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Original article

Incidence and mortality of COVID-19 in Iranian multiple sclerosis patients treated with disease-modifying therapies

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ABSTRACT

Background. – Impaired immunity, in most cases, may render patients more vulnerable to infections and neutralize the effects of vaccines, raising great concerns regarding multiple sclerosis (MS) patients during the coronavirus disease 2019 (COVID-19) pandemic, considering that they are treated with immunosuppressive/immunomodulatory disease-modifying therapies (DMTs). Some studies, however, have suggested a beneficial protective role for these therapies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We aimed to investigate the incidence and mortality of COVID-19 in more than 25,000 MS patients in Iran, who were treated with different DMTs.

Material and methods. – We gathered relevant data pertaining to registered Iranian MS patients from major Iranian pharmaceutical companies, as well as MS societies from all provinces of Iran, who were treated with different DMTs. They were interviewed by nurses via telephone calls, and suspected/confirmed cases of COVID-19 were identified. Furthermore, regarding the deceased patients, it was determined whether or not their death was attributable to COVID-19, or whether they had any other comorbidities.

Results. – 25,436 treated MS patients (7621 males; 30%; 17,815 females; 70%) were identified, with 144 of whom (0.57%) reported as confirmed cases of COVID-19 (45 males; 31.2%, 99 females; 68.8%). A total of 28 deaths (9 males; 32.1%, 19 females; 67.9%), among fingolimod-(one female), dimethyl fumarate- (one female), and rituximab-treated (8 males; 30.8%, 18
1. Introduction

Q In December 2019, a novel cluster of cases of pneumonia of unknown cause were reported in Wuhan, China [1]. Now called the coronavirus disease 2019 (COVID-19), it has affected more than 17 million people around the globe [2]. However, until now, neither a definitive vaccine nor a definitive treatment for this infection has been found. Multiple Sclerosis (MS) is an autoimmune disease characterized by immune-mediated demyelination of nerve fibers in the central nervous system (CNS). Oral medications such as fingolimod (FNG), teriflunomide (TFN), and dimethyl fumarate (DMF); injectable therapies such as Interferon-βs (IFN-βs); and intravenous monoclonal antibodies such as natalizumab (NTZ), ocrelizumab (OCR), and rituximab (RTX), collectively known as disease-modifying therapies (DMTs), are being used to control the disease progression, and thus, ameliorating the patients’ quality of life [3].

Impaired immunity, however, may predispose MS patients to different types of infections, and may neutralize the effects of vaccines, thus raising a great concern for treating MS during the ongoing COVID-19 pandemic [4,5]. Some studies, however, indicate that treatment with DMTs not only does not render MS patients more vulnerable to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but also may improve the prognosis in infected patients [6–11].

In line with previous studies, we aimed to investigate the incidence and the severity of COVID-19 in MS patients treated with different DMTs, and to describe the demographic and clinical characteristics of those who were deceased following a severe course of COVID-19, this time in a much bigger sample size of more than 25,000 patients. Consequently, along with other evidence-based investigations, we believe the current study could be a big step towards a new approach for treating MS patients during the COVID-19 era.

2. Material and methods

In this study, we contacted the major Iranian pharmaceutical companies and MS societies from all provinces of Iran. Demographic and clinical characteristics of the MS patients treated with different DMTs were obtained from their data registries. Special nurses from the follow-up teams interviewed MS patients who were on DMTs (or their clinicians, in case they were already deceased) via telephone calls on a regular basis, from February 25 to June 15, 2020. On each call, patients were asked whether they (1) presented with COVID-19 common manifestations, (2) had a history of journey to endemic regions, or (3) had a history of COVID-19 infection in their families or friends. Nurses considered the patients with at least one of these three criteria as suspected cases of COVID-19 and thus, referred them to a physician. Laboratory, radiological, and clinical information of the patients was then obtained by the nurses (from their physicians), and was registered in the data registries. In this study, we considered a patient with at least one of the following criteria as a confirmed case of COVID-19: (1) ground-glass opacities in chest computed tomography (CT) scan, (2) positive SARS-CoV-2 RNA real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) (oro- or nasopharyngeal swab), or (3) positive anti-SARS-CoV-2 IgM/IgG serum tests. Also, severe cases of COVID-19 were defined as patients who needed hospitalization/intensive care. Regarding deceased patients, we directly contacted their admitting physicians to ascertain whether their death was attributable to COVID-19, and to completely obtain their relevant clinical characteristics. Furthermore, we ensured that there was no overlap between different data registries. This study was approved by the Ethics Committee of the Isfahan University of Medical Sciences. Statistical analyses were carried out using Microsoft Office Excel for Windows 7.

