://abem.org.br/27253-2/?fbclid=IwAR2NCBfORBy1sy9D-WgcXV44Y4zxUWYaZy4Fv98ZvL4og5t2lOVFrg53dxo. Published 2020. Accessed April 14, 2020.

17. Miyazaki Y. Multiple Sclerosis United Nations (MSIF) announces "advice for multiple sclerosis patients about new coronavirus. http://www.neuroimmunology.jp/jpn/news/COVID19_20200315.pdf. Published 2020. Accessed April 14, 2020.

18. Stichting MS Research. Worldwide COVID-19 advice for people with MS. https://msresearch.nl/wereldwijd-covid-19-advies-voor-mensen-met-ms?utm_source=Aanmelding+nieuwsbrief+MS+Research&utm_campaign=acf90a9f4c-EMAIL_CAMPAIGN_2020_03_16_09_24&utm_medium=email&utm_term=0_ec75ab155f-acf90a9f4c-147715973. Published 2020. Accessed April 14, 2020.

19. National Multiple Sclerosis Society. Guidance for the use of disease modifying therapies during the COVID-19 pandemic. https://www.nationalmssociety.org/What-you-need-to-know-about-Coronavirus-(COVID-19)/DMT-Guidelines-for-Coronavirus-(COVID-19)-and. Published 2020. Accessed April 14, 2020.

20. McIntosh K, Chao RK, Krause HE, Wasil R, Mocega HE, Mufson MA. Coronavirus infection in acute lower respiratory tract disease of infants. *J Infect Dis.* 1974;130:502-507.

21. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet.* 2003;361:1319-1325.

22. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012;367:1814-1820.

23. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497-506.

24. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.* 2020.

25. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect.* 2020;9:221-236.

26. Fung SY, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. *Emerg Microbes Infect.* 2020;9:558-570.

27. Wong LY, Lui PY, Jin DY. A molecular arms race between host innate antiviral response and emerging human coronaviruses. *Virol Sin.* 2016;31:12-23.

28. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe.* 2016;19:181-193.

29. Li CK, Wu H, Yan H, et al. T cell responses to whole SARS coronavirus in humans. *J Immunol.* 2008;181:5490-5500.

30. Winkelmann A, Loebermann M, Reisinger EC, Hartung HP, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol.* 2016;12:217-233.

31. Rieckmann P, O'Connor P, Francis GS, Wetherill G, Alteri E. Haematological effects of interferon-beta-1a (Rebif) therapy in multiple sclerosis. *Drug Saf.* 2004;27:745-756.

32. Tan EL, Ooi EE, Lin CY, et al. Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. *Emerg Infect Dis.* 2004;10:581-586.

33. Weber MS, Hohlfeld R, Zamvil SS. Mechanism of action of glatiramer acetate in treatment of multiple sclerosis. *Neurotherapeutics.* 2007;4:647-653.

34. Fox EJ, Buckle GJ, Singer B, Singh V, Boster A. Lymphopenia and DMTs for relapsing forms of MS. *Neurology Clin Pract.* 2019;9:53.

35. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and its mechanism of action in multiple sclerosis. *Drugs.* 2014;74:659-674.

36. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2014;13:247-256.

37. Berkovich R, Weiner LP. Effects of dimethyl fumarate on lymphocyte subsets. *Mult Scler Relat Disord.* 2015;4:339-341.

38. Fox RJ, Chan A, Gold R, et al. Characterizing absolute lymphocyte count profiles in dimethyl fumarate-treated patients with MS: Patient management considerations. *Neurol Clin Pract.* 2016;6:220-229.

39. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med.* 2012;367:1098-1107.

40. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010;362:402-415.

41. Rudnicka J, Czerwiec M, Grywalska E, et al. Influence of fingolimod on basic lymphocyte subsets frequencies in the peripheral blood of multiple sclerosis patients - preliminary study. *Cent Eur J Immunol.* 2015;40:354-359.

42. Kappos L, Cohen J, Collins W, et al. Fingolimod in relapsing multiple sclerosis: An integrated analysis of safety findings. *Mult Scler Relat Disord.* 2014;3:494-504.

43. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391:1263-1273.

44. Koudriavtseva T, Sbardella E, Trento E, Bordignon V, D'Agosto G, Cordiali-Fei P. Long-term follow-up of peripheral lymphocyte subsets in a cohort of multiple sclerosis patients treated with natalizumab. *Clin Exp Immunol.* 2014;176:320-326.

45. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med.* 2006;354:899-910.

46. Mulero P, Midaglia L, Montalban X. Ocrelizumab: a new milestone in multiple sclerosis therapy. *Ther Adv Neurol Disord.* 2018;11:1756286418773025.

47. Ellwardt E, Ellwardt L, Bittner S, Zipp F. Monitoring B-cell repopulation after depletion therapy in neurologic patients. *Neurol Neuroimmunol Neuroinflamm.* 2018;5:e463.

