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The Impact of SARS-CoV-2 Infection in Unvaccinated Multiple Sclerosis Patients on Disease-Modifying Therapies

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Highlights of the Study

- Disease-modifying therapies in multiple sclerosis (MS) do not seem to adversely affect the course and outcome of COVID-19.
- There is no need to withhold these treatments as this could lead to uncontrolled MS.
- Patients on B-cell-depleting therapies should be closely monitored, though the risk of severity following infection is low.

Keywords
Multiple sclerosis · Disease-modifying therapies · COVID-19 infection

Abstract

Objective: Disease-modifying therapies (DMTs) in multiple sclerosis (MS) may affect the course and outcome of COVID-19, but withholding them could permit disease activity. This study aimed to understand the course of COVID-19 in unvaccinated patients with MS on disease-modifying therapies. ***Subjects and Methods:*** This descriptive study examined the course of COVID-19 among infected patients with MS followed up at a large tertiary center in Kuwait between March 1, 2020, and March 1, 2021. All subjects were outpatients at the time of data collection. ***Results:*** We studied 51 patients with MS confirmed to be infected with SARS-CoV-2 using real-time polymerase chain reaction. Of these patients, 33/51 were female, median age was 35 years (IQR 27–39 years), median Expanded Disability Status Scale score was 1.5 (IQR zero–3), and 47/51 had RRMS. B-cell-depleting agents (ocrelizumab and rituximab) were given to 19 patients, another 19 were on immune cell traffickers (fingolimod and natalizumab), and 13 were on other DMT treatments (alemtuzumab, cladribine, interferon-beta, dimethyl fumarate, and teriflunomide). 43/51 of these patients experienced mild COVID-19, not requiring hospitalization. None of the subjects experienced MS relapses during infection. Two patients on rituximab had a moderate course of the illness, which required hospitalization for oxygen support, but did not need mechanical ventilation; the rest of the subjects remained asymptomatic. ***Conclusions:*** These findings suggest that DMT may not adversely affect the course of COVID-19 in MS patients; however, patients on B-cell-depleting agents trended toward a worse outcome.

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Introduction

Multiple sclerosis (MS) is the most common immune-mediated disease leading to disability in young adults [1]. As a means to prevent disability accrual in patients with MS, patients are treated with disease-modifying therapies (DMTs) which modulate a patient's immune system with resultant immunosuppression of varying levels of severity dependent upon the DMT agent. During the COVID-19 pandemic, the risks versus benefits of ongoing immunotherapy in patients with various diseases, inclusive of MS, have been considered and further explored. DMTs may present a formidable challenge to the clinician confronted with how to best manage a patient who becomes infected with COVID-19 while receiving a DMT. Presently, B-cell-depleting therapies have been found to be associated with prolonged COVID-19 hospitalizations; however, no significant difference in mortality rates has been universally reported for patients treated with B-cell-depleting therapies versus other immunosuppressives [2–4]. Similarly, patients receiving treatment with B-cell-depleting therapies have been found to confer a lower vaccine response than patients not treated with B-cell-depleting agents [5]. In our center, we adopted an extended interval dosing of DMT (natalizumab) for MS patients, to reduce hospital visits as recommended by multiple societies, including the Italian MS Society, the European Society for Blood and Bone Marrow Transplantation, and the Association of British Neurologists (ABN), and to mitigate the risk of progressive multifocal leukoencephalopathy [1–3, 6–9]. However, several studies found natalizumab to be safe regarding infection with COVID-19 [4, 5, 10, 11]. However, most studies, including a recently published large registry from North America and Italy, reported that B-cell-depleting antibodies increase the susceptibly to developing COVID-19 or lead to a worse outcome [7, 8, 10, 12–14]. In this paper, we detail the clinical courses of a series of MS patients treated with DMTs who developed COVID-19 while adherent to MS-directed therapy to better inform clinicians of the possible influence of various DMTs on COVID-19 outcomes.

Methods

A descriptive study design was used which included all MS patients registered with the Neurology Service at the Mubarak Al Kabeer Hospital, Kuwait, for initial evaluation of COVID-19 status. All patients on the service are closely monitored on DMT schedules as per standard guidelines. We excluded patients who did not develop COVID-19 during the study period from March 2020 to March 2021. The final study group included subjects who developed COVID-19 defined as any test positive by PCR with or without a symptomatic status. Tests were routinely administered to patients either due to a contact history or suggestive symptoms. It is important to mention that all cases were unvaccinated at the time.

