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REVIEW

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Impact of disease-modifying drugs on the severity of COVID-19 infection in multiple sclerosis patients

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Abstract

Recent evidence suggested that neurological manifestations occur in patients with a severe form of coronavirus disease (COVID-19). On the basis of this issue, neurologists are very concerned about patients with neurological disorders, especially multiple sclerosis (MS), as consumers of immunosuppressive or immune-modulating drugs. Therefore, the administration of proper disease-modifying therapies (DMTs) in MS patients is critical during the pandemic status. On the one hand, both the autoimmune diseases and immunosuppressive drugs increase the risk of infection due to impairment in the immune system, and on the other hand, postponing of MS treatment has serious consequences on the central nervous system. In the present study, we discussed recent literature about the effect of DMTs administration on the severity of COVID-19 in the MS patients. Overall, it seems that DMTs do not provoke the COVID-19 infection in the MS patients by declining immune responses and cytokine storm. However, as a precaution, the supervision of a neurologist is highly recommended.

KEYWORDS

coronavirus, immune system, nervous system

1 | INTRODUCTION

Coronavirus, a causative agent of human COVID-19, has been determined as a global pandemic by the World Health Organization (WHO), which has spread rapidly to many countries around the world.[1] The first report of patients with severe pneumonia was provided by Zhu et al. in January 2020. They described that patients with pneumonia of an unknown cause were epidemiologically linked to a seafood and wet animal wholesale market in the Wuhan province of China.[2] More than 316,732 patients around the world have died from COVID-19, which has become a global fear among the community.

Coronavirus related to COVID-19 is related to a family of betacoronavirus and the same subgenus of SARS-CoV-1 that causes severe acute respiratory syndrome (SARS). On the basis of this similarity, the novel coronavirus (nCoV) was named SARS-CoV-2.[1] Despite the similarity between SARS-CoV-2 and betacoronavirus that have been detected in bats, the nCoV is certainly different from SARS-CoV-1 and the Middle East respiratory syndrome coronavirus (MERS-CoV).[3] It seems that SARS-CoV-2 is matched on the binding site of the human angiotensin-converting enzyme 2 (hACE-2) receptor, which acquires the ability to enter the cells.[1] Viral entry into the lung causes pneumonia, which further results in mild-to-severe COVID-19. The mortality rate of COVID-19 is between 1% and 5%, and elderly patients with comorbidities and immune system deficiency are more susceptible to nCoV.[1,4]

The high expression level of hACE-2 in the olfactory bulb has been proposed as a potential mechanism for coronavirus dissemination in the central nervous system (CNS).[2] Recently, it has been indicated that 36.4% of patients with COVID-19 develop some neurologic symptoms like headache, epilepsy, paresthesia, disturbed consciousness, anosmia, and dysgeusia.[5–7] In some patients, the neurological symptoms are the first signs that occur.[7] Patients with a severe form of COVID-19 most likely show neurological manifestations.[6–8] The first case of a COVID-19 patient with acute necrotizing encephalopathy manifestation[9] has strengthened this hypothesis. Autopsy data from patients who died from COVID-19 also revealed brain edema and partial neuronal degeneration.[10] Furthermore,

genomic sequencing showed the presence of SARS-CoV-2 in the cerebrospinal fluid of patients.[11] Therefore, any pathogenicity that impairs the integrity of the blood–brain barrier may increase the neurological involvement in COVID-19 patients.

To increase the survival of COVID-19 patients with concomitant neurological diseases, especially MS patients, neurologists are looking for effective therapies. Theoretically, MS patients as consumers of immunosuppressive or immune-modulating drugs are at a higher risk for COVID-19.[12] Therefore, the selection of a proper drug to start or continue MS therapies is very important for reducing mortality and morbidity in the MS patients with COVID-19.

In the present review article, we aim to discuss recent reports about the effect of various disease-modifying therapies (DMTs) on the severity of COVID-19 or even prevention of its progression in MS patients.

