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Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies

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Abstract

Background and Aims: The National Multiple Sclerosis Society and other expert organizations recommended that all patients with multiple sclerosis (MS) should be vaccinated against COVID-19. However, the effect of disease-modifying therapies (DMTs) on the efficacy to mount an appropriate immune response is unknown. We aimed to characterize humoral immunity in mRNA-COVID-19 MS vaccinees treated with high-efficacy DMTs.

Methods: We measured SARS-CoV-2 IgG response using anti-spike protein-based serology (EUROIMMUN) in 125 MS patients vaccinated with BNT162b2-COVID-19 vaccine 1 month after the second dose. Patients were either untreated or under treatment with fingolimod, cladribine, or ocrelizumab. A group of healthy subjects similarly vaccinated served as control. The percent of subjects that developed protective antibodies, the titer, and the time from the last dosing were evaluated.

Results: Protective humoral immunity of 97.9%, 100%, 100%, 22.7%, and 3.8%, was observed in COVID-19 vaccinated healthy subjects ($N=47$), untreated MS patients ($N=32$), and MS patients treated with cladribine ($N=23$), ocrelizumab ($N=44$), and fingolimod ($N=26$), respectively. SARS-CoV-2 IgG antibody titer was high in healthy subjects, untreated MS patients, and MS patients under cladribine treatment, within 29.5–55 days after the second vaccine dose. Only 22.7% of patients treated with ocrelizumab developed humoral IgG response irrespective to normal absolute lymphocyte count. Most fingolimod-treated MS patients had very low lymphocyte count and failed to develop SARS-COV-2 antibodies. Age, disease duration, and time from the last dosing did not affect humoral response to COVID-19 vaccination.

Conclusions: Cladribine treatment does not impair humoral response to COVID-19 vaccination. We recommend postponing ocrelizumab treatment in MS patients willing to be vaccinated as a protective humoral response can be expected only in some. We do not recommend vaccinating MS patients treated with fingolimod as a protective humoral response is not expected.

Keywords: COVID-19, humoral immune response, mRNA vaccine, multiple sclerosis, SARS-COV-2 IgG

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has caused a devastating disease with high rates of morbidity and mortality spreading all over the world.[1]

The most effective and safe way to protect people from contagious diseases is by vaccination. The lipid nanoparticle-formulated Pfizer–BioNTech COVID-19 (BNT162b2) vaccine is a new type of vaccine, based on nucleoside-modified mRNA vector vaccine encoding the prefusion spike glycoprotein of SARS-CoV-2. This vaccine proved safe and highly efficient against COVID-19 in a large cohort of patients,[2] and is currently administered all over the world.

We have vaccinated a large cohort of 555 patients with multiple sclerosis (MS) and demonstrated that the vaccine is safe for patients.[3] MS patients had similar rates of adverse reactions to what has been reported in the general population, and we did not observe post-vaccination MS worsening or an immediate increase in the rate of acute relapses. Our findings support the recommendation to MS patients not to delay vaccination during the still-expanding SARS-CoV-2 pandemic.

Although we did not find differences in the adverse events profile between untreated MS patients and patients treated with disease-modifying therapies (DMTs), data related to the ability of MS patients to elicit a protective post-COVID-19 vaccination immune response under high-efficacy DMTs are crucial.

It is well known that high-efficacy DMTs induce immunomodulation associated with lymphocyte depletion involving T cells, B cells, or both.[4,5] Ocrelizumab is an anti-CD20 monoclonal antibody that depletes B lymphocytes and thereby may interfere in the process of antibody production.[6] Fingolimod acts as an antagonist of sphingosine-1-phosphate receptor and therefore prevents lymphocyte egression from secondary lymphoid tissues and marked peripheral blood lymphopenia.[7] Cladribine is a purine analog that targets B cells more than T cells and has been shown to induce long-term selective suppression of certain subtypes of B cells, especially memory B cells.[8,9]

Currently, there are no data regarding the efficacy of the COVID-19 vaccine to induce humoral immunity in MS patients treated with these DMTs.

In the current study, we evaluated the humoral response to the BNT162b2-COVID-19 vaccine in adult MS patients to provide evidence-based guidelines to the MS community regarding the magnitude of protective immunity particularly in patients treated with high-efficacy DMTs.

