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Risk of disease relapse following COVID-19 vaccination in patients with AQP4-IgG-positive NMOSD and MOGAD

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ABSTRACT

Post-vaccination disease relapses have been reported in patients with MOGAD and AQP4-IgG+NMOSD. In this retrospective multicenter Italian study we assessed the frequency of relapses after SARS-CoV-2 vaccination. We included 56 cases: MOGAD, 30; AQP4-IgG+NMOSD, 26. Vaccines received were BNT162b2-Pfizer-BioNTech in 42 patients and mRNA-1273-Moderna in 14 patients. Six patients had a history of SARS-CoV-2 infection; two of them experienced a post-infection disease relapse (MOGAD). The frequency of relapses within one month of SARS-CoV-2 vaccination was 4% (1/26) in the AQP4-IgG+NMOSD group and 0% in the MOGAD group. In these patients the potential benefits of vaccination overcome the risk of relapses.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the related pandemic have posed relevant challenges in the management of patients with demyelinating CNS disorders. In particular, the urgent need for mass vaccination has raised the question whether SARS-CoV-2 vaccines may increase the risk of disease relapse in these patients. While several studies have assessed the safety of SARS-CoV-2 vaccines in patients with multiple sclerosis, (Di Flippo et al., 2021) there are limited data available on patients with aquaporin-4-IgG neuromyelitis optica spectrum disorder -AQP4-IgG+NMOSD- or myelin oligodendrocyte glycoprotein associated disease -MOGAD- (Lotan et al., 2021). This topic is of relevance since a post-vaccination onset or worsening has been reported in both conditions. (Mealy et al., 2018; Kumar et al., 2020)

In this multicentric study we assessed the frequency of disease relapses following SARS-CoV-2 vaccination in patients with AQP4-IgG+NMOSD and MOGAD.

2. Materials and methods

From five Neurology Units in Italy, we retrospectively identified patients with: 1) a diagnosis of AQP4-IgG+NMOSD or MOGAD; and 2) ≥1 month follow-up after receiving at least one dose of one of the approved SARS-CoV-2 vaccines. Demographics, clinical information, and information related to SARS-CoV-2 vaccination and/or preceding infection were collected in a dedicated form at different sites. Relapses were defined as new or worsening neurological symptoms that lasted for ≥24 h, separated by at least one month interval and confirmed with paraclinical investigations (i.e. new or enhancing lesions on MRI scans or abnormalities at visual evoked potentials).

Continuous and categorical variables were reported as median (range) and number (%), and compared by using the Chi square, Fisher's, and Wilcoxon rank sum tests, as appropriate. P-values <0.05 were considered statistically significant (IBM SPSS 26).

3. Results

A total of 56 patients were included from 5 centers: MOGAD, 30; AQP4-IgG+NMOSD, 26 (Supplementary Table 1). Clinical and demographic features, and data related to SARS-CoV-2 infection/vaccination are summarized in Table 1. At the time of SARS-CoV-2 vaccination, patients with AQP4-IgG+NMOSD were more frequently female and older, and had longer disease duration, longer time from last disease attack, and greater disability when compared to MOGAD patients.

3.1. Vaccine-related adverse events and relapse frequency

The SARS-CoV-2 vaccines received were BNT162b2-Pfizer-BioNTech in 42 patients and mRNA-1273-Moderna in 14 patients. Overall, minor side effects were reported by 36 (64.3%) patients after the first dose and by 38 (71.7%) patients after the second dose, with pain at injection site being the most common.

The frequency of relapses within one month of SARS-CoV-2 vaccination was 4% (1/26) in the AQP4-IgG+NMOSD group and 0% in the MOGAD group. The AQP4-IgG-positive patient was a 38-year-old woman under treatment with rituximab who experienced an optic neuritis 10 days after the second dose of BNT162b2-Pfizer-BioNTech vaccination; symptoms resolved completely after intravenous steroids.

Two patients experienced relapses >1 month from vaccination: 1) an untreated 61-year-old woman developed an AQP4-IgG-related myelitis 97 days after her second dose of BNT162b2-Pfizer-BioNTech vaccination; and 2) an untreated 61-year-old man with MOG-IgG positivity who

Abbreviations: AQP4, aquaporin-4-IgG; MOGAD, myelin oligodendrocyte glycoprotein associated disease; NMOSD, neuromyelitis optica spectrum disorder; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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Table 1
Demographic and clinical data of included patients.

