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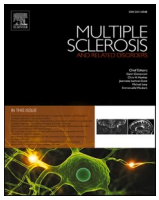

Original article

Quantitative and qualitative features of acute phase-adverse events following SARS-CoV-2 vaccination in a large sample of people with multiple sclerosis

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ABSTRACT

Introduction: Few data are available on adverse events (AE) associated to vaccines in persons with multiple sclerosis (pwMS).
Aims: to study the incidence of acute phase AE (AP-AE) related to SARS-CoV-2 mRNA vaccines in pwMS compared to a control group, and to analyze the association between AP-AE and disease modifying treatments (DMT).
Methods: This was a cross-sectional study on 438 PwMS and 481 age- and sex-matched subjects not affected by dysimmune diseases that underwent two doses of SARS-CoV-2 mRNA BNT162b2 vaccine (Pfizer/BioNtech).
Results: Two hundred and twenty five (51.4%) pwMS complained of ≥1 AP-AE after the first dose, 269 (61.4%) after the second dose. A logistic regression analysis revealed that only pwMS on Fingolimod and Ocrelizumab did not show a higher risk of developing AP-AE. The likelihood to present with ≥1 AP-AE, after correcting for age and sex, was significantly higher in pwMS than controls.
Conclusions: This study reports qualitative and quantitative features of AP-AE associated with the first and second doses of SARS-CoV-2 vaccine in a large sample of pwMS. The only risk factor identified for developing AP-AE is female gender. AntiCD-20 monoclonal antibodies and S1P inhibitors are associated with a lower risk of AP-AE occurrence.

1. Introduction

The outburst of SARS-CoV-2 infection has raised a lot of attention for the potentially severe complications in patients affected by autoimmune diseases, and among them, in people with multiple sclerosis (pwMS). PwMS have an increased risk of all types of infection as compared to the general population and a doubled risk of hospitalization resulting from the same type of infectious pathology as compared to healthy controls (Persson et al., 2020; Ghaderi et al., 2020). For pwMS on immunosuppressive treatments, acute infections can have dangerous sequelae and there is evidence that infections can trigger relapses in MS (Panitch, 1994; Andersen et al., 1993; Ascherio and Munch, 2000; Correale et al., 2006).

With respect to SARS-CoV-2, recent literature data have reported that pwMS have twice the risk of developing a severe form of disease as compared to the general population, mainly related to risk factors such as moderate-to-high disability (expanded disability status scale-EDSS->3), presence of comorbidities and an actively ongoing therapy with antiCD20 medications (Sormani et al., 2022; Schiavetti et al., 2022). Multiple vaccines against SARS-CoV-2 have been developed and approved (Polack et al., 2020; Baden et al., 2021), but they have not been specifically tested in pwMS, raising concerns regarding their efficacy and safety, considering both the dysimmune nature of the disease and the widespread use of immunoactive treatments in pwMS. Several studies have been carried out on the immunogenicity of SARS-CoV-2 vaccines in pwMS undergoing different disease modifying treatments

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(DMT) (Jakubecz et al., 2022; Boekel et al., 2021; Krajnc et al., 2022; Wallach et al., 2022; Iannetta et al., 2021). However, data on the vaccine reactogenicity in terms of adverse events (AE) are still scarce (Briggs et al., 2022; Czarnowska et al., 2022; Achiron et al., 2021; Lotan et al., 2021), and even fewer are the studies that analyzed the effects of vaccines in relationship with different types of DMT (Briggs et al., 2022; Czarnowska et al., 2022), leading to vaccine hesitancy in pwMS (Yap et al., 2021).

With this background, the aims of the present study were to describe the SARS-CoV-2 mRNA vaccine-related acute phase adverse events (AP-AEs) in a large sample of pwMS and to evaluate whether the type of DMT could affect the risk of developing AP-AEs.

