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Humoral Immune Response to COVID-19 mRNA Vaccines in Patients With Relapsing Multiple Sclerosis Treated With Ofatumumab

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SUMMARY

1. **This pilot study showed that patients with RMS treated with ofatumumab (OMB) for ≥4 weeks could subsequently mount a positive HIR after COVID-19 mRNA vaccination (Assay No. 1: 53.9% [14/26]; Assay No. 2: 50.0% [13/26])**
2. **Age appeared to affect response, with 36% (5/14) and 43% (6/14) of patients aged ≥40 years achieving HIR at Assay No. 1 and Assay No. 2, respectively, vs 82% (9/11) and 78% (7/9) of patients aged <40 years**
3. **Although the number of patients identified with previous OCR use was small, decreased HIR achievement was observed with previous OCR use compared with other previous treatments**

INTRODUCTION

- Ofatumumab (OMB; Kesimpta®), a fully human anti-CD20 monoclonal antibody, is approved for the treatment of adults with relapsing multiple sclerosis (RMS) in the United States and European Union[1,2]
- Since the emergence of the coronavirus disease 2019 (COVID-19) global pandemic, there has been speculation that cell-depleting agents, including anti-CD20 therapies such as OMB, may impact the efficacy of COVID-19 vaccination in patients with MS[3,4]
- It is important to understand whether patients treated with OMB can mount a protective immune response to the COVID-19 vaccine

OBJECTIVE

- To report findings of a phase 4 study assessing the effects of OMB on humoral immune response (HIR) to non-live messenger RNA (mRNA) COVID-19 vaccines in patients with RMS

METHODS

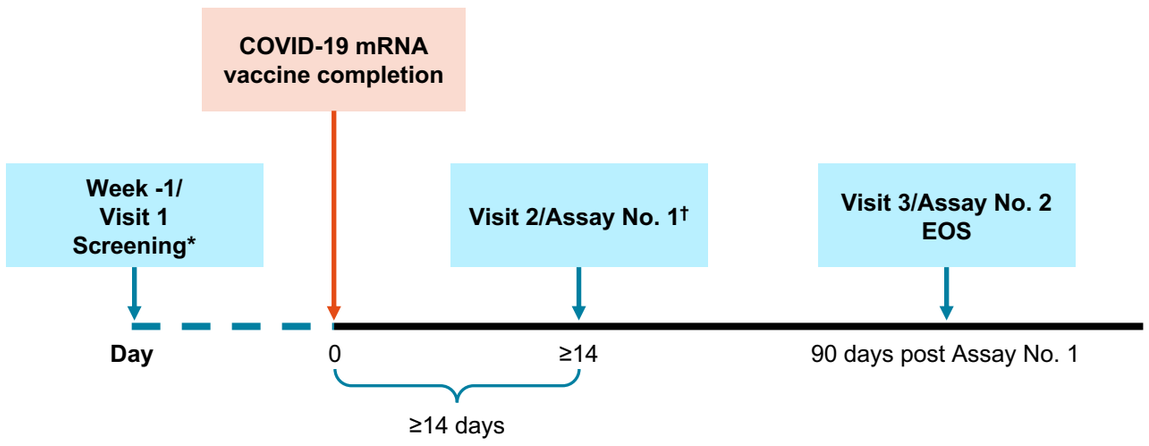
STUDY DESIGN

- This was an open-label, single-arm, prospective pilot study conducted at 5 sites in the United States and Puerto Rico (NCT04847596)
- Eligible patients included patients with RMS aged 18-55 years who received or scheduled mRNA COVID-19 vaccination (Pfizer or Moderna) ≥4 weeks after starting OMB treatment
  - Patients had (i) been scheduled for vaccination, (ii) received a single vaccine with a scheduled second dose or (iii) already completed 2 doses of vaccination
  - Patients who received a third/booster vaccine were also eligible
- 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 90 days after Assay No. 1 (Visit 3/Assay No. 2/end of study; **Figure 1**)
- Qualitative severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) immunoglobulin G (IgG) tests were done/facilitated by local laboratories

STUDY ENDPOINTS

- **Primary endpoint:** Patients achieving HIR to COVID-19 mRNA vaccine at Assay No. 1, as defined by a positive SARS-CoV-2 qualitative IgG antibody assay (yes/no)
- **Secondary endpoints:** Patients achieving HIR to COVID-19 mRNA vaccine at Assay No. 2, adverse events (AEs) and serious AEs (SAEs)

Figure 1. Study Design



COVID-19, coronavirus disease 2019; EOS, end of study; mRNA, messenger RNA
*Vaccine scheduled or first dose already received; †If entry criteria were met at screening, Assay No.1 may be done at Visit 1

RESULTS

PATIENT DEMOGRAPHICS AND DISPOSITION

- Of 26 patients included in the study, the median age was 42 years (range, 27-54) and the majority of patients were female (80.8% [21/26]), White (96.2% [25/26]) and non-Hispanic/Latino (61.5% [16/26]; **Table 1**)
- At screening, the median duration of OMB treatment was 237 days (range, 50-364) and most patients (84.6% [22/26]) had received previous MS disease-modifying therapy before OMB treatment
- 57.7% (15/26) of patients had received 2 vaccine doses and 42.3% (11/26) had received 3 doses

