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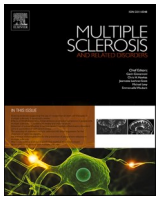
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Comparison of SARS-CoV-2 antibody response after two doses of mRNA and inactivated vaccines in multiple sclerosis patients treated with disease-modifying therapies

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ABSTRACT

Background: Disease-modifying therapy could weaken the immune system and decrease the immune response to vaccines. It is essential to know which vaccine is more protective against SARS-CoV-2 in the multiple sclerosis population.

Objective: To assess immune response after messenger RNA BNT162b2 (Pfizer/BioNTech) and inactivated Sinovac vaccines in people with multiple sclerosis (pwMS) treated with a disease-modifying therapy (DMT) compared to healthy controls.

Methods: This single-center cross-sectional study included 526 MS patients treated with DMT, 44 healthy controls, and 21 untreated patients with MS between May 2021 and September 2021. Serum samples were collected at least two weeks after the second dose of the vaccine.

Results: Participants vaccinated with BNT162b2 had a higher antibody titer than the Sinovac group (95% CI=1.023 – 1.473; $p< .001$). No significant difference between antibody titer of pwMS without treatment and HC was found [95%CI= -0.882; - 0.935 $p > .99$]. In 65 adults without DMT use (HC+pwMSwithout treatment), no seronegative cases were observed in any vaccine group. In patients treated with DMT, BNT162b2 was associated with a 16.3% greater absolute risk of seropositivity than Sinovac.

Conclusion: The mRNA vaccine could be a preferred choice of protection against SARS-CoV-2 in pMS treated with DMT.

1. Introduction

Considering the magnitude of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, vaccine development is one of the effective ways to control the disease. Several vaccines against SARS-CoV-2 are produced globally – messenger Ribonucleic acid (mRNA), inactivated virus, to name a few, but they are not equally available (Sharma et al., 2020). The safety of newer ones is already shown in multiple sclerosis (MS) (A Achiron et al., 2021). The other question is that because of the different effects of the disease-modifying therapy (DMT) on immune cells, the immunogenicity of vaccines was not well predicted in the MS population. Recent papers investigating immune response to mRNA vaccines, which have the advantage of being produced more rapidly and are considered to boost the robust immune response against the SARS-CoV-2, showed a decreased antibody response with fingolimod and ocrelizumab (A Achiron et al., 2021; Sormani et al., 2021), highly active DMT's to treat MS.

On the other hand, some vaccines are produced using inactivated virus technology and do not generate a strong immune response unless used with an adjuvant, such as alum (Sharma et al., 2020). The immunogenicity of inactivated Sinovac in people with multiple sclerosis (pwMS) is relatively unexplored. At the beginning of 2021, Turkey started vaccination with inactivated Sinovac. Primary groups were healthcare workers, the elderly population, and people with chronic diseases. PwMS, who were in the chronic disease group, had early access to the vaccine. The young population without chronic diseases was

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among the last groups to be vaccinated. BNT162b2 (mRNA, Pfizer/BioNTech) became available in Turkey in April 2021, 2.5 months after the Sinovac. People were free to choose between those two. Since the early part of the pandemic, we have connected remotely with most patients in our cohort and have maintained close contact to this day. As soon as vaccination became possible, we motivated the individuals with MS in our cohort to get vaccinated. The main aim of this study is to compare the antibody response between pwMS and healthy controls (HC) after two doses of mRNA (Pfizer/BioNTech) and inactivated Sinovac (CoronaVac) vaccines. Another issue that we are equally curious about is whether the response to these two vaccines is different in MS patients treated with different DMTs.