2. Materials and methods

PwMS were consecutively recruited in this cross-sectional study between May 2021 and January 2022 at IRCCS Mondino Foundation, Pavia, Italy. Inclusion criteria were: 1. diagnosis of clinically definite MS according to the 2017 McDonald's criteria, 2. age >18 years old 3. documented evidence of a vaccination cycle with at least two doses of SARS-CoV-2 mRNA BNT162b2 (Pfizer/BioNtech) 4. A current treatment with any of the disease modifying treatments officially approved for treatment of MS.

The control group was composed by people working at IRCCS Mondino Foundation, Pavia, Italy or at the nearby scientific Institute IRCCS Fondazione Maugeri, Pavia, Italy. The only exclusion criterion considered for the study was the presence of a definite diagnosis of a dysimmune disease.

Demographic data (age, sex) and acute phase adverse events (AP-AEs) possibly occurred after each SARS-CoV-2 vaccine dose (pain at the injection site, fever, asthenia, lymph node swelling, arthralgia, headache, nausea / vomiting, diarrhea, others) were collected for all the people recruited in the study, together with clinical data (disease duration, level of disability quantified by means of Expanded Disability Status Scale-EDSS) only for pwMS. The study was approved by the local Ethical Committee and conducted accordingly to the Declaration of Helsinki. Patients signed an informed consent upon study recruitment (CE code: 2022-3.11/483).

All statistical analysis were conducted using Stata software (version 16.1; StataCorp LP, College Station, TX). For each cohort descriptive statistics were calculated: mean and standard deviation, median and interquartile range (IQR) for continuous variables, frequencies for categorical variables. McNemar's test for paired data was used to compare the proportions of AE after the first and second dose in pwMS and in controls. Student's t-test was performed to compare the mean age in the two groups (at least one AP-AE vs no AP-AE). Multivariate logistic regression models were fitted to estimate the probability of having at least one adverse event or a specific one (i.e. pain surrounding the injection site) compared to those who do not have it, adjusting for covariates (sex, age, DMT only for the analyses related to the pwMS cohort). Finally, *a posteriori* power analysis was performed (Sullivan et al., 2009). For all statistical calculations the threshold for significance was $p < .05$.

3. Results

Four-hundred and thirty eight pwMS (294 women, 67.1%) were recruited in the study, together with 481 controls (332 women, 69%).

3.1. PwMS

Clinico-demographic characteristics are as follows: mean age 46 (SD 12.1) years, median EDSS 2.0 (1.5–3.0), mean disease duration was 15.8 (9.2) years. DMTs' distribution in pwMS is summarized in Table 1.

Two hundred and twenty five (51.4%) pwMS complained of ≥1 AP-AE after the first dose, whereas 269 (61.4%) presented with ≥1 AP-AE after the second dose ($p = .0004$). The frequency of AP-AE after the first and the second dose of vaccines are summarized in Table 2.

Table 1
Disease Modifying Treatments distribution in pwMS.

DMT	pwMS ($n = 438$) *n (%)*
Dimethyl fumarate	103 (23.5)
Teriflunomide	77 (17.6)
Natalizumab	64 (14.6)
Ocrelizumab	50 (11.4)
Fingolimod	46 (10.5)
Glatiramer acetate	34 (7.8)
IM IFN β 1a	24 (5.5)
SC IFN β 1a (once/2 weeks)	22 (5.0)
SC IFN β 1a (3 times/ week)	10 (2.3)
SC IFN β 1b	8 (1.8)

DMT: disease modifying treatments; IM: intramuscular; IFN: interferon; SC: subcutaneous

The most common AP-AE was pain surrounding the injection site (40.2% pwMS after the first dose, 35.2% pwMS after the second dose, 25.3% after both doses), followed by tiredness (12.3% pwMS after the first dose, 18.3% pwMS after the second dose, 6.6% after both doses).

The mean age of pwMS presenting with ≥1 AP-AE was not significantly different from the mean age of pwMS without any AP-AE, neither after the first dose (45.7 years vs 46.3 years, $p = .57$) nor after the second one (45.8 years vs 46.2 years, $p = .76$). Furthermore, the mean age of pwMS complaining about pain surrounding the injection site was not significantly different from the mean age of pwMS without pain surrounding the injection site after the first dose (46.1 years vs 45.9 years, $p = .91$), nor after the second one (46.4 years vs 45.7 years, $p = .57$).

