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Original article

Humoral immune response to COVID-19 mRNA vaccines in patients with relapsing multiple sclerosis treated with ofatumumab

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ABSTRACT

Background: There are limited data available regarding the impact of ofatumumab, an anti-CD20 B-cell−depleting monoclonal antibody for relapsing multiple sclerosis (RMS), on vaccination response. The study objective was to assess humoral immune response (HIR) to non-live coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccination in patients with RMS treated with ofatumumab.

Methods: This was an open-label, single-arm, multicenter, prospective pilot study of patients with RMS aged 18−55 years who received 2 or 3 doses of a COVID-19 mRNA vaccine after ≥1 month of subcutaneous ofatumumab (20 mg/month) treatment. The primary endpoint was the proportion of patients achieving HIR, as defined by local laboratory severe acute respiratory syndrome coronavirus-2 qualitative immunoglobulin G assays. Assay No. 1 was ≥14 days after the second or third vaccine dose. Assay No. 2 was 90 days thereafter.

Results: Of the 26 patients enrolled (median [range] age: 42 [27−54] years; median [range] ofatumumab treatment duration: 237 [50−364] days), HIR was achieved by 53.9% (14/26; 95% CI: 33.4 − 73.4%) at Assay No. 1 and 50.0% (13/26; 95% CI: 29.9 − 70.1%) at Assay No. 2. Patients who received 3 vaccine doses had higher HIR rates (Assay No. 1: 70.0% [7/10]; Assay No. 2: 77.8% [7/9]) than those who received 2 doses (Assay No. 1: 46.7% [7/15]; Assay No. 2: 42.9% [6/14]). Of patients aged <40 years without previous anti-CD20 therapy, HIR was achieved by 90.0% (9/10) at Assay No. 1 and 75.0% (6/8) at Assay No. 2. No serious adverse events were reported.

Conclusion: Patients with RMS treated with ofatumumab can mount HIRs following COVID-19 vaccination. A plain language summary, infographic and a short video summarizing the key results are provided in supplementary material.

Clinical trial registration: ClinicalTrials.gov: NCT04847596 (https://clinicaltrials.gov/ct2/show/NCT04847596)

1. Introduction

Multiple sclerosis (MS) is caused by an inflammatory attack on the central nervous system, leading to neurologic disability (Compston and Coles, 2008). Memory B cells have been strongly implicated in the disease pathophysiology (Baker et al., 2017; Longbrake and Cross, 2016).

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; HIR, humoral immune response; IgG, immunoglobulin G; mRNA, messenger RNA; MS, multiple sclerosis; OCR, ocrelizumab; OMB, ofatumumab; RMS, relapsing multiple sclerosis; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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Ofatumumab (OMB) is a fully human anti-CD20 monoclonal antibody that binds to B cells, resulting in B-cell lysis and cytotoxicity (Kang and Blair, 2022). Two phase 3 trials in patients with relapsing MS (RMS) demonstrated that OMB treatment significantly reduces annualized relapse rate, magnetic resonance imaging activity, and confirmed disability worsening compared with teriflunomide (Hauser et al., 2020). OMB is approved in multiple countries for the treatment of RMS in adults (Novartis AG, 2021; Novartis Pharmaceuticals Corporation, 2020).

Because therapies for MS, including OMB, function by suppressing or modulating immune function, these therapies may potentially reduce vaccine efficacy (Farez et al., 2019). Anti-CD20 therapies may be expected to lower the humoral response to vaccination because they deplete B cells, which are precursors to antibody-producing cells (Du et al., 2017; Nutt et al., 2015). Indeed, patients with RMS treated with the anti-CD20 agent ocrelizumab (OCR) have been shown to mount diminished humoral responses toward tetanus toxoid, pneumococcal, and influenza vaccines compared with patients who were not receiving any disease-modifying therapies (DMTs) (Bar-Or et al., 2020).

Since the development of coronavirus disease 2019 (COVID-19) vaccines, there has been speculation that cell-depleting agents and sphingosine-1-phosphate receptor modulators may impact the efficacy of these vaccines in patients with MS (Houot et al., 2020; Kelly et al., 2021). Studies have reported attenuated humoral responses to COVID-19 vaccines in patients with MS who received B-cell–depleting therapies, including anti-CD20 therapies, compared with patients on other DMTs (Gadani et al., 2021). Reports regarding COVID-19 vaccination responses during OMB treatment are limited (Conte, 2022; Levit et al., 2022). Because OMB's route of administration, dosing, and binding profile differ from other anti-CD20 therapies, it is possible that humoral response following vaccination may also differ.