2. Material and methods

This is a single-center cohort-based cross-sectional study comparing pwMS and healthy controls at Dokuz Eylul University Izmir, Turkey. University's Ethics Committee approved the study (2021/15–14). Patients in our MS cohort who came to our MS unit for any treatment, e.g., natalizumab or ocrelizumab infusion therapy, fingolimod first dose observation, or those who came to the outpatient clinic for routine control and met the inclusion criteria were included in the study. Since control visits of pwMS in our clinic are held twice a year to give every patient an equal chance to be seen and recruited, the selection process was limited by six months between May 2021 and September 2021. Written informed consent was obtained from all the participants. Adult pwMS (>18 years of age, McDonald 2017 criteria) and HC (>18 years of age) vaccinated with two doses of available COVID-19 vaccine at least two weeks before the blood sampling were eligible to participate (Xia et al., 2020; Mulligan et al., 2020). The main exclusion criteria were an immunosuppressive or immunomodulatory drug treatment other than approved DMT for MS. HC group were formed from patients' relatives and healthcare workers and their relatives. Clinical: date of MS diagnosis, latest Expanded Disability Status Scale (EDSS), current DMT (glatiramer acetate [GA], interferons [INF], teriflunomide [TER], dimethyl fumarate [DMF], fingolimod [FNG], cladribine [CLD], natalizumab [NAT], rituximab [RTX], ocrelizumab [OCR]), MS type (Clinically Isolated Syndrome [CIS], Relapsing-remitting Multiple Sclerosis [RRMS], Secondary Progressive Multiple Sclerosis [SPMS], Primary Progressive Multiple Sclerosis [PPMS]), vaccination choice, date of the first and second dose of vaccine, history of COVID-19 exposure (polymerase-chain reaction- confirmed [PCR], Clinically confirmed, Contact with the COVID-19 patient, None) and demographic (age, sex - investigator observed) data were gathered. Interferon beta-1a and ınterferon beta-1b were grouped as 'interferons'. Data on race and ethnicity were not collected. A clinical assessment was made by the neurologist at the MS clinic. PwMS and HC were adjusted by age and sex.

2.1. SARS-CoV-2 IGG antibodies

Serum samples were collected at the MS clinic of Dokuz Eylul University. Serum samples were aliquoted in 1000 μL polypropylene tubes and stored at −80 °C until analyzed. Chemiluminescent microparticle immunoassay (CMIA) was used to quantify IgG antibodies to the receptor-binding domain (RBD) of the S1 subunit of the spike protein of SARS CoV-2. The assay was performed on Abbott Architect İ2000SR system (Abbott laboratories) in accordance with the manufacturer's instructions. The cutoff level or seropositivity is ≥ 50 antibody unit (AU)/ml and linear quantification limits, 21 – 40.000 AU/ml (manufacture defined). CMIA has shown a correlation with the World Health organisation International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136). The mathematical relationship of the Abbott AU/mL unit to the WHO BAU/mL unit follow the equation BAU/mL = 0.142xAU/mL, corresponding to a cutoff at 7.1 BAU/mL (Maine et al., 2020; Kristiansen et al., 2021; https://www.corelaboratory.abbott/us/en/offerings/segments/infectious-disease/sars-cov-2).

2.2. Measurement

The primary outcome was the quantification of antibody response after two doses of the SARS-CoV-2 vaccine. Antibody levels were transformed on a Log10 scale to normalize their distribution, and the 'AU/mL Log' name was used after that. For antibody titer less than the detectable limit of 21AU/mL, in order to prevent missing data during Log10 transformation, a titer of 0.01Au/mL was used. Antibody titer of patients with MS who did not use DMT (pwMSw/oT) was compared as a separate group with pwMS with treatment and HC. Vaccines were grouped into two categories: inactivated Sinovac and mRNA BNT162b2. Using the cutoff titer for seropositivity defined by the manufacturer, the antibody response was divided into two categories: seropositive (antibody titer ≥50AU/mL) and seronegative (antibody titer <50AU/mL). CIS and RRMS were classified as a relapsing group, SPMS with PPMS as a progressive group for multivariable analyses. Each DMT group, HC and pwMSw/oT, was compared in seropositivity, antibody titer, and vaccine type.

2.3. Statistical analyses

After Log transformation, all group comparisons were made by *t*-test and ANOVA. The chi-square test was used for the comparison of the categorical data. A linear regression model was used to compare the antibody titer on a Log10 scale across patients treated with different DMTs, after adjusting for age, sex, EDSS level, disease duration, MS course, vaccine type, and time between second vaccine dose and sample collection dates. For all multiple comparisons, Bonferroni corrections were made. Two-sided hypothesis testing with significance set at $p < .05$ was used. Statistical analysis was run on IBM SPSS STATISTICS software version 26.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

3. Results

In total, 593 people were enrolled. One patient was excluded from the study because a blood sample could not be obtained despite all efforts, and another patient was excluded because the blood sample was hemolyzed. Descriptive statistics and overall comparisons were run with 591 participants. One patient with MS diagnosis used rituximab as a DMT and was excluded from the group analyses due to an insufficient number of patients to evaluate. Demographic and clinical data of vaccinated participants are shown in Table 1.

