INTRODUCTION

The coronavirus disease of 2019 (COVID-19) pandemic created new challenges for persons with Multiple Sclerosis (pwMS). Initial papers presenting COVID-19 cases suggest that clinical presentation is more severe in people with advanced age, immunosuppression, and co-morbidities such as hypertension, diabetes, smoking, obesity. The B-cell depleting drug, ocrelizumab, which is used to treat active and progressive MS, is considered an immunosuppressant. Ocrelizumab was shown to be effective in relapsing-remitting multiple sclerosis (RRMS) and primary-progressive multiple sclerosis (PPMS) in phase 3 of OPERA and ORATORIO clinical trials. Research showed that infectious complications were seen more frequently in ocrelizumab groups than in control groups (interferon-beta-1a or placebo). Most of these infections were mild and moderate, with severe infections being bacterial (pneumonia, urinary tract infections, and cellulitis). Patients with PwMS are usually at a more advanced age (>50) and have restricted ambulation, which causes further problems like obesity, which, in turn, impacts respiratory function. Besides, pwMS are more prone to pulmonary infection.

Immunosuppressant drugs deplete or alter the function of immune cells by different mechanisms. Knowing the pathophysiology...
of COVID-19 infection, we could predict the effect of a particular medication.\(^5\)\(^,\)\(^10\)\(^-\)\(^13\) Firstly, an initial antiviral response during COVID-19 infection is mainly driven by T-cells and B-cells to a lesser extent. So to say B-cell depleting agents may be more favorable than T-cell depleting drugs.\(^11\) Secondly, the acute phase of COVID-19 presenting as acute respiratory distress syndrome (ARDS) is caused by excessive cytokine release; that is why theoretically, immunosuppressants should be helpful in this scenario. Considering immune cells as the main source of cytokines during the infection.\(^14\)\(^,\)\(^15\) Although patients on ocrelizumab survived COVID-19 infection, larger groups are needed to validate this outcome.\(^11\)\(^,\)\(^14\)

Considering the magnitude of COVID-19, it is not unusual that information spreads with great speed, and studies related to this pandemic are framed in a short time. Papers report controversial information and do not present definite answers. The pwMS have access to all this information and wonder what they should do during this pandemic. People with chronic diseases and those older than 65 were officially put on lockdown during the pandemic. Nevertheless, they still risk COVID-19 infection\(^16\) during scheduled ocrelizumab infusion visits, MS-relapse, or other non-emergency visits. However, some centers maintained patient control by telehealth or phone visit.\(^17\) Public health measures managed to flatten the peak of virus spread, but this problem could still be with us for several years. MS progression and disability do not seem to be solved shortly; that is why treatment strategies should not be managed in a short-term fashion; we must consider long-term problems and our patients’ best interests.\(^5\) Turkish Government officially ended some of the social restrictions on 01.06.2020. We aimed to reach out to pwMS on Ocrelizumab treatment by phone and see how they deal with the situation. Did they get a medical consultation to ease their worries, make decisions by themselves considering routine visits and treatment management, how were these decisions related to their disease status in terms of severity, and how were they influenced by their doctor in charge? Overall, we tried to see the whole picture in this specific group of pwMS, which will give us preliminary information on improving patients’ compliance with treatment and seeing challenges from their perspective.

2 | MATERIAL AND METHODS

This is a cross-sectional descriptive study of pwMS on ocrelizumab treatment registered in a tertiary care center in Izmir, Turkey. Approval was obtained from The Ministry of Health of the Turkish Republic and the University’s ethics committee, the requirement for written consent was waived. We included all the 240 pwMS on ocrelizumab treatment registered in our clinic. Participants were interviewed by phone during work hours from 02.06.2020 till 14.07.2020. Phone calls were made by the Multiple Sclerosis Study Group Team. Multiple Sclerosis Study Group Team is a research-oriented team of the Multiple Sclerosis Unit of the University and consists of neurologists, nurses, physiotherapists, and psychologists. Inclusion criteria were a willingness to participate. Exclusion criteria were cognitive decline, which will prevent verbal communication and comprehension.

Before the interview, verbal consent was obtained from all the participants. All the participants were asked the same questions in the same order. We gathered information from 199 of a total of 240 registered pwMS who are on ocrelizumab treatment. Forty-one were out of reach or did not answer the phone call. Several attempts were made each time. Data regarding gender, age, disease duration, marital status, duration of being on ocrelizumab treatment, and information about the number of people they live together were taken. After gathering the answers of all the participants, we accumulated related answers into groups. Questions related to the COVID-19 pandemic were asked: compliance with a stay at home recommendations (Yes, No); have they been tested positive for COVID-19 (Yes, No); how epidemic affected their worries about MS (Nothing changed, Decreased, Increased); did lockdown influenced their planned hospital visits (Was held as scheduled, Canceled but was held by phone, Missed because of fear to go out, Missed because of travel restrictions). “Was held as scheduled” and “Canceled but was held by phone” were grouped as “Had as scheduled.” Scheduled visits do not include appointments for infusion therapy. Because all the participants are registered in the University’s database, we acquired the latest EDSS for each person from our registry. During the phone call, we asked if there were any changes in their condition related to MS. We also looked at the correlation of treatment delay with gender, EDSS, age, disease duration, progressive versus the relapsing-remitting course. Descriptive analyses were performed using IBM SPSS Statistics 26.0 software.

