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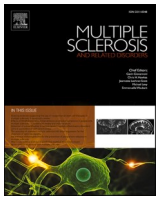

Original article

Incidence of multiple sclerosis relapses and pseudo-relapses following COVID-19 vaccination

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic created an urgency for an effective vaccine. The FDA approved vaccines offered by Pfizer-BioNTech (BNT162b2), ModernaTX (mRNA-1273) and Janssen/Johnson & Johnson (Ad26.COV2.S) have shown minimal side effects (SE) in general population studies. Multiple sclerosis (MS) patients were not specifically represented in the above studies. The MS community is interested in how these vaccines behave in people with MS. In this study, we compare the SE experienced by MS to that of the general population after SARS-CoV-2 vaccination and evaluate their risk of relapses or pseudo-relapses.

Methods: A retrospective, single-site, cohort study of 250 MS patients who received the initial cycle of FDA approved SARS-CoV-2 vaccines with 151 of whom also received an additional booster dose. SE resulting immediately after COVID-19 vaccination were collected as part of the standard clinical care during patient visits.

Results: Out of the studied 250 MS patients, 135 received the first and second doses of BNT162b2 with less than 1% and 4% pseudo-relapses respectively and 79 received the third BNT162b2 dose with a pseudo-relapse rate of 3%. 88 received the mRNA-1273 vaccine with a pseudo-relapse frequency of 2% and 5% after the first and second doses respectively. 70 patients had the mRNA-1273 vaccine booster with a 3% pseudo-relapse rate. 27 received the Ad26.COV2.S first dose, 2 of whom received a second Ad26.COV2.S booster dose, with no reports of MS worsening. No acute relapses were reported in our patient population. All patients experiencing pseudo-relapse symptoms returned to baseline within 96 h.

Conclusion: COVID-19 vaccine is safe in patients with MS. Cases of temporary worsening of MS symptoms following SARS-CoV-2 are rare. Our findings support those reported by other recent studies and the CDC recommendation for MS patients to receive the FDA-approved COVID-19 vaccines, including the boosters.

1. Introduction

The willingness to obtain vaccines in the MS community is lower compared to the general population in the United States (US) (Diem et al., 2021). Two recent studies of MS patients in the US reported that only 66% (Ehde et al., 2021) and 76.6% (Uhr and Mateen, 2022) of the studied MS population were willing to obtain a COVID-19 vaccine. A meta-analysis of various databases including Pubmed and Scopus also showed a willingness of 76% (Yazdani et al., 2022). This contrasts with a vaccination rate of 84.1% in a Canadian MS study (Marrie et al., 2022) and a willingness of 90.5% among Irish MS patients (Yap et al., 2021). This may be attributed to a relatively more concerned US MS population regarding vaccinations in general, and potentially leading to worsening MS symptoms. Studies analyzing Hepatitis B, human papillomavirus, seasonal influenza, measles-mumps-rubella, variola, tetanus, Bacillus Calmette–Guérin, polio, typhoid fever, and diphtheria vaccinations showed no association with increased relapses in patients with MS (Confavreux et al., 2001; Mailand and Frederiksen, 2017 ; Farez and Correale, 2011).

In this study, we evaluated a diverse demographic of MS patients, and compared the prevalence of SE after receiving the first and second doses of BNT162b2 and mRNA-1273, the first dose of Ad26.COV2.S, and the booster dose of BNT162b2 to their respective clinical trial data.