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Table 1 - COVID-19 in Iranian general population as of June 15, 2020.

| Total Iranian population | Total confirmed* Iranian COVID-19 cases | Cumulative incidence of COVID-19 (%)b | Number of COVID-19-related deaths |
|--------------------------|----------------------------------------|--------------------------------------|----------------------------------|
| 83,608,657               | 187,427 [12]                          | 0.22                                 | 8950 [12]                        |

* As stated by the World Health Organization (WHO), "A confirmed COVID-19 case is defined as a person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms."

b The cumulative incidence of COVID-19 among general Iranian population was calculated by dividing total Iranian COVID-19 cases by total Iranian population.

3. Results

We identified 25,436 DMF-treated MS patients (7621 males; 30%, 17,815 females; 70%), 144 patients (0.57%) were reported to be confirmed cases of COVID-19 (45 males; 31.2%, 99 females; 68.8%), with 118 having ground-glass opacities in their chest CT scans, and 68 with positive SARS-CoV-2 RNA RT-PCR test results (naso- or oropharyngeal swabs). Since the risk of SARS-CoV-2 infection in the DMF-treated group was similar to that in the general Iranian population (0.22%; Table 1), we considered this group as the reference to calculate the relative risks (RRs) for others. As a result, the RRs of COVID-19 were greater than 1 in patients treated with TFN, FNG, NTZ, and RTX, with the highest risk among RTX-treated patients (RR: 5.56; 95% confidence interval: 2.45–12.46). The RRs were less than 1 in GA- and IFN-β-treated groups (Table 2).

Furthermore, clinical and demographic data of the infected patients, including their therapies, patterns of MS, and mean ages, are depicted in Table 3. Also, 28 deaths (9 males; 32.1%, 19 females; 67.9%) attributable to COVID-19 were reported; data of the deceased patients are represented in Table 4.

In addition, we identified a total of 70 patients on ocrelizumab (OCR), one of whom presented with COVID-19. Her general conditions improved after a week of self-quarantine at home, with no severe complications. Furthermore, we observed that amongst 474 patients treated with azathioprine, one was diagnosed with COVID-19 and fully recovered. Given that the sample size of these patients (OCR- and azathioprine-treated groups) was relatively small, we did not include them in our evaluations. Similarly, nine patients (two males and seven females) treated with alemtuzumab, were not included (none of them presented with COVID-19).

Table 4 shows some information about the Iranian population and its COVID-19 status, from February 19, 2020; the date of announcement of first reported cases of COVID-19 in Iran, to 15th June 2020[12]. Furthermore, the comparison between our observed incidence risks among MS patients who were on different DMTs is illustrated in Fig. 1.

Table 2 - Distribution of MS patients treated with different disease-modifying therapies during the COVID-19 pandemic.