	All patients($n = 56$)	AQP4-IgG+NMOSD ($n = 26$)	MOGAD($n = 30$)
Age at first dose, years	47 (23–84) *	55 (30–84)	43 (23–74)
Female sex	44 (79%) *	25 (96%)	19 (63%)
Disease duration at first dose, years	3.5 (0–25) *	6 (0–25)	2 (0–17)
EDSS at first dose	2 (0–8) *	4 (0–8)	1.5 (0–7.5)
Time from last attack (months)	20.5 (1–149) *	38 (4–149)	19 (1–117)
History of attacks after vaccination	3 (5%)	1 (4%)	2 (7%)
History of attacks after infection	5 (9%)	1 (4%)	4 (13%)
Number of attacks at first vaccine dose	2 (1–10)	2 (1–10)	1 (1–9)
Ongoing disease modifying treatment at vaccination	No treatment 8 (14.3%) Azathioprine 15 (26.8%) MMF 1 (1.8%) Rituximab 23 (41.4%) Tocilizumab 2 (3.6%) Eculizumab 1 (1.8%) Prednisone 3 (5.4%) Prednisone+IvIg 1 (1.8%) Prednisone+MTX 1 (1.8%) Weekly PLEX 1 (1.8%)	No treatment 3 (11.5%) Azathioprine 4 (15.4%) MMF 1 (3.8%) Rituximab 14 (53.8%) Tocilizumab 2 (7.7%) Eculizumab 1 (3.8%) Weekly PLEX 1 (3.8%)	No treatment 5 (16.7%) Azathioprine 11 (36.7%) Rituximab 9 (30%) Prednisone 3 (10%) Prednisone+IvIg 1 (3.3%) Prednisone+MTX 1 (3.3%)
Previous history of SARS-CoV-2 infection	6 (11%)	1 (4%)	5 (17%)
SARS-CoV-2 infection outcome	Asymptomatic 1 (16.7%) Mild symptoms 5 (83.3%)	Mild symptoms 1 (100%)	Asymptomatic 1 (20%) Mild symptoms 4 (80%)
Attacks after SARS-CoV-2 infection	2	0	2
Time from SARS-CoV-2 infection to attack, days	37 (12–62)	n.a.	37 (12–62)
Clinical features of post-infection relapses	Optic neuritis 1 Optic neuritis + PN 1	n.a.	Optic neuritis 1 Optic neuritis + PN 1
Type of vaccine received	BNT162b2-Pfizer-BioNTech 42 (75%) mRNA-1273-Moderna 14 (25%)	BNT162b2-Pfizer-BioNTech 19 (73%) mRNA-1273-Moderna 7 (27%)	BNT162b2-Pfizer-BioNTech 23 (77%) mRNA-1273-Moderna 7 (23%)
Number of doses received	2 (1–2)	2 (1–2)	2 (1–2)
Side effects after the first dose	No side effects 20 (36%) Local pain 23 (41%) Fever 1 (2%) Fatigue 3 (5%) Nausea 1 (2%) Two or more 8 (14%)	No side effects 12 (46%) Local pain 8 (31%) Fatigue 1 (4%) Nausea 1 (4%) Two or more 4 (15%)	No side effects 8 (27%) Local pain 15 (50%) Fever 1 (3%) Fatigue 2 (7%) Two or more 4 (13%)
Side effects after the second dose	No side effects 15 (28%) Local pain 22 (42%) Fever 6 (11%) Two or more 10 (19%)	No side effects 9 (36%) Local pain 9 (36%) Fever 2 (8%) Two or more 5 (20%)	No side effects 6 (21%) Local pain 13 (46%) Fever 4 (14%) Two or more 5 (18%)
Post-vaccination attacks	3	2	1
Clinical features of post-vaccination relapses	Myelitis 2 Myelitis and cerebellar ataxia 1	Myelitis 2	Myelitis and cerebellar ataxia 1
Time from last dose to attack, days	85 (10–97)	10, 97	85
Follow-up after last dose, months	5 (1–8)	5 (2–8)	5 (1–7)

Data expressed as number (%) or median (range), as appropriate.
EDSS: Expanded Disability Status Scale; MMF: Mofetil Mycophenolate, IvIg: intravenous immunoglobulins; MTX: Methotrexate; PLEX: plasma exchange; PN: peripheral neuropathy * $p<0.05$; ** $p<0.001$.

developed spinal cord dysfunction and cerebellar ataxia 85 days after the second dose of mRNA-1273-Moderna vaccination. None of these patients had an antecedent history of relapses triggered by infections or vaccinations.

Details on the 3 patients who experienced relapses after SARS-CoV-2 vaccination are reported in Table 2.

3.2. Prior SARS-CoV-2 infection

Six patients had a history of SARS-CoV-2 infection (5 before and 1 after vaccination). Of these, one patient was asymptomatic, while 5 cases were mild symptomatic not requiring admission to hospital. Two patients experienced relapses after SARS-CoV-2 infection but before receiving the vaccine. In particular, a 76-year-old woman and a 40-year-old man, both affected by MOGAD, developed optic neuritis 62 and 12 days after the infection, respectively. The first case showed complete symptoms resolution after intravenous steroids, while the second improved after steroids and intravenous immunoglobulins. The second patient had a previous history of post-vaccination and post-infection relapses. Both patients did not relapse after SARS-CoV-2 vaccination.

4. Discussion

We found that SARS-CoV-2 vaccines are safe in patients with MOGAD and AQP4-IgG+NMOSD. The risk of vaccine-related disease relapses is low, even in patients with prior history of relapses following infections (including SARS-CoV-2 infection) or vaccinations.