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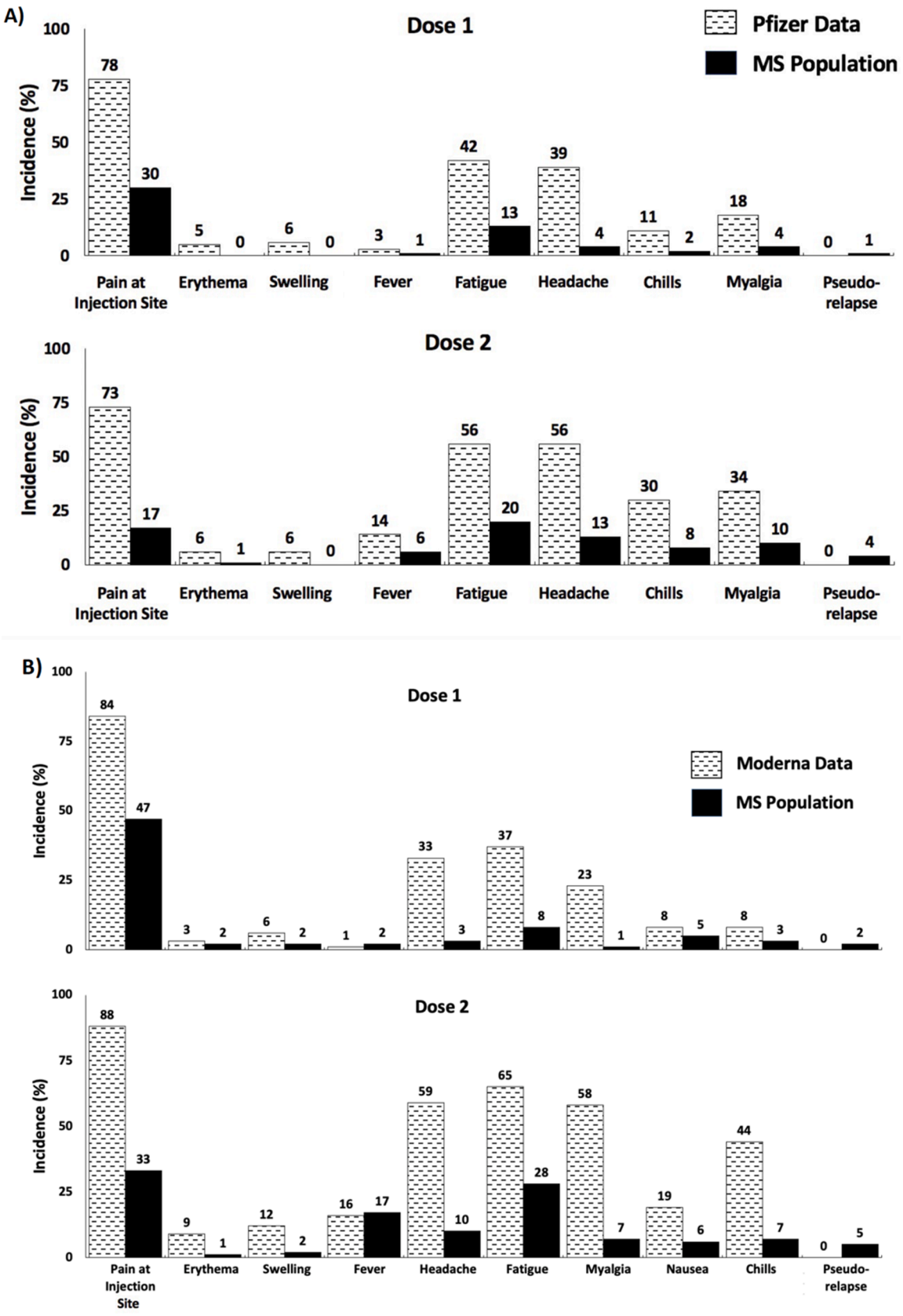

Fig. 1. Local and systemic reactions reported by our MS population compared to Pfizer-BioNTech, ModernaTX and Janssen/J&J phase 3 clinical trial data.

