Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Correspondence

Safety profile of SARS-CoV-2 vaccination in patients with antibody-mediated CNS disorders

ABSTRACT

Objectives: In this retrospective multicenter study, we evaluated the safety of SARS-CoV-2 vaccination in patients harboring autoantibodies targeting neuronal surface and/or synaptic antigens.
Methods: From eight Italian Neurology Units, we included patients with: a) serum and/or CSF positivity for specific neuronal autoantibodies; b) a compatible neurological syndrome; and c) available follow-up ≥ 6 weeks after vaccination with any of the approved SARS-CoV-2 vaccines. Demographics, clinical data, and information regarding previous SARS-CoV-2 infection and vaccination were collected. Disease relapses were considered "post-infectious" or "post-vaccination" when occurring within 6 weeks from infection/vaccination.
Results: We included 66 patients; 7/66 (11%) had a previous history of SARS-CoV-2 infection and 1/7 (14%) had post-infection relapses. BNT162b2-Pfizer-BioNTec was administered in 55 cases (83.3%) and mRNA-1273-Moderna in 11 (16.7%). The median number of doses administered per patient was 2 (1–3) and >50% of patients did not experience side effects. Five patients (8%) had post-vaccination relapses (seizure 3/5); 4/5 improved after immunotherapy, while one did not receive immunotherapy and worsened. Patients with post-vaccination relapses had higher disability scores at vaccination ($p = 0.025$), a trend favoring Leucine-rich glioma-inactivated protein 1 LGI1 glutamic acid decarboxylase 65 (GAD65) antibodies ($p = 0.054$) and shorter time from last relapse ($p = 0.057$).
Discussion: Our data support the safety of SARS-CoV-2 vaccines in patients with neurological disorders associated with antibodies to neuronal and synaptic antigens.

The safety of SARS-CoV-2 vaccines has already been proven in some inflammatory and autoimmune CNS conditions including multiple sclerosis (Di Filippo et al., 2021), aquaporin-4-IgG seropositive neuromyelitis optica, and myelin oligodendrocyte glycoprotein-IgG associated disease (Dinoto et al., 2021).

Recently, single reports described immune-mediated encephalitis as a rare complication of SARS-CoV-2 vaccination (Kaulen et al., 2022; Zuhorn et al., 2021). In agreement, previous studies have shown that other vaccinations, particularly that of Japanese yellow fever, have been associated with antibody-mediated disorders, such as anti--N-Methyl-D-Aspartate receptor (NMDAR) encephalitis (Guedes et al., 2021).

However, no studies have specifically investigated the safety profile of SARS-CoV-2 vaccines in patients with neurological disorders associated with antibodies to neuronal and synaptic antigens.

Methods

We performed a multicenter retrospective study including patients from eight Neurology Units (Supplementary Table 1) with: a) serum and/or cerebrospinal fluid (CSF) positivity for autoantibodies directed against surface/synaptic neuronal antigens; b) a compatible clinical phenotype; and c) ≥ 6 weeks of follow-up after receiving at least one dose of any approved SARS-CoV-2 vaccines.

Demographic and clinical data were retrospectively collected. Detailed data related to vaccinations were obtained at each center through a review of clinical charts, phone interviews and neurological

evaluations and merged in an anonymized shared database. Disease relapses were defined as "post-infection" or "post-vaccination" by the treating physicians as worsening or new-onset of neurological symptoms attributable to the antibody-associated neurological disorder occurring within 6 weeks from SARS-CoV-2 infection/vaccination. Relapse severity was rated by the Clinical Assessment Scale for Autoimmune Encephalitis (CASE), and the modified Rankin Scale (mRS).

Continuous and categorical variables were reported as median (range) and number (%). Comparisons were made with Fisher's exact test, Mann Whitney U, as appropriate. P-values <0.05 were considered statistically significant (IBM SPSS 26).

Results

A total of 66 patients were included. Demographic and clinical data are summarized in Fig. 1 and Table 1.

