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Original article

Safety of disease-modifying treatments in SARS-CoV-2 antibody-positive multiple sclerosis patients

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) raises particular concerns for people with multiple sclerosis (PwMS) on disease-modifying treatments (DMTs), and for physicians caring for them. The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on PwMS receiving DMTs that inhibit immune cell trafficking, such as natalizumab (NTZ) and fingolimod (FTY), remains to be determined, as do the possible effects of these drugs on both the infection and the related disease.

Aims: To describe self-reported COVID-19 symptoms and disease severity in PwMS on NTZ or FTY who received serology confirmation of SARS-CoV-2 infection.

Methods: From 27th April to 3rd May 2020, telephone interviews were conducted with 140 PwMS under treatment with NTZ or FTY in order to collect structured data on multiple sclerosis (MS) and COVID-19. The patients, all followed at our center, were classified as symptomatic, paucisymptomatic or asymptomatic on the basis of their self-reported clinical characteristics. COVID-19 severity was rated on a 7-point ordinal scale. In addition, in the period 4th May to 3rd June 2020 SARS-CoV-2 serology testing, using the Roche SARS-CoV-2 IgG assay (Elecsys®), was performed in 104/140 (74.2%) of the interviewed PwMS (50 treated with NTZ and 54 with FTY).

Results: 14/104 (13.4%) PwMS on NTZ or FTY had anti-SARS-CoV-2 antibodies: 8 met the criteria for asymptomatic, 3 for paucisymptomatic and 3 for symptomatic COVID-19 (COVID-19 severity score lower than 3). None of them required hospitalization or showed severe COVID-19 complications.

Conclusions: Despite the relatively high SARS CoV-2 seroprevalence found in this sample of PwMS, all the positive cases showed either no or only mild COVID-19 symptoms. These reassuring findings indicate a lack of COVID-19 complications in PwMS on DMTs and support the hypothesis that it is safe to maintain ongoing treatment with these drugs in the current setting.

1. Introduction

Coronavirus disease 2019 (COVID-19) raises particular concerns for people with multiple sclerosis (PwMS) receiving disease-modifying treatments (DMTs), and for the physicians caring for them. In particular, the impact of severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection on the progression of multiple sclerosis (MS) is yet to be determined, as are the effects of the related disease, in PwMS under treatment with DMTs.

In the absence of sufficient supportive data, strategies to minimize the risk of transmission of SARS-CoV2 infection in PwMS have been rapidly implemented, while consensus statements have recommended extreme caution in the use of DMTs. In particular, it has been suggested that initiation of DMTs should be delayed and that ongoing treatments [particularly immune reconstitution therapies during the depletion phase of the treatment, sphingosine-1-phosphate (S1P) modulators and

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natalizumab] should be suspended (Brownlee et al., 2020; Giovannoni et al., 2020, p. 1; Multiple Sclerosis International Federation, 2020). However, it has also been hypothesized, on the basis of their mechanisms of action, that some DMTs might be safer than others, or even protective (Amor et al., 2020; Berger et al., 2020; Louapre et al., 2020). In the present study we aimed to verify the impact of SARS-CoV-2 infection on MS patients treated with two common DMTs inhibiting immune cell trafficking, namely natalizumab (NTZ) and fingolimod (FTY), focusing on SARS-CoV-2 antibody-positive PwMS.

2. Material and methods

This study followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and received approval from the medical ethics committee of IRCCS Policlinico San Matteo Hospital in Pavia (n 20,200,052,954, 12 June 2020).

2.1. Patient recruitment

Between 27th April 2020 and 3rd May 2020 (the last week of Italy's national lockdown due to the first wave of COVID-19), neurologists with expertise in MS contacted, by phone, all patients followed at the Multiple Sclerosis Center of the Mondino Foundation, Pavia, Italy who: i) had a diagnosis of MS according to the 2010 revised McDonald diagnostic criteria (Polman et al., 2011); and ii) had been under treatment with NTZ or FTY for at least 3 months.

After obtaining their informed consent, we administered these PwMS a telephone questionnaire. Patients were asked about their current MS condition and about possible COVID-19 symptoms since 1st January 2020. We also collected information on SARS-CoV-2 infection risk, such as contact with known infected individuals, and, if appropriate, information on COVID-19 occurrence and course. If patients were unable to respond in person, information was provided by their caregiver. Additional information regarding their MS clinical status was obtained by calculating their neurological Expanded Disability Severity Scale (EDSS) score, and collecting details of comorbidities and blood tests, including lymphocyte counts, from our electronic records.

At the end of the telephone interview patients were invited to take part in the ancillary study, which included blood sampling at the Multiple Sclerosis Center within 30 days (i.e., between 4th May 2020 and 3rd June 2020, possible quarantine-related restrictions permitting) for the purpose of SARS-CoV-2 IgG testing.