As such, further data are needed to better understand the impact of OMB on the immune response to COVID-19 vaccines in patients with MS. The current study aimed to assess if patients with RMS treated with OMB can mount a humoral immune response (HIR) against COVID-19 messenger RNA (mRNA) vaccination.

2. Materials and methods

2.1. Study design

This was an open-label, multicenter, single-arm, prospective pilot study (NCT04847596) in patients with RMS treated with OMB who received COVID-19 mRNA vaccination as standard of care. The study was conducted at 5 sites in the United States and Puerto Rico. The first post-vaccination serologic assessment occurred ≥14 days after the second or third COVID-19 mRNA vaccine dose (Visit 2/Assay No. 1), followed by a second assessment (Visit 3/Assay No. 2/end of study) 90 days thereafter (Fig. 1).

This clinical study was designed and carried out in accordance with the International Conference on harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki. The trial was approved by institutional review board/independent ethics committees (Copernicus Group IRB, #20211372). Patients gave written informed consent before study participation.

2.2. Patients

The trial enrolled patients aged 18–55 years with a RMS diagnosis (2017 McDonald criteria) who were currently under OMB treatment for ≥4 weeks and were (i) scheduled to receive a COVID-19 mRNA vaccination (Pfizer or Moderna), (ii) had received a single vaccination with a scheduled second dose, or (iii) had already completed 2 vaccine doses. Patients who received a third/booster vaccine dose were also eligible.

Patients were excluded if they had a previous COVID-19 diagnosis, contraindications to COVID-19 mRNA vaccination, immediate allergic reaction to past vaccine or injection, or any safety finding requiring an OMB treatment interruption within 12 weeks of vaccination. Patients were also excluded if they had recent major infections requiring hospitalization or treatment with intravenous antibiotics within 2 weeks of screening, sphingosine-1-phosphate receptor modulator treatment within 2 months of enrollment, natalizumab treatment within 6 months of enrollment, treatment with pre-specified medications (including systemic corticosteroids within 30 days of screening and other treatments listed in Supplementary Appendix A.1), contraindications to OMB treatment, or were a woman of childbearing potential not using highly effective contraception. Patients previously treated with approved anti-CD20 therapy were allowed to enroll. Due to the nature of the pilot study, there was no pre-defined period for discontinuation of prior anti-CD20 therapy required before OMB treatment initiation.

2.3. Study endpoints

The primary endpoint was the proportion of OMB-treated patients achieving HIR to COVID-19 mRNA vaccine at Assay No. 1, defined by a positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) qualitative immunoglobulin G (IgG) antibody test. Secondary endpoints were the proportion of patients achieving HIR at Assay No. 2 and reporting of adverse events (AEs) and serious AEs (SAEs).

Qualitative SARS-CoV-2 IgG (spike or receptor-binding domain) tests were done or facilitated by local laboratories. As such, determination of positive or negative results was by local laboratory threshold.

2.4. Sample size calculation and statistical analysis

Statistical analysis was performed using SAS® version 9.4 or higher.

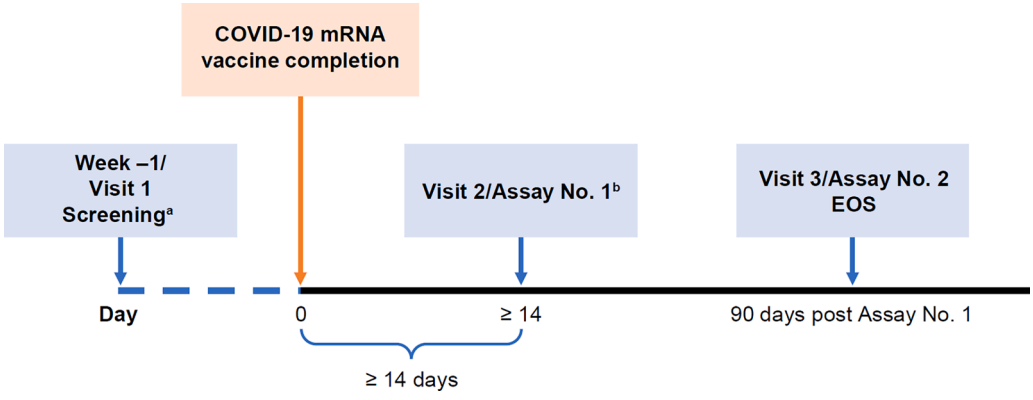

Fig. 1. Study design. [a] COVID-19 mRNA vaccine scheduled, or first dose already received. [b] If entry criteria were met at screening, Assay No. 1 may be done at Visit 1. COVID-19 = coronavirus disease 2019; EOS = end of study; mRNA = messenger RNA.

