DMT41

Immune Response to COVID-19 Vaccine in People With Multiple Sclerosis Treated With Dimethyl Fumarate, Diroximel Fumarate, Natalizumab, Ocrelizumab, or Interferon Therapy

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OBJECTIVE

- To evaluate and compare the effect of DMTs on immune response to mRNA vaccines for prevention of COVID-19.

CONCLUSIONS

- The results suggest that humoral response to mRNA-1273 COVID-19 vaccine (Moderna) is preserved and similar in PwMS treated with natalizumab, fumarates, and interferon.
  - In contrast, the humoral response to mRNA-1273 was dramatically muted in PwMS treated with ocrelizumab.
- Ocrelizumab treatment was associated with a higher proportion of spike-specific T cells compared with natalizumab, fumarates, and interferon. The clinical relevance of this finding is unclear.
- A limitation is the small sample size, which restricts the power of the study.
- The relative importance of both humoral and cell-mediated immunity to SARS-CoV-2 in the context of DMTs is crucial to understand, especially for PwMS who failed to seroconvert.

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Introduction

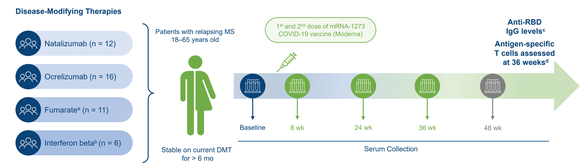
- COVID-19 is a potentially fatal respiratory illness caused by the novel coronavirus, SARS-CoV-2, which has developed into an ongoing global pandemic.[1]
- As of April 2022, more than 975,000 people in the United States and more than 6.1 million worldwide have lost their lives to COVID-19.[2-4]
- Moderna's mRNA-1273 vaccine is directed against the spike glycoprotein required for binding to the angiotensin-converting enzyme-2 receptor and viral entry.[5,6]
- Some disease-modifying therapies (DMTs) used to treat multiple sclerosis (MS) impair immune responses to vaccines.[7-9]
- The ability of vaccines to induce a coordinated induction of both humoral- and cell-mediated arms is key for preventing SARS-CoV-2 infection, particularly among people with MS (PwMS) who are on immunotherapy.[10]
- Data across multiple DMTs are needed to understand both humoral and cellular immune responses to COVID-19 vaccines in PwMS.

Methods

Study Design

- This was an open-label, prospective, observational study (N = 45).
- Participants, aged 18–65 years (inclusive), were treated with natalizumab (n = 12), ocrelizumab (n = 16), dimethyl or diroximel fumarate (n = 11), and interferon beta (n = 6) for at least 6 months (Figure 1).
- Humoral response was assessed:
  - Serum samples were analyzed to measure SARS-CoV-2 spike receptor binding domain (anti-RBD) immunoglobulin G (IgG) titers.
  - IgG levels were measured (sCOVg assay, Siemens Healthineers) at 8, 24, and 36 weeks after first dose of mRNA-1273 (Moderna).
- Cellular response was evaluated:
  - Antigen-specific T cells were assessed using T-Cell Receptor (TCR) sequencing (ImmunoSEQ T-MAP COVID, Adaptive Biotechnologies) at 36 weeks after the first dose of mRNA-1273.
  - Spike-specific TCR templates were used to compare T-cell responses between groups.
- Statistical analyses were performed using GraphPad Prism 9. Chi-squared or Fisher's exact test were used to compare categorical variables. Geometric mean titer (GMT) values and spike-specific T-cell proportion were compared using one-way analysis of variance with Tukey's correction for multiple comparisons.

Figure 1. Study Design



DMT = disease-modifying therapy; Ig = immunoglobulin; MS = multiple sclerosis
[a]Including dimethyl fumarate and diroximel fumarate.
[b]Any interferons and peginterferon beta-1a.
[c]Measured using sCOVg assay (Siemens Healthineers).
[d]Measured using T-Cell Receptor sequencing (ImmunoSEQ T-MAP COVID).

