SHORT COMMUNICATION

Outcome of COVID-19 infection in multiple sclerosis patients receiving disease-modifying therapies

Masoud Etemadifar[1], Ramin Sami[2], Mehri Salari[3], Nahad Sedaghat[4], Amirhossein Akhavan Sigari[4], Ali Aghababaei[5], Mohammadreza Najafi[6], Donya Sheibani Tehrani[7]

[1]Department of Neurosurgery, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Internal Medicine, Khorshid University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Neurology, Shahid Beheshti University, Tehran, Iran, [4]Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [5]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [6]Department of Neurology, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [7]Faculty of Computer Science and Engineering, Shahid Beheshti University, Tehran, Iran

Background: With the spread of COVID-19, treatment of diseases such as multiple sclerosis (MS) should be resumed with caution due to the disease-modifying therapies (DMTs) used in this subset of patients and the immunoregulatory effects of these drugs. We aim to assess the outcome of COVID-19 infection in MS patients receiving DMTs. **Materials and Methods:** This is a cross-sectional study involving 45 COVID-19-infected patients previously diagnosed with MS. The data regarding their MS status and the type of DMT taken by the patients were extracted from the Isfahan MS Institute registry and were summarized. Diagnosis of MS was based on the 2017 McDonald Criteria, and the diagnosis of COVID-19 was based on computed tomography scan and polymerase chain reaction of nasopharyngeal swabs. **Results:** Out of the 45 MS patients infected with COVID-19, 5 had unfavorable outcomes. Two patients deceased and the other three had persistent respiratory complications on the 4-week follow-up visit. Hypertension, diabetes, seizures, and rheumatoid arthritis were among the comorbidities that the patients reported. Both patients who died received rituximab as part of their MS treatment. All other patients recovered completely. **Conclusion:** Each different drug category may possess a distinct risk for infection, therefore until robust evidence are available, the safest drug should be utilized or the therapy should be postponed, if possible, to minimize patient risk. Disease-modifying therapy use in MS patients should be cautiously applied as their effect on COVID-19 infection prognosis is not yet studied.

Key words: COVID-19, disease-modifying therapies, multiple sclerosis, rituximab

How to cite this article: Etemadifar M, Sami R, Salari M, Sedaghat N, Sigari AA, Aghababaei A, *et al*. Outcome of COVID-19 infection in multiple sclerosis patients receiving disease-modifying therapies. J Res Med Sci 2021;26:85.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is spreading at an enormous rate. This rapid surge has caused an urgent need for guidelines on the treatment of diseases in the pandemic era. Disease-modifying therapies (DMTs) form the cornerstone of multiple sclerosis (MS) treatment, and deserve special attention during the COVID-19 pandemic due to their immunomodulatory and immunosuppressive properties.[1] DMTs are a subset of drugs which are now being widely used in various neurologic, immunologic, and hematologic diseases. Fingolimod, dimethyl fumarate, rituximab (RTX), natalizumab, and interferon are examples of DMTs used in MS patients.[2,3]

Early preliminary reports and studies have warned physicians about the potential complications of COVID-19 in patients receiving DMTs. Although these reports are not based on large-scale data and were largely based on theories and knowledge from

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_1047_20

Address for correspondence: Dr. Amirhossein Akhavan Sigari, Alzahra Research Institute, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: amirsigari@aol.com
Submitted: 03-Oct-2020; **Revised:** 15-Dec-2020; **Accepted:** 07-Jun-2021; **Published:** 30-Sep-2021

previous epidemics, they mandate more extensive studies to maximize patient safety during the COVID-19 pandemic.[4] In this study, we report 45 MS patients who were infected with COVID-19 while they were being treated with DMTs.