Because this was a pilot study, the sample size of 20 patients was selected based on the need for early availability of results. This sample size was to provide estimates of the proportion of patients with HIR to the mRNA COVID-19 vaccine with a margin of error (half-width of a 95% confidence interval [CI]) of 20.1%, 19%, and 17.5%, corresponding to HIR response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% of patients with missing Assay No. 2 results, 22 patients were to be enrolled.

Categorical variables are presented as counts and percentages. For the primary endpoint, number and percentage of responders are presented. The 95% CI for the proportion of responders was calculated by using Clopper-Pearson exact method. Non-responder imputation approach was applied to missing post-vaccination antibody assay for the primary endpoint regardless of intercurrent events.

3. Results

3.1. Patient disposition

Of 30 screened patients, 86.7% (26/30) completed the screening phase (Fig. 2). Of the 26 patients enrolled, 88.5% (23/26) completed the study. Reasons for study discontinuation included AE of herpes zoster ($n = 1$) and patient decision ($n = 2$). The patient with the herpes zoster AE came to the site at Visit 3 but did not perform Assay No. 2. One patient who received 3 Moderna vaccine doses and who had previous OCR treatment discontinued after the screening visit, and 1 patient discontinued after Visit 2 and did not perform Assay No. 2.

3.2. Patient demographics and clinical characteristics

Patients had a median (range) age of 42 (27–54) years and the majority were aged >40 years (57.7% [15/26]), female (80.8% [21/26]), and White (96.2% [25/26]); Table 1). At screening, patients had been on OMB treatment for a median (range) duration of 237 (50–364) days. Four patients (15.4%) had not previously received an MS DMT before OMB treatment, whereas the majority of patients (84.6% [22/26]) had, including 23.1% (6/26) who had previously received OCR. Patients had received 2 (57.7% [15/26]) or 3 (42.3% [11/26]) COVID-19 mRNA vaccine doses at screening.

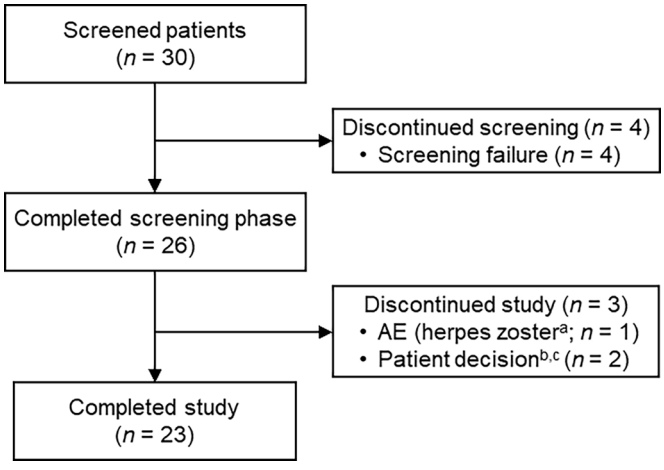

Fig. 2. Patient disposition. [a] Patient came to site at Visit 3 but did not perform Visit 3 assay (last assay performed at Visit 2 was Assay No. 1). [b] One patient (aged 43 years, who received 3 Moderna COVID-19 mRNA vaccine doses, with previous OCR treatment) discontinued after screening visit. [c] One patient discontinued after Visit 2 (last assay performed at Visit 2 was Assay No. 1). AE = adverse event; COVID-19 = coronavirus disease 2019; mRNA = messenger RNA; OCR = ocrelizumab.

Table 1
Patient demographics and clinical characteristics at screening.

Demographic or clinical characteristic	Total ($N = 26$)
Age (years)	
Mean (SD)	42.9 (7.9)
Median (range)	42 (27–54)
Age (years), n (%)	
<40	11 (42.3)
≥40	15 (57.7)
Female, n (%)	21 (80.8)
Race, n (%)	
White	25 (96.2)
Black or African American	1 (3.8)
Ethnicity, n (%)	
Hispanic or Latino	9 (34.6)
Non-Hispanic or Latino	16 (61.5)
Not reported	1 (3.8)
OMB treatment duration at screening (days), median (range)	237.0 (50–364)
No previous MS DMT before OMB treatment[a]	4 (15.4)
Previous MS DMT before OMB treatment	
Any MS DMT (excluding OMB)[b]	22 (84.6)
Glatiramer acetate	9 (34.6)
OCR[c]	6 (23.1)
Natalizumab	5 (19.2)
Dimethyl fumarate	4 (15.4)
Siponimod	4 (15.4)
Fingolimod hydrochloride	2 (7.7)
Interferon beta-1a	2 (7.7)
Immunoglobulins NOS	1 (3.9)
Teriflunomide	1 (3.9)
COVID-19 vaccine doses, n (%)	
2	15 (57.7)
3	11 (42.3)

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; OCR = ocrelizumab; OMB = ofatumumab; mRNA = messenger RNA; MS = multiple sclerosis; NOS = not otherwise specified; SD = standard deviation.
[a] One patient discontinued after Visit 2 (Assay No. 2 was not performed).
[b] Patients could have had more than one DMT before OMB.
[c] One patient (aged 43 years, who received 3 Moderna COVID-19 mRNA vaccine doses, with previous OCR treatment) discontinued after the screening visit.

