Brief Report

Clinical features and outcomes of COVID-19 despite SARS-CoV-2 vaccination in people with multiple sclerosis

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Abstract

Background: Several studies have demonstrated reduced serological response to vaccines in patients treated with anti-CD20 agents. However, limited data exist surrounding the clinical effect of disease modifying therapy (DMT) use on vaccine efficacy.

Objectives: To investigate breakthrough coronavirus disease 2019 (COVID-19) in vaccinated people with multiple sclerosis (PwMS) on DMT.

Methods: PwMS on DMT diagnosed with COVID-19 after full vaccination were identified from an existing Cleveland Clinic COVID-19 registry, supplemented by provider-identified cases. Demographics, disease history, DMTs, comorbidities, exposures, vaccination status, and COVID-19 outcomes were confirmed by review of the electronic medical record.

Results: Thirteen (3.8%) of 344 fully vaccinated people with multiple sclerosis on disease modifying therapy were diagnosed with COVID-19 after vaccination. Ten patients (76.9%) were on an anti-CD20 therapy, the remaining 3 (23.1%) on fingolimod. Only 2 patients (15.4%), both on anti-CD20 therapy, required hospitalization and steroid treatment. Neither required Intensive Care Unit admission.

Conclusion: Patients treated with anti-CD20 agents and sphingosine 1-phosphate receptor modulators may still be at risk for COVID-19 despite vaccination. While still at risk for hospitalization, intubation and death from COVID-19 appear rare. Larger studies analyzing how this may differ in the setting of emerging variants are needed.

Introduction

Three vaccines for coronavirus disease 2019 (COVID-19) were approved in the United States under emergency use authorization; reported efficacies included 95% (Pfizer/BNT162b2), 94% (Moderna/mRNA-1273) and 67% (Janssen/Ad26.COV2.S) in preventing infection.[1] A systematic review of COVID-19 in people with multiple sclerosis (PwMS) estimated the pooled prevalence to be higher than the general population at 4%, with 10% of cases requiring hospitalization.[2] A separate review found that nearly half of COVID-19 cases in PwMS were in the setting of anti-CD20 therapy, raising concern for increased risk of COVID-19 in PwMS on disease-modifying therapy (DMT), and particularly in those on anti-CD20 agents.[3] Subsequent studies demonstrated a reduced serological response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in PwMS on anti-CD20 and sphingosine 1-phosphate receptor modulator (S1PR) DMTs.[4–6] Given these results, questions remained regarding which factors were most important for developing immunity, and how reduced serological vaccine response translated to clinical outcomes. In this study, we investigated breakthrough COVID-19 in fully vaccinated PwMS.

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Table 1. Demographics of fully vaccinated patients by breakthrough COVID-19 status.

SARS-CoV-2 RNA PCR	Negative	Positive	*p* value
n	656	13	
Age (years) (median (IQR))	56 (47–65)	43 (40–50)	0.001
Sex (%)			0.068
Male (%)	121 (18.4)	5 (38.5)	
Female (%)	535 (81.6)	8 (61.5)	
Race (%)			0.135
White	541 (82.5)	11 (84.6)	
Black	84 (12.8)	2 (15.4)	
Multiracial/multicultural	14 (2.1)	0 (0.0)	
Other	4 (0.6)	0 (0.0)	
Unknown	13 (2.0)	0 (0.0)	
BMI (kg/m^2) (median (IQR)	28.3 (24.3–33.3)	30.9 (27.7–35.6)	0.164
MS course (%)			0.602
RRMS	390 (59.4)	11 (84.6)	
SPMS	148 (22.6)	1 (7.7)	
PPMS	67 (10.2)	0 (0.0)	
PRMS	51 (7.8)	1 (7.7)	
Years with MS (median (IQR))	19 (10–28)	12 (6–18)	0.060
On DMT (%)	335 (51.1)	13 (100.0)	0.001
DMT name, *n*			
azathioprine	1	0	
dimethyl fumarate	66	0	
fingolimod	39	3	
glatiramer acetate	33	0	
interferon beta-1a intramuscular	32	0	
interferon beta-1a subcutaneous	2	0	
IVIG	1	0	
methotrexate	2	0	
natalizumab	22	0	
ocrelizumab	102	8	
ozanimod	1	0	
PEGylated interferon beta-1a	2	0	
rituximab	26	2	
siponimod	1	0	
teriflunomide	5	0	
Diabetes (%)	77 (11.7)	0 (0)	0.000
Hypertension (%)	181 (27.6)	5 (38.5)	0.386
Coronary artery disease (%)	45 (6.9)	0 (0)	0.000
Known COVID-19 exposure (%)	61 (9.3)	4 (30.8)	0.010