An increased risk of post-vaccination relapses has been reported for AQP4-IgG+NMOSD, particularly in untreated patients (Mealy et al., 2018) and several studies have reported MOGAD attacks following vaccinations (Kumar et al., 2020). In a large web-based study on SARS-CoV-2 vaccination in patients with neuroimmunological disorders, including MOGAD and AQP4-IgG+NMOSD, no post-vaccination relapses were detected, although 17.8% of patients reported new or worsening of previous symptoms requiring in some cases specific treatment (Lotan et al., 2021). Of note, distinction of relapses vs pseudo-relapses is mandatory and often challenging, since infection or vaccination side effects (as fever) can *per se* cause transient worsening of

Table 2
Clinical features of patients who experienced relapses after SARS-CoV-2 vaccination.

Antibody specificity	Age/ Sex	Number of previous relapses/ disease duration (years)/time from last attack (months)	Treatment at SARS-CoV-2 vaccination	Vaccine received	Time from last dose/infection (days)	Clinical features	Treatment	Outcome
AQP4	38/F	1/0/11	RTX	Pfizer	10	ON	Steroids	Complete recovery
AQP4	61/F	1/1/12	None	Pfizer	97	Myelitis	Steroids	No improvement
MOG	61/M	1/2/26	None	Moderna	85	Myelitis and cerebellar ataxia	Steroids	Improved

RTX: Rituximab; ON: optic neuritis; PN: peripheral neuropathy; IvIg: intravenous immunoglobulins.

symptoms. In this context, MRI scans should be performed to exclude the presence of new or gadolinium enhancing lesions.

Similarly, no attacks were reported among 9 NMOSD patients that received the Beijing/Sinopharm-BBIBP-CorV ($n = 8$) or BNT162b2-Pfizer-BioNTech vaccines ($n = 1$) (Jovicevic et al., 2021). These data are in line with our findings, although we observed a higher frequency of minor side effects, particularly pain at vaccine injection site (Lotan et al., 2021;Jovicevic et al., 2021).

Post-vaccination relapses in our study were rare and occurred at variable intervals following the SARS-CoV-2 vaccinations, with only one case relapsing within one month, making a causal association challenging. Our findings confirm the importance of vaccination in patients with AQP4-IgG+NMOSD and MOGAD to prevent hospitalization and death, given the higher mortality rate reported during SARS-CoV-2 infection (Newsome et al., 2021). Moreover, we observed an overall higher relapse rate during the first month in patients who developed SARS-CoV-2 infection before receiving the vaccine (20%; 1/5) compared to that observed after vaccination (2%; 1/56), although this difference was not statistically significant.

Our study is limited by the small sample size, the retrospective design, and exclusive exposure to mRNA-based vaccines (the incidence of relapses might be different following other types of vaccines) (Fragoso et al., 2021). In addition, patients did not perform brain or spinal cord imaging during the post-vaccination follow-up, but clinically silent lesions are rare in these conditions and MOGAD lesions frequently resolve over time limiting the utility of MRI for disease activity monitoring (Fadda et al., 2021; Sechi et al., 2021).

5. Conclusions

SARS-CoV-2 vaccination is safe in patients with MOGAD and AQP4-IgG+NMOSD. The benefits of the vaccination in these patients clearly outweigh the risk of potential vaccine-related disease reactivations.

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Availability of data and material

Data are available upon reasonable request.

Ethics approval

The study was approved by the local ethical committee (Prog.56COVIDCESC)

Consent to participate

Patients gave their informed consent to participate.

Consent for publication

Patients gave their informed consent for publication.

CRediT authorship contribution statement

Alessandro Dinoto: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Elia Sechi:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Resources. **Sergio Ferrari:** Investigation, Resources, Writing – review & editing. **Alberto Gajofatto:** Investigation, Resources, Writing – review & editing. **Riccardo Orlandi:** Investigation, Resources, Writing – review & editing. **Paolo Solla:** Investigation, Resources, Writing – review & editing. **Alessandra Maccabeo:** Investigation, Resources, Writing – review & editing. **Giorgia Teresa Maniscalco:** Investigation, Resources, Writing – review & editing. **Vincenzo Andreone:** Investigation, Resources, Writing – review & editing. **Arianna Sartori:** Investigation, Resources, Writing – review & editing. **Paolo Manganotti:** Investigation, Resources, Writing – review & editing. **Sarah Rasia:** Investigation, Resources, Writing – review & editing. **Ruggero Capra:** Investigation, Resources, Writing – review & editing. **Chiara Rosa Mancinelli:** Investigation, Resources, Writing – review & editing. **Sara Mariotto:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Resources.

Declaration of Competing Interest

A Dinoto has received funding for travel from Novartis, Genzyme, Biogen.

E Sechi declares no competing interests.

S Ferrari declares no competing interests.

A Gajofatto declares no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103424.

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