3 | RESULTS

A total of 199 pwMS participated in this survey. Mean duration of phone call is 5.2 minutes (SD 2.2; min-1.6, max-15.1). 121 (60.8%) of participants were female, 78 (39.2%) were male. Mean age 48 (SD 11; min-22, max-78). Nine (4.5%) were living alone. 76(38.2%) have relapsing-remitting, 123 (61.9%) have either secondary or primary-progressive form of MS. Mean disease duration was 17.1 (SD 8.4; min-2, max-44) years. Mean baseline EDSS was 5.3 (SD 1.7; min-0, max-8.5). Participants’ demographic data are also shared in Table 1.

12 (6%) missed their scheduled control visit: 7 (3.5%) because they were afraid to go out, and only 5 (2.5%) because of travel restrictions (Table 2). 33 (16.6%) responded that their scheduled control was held by phone. Two of them did not get the infusion because they were afraid to go to the hospital, and one was afraid to go out. 177 (89%) of participants continued their treatment during the pandemic. 22 (11%) missed their ocrelizumab infusion because of fear of going out or fear of hospital visits, including those three whose scheduled control visits were canceled but were held by phone (Table 3).

Of those 115 (57.8%) who were doing physical exercises before the pandemic as part of their treatment or healthy lifestyle, no one...
discontinued exercising. However, 31 (15.6%) spent less time doing sports than before the pandemic, and 18 (9%) increased exercise time. None were diagnosed with COVID-19, though 6 (3%) underwent a test to detect COVID-19; the results were negative. 18 (9.1%) said that the epidemic and the lockdown that ensued positively influenced their MS: because of work closure, they can spend more time at home, as going out was increasing their stress, their MS was more protected during the lockdown, and there is more time for physical exercises. However, 53 (26.6%) said that the lockdown increased their level of stress. Normality requirements were not met (Kolmogorov-Smirnov Sig. = 0.000). Spearman’s correlation analyses were done. The correlation between treatment delay and loneliness status was statistically significant (P = .029; Figure 1). Loneliness was determined as “living alone.” All other patients were grouped as “not alone.”

4 | DISCUSSION

We surveyed pwMS on ocrelizumab treatment, registered in tertiary MS clinic in Turkey, during lockdown because of the COVID-19 pandemic. Though this was not a comparative study, the information we gathered is valuable for us and gives us insight into what matters for patients. Every Monday is a Demyelinating Disease control day in our clinic, which was canceled during the pandemic through March 2020 till June 1, 2020. Nevertheless, we called all patients who had scheduled visits for Mondays during these three months out of the present study’s scope. Furthermore, during this period, patients had plenty of questions about MS drugs and hospital visits. We answered all these questions via phone or e-mail. Because there were no research-based definite recommendations about the use of immunosuppressive medications and

---

TABLE 1  Demographic and clinical data of participants

|                          | All participants N = 199 | Patients With Treatment Delay* N = 22 |
|--------------------------|--------------------------|--------------------------------------|
| Female, n (%)            | 121 (60.8)               | 14 (63.6)                            |
| Male, n (%)              | 78 (39.2)                | 8 (36.4)                             |
| Age mean, y (SD)         | 48 (11)                  | 46.3 (10.5)                          |
| Disease course, n (%)    |                          |                                      |
| Relapsing-Remitting      | 76 (38.2)                | 8 (36.4)                             |
| Progressive              | 123 (61.9)               | 14 (63.6)                            |
| Disease duration mean, y (SD) | 17.1 (8.4)           | 17.3 (7.9)                           |
| EDSS mean, n (SD)        | 5.3 (1.7)                | 5.6 (1.5)                            |
| EDSS 4 or less, n (%)    | 49 (24.6)                | 4 (18.2)                             |
| EDSS 4, 5 or more, n (%) | 150 (75.4)               | 18 (81.8)                            |

*Numbers and percentages are representing participants who experienced a delay in treatment (n = 22).