3.3. HIR by assay time point

The proportion of patients who achieved a positive HIR at Assay No. 1, as assessed by qualitative SARS-CoV-2 IgG test, was 53.9% (14/26 [95% CI: 33.4–73.4%]; Table 2). Quantitative SARS-CoV-2 IgG tests were also carried out by some local laboratories, but because test methodologies differed between sites, results varied widely (data not shown).

The proportion of patients who achieved a positive HIR at Assay No. 2, as assessed by qualitative SARS-CoV-2 IgG test, was 50.0% (13/26 [95% CI: 29.9–70.1%]; Table 2). Of the 13 patients with a positive HIR at Assay No. 2, 10 had maintained HIR and 3 additional patients had achieved HIR since Assay No. 1, whereas 2 patients who had achieved HIR at Assay No. 1 were negative at Assay No. 2, and 2 patients were missing Assay No. 2 data.

3.4. HIR by number of COVID-19 vaccine doses and patient subgroups

The proportion of patients achieving a positive HIR appeared to increase with 3 versus 2 doses of COVID-19 mRNA vaccine, with 70.0% (7/10) versus 46.7% (7/15) achieving a positive HIR at Assay No. 1 and 77.8% (7/9) versus 42.9% (6/14) achieving a positive HIR at Assay No. 2, respectively (Table 2).

The impact of age on achieving a positive HIR was assessed in patients aged <40 or ≥40 years; this cutoff was chosen because the median age was 42 years. The proportion of patients aged <40 years who achieved a positive HIR was 81.8% (9/11) at Assay No. 1 and 77.8% (7/9) at Assay No. 2. For patients aged ≥40 years, these numbers were

Table 2
Humoral immune response (positive SARS-CoV-2 qualitative IgG) after non-live COVID-19 mRNA vaccination at Visit 2/Assay No. 1 and Visit 3/Assay No. 2/EOS.

	Response rate, n/M (%)[a]	
Category/subgroup	Visit 2/Assay No. 1	Visit 3/Assay No. 2/EOS
Overall	14/26 (53.9) 95% CI: 33.4 – 73.4	13/26 (50.0) 95% CI: 29.9 – 70.1
Number of COVID-19 mRNA vaccine doses		
2	7/15 (46.7)	6/14 (42.9)
3	7/10 (70.0)	7/9 (77.8)
Previous MS DMT before OMB treatment[b]		
OCR	1/5 (20.0)	3/5 (60.0)
Other[c]	13/18 (72.2)	11/17 (64.7)
Age (years)		
<40	9/11 (81.8)	7/9 (77.8)
≥40	5/14 (35.7)	6/14 (42.9)
Age <40 years, no previous OCR	9/10 (90.0)	6/8 (75.0)
Age ≥40 years, no previous OCR	4/10 (40.0)	4/10 (40.0)
Length of OMB treatment at time of Assay No. 1 (days)		
<182	5/9 (55.6)	2/7 (28.6)
≥182	9/16 (56.3)	11/16 (68.8)
Type of COVID-19 mRNA vaccine		
Moderna	4/7 (57.1)	5/7 (71.4)
Pfizer	10/18 (55.6)	8/16 (50.0)

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; EOS = end of study; IgG = immunoglobin G; OCR = ocrelizumab; OMB = ofatumumab; *M* = number of patients with laboratory data; mRNA = messenger RNA; MS = multiple sclerosis; *n* = number of patients with positive qualitative response; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
[a] Non-responder imputation for overall response rate (*N* = 26); the rest of the table shows observed case data (*N* = 25).
[b] Patients could be included in more than one category of previous DMT.
[c] Other: glatiramer acetate, natalizumab, dimethyl fumarate, siponimod, fingolimod hydrochloride, interferon beta-1a, immunoglobulins not otherwise specified, teriflunomide.

Table 3
Humoral immune response (positive SARS-CoV-2 qualitative IgG) after non-live COVID-19 mRNA vaccination by number of COVID-19 mRNA vaccine doses at Visit 2/Assay No. 1 and Visit 3/Assay No. 2/EOS.