2 | IMMUNE RESPONSES IN COVID-19 CASES

The immune responses against coronavirus include innate and adaptive immunities. The innate immunity is the first response in the circulatory system and peripheral tissue, especially lung alveolar.[13] Lymphopenia and cytokine storm are the major hallmarks of patients with a severe form of COVID-19. Recently, a lower level of T-helper (Th) cells, dysregulation between Th1 and Th2, and an increased level of naïve Th cells have been reported in COVID-19 patients. In addition to lymphocytes, higher levels of B cells, innate immune cells, and inflammatory cytokines have also been found in severe cases of COVID-19.[14,15] In this regard, the levels of antinucleocapsid and antispike protein antibodies were enhanced in the circulatory system of COVID-19 cases. A previous report has indicated that the risk of COVID-19 infection increases in individuals with X-linked agammaglobulinemia. This evidence indicates that B-cell activity is not indispensable for protection against SARS-CoV-2 infection.[16] A recent study on 99 patients with COVID-19 showed the elevation of neutrophils (38%), IL-6 (52%), and C-reactive protein (CRP; 84%) versus reduced total lymphocytes (35%).[15] Other cytokines such as IL-10, IL-2R, and TNF-α have also been observed to be drastically elevated in the severe form of COVID-19.[17]

3 | THE POTENTIAL RISK OF INFECTION IN MS PATIENTS

Both autoimmune diseases and immunosuppressive drugs increase the risk of infection due to impairment in the immune system. Although the use of immunosuppressive drugs was a major leap in the control of MS progression, but due to the nature of these drugs, MS patients are at a higher risk of bacterial, fungal, parasitic, and viral infections. Studies revealed that immunosuppressive drugs increase the risk of hepatitis B virus, hepatitis C virus, cytomegalovirus, and herpes virus by leukocytosis, lymphopenia, lymphoid redistribution, and diminishing immune surveillance in the CNS.[18] Therefore, the inflammatory status of patients before drug administration, during consumption, and at the end of treatment should be precisely monitored.[18] It should be also noted that other factors such as older age, sex, worse physical disability, and lower concomitant status increase the risk of infection and hospitalization in MS patients.[18,19] In the current situation where COVID-19 has rapidly spread around the world, it could theoretically be admitted that MS patients are at a higher risk of infection and health anxiety.[20] Furthermore, during the COVID-19 crisis, the access of MS patients to their therapist teams, psychologists, and physiotherapists is restricted, which exacerbates the severity of the disease. To reduce the mental and physical impairments in MS patients, it has been suggested that regular exercise, yoga, and other therapeutic options such as online support are very helpful during the pandemic condition. However, the lack of pragmatic methods raises the concern of neurologists about severe infections in the MS patients.[20]

4 | THE EFFECT OF DMTS ON MS PATIENTS WITH COVID-19

We have performed a PubMed search to find articles, which have been published recently (2019–2020), about the effect of DMTs on the severity of COVID-19 in MS patients.

Fingolimod (FTY720) as an agonist of sphingosine-1-phosphate (S1P) receptor internalizes S1P and leads to the redistribution of lymphocytes, thus reducing their entry into the CNS.[21] It has not been reported that FTY720 increases the infectionary rate in participants enrolled in the initial multisite randomized phase 3 controlled trials,[22] but post-marketing surveillance suggested that long-term consumption of FTY720 may increase the risk of several infections.[23]

Foerch et al. reported a 58-year-old female relapsing–remitting multiple sclerosis (RRMS) patient with severe COVID-19 infection under FTY720 treatment. Five days after stopping FTY720 and performing the necessary medical care in the intensive care unit (ICU), the patient was transferred to a normal ward. It has been suggested that FTY720 has complex effects on COVID-19 through S1P receptor. It has been shown that S1P receptor is an angiogenic factor that improves endothelial integrity, vascular permeability, and alveolar flooding. Furthermore, FTY720 as an immunosuppressive agent prevents cytokine storm by reducing naïve T cells and memory T cells. Hence, it might be considered as an effective therapy for reducing the mortality rate of COVID-19 cases.[24]

Barzegar and colleagues reported a 61-year-old female RRMS patient under FTY720 therapy. The patient was transferred to the hospital after the symptoms of relapse or pseudoexacerbation and clinical and paraclinical findings of COVID-19. Clinicians speculated that the nCoV was likely to cause pseudoexacerbation or relapse without a clear etiology in the MS case. Despite multiple comorbidities in this patient, the COVID-19 infection was resolved with a favorable outcome.[25] It seems that MS and FTY720 consumption did not complicate the treatment procedure in COVID-19 patients.