A retrospective chart review was performed for the 51 patients who met inclusion criteria for this study. Informed consent was obtained from all patients. The following details were extracted from chart review: demographics, medical comorbidities, laboratory data (vitamin D levels, CD19+ cell count when applicable, absolute lymphocyte counts), MS phenotype, Expanded Disability Status Scale (EDSS) scores of the patient, DMT regimen and details pertaining to COVID-19 history inclusive of household contacts, symptoms, disease severity, and COVID-19 outcomes. All patients were outpatients at the time of data collection.

COVID-19 outcomes were pre-defined as asymptomatic, mild (when the patient was not hospitalized), moderate (when the patient was hospitalized), and severe/critical when the patient was admitted to ICU/mechanical ventilation or died. The DMT regimen was categorized into the following subgroups as per mechanism of action: B-cell-depleting therapies (rituximab and ocrelizumab), immune cell trafficking inhibitors (fingolimod and natalizumab), and other DMTs (alemtuzumab, cladribine, interferon-beta, dimethyl fumarate, and teriflunomide). The mild cases were isolated at home and prescribed simple analgesics, antipyretics, vitamin C, and zinc supplements.

Statistical Analyses

All data were analyzed descriptively, and group comparisons were made using hypothesis testing (Kruskal-Wallis or Fisher's exact test as appropriate). The analysis utilized Stata version 15, College Station, TX, USA.

Results

Demographic data, baseline characteristics, and severity of COVID-19 are presented in Table 1. This series of patients had a wide range of age (17–61 years; median 35 years; IQR 27–39 years) as well as of years since diagnosis (1–21 years; median 9 years; IQR 4–13); most were female (N = 33, 64.71%) with an EDSS score 0–6.5 (median 1.5; IQR zero–3). 47/51 (92%) cases had RRMS. Patients were on various DMTs (Table 1) with approximately equal numbers on B-cell depleters, immune cell traffickers, and other medications. Eight cases had ideal levels of 25[OH] Vit D (125–175 nmol/L), 27 patients had sufficient vitamin D levels (75–125 nmol/L), 11 cases had insufficient (50–75 nmol/L) vitamin D levels, and 5 patients had low vitamin D levels (<50 nmol/L). A majority of our patients (N = 31, 60.8%) did not report any comorbidities. However, 5 (9.8%) patients had asthma; 4 (7.8%) were suffering from hypothyroidism and migraine; 2 (3.9%) were pregnant; dyslipidemia and epilepsy were found in 2 (3.9%) patients each. We did not find any association of comorbidities with COVID-19 outcomes. The type of DMT, including B-cell-depleting agents, had minimal bearing on disease severity,

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Table 1. Comparative representation of baseline demographic, phenotypic, and clinical characteristics of study subjects based on their disease-modifying therapy

Characteristic	B-cell depleters (*N* = 19)	Immune cell traffickers (*N* = 19)	Other (*N* = 13)	*p* value
Age	34 (23, 38)	35 (27, 38)	36 (30, 42)	0.698
Female gender, *n* (%)	12 (63.2)	13 (68.4)	9 (69.2)	1
Arab ethnicity, *n* (%)	17 (89.5)	17 (89.5)	10 (76.9)	0.522
RRMS phenotype, *n* (%)	17 (89.5)	19 (100)	11 (84.6)	0.285
Duration of MS, years	6 (3, 12)	9 (3, 14)	10 (8, 13)	0.375
Duration of current DMT, years	2 (1.5, 3)	5 (1.5, 7)	3 (1.9, 5)	0.093
EDSS	2.5 (1, 3.5)	1 (0, 2)	1 (0, 3)	0.19
CD19 count, %	1.98 (1.05, 3.26)			
Lymphocyte count, 10^3/μL	2.3 (1.8, 2.7)	1 (0.5, 3.5)	2 (1.5, 2.1)	0.182
25[OH] Vit D, nmol/L	79 (70, 109)	95 (68, 104)	93 (80, 124)	0.589
Severity of COVID-19 disease, *n* (%)				
Asymptomatic	4 (21.1)	1 (5.6)	0	0.067
Mild	13 (68.4)	17 (94.4)	13 (100)	
Severe	2 (10.5)	0	0	
Critical	0	0	0	
Duration of COVID-19, days	8.5 (5, 10)	7 (6, 10)	7 (5, 10)	0.979
Post-COVID-19 symptoms, *n* (%)	5 (26.3)	5 (27.8)	3 (23.1)	1

Median (IQR) or *N* (%) is reported; *p* based on the Fisher's exact test or the Kruskal-Wallis test (as appropriate).

and the majority (43/51 cases) in this series "Table 1" had a mild illness, with no need for hospitalization. None of these patients had an exacerbation of their MS before or during the COVID-19 illness. They continued to receive their DMTs on schedule during and after the COVID-19 illness. In addition, 5 cases were asymptomatic, with four on B-cell-depleting agents and one on immune cell trafficking drugs.