Response rate by category/subgroup, n/M (%)[a]	Visit 2/Assay No. 1		Visit 3/Assay No. 2/EOS	
	2 doses (*n* = 15)	3 doses (*n* = 11)	2 doses (*n* = 15)	3 doses (*n* = 11)
Overall	7/15 (46.7)	7/10 (70.0)	6/14 (42.9)	7/9 (77.8)
Previous MS DMT before OMB treatment[b]				
OCR	0/3 (0.0)	1/2 (50.0)	0/3 (0.0)	1/2 (50.0)
Other[c]	7/10 (70.0)	6/8 (75.0)	7/10 (70.0)	5/7 (71.4)
No previous OCR	7/12 (58.3)	6/8 (75.0)	4/11 (36.4)	6/7 (85.7)
Age (years)				
<40	4/6 (66.7)	5/5 (100.0)	3/5 (60.0)	4/4 (100.0)
≥40	3/9 (33.3)	2/5 (40.0)	3/9 (33.3)	2/5 (40.0)
Age <40 years, no previous OCR	4/5 (80.0)	5/5 (100.0)	2/4 (50.0)	4/4 (100.0)
Length of OMB treatment at time of Assay No. 1 (days)				
<182	4/7 (57.1)	1/2 (50.0)	3/6 (50.0)	0/1 (0.0)
≥182	3/8 (37.5)	6/8 (75.0)	3/8 (37.5)	6/8 (75.0)
Type of COVID-19 mRNA vaccine				
Moderna	1/4 (25.0)	3/3 (100.0)	1/4 (25.0)	3/3 (100.0)
Pfizer	6/11 (54.5)	4/7 (57.1)	5/10 (50.0)	3/6 (50.0)

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; EOS = end of study; IgG = immunoglobin G; OCR = ocrelizumab; OMB = ofatumumab; *M* = number of patients with laboratory data; mRNA = messenger RNA; MS = multiple sclerosis; *n* = number of patients with positive qualitative response; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
[a] Observed case data (*N* = 26).
[b] Patients could be included in more than one category of previous DMT.
[c] Other: glatiramer acetate, natalizumab, dimethyl fumarate, siponimod, fingolimod hydrochloride, interferon beta-1a, immunoglobulins not otherwise specified, teriflunomide.

Table 4
Adverse events.[a]

AE, n (%)	Total ($N = 26$)
Any AE	5 (19.2)
Grade 1	4 (15.4)
Grade 2[b]	1 (3.8)
Infections and infestations	5 (19.2)
COVID-19	4 (15.4)
Herpes zoster	1 (3.8)
Streptococcal pharyngitis	1 (3.8)
Nervous system disorders	1 (3.8)
Headache	1 (3.8)
Any serious AE	0 (0.0)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events. A patient with multiple AEs within a primary System Organ Class is counted only once in the total row. A patient with multiple occurrences within the same category is counted only once. System Organ Classes are presented in alphabetical order; Preferred Terms are sorted within System Organ Class in descending frequency of AEs. A patient experiencing multiple AEs of different severity was counted once with the maximum CTCAE grade only.

[a] None of the AEs were considered to be related to treatment.

[b] The only grade 2 AE was COVID-19 infection.

35.7% (5/14) and 42.9% (6/14), respectively.

The proportion of patients with previous other treatment (glatiramer acetate, natalizumab, dimethyl fumarate, siponimod, fingolimod, interferon beta-1a, immunoglobulins, teriflunomide) who achieved a positive HIR was 72.2% (13/18) at Assay No. 1 and 64.7% (11/17) at Assay No. 2. The numbers of patients identified with either previous OCR or no previous treatment were small. For patients who received previous OCR, a positive HIR was achieved by 20.0% (1/5) at Assay No. 1 and 60.0% (3/5) at Assay No. 2. Of patients aged <40 years with no previous OCR, HIR was achieved by 90.0% (9/10) at Assay No. 1 and 75.0% (6/8) at Assay No. 2.

Length of OMB treatment and brand of COVID-19 mRNA vaccine did not appear to impact the proportion of patients achieving a positive HIR at Assay No. 1. Response appeared to be better in those receiving the Moderna mRNA vaccine (response in 71.4% [5/7]) compared with the Pfizer vaccine (response in 50.0% [8/16]) at Assay No. 2, although numbers were small. Data based on full versus half doses of the Moderna vaccine are not available for this study.