| Disease-modifying therapya | Total number of treated patients (male, female) | Pattern of MS in treated patients | Total number of confirmed COVID-19 patientsa (male, female) | Incidence risk of COVID-19 (%) | Relative risk of infection (95% confidence interval) |
|---------------------------|-------------------------------------------------|----------------------------------|-----------------------------------------------------------|-------------------------------|---------------------------------------------------|
| IFN-β 1a (IM)            | 2599 (780, 1819)                                | RR: 2599                         | 5 (2, 3)                                                  | 0.19                          | 0.89 (0.36–2.18)                                   |
| IFN-β 1a (SC)            | 2520 (806, 1714)                                | RR: 2470                         | 4 (0, 4)                                                  | 0.16                          | 0.73 (0.21–2.60)                                   |
| IFN-β 1b                 | 1837 (447, 1390)                                | RR: 1716                         | 3 (1, 2)                                                  | 0.16                          | 0.76 (0.19–3.02)                                   |
| GA                       | 2245 (566, 1679)                                | RR: 2245                         | 3 (1, 2)                                                  | 0.13                          | 0.62 (0.15–2.47)                                   |
| FNG                      | 1982 (399, 1583)                                | RR: 1721                         | 8 (3, 5)                                                  | 0.40                          | 1.87 (0.61–5.70)                                   |
| DMF                      | 2777 (786, 1991)                                | RR: 2705                         | 6 (2, 4)                                                  | 0.22                          | Reference                                         |
| TFN                      | 1755 (371, 1384)                                | RR: 1755                         | 6 (1, 5)                                                  | 0.34                          | 1.58 (0.51–4.90)                                   |
| NTZ                      | 984 (157, 827)                                  | RR: 800                          | 4 (1, 3)                                                  | 0.41                          | 1.88 (0.42–8.39)                                   |
| RTX                      | 8737 (3310, 5427)                               | RR: 2725                         | 105 (34, 71)                                              | 1.20                          | 5.66 (2.45–12.65)                                  |
| Total                    | 25436 (7621, 17815)                             | RR: 18736                        | 144 (45, 99)                                              | 0.57                          | –                                                 |

RTX: rituximab; NTZ: natalizumab; FNG: fingolimod; TFN: teriflunomide; DMF: dimethyl fumarate; IFN-β: interferon beta; GA: glatiramer acetate; IM: intramuscular; SC: subcutaneous; RR: relapsing-remitting; PP: primary progressive; SP: secondary progressive.

a COVID-19 was confirmed if the patients had (1) ground-glass opacities in their chest computed tomography (CT) scan; or (2) positive oropharyngeal swab real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) for SARS-CoV-2 RNA; or (3) positive anti-SARS-CoV-2 RNA IgM/IgG serum tests.

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Table 3 – clinical information of treated MS patients with confirmed COVID-19.

| Disease-modifying therapy* | Number of confirmed COVID-19 patients (male, female) | Mean age (± SD) | MS patternb | Number of hospitalized patients sorted by MS pattern (male, female)b | Number of deaths due to COVID-19 (male, female) |
|----------------------------|-----------------------------------------------|-----------------|--------------|-------------------------------------------------|-----------------------------------------------|
| IFN-β 1a (IM)              | 5 (2, 3)                                       | 48 ± 6.2        | RR: 5        | 0                                               | 0                                             |
| IFN-β 1a (SC)              | 4 (0, 4)                                       | 47.5 ± 6.4      | RR: 4        | 0                                               | 0                                             |
| IFN-β 1b                   | 3 (1, 2)                                       | 39 ± 7.54       | RR: 3        | 0                                               | 0                                             |
| GA                         | 3 (1, 2)                                       | 33.33 ± 6.66    | RR: 3        | 0                                               | 0                                             |
| FNG                        | 8 (3, 5)                                       | 40 ± 9.59       | RR: 6        | RR: 2 (female)                                  | 1 (female)                                    |
| DMF                        | 6 (2, 4)                                       | 35.17 ± 8.49    | RR: 6        | RR: 1 (female)                                  | 1 (female)                                    |
| TFN                        | 6 (1, 5)                                       | 37.5 ± 4.95     | RR: 6        | 0                                               | 0                                             |
| NTZ                        | 4 (1, 3)                                       | 39.5 ± 8.1      | RR: 3        | SP: 1 (female)                                  | 0                                             |
| RTX                        | 105 (34, 71)                                   | 44.6 ± 7.44     | RR: 21       | RR: 8 (3, 5)                                    | 26 (9, 17)                                    |
| Total                      | 144 (45, 99)                                   | 41.5 ± 7.88     | PP: 45       | PP: 17 (4, 13)                                  | 28 (9, 19)                                    |

RTX: rituximab; NTZ: natalizumab; FNG: fingolimod; TFN: teriflunomide; DMF: dimethyl fumarate; IFN-β: interferon beta; GA: glatiramer acetate; IM: intramuscular; SC: subcutaneous; RR: relapsing-remitting; PP: primary progressive; SP: secondary progressive.

