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ORIGINAL COMMUNICATION

Risk of breakthrough COVID-19 after vaccination among people with multiple sclerosis on disease-modifying therapies

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Abstract

Background Disease-modifying therapies (DMTs) for people with multiple sclerosis (pwMS) may decrease vaccine effectiveness. We aimed to explore the association between various DMTs and the risk for breakthrough COVID-19.

Methods Population-based data from Clalit Health Services, Israel's largest healthcare organization, were used. PwMS treated with DMTs without prior COVID-19 were followed from the commencement of the mass vaccination campaign in December 2020. The end of follow-up was at the time of COVID-19 infection, the receipt of a third vaccine dose or until the end of August 2021. Time-dependent multivariate Cox proportional hazard models were used to estimate hazard ratios for COVID-19 according to vaccination, DMT, age, gender, disability and comorbidities.

Results 2511 PwMS treated with DMTs were included (Age: 46.2 ± 14.6, 70% Female, EDSS: 3.0 ± 2.1). Of whom, 2123 (84.5%) received 2 vaccine doses. On multivariate models that included all pwMS, vaccination was protective (HR = 0.41, $P < 0.001$). On multivariate models that included only fully vaccinated pwMS cladribine, ocrelizumab, S1P receptor modulators and natalizumab were associated with breakthrough COVID-19 (HR = 6.1, 4.7, 3.7 and 3.3; $P = 0.004$, 0.008, 0.02 and 0.05, respectively). On multivariate models that included unvaccinated and fully vaccinated pwMS on each DMT separately, a protective trend was noted for vaccination on all DMTs ($0.09 < HR < 0.65$), except for cladribine (HR = 1.1). This protective trend was not statistically significant on ocrelizumab, S1P receptor modulators and natalizumab. COVID-19 among pwMS was generally mild. Only 2 vaccinated pwMS had a severe infection with eventual recovery.

Conclusions Vaccination effectively protects pwMS from COVID-19. An increased risk of breakthrough infection was noted on high-efficacy DMTs, however COVID-19 after vaccination was usually mild.

Keywords Multiple sclerosis · Covid-19 · Vaccination · Immunodeficiency · Disease modifying treatment

Introduction

Disease-modifying therapies (DMTs) for multiple sclerosis (MS) have proven efficacy in preventing relapses and slowing disability progression. However, these medications interfere with the immune system, which may lead to increased susceptibility to infections [1] and to reduced response to vaccinations [2].

The outbreak of the Coronavirus disease 2019 (COVID-19) pandemic has highlighted the potential impact of DMTs on infection risk of people with MS (pwMS). In particular, early evidence has shown that pwMS who are treated with anti-CD20 therapies are at increased risk of COVID-19-related morbidity [3]. Furthermore, these patients have demonstrated weaker humoral responses after COVID-19 infection, raising concerns about their response to future vaccination [4, 5].

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On December 20, 2020, the Israeli vaccination campaign was launched, after the government had signed a contract with Pfizer. Since the beginning of the campaign, each adult MS patient was entitled to receive the BNT162b2 vaccine, a spike-encoding nucleoside-modified mRNA vaccine. On August 1, 2021, Israel began vaccinating patients with a third dose (booster).

The new vaccination was reported as safe for pwMS [6, 7] and pwMS seemed willing to receive it [8], however doubts remained regarding its efficacy due to the immunocompromised status of these patients. Several studies investigated the immune response to vaccination among pwMS treated with DMTs. Suboptimal humoral response has been reported for pwMS who were treated with ocrelizumab and fingolimod, a sphingosine-1-phosphate receptor modulator (S1PRM) [9]. Tortorella et al. reported similar findings, and noted that S1PRM treatment was also associated with a weak T-cell response [10]. On the other hand, adequate virus specific T-cell response to vaccination has been demonstrated for pwMS who were treated with anti-CD20 medication [11, 12]. Follow-up studies were in agreement with initial results [13, 14].

Epidemiological studies from Italy reported that low SARS-CoV-2 antibody level after the second vaccine dose predicted breakthrough COVID-19 infection among pwMS who were treated with DMTs during the delta and omicron waves [15]. Accordingly, breakthrough infection was more common among pwMS who were treated with fingolimod, as well as with anti-CD20s compared to all other DMTs [15, 16]. According to population based data from England, the incidence rate ratio of COVID-19 (incidence rate of infection among pwMS taking DMTs divided by incidence rate among the general population) increased after the start of mass vaccination for people who were treated with fingolimod and ocrelizumab, but not with other DMTs [17].