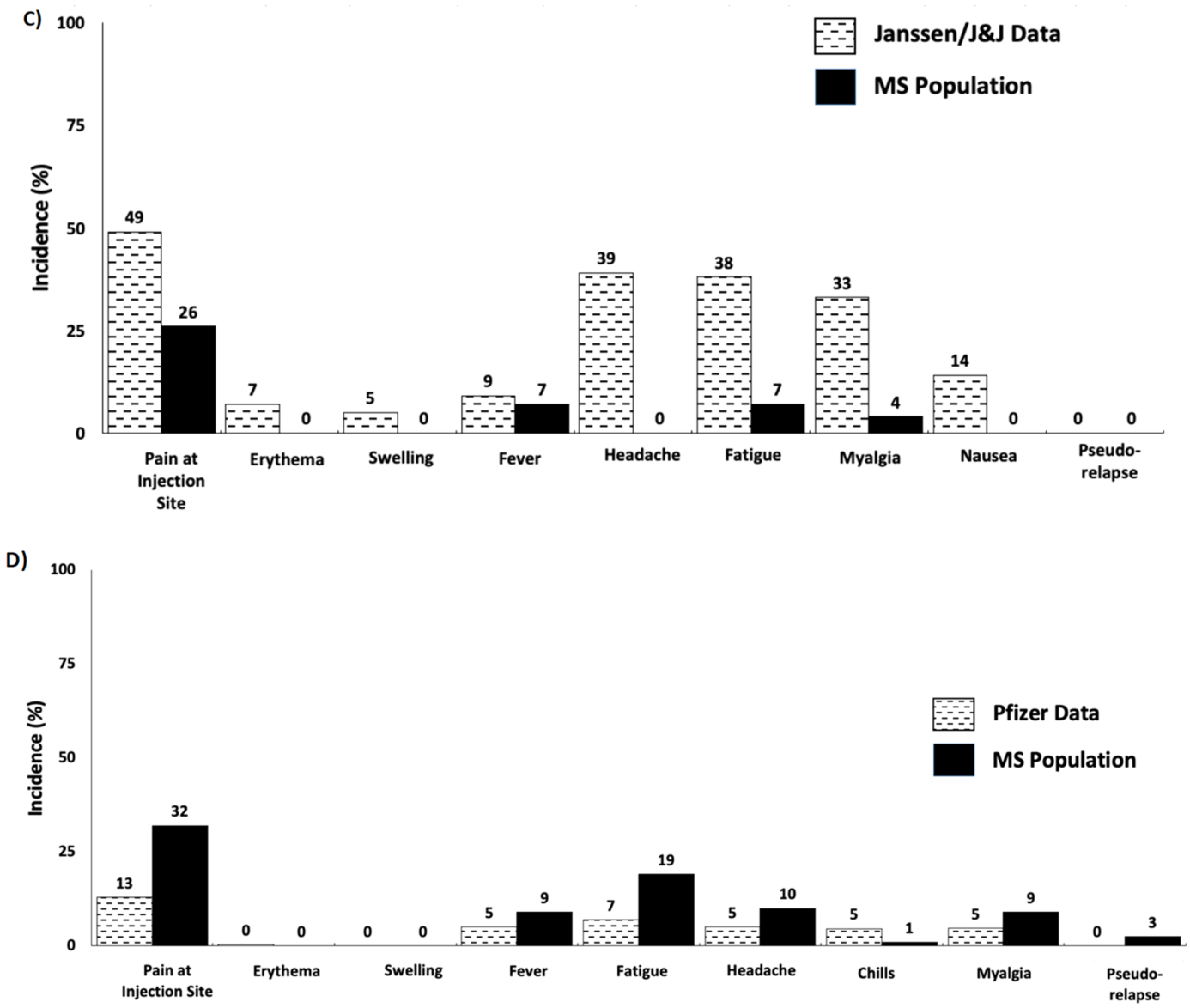

Fig. 1. (*continued*).

2. COVID-19 vaccine mechanisms

The BNT162b2 and mRNA-1273 vaccine variants introduce lipid-nanoparticle mRNA transcripts encoding the prefusion spike glycoprotein of SARS-CoV-2 to host cells (Polack et al., 2020; Baden et al., 2021). The Ad26.COV2.S introduce a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector encoding a full-length, membrane-bound SARS-CoV-2 spike protein in a prefusion-stabilized conformation (Sadoff et al., 2021). All vaccine variants allow for the host to develop strong immunity to the SARS-CoV-2 virus (Polack et al., 2020; Baden et al., 2021; Sadoff et al., 2021).