Methods

Study participants and study design

We established guideline recommendations for COVID-19 vaccination for MS patients.[3] Briefly, these guideline recommendations for COVID-19 vaccination were to promote vaccination and pre-vaccination lymphocyte count for all MS patients. Patients were recommended to be vaccinated regardless of the lymphocyte count and without stopping their current immunomodulatory treatment; specifically, patients treated with B-cell depletion therapies such as alemtuzumab or ocrelizumab and patients treated with cladribine were recommended to be vaccinated at least 3 months after the last treatment dose. We included in the current observational cohort study MS patients that performed pre-vaccination lymphocyte count and received the full COVID-19 vaccination paradigm. Blood samples were evaluated for the presence of SARS-CoV-2 IgG antibodies 1 month after the second vaccine dose. A group of healthy subjects similarly vaccinated against COVID-19 served as control.

COVID-19 vaccination

Subjects received two intramuscular injections, 21 days apart, delivered in the deltoid muscle. Each injection contained 30 µg of BNT162b2 (0.3 ml volume per dose).

Detection of SARS-CoV-2 IgG antibodies

Immunoassay for the detection of SARS-CoV-2 IgG antibodies in blood samples was performed using EUROIMMUN (EI, Lubeck, Germany) anti-SARS-CoV-2 IgG quantitative ELISA kit based on a recombinant S1 subunit of the SARS-CoV-2 spike protein. The assay was performed following the manufacturer's instructions,[10] using the AGILITY® automated ELISA analyzer (DYNEX Technologies Inc., Chantilly, VA),

1 month following COVID-19 s vaccine dose. An index value higher than 1.1 was considered positive.

Ethics and data collection

The study was approved by Sheba Medical Center Institutional Review Board (Sheba.SMC - 5596-08), and the need for informed consent was waived. Each patient record was coded anonymously to ensure confidentiality during statistical analyses.

Statistical analysis

Categorical variables are described as frequency, and percentage and continuous variables were reported by their median and interquartile range. Data were compared between the healthy subjects group and the untreated MS group, and between each DMT group and untreated MS group. Fisher's exact test was applied to test the statistical significance of the difference in categorical variables between the study groups. An analysis of variance (ANOVA) model was applied to test the differences in SARS-CoV-2 IgG antibody titers between groups adjusted to suspected confounders. *P*-value cutoffs of 0.05 indicated significance. Data analyses were performed using Python (version 3.0) and SAS® (version 9.4 SAS Institute, Cary, NC).

Results

MS vaccinees

The demographic and clinical variables of the 172 study participants are presented in Table 1. We assessed 47 healthy vaccinees and 125 COVID-19 MS vaccinees comprised 72 (57.6%) females and 53 (42.4%) males; there were 76 (60.8%) relapsing-remitting, 24 (19.2%) primary-progressive, 18 (14.4%) secondary-progressive, 4 (3.2%) clinically isolated syndrome, and 3 (2.4%) radiologically isolated syndrome patients.

SARS-CoV-2 anti-spike IgG

Protective humoral immunity was demonstrated in 46/47 (97.9%) of healthy subjects and all untreated MS patients. Similarly, all MS patients under cladribine treatment developed a high level of antibodies post-COVID-19 vaccination ($p = 0.99$).

MS patients treated with fingolimod failed to develop a post-vaccination humoral response, and only 1/26 (3.8%) had an antibody response that, although attenuated, was above the cut-off value for a positive response ($p < 0.0001$).

Most patients under treatment with ocrelizumab failed to develop a post-vaccination humoral response, and only 10/44 (22.7%) demonstrated a protective antibody titer ($p < 0.0001$).

Lymphocyte count

Absolute lymphocyte count presented as three gradings (>1000 cells/mm^3, between 500 and 1000 cells/mm^3, and <500 cells/mm^3) in relation with post-vaccination SARS-CoV-2 IgG antibody titer by DMT treatment, is presented in Figure 1. The failure to develop SARS-CoV-2 IgG antibody response in fingolimod-treated MS patients could be related to the very low lymphocyte count in the majority of patients; 10/26 (38.5%) had a lymphocyte count below 500 cells/mm^3, and an additional 13/26 (50%) had lymphocyte count between 500 and 1000 cells/mm^3. Only one patient treated with Fingolimod (3.8%) showed a humoral response, but even in this subject, the SARS-CoV-2 titer was at the low protective level. This patient had a lymphocyte count of 700 cells/mm^3, while three patients (11.5%) with rates >1000 cells/mm^3 (see Figure 1) did not mount an immune response.

In ocrelizumab-treated MS patients, the failure to develop a humoral response to COVID-19 vaccine was not related to the absolute lymphocyte count as it occurred while 42/44 (95.5%) of patients had lymphocyte counts above 1000 cells/mm^3.