We aimed to further explore the risk of breakthrough COVID-19, despite vaccination, among pwMS who were treated with DMTs during the COVID-19 wave caused by the alpha variant in Israel.

Methods

A population-based retrospective cohort study, utilizing the computerized database of Clalit Health Services (CHS), the largest of four integrated healthcare organizations in Israel, which provides obligatory healthcare to more than 50% of the population. This insured population is geographically and socioeconomically diverse. CHS's electronic medical record system extracts data from inpatient and outpatient care facilities, laboratories, and pharmacies. This database includes demographic information, diagnoses, laboratory measurements, and medication dispensing.

PwMS actively treated with DMTs were included in this study. Active treatment was identified by medication dispensing within 12 months, 9 months and 3 months prior to the beginning of follow-up for cladribine and alemtuzumab, ocrelizumab and all other DMTs, respectively. COVID-19 diagnosis was based on a polymerase chain reaction (PCR) test. PwMS who had COVID-19 prior to the beginning of follow-up were excluded. Severe COVID-19 was coded in CHS database according to the national institutes of health (NIH) definitions, namely the presence of one or more of the following indicators: oxygen saturation less than 94%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of less than 300 mmHg, a respiratory rate exceeding 30 breaths per min or the observation of lung infiltrates accounting for over 50% of the lung area (https://www.covid19treatmentguidelines.nih.gov).

Clinical data on age, gender, expanded disability status scale (EDSS), comorbidities, vaccination status, COVID-19 infection and severity were extracted from CHS database.

This study has been approved by the institutional review board (IRB) of the Lady Davis Carmel Medical Center. Because this was a retrospective cohort study, based on automatically and routinely collected administrative and clinical data in a coded database, informed consent has been waived by the IRB.

Statistical analysis

Multivariate stepwise cox proportional hazard regression models were used. In the first analysis, all pwMS were included, regardless of their vaccination status. In this model the dependent variable was COVID-19 infection. Independent variables were vaccination status (entered as a time-dependent variable), age, sex, EDSS, specific DMTs and various comorbidities. In the second analysis only pwMS who were vaccinated with 2 doses of BNT162b2 mRNA Covid-19 vaccine were included and the predictors were age, sex, EDSS, specific DMTs and comorbidities. The third analysis compared pwMS who were vaccinated with two doses, on each DMT separately, with unvaccinated pwMS. Independent variables were vaccination status (entered as a time-dependent variable), age, sex, EDSS and various comorbidities.

In the first and third analyses, which included vaccinated and unvaccinated PwMS, participants were followed since the commencement of the mass vaccination campaign on December 20, 2020. Participants were considered vaccinated in time-dependent analyses from 2 weeks after receiving the second vaccine dose. Importantly, COVID-19 infections, which had occurred after December 20, 2020 but before 2 weeks after receiving the second vaccine contributed to the hazard rate of the unvaccinated group. In the second analysis, which included only vaccinated pwMS, participants

were followed from two weeks after receiving the second vaccine dose. The end of follow-up in all analyses was at the time of COVID-19 infection, the receipt of a third vaccine dose (booster), or until the end of August 2021, whichever came first. Patients who were vaccinated with only one dose were categorized as not vaccinated.

Statistical analyses were performed using SPSS (IBM, Chicago, Illinois).

A two-sided p-value of less than 0.05 was considered statistically significant in all analyses. Descriptive statistics are presented as means and standard deviations.

Table 1 Patients' characteristics

N	2511
Age (years)	46.2 ± 14.6
Gender	Female: 1749 (70%)
EDSS	3.0 ± 2.1
Comorbidities	Obesity: 483 (19%)
	Hypertension: 374 (15%)
	Diabetes Mellitus: 209 (8%)
	Kidney disease: 192 (8%)
	Heart disease: 181 (7%)
	Cerebrovascular disease: 167 (6%)
	Asthma and COPD: 158 (6%)
	Cancer: 71 (3%)
	Liver disease: 34 (1%)
Disease modifying treatments	N (%)
Dimethyl fumarate	586 (23)
Interferon beta	546 (21)
Ocrelizumab	373 (15)
Glatiramer acetate	244 (10)
Teriflunomide	230 (9)
S1P receptor modulators	226 (9)
Natalizumab	182 (7)
Cladribine	113 (5)
Alemtuzumab	11 (1)