Table 4 – Demographic and clinical characteristics of the MS patients who were on disease modifying therapies and were deceased due to COVID-19 (n = 28).

| Disease-modifying therapy | Sex            | Age (mean ± SD) | Pattern of MS | Duration of MS (mean) (years) | Other possible risk factors                        |
|---------------------------|----------------|-----------------|---------------|-------------------------------|---------------------------------------------------|
| Fingolimod               | Female 42      | 42              | RR            | 10                            | None                                              |
| Dimethyl fumarate        | Female 45      | 45              | RR            | 12                            | None                                              |
| Rituximab                | Female: 17 M: 9| 41.5 ± 9.37     | RR: 5         | PP: 15                        | Primary hypertension: 1 Diabetes mellitus: 1 History of smoking: 1 Obesity: 1 Ischemic heart disease: 1 |

SD: standard deviation; RR: relapsing-remitting; PP: primary progressive; SP: secondary progressive.

Fig. 1 – Graph depicting the Cumulative incidences of COVID-19 among patients with MS and general Iranian population (February 2020–June 2020).

4. Discussion

We studied 25,436 Iranian MS patients who were treated with different DMTs, of whom 144 patients contracted COVID-19 (Table 2). Importantly, the risk of COVID-19 was significantly higher in RTX-treated patients compared to the patients on other DMTs (Table 2). Moreover, among 105 RTX-treated patients with confirmed COVID-19, 26 (25%) were deceased.

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Regarding the decreased risks in IFN-β- and GA-treated patients (relative to the general population), should they be observed in future studies as well, some probable protective effects of these therapies (e.g. the anti-viral effects of IFN-β) could be taken into account. Notably, such large population of DMT-treated MS patients has not been studied previously with respect to their therapy, during the COVID-19 pandemic.

The risk of infections is reported to be higher in patients with MS compared to the general population, regardless of their treatment [13,14]. Additionally, systemic infections could exacerbate the pre-existing MS or may increase the risk of relapses [15]. Some studies have indicated that DMTs may add to the background risk of infection in patients with MS [16–18]. However, since many MS patients receive DMTs, the precise background risk of infections in MS patients, independent from their treatments, is difficult to assess. Findings from some placebo-controlled studies have shown that the risk of serious infections in MS patients could range between 0.2 and 2.6% [16]. Regarding the degrees to which different DMTs could predispose patients to infections, a nationwide Swedish cohort study suggested that RTX-treated patients had a higher risk of developing severe infections, compared with those on IFN-β, GA, FNG, and NTZ therapies [17]. They also reported that an increased risk of infection was associated with FNG and NTZ, compared with the injectable therapies. Similar to their results, RTX, NTZ, and FNG-treated patients had the highest risks of COVID-19 in our study.

Our experience with SARS-CoV-1 and MERS-CoV epidemics should also be taken into account; in many studies from those epidemics, immunosuppressive treatments showed an association with neither an increased risk of infection nor a more severe disease course [19]. However, there still is a lack of evidence in this regard, since case reports from the previous epidemics are limited in number, and some DMTs, such as anti-CD20 monoclonal antibodies, were not prescribed as extensively as they are nowadays.

The immune response to viral pathogens, including SARS-CoV-2, involves both innate and adaptive immune systems. The secretion of cytokines such as IL-1β by infected cells and eventually their lysis leads to recognition of pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) by local cells such as alveolar epithelial cells and alveolar macrophages. This eventually leads to secretion of T helper 1 (Th1) cell-mediated pro-inflammatory cytokines, such as IL-6. These cytokines primarily attract monocytes and T lymphocytes from the circulation to the tissue, explaining the lymphopenia seen in COVID-19 patients [20]. In most cases, the immune response is adequate to eliminate the virus; however, over-activation of the immune system may play a role in exacerbation of COVID-19. Oxidative stress caused by immune cells to eliminate the infection, also contributes to the alveolar tissue damage, resulting severe respiratory problems [20]. Also, over-secretion of cytokines, known as cytokine storm, causes a systemic inflammation and a sepsis-like shock, which eventually leads to multi-organ failures and death. Blood levels of the cytokines such as IL-6 were reported to be higher in severe cases needing intensive care [21]. Furthermore, there is an increasing number of case reports of patients developing post-infectious autoimmunity after COVID-19 [22]. Considering the above arguments, a lot of ongoing studies and clinical trials are evaluating the effects of immune-modifying medications on COVID-19 [6,9,22,23]. Also, in this regard, our observations may help the scientific community to see the big picture more transparent.