2.2. SARS-CoV-2 antibody detection

Serum samples from all the patients who agreed to participate were tested using the Roche SARS-CoV-2 IgG assay (Elecsys®). Tests were classified as positive or negative according to the manufacturer's instructions.

2.3. Classification of COVID-19 by self-reported clinical characteristics

On the basis of the self-reported clinical characteristics, the PwMS were classified as: i) asymptomatic (no symptoms); ii) paucisymptomatic (1–2 symptoms, e.g. fever and cough, but without anosmia or ageusia), or iii) symptomatic (anosmia or ageusia, or at least three of the following symptoms: fever, chills, severe tiredness, sore throat, cough, shortness of breath, headache, nausea, vomiting, diarrhea) (Pollán et al., 2020).

2.4. COVID-19 severity score

A seven-point scale was used to assign COVID-19 severity scores to the PwMS (**Table 1**) (Cao et al., 2020).

2.5. Statistical analysis

The variables in our sample were analyzed using descriptive statistics. Mean and standard deviation (SD) were calculated for continuous variables, and frequencies for categorical ones. Median and interquartile range were used to describe non-normally distributed variables. Statistical analyses were carried out using STATA 14 (Texas, USA).

3. Results

In the period 27th April to 3rd May 2020, 140 PwMS (60 on NTZ and 80 on FTY) were contacted by phone by MS neurologists. A total of 104 PwMS (50 treated with NTZ and 54 with FTY) agreed to be enrolled in the ancillary study and undergo SARS-CoV-2 serology testing. Their baseline characteristics are reported in supplementary Table 1.

Of the 36 PwMS who refused to be included in the ancillary study, none met the criteria for symptomatic or paucisymptomatic COVID-19, either at the time of the phone call or 30 days later (Pollán et al., 2020).

Fourteen of the remaining 104 (13.46%) patients tested positive for SARS-CoV-2 antibodies. Among these, 3 (21.4%) reported anosmia or three or more symptoms compatible with COVID-19, and 3 individuals (21.4%) were paucisymptomatic. Eight of the 14 (57.1%) seropositive PwMS were asymptomatic (**Fig. 1**). **Table 2** reports the demographic and clinical characteristics of the 14 SARS-CoV-2 antibody-positive PwMS. As regards the management of DMTs, in accordance with the Italian guidelines, we prescribed treatment withdrawal until recovery in the paucisymptomatic and symptomatic PwMS who contacted the MS Center at the onset of, or during, possible COVID-19 (AISM).

4. Discussion

The majority of DMTs in MS have an immunomodulatory effect, aimed at minimizing the possible autoimmune response while preserving exogenous immunosurveillance. Nevertheless, some DMTs are associated with a relatively increased risk of opportunistic viral infections, for example NTZ carries a relatively increased risk of JCV-related progressive multifocal leukoencephalopathy (PML) and FTY of recurrent varicella zoster-related lesions.

There is still no strong evidence of the impact of DMTs on COVID-19. What is more, it is not well established whether PwMS have a greater risk of developing severe COVID-19, or of developing symptomatic as opposed to asymptomatic infection. In addition, the impact of SARS-CoV-2 infection on MS progression is still unknown. Above all, it remains to be determined whether the use of DMTs (in general or specific classes) affects the risk of developing severe COVID-19.

The current gold standard diagnostic test for acute SARS-CoV-2 infection is the upper respiratory tract swab, used to detect viral RNA with real-time RT-PCR. However, a swab test can only diagnose an ongoing infection. Although serological tests do not tell us a patient's current infectious status, seroprevalence studies allow investigation of exposure to the virus.

To date, a number of case reports and a few cohort studies have

Table 1
Seven-point ordinal scale for grading clinical status.

Grade*	Description
1	No hospitalization and no limitation of activities
2	No hospitalization but limitation of activities
3	Hospitalization without supplemental oxygen
4	Hospitalization with supplemental oxygen
5	Hospitalization with non-invasive ventilation or high-flow oxygen therapy
6	Hospitalization with invasive mechanical ventilation or extracorporeal membrane oxygenation
7	Death

* COVID-19 severity score.