3. Methods

We retrospectively identified 250 MS patients at our institution who had received the initial vaccination cycle of the currently approved COVID-19 vaccines in the US. 151 of these patients also received a booster dose. SE attributed to the COVID-19 vaccinations during a 90-day post-vaccination observation period were collected as part of the standard clinical care. We compared the SE prevalence in our patients with the clinical trial data from Pfizer-BioNTech, ModernaTX and Janssen/J&J for the initial vaccination cycle and the third dose of BNT162b2. Approximately 1.5% of our study population had suffered from a clinical MS relapse within 12 months prior to vaccination. Only a very small fraction of our subjects (<5%) self-reported prior COVID19 infections.

Categorization of SE were adapted from the BNT162b2, mRNA-1273 and Ad26.COV2.S clinical trial publications (Polack et al., 2020; Baden et al., 2021; Sadoff et al., 2021; Moreira et al., 2022). Local reactogenicity included injection site pain, swelling, erythema or pruritus. Systemic reactogenicity included fever (>38 °C/100.4°F), fatigue, headache, chills, myalgia, joint pain, vomiting, diarrhea, and nausea. We added an additional MS specific category termed “pseudo-relapse” to encompass any transient exacerbation of previously reported neurological symptoms that lasted less than 21 days with subsequent full recovery. Pseudo-relapses did not result in new MRI lesions. Safety data from general population studies were adapted from the phase 3 BNT162b2, mRNA-1273, and Ad26.COV2.S clinical trials (Polack et al., 2020; Baden et al., 2021; Sadoff et al., 2021; Moreira et al., 2022).

We excluded presenting the parameters diarrhea and arthralgia pain from the BNT162b2 data set and excluded lymphadenopathy and arthralgia from the mRNA-1273 data set. Our study population did not

report any of the above symptoms.

4. Results

4.1. Worsening of MS symptoms

135 MS patients received the first and second dose of BNT162b2. There was 1 case of pseudo-relapse after the first dose and 6 cases after the second dose (Fig. 1A). following the first dose, 1 patient experienced acute unilateral ptosis for 24 h after first dose administration. The subjects did not experience the same SE following the second dose administration. Pseudo-relapse symptoms after the second dose of BNT162b2 included tingling (x3), numbness (x2), blurred vision (x1) lower extremity (LE) weakness (x1), worsening of spasticity (x1), and dysarthria (x1). 79 patients received a third dose of BNT162b2 with 2 patients reporting pseudo-relapse consisting of LE weakness (Fig. 1D). Overall, 1% of our studied BNT162b2 population experienced pseudo-relapse symptoms following the first dose as compared to 4% with the second dose and 3% with the booster.

88 MS patients received the first and second doses of the mRNA-1273 vaccine (Fig. 1b). There were 2 cases of pseudo-relapse after the first mRNA-1273 dose and 4 cases following the second mRNA-1273 dose. Symptoms mainly consisted of weakness and severe fatigue. 70 patients received the mRNA-1273 booster dose with 2 reports of pseudo-relapse. Symptoms included difficulty with mobility and balance. Overall, 2% of our studied mRNA-1273 population experienced pseudo-relapse symptoms following the first dose as compared to 5% after the second dose, and 3% with the booster.

22 of our patients swapped between the mRNA vaccines for their initial vaccination cycle and the booster dose. One reported pseudo-relapse symptoms after the mRNA-1273 booster which involved worsening balance lasting for 15 days. She also experienced a pseudo-relapse following her second BNT162b2 dose with similar symptoms. Pseudo-relapse following more than one vaccination event was reported by only one other patient who received the mRNA-1273 vaccine. Each time, gait difficulty lasted 24 h after the first and second doses and 7 days after the booster dose. It is worth mentioning that this patient reported testing positive for SARS-CoV-2 one day after her first mRNA-1273 dose with worsening fatigue that lasted approximately 12 days.

27 MS patients received the Ad26.COV2.S first dose and 2 MS patients received the second Ad26.COV2.S booster dose with no reports of MS or neurological worsening (Fig. 1C).

Of note, most patients reporting a pseudo-relapse returned to baseline within less than 96 h except for the 2 cases discussed above. There was no permanent neurological disability or severe, life-threatening adverse events reported. No treatment was recommended or performed during any of our pseudo-relapse cases. No acute cases of MS relapse were noted in our studied population that could be confirmed by clinical or radiological findings.

