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COMMENTARY

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Multiple sclerosis and COVID-19: How could therapeutic scenarios change during the pandemic?

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We read with great interest the review by Rostami Mansoor and Ghasemi-Kasman entitled "Impact of disease-modifying drugs on the severity of coronavirus disease 2019 (COVID-19) infection in multiple sclerosis patients" in your journal.[1] After examining the papers published on this topic, they conclude that it seems that disease-modifying drugs (DMTs) do not confer an increased risk or provoke COVID-19 infection in multiple sclerosis (MS) patients.

In this commentary, we want to focus the attention on the modification of prescribing habits by neurologists in MS patients during the pandemic. Case reports or case series of MS patients with COVID-19 in both first-line (teriflunomide and dymethil fumarate) and second-line treatment (fingolimod, natalizumab, ocrelizumab, alemtuzumab, and cladribine) have been reported in the literature.[2–13] Nevertheless, the risk and course of COVID-19 in patients with MS is unclear, and neurologists have to face different decisions when considering to initiate or continue therapies in these patients. Indeed, MS clinicians know that their patients are at a generally increased risk of infections and are twice as likely to be hospitalized for infections than the general population.[14]

At the beginning of the pandemic, Brownlee and colleagues[15] published a paper highlighting the implications of COVID-19 for people with MS and related disorders. The authors considered MS patients with and without COVID-19 infection. For MS patients with COVID-19 infection, the authors suggested that clinicians consider stopping highly immunosuppressive treatments in patients who have risk factors for severe COVID-19 disease, have severe symptoms, or have a complicated COVID-19 infection. On the other hand, they suggested continuing treatment in those with documented mild COVID-19 infection. For patients without COVID-19 infection, they speculated that therapies with immunosuppressive effects and alterations in lymphocyte number, trafficking, proliferation, and function might predispose to a greater risk of COVID-19 infection and potentially more severe infection. The authors suggest to continue the therapies with a low risk of systemic immunosuppression, monitor blood test, consider transitioning to extended-interval dosing for anti-CD20 agents, consider avoiding initiation of or delaying current use of cladribine and alemtuzumab (considered at high risk of systemic immunosuppression).

More recently, Giovannoni et al.[16] affirmed that it is essential to consider the potential risk of morbidity and possible mortality for each MS patient, pondering the individual's multifactorial risk profile. Any decision to initiate a DMT during the COVID-19 pandemic will need to be made carefully, considering the COVID-19 pandemic status. However, they suggested suspending a dose of alemtuzumab and assessing anti-CD20 and cladribine risk, considering suspending dosing.

Hamdy and colleagues suggested that, in patients with active COVID-19 infection, it is mandatory to stop all DMTs, and the timing of resuming treatment is not well defined.[17]

In a recent work by the Italian MS group, a large majority of deaths occurred in patients with advanced disease and disability due to MS, and anti-CD20 treatment was associated with a higher risk of developing COVID-19 symptoms and severe COVID-19 course, with an association with treatment duration. Moreover, methylprednisolone in the month preceding COVID-19 infection was significantly associated with a worse disease outcome.[18] Even Safavi et al.[19] reported that B-cell depleting antibodies might increase susceptibility to acute respiratory illness in MS patients. In a pharmacovigilance-based case series of 100 COVID-19 patients treated with ocrelizumab, 28 of them presented a severe or critical course of infection.[20]

Our group has recently published data from our patients in the first phase of the pandemic in Italy (from March to May 2020).[21] At that time, 15 of 275 patients reported symptoms suggestive of COVID-19 infection; 14 patients were qualified by their reported symptoms and one patient reported a positive PCR test. They all improved without receiving any specific treatment; none of them required hospitalization, intensive care unit, or intubation. No patients had to change/delay the ongoing treatment in our cohort.