BMI: body mass index; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; PRMS: progressive-relapsing multiple sclerosis; DMT: disease-modifying therapy; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction.

Methods

PwMS diagnosed with COVID-19 after full vaccination were identified from an existing Institutional Review Board-approved Cleveland Clinic COVID-19 registry,[7] supplemented by provider-identified cases diagnosed at outside hospitals. All cases were confirmed by SARS-CoV-2 polymerase chain reaction (PCR) testing of nasal swabs. Demographics, disease history, DMT, comorbidities, vaccination status and COVID-19 outcomes were

Table 2. Demographics and COVID-19 outcomes per patient.

Case	Age (years)	Race	Years since MS Onset	PDDS	DMT at time of vaccination	Smoking Status	Comorbidities	DMT to vaccine (months)[a]	Vaccine	Vaccine to diagnosis (days)[b]	CV-19 treatment	H	O$_2$	MV	PNA	Death
1	40	White	18	0-Normal	Ocrelizumab	NS	Sinus tachycardia	4.5	Moderna	101	No	No	No	No	No	No
2	42	White	12	0-Normal	Fingolimod	NS	None	0.0	Pfizer	26	No	No	No	No	No	No
3	48	Black	3	0-Normal	Rituximab	FS	Diabetes, hypertension	4.6	Pfizer	27	Steroids, remdesivir	Yes	Yes	No	Yes	No
4	43	White	11	4-Early cane	Fingolimod	FS	Hypertension	0.0	Moderna	92	No	No	No	No	No	No
5	55	White	10	NA	Ocrelizumab	FS	None	6.5	Janssen	19	No	No	No	No	No	No
6	35	White	15	1-Mild disability	Ocrelizumab	NS	None	4.0	Moderna	110	No	No	No	No	No	No
7	40	White	6	NA	Ocrelizumab	NS	None	4.2	Pfizer	51	No	No	No	No	No	No
8	53	White	23	0-Normal	Ocrelizumab	NS	None	3.1	Janssen	48	No	No	No	No	No	No
9	41	White	18	0-Normal	Fingolimod	NS	Hypertension	0.0	Pfizer	13	No	No	No	No	No	No
10	47	White	18	6-Bilateral support	Ocrelizumab	NS	Hypertension	3.2	Pfizer	11	Steroids, remdesivir	Yes	No	No	No	No
11	31	White	6	0-Normal	Rituximab	NS	None	3.4	Moderna	79	Inhaled cortico-steroids	No	No	No	Yes	No
12	50	Black	24	6-Bilateral support	Ocrelizumab	NS	Hypertension	1.7	Pfizer	8	No	No	No	No	No	No
13	65	White	6	0-Normal	Ocrelizumab	NS	Mycosis fungoides	0.3	Moderna	110	No	No	No	No	No	No

PDDS: Patient-Determined Disease Steps; MS: multiple sclerosis; DMT: disease-modifying therapy; CV-19: coronavirus disease 2019; H: hospitalized; O$_2$: supplemental oxygen; MV: mechanical ventilation; PNA: pneumonia; NS: never smoker; FS: former smoker; NA: not available; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction.
[a]Time interval from the last dose of disease-modifying therapy to the first dose of a vaccine, measured in months.
[b]Time interval from the last dose of a vaccine to the date of the positive SARS-CoV-2 PCR result, measured in days.

either confirmed (for existing registry patients) or abstracted (for provider-identified cases) by review of the electronic medical record.