4.2. Local and systemic reactogenicity

Overall, our patient population reported significantly lower occurrences of SE for the initial vaccination cycle of each vaccine variant as compared to the general population studies except for a higher incidence of fever in mRNA-1273 recipients. Interestingly, our study population experienced SE more frequently with the BNT162b2 booster dose than was reported by its clinical trial for the general population.

Fig. 1 depicts adverse events from general population studies versus our studied MS population after dose 1 and 2 of BNT162b2, $n = 135$ (**A**), dose 1 and 2 of mRNA-1273, $n = 88$ (**B**), dose 1 of Ad26.COV2.S, $n = 27$ (**C**) and dose 3 of BNT162b2, $n = 79$ (**D**). General population percentages were adapted from the phase 3 clinical trial data reported in *Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine* (Polack et al., 2020), *Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine* (Baden et al., 2021), *Safety and Efficacy of Single-Dose Ad26.COV2 Vaccine against Covid-19*[12], and *Safety and efficacy of a third dose of BNT162B2 covid-19 vaccine* (Moreira et al., 2022).

5. Discussion

In this study, we evaluated a diverse demographic of MS patients, and compared the prevalence of SE after receiving BNT162b2, mRNA-1273 and Ad26.COV2.S vaccines to their respective clinical trial data. It is worth mentioning that the average age of our study population was significantly higher than in typical multiple sclerosis treatment trials. When COVID-19 vaccines first became available in the United States, the following groups were generally prioritized for vaccination: Adults aged 65 years and older, and frontline essential workers. That is the main reason for the advanced age and longer disease duration in our study population.

Overall, our cohort of MS patients reported lower instances of local and systemic reactogenicity with the first and second doses of the mRNA vaccines and the first dose of Ad26.COV2.S with only a slightly higher incidence of fever following the first and second administrations of mRNA-1273. Higher instances of local and systemic reactogenicity were reported with the third dose of BNT162b2. There was a higher incidence of local and systemic SE in our patient population after the second dose of mRNA vaccinations as compared to the first dose which is in line with the general population studies (Polack et al., 2020; Baden et al., 2021).

The reported pseudo-relapses largely consisted of a transient resurgence of MS symptoms, including paresthesia, lower extremity weakness, dysarthria, and cognitive impairment. However, we observed a single case of a new left eye ptosis in a patient that resolved within 24 h after their first BNT162b2 dose. Altogether, the risk of having a pseudo-relapse after receiving BNT162b2 and mRNA-1273 is low. There did not appear to be an increased incidence of fever in our subjects who experienced a pseudo-relapse. Furthermore, it cannot be determined if the mRNA vaccine variants directly caused a pseudo-relapse in our MS population. SE from the vaccine such as fever or myalgia could temporarily provoke old symptoms similar to a systemic infection. Most cases of pseudo-relapses resolved completely within 96 h except for 2 cases that lasted for 1–2 weeks.

One patient on ocrelizumab tested positive for COVID-19 one day after the first dose of mRNA-1273 and experienced unilateral lower extremity weakness following the second dose of mRNA-1273 that spontaneously resolved within 96 h. There is a possibility that the patient contracted COVID-19 after their first dose due to the possible decreased immune-response for patients on B-cell therapy. Alternatively, the patient could have had asymptomatic COVID-19 prior to first dose administration. In general, we did not identify a clear correlation between a type of disease modifying therapy (DMT) and incidence of SE.

