Rates of Multiple Sclerosis Relapse, Severe Relapse, and Health Care Resource Utilization Following COVID-19 Vaccination: Real-World Evidence from a US EMR Network

S. Kuranz[1], P. Landsman-Blumberg[1], S.L. Wong[2], N.L. Tundia[2]

[1]TriNetX, LLC, Cambridge, MA, USA; [2]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA

CONCLUSION

Among patients receiving DMTs, rate of relapses and HCRU after COVID-19 vaccination were greatest for patients treated with ocrelizumab, ofatumumab, siponimod, or fingolimod, compared to those treated with other DMTs or untreated patients.

INTRODUCTION

- Effectiveness of coronavirus disease 2019 (COVID-19) vaccines in patients with multiple sclerosis (MS) is already proven, and guidelines suggest all patients should be vaccinated.[1]
- However, studies consistently show that patients treated with anti-CD20 therapies (such as ocrelizumab) have a reduced humoral response to such vaccines.[2–4]
- These studies also reported a blunted serological response – compared with untreated patients – for those treated with the sphingosine-1-phosphate receptor modulator fingolimod.[2–4]
- To date, few studies have characterized MS outcomes among COVID-19-vaccinated patients who are receiving disease-modifying therapies (DMTs).

OBJECTIVES

This study described and compared MS outcomes (relapse, severe relapse) and rates of health care resource utilization (HCRU) between cohorts of vaccinated MS patients defined as:

- **Treated with ocrelizumab, ofatumumab, siponimod, or fingolimod (Cohort 1)**
- **Treated with other DMTs (Cohort 2)**
- **Untreated (Cohort 3)**

METHODS

- Retrospective study of adult MS patients in the TriNetX Dataworks EMR Network with complete COVID-19 vaccination between January 1 and July 31, 2021.
  - Complete vaccination was defined as receipt of the second dose of an mRNA vaccine or single dose of a vector-based vaccine
  - Cohorts 1, 2, and 3 were defined based on the treatment status closest to the index date (visit date ≥6 months before complete vaccination)
  - Patients were excluded when complete vaccination was undetermined, or a patient switched treatment over follow-up
- **Relapses and severe relapses** were defined as steroid use in any setting and in an inpatient setting, respectively, recorded ≥14 days after the index date. **HCRU** was defined as MS care in any inpatient setting.
- Person-days (PDs) were accrued from index date to relapse and HCRU.
- Poisson models comparing cohorts were adjusted for baseline characteristics (demographics, HCRU, steroid use, COVID-19 diagnosis, comorbidities, and Expanded Disability Status Scale [EDSS] scores) using inverse probability of treatment weights.
  - Adjusted incidence rates (IR) per 1000 PDs and incidence rate ratios (IRR) are reported with 95% confidence intervals

RESULTS

Table 1. Patient Characteristics at Index Date

Characteristic	Cohort 1 (n=518)	Cohort 2 (n=1312)	Cohort 3 (n=3630)
Age at index, years (mean, SD)	50.8 (12.0)	53.7 (12.4)	58.6 (14.1)
Female, n (%)	374 (72.2)	1021 (77.8)	2702 (74.4)
EDSS score, n (%)			
0	265 (51.2)	776 (59.1)	2300 (63.4)
≤2.5	41 (7.9)	93 (7.1)	210 (5.8)
3.0–5.5	120 (23.2)	312 (23.8)	746 (20.6)
≥6.0	92 (17.8)	131 (10.0)	374 (10.3)
DMT closest to index event (n, %)			
Ocrelizumab	320 (61.8)	-	-
Fingolimod	182 (35.1)	-	-
Siponimod	11 (2.1)	-	-
Ofatumumab	5 (1.0)	-	-
Glatiramer acetate	-	398 (30.3)	-
Dimethyl fumarate	-	391 (29.8)	-
Interferon beta-1a	-	187 (14.3)	-
Teriflunomide	-	167 (12.7)	-
Natalizumab	-	115 (8.8)	-
Interferon beta-1b	-	21 (1.6)	-
Peginterferon beta	-	14 (1.1)	-
Diroximel fumarate	-	11 (0.8)	-
Alemtuzumab	-	7 (0.5)	-
Cladribine	-	1 (0.1)	-
Steroid use, n (%)			
Any steroid	334 (64.5)	463 (35.3)	1162 (32.0)
Methylprednisolone	284 (54.8)	242 (18.4)	536 (14.8)
Prednisone	54 (10.4)	184 (14.0)	432 (11.9)
Dexamethasone	53 (10.2)	144 (11.0)	406 (11.2)
Betamethasone	11 (2.1)	36 (2.7)	108 (3.0)
Prednisolone	26 (5.0)	41 (3.1)	85 (2.3)
Corticotropin	1 (0.2)	0 (0)	2 (0.1)

DMT, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **SD**, standard deviation