Results

A total of 2612 pwMS who were actively treated with DMTs were found in the database on December 20, 2020. Of whom, 101 patients were excluded due to a documented COVID-19 prior to the beginning of follow-up period. Among the included patients, 2123 (84.5%) received 2 vaccine doses, 41 (1.5%) received only 1 vaccine dose and 347 (14.0%) declined vaccination. The study participants' baseline demographic and clinical characteristics are presented in Table 1 and the characteristics of the COVID-19-infected patients are presented in Table 2. The average age of patients at the beginning of follow-up was 46.2 ± 14.6, 70% were females. 137 patients developed COVID-19 infection during follow-up, 28% of whom were vaccinated. The mean duration of follow-up from the commencement of mass vaccination campaign

Table 2 Characteristics of COVID-19 cases during follow-up

N	137	
Age (years)	43.9 ± 13.4	
Gender	Female: 87 (63.5)	
EDSS	2.9 ± 2.12	
Comorbidities	Obesity: 26 (19.0%)	
	Hypertension: 21 (15.3%)	
	Diabetes mellitus: 11 (8.0)	
	Kidney disease: 16 (11.7%)	
	Heart disease: 8 (5.8%)	
	Cerebrovascular disease: 11 (8.0%)	
	Asthma and COPD: 12 (8.7%)	
	Cancer: 5 (3.6%)	
	Liver disease: 4 (2.9)	
Vaccinated with 2 doses (n,%)	38 (28%)	
Disease modifying treatments	COVID-19 throughout follow-up (n)	Breakthrough COVID-19 following vaccination with 2 doses (n)
Ocrelizumab	28	8
S1P receptor modulators	18	4
Natalizumab	11	5
Cladribine	10	4
Other DMTs	70	17

was 239 ± 43 days. The mean duration of follow-up from 2 weeks after receiving 2 vaccine doses was 174 ± 31 days.

Risk factors for COVID-19 infection in multivariate analyses are reported in Table 3. Vaccination with 2 doses of mRNA BNT162b2 was protective from COVID-19, with a HR of 0.41 (95% CI 0.24–0.69) among pwMS who were treated with DMTs. Notably, treatment with ocrelizumab as well as with S1PRM was associated with higher rates of COVID-19 (Table 3).

In the analysis that included only the vaccinated population, treatment with ocrelizumab, S1PRM and cladribine emerged as potential risk factors for breakthrough COVID-19 on stepwise multivariate analysis (Table 4). In the model that included all predictors, natalizumab was also associated with increased risk of breakthrough COVID-19 (Table 4; Fig. 1).

On multivariate models that included unvaccinated and fully vaccinated pwMS on each DMT separately, a protective trend was noted for vaccination on all DMTs ($0.09 < HR < 0.65$), except for cladribine ($HR = 1.1$, $P = 0.87$). This protective trend was not statistically significant for pwMS on ocrelizumab, S1P receptor modulators and natalizumab (Table 5).

Only 8 pwMS had a severe COVID-19 infection, just 2 of them were fully vaccinated. Their characteristics are presented in Table 6. There were no cases of COVID-19-related mortality during follow-up.

Discussion

In this population-based study of pwMS who were actively treated with DMTs, mRNA vaccination against COVID-19 was protective. Although active treatment with ocrelizumab, S1PRM, cladribine and natalizumab was associated with increased risk of breakthrough COVID-19, the infection was generally mild, regardless of DMT.

The findings support the effectiveness of COVID-19 mRNA vaccine among pwMS who are using DMTs, with an HR of 0.41. The degree of protection is consistent with a previously reported HR of 0.51 during the delta wave in Italy [15], but much less than vaccine effectiveness of 92% that has been reported for the general Israeli population [18]. This difference in vaccine effectiveness may be due to disability and immune suppression of pwMS.

In the current study treatment with ocrelizumab and S1PRMs was found as a risk factor for COVID-19 infection

Table 3 Multivariate Cox regression model evaluating risk factors for SARS-CoV-2 infection among pwMS ($N = 2511$)

