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Evaluating Humoral Immune Response to mRNA COVID-19 Vaccines in Siponimod-treated Patients with Advancing Forms of Relapsing Multiple Sclerosis: A COVID-19 Vaccine Sub-study of Phase 3b EXCHANGE Trial

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SUMMARY

1 **A single-arm pilot sub-study was conducted to understand COVID-19 vaccine response in subjects switching to siponimod in the EXCHANGE study**

2 **These preliminary findings offer emerging evidence that the majority of siponimod-treated patients seroconvert following two doses of COVID-19 vaccination, demonstrating IgG towards SARS-Cov-2 spike protein**

3 **This study also suggests that while younger patients (<40 years old) are more likely to develop a vaccine response, some patients may benefit from a COVID-19 booster where the vaccine response rate is highest**

BACKGROUND

- Siponimod (SIPO, Mayzent®), an oral S1P receptor type 1, 5 modulator approved in the USA for adults with RMS (including CIS, RRMS, and active SPMS), reduces relapses and disability progression in patients with SPMS[1-3]
- EXCHANGE (NCT03623243) is a 6-month, open-label, single-arm Phase 3b trial of safety and tolerability of immediate conversion to dose-titrated SIPO from other DMTs in patients with advancing RMS
- Given the ongoing COVID-19 global pandemic, it is important to assess if patients can mount an immune response to COVID-19 vaccines while receiving or switching to SIPO
- While data suggests there is limited effect of SIPO on development of the immune response following influenza and pneumococcal vaccinations,[4] this COVID-19 vaccination sub-study will provide early evidence on considerations under the SARS-CoV-2 pandemic and beyond

OBJECTIVE

- To report results of a sub-study assessing humoral immune response to mRNA COVID-19 vaccines (Pfizer/Moderna) in a subset of patients enrolled in EXCHANGE

METHODS

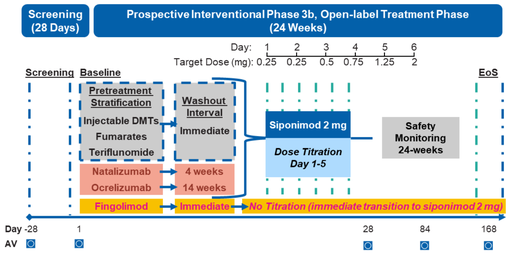
STUDY DESIGN

- EXCHANGE enrolled patients aged 18-65 years with advancing forms of RMS, EDSS score 2.0–6.5, and on continuous oral/injectable/infusion DMTs for ≥3 months at time of consent (**Figure 1**)
- SARS-CoV-2 spike IgG was used to assess vaccine response; SARS-CoV-2 nucleocapsid IgG was assessed simultaneously to inform any confounding COVID-19 infection and natural immunity

COVID-19 VACCINATION SUB-STUDY

- A single-arm pilot sub-study in patients currently participating in the core EXCHANGE study who have received at least a full course (2 doses) of mRNA COVID-19 vaccine
  - Notably, some patients were vaccinated prior to switching to SIPO and some patients once commencing SIPO on study, and is reflected in these data
- Patients with known prior COVID-19 diagnosis (clinically or by lab test with negative nucleocapsid Ab) or contraindication to receiving an mRNA COVID-19 vaccine will be excluded from the sub-study
- Patients in the sub-study will continue taking 2-mg SIPO as per the EXCHANGE study protocol
- The sub-study will evaluate the number of patients achieving positive IgG response to SARS-CoV-2 spike protein ≥14 days after full course vaccination
- Exploratory endpoints include rate of seroconversion and evaluation of magnitude of humoral response to COVID-19 vaccination

Figure 1. EXCHANGE study design



*Injectable DMTs: IFN beta-1a, IFN beta-1b, GA, pegIFN beta-1a; †Defined as cessation of existing DMT and initiation of SIPO within 24 hours, followed by subsequent 5-day dose titration; AV, Assessment Visit

RESULTS

PATIENT DEMOGRAPHICS AND DISPOSITION

- Patient demographics and disposition described in **Table 1**

Table 1. Patient demographics and disposition

At screening	Total (N=10)
Disposition / Reason, n (%)	
Completed study	5/10 (50.0)
Ongoing	3/10 (30.0)
Discontinued*	2/10 (20.0)
Age, years	
median (range)	47.0 (27–60)
≤40, n (%)	4 (40.0)
>40, n (%)	6 (60.0)
Female, n (%)	7 (70.0)
Race, n (%)	
White	7 (70.0)
Black or African American	2 (20.0)
American Indian or Alaska Native	1 (10.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (20.0)
Not Hispanic or Latino	8 (80.0)
MS DMT at time of vaccination	
SIPO	5 (50.0)
FIN	1 (10.0)
OCR	1 (10.0)
TER	1 (10.0)
GA	1 (10.0)
Any IFN-β	1 (10.0)
Number of vaccine doses	
2	7 (70.0)
3	3 (30.0)

Study discontinuations were due to subject decision (n=1) and physician decision (n=1)

HUMORAL IMMUNE RESPONSE TO mRNA COVID-19 VACCINE

- Characteristics of the patients achieving immune response as defined by a positive SARS-CoV-2 qualitative IgG ≥14 days after full course vaccination (responders) are described in **Table 2**
- Overall, 70% (7/10) achieved a positive humoral immune response to COVID-19 vaccine at the post-vaccination assessment (**Table 2**)
- 57.1% (4/7) and 100% (3/3) achieved a positive response after two and three vaccine doses, respectively (**Table 2**)
- 75% (3/4) and 66% (4/6) of patients ≤40 and >40 years, respectively, had a positive humoral response post-vaccination (**Table 2**)
- 80% (4/5) of patients on SIPO treatment at time of vaccination had a positive humoral response (**Tables 2-4**)
  - 100% (3/3) response rate among SIPO-treated patients <40 years