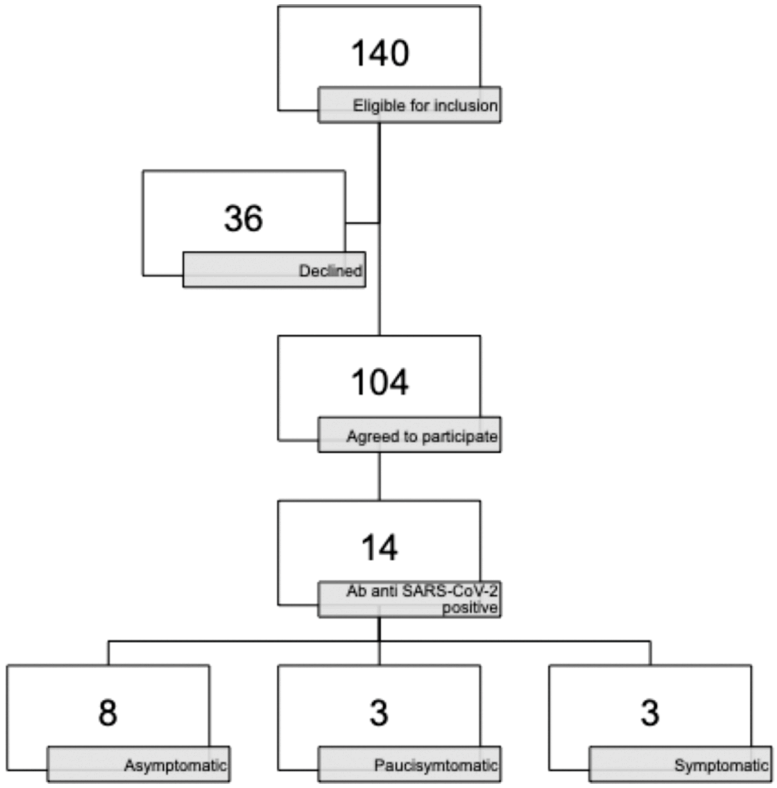

Fig. 1. one hundred-forty patients were eligible for inclusion in the study and 104 were included in the analysis. The flowchart shows the number of patiens selected for their poitive antibody status and their COVID-19 status based on their self reported clinical characterstics.

examined COVID-19 outcomes in PwMS receiving DMTs.

In particular, a French paper described the course of MS and COVID-19 in a cohort of 347 PwMS on DMTs. It showed that disability, age and obesity were the main risk factors for severe COVID-19 and that the use of DMTs did not increase the risk of a severe outcome. Conversely, patients with high EDSS scores and older age were at highest risk of severe COVID-19 (Louapre et al., 2020).

The Netherlands Society of Neurology collected data on a total of 86 MS patients with COVID-19, confirmed or suspected. Their findings did not seem to show a difference in DMT use and COVID-19 progression and outcome in their MS patients. Additionally, they found no clear link between low lymphocyte count and severe COVID-19 (Loonstra et al., 2020).

However, the above paper did not include asymptomatic patients, which, according to a recent review, can be conservatively estimated to account for up to 30% of total cases in the general population (Oran and Topol, 2020). Recent studies have shown that the asymptomatic subgroup consists primarily of younger individuals and females (Meng et al., 2020; Peckham et al., 2020), which suggests that seroepidemiological studies could help to shed light on SARS-CoV-2 exposure in PwMS (a generally young and female population).

The overall frequency of SARS-CoV-2 antibody-positive PwMS in our study was 13.46%, which is almost twice the rate (7.5%) found between 25th May 2020 and 15th July 2020 in blood donors in Lombardy, the region where all our patients resided. Notably, 57.14% of the seropositive PwMS in our cohort were asymptomatic (ISTAT). However, despite the advantages of having a study population drawn from the same environment (with the same SARS-CoV-2 contagion risk, same SARS-CoV-2 restrictions and same medical doctors), due to the small sample size of this study, its results should be interpreted with caution.

The risk of a severe COVID-19 course in PwMS using DMTs remains a major concern. Although international consensus and guidelines have provided some reassurance about the use of self-injectable DMTs and dimethyl fumarate and teriflunomide, warnings have been issued for immune suppressants (i.e., alemtuzumab, ocrelizumab and cladribine) during the depletion phase of these treatments, which can even last up to one year. Use of the most common treatments inhibiting immune cell trafficking (i.e. NTZ and FTY) has been suggested to carry intermediate risk (Baker et al., 2020). On the other hand, unnecessary withdrawal of a DMT can expose the patient to a higher risk of relapse and further disability progression.

One of the major safety issues concerning the use of NTZ during the COVID-19 pandemic seems to be the neurotrophism of SARS-CoV-2, given that the reduction of viral immunosurveillance of the CNS due to NTZ could increase the risk of COVID-19-related encephalitis, a very rare neurological complication described only in few case reports (Ellul et al., 2020). Even FTY treatment has some safety issues, since varicella zoster virus encephalitis and PML have been described in rare MS cases treated with FTY.

Conversely, albeit through very different mechanisms, both NTZ and FTY might also be protective against SARS-CoV-2 infection (Baker et al., 2020). NTZ could be beneficial by limiting monocyte and T-cell damage to the lung and also by blocking host cell entry by SARS-CoV-2 (some evidence points to integrins as alternative receptors). Similarly, FTY, a non-selective S1P receptor (S1PR) modulator, could prevent excessive recruitment by S1PR-3 of monocytes and macrophages during an abnormal inflammatory response in COVID-19. Of note, in this study we report no severe case of COVID-19.