Variable	Multivariate analysis (all variables included)		Stepwise multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Vaccination with 2 doses of mRNA BNT162b2 (yes vs. no)	**0.43 (0.25–0.74)**	**0.002**	**0.41 (0.24–0.69)**	**< 0.001**
Age (years)	1.00 (0.98–1.01)	0.57		
Sex (Female vs. Male)	0.80 (0.56–1.14)	0.22		
EDSS (1 point score)	0.93 (0.84–1.03)	0.17		
Ocrelizumab (yes vs. no)	1.49 (0.73–3.01)	0.27	**1.53 (1.001–2.33)**	**0.049**
S1P receptor modulators (yes vs. no)	1.62 (0.80–3.30)	0.18	**1.80 (1.08–2.84)**	**0.020**
Cladribine (yes vs. no)	1.60 (0.73–3.52)	0.25		
Dimethyl fumarate (yes vs. no)	0.75 (0.38–1.46)	0.39		
Interferon beta (yes vs. no)	0.78 (0.39–1.54)	0.47		
Natalizumab (yes vs. no)	1.15 (0.51–2.56)	0.74		
Glatiramer acetate (yes vs. no)	0.94 (0.44–2.01)	0.87		
Teriflunomide (yes vs. no)	0.88 (0.40–1.94)	0.75		
Alemtuzumab (yes vs. no)	0.00	0.96		
Obesity (yes vs. no)	0.91 (0.57–1.43)	0.67		
Hypertension (yes vs. no)	1.27 (0.71–2.27)	0.41		
Diabetes mellitus (yes vs. no)	1.05 (0.51–2.15)	0.90		
Kidney disease (yes vs. no)	1.65 (0.95–2.84)	0.07		
Heart disease (yes vs. no)	0.78 (0.36–1.66)	0.51		
Cerebrovascular disease (yes vs. no)	1.27 (0.67–2.42)	0.46		
Asthma and COPD (yes vs. no)	0.97 (0.52–1.80)	0.92		
Cancer (yes vs. no)	1.39 (0.56–3.44)	0.48		
Liver disease (yes vs. no)	2.19 (0.78–6.15)	0.14		

Table 4 Multivariate Cox regression model evaluating risk factors for SARS-CoV-2 infection among vaccinated pwMS ($N=2123$)

Variable	Multivariate analysis (all variables included)		Stepwise multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.00 (0.97–1.03)	0.73		
Sex (Female vs. Male)	0.65 (0.33–1.28)	0.22		
EDSS (1 point score)	0.85 (0.69–1.04)	0.11		
Ocrelizumab (yes vs. no)	**4.74 (1.49–15.06)**	**0.008**	**3.48 (1.40–8.67)**	**0.007**
S1P receptor modulators (yes vs. no)	**3.72 (1.19–11.69)**	**0.024**	**2.70 (1.09–6.68)**	**0.032**
Cladribine (yes vs. no)	**6.10 (1.78–20.86)**	**0.004**	**4.40 (1.53–12.68)**	**0.006**
Dimethyl fumarate (yes vs. no)	1.35 (0.47–3.86)	0.57		
Interferon beta (yes vs. no)	1.94 (0.67–5.62)	0.22		
Natalizumab (yes vs. no)	**3.26 (1.01–10.54)**	**0.049**		
Glatiramer acetate (yes vs. no)	0.43 (0.05–3.63)	0.44		
Teriflunomide (yes vs. no)	1.26 (0.32–4.98)	0.74		
Obesity (yes vs. no)	0.72 (0.27–1.90)	0.50		
Hypertension (yes vs. no)	0.87 (0.26–2.89)	0.82		
Diabetes mellitus (yes vs. no)	1.68 (0.53–5.33)	0.38		
Kidney disease (yes vs. no)	0.95 (0.28–3.24)	0.93		
Heart disease (yes vs. no)	0.79 (0.18–3.53)	0.76		
Cerebrovascular disease (yes vs. no)	1.01 (0.23–4.37)	0.99		
Asthma and COPD (yes vs. no)	1.60 (0.62–4.17)	0.33		
Cancer (yes vs. no)	2.92 (0.86–9.88)	0.09		