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 (3.9)
Ethnicity, n (%)	
Hispanic or Latino	9 (34.6)
Non-Hispanic or Latino	16 (61.5)
Not reported	1 (3.9)
OMB treatment duration at screening, days, median (range)	237 (50-364)
Previous MS DMT before OMB treatment	
Any MS DMT (excluding OMB)	22 (84.6)
Glatiramer acetate	9 (34.6)
OCR*	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)
Treatment naïve before OMB start†	4 (15.4)
COVID-19 vaccine doses, n (%)	
2	15 (57.7)
3	11 (42.3)

COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; MS, multiple sclerosis; NOS, not otherwise specified; OCR, ocrelizumab; OMB, ofatumumab; SD, standard deviation
*1 patient (aged 43 years, who received 3 Moderna COVID-19 mRNA vaccine doses, with previous OCR treatment) discontinued after screening visit; †1 patient discontinued after Visit 2 (last assay performed at Visit 2 was Assay No. 1)

ACHIEVEMENT OF HIR TO COVID-19 mRNA VACCINE BY ASSAY TIME POINT

- At Assay No. 1, 53.9% (14/26 [95% CI: 33.4-73.4%]) of patients achieved a positive HIR (**Table 2**)
- At Assay No. 2, 50.0% (13/26 [95% CI: 29.9-70.1%]) of patients achieved a positive HIR (**Table 2**)
  - Of these patients, 10 had maintained HIR, and 3 additional patients had achieved HIR since Assay No. 1
  - 2 patients who achieved HIR at Assay No. 1 were negative at Assay No. 2, and 2 were missing Assay No. 2 data

ACHIEVEMENT OF HIR BY NUMBER OF COVID-19 VACCINE DOSES AND PATIENT SUBGROUPS

- The proportion of patients achieving a positive HIR increased with 3 vs 2 doses of the vaccine (Assay No. 1: 70.0% [7/10] vs 46.7% [7/15]; Assay No. 2: 77.8% [7/9] vs 42.9% [6/14], respectively; **Table 2**)
- Patients aged ≥40 years had lower HIR achievement rates (Assay No. 1: 35.7% [5/14]; Assay No. 2: 42.9% [6/14]) compared with patients aged <40 years (Assay No. 1: 81.8% [9/11]; Assay No. 2: 77.8% [7/9])
- Although the number of patients identified with previous ocrelizumab (OCR) use was small, decreased HIR achievement was observed with previous OCR use compared with other previous treatments
- Patients aged <40 years with no prior OCR who received 2 vaccine doses had lower HIR achievement rates (Assay No. 1: 80.0% [4/5]; Assay No. 2: 50.0% [2/4]) compared with those who received 3 vaccine doses (Assay No. 1: 100.0% [5/5]; Assay No. 2: 100.0% [4/4])
- Length of OMB treatment and brand of vaccine did not appear to impact the proportion of patients achieving a positive HIR at Assay No. 1
- The Moderna vaccine appeared to have a more sustained humoral response over time, in terms of a higher proportion of patients achieving a positive HIR after 3 months (at Assay No. 2) than the Pfizer vaccine, albeit with small numbers of patients receiving the Moderna vaccine

Table 2. HIR (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 (%)*	
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		
OCR	1/5 (20.0)	3/5 (60.0)
Other†	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 prior OCR		
2 doses	4/5 (80.0)	2/4 (50.0)
3 doses	5/5 (100.0)	4/4 (100.0)
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)

COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; EOS, end of study; IgG, immunoglobin G; OMB, ofatumumab; M, number of patients with lab data; MS, multiple sclerosis; n, number of patients with positive assay; NOS, not otherwise specified; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus-2
*Non-responder imputation for overall response rate (N=26); the rest of the table shows observed case data (N=25); †Other: glatiramer acetate, natalizumab, dimethyl fumarate, siponimod, fingolimod hydrochloride, interferon beta-1a, immunoglobulins NOS, teriflunomide; ‡Data based on full vs half doses of the Moderna vaccine were not available in this study

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 3.9% (n=1) each (**Table 3**)
- AEs were mostly (80% [4/5]) Grade 1, with 1 Grade 2 AE of COVID-19 infection
- No AEs were considered related to treatment and no SAEs were reported

Table 3. Summary of AEs*

AE, n (%)	Total (N=26)
Any AE	5 (19.2)
Grade 1	4 (15.4)
Grade 2†	1 (3.9)
Infections and infestations	5 (19.2)
COVID-19	4 (15.4)
Herpes zoster	1 (3.9)
Streptococcal pharyngitis	1 (3.9)
Nervous system disorders	1 (3.9)
Headache	1 (3.9)
Any serious AE	0

AE, adverse event; COVID-19, coronavirus disease 2019
*None of the AEs were considered related to treatment; †The only Grade 2 AE was COVID-19 infection

ABBREVIATIONS: AE, adverse event; **CI**, confidence interval; **COVID-19**, coronavirus disease 2019; **DMT**, disease-modifying therapy; **EOS,** end of study; **HIR**, humoral immune response; **IgG**, immunoglobulin G; **mRNA**, messenger RNA; **MS**, multiple sclerosis; **NOS**, not otherwise specified; **OCR**, ocrelizumab; **OMB**, ofatumumab; **RMS**, relapsing multiple sclerosis; **SAE**, serious adverse event; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus-2; **SD**, standard deviation.

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