The likelihood to present with ≥1 AP-AE was lower for men as compared to women (27.6% lower after the first dose of vaccine, 25.2% lower after the second one, 38.4% after at least one dose) after correcting for age ($p = .12$, $p = .16$, $p = .03$, respectively).

Table 3 shows the distribution of ≥1 AP-AE at the first, at the second and at least one dose by DMT. Since SC INF β 1a showed the lowest percentage of AP-AE, we used this DMT as reference category in the logistic regression models. No significant effect of DMT on AP-AE or of pain surrounding the injection site is shown after the first dose of vaccine.

Table 2
Adverse Events distribution in pwMS and controls.

	pwMS ($n = 438$) *n (%)*		Controls ($n = 481$) *n (%)*	
	After first dose	After second dose	After first dose	After second dose
AE				
At least one	225 (51.4)	269 (61.4)	103 (21.4)	209 (43.5)
Pain surrounding the injection site				
Yes	176 (40.2)	154 (35.2)	46 (9.6)	37 (7.7)
Fever (T°)				
Yes	19 (4.3)	79 (18.0)	13 (2.7)	86 (17.9)
Tiredness				
Yes	54 (12.3)	80 (18.3)	31 (6.4)	72 (15.0)
Enlargement of lymph nodes				
Yes	1 (0.2)	4 (0.9)	3 (0.6)	8 (1.7)
Arthralgia				
Yes	18 (4.1)	32 (7.3)	14 (2.9)	64 (13.3)
Headache				
Yes	16 (3.7)	25 (5.7)	23 (4.8)	55 (11.4)
Nausea/vomiting				
Yes	6 (1.4)	7 (1.6)	6 (1.2)	23 (4.8)
Diarrhea				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

AE: Adverse Events.

Table 3
Adverse Events distribution by DMT in pwMS.

	AE after first dose (n = 225) *n (%)* At least one	AE after first dose (n = 269) *n (%)* At least one	AE after at least one dose (n = 322) *n (%)* At least one
DMT			
Dimethyl fumarate	50 (22.22)	67 (24.90)	81 (25.16)
Teriflunomide	40 (17.78)	55 (20.45)	63 (19.57)
Natalizumab	45 (20.0)	45 (16.73)	52 (16.15)
Ocrelizumab	20 (8.89)	27 (10.04)	28 (8.70)
Fingolimod	25 (11.10)	24 (8.92)	31 (9.63)
Glatiramer acetate	15 (6.67)	16 (5.95)	24 (7.45)
IM IFN β 1a	13 (5.78)	12 (4.46)	15 (4.65)
SC IFN β 1a (once/2 weeks)	9 (4.0)	13 (4.83)	16 (4.97)
SC IFN β 1a (3 times/ week)	4 (1.78)	3 (1.12)	5 (1.55)
SC IFN β 1b	4 (1.78)	7 (2.60)	7 (2.17)

IM: intramuscular; IFN: interferon; SC: subcutaneous

After the second dose of vaccine, the logistic regression analysis showed a higher probability to develop symptoms in pwMS treated with IFN®-1b (OR = 16.3, 95% CI 1.35–197.77, p = .028), Teriflunomide (OR = 5.83, 95% CI 1.38–24.62, p = .016), Natalizumab (OR = 5.52, 95% CI 1.29–23.68, p = .021), Dymethilfumarate (OR = 4.34, 95% CI 1.06–17.82, p = .041). The same analysis investigating a possible association between pain surrounding the injection site and the type of DMT did not show any significant result.

Finally, the same analyses were performed on pwMS that developed ≥1 AP-AE after *at least one* dose of vaccine, with the following results: the mean age of pwMS with ≥1 AP-AE was not statistically different as compared to pwMS without AP-AE (45.8 years vs 46.5 years, p = .61).