48. Zhang X, Tao Y, Chopra M, et al. Differential reconstitution of T cell subsets following immunodepleting treatment with alemtuzumab (anti-CD52 monoclonal antibody) in patients with relapsing-remitting multiple sclerosis. *J Immunol.* 2013;191:5867-5874.

49. Wray S, Havrdova E, Snydman DR, et al. Infection risk with alemtuzumab decreases over time: pooled analysis of 6-year data from the CAMMS223, CARE-MS I, and

CARE-MS II studies and the CAMMS03409 extension study. *Mult Scler.* 2019;25:1605-1617.

50. Deeks ED. Cladribine tablets: a review in relapsing MS. *CNS Drugs.* 2018;32:785-796.

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Table 1. **Summary of the recommendations regarding disease-modifying therapies**

Clinical situation	Summary of recommendations
Newly diagnosed with MS	• Start DMT after discussing individual risk and benefit,[19] preferably IFNs, glatiramer acetate, and natalizumab.[4,6,7] • Avoid or delay starting cell-depleting DMTs such as alemtuzumab, anti-CD20 monoclonal antibodies, and cladribine.[4-6,14] • Ocrelizumab may be considered in patients requiring high-efficacy therapy who contraindicated to natalizumab.[14] • The expert opinions regarding teriflunomide and dimethyl fumarate are different.[6,14,15,19]
Patients currently taking a DMT	• Discussing individual risk and benefit of DMTs • Continue the current DMT [4-11,13-15,19] • Consider extended interval dosing for cell-depleting therapies and natalizumab[4-10,13-15]
Patients with active COVID-19 infection	• Discussing individual risk and benefit • Holding all injectable and oral DMTs, as well as delaying cell-depleting DMTs[5,10,14] • May consider continuing IFN because of the potential anti-viral effect[10]

Abbreviations: MS: Multiple sclerosis; DMT: disease-modifying therapy; IFNs: interferons, COVID-19: a novel coronavirus

Table 2. **The expert opinions regarding the risk of novel coronavirus infection in patients with disease-modifying therapies**

	MS-Ireland	Swiss MSS	ABN	MSS-UK	NMSS
Interferons	↔	↔	↔	↔	↔
Glatiramer acetate	↔	↔	↔	↔	↔
Teriflunomide	↔	↑	↔	↔	↑
Dimethyl fumarate	↔	↑	↔	↔	↑
Fingolimod	↑	↑	↑	↑	↑
Siponimod	N/A	N/A	N/A	↑	↑
Natalizumab	↔	↔	N/A	N/A	↔
Ocrelizumab	↑	↑	↑	↑	↑
Rituximab	↑	N/A	N/A	↑	↑
Alemtuzumab	↑	↑	↑	↑	↑
Cladribine	↑	↑	↑	↑	↑

Abbreviation: ↔ not significantly increased; ↑ may increase; MS-Ireland: Multiple Sclerosis Society of Ireland; Swiss MSS: Swiss Multiple Sclerosis Society; ABN: Association of British Neurologist; MSS-UK: Multiple Sclerosis Society (United Kingdom); NMSS: National Multiple Sclerosis Society (United States); N/A: not available

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Table S1. **Search strategy**

Ovid/MEDLINE	1. exp Coronavirus/ or exp Coronavirus Infections/ 2. novel coronavirus 2019.mp. 3. 2019 ncov.mp. 4. COVID-19.mp. 5. Wuhan coronavirus.mp. 6. Wuhan pneumonia.mp. 7. SARS-CoV2.mp. 8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 9. exp multiple sclerosis/ 10. 8 AND 9
EMBASE	1. coronavirus OR 'coronavirus'/exp 2. 'novel coronavirus 2019' OR 'novel coronavirus 2019'/exp 3. '2019 ncov' 4. 'covid-19' OR 'covid 19'/exp 5. 'wuhan coronavirus' 6. 'wuhan pneumonia' 7. 'sars cov2' 8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 9. 'multiple sclerosis' OR 'multiple sclerosis'/exp 10. 8 AND 9
Cochrane databases	(coronavirus OR "novel coronavirus 2019" OR "2019 nCoV" OR "COVID-19" OR "Wuhan coronavirus" OR "Wuhan pneumonia" OR "SARS-CoV2") AND "Multiple sclerosis"
Google search	(coronavirus OR "novel coronavirus 2019" OR "2019 nCoV" OR "COVID-19" OR "Wuhan coronavirus" OR "Wuhan pneumonia" OR "SARS-CoV2") AND "Multiple sclerosis"

Table S2. **International and national multiple sclerosis associations and their websites**