Our findings suggest that some DMTs (IFN-β 1a/1b and GA) may improve COVID-19 prognosis, as the risk of infection in patients treated with these therapies was lower than the general population (Tables 1 and 2, Fig. 1). However, a significant number of RTX-treated patients had contracted COVID-19, of whom a considerable proportion (25%) were deceased. We did not expect such outcome, keeping in mind that a number of previous studies suggested that it may be safe to initiate or continue anti-CD20 therapy during the ongoing COVID-19 pandemic [6–8,10,24]. Furthermore, some other studies in larger scales have reported no association between DMTs and COVID-19 severity (or the risk of COVID-19 contraction) [25–27]. In one of these studies, however, a considerable proportion (44.7%) of patients with COVID-19 were on anti-CD20 therapies [26]. It is important to note that since the aforementioned studies had several limitations, their results should be interpreted with caution.

As the host main immune response to SARS-CoV-2 is thought to be mainly directed by CD 8+ T cells and natural killer cells, B-cell-depleting anti-CD20 monoclonal antibodies are theoretically not considered to increase the incidence and mortality of COVID-19. Furthermore, some studies have indicated that anti-CD20 therapies may even have a protective role against a more severe disease course [6,7,28], possibly since they inhibit a B-cell induced cytokine storm [28]. Several reports have described OCR- and RTX-treated MS patients with COVID-19 who finally had a favorable outcome [6–8,28–30]. Besides, in another report, a number of X-linked agammaglobulinemia patients who were infected with SARS-CoV-2 fully recovered [31]. These observations seem to theoretically reinforce the notion that B cell-depleting therapies are safe to be initiated or continued during the pandemic. However, still not all studies fully support this conclusion. In a cross-sectional study, 21 out of 34 suspected COVID-19 patients were on RTX; interestingly, the only two hospitalized patients were also treated with RTX/OCR. Furthermore, the authors reported that the risk of SARS-CoV-2 infection in RTX-treated patients was 3.6 times as high as that in those on other DMTs [32]. In a study by Sormani et al., three out of the total 10 COVID-19 patients with critical/severe disease courses, were among the 28 patients who were treated with anti-CD20 therapies (26 with OCR and 2 with RTX). Furthermore, one patient on RTX was deceased [33]. Moreover, a high proportion of the U.S. and Canadian MS-focused neurologists stated that they would avoid prescribing OCR (38%) and/or RTX (35%) during the pandemic. Furthermore, most of them believed that OCR and RTX may prevent the future potential COVID-19 vaccines to induce a protective immune response [34]. In our study, the risk of infection in RTX-treated patients was nearly 5.6 times as high as that in the DMT-treated patients (the group with a similar risk with the general population). Also, the mortality of COVID-19 amongst RTX-treated patients was remarkably higher, compared to that in patients on other DMTs and the general population.

There may be several explanations to this scenario. Möhn et al. suggested some mechanisms through which B
cell-depleting therapies could affect the risk of a more severe course of COVID-19 [19]. Depletion of the minor CD20+ T cell population which probably exert crucial effects in inflammatory processes [35] might play a critical role in worsening the course of COVID-19. Furthermore, Bacterial co-infections are also more likely to occur when B cells are depleted [17]. However, some important, well-established risk factors for severe COVID-19, including obesity, diabetes mellitus, and cardiovascular/pulmonary comorbidities, were not assessed among all the confirmed infected patients. Therefore, the majority of the RTX-treated patients with COVID-19 (84 out of 105 patients; Table 3) had progressive forms of MS. Thus, the significantly elevated incidence of COVID-19 in RTX-treated patients may simply be attributable to the fact that they had some underlying predisposing factors, irrespective of their therapy (e.g., progressive patterns of MS). Nevertheless, the mean age of these patients was not considered old; thus, one important risk factor (i.e., older age) might have had a rather minor role in rendering them more susceptible to COVID-19. Although most of them were under 65 years old, the majority of the deceased RTX-treated patients (21 out of 26 patients; Table 4) had progressive forms of MS and some important comorbidities, indicating that their deaths may possibly not be associated with the RTX therapy. Therefore, the probable role of anti-CD20 therapies in increasing the risk of COVID-19 contraction and/or severity, regardless of other well-established risk factors, remains to be further investigated. Nevertheless, considering that B cell depletion may also increase the risk of reinfection and impair the protective effects of a possible COVID-19 vaccine [36], it seems reasonable to exercise caution regarding the application of anti-CD20 therapies during the COVID-19 pandemic, until a firmer body of evidence becomes available.