Nineteen subjects were on B-cell-depleting agents (Table 1), 11 were on ocrelizumab, and 8 were on rituximab. All had adequate CD19 (>1%) levels and received their DMT on schedule. Although only 2 moderate cases noted, both were in this group on B-cell-depleting agents and had gastrointestinal and respiratory involvement, requiring hospitalization for supplemental oxygen. The first was a female patient who had been on rituximab for a year and a half. She presented with hypoxic respiratory failure symptoms several days after testing positive for COVID-19. She was hospitalized and required supplemental oxygen. A high-resolution computerized tomography scan of the chest showed bilateral ground-glass opacities but no infarctions. She eventually recovered from her respiratory illness. The second patient was a young male who developed gastrointestinal symptoms after testing positive for COVID-19. On day four of his symptoms after developing hypoxic respiratory failure, he was admitted to the hospital and was kept on supplemental oxygen. He was discharged from the hospital after 10 days and recovered well. He received his DMT on schedule, a week later.

Four percent of the subjects were pregnant when they contracted COVID-19. One of these cases did not realize that she was pregnant while on fingolimod. Her DMT was discontinued when she reported pregnancy. She had an insufficient vitamin D level and reported a mild upper respiratory illness but experienced excessive fatigue and bone pains, extending up to 4 weeks. The other subject was on natalizumab, just at the start of the third trimester of pregnancy, had a mild COVID-19 illness, and reported a spontaneous miscarriage after 11 days of testing positive on real-time polymerase chain reaction.

Table 2 presents a brief description of the population of MS patients (*N* = 467) registered in the hospital during the period of our study. Among them, 51 (10.9%) included in our study had COVID-19. Table 3 represents a description of the population of MS patients who were not on any DMT during the period of our study (*N* = 38); 8 (21%) of them reported mild COVID-19 infection.

Discussion

Initial reports on the risk associated with COVID-19 infection in patients with MS were mostly reassuring and highlighted the importance of initiating and maintaining DMTs in patients with MS when indicated, despite the pandemic [12–14]. Our patients had comorbidities like dyslipidemia and hypertension yet had mild illnesses and

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Table 2. Baseline demographic, phenotypic characteristics of MS patients (*N* = 467) on disease-modifying therapy

Characteristic	B-cell depleters (*N* = 152)	Immune cell traffickers (*N* = 245)	Other (*N* = 70)
Age	36 (27, 45)	35 (29, 42)	43 (34, 53)
Female gender, *n* (%)	93 (61.2)	143 (58.4)	40 (57.1)
Arab ethnicity, *n* (%)	118 (76.3)	195 (79.6)	59 (84.3)
RRMS phenotype, *n* (%)	46 (30.3)	237 (96.7)	69 (98.6)
Duration of MS, years	3 (1, 10)	8 (5, 12)	11 (6, 14)
Duration of current DMT, years	2 (1, 3)	5 (1.5, 7)	3 (2, 5)

Median (IQR) or *N* (%) is reported.

Table 3. Baseline demographic, phenotypic characteristics of patients not on disease-modifying therapy

Characteristic	Patients who reported COVID-19 disease (*N* = 8)	Patients who did not report COVID-19 (*N* = 30)
Age	45 (31–49)	43 (36–72)
Female gender, *n* (%)	5 (55.6)	27 (71.1)
Arab ethnicity, *n* (%)	8 (100)	33 (86.8)
RRMS phenotype, *n* (%)	8 (100)	29 (76.3)
Duration of MS, years	8 (3, 10.5)	11.5 (7, 24)
EDSS	0 (0–8)	2 (0, 9.5)
COVID severity		
Asymptomatic		
Mild, *n* (%)	8 (100)	
Severe		

Median (IQR) or *N* (%) is reported.

favorable outcomes even though they were on immune-modulating agents, had a wide age distribution, and varied duration of DMTs (Table 1). Surprisingly, of the patients who were not on DMT, a higher percentage was noted to have contacted COVID-19 infection (21%) as compared to those who were on DMTs (10.9%). The small number of patients off DMTs (*N* = 38) may have introduced bias in our observations.