Time from last DMT dose

For MS patients under treatment with cladribine or ocrelizumab, we specifically evaluated the time from the last treatment dose to the time of COVID-19 vaccination. The results are presented in Figure 2. All patients treated with cladribine were efficiently vaccinated and developed a protective SARS-CoV-2 antibody titer being vaccinated as early as 4.4 months after the last treatment dose. However, for MS patients treated with ocrelizumab, the relation between the last treatment dose and an effective post-vaccination humoral response demonstrated that the

Table 1. Clinical and demographic variables of patients with multiple sclerosis that received COVID-19 vaccination under high-efficacy DMTs.

Study population	MS patients *N* = 125				Healthy subjects *N* = 47
	Cladribine *N* = 23	Fingolimod *N* = 26	Ocrelizumab *N* = 44	Untreated *N* = 32	
Follow-up after second vaccine, days					
Median	33	39.5	37	46.5	44
25–75 IQR	29.5–35.5	33.2–51.5	32–42.2	35–55	34.5–50
Gender, *n* (%)					
Females	17 (73.9)	12 (46.2)	20 (45.5)	23 (71.9)	30 (63.8)
Males	6 (26.1)	14 (53.8)	24 (54.5)	9 (28.1)	17 (36.1)
Age, years					
Median	43.1	44.9	53.2	50.5	54.3
25–75 IQR	36.3–47.9	41.3–52.0	46.4–61.7	37.1–58.9	43.1–61.9
Disease duration, years					
Median	11.0	15.7	13.4	12.5	___
25–75 IQR	6.8–21.8	8.3–20.7	5.5–20.2	6.6–18.8	
Disability by EDSS					
Median	3.0	2.0	5.5	2.0	___
25–75 IQR	1.3–4.7	1.1–3.4	4.0–6.0	1.0–5.3	
Time from last Tx dose to vaccination, months					
Median	7.1	NA	4.9	___	___
25–75 IQR	6.1–9.4		4.1–5.3		
Patients with positive SARS-CoV-19 IgG					
N, (%)	23 (100)	1 (3.8)	10 (22.7)	32 (100)	46 (97.9)
SARS-CoV-2 IgG titer					
Median	7.0	0.27	0.29	8.1	7.4
25–75 IQR	6.5–8.1	0.12–0.45	0.06–0.89	7.5–8.4	6.4–8.1
Absolute lymphocyte count					
Median	900	555	1940	1870	
25–75 IQR	630–1305	402–722	1395–2370	1650–2310	

DMTs, disease-modifying therapies; IQR, Interquartile range; EDSS, Expanded Disability Status Scale

majority 34/44 (77.3%) of patients did not develop a protective SARS-CoV-2 antibody titer when vaccinated up to 8.9 months after the last treatment dose. Those that did develop protective antibody response were vaccinated between 3.7 and 6.4 months after the last treatment dose.

Variables affecting humoral response to COVID-19 vaccine

ANOVA model analysis of SARS-CoV-2 antibody titer by DMT adjusted for age, time from the last dose to COVID-19 vaccination, and lymphocyte count, demonstrated a significant effect of time from last treatment dose to vaccination for MS patients treated with cladribine ($p=0.0211$) and for ocrelizumab ($p=0.0361$). No effect on the humoral IgG response to the COVID-19 vaccine was demonstrated for age or lymphocyte count for cladribine, ocrelizumab, or fingolimod. Compared with the other DMTs groups, ocrelizumab-treated patients had higher neurological disability by the Expanded Disability Status Scale score and 23/44 (52.2%) had a primary-progressive disease course, whereas fingolimod-treated patients had longer disease duration. These differences did not significantly affect the COVID-19 vaccine humoral response.