The logistic regression analysis after *at least one* dose of vaccine showed a significantly higher probability to develop symptoms in pwMS treated with Teriflunomide (OR = 4.5, 95% CI 1.15–17.68, p = .031) and Natalizumab (OR = 4.3, 95% CI 1.08–17.39, p = .039), and a trend towards significance for Dymethilfumarate (OR = 3.68, 95% CI 0.98-13.87, p = .05). Instead, pwMS on Fingolimod and on Ocrelizumab did not show a higher risk of developing AP-AE.

3.2. Controls

Mean age was 43.9 (SD 12.9) years. One hundred and three (21.4%) controls complained of ≥1 AP-AE after the first dose, whereas 209 (43.5%) presented with ≥1 AP-AE after the second dose (p < .0001). The frequency of AP-AE after the first and the second dose of vaccines are summarized in Table 2.

The most common AP-AE after the first dose was pain surrounding the injection site (9.6% controls), fever after the second dose (17.9%) as well as after both doses (18.1%), followed by tiredness (6.4% after the first dose, 15% after the second dose).

The mean age of controls presenting with ≥1 AP-AE after the first dose was not significantly different from the mean age of controls without any SE (43.7 years vs 43.8 years, p = .90), whereas there was a statistically significant difference after the second dose (42 years vs 45.2 years, p = .008), and also after at least one dose (42 years vs 45.6 years, p = .002).

The likelihood to present with ≥1 AP-AE was lower for men as compared to women after correcting for age (53.6% lower in men after the first dose of vaccine, 53.5% after the second one, 63.9% after at least one dose; all $p \leq .005$).

3.3. PwMS versus controls

The likelihood to present with ≥1 AP-AE, after correcting for age and sex, was significantly higher in pwMS than controls (4 times higher after the first dose of vaccine, OR = 4, 95% CI 2.99 – 5.36; twice higher after the second dose, OR = 2.16, 95% CI 1.65 – 2.83; about three times higher after at least one dose, OR = 2.9, 95% CI 2.18 – 3.88, all p < .001).

The *a posteriori* power analysis showed that the analyzed sample size is sufficient to detect a difference in the proportion of AE of at least 15% with a power of 99%.

4. Discussion

In the current study we analyzed data regarding acute-phase adverse events of the first two doses of mRNA BNT162b2 vaccine for SARS-CoV-2 (Pfizer BioNTech) in a cohort of 438 pwMS and 481 control cases. BNT162b2 is a nucleoside-modified mRNA vaccine encoding the SARS-CoV-2 spike glycoprotein, that does not contain live virus, does not integrate with the human genome, and cannot cause SARS-CoV-2 infection (Polack et al., 2020; Pardi et al., 2018). The associated adverse effects are generally minor (injection-site pain and short-lived febrile symptom), while severe adverse events are rare (Polack et al., 2020). Nevertheless, because immunocompromised patients and those on immunomodulators were excluded from the original randomized controlled trials, there is the need for continuous clinical surveillance in these subpopulations of patients.

In the current study, the likelihood to present at least one AP-AE was significantly higher in pwMS than controls, and increased significantly with the second dose of vaccine in both groups. This is the first study directly comparing pwMS with age- and sex-matched HC, but the frequency of AP-AE in pwMS is similar to the one reported in previous studies and to the original RCT (Polack et al., 2020; Briggs et al., 2022; Lotan et al., 2021; Wieske et al., 2022). The reason for a reduced incidence of AP-AEs in our cohort of controls might reside in ethnic, demographic or social differences from the general population of the original RCT.

The increased incidence of AP-AE might be interpreted considering the timing of vaccine-induced immune system response. In particular, the first dose elicits the innate immune system and subsequently the adaptive immune system, whereas the second dose promotes a stronger and quicker response from the adaptive immune system. This latter is far more complex and effective in building up an immunological defense against the pathogen, and for the same reasons, more likely to induce side effects (Clem, 2011; Kang and Compans, 2009).