TABLE 2  Survey data of participants

|                          | All participants N = 199 | Patients With Treatment Delay* N = 22 (11%) |
|--------------------------|--------------------------|--------------------------------------------|
| *How pandemic affected your life,* n (%) |                      |                                            |
| Positively               | 18 (9.1)                 | 2 (9.1)                                   |
| Negatively               | 53 (26.6)                | 6 (27.3)                                  |
| No change                | 128 (64.3)               | 14 (63.6)                                 |
| *What matters most during the pandemic in terms of disease,* n (%) |                      |                                            |
| More worried about contracting COVID-19 | 11 (5.5)               | 1 (4.5)                                   |
| MS could get worse       | 51 (25.6)                | 5 (22.7)                                  |
| No change                | 137 (68.8)               | 16 (72.7)                                 |
| Scheduled visits, n (%)  |                         |                                            |
| Missed because of fear to go out | 7 (3.5)                | 3 (13.6)                                  |
| Missed because of travel restriction | 5 (2.5)                | 4 (18.2)                                  |
| Had as scheduled         | 187 (94)                 | 15 (68.2)                                 |

*Numbers and percentages are representing participants who experienced a delay in treatment (n = 22).

***Was held as scheduled” and “Canceled but was held by phone” were grouped as “Had as scheduled”. Scheduled visits does not include appointments for infusion therapy.
controversies in the published literature, we did not stop or change current treatment options. We think that the risk of MS worsening, which will inevitably arise with the withdrawal or prolonged delay of ocrelizumab infusion, would be more severe than the threats from the pandemic. Because ocrelizumab is an infusion that must be given once in 6 months, one would expect its protective effects to decrease gradually after 6 months from the last infusion. However, to reduce COVID-19 risk to a minimum, we postponed some scheduled appointments for infusion therapy for a week or 2 weeks. We set up these infusion visits in local clinics close to patients' addresses whenever possible. None of the respondents said that they were afraid of the immunosuppressive effect of ocrelizumab. And out of 11 (5.5%) persons, who were more desperate for contracting COVID-19 infection than their MS exacerbation, only one discontinued the treatment. We may hypothesize that the treatment delay of 22 (11%) participants during the lockdown was not caused by fear of immunosuppressive drug use but rather by a general fear of contracting a fatal disease.

The fact that there was not a single positive case of COVID-19 complies with other observations that the incidence of COVID-19 among those on immunosuppressive treatment is not different from the general population or even protected. However, this could also result from the fact that people with chronic diseases and immunosuppressants could be more consistent with public health regulations during the pandemic. Which logically could lead to the fewer incidence of COVID-19 infection among this specific group of people. However, this should be demonstrated in population-based studies.

Interestingly, 18 (9.1%) of participants noted the positive effect of governmental restrictions. They have more time for themselves, are engaged in exercises, and were protected from stressful work and outdoor environments. In contrast, 53 (26.6%) reported that staying at home increased their level of stress. It shows that lifestyle change could be favorable for some and detrimental for others, stressing patient-based decision making and the importance of issues other than drugs regarding disease management.

Discontinuation of DMT for more than six months leads to increased progression rate in older patients and higher relapse rates in younger patients. Because COVID-19 spread continues to be an issue, treatment discontinuation will face us with other problems in future, and we should not forget that it takes time for DMT to be effective. Adherence rates for treatment in pwMS vary from 41% to 88% across studies. In the present study, the adherence rate was 89%, which is more valuable because it was achieved during the pandemic. We looked at the correlation between therapy delay and other factors. We find out that living alone and treatment delay are positively correlated. This relation was statistically significant, but this statement and its clinical significance should be tested in larger groups.

Living alone does not mean that a person does not have family or social support, but having someone around could be more supportive during the pandemic. Studies show that treatment adherence is high if patients have external support from spouses and friends. We do not know if family members were more educated about continuing treatment because MS drugs do not pose a risk during the pandemic,
or patients themselves were more worried about their MS. Maybe the presence of another person at home made them feel more secure in terms of COVID-19. In addition to the notion mentioned above that people with chronic diseases are more stringent with public health regulations during the pandemic, other limitations are worth mentioning. We tried but could not reach 41 of 240 pwMS on ocrelizumab treatment, which compose 17% of registered patients. They could have dramatically changed the numbers in a favorable or unfavorable direction. We did not ask the respondents whether they would have gotten the infusion provided in a safe environment at home. We assumed that there was no fear of the immunosuppressive effect of ocrelizumab because it was not why patients discontinued the treatment. This research reflects the conditions of patients of one center, lacking a multicenter study’s power. Moreover, it is a short time for observations. We need more time and more extensive studies to see the actual results of the pandemic on disease course and treatment management.

5 | CONCLUSIONS

In conclusion, because ocrelizumab is a comparatively novel treatment, it could lead to more concerns during the pandemic; this was one reason we focused our attention on this group of patients. We managed to monitor our patients closely during this pandemic. We understand the importance of good conductance and keeping patients informed about the situation before they fall under the influence of false or unproven news. MS is a progressive and disabling disease, and doctors should think twice before discontinuing the treatment.