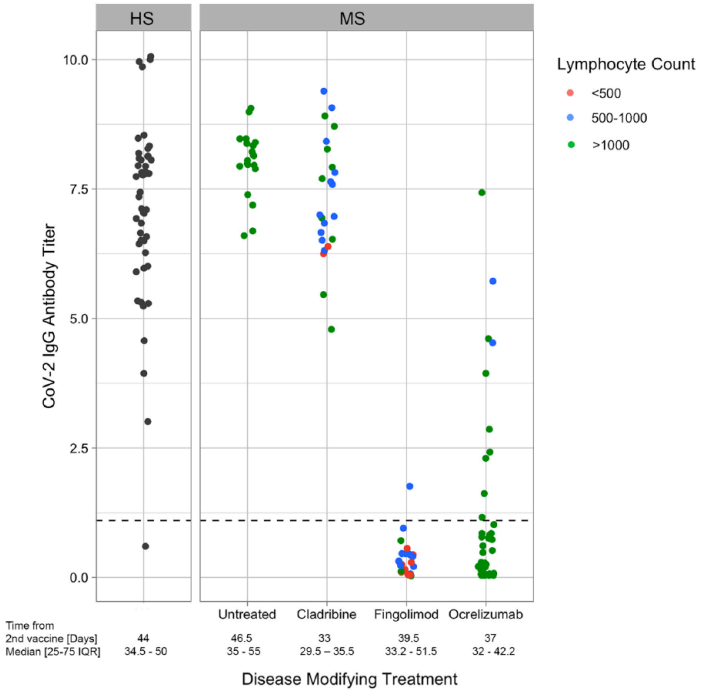

Figure 1. Post-vaccination SARS-CoV-2 IgG antibody titer by disease-modifying treatment in relation to absolute lymphocyte count presented as grading >1000 cells/mm^3 (green circles), between 500 and 1000/cells mm^3 (red), and <500 cells/mm^3 (blue).

Discussion

Vaccination against the SARS-CoV-2 pandemic is currently ongoing in large populations all over the world, and among them, many MS patients are being vaccinated. It was suggested that MS patients under DMTs might show reduced humoral response to the vaccine.[11] Our study provides first-ever real-world data on the efficacy for MS patients to develop protective humoral response following Pfizer-BNT162b2-COVID-19 vaccination. Specifically, we compared the induction of immune responses between healthy vaccinees, untreated MS vaccines, and MS vaccinees treated with high-efficacy DMTs, within 4.5–6.5 weeks following the second vaccine dose, by measuring SARS-CoV-2 IgG antibodies.

It is well known that antibody levels correlate with protection against many viruses including SARS-CoV-2, and recent data suggest that high neutralizing titers are particularly important for protection against the novel SARS-CoV-2 causing the COVID-19 pandemic.[12,13] In the current study we used the Euroimmune ELISA assay to quantify SARS-CoV-2 antibody level as it was reported to highly correlate with the neutralizing antibody assay.[14]

Our findings demonstrated that untreated COVID-19-vaccinated MS patients developed protective SARS-CoV-2 humoral responses similarly to healthy vaccinees, and similarly to the

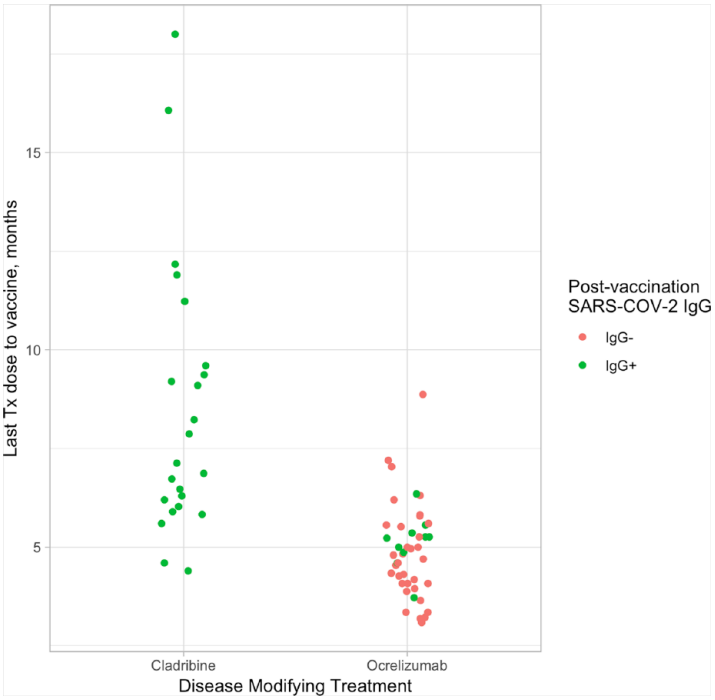

Figure 2. Time in months from last treatment dose to COVID-19 vaccination for patients with multiple sclerosis treated with cladribine or ocrelizumab in relation to post-vaccination SARS-CoV-2 IgG.
Positive post-vaccination SARS-CoV-2 IgG antibody titer is presented by a green circle; negative post-vaccination SARS-CoV-2 IgG antibody titer is presented by a red circle.

findings recently reported in the literature for non-MS vaccinees.[15]

However, for MS patients treated with high-efficacy DMTs, the immune response to COVID-19 vaccination varied.