Importantly, we were not able to gather all clinical and demographic data of every individual in such large sample size. Thus, it was not possible for us to assess some factors that could have affected the possible association of different DMTs with increased/decreased susceptibility to COVID-19 contraction/severity. Furthermore, we could collect data on neither untreated MS patients, nor the through population of Iranian MS patients treated with different DMTs, partly because we had access not to all Iranian pharmaceutical companies. Further studies on untreated MS patients who contracted COVID-19 can determine if progressive MS pattern, as a probable risk factor, could affect the incidence and/or mortality of COVID-19, independently from therapy. Nevertheless, our report covers a sample size of more than 25,000 DMT-treated MS patients, which is nearly one-third of all Iranian MS patients (treated or untreated), according to the statistics announced in May 2020 by the Iranian Ministry of Health. Additionally, all the patients were studied particularly with respect to their therapies, and the COVID-19 diagnoses were firmly made by physicians. Thus, although not completely controlled, we believe that this study could considerably add to the growing body of evidence regarding the use of DMTs in the COVID 19 era.

5. Conclusion

Compared to the general population, the risk of COVID-19 contraction was observed to be lower in IFN-β- and GA-treated patients, suggesting possible favorable effects of these therapies in COVID-19. On the other hand, the risk was higher among patients treated with RTX, NTZ, and FNG. Importantly, the increased risk of infection was statistically significant only in RTX-treated patients, the majority of whom had a progressive pattern of MS. Also, a notable proportion of RTX-treated patients presented with severe or fatal courses of disease. However, as some underlying risk factors other than MS DMTs were not assessed among the infected patients, drawing a firm conclusion regarding the probable association of anti-CD20 therapies with COVID-19 contraction/severity is not possible yet. Nevertheless, keeping in mind that anti-CD20 therapies may increase the risk of reinfection and may impair protective effects of a possible COVID-19 vaccine, we advise clinicians to exercise caution when confronting the decision to initiate/continue anti-CD20 therapies, especially in patients with progressive patterns of MS and/or other well-established predisposing factors. We would certainly recommend more controlled studies to be performed, evaluating the positive/negative effects of DMTs on the risk of COVID-19 contraction or severity, irrespective of other possible risk factors.

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Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] WHO. Pneumonia of unknown cause–China; 2020 [Accessed June 5th 2020]https://www.who.int/csr/don/05-january-2020-pneumonia-of-unknown-cause-china/en/.

[2] Coronavirus disease (COVID-19) situation reports; 2020, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[3] Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav 2015;5(9):e00362.

[4] Brownlee W, Bourdette D, Brodsky S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. Neurology 2020. http://dx.doi.org/10.1212/WNL.0000000000005957.

[5] Carnero Contentti E, Correa J. Immunosuppression during the COVID-19 pandemic in neuromyelitis optica spectrum disorders patients: a new challenge. Mult Scler Relat Disord 2020;41:102097.

[6] Novi G, Mikulska M, Brianz F, Toscanini F, Tazza F, Uccelli A, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? Mult Scler Relat Disord 2020;42:102120.

[7] Giovannoni G. Anti-CD20 immunosuppressive disease-modifying therapies and COVID-19. Mult Scler Relat Disord 2020;41:102155.

[8] Montero-Escribano P, Matias-Guiu J, Gómez-Iglesias P, Porta-Etessam J, Pytel V, Matias-Guiu JA. Anti-CD20 and COVID-19 in multiple sclerosis and related disorders: a case series of 60 patients from Madrid, Spain. Mult Scler Relat Disord 2020;42:102185.

[9] Maghzi AH, Houtchens MK, Preziosa P, Itonete C, Beretich BD, Stankiewicz JM, et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. J Neurol 2020.