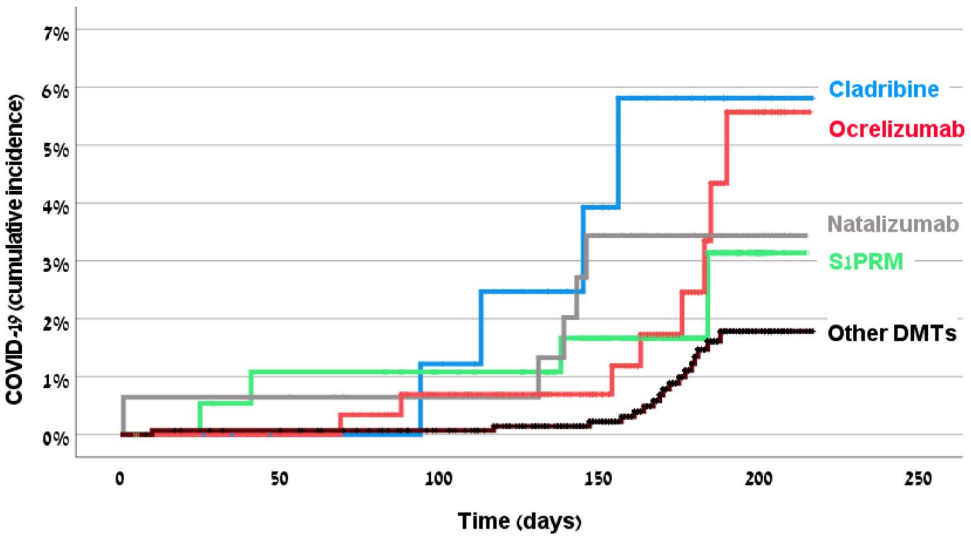

Fig. 1 Cumulative incidence of breakthrough COVID-19 on various DMTs. Cumulative incidence of breakthrough COVID-19 on various disease modifying treatments (DMTs), among 2123 participants with multiple sclerosis, who were vaccinated with 2 doses. Follow up time was from 2 weeks after receiving the second vaccine dose, until COVID-19 infection, receipt of a third vaccine dose or the end of August 2021, whichever came first. *S1PRM* Sphingosine-1-phosphate receptor modulators, Other DMTs include dimethyl fumarate, interferon beta, glatiramer acetate and teriflunomide. For statistics refer to Table 4

in the post-vaccination era (Table 3). Since this analysis included vaccinated as well as unvaccinated pwMS, it is impossible to determine if the risk was due to breakthrough infection or owing to infection in those who had not been vaccinated. In line with our findings, treatment with anti-CD20 medications, has been found as an independent risk factor for COVID-19 in the pre-vaccination era [3, 19–21], while both S1PRM and anti-CD20 medications have been associated with COVID-19 after mass vaccination against COVID-19 took place [15–17]. The higher risk

Table 5 Multivariate Cox regression models evaluating hazard ratios for SARS-CoV-2 infection among fully vaccinated pwMS on each DMT separately, compared to unvaccinated pwMS [a]

Disease modifying treatment (DMT) [b]	Vaccinated pwMS on a specific DMT (*n*)	Participants [c] (*n*)	Multivariate analysis [d]	
			HR (95% CI)	*P* value
Cladribine	86	474	1.09 (0.37–3.17)	0.87
Ocrelizumab	301	689	0.65 (0.29–1.47)	0.30
Natalizumab	154	542	0.58 (0.22–1.50)	0.25
S1P receptor modulators	186	574	0.37 (0.13–1.06)	0.06
Interferon beta	467	855	0.34 (0.15–0.80)	0.01
Dimethyl fumarate	502	890	0.25 (0.10–0.62)	0.006
Teriflunomide	202	590	0.24 (0.07–0.78)	0.02
Glatiramer acetate	217	605	0.09 (0.01–0.65)	0.02

a) Predictors in the model: vaccination on specific DMTs (one at a time) as a time-dependent variable (pwMS were considered vaccinated from 2 weeks after receiving two vaccine doses), age, sex, EDSS, comorbidities

b) Alemtuzumab was not included since only 8 patients were vaccinated on this DMT

c) PwMS in the model: vaccinated with 2 doses on a specific DMT as specified in each row and unvaccinated on any DMT ($n = 388$)

d) Hazard ratios (HR) represent the ratios of the hazard rates of breakthrough COVID-19 after receiving two vaccine doses on a specific DMT as specified in each row, to the hazard rates in the unvaccinated group, after controlling for covariates

Table 6 Characteristics of the patients with severe COVID-19 despite vaccination

Patient	Age	Sex	EDSS	DMT	Comorbidities
1	54	Male	7	Ocrelizumab	Diabetes mellitus, Chronic renal failure
2	51	Female	4	Fingolimod	Hypertension

of infection is probably due to weakened humoral response to mRNA vaccines against SARS-CoV-2 for both S1PRM and anti-CD 20 medications, while pwMS on S1PRM had impaired cellular response as well [10, 14, 22, 23]. Diminished humoral response was also described after natural infection with SARS-CoV-2 on both anti-CD20 therapies and S1PRM [24, 25].