Of 591 analysed participants 526 (89%) pwMS were using DMT, 21 (3.6%) persons with MS were without treatment (pwMSw/oT) and 44 (7.4%) were HC. In the study, the proportion of people in the various treatment groups was consistent with our cohort's rate of MS drug use. Thus, the study population was representative of our cohort in terms of treatment distribution (data not shown). In total, 374 (63.3%) participants received two doses of inactivated Sinovac, and 217(36.75%) received two doses of BNT162b2.

All of HC ($n = 44$, 100%), pwMSw/oT ($n = 21$, 100%), and all patients on dimethyl fumarate ($n = 42$, 100%) and cladribine ($n = 10$, 100%) treatment have seropositive results in both vaccine types. Of 526 patients who were treated with DMT, inactivated Sinovac resulted in 121 (35.1%) seronegative and 224 (64.9%) seropositive cases; in the BNT162b2 group, 34 (18.8%) were seronegative, and 147 (81.2%) were seropositive (Fig. 1).

Only one (3.7%) patient treated with natalizumab, 14 (27.5%) treated with fingolimod, and 19 (70.4%) treated with ocrelizumab had seronegative antibody titer after the BNT162b2. In the Sinovac group, one (2.2%) patient treated with interferon, two (6.7%) treated with glatiramer acetate, four (22.2%) treated with teriflunomide, five (10.6%) treated with natalizumab, 49 (52.1%) treated with fingolimod, and 60 (72.3%) treated with ocrelizumab have seronegative results

Table 1
Demographic and clinical data of study participants.

	Sex(%)		Age-Mean (SD)	Disease duration Mean-year (SD)	MS type (%)				EDSS[a] (SD)	Vaccine type (%)		TBVS[b] Mean-day (SD)
	Female	Male			CIS[e]	RRMS[f]	SPMS[g]	PPMS[h]		Inactivated Vaccine	mRNA Vaccine	
pwMS DMT[c]	371 (70.5)	155 (29.5)	41.62 (11.4)	11.35 (7.6)	0	453 (86.2)	56 (10.7)	17 (3.2)	2.1 (2.1)	345 (65.5)	181 (34.5)	38.6 (30.2)
pwMS w/o T[d]	13 (61.9)	8 (38.1)	40.81 (11.5)	6.32 (5.8)	10 (47.6)	10 (47.6)	0	1 (4.8)	1.19 (1.4)	9 (42.8)	12 (57.2)	24.3 (13.1)
Healthy Controls	31 (70.5)	13 (29.5)	41.02 (8.1)	0	–	–	–	–	–	20 (45.4)	24 (54.6)	51.6 (46.6)
Glatiramer Acetate	36 (75)	12 (25)	45.08 (10.1)	9.62 (7.8)	0	46 (95.8)	2 (4.2)	0	1.22 (1.42)	30 (62.5)	18 (37.5)	43.6 (26)
Interferons	53 (73.6)	19 (26.4)	38.92 (9.9)	8.65 (6.3)	0	72 (100)	0	0	0.78 (1)	46 (63.8)	26 (36.2)	39.2 (31.9)
Teriflunomide	17 (68)	8 (32)	46.76 (12.9)	11.58 (8.1)	0	24 (96)	1 (4)	0	1.7 (1.7)	18 (72)	7 (28)	36.8 (23.6)
Dimethyl Fumarate	24 (57.1)	18 42.9)	35.07 (11.8)	4.52 (7.1)	0	41 (97.6)	0	1 (2.4)[i]	1.29 (0.9)	20 (47.6)	22 (52.4)	36.2 (35.4)
Cladribine	8 (80)	2 (20)	31.1 (10.4)	5.3 (3.9)	0	10 (100)	0	0	0.65 (1.1)	7 (70)	3 (30)	49.6 (45.5)
Fingolimod	106 (73.1)	39 (26.9)	40.57 (10.3)	11.89 (6.8)	0	138 (95.1)	4 (2.7)	3 (2.2)[i]	1.65 (1.8)	94 (64.8)	51 (35.2)	42.9 (32.8)
Natalizumab	60 (81.1)	14 (18.9)	37.97 (10.1)	10.5 (5.8)	0	73 (98.6)	1 (1.4)	0	1.61 (1.1)	47 (63.5)	27 (36.5)	29.7 (28.8)
Rituximab	1	0	43	3	0	1	0	0	1	1	0	29
Ocrelizumab	66 (60.6)	43 (39.4)	48.05 (10.6)	16.9 (7.2)	0	48 (44)	48 (44)	13 (12)	4.89 (1.8)	82 (75.2)	27 (24.8)	36.8 (24.6)
Total	415 (70.2)	176 (29.8)	41.5 (11.1)	–	10 (1.7)	463 (78.3)	56 (9.5)	18 (3)	–	374 (63.3)	217 (36.7)	39.1 (31.6)