Thus, contrary to worsening neurologic symptoms, which is often the case in MS patients suffering from an infection, the outcome in this cohort was generally similar to the general population. The results of this study suggest that there is a possibility of several beneficial aspects of immunotherapies in COVID-19 infection, including purported antiviral effects conferred by interferon, glatiramer acetate, and teriflunomide; leukocyte sequestration as a result of natalizumab or sphingosine-1-phosphate receptor antagonists; and potential immunoregulatory effects in terms of a cytokine storm from IVIG or glucocorticosteroids [11, 15]; although a worsening outcome with methylprednisolone infusion up to 1 month preceding COVID-19 infection has also been reported [8, 12], none of our patients had received corticosteroids in the months before developing COVID-19 infection.

The anti-CD20 agents ocrelizumab and rituximab selectively deplete B lymphocytes. Compared to other DMTs, these agents entail a higher risk associated with infection, which may be associated with a more severe disease course [12, 16]. In one report, findings showed increased severity of COVID-19 disease in patients receiving ocrelizumab and rituximab [8, 13]. Another study found that anti-CD20-antibodies impede the production of neutralizing antibodies, which led to a protracted course and a worse outcome [13, 17]. In our study, 2 of the 19 patients who had been on B-cell-depleting agents developed moderate disease, of whom, only 1 patient had been on rituximab for approximately 18 months. These findings do not support the assumption that B-cell-depleting agents have consistent adverse outcomes, contrary to studies that suggest a worse outcome [8, 12, 13, 16, 17]. One possible explanation for this may be selection criteria, host genetics, or SARS-CoV-2 strain virulence.

It is now well established that coronaviruses trigger the inflammatory host response, significantly contributing to the disease severity. Dysregulated immune responses appear to be crucial drivers of tissue damage after the initial infection. While speculative, the role of immunomodulatory therapy may have a protective effect by attenuating the

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damage caused by the viral-induced excessive response. However, this mode of action is seen in treatment that targets IL-6, i.e., tocilizumab, which mitigates the cytokine storm seen in severe COVID-19 pneumonia [11, 15].

Vitamin D deficiency is present in up to 80% of populations in Middle Eastern countries, occurring more frequently with obesity and diabetes [14, 18]. Vitamin D is an essential immune modulator through multiple mechanisms and effects on immune pathways, and several studies are hypothesizing an association of vitamin D deficiency with greater severity of COVID-19 infection [19, 20]. Regulatory T lymphocytes (which are a principal defense against uncontrolled inflammation) are reported to be low in many COVID-19 patients and can be increased by vitamin D supplementation [21, 22]. The efficacy of vitamin D supplements is best demonstrated with the chronic intake of low doses rather than bolus administration of large amounts [23].

In the current study, MS patients have had regular monitoring and supplementation with vitamin D, and the majority of cases had sufficient vitamin D levels before COVID-19 infection. One of the patients who had insufficient vitamin D, and was pregnant, experienced a prolonged course. Our data, though based on a small sample size, suggest that pregnancy may not necessarily negatively affect the course and outcome of COVID-19. Natalizumab may contribute to miscarriage as it is a known association.

These results must be interpreted with caution because of the small size of the sample and with no comparative populations to draw any conclusions. We can hypothesize that sufficient vitamin D levels through regular supplementation may well have contributed to their mild response and course of COVID-19 infection. However, this is an area for future research. The study is limited by the single center design and small sample size. Also, the retrospective nature could have been responsible for missing some data.

Conclusion

In conclusion, our findings concur with reports that patients whose disease process is controlled under current immunotherapies should continue their medications and, overall, use of a DMT that is not a B-cell-depleting agent does not appear to confer worse COVID-19 outcome whereas B-cell-depleting agents may do. Hereby, present results are confirmatory of previous studies, which were however obtained on different populations (e.g., mostly Europe and the USA) [6–8, 13, 16]. The influence of DMTs [18] and vitamin D status on the clinical course of COVID-19 in patients with MS requires further study.

Statement of Ethics

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was taken from all the patients included in this study. This study protocol was reviewed and approved by Ethics Committee, Ministry of Health, Kuwait.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Suhail Al Shammri designed the experiments and prepared the manuscript. Geeti Chadha collected the data and contributed in preparation of manuscript. Arpita Chattopadhyay and Suhail Doi analyzed the data and prepared the final manuscript. All the authors approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request.

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