When comparing the proportion of patients achieving a positive HIR by 2 or 3 doses of COVID-19 mRNA vaccine, response rates were generally higher with 3 versus 2 doses of vaccine across subgroups at both Assay No. 1 and Assay No. 2 (Table 3). The proportion of patients with no previous OCR who received 3 doses of COVID-19 mRNA vaccine and who achieved a positive HIR was 75.0% (6/8) at Assay No. 1 and 85.7% (6/7) at Assay No. 2. Notably, all patients aged <40 years who received 3 doses of mRNA vaccine without previous anti-CD20 therapy achieved a positive HIR at both Assay No. 1 (5/5) and Assay No. 2 (4/4).

3.5. Safety

Overall, 19.2% (5/26) of patients reported ≥1 AE, including COVID-19 infection in 15.4% ($n = 4$), and herpes zoster infection, streptococcal pharyngitis, and headache in 3.8% ($n = 1$) each (Table 4). AEs were mostly (80.0% [4/5]) grade 1, with the exception of 1 grade 2 AE of COVID-19 infection. None of the AEs were considered to be related to treatment. No SAEs were reported.

All 4 patients who contracted COVID-19 infection in this study did so in Q1 2022. These infections occurred 5–9 months after the last vaccination in 3 patients who received 2 Moderna vaccine doses and in 1 patient who received 3 Pfizer vaccine doses. Two patients had a negative HIR following COVID-19 vaccination at both Assay No. 1 and Assay No. 2. All infections resolved within 3 weeks. No patients received preventative antibody-based combination treatment with tixagevimab and cilgavimab. One patient received nirmatrelvir and ritonavir antiviral treatment for COVID-19 infection.

4. Discussion

This study showed that a proportion of patients with RMS treated with OMB for ≥4 weeks, and as long as 364 days, could subsequently mount a positive HIR after COVID-19 mRNA vaccination. The HIR rate was similar to the 60% seropositivity rate previously reported in 11 (Sabatino et al., 2023) and 5 (Ziemssen et al., 2022) OMB-treated patients. The observed response rate is also consistent with the humoral qualitative response rates reported in several OCR studies (Achiron et al., 2021; Apostolidis et al., 2021; Brill et al., 2021; Oreja-Guevara et al., 2022). In one such study, only 3 of 20 patients treated with OCR developed a humoral response after receiving both doses of the Pfizer vaccine (Oreja-Guevara et al., 2022). In other studies, HIR rates of 23–56% have been reported for OCR-treated patients following completion of their COVID-19 vaccination course (Achiron et al., 2021; Brill et al., 2021; Gadani et al., 2021; Karussis et al., 2021; Sabatino et al., 2023). However, one study with 25 OCR-treated patients reported a higher rate of HIR positivity (85%) (Sabatino et al., 2023). Notably, these comparisons should be interpreted with caution because the studies used varying immunoassays, and positive testing thresholds between laboratories can be highly variable. Factors that appeared to impact HIR development in this study included the number of COVID-19 mRNA doses, previous OCR treatment, and age. All OMB-treated patients aged <40 years in the current study who received 3 doses of COVID-19 mRNA vaccine and who had not received previous OCR treatment could mount a positive HIR after COVID-19 mRNA vaccination, although this particular cohort was small (Assay No. 1: $n = 10$; Assay No. 2: $n = 8$). Higher positive HIR rates were observed in patients who received 3 versus 2 vaccine doses and no previous OCR treatment versus previous OCR treatment, as well as in younger (<40 years) versus older (≥40 years) patients. Notably, 3 patients who were negative at Assay No 1 had achieved HIR at Assay No. 2. One of these patients had received a booster vaccine dose after Assay No. 1, whereas the results for the other 2 patients were likely attributed to varying testing methodologies.

In previous studies, patients with MS receiving OCR or OMB demonstrated a reduced HIR following SARS-CoV-2 vaccination, compared with healthy controls (Faissner et al., 2022; Sabatino et al., 2023) and those receiving beta-interferon, glatiramer acetate, dimethyl fumarate, teriflunomide, or no DMT (Ziemssen et al., 2022). Nonetheless, in COVID-19–vaccinated patients with MS receiving OMB, an increase in neutralizing antibody levels and the presence of a T cell response were identified (Faissner et al., 2022; Ziemssen et al., 2022). Additionally, a recent study in patients with RMS treated with OMB reported that the proportion of fully or partially vaccinated patients who experienced a breakthrough COVID-19 infection was small (Cross et al., 2022). This suggests that an appropriate HIR can be mounted even in the presence of a B-cell–depleting therapy, such as OMB, and is consistent with the findings of the present study.