Various recent studies provide further evidence towards a low incidence of pseudo-relapses and relapses in MS patients following COVID-19 vaccinations. A study of 2261 Polish MS patients reported only one severe adverse event with the AstraZeneca vaccine, a relapse rate of 4.4%, and a pseudo-relapse rate of 2.7% (Czarnowska et al., 2022). An Israeli study showed no increased risk of relapses in 555 MS patients who received the first dose of BNT16b2 (2.1% relapse rate) and 435 MS who received the second BNT16b2 dose (1.6% relapse rate) as compared to MS patients who did not receive the COVID-19 vaccine (Achiron et al., 2021). Another Israeli study of 211 MS patients reported MS exacerbation rates of 4.8% and 3.8% after the second and third BNT162b2 doses respectively, and a relapse rate of 1.4% within 30 days of receiving the third dose (Dreyer-Alster et al., 2022). Similarly, a study of 324 Italian MS patients did not find any significant difference in relapse rates during the two-month period prior to SARS-CoV-2 vaccination (1.9% relapse rate) and the two months following vaccination (2.2% relapse rate) (Di Filippo et al., 2022). Our reported data appears in line with reports from the other countries.

Individual cases of relapses or diagnosis of MS following SARS-CoV-2 have also been previously reported (Havla et al., 2022; Kataria et al.,

Table 1
Demographic and clinical characteristics of multiple sclerosis patients Categorized by vaccine variant.

Initial Vaccination Characterisitics	BNT162b2 (*n* = 135)	mRNA-1273 (*n* = 88)	Ad26.COV2.S (*n* = 27)	Total (*n* = 250)	Booster Characterisitics	BNT162b2 (*n* = 79)	mRNA-1273 (*n* = 70)	Ad26.COV2.S (*n* = 2)	Total (*n* = 151)
Sex — no. (%)					**Sex — no. (%)**				
Male	39 (28.9%)	14 (15.9%)	6 (22.2%)	59 (23.6%)	Male	23 (30.0%)	14 (15.9%)	1 (22.2%)	38 (25.0%)
Female	96 (77.1%)	74 (84.1%)	21 (77.8%)	191 (76.4%)	Female	56 (71.0%)	56 (84.1%)	1 (77.8%)	113 (75.0%)
Mean Age (s.d.)	63.2 (13.2)	56.6 (12.9)	53.4 (11.1)	57.7 (12.4)	Mean Age (s.d.)	60.4 (11.9)	55.3 (12.9)	60.0 (8.5)	58.6 (12.4)
Race or ethnic group — no. (%)					**Race or ethnic group — no. (%)**				
Caucasian	96 (71.1%)	66 (75%)	18 (66.7%)	84 (33.6%)	Caucasian	59 (74.7%)	51 (73.0%)	2 (100%)	112 (74.0%)
African American	37 (27.4%)	19 (21.5%)	9 (33.3%)	28 (11.2%)	African American	19 (24.0%)	17 (24.2%)	0 (0%)	36 (24.0%)
Other	2 (1.48%)	3 (3.4%)	0 (0%)	3 (1.2%)	Other	1 (1.3%)	2 (2.8%)	0 (0%)	3 (2.0%)
Disease-Modifying Therapies — no. (%)					**Disease-Modifying Therapies — no. (%)**				
B-Cell Therapies †	55 (40.7%)	38 (43.2%)	13 (48.1%)	106 (42.4%)	B-Cell Therapies †	33 (41.7%)	38 (54.3%)	1 (50.0%)	72 (48%)
Alemtuzumab	29 (21.5%)	16 (18.2%)	3 (11.1%)	48 (19.2%)	Alemtuzumab	16 (20.2%)	5 (7.1%)	0 (0%)	21 (13.9%)
S1P-modulators *	15 (11.1%)	8 (9.1%)	3 (11.1%)	26 (10.4%)	S1P-modulators *	11 (14.0%)	8 (11.4%)	1 (50.0%)	20 (13.2%)
Teriflunomide	13 (9.6%)	8 (9.1%)	4 (14.8%)	25 (10%)	Teriflunomide	7 (9.0%)	4 (5.7%)	0 (0%)	11 (7.3%)
Fumarates ‡	1 (0.7%)	5 (5.7%)	1 (3.7%)	7 (2.8%)	Fumarates ‡	1 (1.2%)	2 (3.0%)	0 (0%)	3 (2.0%)
Natalizumab	5 (3.7%)	7 (8.0%)	1 (3.7%)	13 (5.2%)	Natalizumab	4 (5.0%)	7 (10.0%)	0 (0%)	11 (7.3%)
Glatiramer acetate	4 (3.0%)	3 (3.4%)	1 (3.7%)	8 (3.2%)	Glatiramer acetate	4 (5.0%)	5 (7.1%)	0 (0%)	9 (6.0%)
Interferons	1 (0.7%)	1 (1.1%)	0 (0%)	2 (0.8%)	Interferons	1 (1.2%)	0 (0%)	0 (0%)	1 (0.7%)
Cladribine	3 (6.7%)	0 (0%)	0 (%)	3 (1.2%)	Cladribine	0 (0%)	1 (1.4%)	0 (0%)	1 (0.7%)
Treatment Naïve	9 (2.2%)	2 (2.3%)	1 (3.7%)	12 (4.8%)	Treatment Naïve	2 (2.7%)	0 (0%)	0 (0%)	2 (1.3%)
Multiple Sclerosis Subtype — no. (%)					**Multiple Sclerosis Subtype — no. (%)**				
RRMS	116 (85.9%)	71 (80.7%)	21 (77.8%)	208 (83.2%)	RRMS	68 (86.1%)	62 (88.6%)	1 (50%)	131 (86.8%)
PPMS	10 (7.5%)	12 (13.6%)	2 (7.4%)	24 (9.6%)	PPMS	3 (3.8%)	7 (10.0%)	1 (50%)	11 (7.3%)
PRMS	6 (4.4%)	2 (2.3%)	3 (11.1%)	11 (4.4%)	PRMS	6 (7.6%)	1 (1.4%)	0 (0%)	7 (4.6%)
SPMS	3 (2.2%)	3 (3.4%)	1 (3.7%)	7 (2.8%)	SPMS	2 (2.5%)	0 (0%)	0 (0%)	2 (1.3%)
Age - average									
Male age	59.1	63.1	50.5	59.1					
Female age	58.5	57.4	56.7	57.9					