METHODS

This is a cross-sectional study involving 45 COVID-19-infected individuals previously diagnosed with MS who were identified using the Isfahan MS Institute registry. A total of 870 patients (212 males and 658 females) with a mean age of 32.41 ± 9.02 years were screened for COVID-19 between March 1 and the end of July 2020. All the patients received DMTs as part of their MS treatment protocol. All data regarding their MS disease and COVID-19 status were collected. Diagnosis of COVID-19 was made based on an evaluation of signs and symptoms, history of contact with an infected individual, computed tomography (CT) scan of the lung reviewed by a board-certified radiologist for typical COVID-19 features, and polymerase chain reaction (PCR) testing from a nasopharyngeal and an oropharyngeal swab. Symptomatic patients with typical features of COVID-19 on CT scan or a positive PCR test were identified as being infected with COVID-19. The diagnosis of MS was based on the 2017 modified McDonald criteria which takes into account clinical manifestations and neuroimaging features.[5]

RESULTS

A total of 45 MS cases with a mean age of 37.7 years and a mean Expanded Disability Status Scale of 1.92 that were confirmed to have COVID-19 infection were reported. The mean duration of MS since diagnosis was 7.6 years. Fever, dyspnea, and myalgia were the most common reported symptoms of COVID-19 infection. Thirty patients (66.6%) followed preventative measures such as social distancing, using a face mask in public locations, and proper handwashing. Fifteen patients were admitted to the hospital, of which six had underwent mechanical ventilation. Of the six ventilated patients (severe disease course), four received RTX, one received fingolimod, and one received interferon. Two of the patients had hypertension, one had diabetes mellitus, one had epilepsy, and one suffered from rheumatoid arthritis as a comorbid condition. All of these patients recovered without any complications on the 4-week follow-up visit.

Among the entire cohort, 35% and 17% of the patients were receiving dimethyl fumarate (DMF) and RTX for their MS, respectively. Two patients expired during their hospital stay: a 35-year-old female with a 7-year history of relapsing-remitting MS and a 45-year-old female with a 9-year history of secondary progressive MS. Both patients were receiving RTX and they had no other comorbidities besides their underlying neurological disorder. Forty patients recovered completely and were asymptomatic on the 4-week follow-up visit, and three had residual respiratory complications. The patients with respiratory complications on follow-up visits did not report any comorbid conditions besides MS such as obesity, hypertension, and diabetes mellitus. A summary of patients' data are reported in Table 1.

Table 1: Summary of patients' data

Criteria	Data, number of patients (out of 45), *n* (%)
Sex	
Female	36 (80)
Male	9 (20)
Positive PCR for COVID-19	37 (82.2)
CT scan consistent with COVID-19	35 (77.7)
Patients admitted to the hospital	15 (33.3)
Relevance of symptoms	
Fever	40 (88.8)
Dyspnea	27 (60)
Myalgia	23 (51.1)
Headache	13 (28.8)
Cough	11 (24.4)
Anosmia	9 (20)
Ageusia	6 (13.3)
Sore throat	4 (8.8)
Diarrhea	3 (6.6)
Vomiting	2 (4.4)
Fatigue	2 (4.4)
Rhinitis	1 (2.2)
DMT	
Dimethyl fumarate	16 (35.5)
Interferon-beta	8 (17.7)
Rituximab	8 (17.7)
Fingolimod	6 (13.3)
Teriflunomide	3 (6.6)
Azathioprine	2 (4.4)
Glatiramer acetate	1 (2.2)
Natalizumab	1 (2.2)
Type of MS	
RR-MS	38 (84.4)
SP-MS	6 (13.3)
PP-MS	1 (2.2)
Patients with lymphopenia	33 (73.3)
4-week follow-up	
Recovered	40 (88.8)
Respiratory complications	3 (6.6)
Expired	2 (4.4)
Use of preventative actions	28 (62.2)
Mechanical ventilation	6 (13.3)
Patients with comorbidities	5 (11.1)

COVID-19=Coronavirus disease 2019; CT=Computed tomography; MS=Multiple sclerosis; PCR=Polymerase chain reaction; PP=Primary-progressive; RR=Relapsing-remitting; SP=Secondary-progressive; DMT=Disease-modifying therapy

DISCUSSION

DMTs have been essential for the treatment of many diseases such as MS. Although the definite risks and severity of COVID-19 infection in MS patients on DMTs are currently unknown, when deciding on initiating or continuing DMTs in MS patients, the pathophysiology and prognostic factors for severe COVID-19 infection should be foreseen.[6]

Out of the five patients with unfavorable outcomes in our study, two were being treated with RTX, out of which two deceased. All hospitalized patients received standard COVID-19 treatment based on the national protocol. Hydroxychloroquine, ceftriaxone, and azithromycin along with oxygen therapy were the mainstay of therapy in the study's time period. None of the patients received remdesivir due to unavailability and none received corticosteroids as it had not yet been approved for COVID-19.