Upon inclusion of only pwMS who received 2 doses of mRNA vaccine, the increased risk with ocrelizumab and S1PRMs remained, while cladribine and natalizumab appeared to increase the risk of breakthrough COVID-19 as well (Table 4; Fig. 1). While adequate humoral response to mRNA vaccination on cladribine has been reported by some [9], others have noted diminished immune responses with this medication: post vaccination anti-Region-Binding-Domain median titter was lower in patients treated with cladribine compared to healthy people [10]. Interferon-γ-T-cell-specific responses were also found to be significantly lower in cladribine treated patients compared to healthy controls [10]. Moreover, a proportion of convalescent COVID-19 pwMS on cladribine did not develop IgG SARS-CoV-2 antibodies [13, 24, 26]. Data on the immunogenicity to COVID-19 vaccine among pwMS on natalizumab attest to preserved humoral and T-cell responses [27]. However, one study did show a significantly lower post-vaccine antibody levels in pwMS on natalizumab compared with untreated people [28]. Moreover, natalizumab may impair alpha-4-integrin mediated migration of monocytes into respiratory tissues during SARS-CoV-2 infection, which may contribute to increased risk of breakthrough COVID-19 despite adequate vaccine responses [29].

The aforementioned increased risk of breakthrough COVID-19 for people on ocrelizumab, S1PRM, natalizumab and cladribine must be interpreted with caution. One inherent limitation to the Cox regression approach is guarantee-time bias: events of COVID-19 were excluded from the analysis during the 'guarantee' time, from the start of follow-up on December 20, 2020, until the date of actual vaccination. Thus, guarantee-time differences between pwMS on different DMTs could potentially bias the results. To control for this potential bias, pwMS who were vaccinated with two doses, on each DMT separately, were compared with unvaccinated pwMS. In this analysis, vaccination status, on each DMT was entered as time-dependent variable, so that COVID-19 events after the start of follow-up and before vaccination were not excluded, but contributed to the hazard rate of the unvaccinated group [30]. Even after taking guarantee-time into account, the protective trend of vaccination was not statistically significant for people on cladribine, ocrelizumab, S1PRM and natalizumab (Table 5).

It is noteworthy and reassuring that probably due to vaccination COVID-19 among the participants of this study was generally mild. Only 2 severe infections were observed in vaccinated patients (Table 6) and no deaths were recorded. Indeed, the importance of vaccination is

mainly to prevent severe infection. The paucity of severe breakthrough COVID-19 among vaccinated pwMS, regardless of DMT type was reported by others, and decreased significantly compared to the pre-vaccination era [15, 31]. As the virulence of SARS-CoV-2 variants decreases over time [32, 33], the odds of severe infection, despite vaccination, due to DMT use among pwMS is expected to decrease even further. Perhaps the retained ability to mount a vaccine-specific T-cell response on anti-CD20 therapies [11, 12, 34], might provide protection from severe disease by limiting viral replication to the upper respiratory tract [35]. In the case of S1PRM, it is possible that the diminished T-cell and humoral responses to vaccination that are detected in the peripheral circulation, do not adequately represent the capacity of the immune system to respond to severe infections, since lymphocytes are sequestered in lymph nodes, rather than abolished by these medications.

The COVID-19 pandemic introduced new uncertainties into clinical decision making with pwMS regarding the balance between efficacy and safety of DMTs. Our results support the notion that DMT choice in the COVID-19 era should still be guided first and foremost by MS disease activity, as COVID-19 vaccines seems effective in preventing severe infection, regardless of DMT. The signal of increased risk of breakthrough infection with ocrelizumab, S1PRM, natalizumab and cladribine call for considering personal risk of infection during therapeutic decision making, especially if MS is not highly active.

The strengths of this study are the use of population-based data, control of individual-level confounding factors, solid case definitions of COVID-19 by PCR testing and classification of COVID-19 severity according to NIH definitions, rather than by hospitalization status, which may be influenced by factors other than disease severity per se, such as background illnesses and use of immunosuppressive medications. Among the limitations are unknown antibody levels and the short follow-up time, dictated by the introduction of a mass vaccination campaign for a third vaccine dose (booster) and by the emergence of the delta wave. The short follow-up time, together with the limited number of participants resulted in small absolute numbers of breakthrough COVID-19 cases per DMT (Table 2). Small number of cases carry the risk of unstable results, as change of only few cases per DMT could have changed statistical significance. The short follow-up and small number of breakthrough infections also decreased the power of statistical analyses, explaining why protective trend of vaccination on some DMTs, demonstrated by HR < 1, did not reach statistical significance (Table 5).