Furthermore, previous studies revealed that discontinuation of immunotherapies such as FTY720 leads to rebound MS disease activity.[26] Therefore, FTY720 cessation may initiate severe relapse in MS patients with COVID-19.

Valencia-Sanchez et al. reported a 58-year-old female patient with RRMS who was hospitalized in the ICU due to acute respiratory distress syndrome (ARDS). FTY720 as a main used drug in the last 4 years was stopped and one dose of tocilizumab was administered intravenously. As a result, the levels of IL-6, CRP, ferritin, D-dimer, and lactate dehydrogenase were dramatically enhanced in the patient. After more than 6 days, all the markers were reduced and there was an improvement in the infection. It has been suggested that FTY720 suppresses the immune system through egressing of lymphocytes from secondary lymphoid organs into the circulation and initiates the severe form of COVID-19.[27]

Borriello et al. reported a 48-year-old male RRMS patient under natalizumab treatment who tested positive for nCoV. They indicated that the patient recovered without any complications. After recovery, treatment was followed by extended interval dosing of natalizumab without any new symptoms.[28]

Novi et al. reported a 58-year-old male patient with primary progressive MS under periodic 6-month ocrelizumab infusions who developed COVID-19 symptoms. They indicated that despite B-cell depletion caused by ocrelizumab, the symptoms of the disease were significantly reduced few days after hospitalization. They suggested that the persistence of B cells in secondary lymphoid organs and reduction in peripheral B cells lead to moderate immune responses in ocrelizumab-treated patients.[29]

Carandini et al. reported a 28-year-old female RRMS patient under the second cycle of alemtuzumab treatment. The mentioned case showed mild symptoms of confirmed COVID-19 with normal oxygen saturation. Although due to the immunosuppressive effect of alemtuzumab, the blood test revealed severe leukopenia without elevation of inflammatory factors. This drug leads to the depletion of CD52-expressing cells and reduces the lymphocyte trafficking and activity after each course. However, the patient recovered 2 weeks later without hospitalization.[30] Despite the recent recommendations by Brownlee et al.,[31] about the prohibition of alemtuzumab infusion in the pandemic status, this patient did not show a severe form of COVID-19 infection. However, it should be noted that the patient was young and had no underlying disease other than MS.[30]

Guevara et al. published a case report about alemtuzumab treatment in 32-year-old male RRMS patient who was infused with alemtuzumab two and a half months before COVID-19 infection. Despite severe depletion of lymphocyte, B cells, and natural killer cells were normal and patient showed mild symptoms of COVID-19 infection. The patient stayed at home until he was recovered.[32]

Fernández-Díaz et al. revealed alemtuzumab as a safe drug in two young RRMS patients under COVID-19 infection. Both patients (a female aged 30 and a male aged 43) showed mild clinical symptoms of COVID-19. However, one of them due to a significant immunosuppression state was hospitalized. They reported that in the male patient, $CD8^+$-T cells and $CD4^+$-T cells were increased after infection, and in the female patient, monocytes and neutrophils were enhanced during the acute phase of the infection. They suggested that these immune cells respond adequately to SARS-CoV-2.[33]

Maghzi et al. reported a case series of five RRMS patients ($n = 2$ females and $n = 3$ males), in the age range of 38–79 years, under teriflunomide therapy. Two of them had other medical conditions such as hypertension, recurrent urinary tract infection, and depression. The patients showed mild symptoms of COVID-19 and all tested were positive by nasal swab. Their neurologist advised them to continue the intake of teriflunomide at the same dose. All of the patients gradually recovered without hospitalization.[34] Teriflunomide is an immune modulator drug that reduces immune activation without cell lysis and immunosuppression. The immune responses and cytokine storm as a common feature of COVID-19 infection were declined in the patients.[35]

In another case of RRMS patient under teriflunomide therapy, Möhn et al. reported a 42-year-old man who was admitted to the hospital due to sore throat, weakness, ataxia, nausea, and vomiting. The chest X-ray and urine analysis were normal, and inflammatory parameters were drastically increased. Brain magnetic resonance imaging showed a new T2 lesion within the right cerebellum, reflecting a new relapse. The patient received high-dose methylprednisolone, and 4 days later, he was ready to be discharged. However, the next day, he showed worse neurological symptoms, fever, and hypotension with increased IL-6 and ferritin. The nasal swab test confirmed COVID-19 infection. They assumed that the patient had both relapse and COVID-19 infection in the first admission. However, despite receiving a high dose of methylprednisolone and relapse therapy, he did not show a severe form of COVID-19.[36]