a. EDSS: Expanded Disability Status Scale.
b. TBVS= Time between second vaccine dose and sample collection dates.
c. pwMS DMT = Persons with MS on Disease Modifying Therapy.
d. pwMS w/o *T* = Persons with MS without treatment.
e: CIS: Clinically Isolated Syndrome.
f: RRMS: Relapsing Remitting Multiple Sclerosis.
g. SPMS: Secondary Progressive Multiple Sclerosis.
h. PPMS: Primary Progressive Multiple Sclerosis.
i. Patients were new to our cohort. After the thorough evaluation were classified as having PPMS, and their treatment strategy was changed accordingly. They were treated with dimethyl fumarate and fingolimod at the time of vaccination.

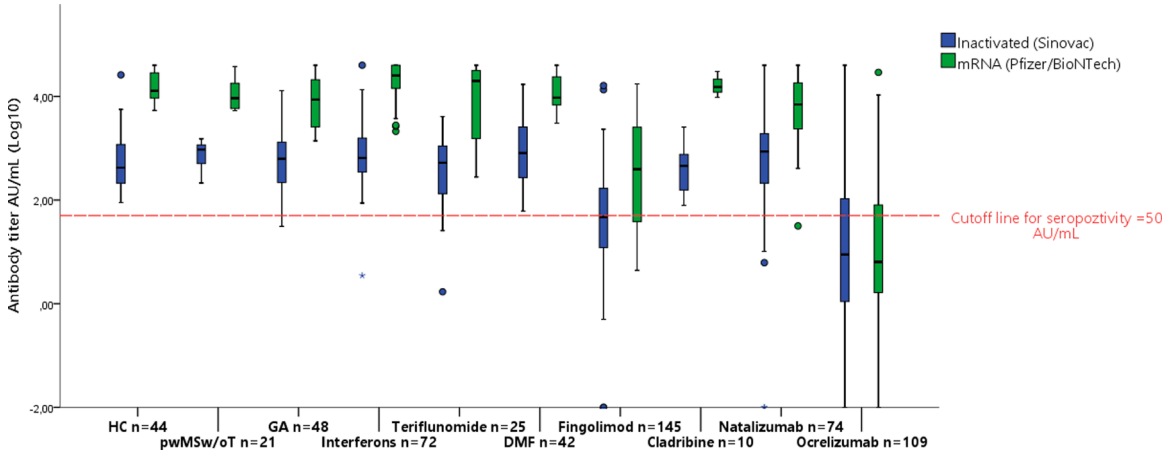


Fig. 1. Antibody levels (AU/mL Log) regarding vaccine type across the groups HC-healthy controls, pwMSw/oT=persons with multiple sclerosis without disease modifying therapy GA=glatiramer acetate, n-number of cases per group.

(Fig. 2).

Mean antibody titer Log between mRNA and inactivated vaccines was greater for mRNA group [mean difference (MD) standard error (SE)= 1.250 (0.114) 95%CI=1.026 – 1.475; $p< .001$]. No significant difference in antibody titer between pwMSw/T and HC was found [MD (SE)= 0.26 (0.379) 95%CI= −0.882; - 0.935 $p > .99$] (Fig. 3).

Of 526 patients who were on any DMT, vaccine type significantly correlated with seropositivity. (r~ 0.170 $p< .001$). Participants treated with DMT have a 16.3% greater absolute risk (probability) of seropositivity in the BNT162b2 group than in the inactivated vaccine group. The results of the multivariable regression are reported in Table 2.