The average duration of MS illness was 14 years for men and 16 years for women.
† B-cell Therapies included ocrelizumab and rituximab
* S1P-modulators included fingolimod and ozanimod.
‡ Fumarates included dimethyl fumarate and diroximel fumarate.

2022; Khayat-Khoei et al., 2022; Toljan et al., 2022; Finsterer, 2022). However, none of these reports claims to have found a causal relationship between COVID-19 vaccination and relapse/exacerbation of MS. In contrast, COVID-19 infection has been associated with an increased risk of MS relapses (Barzegar et al., 2021). Additionally, any risk of MS exacerbation with the COVID-19 vaccine seems to be miniscule in contrast to the risk of disease reactivation in the setting of COVID-19 infections (Havla et al., 2022).

Further longitudinal studies will be necessary to evaluate the enduring immunogenicity of COVID-19 vaccines for untreated MS patients, and those on the various MS therapies. Vaccine response has been shown to be detectable with the majority of MS DMTs (Tortorella et al., 2022). However, many studies have reported a blunted humoral response in patients on anti-CD20[24–32] and sphingosine 1-phosphate (S1P) therapies (Jakimovski et al., 2022) particularly with fingolimod (Tortorella et al., 2022; Tallantyre et al., 2022; Iannetta et al., 2022; Garjani et al., 2022) and siponimod (Skorić et al., 2022). This attenuated humoral response also applies to the immunity gained from the SARS-CoV-2 infections (Kister et al., 2022) and the attenuation period could last for up to 18 months after discontinuation of anti-CD20 infusion therapies (Moser et al., 2022). Among anti-CD20 DMTs, the highest percentage of seroconversion has been reported for ofatumumab (Levit et al., 2022). Seroconversion does seem to increase with a second vaccine dose (Tallantyre et al., 2022) and with time from the last anti-CD20 treatment (Tallantyre et al., 2022; Katz et al., 2022; Schwarz et al., 2022). Additionally, recall response to SARS-CoV-2 antigen seems to be better preserved when anti-CD20 therapy and booster doses are received after the completion of the initial vaccination cycle as compared to receiving all COVID-19 vaccine doses following anti-CD20 therapy initiation (Moser et al., 2022). Humoral response is reportedly not diminished in patients receiving natalizumab infusions (Katz et al., 2022; Levit et al., 2022; Iannetta et al., 2022).

