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SARS-CoV-2 serology after COVID-19 in multiple sclerosis: An international cohort study

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Abstract

Background: The MuSC-19 project is an Italian cohort study open to international partners that collects data on multiple sclerosis (MS) patients with COVID-19. During the second wave of the pandemic, serological tests became routinely available.

Objective: To evaluate the seroprevalence of anti-SARS-CoV-2 antibodies according to the use of disease-modifying therapy (DMT) in a subset of patients included in the MuSC-19 data set who had undergone a serological test.

Methods: We evaluated the association between positive serological test results and time elapsed since infection onset, age, sex, Expanded Disability Status Scale score, comorbidities and DMT exposure using a multivariable logistic model.

Results: Data were collected from 423 patients (345 from Italy, 61 from Turkey and 17 from Brazil) with a serological test performed during follow-up. Overall, 325 out of 423 tested patients (76.8%) had a positive serological test. At multivariate analysis, therapy with anti-CD20 was significantly associated with a reduced probability of developing antibodies after COVID-19 (odds ratio (OR) = 0.20, $p = 0.002$).

Conclusion: Patients with MS maintain the capacity to develop humoral immune response against SARS-COV-2, although to a lesser extent when treated with anti-CD20 drugs. Overall, our results are reassuring with respect to the possibility to achieve sufficient immunization with vaccination.

Keywords: Multiple sclerosis, coronavirus, Sars-COV-2, immunomodulatory therapies, immunosuppressive therapies

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Introduction

The MuSC-19 project is an Italian cohort study open to international partners that collects data on people with multiple sclerosis (PwMS) and COVID-19.[1,2] This study evaluated risk factors for severe COVID-19 in PwMS, with a focus on the role of different disease-modifying therapies (DMTs).[2] The MuSC-19 cohort included both suspected and confirmed COVID-19 cases since it was not possible to test all symptomatic patients during the first wave of the pandemic.

During the second wave, real-time polymerase chain reaction (RT-PCR) on nasal and pharyngeal swabs for SARS-CoV-2 and serological tests became routinely available. Serological tests are useful tools to diagnose prior SARS-CoV-2 infection. Prior infection may reflect acquired protection, although our understanding of the significance of antibody response to SARS-CoV-2 is still limited.[3] This protection may be reduced in PwMS receiving immunomodulating/suppressive DMT, which may be reflected by decreased antibody response against SARS-CoV-2. This information may

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integrate similar data obtained in PwMS after the administration of anti-SARS-CoV-2 vaccines. To date, very limited data are available regarding the rate of seroconversion in large cohorts of PwMS previously infected with SARS-CoV-2. The aim of this study was to evaluate the seroprevalence of anti-SARS-CoV-2 antibodies according to DMT in a sample of PwMS and COVID-19 enrolled in the MuSC-19 database.

Materials and methods

Data of PwMS with suspected or confirmed COVID-19 were retrospectively collected in Italy, Turkey and Brazil. Details on data collection methods and inclusion criteria were previously reported.[1,2] Briefly, we included adult MS patients in the MuSC-19 study who had been in contact with their neurologist due to confirmed or suspected SARS-CoV-2 infection during the observation period (15 January 2020 to 10 April 2021). Confirmed cases were those with a molecular positive test (RT-PCR on nasal and pharyngeal swabs) for SARS-CoV-2 or a positive serological test obtained at any point during the observation period. Suspected cases were those with radiological findings and/or symptoms highly suggestive of SARS-CoV-2 infection according to clinical judgement (cough, fever, shortness of breath, sudden onset of anosmia, ageusia and dysgeusia) and/or close contact with a confirmed COVID-19 case in the 14 days prior to symptom onset. For this analysis, we selected a subset of patients included in the MuSC-19 data set who had performed a serological test evaluating antibodies (IgG) against different SARS-CoV-2 antigens (nucleocapsid or spike) at any point during the follow-up period, as per clinical practice. Patients were considered to have either a positive or negative serological test result based on the reference values of each laboratory.

We evaluated the association between the probability of having a positive IgG test and the time elapsed since symptom onset/positive swab (for asymptomatic patients), age, sex, Expanded Disability Status Scale (EDSS) score, RT-PCR status (positive vs negative vs not done), comorbidities and DMT exposure using a multivariable logistic model stratified by country. The level of significance was set at 5%. COVID-19 severity was categorized as follows: level 0 = asymptomatic patients, level 1 = patients without pneumonia and not requiring hospitalization or level 2 = patients who had documented pneumonia or who were hospitalized or who were admitted to an intensive care unit (ICU) or who died (grouped together due to their small individual sample sizes). The treatment duration of patients on anti-CD20 therapy was compared between serologically positive and negative patients using the Mann–Whitney *U* test. The study was approved by the regional ethics committee of Liguria (University of Genoa) (n 130/2020 – DB id 10433) and on a national level by Agenzia Italiana del Farmaco (AIFA).