Factors significantly associated with the SARS CoV-2 antibody titers were the age (β= −0.015 95%CI= −0.026;−0.003), type of vaccine (β= 0.918 95%CI= 0.701;1.135 inactivated vaccine being the reference

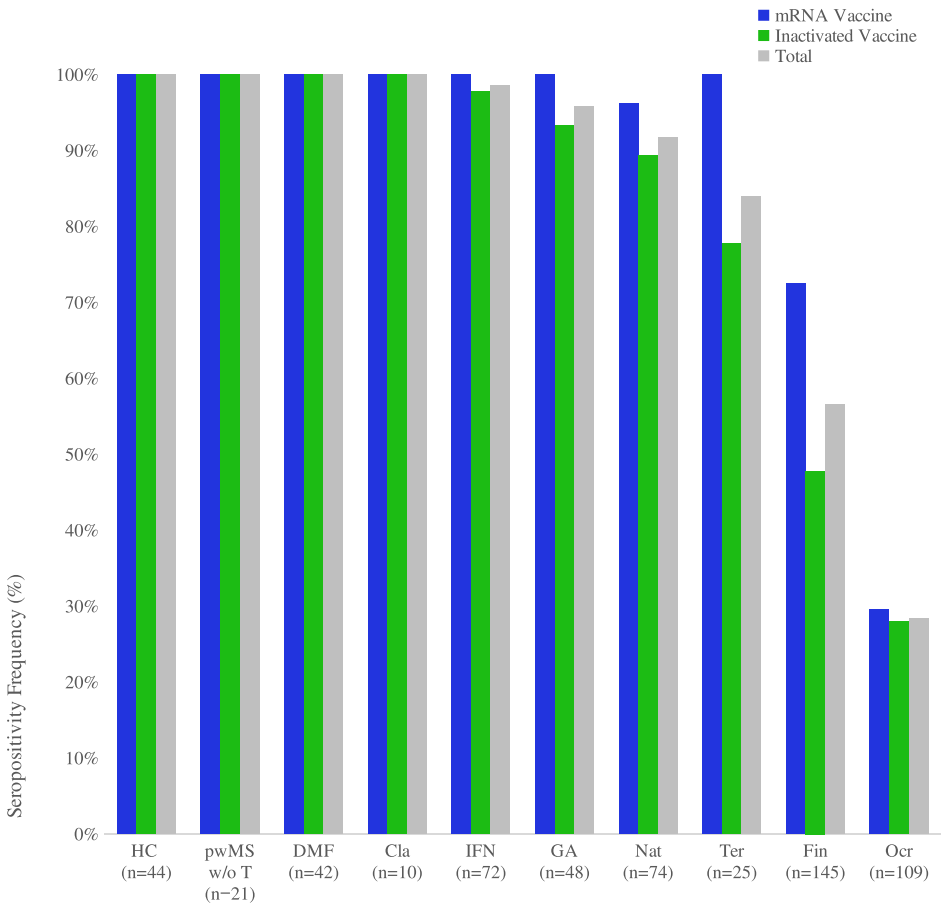


Fig.. 2. Seropositivity frequency across the groups(≥50AU/ml)
HC: Healthy Controls, pwMSw/oT: People with MS without treatment, DMF: Dimethyl fumarate, Cla: Cladribine, IFN: Interferon-beta 1a or interferon-beta 1b, GA: Glatiramer acetate, Nat: Natalizumab, Ter: Teriflunomide, Fin: Fingolimod, Ocr: Ocrelizumab, n: number of cases per group.

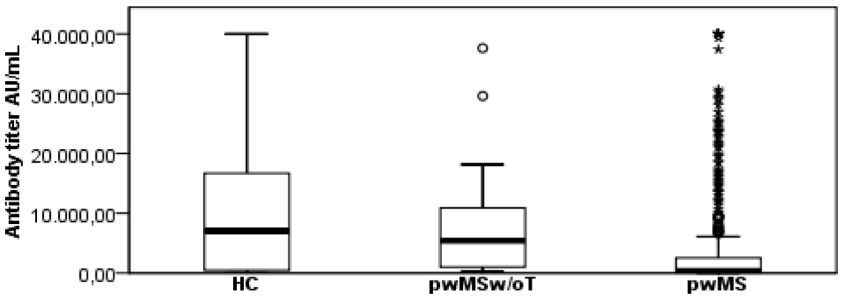


Fig. 3. Pairwise comparisons between groups for SARS-Cov-2 antibody titer (AU/mL Log)
Pairwise comparison: pwMS* – HC** [MD (SE)= −1.148 (0.224) 95%CI= −1.688; −0.610 p <0.001] pwMS – pwMSw/oT*** [MD(SE)= −1.175 (0.318) 95%CI= −1.937; - 0.412 p<.001] pwMSw/oT - HC [MD(SE)= 0.026 (0.379) 95%CI= -0.882; 0.935 p>.99] Significance values have been adjusted by the Bonferroni correction for multiple tests
*patients with multiple sclerosis using disease modifying therapy **healthy controls ***patiens with multiple sclerosis without treatment.