Mantero et al. reported a case series of six RRMS patients ($n = 4$ females and $n = 2$ males), in the age range of 37–57 years, under teriflunomide treatment. All of the patients showed a mild form of confirmed COVID-19 infection without lymphopenia, neutropenia, or leukopenia and recovered progressively in their house.[37]

Mantero et al. published another case series about seven RRMS patients ($n = 5$ females and $n = 2$ males), in the age range of 23–51 years, treated with dimethyl fumarate (DMF). All of them after showing the symptoms of dry cough, anosmia, ageusia, fever, asthenia, and shortness of breath were diagnosed with COVID-19 without confirmation by nasal swab and chest X-ray/computed tomography. They continued their therapy with DMF at the same dose. The symptoms gradually improved without severe lymphopenia, hospitalization, ICU care, and intubation.[38] Theoretically, DMF increases the risk of COVID-19 infection and severity due to the reduction of lymphocyte count. However, Brownlee et al.[31] have advised DMF as a safe drug during the COVID-19 pandemic. It seems that DMF as an immune modulator agent increases the memory T- and B-cell apoptosis, induces Th_1 to Th_2 shift, and protects from COVID-19 by reducing cytokine storm.[39,40]

Dersch et al. reported a 59-year-old male RRMS patient with cladribine therapy 2 weeks before COVID-19 infection. Despite severe lymphopenia after cladribine therapy and increased

inflammatory markers, patient showed mild-to-moderate symptoms of infection. Sixteen days after the onset of COVID-19 infection, the inflammatory markers were declined and clinical symptoms were resolved. However, the neurologist postponed the second cycle of cladribine infusion. Cladribine is an immunosuppressive drug that reduces the number of B and T cells (5), but cladribine did not cause a severe form of COVID-19 in the aforementioned report. It has been suggested that the severity of COVID-19 is not directly dependent on the virus, rather the host response and immune system over-activation damage different tissues by releasing cytokines.[41]

De Angelis et al. reported two RRMS patients (a female aged 61 and a male aged 29) under periodic cladribine infusions who developed COVID-19 infection. The young man showed mild symptoms of SARS-CoV-2 with lymphopenia; however, he fully recovered without hospitalization. The old woman had no symptoms of COVID-19 infection, but her test was positive for nasal swab SARS-CoV-2. Both patients were positive for anti-SARS-CoV-2 IgG antibodies. In this regard, it seems that cladribine does not increase the severity of COVID-19 and does not disturb anti-SARS-CoV-2 antibody production. Therefore, it has been suggested that cladribine could be considered as a proper drug in terms of COVID-19 vaccination.[42]

However, the conclusion of this issue may be reversed if addressed from another perspective. As mentioned above, the severity of COVID-19 is associated with the immune response to SARS-CoV-2. The invasion of inflammatory cytokines in systemic circulation causes damage to several tissues, especially lung. IL-6 is regarded as one of the principal cytokines that triggers the inflammatory cascade and leads to worse outcomes in COVID-19 patients.[43] Furthermore, IL-6 is involved in the pathogenicity of MS by stimulating T cells to produce IL-17.[44] It has even been reported that rheumatoid arthritis progressed to MS under repeated tocilizumab treatment.[45] Therefore, it seems that tocilizumab administration in MS patients with COVID-19 not only enhances the severity of COVID-19, but also exacerbates the MS-related neurological manifestations. Giovani et al. mentioned that immunosuppressive and immune modulator agents could mitigate the severity of COVID-19. They suggested that ARDS that occurs in a severe form of COVID-19 is an immune-mediated response. Therefore, reduced severe immune reactions against the virus could alleviate the mortality rate in MS patients under immunosuppressive treatment.[12] On the basis of this evidence, several routine drugs for MS patients are being evaluated to reduce the severity of COVID-19.

There are several drugs for MS treatment to prevent relapses and disability progression.[46] The mechanisms of these drugs are different and complex, and each of them may increase the risk of infection and reduce the response rate of patients to the therapies. Therefore, there are several recommendations for the treatment of the MS patients infected with COVID-19.