Confirming previous findings on MS and other dysimmune diseases, females of both groups presented a significantly higher risk of developing AP-AE after at least one dose of vaccine (Briggs et al., 2022; Wieske et al., 2022). This might be explained taking into account that females are more prone to mount a stronger immune response to infectious diseases, resulting in a faster clearance of pathogens, but also representing a risk factor for developing dysimmune diseases(Klein and Flanagan, 2016), as well as vaccines-related side effects (Klein and Flanagan, 2016; Klein et al., 2010; Cook, 2008; Giefing-Kroll et al., 2015).

Interestingly, the likelihood for at least one AP-AE to occur after the second vaccination dose or at least one vaccination dose is lower in pwMS taking B cell depletors and S1P inhibitors with respect to pwMS on other DMTs.

Previous studies have already highlighted how different DMTs could determine a different vaccine response and therefore its different effectiveness and risk of adverse reactions, because of their mechanism of action (Iannetta et al., 2021).

Sphingosine-1-phosphate (S1P) modulators such as fingolimod prevent egress of T and B cells from lymph nodes. Fingolimod has been shown to dampen the cellular and humoral immune responses against vaccines, including the case of pwMS receiving the inactivated influenza vaccine (Kappos et al., 2015; Metze et al., 2019; Olberg et al., 2018). In addition, pwMS on fingolimod that got infected with SARS-CoV2 were reported to have attenuated anti-SARS-CoV-2 antibodies (Bollo et al.,

2020). Based on this evidence and the fact that S1P modulators segregate lymphocytes in secondary lymphoid tissues, it is plausible to hypothesize that pwMS taking S1P modulators produce an attenuated immune response to vaccines, and therefore, are less exposed to AP-AE.

Ocrelizumab is a humanized anti-CD20 monoclonal antibody that causes selective B-cell depletion (Cross and Naismith, 2014). By its effect on B and CD20+ T cells, ocrelizumab can dampen both cellular and humoral response to vaccines. Several studies have shown a reduced immunogenicity of SARS-CoV-2 infection in pwMS on Ocrelizumab, in particular with respect to their humoral response (Wallach et al., 2022; Allman et al., 2022; Zabalza et al., 2022). For the same reason, these patients might be at a lower risk of developing AP-AE. Moreover, these findings indirectly support the relationship between the role of the adaptive immune system response elicited by the vaccine and the occurrence of AP-AE. Indeed, we did not find an association between the likelihood of AP-AE and the type of DMT after the first dose of vaccine, which is known to elicit the innate immune system, but only after the second one, mediated by the same adaptive immune system that is altered by antiCD-20 therapies and S1P modulators.

Our study has some strengths, such as the presence of an age- and sex-matched control group, and the possibility to analyze the effect of different DMT on the occurrence of AP-AE in a large sample of pwMS. Some limitations need also to be considered: first of all, only pwMS that were administered BNT162b2 vaccine were included in the study, preventing us from drawing any conclusion on the reactogenicity of different vaccines. Due to the decision of the Italian Health authorities, pwMS were eligible only to treatment with mRNA-based vaccines, and BNT162b was the first choice of treatment. Second, we do not have data on previous infection with SARS-CoV-2 in pwMS treated with vaccines, making it impossible to compare vaccine reactogenicity related to a previous contact with the virus itself. Third, the questionnaires administered to pwMS did not include questions refereeing to worsening of neurological symptoms or occurrence of MS relapses. However, the aim of the current study was to characterize quantitatively and qualitatively the occurrence of AP-AE in pwMS and not aspects related to a transient worsening of MS itself.

In conclusion, the current study presents qualitative and quantitative results on AP-AE associated with the first and second doses of SARS-CoV-2 vaccine in a large Italian sample of pwMS. The only risk factor identified for developing AP-AE is female sex, whereas specific types of DMT, such as angtiCD-20 monoclonal antibodies and S1P inhibitors, are associated with a lower risk of AP-AE occurrence.

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Declaration of Competing Interest

ET, GDP, FS RDC, LG, EG, MATC, AF, CM declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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