RTX is a monoclonal antibody against CD20 and therefore causes a decrease in B cells of the immune system, decreasing MS disease relapses. An increased infection risk in patients treated with this drug has been reported.[6] The drug is also used to treat other diseases besides MS such as rheumatic diseases, and unfavorable outcomes have been reported in COVID-19-infected patients receiving the drug.[7-9]

Based on a nationwide study carried out by Sormani *et al*., anti-CD20 therapies such as RTX and ocrelizumab were significantly associated with a severe COVID-19 infection course.[10] However, in another study, Berger *et al*. stated that overall mortality in MS patients receiving DMTs is no different from the population at large, however the statements are made at the beginning of the pandemic when robust evidence was not available.[11]

Nonetheless, no definite conclusions can be drawn based on limited case reports and letters. Therefore, until more evidence is available, the use of DMTs especially CD-20 inhibitors such as RTX should be cautiously applied and/or application should be delayed on a case-by-case basis.[12] Moreover, patients with persistent lymphopenia evident in their complete blood count should be reassessed regarding their treatment if they are receiving drugs such as fingolimod or RTX as they can cause lymphopenia as it further compromises the immune system at least, theoretically.

CONCLUSION

DMTs, especially RTX, may increase infection risk and complicate COVID-19 infection course, therefore until wide-scale studies are carried out to evaluate these therapies on COVID-19 infection course and sufficient data are available, RTX and other DMTs should be cautiously applied.

Acknowledgments

We appreciate the help of the ethical board of the Isfahan University of Medical Sciences. This article has been approved by the ethics committee of the Isfahan University of Medical Sciences under the registration #IR.MUI.MED.REC.1399.259.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wijnands JM, Kingwell E, Zhu F, Zhao Y, Fisk JD, Evans C, *et al.* Infection-related health care utilization among people with and without multiple sclerosis. Mult Scler 2017;23:1506-16.
2. Carden MA, Little J. Emerging disease-modifying therapies for sickle cell disease. Haematologica 2019;104:1710-9.
3. Vargas DL, Tyor WR. Update on disease-modifying therapies for multiple sclerosis. J Investig Med 2017;65:883-91.
4. Giovannoni G. Anti-CD20 immunosuppressive disease-modifying therapies and COVID-19. Mult Scler Relat Disord 2020;41:102135.
5. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
6. Zrzavy T, Wimmer I, Rommer PS, Berger T. Immunology of COVID-19 and disease-modifying therapies: The good, the bad and the unknown. Eur J Neurol 2020.
7. Avouac J, Airó P, Carlier N, Matucci-Cerinic M, Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Ann Rheum Dis 2020;217864.
8. Guilpain P, Le Bihan C, Foulongne V, Taourel P, Pansu N, Maria AT, *et al.* Rituximab for granulomatosis with polyangiitis in the pandemic of COVID-19: Lessons from a case with severe pneumonia. Ann Rheum Dis 2021;80:e10.
9. Schulze-Koops H, Krueger K, Vallbracht I, Hasseli R, Skapenko A. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. Annals of the rheumatic diseases. 2021 May 1;80(5):e67-.
10. Sormani MP, De Rossi N, Schiavetti I, Carmisciano L, Cordioli C, Moiola L, *et al.* Disease modifying therapies and COVID-19 severity in multiple sclerosis. SSRN electronic journal 2020.
11. Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-modifying therapies. Neurol Neuroimmunol Neuroinflamm 2020;7:e761.
12. Maarouf A, Rico A, Boutiere C, Perriguey M, Demortiere S, Pelletier J, *et al*. Extending rituximab dosing intervals in patients with MS during the COVID-19 pandemic and beyond? Neurol Neuroinflamm 2020;7:e825.