In conclusion, vaccination against COVID-19 is effective for pwMS on various DMTs, significantly reduces the risk of infection, and particularly of severe infection. Although a signal of increased risk of breakthrough COVID-19, despite vaccination emerged with ocrelizumab, S1P receptor modulators, natalizumab and cladribine, the absolute number of infections was small, and COVID-19 was generally mild. Additional studies with longer follow-up times are needed to fully understand the risk of breakthrough COVID-19 and its consequences among pwMS who are treated with high-efficacy DMTs.

Data availability statement

Anonymized data will be shared by request from any qualified investigator.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Luna G, Alping P, Burman J et al (2020) Infection risks among patients with multiple sclerosis treated with Fingolimod, Natalizumab, Rituximab, and injectable therapies. JAMA Neurol 77:184–191. https://doi.org/10.1001/jamaneurol.2019.3365
2. Farez MF, Correale J, Armstrong MJ et al (2019) Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis: report of the Guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology 93:584–594. https://doi.org/10.1212/WNL.0000000000008157
3. Simpson-Yap S, De Brouwer E, Kalincik T et al (2021) Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. Neurology 97:e1870–e1885. https://doi.org/10.1212/WNL.0000000000012753
4. Louapre C, Ibrahim M, Maillart E et al (2022) Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 in patients with multiple sclerosis or neuromyelitis optica spectrum disorders. J Neurol Neurosurg Psychiatry 93:24–31. https://doi.org/10.1136/jnnp-2021-326904
5. Thornton JR, Harel A (2020) Negative SARS-CoV-2 antibody testing following COVID-19 infection in Two MS patients treated with ocrelizumab. Mult Scler Relat Disord 44:102341. https://doi.org/10.1016/j.msard.2020.102341
6. Achiron A, Dolev M, Menascu S et al (2021) COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by February 2021. Mult Scler 27:864–870. https://doi.org/10.1177/13524585211003476
7. Lotan I, Wilf-Yarkoni A, Friedman Y et al (2021) Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis (MS): Early experience from a tertiary MS center in Israel. Euro J Neurol 28:3742–3748. https://doi.org/10.1111/ene.15028
8. Xiang XM, Hollen C, Yang Q et al (2021) COVID-19 vaccination willingness among people with multiple sclerosis. Mult Scler J Experim Translat Clin 7:205521732110171. https://doi.org/10.1177/20552173211017159
9. Achiron A, Mandel M, Dreyer-Alster S et al (2021) Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying

therapies. Ther Adv Neurol Disord 14:175628642110128. https://doi.org/10.1177/17562864211012835
10. Tortorella C, Aiello A, Gasperini C et al (2022) Humoral- and T-Cell–specific immune responses to SARS-CoV-2 mRNA vaccination in patients with MS using different disease-modifying therapies. Neurology 98:e541–e554. https://doi.org/10.1212/WNL.0000000000013108
11. Apostolidis SA, Kakara M, Painter MM et al (2021) Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat Med 27:1990–2001. https://doi.org/10.1038/s41591-021-01507-2
12. Brill L, Rechtman A, Zveik O et al (2021) Humoral and T-cell response to SARS-CoV-2 vaccination in patients with multiple sclerosis treated with Ocrelizumab. JAMA Neurol 78:1510. https://doi.org/10.1001/jamaneurol.2021.3599
13. Milo R, Staun-Ram E, Karussis D et al (2022) Humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination in patients with Multiple sclerosis: An Israeli multi-center experience following 3 vaccine doses. Front Immunol 13:868915. https://doi.org/10.3389/fimmu.2022.868915
14. Zabalza A, Arrambide G, Tagliani P et al (2022) Humoral and cellular responses to SARS-CoV-2 in convalescent COVID-19 patients with multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 9:e1143. https://doi.org/10.1212/NXI.0000000000001143
15. Sormani MP, Schiavetti I, Inglese M et al (2022) Breakthrough SARS-CoV-2 infections after COVID-19 mRNA vaccination in MS patients on disease modifying therapies during the Delta and the Omicron waves in Italy. eBioMedicine 80:104042. https://doi.org/10.1016/j.ebiom.2022.104042
16. Schiavetti I, Cordioli C, Stromillo ML et al (2022) Breakthrough SARS-CoV-2 infections in MS patients on disease-modifying therapies. Mult Scler 28:2106–2111. https://doi.org/10.1177/13524585221102918
17. Garjani A, Patel S, Bharkhada D et al (2022) Impact of mass vaccination on SARS-CoV-2 infections among multiple sclerosis patients taking immunomodulatory disease-modifying therapies in England. Mult Scler Relat Disord 57:103458. https://doi.org/10.1016/j.msard.2021.103458
18. Dagan N, Barda N, Kepten E et al (2021) BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 384:1412–1423. https://doi.org/10.1056/NEJMoa2101765
19. Reder AT, Centonze D, Naylor ML et al (2021) COVID-19 in Patients with Multiple sclerosis: associations with disease-modifying therapies. CNS Drugs 35:317–330. https://doi.org/10.1007/s40263-021-00804-1
20. Safavi F, Nourbakhsh B, Azimi AR (2020) B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. Mult Scler Relat Disord 43:102195. https://doi.org/10.1016/j.msard.2020.102195
21. Sormani MP, De Rossi N, Schiavetti I et al (2021) Disease-modifying therapies and coronavirus disease 2019 severity in Multiple SCLEROSIS. Ann Neurol 89:780–789. https://doi.org/10.1002/ana.26028
22. Cohen JA, Bermel RA, Grossman CI et al (2022) Immunoglobulin G immune response to SARS-CoV-2 vaccination in people living with multiple sclerosis within Multiple sclerosis partners advancing technology and health solutions. Mult Scler 28:1131–1137. https://doi.org/10.1177/13524585211061343
23. Capuano R, Bisecco A, Conte M et al (2022) Six-month humoral response to mRNA SARS-CoV-2 vaccination in patients with multiple sclerosis treated with ocrelizumab and fingolimod. Mult Scler Relat Disord 60:103724. https://doi.org/10.1016/j.msard.2022.103724
24. Habek M, Jakob Brecl G, Bašić Kes V et al (2021) Humoral immune response in convalescent COVID-19 people with multiple sclerosis treated with high-efficacy disease-modifying therapies: a multicenter, case-control study. J Neuroimmunol 359:577696. https://doi.org/10.1016/j.jneuroim.2021.577696
25. van Kempen ZLE, Strijbis EMM, Al MMCT et al (2021) SARS-CoV-2 antibodies in adult patients with multiple sclerosis in the Amsterdam MS cohort. JAMA Neurol 78:880. https://doi.org/10.1001/jamaneurol.2021.1364
26. Bsteh G, Dürauer S, Assar H et al (2021) Humoral immune response after COVID-19 in multiple sclerosis: a nation-wide Austrian study. Mult Scler 27:2209–2218. https://doi.org/10.1177/13524585211049391
27. Etemadifar M, Nouri H, Pitzalis M et al (2022) Multiple sclerosis disease-modifying therapies and COVID-19 vaccines: a practical review and meta-analysis. J Neurol Neurosurg Psychiatry 93:986–994. https://doi.org/10.1136/jnnp-2022-329123
28. Pitzalis M, Idda ML, Lodde V et al (2021) Effect of different disease-modifying therapies on humoral response to BNT162b2 vaccine in sardinian multiple sclerosis patients. Front Immunol 12:781843. https://doi.org/10.3389/fimmu.2021.781843
29. Baker D, Amor S, Kang AS et al (2020) The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. Mult Scler Relat Disord 43:102174. https://doi.org/10.1016/j.msard.2020.102174
30. Cho IS, Chae YR, Kim JH et al (2017) Statistical methods for elimination of guarantee-time bias in cohort studies: a simulation study. BMC Med Res Methodol 17:126. https://doi.org/10.1186/s12874-017-0405-6
31. Capuano R, Prosperini L, Altieri M et al (2023) Symptomatic COVID-19 course and outcomes after three mRNA vaccine doses in multiple sclerosis patients treated with high-efficacy DMTs. Mult Scler. https://doi.org/10.1177/13524585231167515
32. Wang C, Liu B, Zhang S et al (2023) Differences in incidence and fatality of COVID-19 by SARS-CoV-2 Omicron variant versus Delta variant in relation to vaccine coverage: a world-wide review. J Med Virol 95:e28118. https://doi.org/10.1002/jmv.28118
33. Trunfio M, Portesani F, Vicinanza S et al (2022) Real-life evidence of lower lung virulence in COVID-19 inpatients infected with SARS-CoV-2 omicron variant compared to wild-type and delta SARS-CoV-2 pneumonia. Lung 200:573–577. https://doi.org/10.1007/s00408-022-00566-7
34. Gadani SP, Reyes-Mantilla M, Jank L et al (2021) Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy. EBioMedicine 73:103636. https://doi.org/10.1016/j.ebiom.2021.103636
35. Sette A, Crotty S (2021) Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 184:861–880. https://doi.org/10.1016/j.cell.2021.01.007