category), EDSS (β= −0.108 95%CI= −0.186;−0.030), and DMT used by the patient (β= −0.195 95%CI= −0.247;−0.143). Only fingolimod and ocrelizumab significantly differed among treatment groups and participants without treatment. Of 74 (%100) progressive MS patients 61(%82.43) were treated with ocrelizumab. As an explorative analysis after running multivariable regression excluding ocrelizumab from the DMT group, EDSS association was not significant (β= −0.055 95%CI= −0.13; 0.020; analyses not shown) no change in other factors in the model were observed. No significant difference was found in antibody response between pwMS treated with ocrelizumab in terms of vaccine type used (MD= 0.186; 95%CI= −0.521; 0.893; p= .60). In patients treated with fingolimod (n = 145) proportion of antibody titer Log in BNT162b2 group were significantly higher (MD= 0.886; 95%CI= 0.540; 1.232; p< .001). In fingolimod group absolute risk reduction for seronegativity with mRNA was 24.6%.

4. Discussion

In this study, antibody response to two different types of SARS CoV-2 vaccines [mRNA BNT162b2 (Pfizer/BioNTech) and inactivated Sinovac] in people with MS on different DMT was compared with healthy controls and patients without DMT at a single centre's MS population. Study results show that antibody titer was higher for mRNA vaccine (md= 1.248; 95%CI=1.023 – 1.473; p< .001). Of patients who were on any DMT and got two doses of Sinovac, 121 (%3.1) were seronegative, and in the BNT162b2 group, only 34 (%18.8) were seronegative. Although the inactivated vaccine produced by Sinovac uses alum adjuvant as an immunogenic booster, BNT162b2 appeared to have a greater response even in participants with DMT (Dong et al., 2020). In clinical trials of both vaccines, the immunogenicity response was compared to serum antibody levels of patients recovered after SARS-CoV-2. Both vaccines

Table 2
Multivariable regression analysis assessing factors associated with antibody levels (AU/mL Log).

Variable	β (SE)	%95 CI	P
Sex (female vs male)	0.033 (0.113)	−0.187- 0.256	.77
Age	***−0.015 (0.006)***	***−0.026 - −0.003***	***.01***
Vaccine type			
İnactivated vaccine	reference		
mRNA	***0.918(0.110)***	***0.701 – 1.135***	***<0.001***
TBVS[a]	−0.003 (0.002)	−0.007 - −0.000027	.05
EDSS	***−0.108 (0.040)***	***−0.186 - −0.030***	***.007***
Disease duration	−0.012 (0.009)	−0.030 – 0.005	.16
MS course (Relapsing vs progressive)	−0.173 (0.213)	−0.593 – 0.247	.42
DMT[b]			***<0.001***
	Mean difference		
No treatment[c]	reference		
Glatiramer acetate	0.364 (0.213)	−0.322 – 1.050	>0.99
Interferons	0.163 (0.192)	−0.454 – 0.780	>0.99
Teriflunomide	0.677 (0.264)	−0.172 – 1.525	.38
Dimethyl fumarate	−0.016 (0.222)	−0.730 – 0.698	>0.99
Fingolimod	***1.619(0.168)***	***1.080 – 2.157***	***<0.001***
Cladribine	0.457 (0.381)	−0.768 – 1.681	>0.99
Natalizumab	0.506 (0.191)	−0.107 – 1.119	.30
Ocrelizumab	***2.616(0.176)***	***2.051 – 3.181***	***< 0.001***

[a] TBVS= Time between second vaccine dose and sample collection dates.
[b] Disease Modifying Therapy.
[c] For multiple comparisons Bonferroni correction was used.

were able to produce immune response (Xia et al., 2020; Mulligan et al., 2020). However, the protective titer of IgG against SARS-CoV-2 is not established.