[10] Creed M, Ballesteros E, Jr JG, Imiola J. Mild COVID-19 infection despite chronic B cell depletion in a patient with aquaporin-4-positive neuromyelitis Optica spectrum disorder. Mult Scler Relat Disord.

[11] Gencioğlu E, Davutoğlu M, Ozdemir EE, Erden A. Are type 1 interferons treatment in Multiple Sclerosis as a potential therapy against COVID-19? Mult Scler Relat Disord 2020;42:102196.

[12] Iran (Islamic Republic of): WHO Coronavirus Disease (COVID-19) Dashboard; 2020, https://www.covid19.who.int/region/emro/country/ir.

[13] Montgomery S, Hillert J, Bahmanyar S. Hospital admission due to infections in multiple sclerosis patients. Eur Neurol 2013;60(4):115–60.

[14] Wijnands JMA, 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 J 2016;23(11):1506–16.

[15] Steelman AJ. Infection as an environmental trigger of multiple sclerosis disease exacerbation. Front Immunol 2015;6:520.

[16] Winkelmann A, loebermann M, Reisinger EC, Hartung HP, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. Nat Rev Neurol 2016;12(4):217–33.

[17] Luna G, Alping P, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol 2019.

[18] Wijnands JMA, Zhu F, Kingwell E, Fisk JD, Evans C, Marrie RA, et al. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. J Neurol Neurosurg Psychiatry 2018;89(10):1050.

[19] Möhn N, Fül R, Kleinschitz C, Prüss H, Witte T, Stangel M, et al. Implications of COVID-19 outbreak on immune therapies in multiple sclerosis patients—lessons learned from SARS and MERS. Front Immunol 2020;11:1059.

[20] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20(6):363–74.

[21] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

[22] Ottaviani D, Boso F, Tranquillini E, Gepeni I, Pedrotti G, Cazzio S, et al. Early Guillin-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital. Neurol Sci 2020;41(6):1351–4.

[23] Zhang C, WU Z, Li J-Wei Zhao H, Wang G-Q. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020;55(5):10594.

[24] 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.

[25] Louapre C, Collongues N, Stankoff B, Giannesini C, Papeix C, Bensa C, et al. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol 2020.

[26] Parrotta E, Kister I, Charvet L, Sammarco C, Saha V, Charlson RE, et al. COVID-19 outcomes in MS: observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. Neurol Neuroimmunol Neuroinflamm 2020;7(5).

[27] Fan M, Qiu W, Bu B, Xu Y, Yang H, Huang D, et al. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. Neurol Neuroimmunol Neuroinflamm 2020;7(5).

[28] Suwanwongse K, Shabarek N. Benign course of COVID-19 in a multiple sclerosis patient treated with Ocrelizumab. Mult Scler Relat Disord 2020;42:102201.

[29] Hughes R, Pedrotti R, Koendgen H. COVID-19 in persons with multiple sclerosis treated with ocrelizumab — A pharmacovigilance case series. Mult Scler Relat Disord 2020;42:102192.

[30] Devogelaere J, D’Hooghe MB, Vanderhaeurnt F, D’Haeleele M. Coronavirus disease 2019: favorable outcome in an immunosuppressed patient with multiple sclerosis. Neurol Sci 2020;41(8):1981–3.

[31] Soresina A, Moratto D, Chiarini M, Paolillo C, Baresi G, Foca E, et al. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. Pediatr Allergy Immunol 2020.

[32] Safavi F, Nourbaksh 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.

[33] Sormani MP, Italian Study Group on C-ims. An Italian programme for COVID-19 infection in multiple sclerosis. Lancet Neurol 2020;19(6):481–2.

[34] Mateen FJ, Rezaei S, Alakel N, Gazdag B, Kumar AR, Vogel A. Impact of COVID-19 on U.S. and Canadian neurologists’ therapeutic approach to multiple sclerosis: a survey of knowledge, attitudes, and practices. J Neurol 2020.

[35] Chen Q, Yuan S, Sun H, Peng L. CD3 + CD20 - T cells and their roles in human diseases. Human Immunol 2019;80(3):191–4.

[36] Thornton JR, Harel A. Negative SARS-CoV-2 antibody testing following COVID-19 infection in Two MS patients treated with ocrelizumab. Mult Scler Relat Disord 2020;44:102341.