Results

Demographics

- There were 45 participants in this study, grouped based on DMT:
  - Natalizumab (n = 12)
  - Ocrelizumab (n = 16)
  - Fumarates (n = 11): 10 dimethyl fumarate and 1 diroximel fumarate
  - Interferon-beta (n = 6).
- The mean age ± SD (range) of participants was 48.7 ± 10.9 (20–65) years; 73% were White, and 82% were female.
- Baseline demographics and clinical characteristics are summarized in Table 1. Baseline characteristics among treatment groups were generally comparable.
  - The only statistically significant imbalances between treatment group were race and duration of exposure to current DMT.
  - The imbalance was a consequence of a lack of racial heterogeneity in the ocrelizumab group, and significantly longer interferon exposure relative to other treatments.

Post-Vaccination Humoral Response by DMT

- At 8 weeks post-vaccination, all natalizumab-, interferon-, and fumarate-treated patients generated detectable anti-RBD IgG titers with similar GMT between these treatments (Figure 2).
  - Anti-RBD IgG titers continued to be detectable at 36 weeks post-vaccination.
- In ocrelizumab-treated patients:
  - At 8 weeks post-vaccination, only 25% of participants generated detectable anti-RBD titers.
  - At 24 weeks and 36 weeks post-vaccination, no participants (0%) had detectable anti-RBD IgG titers.
- Duration of ocrelizumab, natalizumab, and fumarate treatment did not correlate with anti-RBD titer.
  - A positive correlation was observed between duration of interferon treatment and anti-RBD titers (p = 0.042).

Post-Vaccination Cell-Mediated Response by DMT

- Samples from patients treated with natalizumab had a higher number of T cells relative to the samples from the ocrelizumab, fumarate, and interferon groups (Table 2).
- The ocrelizumab sample had a higher proportion of spike-specific T cells compared with samples from other treatment groups (Table 2, Figure 3).

Safety

- No anaphylactic events or life-threatening responses occurred after the first or second doses of mRNA-1273 vaccine.
- The most commonly reported adverse events were injection site pain and fatigue (Table 3).
- Ocrelizumab participants were more likely to experience myalgias following vaccination ($p < 0.05$), with a trend toward higher rates of all side effects except injection site pain.
- No symptomatic breakthrough COVID-19 cases were reported in the study participants at the time of the 36-week serum collection.
  - Two asymptomatic exposures (both on natalizumab) were detected and confirmed with nucleocapsid antibody testing (excluded from 36-week serum and T-cell analysis).
- At 48 weeks, nearly all participants had 1 or more exclusions from serum analysis, including: 20 receiving a third vaccine dose, 2 asymptomatic exposures, 9 symptomatic COVID-19 infections, and 5 participants receiving pre-exposure prophylactic monoclonal antibody treatment (Evusheld, AstraZeneca).

Table 1. Baseline Demographics and Clinical Characteristics

	Ocrelizumab	Natalizumab	Fumarate	Interferon	p-value
n	16	12	11	6	
Age, y, mean ± SD (range)	52.6 ± 7.3 (38–64)	42.9 ± 13.7 (20–59)	48.5 ± 11.5 (27–62)	50.2 ± 9.3 (40–65)	0.135
Female, n (%)	12 (75)	10 (83.3)	10 (90.9)	5 (83.3)	0.764
Race[a]					
White, n (%)	16 (100)	5 (50)	6 (67)	3 (50)	0.015
Black, n (%)	0 (0)	5 (50)	3 (33)	3 (50)	0.015
Body mass index, mean ± SD	32.8 ± 9.9	27.3 ± 6.2	27.3 ± 4.1	27.0 ± 6.4	0.112
Time since MS onset, y, mean ± SD (range)	16.3 ± 7.3 (4.5–29.4)	14.3 ± 12.3 (2.4–39.2)	15.8 ± 9.5 (4.1–33.2)	10.6 ± 4.6 (5.2–17.2)	0.603
Time since MS diagnosis, y, mean ± SD (range)	10.5 ± 8.1 (2.2–24.4)	10.8 ± 9.5 (1.4–26.1)	12.8 ± 9.2 (3.1–30.2)	10.1 ± 5.0 (5.2–17.2)	0.721
EDSS, mean ± SD (range)[a]	2.8 ± 1.6 (1.5–6.0)	1.9 ± 1.2 (1.0–4.5)	2.1 ± 0.5 (1.5–3.0)	2.5 ± 1.1 (1.5–4.0)	0.445
Duration of DMT exposure, mo, mean ± SD (range)	27.3 ± 8.7 (16–42)	51.2 ± 50.8 (10–185)	49.8 ± 35.1 (12–95)	108.0 ± 54.1 (61–206)	0.0007
DMT washout, d, mean ± SD (range)[b]	129.8 ± 34.1 [83–192]	NA	NA	NA	

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NA = not available
[a]Two samples excluded due to asymptomatic COVID-19.
[b]Days from last dose of ocrelizumab to initial dose of mRNA-1273.