In studies of healthy adults vaccinated with COVID-19 mRNA vaccines, 95.7–100% developed antibody immune responses in the weeks following 2 doses of the Moderna (Jackson et al., 2020) and Pfizer (Favresse et al., 2021) vaccines. For both vaccine types, the level of COVID-19 antibodies waned after ~40 days (Doria-Rose et al., 2021; Favresse et al., 2021; Jackson et al., 2020) and could be boosted by a third vaccination to the same or a greater level than the highest levels seen after 2 vaccinations (Chu et al., 2022; Rastawicki et al., 2022). This study's findings demonstrated that the proportion of patients with RMS with a positive HIR reduced slightly over time and increased with 3 versus 2 vaccine doses.

The age of patients in this study was similar to that in the phase 3 OMB trials (mean age of 38–39 years, depending on treatment group) (Hauser et al., 2020), and HIR was higher with younger patients (<40 years). Older patients (≥65 years) have been shown to exhibit reduced functions in some aspects of their immune systems and lower primary vaccine response rates compared with younger patients, which has been attributed to immunosenescence (Crooke et al., 2019). With the hepatitis A vaccine, a lower initial immune response rate could be seen in individuals aged >40 years versus those who were younger (Link-Gelles et al., 2018), suggesting that age effects are not limited to the most elderly; however, these differences were not typically seen after 30 days. In healthy adults, lower COVID-19 antibody levels have been seen in those aged >56 versus 18–55 years following 2 Pfizer vaccine doses (Doria-Rose et al., 2021); however, a qualitatively positive HIR could still be detected in 95% of individuals aged >60 years (Bag Soytas et al., 2022).

In this study, only 20% of 5 patients who received previous OCR had a positive HIR ≥14 days post full vaccination versus 75% in those who received other treatment. Previous studies have shown attenuated humoral responses to COVID-19 vaccines in patients with MS who received B-cell–depleting therapies, including OMB, compared with patients on other DMTs (Conte, 2022; Levit et al., 2022). In a retrospective study by Levit et al. on COVID-19 vaccination seroconversion in patients with MS (Levit et al., 2022), the subcutaneous B-cell–depleting therapy, OMB, had a seropositivity of 75% in the small number of patients tested ($n = 4$), whereas the infused B-cell–depleting therapies, OCR and rituximab, had a seropositivity of 43% (19/44) and 11%#x00A0;(1/9), respectively. Recent data have shown that few patients with MS treated with OCR repopulate their B cells by the end of the standard 6-month OCR dosing interval (Baker et al., 2022), whereas model-based predictions showed that 50% of patients repleted to ≥110 B cells/μL or baseline levels ~9 months since last OMB dose compared with 11% for OCR (Savelieva et al., 2017), and B-cell levels can begin to increase as soon as 2 months after OMB dose (Bar-Or et al., 2018). Thus, OCR may have a more sustained impact on the B-cell population than OMB after discontinuation (Savelieva et al., 2017). Nonetheless, with monthly dosing, circulating B-cell levels remain low or absent (Savelieva et al., 2017; Yu et al., 2022). Additionally, circulating B-cell levels may not indicate the varying degrees of depletion and repletion in tissues (Hausler et al., 2018). Several other factors may also play a role in differential immune effects. Improved lymph node targeting with subcutaneously administered anti-CD20 therapies was observed in a mouse model, compared with intravenous administration (Torres et al., 2022). Preclinical animal data have also shown that marginal zone B cells in the spleen and lymph nodes are spared with OMB treatment, demonstrating different susceptibility of B-cell subtypes, which is consistent with other anti-CD20 therapies (Theil et al., 2019). Different mechanisms of B-cell lysis among anti-CD20 therapies may also lead to their varying effects on immune cells (Beers et al., 2010). These complex interactions result in different effects on humoral immunity among the various B-cell therapies.

Both cellular responses and HIR have been shown to contribute to immunity against COVID-19 generated by vaccination in healthy individuals (Anderson et al., 2020; Sahin et al., 2020). Previous studies in patients with MS on OCR have shown that although antibody responses can be attenuated or even absent, T-cell responses were relatively normal (Apostolidis et al., 2021; Gadani et al., 2021; Iannetta et al., 2022; Katz et al., 2022). Notably, immunoassays used to assess T-cell responses varied among these studies. Therefore, further study is warranted into T-cell responses to COVID-19 mRNA vaccines in OMB-treated and other anti-CD20–treated patients with RMS. In 4 patients with MS treated with OMB from a single center in the ALITHIOS phase 3b trial who had mild COVID-19 infections, T-cell immunity, as assessed by interferon-gamma ELISpot, was present in all 3 patients who were tested (Adamec et al., 2022). Interim findings from the open-label multicenter KYRIOS trial showed T-cell response was not affected by OMB treatment after initial and booster vaccination, as assessed by ELISpot (Ziemssen et al., 2022). KYRIOS is 1 of 2 phase 4 trials (NCT04869358, NCT04878211) that are currently ongoing to further assess humoral and cell-mediated immune response to COVID-19 mRNA vaccines in OMB-treated patients with RMS.