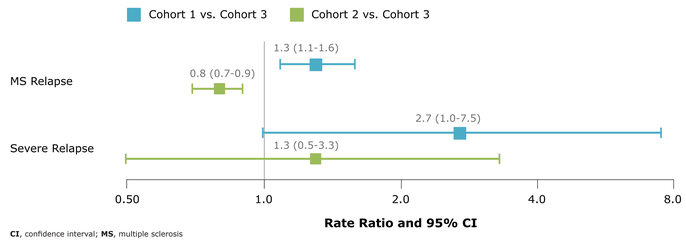
- The most common DMTs used in Cohort 1 were ocrelizumab (61.8%) and fingolimod (35.1%), while glatiramer acetate (30.3%) and dimethyl fumarate (29.8%) were the most common DMTs in Cohort 2 (**Table 1**).
- A larger proportion of patients in Cohort 1 had previous steroid use (64.5%) compared with Cohort 2 (35.3%) and Cohort 3 (32.0%) (**Table 1**).
- In vaccinated MS patients, while rates of relapses were significantly higher in Cohort 1 vs. Cohort 3, rates of relapses were significantly lower in Cohort 2 vs. Cohort 3. Additionally, severe relapses were numerically higher in both Cohort 1 and 2 vs. 3 (**Table 2** and **Figure 1**).
- In terms of MS-related total HCRU and inpatient visits, higher rates were seen for Cohort 1 vs. Cohort 3 than for Cohort 2 vs. Cohort 3 (**Table 3**).

Table 2. Adjusted Analyses: MS Relapse

	Total person-time (days)	Median person-days	Total (N)	Relapse/ severe relapse* (n, %)	Adjusted event rates per 1,000 person-days (95% CI)	Rate ratio (95% CI)
Relapses						
Cohort 1	35,391	67	518	173 (33.4)	3.1 (2.5, 3.7)	**1.3 (1.1, 1.6)**
Cohort 2	101,320	84	1312	194 (14.8)	1.8 (1.5, 2.0)	**0.8 (0.7, 0.9)**
Cohort 3	240,927	66	3630	535 (14.7)	2.3 (2.1, 2.5)	Reference
Severe relapses						
Cohort 1	43,553	94	518	8 (1.5)	0.2 (0.1, 0.3)	**2.7 (1.0, 7.5)**
Cohort 2	112,251	91	1312	7 (0.5)	0.1 (0.0, 0.1)	**1.3 (0.5, 3.3)**
Cohort 3	273,198	82	3630	13 (0.4)	0.1 (0.0, 0.1)	Reference

Note: Models comparing Cohorts 1 and 2 to Cohort 3 were run separately.
Person-time defined as the number of days between the index event (i.e., being fully vaccinated) and the date of the outcome event.
CI, confidence interval; **MS**, multiple sclerosis

Figure 1. Rates of Relapse and Severe Relapse Among Cohorts 1 and 2 Versus Cohort 3



CI, confidence interval; **MS**, multiple sclerosis

Table 3. Adjusted Analyses: MS-Related HCRU

	Total person-time (days)	Median person-days	Total (N)	Mean number of visits (SD)	Adjusted event rates per 1,000 person-days (95% CI)	Rate ratio (95% CI)
MS-related total HCRU						
Cohort 1	44,217	92	518	2.8 (3.3)	32.2 (29.1, 35.6)	**1.5 (1.3, 1.7)**
Cohort 2	112,777	95	1312	2.5 (3.3)	28.1 (26.3, 30.0)	**1.3 (1.2, 1.5)**
Cohort 3	274,507	83	3630	1.6 (3.3)	21.4 (20.1, 22.8)	Reference
MS-related inpatient visits						
Cohort 1	44,217	92	518	0.7 (1.0)	7.6 (6.4, 8.9)	**1.7 (1.4, 2.0)**
Cohort 2	113,526	95	1312	0.5 (0.9)	6.0 (5.5, 6.6)	**1.4 (1.2, 1.6)**
Cohort 3	274,507	83	3630	0.3 (0.8)	4.5 (4.2, 4.8)	Reference

CI, confidence interval; **HCRU**, health care resource utilization; **MS**, multiple sclerosis; **SD**, standard deviation

Limitations:

- Weighted models adjusted for baseline characteristics in the cohorts (including steroid use, i.e. relapse). However, certain confounding biases may remain, similar to other studies with retrospective longitudinal analysis.

REFERENCES
1. Yamout BI, et al. *Mult Scler Relat Disord*. 2021;56:103225. 2. Sormani MP, et al. *EBioMedicine*. 2021;72:103581. 3. Achiron A, et al. *J Neuroimmunol*. 2021;361:577746. 4. Capone F, et al. *Neurotherapeutics*. 2021; Epub ahead of print (doi: 10.1007/s13311-021-01165-9).

FOR REACTIVE MEDICAL USE ONLY

Disclosures: **SK** and **PL-B** are employees of TriNetX and contracted to provide consulting services to EMD Serono. **SLW** and **NLT** are employees of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA.

Medical writing assistance was provided by Joseph Ward of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

Presented at ACTRIMS 2022 Forum | 24–26 February | West Palm Beach, Florida, USA

Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)