Results

Data were collected from 423 PwMS (345 from Italy, 61 from Turkey and 17 from Brazil) presenting symptoms of COVID-19 or with a positive RT-PCR nasal and pharyngeal swab and a serological test performed during follow-up.

Out of 423 PwMS, 38 were asymptomatic (9%) and 71 experienced severe COVID-19 (17%), with two ICU admissions and one death. Demographic and clinical characteristics of the three cohorts are reported in Table 1. The three cohorts were homogeneous except for the following: Turkish patients were younger than Italian and Brazilian patients; the most widely used DMT was natalizumab in Italy (20%), fingolimod in Turkey (31.1%) and glatiramer acetate in Brazil (29.4%); there was a higher prevalence of hypertension in Brazil (41.2%) than in Italy (10.9%) and Turkey (9.7%).

Table 2 reports positive results of RT-PCR swabs and serological tests. Overall, 325 out of 423 tested patients (76.8%) had a positive serological test. Serological tests were positive in 73.5% of patients who had a positive RT-PCR test, in 80.4% of those who had a negative RT-PCR test and in 81% of those who did not receive an RT-PCR test. Only 22 patients (5.2%) had both a negative serological and RT-PCR test.

Serological tests were performed within a median time of 75 days after symptom onset (range = 0–401 days). Only 20 patients (4.7%) took the test within 1 week of symptom onset (11 were positive (55%) and 9 were negative (45%)). Approximately 65% of patients had a positive serological test within the first 15 days after symptom onset or a positive swab (for asymptomatic patients) ($n = 37$), 91% had a positive serological test between days 15 and 30 ($n = 42$), 79% had a positive serological test during the second month ($n = 85$), 80% during the third month ($n = 115$), 74% between months 3 and 6 ($n = 115$) and 66% after 6 months ($n = 29$) ($p = 0.07$ for heterogeneity) (Figure 1). The number and percentage of positive patients according to DMT are reported in Table 3. There were no differences in

Table 1. Clinical and demographic characteristics of the enrolled cohort.

Characteristic	Overall (*N*=423)	Italy (*N*=345)	Turkey (*N*=61)	Brazil (*N*=17)	*p*
Age — mean (SD)	42.5 (10.9)	43.3 (10.9)	37.9 (9.7)	42.8 (11.5)	0.001
Female sex — number (%)	300 (70.9)	241 (69.9)	43 (70.5)	16 (94.1)	0.099
BMI — mean (SD)	23.9 (3.9)	23.7 (4.0)	23.8 (3.2)	26.3 (4.9)	0.074
Comorbidities — number (%)					
Hypertension	39 (9.2)	29 (8.4)	3 (4.9)	7 (41.2)	<0.001
Major depressive disorder	13 (3.1)	11 (3.2)	1 (1.6)	1 (5.9)	0.642
Haematological disease	5 (1.2)	3 (0.9)	2 (3.3)	0 (0.0)	0.248
Diabetes	8 (1.9)	7 (2.0)	1 (1.6)	0 (0.0)	0.825
Cancer	7 (1.7)	7 (2.0)	0 (0.0)	0 (0.0)	0.447
Coronary heart disease	3 (0.7)	2 (0.6)	1 (1.6)	0 (0.0)	0.621
MS phenotype — number (%)					0.427
Primary progressive	16 (3.8)	16 (4.6)	0 (0.0)	0 (0.0)	
Relapsing remitting	382 (90.3)	308 (89.3)	57 (93.4)	17 (100.0)	
Secondary progressive	21 (5.0)	17 (4.9)	4 (6.6)	0 (0.0)	
Missing data	4 (0.9)	4 (1.2)	0 (0.0)	0 (0.0)	
MS duration — median (IQR)	8.8 (3.5–14.2)	9.3 (4.0–14.4)	5.7 (2.3–14.2)	7.1 (2.3–11.4)	0.049
EDSS — median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	1.5 (1.0–2.5)	2.0 (0.0–3.0)	0.131
MS treatment — number (%)					<0.001
Natalizumab	73 (17.3)	69 (20.0)	2 (3.3)	2 (11.8)	
Dimethyl fumarate	61 (14.4)	52 (15.1)	5 (8.2)	4 (23.5)	
Fingolimod	52 (12.3)	31 (9.0)	19 (31.1)	2 (11.8)	
Ocrelizumab	51 (12.1)	45 (13.0)	6 (9.8)	0 (0.0)	
Interferon	49 (11.6)	34 (9.9)	11 (18.0)	4 (23.5)	
Teriflunomide	42 (9.9)	35 (10.1)	7 (11.5)	0 (0.0)	
Glatiramer acetate	35 (8.3)	24 (7.0)	6 (9.8)	5 (29.4)	
Cladribine	9 (2.1)	9 (2.6)	0 (0.0)	0 (0.0)	
Alemtuzumab	6 (1.4)	6 (1.7)	0 (0.0)	0 (0.0)	
Rituximab	5 (1.2)	4 (1.2)	1 (1.6)	0 (0.0)	
Azathioprine	2 (0.5)	2 (0.6)	0 (0.0)	0 (0.0)	
None	38 (9.0)	34 (9.9)	4 (6.6)	0 (0.0)	
Methylprednisolone — number (%)	7 (1.7)	5 (1.4)	0 (0.0)	2 (11.8)	0.003
Asymptomatic — number (%)	38 (9.0)	28 (8.1)	8 (13.1)	2 (11.8)	0.001
No pneumonia nor hospitalization – number (%)	314 (74.2)	278 (80.6)	27 (44.3)	9 (52.9)	
Pneumonia, hospitalization, ICU, death – number (%)	71 (16.8)	39 (11.3)	26 (42.6)	6 (35.3)	