A recent study investigated the risk of infection in the MS patients under different DMTs including interferon-beta (IFN-β), glatiramer acetate, fingolimod, natalizumab, and rituximab. The increased risk of infection in patients under rituximab treatment and enhanced antibiotic use was observed in rituximab- and natalizumab-treated patients. There was no difference between patients receiving IFN-β, glatiramer acetate, and fingolimod and no exposure patients. Furthermore, natalizumab was the only drug associated with a higher risk of upper respiratory tract infection as compared with no exposure patients. None of the drugs have a significant association with infection-related hospitalization.[47] Therefore, it seems that DMTs, especially the first-generation drugs such as IFN-β and glatiramer acetate, are not related to severe infection in MS patients. However, very recent reports about the risk of COVID-19 infection in MS patients demonstrated that there is no correlation between incidences of COVID-19 in the MS patients.[48–50] However, Sahraian et al.[48] showed a higher risk of hospitalization in the MS patients infected by COVID-19 as compared with the general population.

IFN-β and glatiramer acetate are immune modulator drugs without any immunosuppressive effects. Therefore, these therapies are considered as safe drugs to start or continue treatment in MS patients. It has been shown that first-generation drugs do not interfere with response to the seasonal influenza vaccine.[51] Therefore, it seems promising that their administration will be unrestricted after the production of the SARS-CoV-2 vaccine.

Natalizimab has been introduced as an antagonist of α4 subunit of the cell adhesion molecule. It has been reported that "very late antigen 4" (VLA-4) has a partial effect on the suppression of the immune system.[46] However, it has been shown that natalizimab is a proper drug to start MS treatment in pandemic status, but previous studies have reported a higher risk of respiratory infection in natalizimab-receiving patients.[47,52,53] It has been postulated that reduced traffic of lymphocytes in the lungs and mucosa may increase the risk of respiratory infection. The treatment interval for natalizumab in MS patients is 4 weeks, but some studies revealed that no changes occur in MS patient's stability by extending the interval dosage to 8 weeks. Therefore, it has been recommended that the treatment interval for natalizumab should be 6 weeks in the pandemic situation.[28,51] Similarly, the interval between rituximab dosages could be increased from 6 months to 9–12 months.[51]

Rituximab and ocrelizumab as moderate immunosuppressive drugs have a remarkable effect on B-cell depletion.[4,54] In this regard, Safavi et al. reported that B cell-depleting antibodies increase the incidence of COVID-19 infection in MS patients. However, this infection was mild to moderate and there was no correlation between B cell-depleting antibodies and hospitalization.[55] In another study, Sahraian et al.[48] showed that rituximab enhances the rate of COVID-19 infection in the MS patients without any effect on the hospitalization rate. However, Crescenzo et al.[56] observed no correlation between specific DMT and a higher risk of COVID-19 in the MS patients. Furthermore, it should be noted that rituximab may impair the response to SARS-CoV-2 vaccine, as it has previously impaired the effect of seasonal influenza vaccine.[57,58]

The highest risk of infection is due to the immune reconstitution therapies during the depletion phase of the treatment.[57] Cladribine, alemtuzumab, and hematopoietic stem cell transplantation (HSCT) are the most important therapeutic approaches in this category. The mentioned therapies lead to complete lymphocyte depletion and increase the risk of viral infection until the total lymphocyte count reaches over

1.1×10^9/L, followed by which the infection rate may gradually decrease and reach the level of normal condition.[59] However, as mentioned above, MS patients under cladribine and alemtuzumab therapies show mild-to-moderate symptoms of COVID-19 infection.

5 | CONCLUSION

SARS-CoV-2 is a pandemic infection and may take several years to subside. In addition, at best, vaccine production may take 12–18 months. Therefore, failure to use the appropriate dose of the immunosuppressive drugs or postponing treatment of MS patients may have serious consequences on the CNS as a precious tissue. Therefore, patient's follow-up and observance of hygienic principles are the most important strategies to alleviate the SARS-CoV-2 infection rate in the MS patients. Patient's follow-up is especially important in patients who have been treated by HSCT, alemtuzumab, and cladribin, or have other risk factors such as ambulatory status, old age, overweight, cancer, diabetes, and heart failure.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Sahar Rostami Mansoor wrote the manuscript and Maryam Ghasemi-Kasman designed and supervised the study.