Table 2. T-Cell Analysis (36 Weeks)

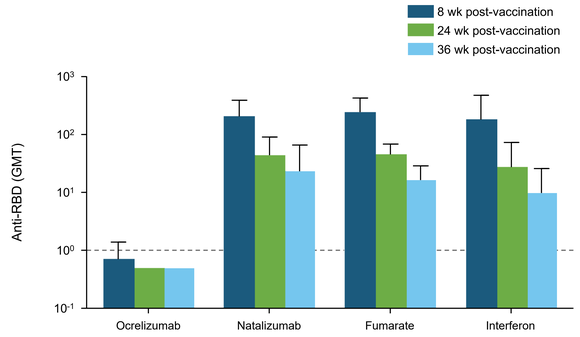
	Ocrelizumab	Natalizumab	Fumarate	Interferon	p-value
n	10	7[a]	5	3	
T cells per sample, mean ± SD	150,639 ± 57,275	234,587 ± 38,830	122,911 ± 82,295	137,531 ± 23,885	0.03
Spike-specific T cells per sample, mean ± SD	943.9 ± 486.2	551.0 ± 237.7	195.8 ± 156.6	174.0 ± 21.1	0.003
Proportion of spike-specific T cells, mean ± SD	0.0065 ± 0.0029	0.0024 ± 0.0012	0.0015 ± 0.0003	0.0013 ± 0.0001	0.0003

[a]Two samples excluded due to asymptomatic COVID-19.

Table 3. Vaccine Side Effects

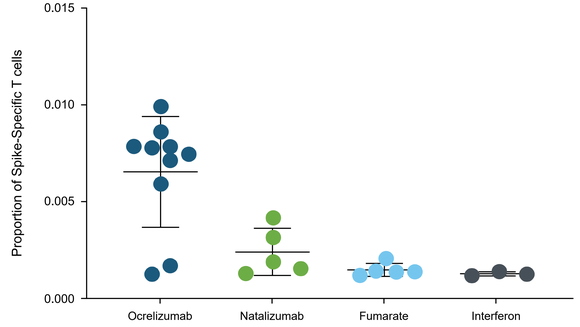
	Ocrelizumab n = 16	Natalizumab n = 12	Fumarate n = 11	Interferon n = 6	p-value
All side effects, n (%)	15 (93.8)	9 (75.0)	10 (90.9)	6 (100)	0.318
Injection site pain, n (%)	12 (75.0)	7 (58.3)	8 (72.7)	5 (83.3)	0.677
Fatigue, n (%)	14 (87.5)	7 (58.3)	6 (54.5)	4 (66.7)	0.233
Headache, n (%)	9 (56.3)	5 (41.7)	3 (27.3)	0 (0)	0.087
Myalgia, n (%)	11 (68.8)	2 (16.7)	6 (54.5)	2 (33.3)	0.043
Arthralgia, n (%)	7 (43.8)	2 (16.7)	2 (18.2)	0 (0)	0.122
Fever, n (%)	7 (43.8)	3 (25.0)	1 (9.1)	0 (0)	0.087
Chills, n (%)	8 (50.0)	2 (16.7)	4 (36.4)	2 (33.3)	0.342

Figure 2. Humoral Response to mRNA-1273 COVID-19 Vaccine



Anti-RBD = SARS-CoV-2 spike receptor binding domain; GMT = geometric mean titer
Dashed line indicates limit of detection (LOD). Per protocol, samples below LOD were imputed as 0.5.

Figure 3. Total T-cell Responses 36 Weeks After SARS-CoV-2 Vaccination in PwMS Treated With DMTs



DMT = disease-modifying therapy; PwMS = people with multiple sclerosis
Outlier values were among the older participants in the ocrelizumab group.

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