Despite the attenuated B-cell response in patients on S1P or anti-CD20 therapies, various studies suggest that protection against SARS-CoV-2 can be preserved due to an intact T-cell response. Clinical outcomes with these agents appear similar to other disease modifying therapies, though risk of hospitalization appears higher in anti-CD20 therapies. Generation of antigen-specific CD4 and CD8 T cells after COVID-19 vaccination have been observed in MS patients along with a compromised follicular helper T-cell response, enhanced CD8 T-cell induction, and unchanged type 1 helper T-cell priming in MS patient on anti-CD20 DMTs (Apostolidis et al., 2021). The role of CD4 and CD8 T-cells in viral responses has been confirmed in a recent study with a measurable T-cell response being detected in 1 out 6 fingolimod patients and 4 out 8 patients on B-cell depleting therapies (4 out 6 on Ocrelizumab and 0 out of 2 on Rituximab) (Tallantyre et al., 2022). Another study of 108 MS patients and 78 healthy controls observed a reduced albeit adequate T-cell response in 14% of fingolimod patients vs 92% with ocrelizumab, 89% with interferon beta, and 70% with cladribine (Tortorella et al., 2022). Similar results on SARS-CoV-2-specific T-cell response in ocrelizumab patients has been published in other studies (Brill et al., 2021; Iannetta et al., 2022; Schwarz et al., 2022). Further

reports suggest that cellular responses might also be enhanced or at least comparable in patients on natalizumab (Kister et al., 2022; Iannetta et al., 2022) while remaining intact with ocrelizumab and diminished with S1P therapies as compared to controls (Kister et al., 2022). Unlike the humoral response, cellular response after SARS-CoV-2 seems to be entirely independent of time passed from the last anti-CD20 treatment (Kister et al., 2022).

Seroconversion to SARS-CoV-2 in most MS patients seems to increase significantly after receiving a booster dose (Milo et al., 2022; Tallantyre et al., 2022.). However, there are conflicting reports on the seroconversion of MS patients on anti-CD20 and S1P therapies. Some studies indicated lower post-booster seroconversion rates with both anti-CD20 therapies (Milo et al., 2022; Achtnichts et al., 2021) and fingolimod (Milo et al., 2022) while an increased humoral response in ocrelizumab and fingolimod patients has also been noted (Maglione et al., 2022). Lastly, higher seroconversion rates in patients on fingolimod vs. those on anti-CD20 DMTs (Tallantyre et al., 2022) and vice versa (König et al., 2022) have also been reported. Further studies will be needed to better inform our knowledge of booster responses in MS patients on S1P or anti-CD20 therapies.

5.1. Limitations

This is a single center observational cohort study with results based on subjective patient-reported SE. The main limitations of the present study are the relatively small sample size, not having serological status before vaccination, lack of EDSS assessment, and the short follow-up period. Single center studies are limited by the specific population that is being studied. Therefore, the results may not be generalizable to other populations. Observational studies are prone to confounding variables that can affect the relationship between the exposure and outcome being studied. Another weakness is that we are unable to establish causation, though we believe that the COVID19 vaccination was the trigger for the reported outcomes. Additionally, out of the studied population, relatively few MS patients received the Ad26.COV2.S vaccine with only 2 of them obtaining a Ad26.COV2.S booster. Larger multicentric prospective studies with longer follow-up evaluating the COVID19 vaccines impact on MS patients are still needed (Table 1).

6. Conclusion

COVID-19 vaccination is safe in patients with MS with a comparable SE spectrum to the general population. The risk for clinical relapses was absent in our cohort. Cases of temporary worsening of MS symptoms following SARS-CoV-2 are rare. Our findings support those reported by other recent studies and the CDC recommendation for MS patients to receive the FDA-approved COVID-19 vaccines, including the boosters.

CRediT authorship contribution statement

Amir Labani: Writing – original draft, Data curation, Formal analysis, Investigation. **Scott Chou:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Kasra Kaviani:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Brenda Ropero:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Katharine Russman:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Daniel Becker:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

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