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REFERENCES

1. Mansoor S, Kelly S, Murphy K, Waters A, Siddiqui NS. COVID-19 pandemic and the risk of infection in multiple sclerosis patients on disease modifying therapies: "what the bleep do we know?". *Egypt J Neurol Psychiatr Neurosurg*. 2020;56:1–3.
2. 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.
3. Manji H, Carr AS, Brownlee WJ, Lunn MP. *Neurology in the Time of COVID-19*. BMJ Publishing Group Ltd; 2020.
4. Rejdak K, Grieb P. Adamantanes might be protective from COVID-19 in patients with neurological diseases: multiple sclerosis, parkinsonism and cognitive impairment. *Mult Scler Relat Disord*. 2020;42:102163.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
6. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun*. 2020;87:18–22.
7. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683.
8. Yavarpour-Bali H, Ghasemi-Kasman M. Update on neurological manifestations of COVID-19. *Life Sci*. 2020;257:118063.
9. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*. 2020;296:E119–E120.
10. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420–422.
11. Xiang P, Xu X, Gao L, Wang H, Xiong H, Li R. First case of 2019 novel coronavirus disease with encephalitis. *ChinaXiv*. 2020;202003:00015.
12. Giovannoni G. Anti-CD20 immunosuppressive disease-modifying therapies and COVID-19. *Mult Scler Relat Disord*. 2020;41:102135.
13. Baker D, Amor S, Kang AS, Schmierer K, Giovannoni G. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. *Mult Scler Relat Disord*. 2020;43:102174.
14. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate forms of coronavirus disease. *J Clin Invest*. 2019:137244.
15. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–273.
16. Soresina A, Moratto D, Chiarini M, et al. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. *Pediatr Allergy Immunol*. 2020;31:565–569.
17. Contentti EC, Correa J. Immunosuppression during the COVID-19 pandemic in neuromyelitis optica spectrum disorders patients: a new challenge. *Mult Scler Relat Disord*. 2020;41:102097.
18. Winkelmann A, Loebermann M, Reisinger EC, Hartung H-P, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol*. 2016;12(4):217–233.
19. Marrie RA, Elliott L, Marriott J, et al. Dramatically changing rates and reasons for hospitalization in multiple sclerosis. *Neurology*. 2014;83(10):929–937.
20. Akhoundi FH, Sahraian MA, Moghadasi AN. Neuropsychiatric and cognitive effects of the COVID-19 outbreak on multiple sclerosis patients. *Mult Scler Relat Disord*. 2020;41:102164.
21. Samudralwar RD, Spec A, Cross AH. Fingolimod and cryptococcosis: collision of immunomodulation with infectious disease. *Int J MS Care*. 2019;21:275–280.
22. Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387–401.
23. Arvin AM, Wolinsky JS, Kappos L, et al. Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management. *JAMA Neurol*. 2015;72(1):31–39.
24. Foerch C, Friedauer L, Bauer B, Wolf T, Adam EH. Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. *Mult Scler Relat Disord*. 2020;42:102180.
25. Barzegar M, Mirmosayyeb O, Nehzat N, et al. COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(4):e753.
26. Barry B, Erwin AA, Stevens J, Tornatore C. Fingolimod rebound: a review of the clinical experience and management considerations. *Neurol Ther*. 2019;8:1–10.
27. Valencia-Sanchez C, Wingerchuk DM. A fine balance: immunosuppression and immunotherapy in a patient with multiple sclerosis and COVID-19. *Mult Scler Relat Disord*. 2020;42:102182.
28. Borriello G, Ianniello A. COVID-19 occurring during natalizumab treatment: a case report in a patient with extended interval dosing approach. *Mult Scler Relat Disord*. 2020;41:102165.
29. Novi G, Mikulska M, Briano F, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? *Mult Scler Relat Disord*. 2020;42:102120.
30. Carandini T, Pietroboni AM, Sacchi L, et al. Alemtuzumab in multiple sclerosis during the COVID-19 pandemic: a mild uncomplicated infection despite intense immunosuppression. *Mult Scler*. 2020;26:1268–1269.

31. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology*. 2020;94:949–952.
32. Guevara C, Villa E, Cifuentes M, Naves R, de Grazia J. Mild COVID-19 infection in a patient with multiple sclerosis and severe depletion of T-lymphocyte subsets due to alemtuzumab. *Mult Scler Relat Disord*. 2020;44:102314.
33. Fernández-Díaz E, Gracia-Gil J, García-García JG, Palao M, Romero-Sánchez CM, Segura T. COVID-19 and multiple sclerosis: a description of two cases on alemtuzumab. *Mult Scler Relat Disord*. 2020;45:102402.
34. Maghzi AH, Houtchens MK, Preziosa P, et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. *J Neurol*. 2020;267:2790–2796.
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(6):659–674.
36. Möhn N, Saker F, Bonda V, et al. Mild COVID-19 symptoms despite treatment with teriflunomide and high-dose methylprednisolone due to multiple sclerosis relapse. *J Neurol*. 2020;267:2803–2805.
37. Mantero V, Baroncini D, Balgera R, et al. Mild COVID-19 infection in a group of teriflunomide-treated patients with multiple sclerosis. *J Neurol*. 2020:1–2.
38. Mantero V, Abate L, Basilico P, et al. COVID-19 in dimethyl fumarate-treated patients with multiple sclerosis. *J Neurol*. 2020:1–3.
39. Lückel C, Picard F, Raifer H, et al. IL-17+ CD8+ T cell suppression by dimethyl fumarate associates with clinical response in multiple sclerosis. *Nat Commun*. 2019;10(1):1–15.
40. Spencer CM, Crabtree-Hartman EC, Lehmann-Horn K, Cree BA, Zamvil SS. Reduction of CD8+ T lymphocytes in multiple sclerosis patients treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e76.
41. Dersch R, Wehrum T, Fähndrich S, Engelhardt M, Rauer S, Berger B. COVID-19 pneumonia in a multiple sclerosis patient with severe lymphopenia due to recent cladribine treatment. *Mult Scler*. 2020;26(10):1264–1266.
42. De Angelis M, Petracca M, Lanzillo R, Morra VB, Moccia M. Mild or no COVID-19 symptoms in cladribine-treated multiple sclerosis: two cases and implications for clinical practice. *Mult Scler Relat Disord*. 2020;45:102452.
43. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. 2020;92:814–818.
44. Serada S, Fujimoto M, Mihara M, et al. IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci U S A*. 2008;105(26):9041–9046.
45. Beauchemin P, Carruthers R. MS arising during tocilizumab therapy for rheumatoid arthritis. *Mult Scler*. 2016;22(2):254–256.
46. Finkelsztejn A. Multiple sclerosis: overview of disease-modifying agents. *Perspect Medicin Chem*. 2014;6:65–72.
47. Willis M, Robertson N. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. *J Neurol*. 2020;267(5):1567–1569.
48. Sahraian MA, Azimi A, Navardi S, Ala S, Moghadasi AN. Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102472.
49. Parrotta E, Kister I, Charvet L, et al. COVID-19 outcomes in MS: observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. *Neurolo Neuroimmunol Neuroinflamm*. 2020;7(5):e835.
50. Mantero V, Abate L, Balgera R, Basilico P, Salmaggi A, Cordano C. Assessing the susceptibility to acute respiratory illness COVID-19-related in a cohort of multiple sclerosis patients. *Mult Scler Relat Disord*. 2020;46:102453.
51. Holmøy T, Torkildsen Ø, Bø L. Treatment of multiple sclerosis under the COVID-19 pandemic. *Tidsskr Nor Laegeforen*. 2020;140:1–6
52. Kapoor R, Ho P-R, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *Lancet Neurol*. 2018;17(5):405–415.
53. 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(9):899–910.
54. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209–220.
55. 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.
56. Crescenzo F, Marastoni D, Bovo C, Calabrese M. Frequency and severity of COVID-19 in multiple sclerosis: a short single-site report from northern Italy. *Mult Scler Relat Disord*. 2020;44:102372.
57. Giovannoni G, Hawkes C, Lechner-Scott J, Levy M, Waubant E, Gold J. The COVID-19 pandemic and the use of MS disease-modifying therapies. *Mult Scler Relat Disord*. 2020;39:102073.
58. Stokmaier D, Winthrop K, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis. *Neurology*. 2018;90(15 suppl).
59. Warny M, Helby J, Nordestgaard BG, Birgens H, Bojesen SE. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. *PLOS Med*. 2018;15(11):e1002685.

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