ACKNOWLEDGMENT
Not applicable.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
The study conception and methodology were designed by CB, PY, and SO. All authors contributed to the material preparation, data collection. CB performed the formal analysis, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL
The research protocol was approved by Dokuz Eylul University Ethics Committee (code: 2020/15-32).

CONSENT TO PARTICIPATE
Verbal consent was obtained from all the participants.

CONSENT FOR PUBLICATION
Verbal consent was obtained from all the participants.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon request. The datasets generated and analyzed during the current study are available from the corresponding author on request.

ORCID
Cavid Baba  https://orcid.org/0000-0001-5455-7080

REFERENCES
1. Wu C, Chen X, Cai Y et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934. https://doi.org/10.1001/jamainternmed.2020.0994
2. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-848. https://doi.org/10.1007/s00134-020-05991-x
3. Hauser SL et al. Ocrelizumab versus Interferon Beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376(3):221-234. https://doi.org/10.1056/nejmoa1601277
4. Riederer F. Ocrelizumab versus placebo in primary progressive multiple sclerosis. J. Fur Neurol. Neurochir. Und Psychiatr. 2017;18(1):30-31. doi:https://doi.org/10.1056/nejmoa1606468
5. 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 Dis. 2020;39:102073-https://doi.org/10.1016/j.msard.2020.102073
6. Guillemin F, Baumann C, Epstein J, et al. Older age at multiple sclerosis onset is an independent factor of poor prognosis: a population-based cohort study. Neuroepidemiology. 2017;48(3-4):179-187. https://doi.org/10.1159/000479516
7. Polläck ML, Barak Y, Achiron A. Late-onset multiple sclerosis. J Am Geriatr Soc. 2001;49:168-171. https://doi.org/10.1046/j.1532-5415.2001.49038.x
8. Nelson RE, Xie Y, DuVall SL, et al. Multiple sclerosis and risk of infection-related hospitalization and death in US veterans. Int J MS Care. 2015;17(5):221-230. https://doi.org/10.7224/1537-2073.2014-035
9. Wijnands JMA, Kingwell E, Zhu F, et al. Infection-related health care utilization among people with and without multiple sclerosis. Mult Scler. 2017;23(11):1506-1516. https://doi.org/10.1177/135245851661198
10. Suwangoze K, & Shabarek, N. Benign course of COVID-19 in a multiple sclerosis patient with Ocrelizumab. Mult Scler Relat Disord. 2020;42:102201. https://doi.org/10.1016/j.msard.2020.102201
11. 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;42:9-10. https://doi.org/10.1016/j.msard.2020.102120
12. 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
13. Saari TT. An Italian programme for COVID-19 infection in multiple sclerosis A call from the European Academy of Neurology on COVID-19 A call for a global COVID-19 Neuro Research Coalition. Lancet Neurol. 2020;19(6):481-482. https://doi.org/10.1016/s1474-4422(20)30301-0
14. Giovannoni G. Anti-CD20 immunosuppressive disease-modifying therapies and COVID-19. Mult Scler Relat Disord. 2020;41:102135.
15. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol.* 2020;20(5):269-270. https://doi.org/10.1038/s41577-020-0308-3

16. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA - J Am Med Assoc.* 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585

17. Collins TR. COVID-19: how neurologists are defining those ‘essential’ visits in migraine, stroke, epilepsy, and multiple sclerosis. *Neurology Today.* 2020;6(9):1-23. https://doi.org/10.1097/01.NT.0000666948.60903.9e

18. Giovannoni G, Rhoades RW. Individualizing treatment goals and interventions for people with MS. *Curr Opin Neurol.* 2012;25:520-527. https://doi.org/10.1097/01.wco.0000413321.32834.a

19. Hajjaj FM, Salek MS, Basra MKA, Finlay AY. Non-clinical influences on clinical decision-making: a major challenge to evidence-based practice. *J R Soc Med.* 2010;103(5):178-187. https://doi.org/10.1258/jrsm.2010.100104

20. Kister I, Spelman T, Patti F, et al. Predictors of relapse and disability progression in MS patients who discontinue disease-modifying therapy. *J Neurol Sci.* 2018;391:72-76. https://doi.org/10.1016/j.jns.2018.06.001

21. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *J Manag Care Pharm.* 2013;19(SUPPL):1. https://doi.org/10.18553/jmcp.2013.19.s1.s24

22. Klauer T, Zettl UK. Compliance, adherence, and the treatment of multiple sclerosis. *J Neurol.* 2008;255(SUPPL. 6):87-92. https://doi.org/10.1007/s00415-008-6016-8

How to cite this article: Baba C, Yigit P, Dastan S, et al. Challenges of persons with multiple sclerosis on ocrelizumab treatment during COVID-19 pandemic. *Neurol Clin Neurosci.* 2022;10:3-8. https://doi.org/10.1111/ncn3.12561