SD: standard deviation; BMI: body mass index; MS: multiple sclerosis; IQR: interquartile range; EDSS: Expanded Disability Status Scale; ICU: intensive care unit.

the percentage of patients with a positive serological test between patients with a negative RT-PCR (80%), patients with a positive RT-PCR (74%) and patients who had not undergone an RT-PCR (81%) ($p=0.11$).

According to the results of multivariate analysis, after adjusting for the time elapsed between symptom onset or RT-PCR test (for asymptomatic subjects), anti-CD20 therapy versus no therapy was the only factor significantly associated with a lower probability of developing antibodies after COVID-19 (odds ratio (OR)=0.20, $p=0.002$), with a trend for female versus male sex (OR=0.61, $p=0.10$) (Table 4). As compared to asymptomatic patients, symptomatic disease was associated with a higher probability of seroconversion (OR=2.07, $p=0.12$), which was not affected by the presence of more severe disease (OR=1.84, $p=0.25$). However, a larger sample is

Table 2. RT-PCR swab and serological test outcomes.

RT-PCR swab	Serology		Total
	Negative	Positive	
Negative	22	90	112
	19.6%	80.4%	100.0%
Positive	60	167	227
	26.4%	73.6%	100.0%
Not done	16	68	84
	19.0%	81.0%	100.0%
Total	98	325	423
	23.2%	76.8%	100.0%

RT-PCR: real-time polymerase chain reaction.

needed to confirm this association, which contrasts with results obtained by Chen et al.,[4] where individuals with greater response recovered more rapidly from symptomatic COVID-19. Figure 2 reports serological test positivity according to DMT (anti-CD20 vs others). The results did not change when the 22 symptomatic patients with both a negative RT-PCR and serological test were excluded from analysis (data not shown). Of the 56 patients treated with anti-CD20 therapy, 52 had information regarding the duration of therapy. The median treatment duration for those who tested negative ($n = 29$) was 1.49 years (range = 0.4–5.3 years), while it was shorter for those who tested positive ($n = 23$) (median treatment duration 1.15 years (range = 0.4–3.5 years), $p = 0.06$).

Discussion

This study evaluated the seroprevalence of anti-SARS-CoV-2 antibodies in PwMS who had symptomatic COVID-19 or a positive RT-PCR in a real-life setting. The study setting has a major limitation. Serological tests were conducted according to clinical practice, not a pre-planned time schedule. Therefore, there was heterogeneity in the time and frequency of serological testing after COVID-19 symptom onset. Even if neurologists were asked to report all serological evaluations performed on PwMS who had COVID-19, a reporting bias can be expected, with a higher probability of having a positive test reported than a negative one. This could have inflated the estimated positivity rate recorded in this study. However, this bias should not have affected internal comparisons between different DMTs. In addition, there was not a centralized assessment of serological tests, and different types of antibody tests were performed. Therefore, we could only assess test positivity/negativity without a quantitative assessment.