Results

We identified 669 patients who received a full SARS-CoV-2 vaccination series; 176 (26.3%) patients received two doses of the Moderna, 456 (68.2%) received two doses of the Pfizer and 37 (5.5%) received the single dose of the Janssen vaccine. Of 669 fully vaccinated PwMS, 344 (51.4%) were on DMT at the time of vaccination. There were no breakthrough COVID-19 infections in PwMS off DMT. Of 344 PwMS on DMT, 13 (3.8%) developed confirmed COVID-19 despite full vaccination with Moderna ($n = 5$), Pfizer ($n = 6$), or Janssen ($n = 2$) vaccine.

Demographics of the 13 PwMS with breakthrough COVID-19 are as follows. Most were white (84.6%), female (61.5%) and had a relapsing-remitting course (84.6%). The mean age was 45.4 years. All breakthrough occurred on DMT. Ten patients (76.9%) were on an anti-CD20 therapy, and three (23.1%) were on fingolimod. There was a wide range of values for time to positive PCR after the final dose of vaccine (median 48 days; interquartile range [19–92]). The most prevalent comorbidity was hypertension (five patients; 38.5%). No patients were current smokers or had chronic obstructive pulmonary disease, coronary heart disease, heart failure or other autoimmune conditions.

Comparative demographics between those with and without breakthrough COVID-19 are summarized in Table 1. Comprehensive COVID-19 outcomes are in Table 2. Only two (15.4%) of the 13 patients required hospitalization; Both were on anti-CD20 therapy. One stayed three days, and the other stayed 13 days after the development of pneumonia. Neither required intensive care unit (ICU) admission or mechanical ventilation; both were discharged home. Both received steroid treatment, and the patient with pneumonia was additionally treated with remdesivir. Another patient, also on anti-CD20 treatment, developed pneumonia but was managed as an outpatient on inhaled corticosteroids. The three patients on fingolimod did not require COVID-targeted treatment or hospitalization. The times from last infusion to first vaccination were similar for patients on anti-CD20 therapy with breakthrough infection compared to those without, median 119 days; interquartile range (95–133) versus 137; interquartile range (95–152), respectively.

Discussion

Prior pre-vaccination studies estimated the prevalence of COVID-19 in PwMS to be 4%. Although of limited sample size, our post-vaccination prevalence occurred exclusively in PwMS on DMT and was similar at 3.8%, suggesting that the 67%–95% reported vaccine efficacy may not fully apply to this population. Despite disease breakthrough, our patients had good outcomes. Most did not require hospitalization or COVID-19 treatment, none required ICU admission and none died.

In line with prior reports of reduced response to inactivated viral vaccines and higher breakthrough COVID-19 infections, particularly in those on anti-CD20 and S1PR DMTs, all observed breakthrough infections occurred in this subpopulation. However, in contrast to a report of lower humoral immunity in those on an S1PR modulator compared to anti-CD20, 22.7% and 3.8%, respectively,[6] and limited by the absence of available SARS-CoV-2 antibody titers from our patients, those requiring hospitalization in our study were all on anti-CD20 therapy. Such discrepancy highlights the range of anti-SARS-CoV-2 immune response and the remaining uncertainty surrounding which aspects of protective immunity translate to more favourable clinical outcomes – humoral versus cell-mediated processes. Recent data suggest patients on anti-CD20 have a preserved T-cell response to vaccination, albeit with shifts in lymphocyte subpopulations,[8,9] yet these patients remain at higher risk for clinically significant breakthrough. Larger studies are required to analyze the range of vaccine response on DMT and if breakthrough COVID-19 outcomes differ in the setting of emerging variants. Nevertheless, PwMS on anti-CD20 and S1PR therapies appear at higher risk for breakthrough disease. Although still at risk for hospitalization, intubation and death from COVID-19 appear rare.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or

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