However, this pandemic has undoubtedly changed the way many neurologists treat MS patients. The risk of new waves of pandemics may make neuro-immunologists more prudent in choosing drugs for their at-risk patients, particularly if the therapies have a higher toxicity profile and are less manageable. The second-line drug that indeed finds the most benefit at the moment is natalizumab, which appears to be the safest for its mechanism of action due to the low risk of systemic immunosuppression. Brownlee et al.[15] recommend that wherever there is a need for a high-efficacy treatment, starting or switching to natalizumab is preferable to alemtuzumab, cladribine, or ocrelizumab because the risk of systemic immunosuppression is low and prolonged lymphocyte depletion does not occur. Giovannoni et al.[16] considered natalizumab low risk, but the authors raised theoretical concerns of creating an environment in mucosal surfaces and the gut with a danger of prolonged viral shedding.

Another problem we wish to focus on is the flu-like syndrome (as fever, muscle aches, chills, and fatigue), which is known to be associated with some drugs for MS treatment, particularly interferons. Today in Italy, as in other countries, to go to work and in restaurants and bars, body temperature measurement is required. How can patients with flu-like syndrome solve this problem? Will they lose more business days? Will they have less adherence to the drug? Neurologists should be careful in evaluating these implications and be ready to vary therapy if necessary and indicated.

To conclude, the therapeutic scenario for MS has certainly changed with the pandemic, and probably also in the future, the attitude of neurologists will be different. However, in the past, we were already used to changing our habits with other infectious diseases. For example, when the correlation between natalizumab and progressive multifocal leukoencephalopathy was discovered, the quantification of anti-JCV antibodies was introduced; or, after cases of chickenpox virus infection identified after fingolomod administration in patients with absent varicella-zoster virus antibodies, the VZV vaccination was required before use.

As suggested by Giovannoni et al.,[16] the COVID-19 pandemic may trigger a large number of neurologists and patients to reconsider the treatment strategy and opt for less effective DMTs, but we must not forget the goal of treatment. Therefore, it is necessary to always use the most suitable drug for the patient while paying attention to safety. Relying on safety alone can do long-term harm to patients.

CONFLICT OF INTERESTS

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

1. Rostami Mansoor S, Ghasemi-Kasman M. Impact of disease-modifying drugs on severity of COVID-19 infection in multiple sclerosis patients. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.26593
2. Maghzi AH, Houtchens MK, Preziosa P, et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. *J Neurol*. 2020;267:2790-2796.
3. Mantero V, Abate L, Basilico P, et al. COVID-19 in dimethyl fumarate-treated patients with multiple sclerosis [published online ahead of print June 25, 2020]. J Neurol. 1–3. https://doi.org/10.1007/s00415-020-10015-1
4. Mantero V, Baroncini D, Balgera R, et al. Mild COVID-19 infection in a group of teriflunomide-treated patients with multiple sclerosis [published online ahead of print August 31, 2020]. J Neurol. 1–2. https://doi.org/10.1007/s00415-020-10196-9
5. 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.
6. 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:e753.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. Wijnands JM, Kingwell E, Zhu F, et al. Infection-related health care utilization among people with and without multiple sclerosis. *Mult Scler*. 2017;23:1506-1516.
15. 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.
16. 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 [published online ahead of print March 27, 2020]. Mult Scler Relat Disord. 39 102073https://doi.org/10.1016/j.msard.2020.102073
17. Hamdy SM, Abdel-Naseer M, Shehata HS, et al. Managing disease-modifying therapies and breakthrough activity in multiple sclerosis patients during the COVID-19 pandemic: toward an optimized approach. *Ther Clin Risk Manag*. 2020;16:651-662.
18. Sormani MP, Rossi ND, Schiavetti I, Musc-19 Study Group, et al. Disease Modifying Therapies and COVID-19 Severity in Multiple Sclerosis. SSRN: https://www.ssrn.com/abstract=3631244. https://doi.org/10.2139/ssrn.3631244. Accessed June 15, 2020.

19. 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. https://doi.org/10.1016/j.msard.2020.102195
20. Hughes R, Pedotti R, Koendgen H. COVID-19 in persons with multiple sclerosis treated with ocrelizumab—a pharmacovigilance case series. *Mult Scler Relat Disord*. 2020;42:102192. https://doi.org/10.1016/j.msard.2020.102192
21. 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. https://doi.org/10.1016/j.msard.2020.102453

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