This study showed that COVID-19 mRNA vaccination given alongside OMB treatment was well tolerated in patients with MS; AEs were mostly grade 1 and there were no SAEs reported. Four patients experienced COVID-19 infections 5–9 months after their last vaccination. Given the timing of these infections (January/February 2022), they are likely to have been due to the Omicron variant. The efficacy of COVID-19 mRNA vaccines against Omicron variants has been controversial, but many studies show some effectiveness (Link-Gelles et al., 2022, 2023).

5. Limitations

This was an open-label single-arm pilot study with a limited sample size, and most patients were female and White. There was no control arm of patients on other DMTs or healthy individuals for direct comparisons. SARS-CoV-2 IgG tests were performed qualitatively by local and not central laboratories, using local procedures and different assays, with thresholds set according to the particular IgG test used in each laboratory; this may have resulted in variation of testing outcomes. Data on B- and T-cell responses to vaccination were not collected. Additionally, only the OMB start date was collected at baseline, so information is lacking on exact timing of ongoing OMB injections in relation to COVID-19 vaccination. This study did not assess the relationship between measured HIR and protection from COVID-19 infection. As such, no conclusions can be drawn on whether the HIRs seen in this study were protective. Currently, the HIR threshold for seroprotection after COVID-19 mRNA vaccination in the general population is unknown and may depend upon factors unrelated to vaccine response (such as virus variant). Further studies are required to assess whether the HIR to COVID-19 mRNA vaccinations in individuals with RMS receiving OMB is clinically meaningful.

6. Conclusions

The findings of this study suggest that many OMB-treated patients with RMS can mount an HIR after COVID-19 mRNA vaccination. The findings are encouraging, indicating that patients with RMS treated with OMB should receive COVID-19 mRNA vaccinations. Given that a sizable proportion of OMB-treated patients did not respond with HIR, continued vigilance against COVID-19 infection by patients with RMS receiving OMB treatment is recommended.

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CRediT authorship contribution statement

Amit Bar-Or: Conceptualization, Validation, Data curation, Writing – review & editing, Visualization. **Rany Aburashed:** Conceptualization, Investigation, Writing – review & editing, Visualization. **Angel R. Chinea:** Conceptualization, Investigation, Writing – review & editing, Visualization. **Barry A. Hendin:** Conceptualization, Investigation, Writing – review & editing, Visualization. **Elisabeth Lucassen:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration. **Xiangyi Meng:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing, Visualization. **James Stankiewicz:** Conceptualization, Writing – review & editing, Visualization. **Mark J. Tullman:** Conceptualization, Investigation, Writing – review & editing, Visualization. **Anne H. Cross:**

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Declaration of Competing Interest

Amit Bar-Or has been a speaker in meetings sponsored by and received consulting fees and/or grant support from Atara Biotherapeutics, Biogen, Celgene/Receptos, Janssen/Actelion, Mapi Pharma, MedImmune, Merck/EMD Serono, Novartis, Roche/Genentech, and Sanofi Genzyme. **Rany Aburashed** has received consulting fees, research grants, and/or speaker honoraria from and served on scientific advisory boards for Bayer, Biogen, Genentech, Novartis, Sanofi, and Teva Pharmaceuticals. **Angel R. Chinea** has been a speaker for Allergan, Biogen, EMD Serono, Genentech, Novartis, Sanofi Genzyme, and Teva Pharmaceuticals. **Barry A. Hendin** has received advisory and speaking honoraria from Alexion Pharmaceuticals, Biogen, EMD Serono, Genentech, Genzyme, Horizon Therapeutics, Novartis, and TG Therapeutics. **Elisabeth Lucassen** and **James Stankiewicz** are employees of and stockholders in Novartis Pharmaceuticals Corporation. **Xiangyi Meng** was an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, at the time of this analysis and during the development of this article. **Mark J. Tullman** has received consulting fees, research support, and/or speaking honoraria from Banner Life Sciences, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Genzyme, Horizon Therapeutics, Novartis, and TG Therapeutics. **Anne H. Cross** has received consulting fees and/or research support from Biogen, Bristol Myers Squibb, Celgene, Horizon Therapeutics, Janssen/Actelion, Jazz Pharmaceuticals, Merck/EMD Serono, Novartis, Roche/Genentech, and TG Therapeutics.

Data availability

The trial data are available on reasonable request, provided that it is in line with current ethical and intellectual property requirements surrounding the use of data. Requests should be directed through ClinicalStudyDataRequest.com.

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Supplementary materials

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