To date, it is known that a detectable IgG antibody response to SARS-CoV-2 is usually present within a few days after symptom onset.[5] IgG response is maintained, with a slow decline, for at least 90 days post-disease onset in the majority of COVID-19 patients.[3,6] These antibodies may be linked to COVID-19 severity since higher ratios were detected in patients with mild disease compared to severely ill patients (although antibody affinity to specific spike protein epitopes may also play a role in defining clinical outcome).[7] Nevertheless, humoral immune response in PwMS may also be variably conditioned by DMTs based on the mechanism of action of each drug.

Overall, the majority of PwMS in our cohort developed anti-SARS-CoV-2 antibodies regardless of whether or not they were treated with DMTs. Notably, seroconversion was detected in patients treated with cladribine, fingolimod and alemtuzumab, as already described in smaller cohorts[8,9] or pharmacovigilance reports.[10] These drugs may reduce the peripheral count or circulation of both T and B cells. Our data partially mitigate the initial concerns raised regarding the capacity of infected/vaccinated patients treated with these drugs to develop antibodies.[11]

Conversely, this study shows that PwMS under anti-CD20 therapy may have reduced antibody titres following symptomatic or RT-PCR-confirmed COVID-19, in accordance with previous case reports.[12–14] This result is consistent with our previous finding of an increased risk of severe COVID-19 in PwMS treated with anti-CD20.[1] Whether or not lower antibody titres are predictive of an increased risk of reinfection is still not established. Adaptive and innate immune responses interact in different ways in different viral infections and after vaccination. In COVID-19, the relative importance of the many arms of immune response remains unclear.[15] Indeed, patients on anti-CD20 therapy coped relatively well with viral infections. Since immune memory involves B lymphocytes as well as CD4+ and CD8+ T cells, the attainment of protection against reinfection is plausible in these patients. Follow-up studies and comparison with data on vaccinated PwMS will clarify the role of B cells with respect to different immune challenges (COVID-19 or vaccination). These results are consistent with a recently published study on vaccinated MS patients in Israel[16] who showed a reduced response to vaccination when treated with anti-CD20 therapy. Conversely, we did not detect any response differences in patients treated with fingolimod, who showed a reduced response to vaccination in the aforementioned study,[16] but the lack of any difference may be due to the qualitative nature of our assessment.

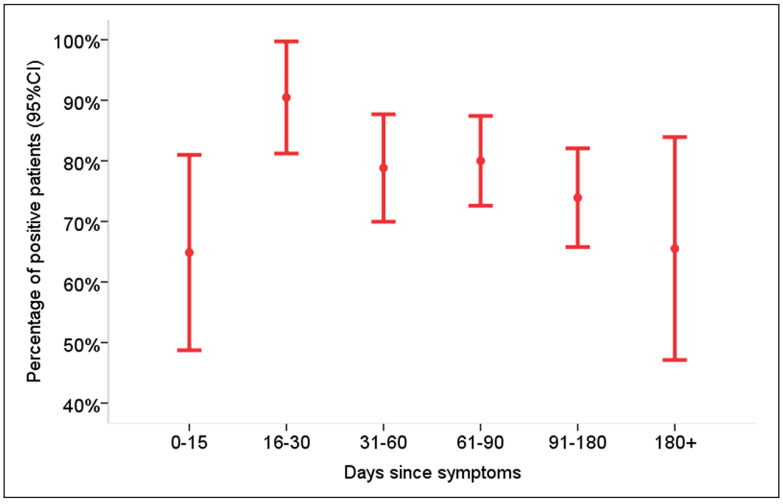

Figure 1. Percentage of positivity to serological test according to the time passed since COVID-19 symptoms or positivity to the RT-PCR test (for asymptomatic patients).

Table 3. Patients with a positive serological test according to disease-modifying therapy.