All cladribine-treated MS patients demonstrated a protective humoral immune response to the COVID-19 vaccine. SARS-CoV-2 antibody response was already evident within 4.4 months after the last treatment dose, and the SARS-CoV-2 antibody titer did not differ from that of untreated MS patients and healthy subjects. These encouraging findings suggest that cladribine treatment does not prevent the induction of appropriate post-COVID-19 vaccination response, similar to what has been reported for cladribine-treated patients that were vaccinated against seasonal influenza and varicella-zoster.[16,17]

Post-COVID-19 vaccination humoral responses were impaired in MS patients treated with ocrelizumab or with fingolimod. The majority of vaccinated patients these medications failed to show a protective level of SARS-CoV-2 spike-specific IgG following COVID-19 vaccination protocol.

For ocrelizumab-treated patients, the failure to mount appropriate IgG immune response was regardless of the absolute lymphocyte counts that were in the normal range, or to the time-interval from the last ocrelizumab treatment dose that was from 3.1 to 8.9 months, suggesting the need to postpone the next dosing to enable an effective post-vaccination humoral response.

For fingolimod-treated COVID-19-vaccinated MS patients, the low absolute lymphocyte count in the majority of patients—88.5% had a lymphocyte count less than 1000 cells/mm^3—may be the cause for failing to mount an immune response. Moreover, even in the small group of 11.5% fingolimod-treated MS patients with an absolute lymphocyte count $>$1000 cells/mm^3, no humoral response was detected. This concerning finding suggests that a decrease in CD19+ B cells occurs irrespective of the degree of lymphopenia as was previously described.[18]

It is well described that MS patients treated with ocrelizumab or fingolimod not only have higher rates of morbidity due to viral infections,[19] but also respond less to vaccinations. Immunizing patients against influenza using the inactivated virus vaccine and the toxoid tetanus resulted in decreased vaccination-induced immune responses,[20,21] mainly due to a decline in humoral immunity. Similarly, the consequence of immunosenescence resulted in reduced adaptive immune responses to COVID-19 vaccination.

Our findings raise two major questions related to the induction of humoral responses following COVID-19 vaccination in MS patients under treatment with fingolimod or ocrelizumab.

It is not surprising that in the presence of low lymphocyte counts, as occurs in MS patients treated with fingolimod where lymphocytes are reduced by number in the peripheral blood and segregated in secondary lymphoid tissues, a failure to mount an appropriate humoral response happens. Therefore, the relevant question is related to the need to stop or switch fingolimod treatment for the purpose of re-populating the peripheral blood and with time enable patients to appropriately be vaccinated.

The second intriguing question is why ocrelizumab-treated MS patients, despite normal lymphocyte counts, fail to develop an anti-SARS-CoV-2 humoral response, even many months after the last dosing. We suggest that this failure is related to depletion of naive and memory B lymphocytes that occurs under ocrelizumab treatement.[22] These cells are responsible for the generation of antibody production, and therefore their depletion harms humoral protection.

The limitations of our study are that although it presents the first data on the efficacy of COVID-19 vaccinations in patients with MS treated with high-efficacy DMTs, the total number of vaccinated patients in each medication group is rather low. This is because of the acuity of the situation but limits the impact of the outcome, even though statistical analyses were strongly positive. Another limitation of the study is that vaccine-specific memory T- or B-cell responses were not assessed. This is of importance especially in MS patients that did not develop humoral immunity, as the absence of specific S1 spike antibodies does not necessarily mean an absence of adaptive immune response.

Our study presents the worldwide first comprehensive data on humoral COVID-19 vaccination response in patients with MS treated with high-efficacy DMTs.

In practice, following the findings of our study, we have updated our COVID-19 vaccination guideline recommendations for patients with MS. We recommend the policy of vaccinating untreated MS patients without any limitations and vaccinating cladribine-treated MS patients at least 4.4 months after the last dosing. For MS patients treated with fingolimod, we currently do not promote COVID-19 vaccination unless their lymphocyte count is above 1000 cells/mm^3. In the small percentage of fingolimod-treated patients with higher lymphocyte counts, caution is recommended as the level of lymphocytes did not confirm a correlation with a protective humoral response.

Patients treated with ocrelizumab that are at especially high risk for severe disease and death from COVID-19[23] are recommended to postpone their upcoming treatment and be vaccinated at least 9 months after the last dosing.

It is of note that fingolimod and ocrelizumab unvaccinated MS patients might be at risk either for getting infected with SARS-CoV-2 virus while being vaccination-paused or by experiencing rebound disease activity while being switched to another DMT. However, as there are countries with a shortage of COVID-19 vaccinations, our findings are of importance for health decisions for appropriately prioritizing the management of MS patients that will best benefit from COVID-19 vaccination.

Future studies are needed to further evaluate the longevity of humoral response following COVID-19 vaccination in MS patients and to further elucidate B-cell and T-cell memory responses in the DMTs-treated MS population.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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