Country/ Region	Organization	Website
Global	Multiple Sclerosis International Federation	https://www.msif.org
Europe	European Academy of Neurology	https://www.ean.org/
Europe	European Multiple Sclerosis Platform	http:/www.emsp.org
Australia	Multiple Sclerosis Australia	https://www.msaustralia.org.au/
Brazil	Brazilian Multiple Sclerosis Association	http://abem.org.br/
France	Francophone Society of Multiple Sclerosis	https://sfsep.org/
Ireland	Multiple Sclerosis Society of Ireland	https://www.ms-society.ie/
Italy	Italian Multiple Sclerosis Association	https://www.aism.it/
Japan	The Japanese Society of Neuroimmunology	http://www.neuroimmunology.jp/
New Zealand	Multiple Sclerosis Society of New Zealand	https://www.msnz.org.nz/
Spain	Multiple Sclerosis Spain	https://www.esclerosismultiple.com/
Switzerland	Swiss Multiple Sclerosis Society	https://www.multiplesklerose.ch/
The Netherlands	Stichting MS Research	https://msresearch.nl/
United Kingdom	Association of British Neurologist	https://www.theabn.org/
United Kingdom	Multiple Sclerosis Society	https://www.mssociety.org.uk/
United States	National Multiple Sclerosis Society	http://www.nationalmssociety.org/

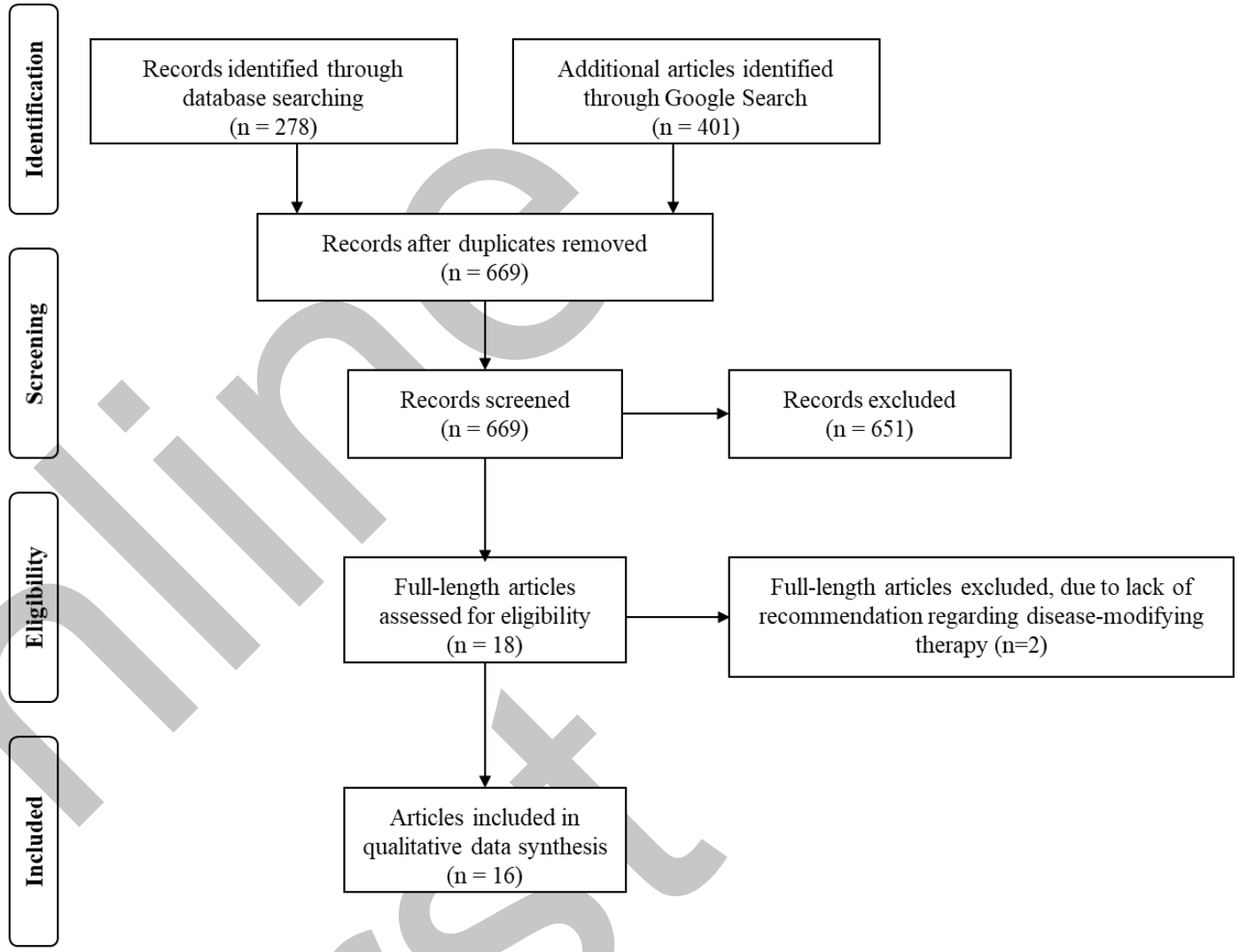

Figure S1. **Flow diagram of literature search result, article screening, and article inclusion numbers**