People with MS who were not using DMT did not differ significantly from HC [MD(SE)= 0.26 (0.379) 95%CI= −0.882; - 0.935 $p > .99$]. It seems that although abnormal functioning of the immune system is a culprit in the pathogenesis of MS, it does not affect the cellular and humoral response against pathogens, and reported results of immune response in pwMS are consistent with the notion that DMT is one of the risk factors for absent or decreased seroconversion (Ciotti et al., 2020). The association between higher age and lower antibody titer could be explained by diminished vaccine responses in the elderly, who also have more rapid waning of antibodies (Zimmermann and Curtis, 2019). Nevertheless, inconsistent results were reported regarding immune response to SARS-CoV-2 vaccine and its association with age (A Achiron et al., 2021; Brill et al., 2021). Our results support the previous reporting about diminished antibody response to SARS-CoV-2 vaccination in pwMS treated with fingolimod and CD-20 depleting drugs, such as ocrelizumab and rituxsimab (A Achiron et al., 2021; Sormani et al., 2021; Brill et al., 2021; Disanto et al., 2021). Some of the studies have a lower number of participants, but similar results could be attributed to the unchanged effects of those drugs. All of the research mentioned above presented the mRNA vaccine results. Only one showed results of two different mRNA vaccines (BNT162b2, Pfizer/BioNTech, Inc or mRNA-1273 Moderna Tx, Inc) [4]. Another study indicates issues with fingolimod and ocrelizumab treatment in people with multiple sclerosis after adenovirus and mRNA vaccines (Tallantyre et al., 2021). With the increasing availability of vaccines, although the opportunity to choose between them seems to be preferential, knowledge of the differences between the effects of different SARS-CoV-2 vaccines in the MS population could strengthen the scientific explanation behind the vaccine choice. Turkey is one of the countries that has been using mRNA vaccine alongside the inactivated one, which gave us the opportunity for comparison.

Although in patients treated with fingolimod, the immune response with BNT162b2 was significantly higher than for Sinovac (MD= 0.886; 95%CI= 0.540; 1.232; $p< .001$), we did not observe the same association in ocrelizumab group (MD= 0.186; 95%CI= −0.521; 0.893; $p= .60$). In the study looking for T-cell levels after the mRNA vaccine in patients treated with ocrelizumab, the response was similar to HC independent of the SARS CoV-2 antibody titer (Brill et al., 2021). Whether T-cell response would be enough to protect from severe SARS-CoV-2 infection is yet to be determined. Despite this, it has been suggested that both fingolimod and ocrelizumab treated vaccinated individuals may be at risk from symptomatic COVID-19 (Garjani et al., 2022).

One of the limitations is the lack of the generalisability of the findings of a single-center study, but enrolling a large number of patients and HC, and the fact that the data are based on a cohort of more than 3000 people with MS on active treatment can ensure homogeneity and increase the significance of the results. The study also suffers from selection bias and limitations related to the design. We did not standardize the serum sampling time. Although there was a minimum time limit of two weeks, absence of the precise information about the peak immune response time and duration of time antibodies stay at least detectable could lead to erroneous results. The other drawback is the lack of data on T-cell immunity; we did not look for lymphocyte count and specific immune cells and their relation with antibody titer, which could add to the understanding of different antibody responses in DMT groups. Single-time serum sampling is another limitation. We did not know how antibody titer would change with time and which vaccine response would last longer. We also do not know the prevaccination history of participants. In a recent study, 66.7% of seropositive patients before the vaccination were unaware of their past SARS-CoV- 2 infection (Sormani et al., 2021). Reconvalescents from SARS-CoV-2 infection could have increased immunogenicity after the vaccines.

5. Conclusions

Overall, in all the comparisons, the mRNA vaccine showed a higher antibody response than the inactivated vaccine (Khoury et al., 2021), except for the ocrelizumab group. Based on this data alone, we can not conclude which vaccine is protective against SARS-CoV-2 in pwMS treated with DMT. However, mRNA vaccines show more favourable results in this specific population of patients. Further studies regarding protective antibody titer and rate of the SARS-CoV-2 infection in vaccinated pwMS are needed to make definitive conclusions about SARS-CoV-2 vaccine choice.

Author statement

The study conception and methodology were designed by Serkan O., Yavuz D., Cavid B.

Yavuz D., Sumeyye C., Sinem O., and Ergi K. performed the material preparation and data collection.

Cavid B. and Sinem O. performed the formal analysis.

Serkan O. and Cavid B. wrote the draft.

All authors contributed to data interpretation, revising the draft and approved the final version for publication.

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Research data and material

The data that support the findings of this study are available from the corresponding author upon request if deemed appropriate.

Role of the funder/sponsor

Multiple Sclerosis Research Association (Izmir, Turkey) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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Not applicable.

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