Table 2. Immune response to COVID-19 vaccine

	Responders, n/M (%)
Overall	7/10 (70.0) 95% CI: (35.4, 91.9)
Number of vaccine doses	
2	4/7 (57.1)
3	3/3 (100.0)
Age (years)	
≤40	3/4 (75.0)
>40	4/6 (66.7)
MS DMT at time of vaccination	
SIPO	4/5 (80.0)
Other*	3/5 (60.0)
Type of COVID-19 vaccine†	
Moderna	5/10 (50.0)
Pfizer	6/10 (60.0)

n=number of patients with positive; M=number of patients with lab data
*Other: FIN (n=1), OCR (n=1), TER (n=1), GA (n=1), Any IFN-β (n=1)
†One patient received 2 doses of the Moderna vaccine and a booster dose of the Pfizer vaccine

Table 3. Patient characteristics for those who achieved a positive humoral immune response to COVID-19 vaccine at the post-vaccination assessment (responders, n=7)

Patient #	Age (y)	COVID-19 vaccine	Prior MS DMT	MS DMT at time of vacc	Ab titer
Received two vaccine doses					
1044007	27	Moderna	DMF	SIPO	1616
1065018	34	Moderna	TER	SIPO	1616
1026001	51	Pfizer	NAT	SIPO	101
1076005	38	Pfizer	OCR	SIPO	404
Received three vaccine doses					
1013005*	47	Moderna/ Pfizer	GA	GA	1) 3232 2) 6464
1026003	49	Pfizer	TER	TER	3232
1026004	60	Pfizer	Any IFN-β	Any IFN-β	3232

*Patient received 2 doses of the Moderna vaccine and a booster dose of the Pfizer vaccine; Ab titer captured while still on GA (assessment 1), and ~1 month after switching to SIPO (assessment 2); patient was positive for SARS-CoV-2 nucleocapsid IgG suggesting prior COVID-19 exposure. Ab, antibody; vacc, vaccination; y, year

- Patient 1013005 was on GA at time of all vaccinations, and Ab titers were captured while still on GA (at screening, assessment 1) and ~1 month after switching to SIPO (assessment 2)
  - The increased Ab titer at assessment 2 suggests that expansion of the immune response following vaccination was not restricted under SIPO (**Table 3**)
  - Patient was negative for nucleocapsid IgG at time of both assessments, which suggest that the patient had not had prior COVID-19 exposure at the assessment timepoints, although they developed COVID-19 infection afterwards
- 90% (9/10) of patients were negative for SARS-CoV-2 nucleocapsid IgG, indicating no confounding prior COVID-19 infection and natural immunity
  - Patient #1026003 demonstrated a positive response to nucleocapsid IgG suggesting prior COVID-19 exposure
- The 3 non-responders were each on OCR, SIPO, or FIN at time of vaccination; 66.7% (2/3) were >40 years (**Table 4**)

Table 4. Patient characteristics for those who did not achieve a positive humoral immune response to COVID-19 vaccine at the post-vaccination assessment (non-responders, n=3)

Patient #	Age (y)	COVID-19 vaccine	Prior MS DMT	MS DMT at time of vacc	Ab titer
Received two vaccine doses					
1017006	47	Moderna	GA	OCR	Negative
1041014	29	Moderna	FIN	FIN	Negative
1037010	47	Pfizer	OCR	SIPO	Negative

Ab, antibody; vacc, vaccination; y, year

SAFETY

- Five (50.0%) patients experienced AEs during the study
  - AEs by preferred term included increased blood alkaline phosphatase, COVID-19, dyspnea, headache, increased hepatic enzyme, influenza-like illness, nasopharyngitis, peripheral swelling, rash, and upper-airway cough syndrome, each by n=1 (10.0%), 95% CI: (0.5, 45.9)
  - 1 patient (#1013005, received booster under GA therapy) developed COVID-19 infection shortly after switching to SIPO, infection was mild and resolved; patient was negative for nucleocapsid IgG at time of titer assessment, indicating titer values reported here were captured prior to COVID-19 exposure
  - AEs leading to permanent SIPO discontinuation included peripheral swelling and rash, each by n=1 (10.0%), 95% CI: (0.5, 45.9)
- No SAEs were reported

CONCLUSIONS

- **Albeit limited by small sample size, this preliminary sub-study adds to our understanding of humoral immune responses to mRNA COVID-19 vaccination in patients with advancing forms of RMS who switched to SIPO treatment**
- **These findings offer emerging evidence that the majority of SIPO-treated patients seroconvert following two doses of COVID-19 vaccination**
- **Patient's age and number of vaccine doses may contribute to the positive humoral immune response to mRNA COVID-19 vaccines**

ABBREVIATIONS: AE, adverse event; **CIS,** clinically isolated syndrome; **COVID-19,** coronavirus disease 2019; **DMF**, dimethyl fumarate; **DMT**, disease-modifying therapy; **EoS,** end of study; **FIN**, fingolimod hydrochloride; **GA**, glatiramer acetate; **IFN**, interferon; **IgG,** immunoglobulin G; **MS,** multiple sclerosis; **NAT**, natalizumab; **OCR**, ocrelizumab; **RMS,** relapsing multiple sclerosis; **RRMS,** relapsing-remitting multiple sclerosis; **SPMS,** secondary progressive multiple sclerosis; **SAE,** serious adverse event; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2; **SIPO**, siponimod; **S1P,** sphingosine-1-phosphate; **TER**, teriflunomide; **y**, year.

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