	IgG negative	IgG positive	Total
No therapy	8	30	38
	21.1%	78.9%	100.0%
Alemtuzumab	1	5	6
	16.7%	83.3%	100.0%
Azathioprine	0	2	2
	0.0%	100.0%	100.0%
Cladribine	2	7	9
	22.2%	77.8%	100.0%
Glatiramer acetate	7	28	35
	20.0%	80.0%	100.0%
Dimethyl fumarate	9	52	61
	14.8%	85.2%	100.0%
Fingolimod	11	41	52
	21.2%	78.8%	100.0%
Interferon	7	42	49
	14.3%	85.7%	100.0%
Natalizumab	15	58	73
	20.5%	79.5%	100.0%
Ocrelizumab	27	24	51
	52.9%	47.1%	100.0%
Rituximab	4	1	5
	80.0%	20.0%	100.0%
Teriflunomide	7	35	42
	16.7%	83.3%	100.0%
Total	98	325	423
	23.2%	76.8%	100.0%

In conclusion, PwMS maintain the capacity to develop humoral immune response against SARS-CoV-2 regardless of whether or not they are treated with DMTs, although this capacity is reduced with anti-CD20 drug treatment. Overall, these results are reassuring with respect to the possibility to achieve sufficient immunization with vaccination, although direct verification is needed and will be available soon.

Table 4. Multivariate analysis evaluating factors associated with the probability to have positive serological test.

Variable	Multivariate analysis[a]	*p*
	OR (95% CI)	
Age (years)	1.00 (0.97–1.03)	0.92
Sex (female vs male)	0.61 (0.34–1.11)	0.10
EDSS	1.00 (0.85–1.18)	0.99
Presence of comorbidities	0.72 (0.36–1.43)	0.35
COVID-19 severity		
Asymptomatic	Reference	
Symptoms but no pneumonia nor hospital	2.07 (0.82–5.21)	0.12
Pneumonia/hospitalization/ICU/death	1.84 (0.65–5.17)	0.25
PCR		
Positive	Reference	
Negative	0.97 (0.50–1.86)	0.92
Not done	1.06 (0.50–2.21)	0.88
Disease-modifying therapy		
No therapy[b]	Reference	
Interferon	1.83 (0.57–5.87)	0.30
Glatiramer acetate	1.29 (0.40–4.02)	0.67
Teriflunomide	1.27 (0.38–3.76)	0.68
Dimethyl fumarate	1.70 (0.57–5.25)	0.34
Natalizumab	1.06 (0.38–2.91)	0.91
Fingolimod	1.14 (0.39–3.32)	0.81
Ocrelizumab or rituximab (anti-CD20)	0.20 (0.07–0.55)	0.002
Other	1.17 (0.21–6.72)	0.85

OR: odds ratio; EDSS: Expanded Disability Status Scale; PCR: polymerase chain reaction; ICU: intensive care unit; 95% CI: confidence interval.
[a]All the analyses are adjusted for time since symptoms onset/positive swab.
[b]No therapy was chosen as the reference class.

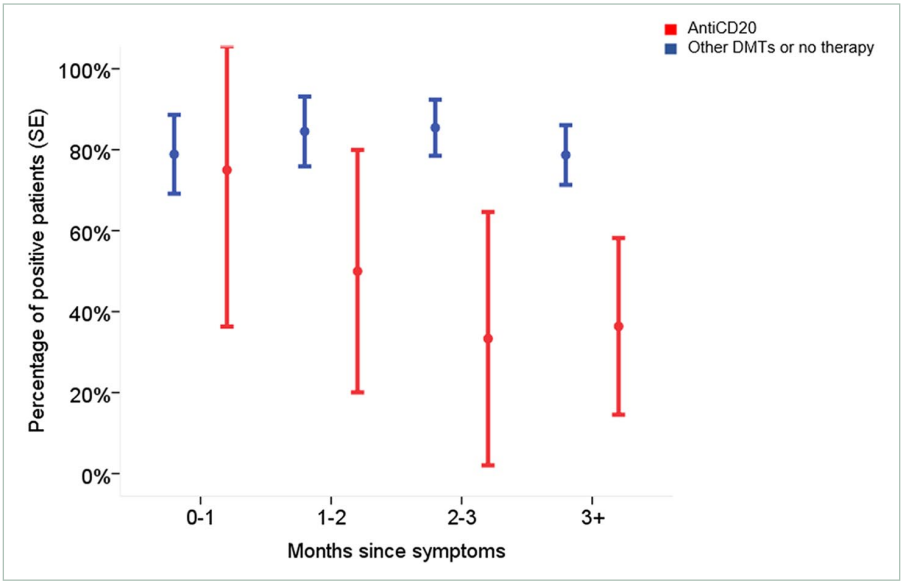

Figure 2. Percentage of positivity to serological test over time according to anti-CD20 therapy.

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Author Contributions
The MuSC-19 Study Group participants are listed in Supplementary Material.

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Supplemental Material
Supplemental material for this article is available online.

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