Some observational data have been published about the course of COVID-19 in PwMS on NTZ and FTY (Supplementary Table 2). In an early report from the Italian Study Group on COVID-19 infection in MS, the clinical course was good in 30 patients on FTY and 24 on NTZ, and only two severe cases of COVID-19 were reported across both groups receiving these drugs that inhibit immune cell trafficking (Sormani and Italian Study Group on COVID-19 infection in multiple sclerosis, 2020). In the Covisep registry of symptomatic COVID-19 patients, 42 on FTY and 57 on NTZ were found to have a lower risk of developing severe COVID-19, with a mean odds ratio of 0.37 and 0.18, respectively

Table 2
Demographic and clinical characteristics of 14 SARS-CoV-2 antibody-positive people with multiple sclerosis (PwMS) divided by symptom severity: symptomatic, paucisymptomatic and asymptomatic.

Patient ID number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (yrs)	48	42	55	32	35	50	28	39	45	37	38	34	36	37
Gender	F	F	M	F	F	F	F	F	M	F	F	F	F	F
MS duration (yrs)	9	10	22	13	16	24	5	15	12	5	20	17	15	16
EDSS score at last visit	1.0	4.0	2.5	1.0	1.0	5.5	1.0	2.0	1.0	3.0	5.5	4.5	2.0	2.0
COVID-19 classification	asymptomatic	asymptomatic	asymptomatic	asymptomatic	asymptomatic	asymptomatic	asymptomatic	asymptomatic	paucisymptomatic	paucisymptomatic	paucisymptomatic	symptomatic	symptomatic	symptomatic
COVID-19 severity score	na	na	na	na	na	na	na	na	1	2	1	2	2	2
Nasopahryngeal swab	Not performed	Not performed	Not performed	Not performed	Not performed	Positive*	Not performed	Positive*	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
COVID-19 treatment	na	na	na	na	na	na	na	na	none	paracetamole	none	paracetamole	paracetamole	paracetamole
DMT for MS	NTZ	NTZ	FTY	NTZ	FTY	FTY	NTZ	FTY	NTZ	FTY	NTZ	NTZ	FTY	NTZ
DMT modification during COVID-19	na	na	na	na	na	temporary withdrawal until full recovery	na	temporary withdrawal until full recovery	temporary withdrawal until full recovery	no	temporary withdrawal until full recovery	temporary withdrawal until full recovery	no	temporary withdrawal until full recovery
Comorbidities	none	Hashimoto's disease	none	none	none	none	none	none	none	none	psoriatic arthritis	tetralogy of Fallot	none	none
MS during COVID-19	na	na	na	na	na	na	na	na	stable	stable	stable	stable	stable	stable
Lymphocyte count (per μL)	3800	3300	600	4400	1190	400	4300	680	3100	490	5300	2500	1800	4200
Smoker	no	no	yes	yes	yes	no	no	no	no	no	no	no	no	no

COVID-19: coronavirus disease 2019; DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; F: Female; FTY: fingolimod; M: Male; Na: not applicable; MS: multiple sclerosis; NTZ: natalizumab.
* Nasal swab tested with SARS-CoV2-real-time PCR was performed at least 30 days before the serological test. Nasal swab was performed due to the presence of family members with confirmed COVID-19.

(Louapre et al., 2020).

Moreover, we have previously reported two cases of asymptomatic infection in PwMS on FTY (Mallucci et al., 2020), whereas to date there are no published data on asymptomatic infection in persons treated with NTZ.

In conclusion, although we found a relatively high frequency of positive SARS-CoV-2 antibody tests, our entire cohort of PwMS was asymptomatic or had mild symptoms of COVID-19. These findings indicate that DMTs inhibiting immune cell trafficking, such as NTZ and FTY, are likely safe and suggest that they could be a good therapeutic choice for PwMS with active disease, also during COVID-19 pandemic.

Disclosure statement

Dr. Mallucci and Dr. Bergamaschi received general and non-related consultancy fees from Novartis and Biogen, manufacturers and marketing authorization holders of the compounds dealt with in this report.

Prof. Baldanti, Dr. Dal Fabbro, Dr. Zito reported no potential conflict of interest

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Statement of ethics

Observational cohort study approved from the medical ethics committee of IRCCS Policlinico San Matteo of Pavia (n 20,200,052,954; 12 June 2020).

Author contributions

GM: study concept, data acquisition, analysis and interpretation of data, drafting/revising the manuscript.

AZ and BDF: data acquisition and revising the manuscript.

FB, MG and DG: study concept, drafting/revising the manuscript

RB: study concept, data interpretation study supervision, drafting/revising the manuscript.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.102754.

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