Seven (10.6%) patients had a previous history of SARS-CoV-2 infection, and 4 of them (57.1%) experienced mild flu-like symptoms while the remaining 3 were asymptomatic. One patient with glutamic acid decarboxylase 65 (GAD65) antibodies worsened (with psychiatric disturbances, tremor and seizures) 31 days after the infection without improvement after treatment with benzodiazepines and levetiracetam.
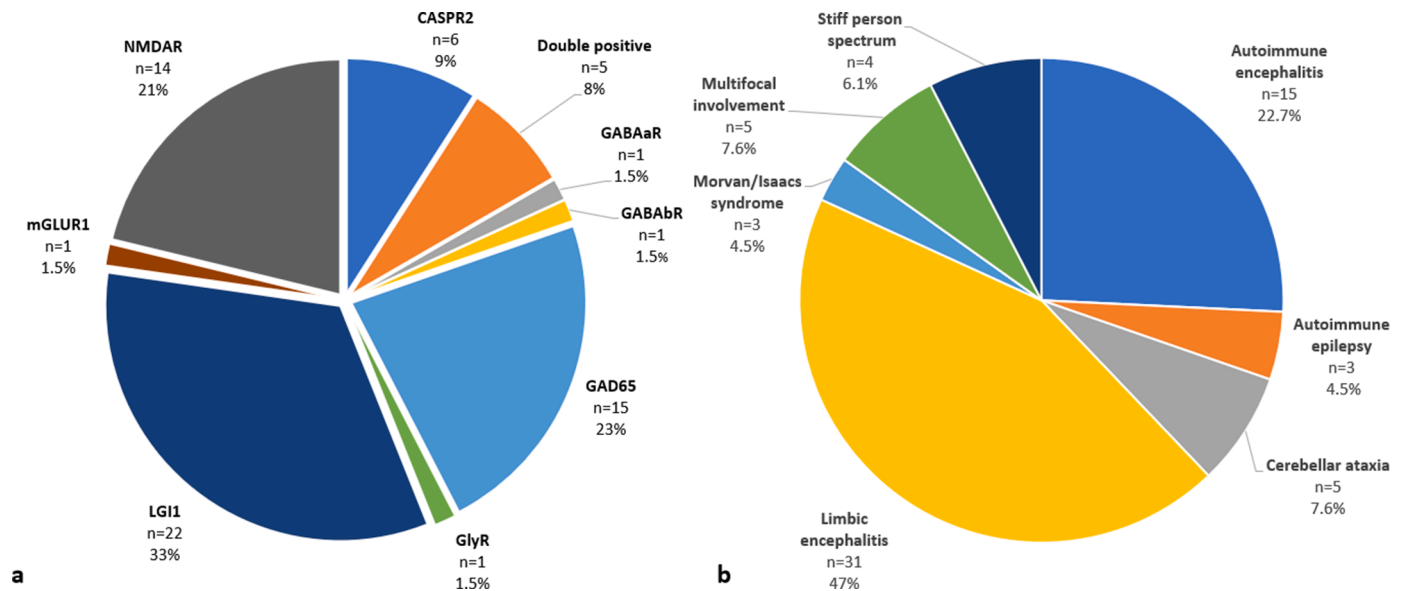
Regarding vaccination, the median number of doses administered was 2 (1–3); 55 (83.3%) patients received BNT162b2-Pfizer-BioNTech, whilst 11 (16.7%) mRNA-1273-Moderna. Around half of the patients did not experience side effects (53% and 63.8% after the first and second dose, respectively). Among the side effects, pain at injection site was the

Fig. 1. (a) antibody positivity and (b) clinical phenotype of included patients. Double positive patients harbored the following antibodies: CASPR2+LGI1 $n = 2$; GABAbR+GAD65 $n = 1$; GAD65+AChR $n = 1$; IgLON5+GAD65 $n = 1$. Those with multifocal involvement had: autoimmune encephalitis and myasthenia gravis $n = 1$; stiff person syndrome and cerebellar ataxia $n = 1$; overlapping features between IgLON5 and GAD65 (double positive patient) $n = 1$; limbic encephalitis and chorea $n = 1$; cerebellar ataxia and progressive encephalomyelitis with rigidity and myoclonus $n = 1$. NMDAR: N-Methyl-D-Aspartate receptor, CASPR2: contactin-associated protein-like 2, GABAaR: gamma-aminobutyric acid A receptor, GABAbR: gamma-aminobutyric acid B receptor, GAD65: glutamic acid decarboxylase 65, GlyR: glycine receptor, LGI1: leucine-rich glioma-inactivated protein 1, mGLUR: metabotropic glutamate receptor 1, AChR: acetylcholine receptor, IgLON5: immunoglobulin-like cell adhesion molecule 5.

most frequently reported (24.2% and 15.5% after the first and second dose, respectively).

Five patients (5/66, 7.6%) experienced post-vaccination relapses a median of 7 days after vaccination (range, 2–45), and 2/5 were receiving chronic immunotherapy at the time of vaccination (all oral steroids). Clinical features of relapses included seizures ($n = 2$), worsening of ataxia ($n = 1$), seizure + altered mental status ($n = 1$), and abnormal behavior + movement disorders ($n = 1$). All patients who experienced seizures (3/3) were already affected by epilepsy as part of their autoimmune disorder. At last follow-up, outcome was as follow: complete recovery ($n = 1$), partial improvement ($n = 3$), worsening ($n = 1$). Four patients received intravenous steroids while one subject was not treated and worsened. The GAD65 positive patient who had a flare after SARS-CoV-2 infection also experienced a relapse after vaccination. Individual data of relapsing patients are reported in Supplementary Table 2.

When comparing patients with and without post-vaccination relapses, relapsing cases had higher CASE scores at vaccination ($p = 0.021$) and a trend favoring Leucine-rich glioma-inactivated protein 1 LGI1 GAD65 antibodies positivity ($p = 0.054$) and a shorter time from last relapse ($p = 0.057$), Supplementary Table 3.

Discussion

Our multicenter retrospective study shows that SARS-CoV-2 vaccination is safe in patients with neurological disorders associated with antibodies to neuronal and synaptic antigens since 1. vaccine-related side effects occur in about half of patients but are typically mild and showed a rate comparable with other autoimmune neurological conditions (Dinoto et al., 2021; I Lotan et al., 2021); 2. post-vaccination relapses rarely occur in these conditions (7.6%); 3. post-vaccination relapses generally show a favorable outcome to immunotherapy.

Of note, additional factors have to be considered as possible contributors to the few relapses herein observed after vaccination. In this context, seizures were a common manifestation in post-vaccination relapses and always occurred in patients with a known history of epilepsy.

Since an increase in seizure frequency after vaccination has also been reported in a minority of patients with non-autoimmune epilepsy, the possibility that systemic/structural rather than autoimmune factors might be the leading cause of this post-vaccine symptom should be considered (Steriade et al., 2020; Lu et al., 2022). The association between pre-vaccination disease severity, which represents a risk factor for remote symptomatic seizures, and the occurrence of post-vaccination worsening further reinforces this hypothesis. Similarly, the worsening of ataxia and movement disorder associated with psychiatric disturbances after vaccination may be related to the progressive course of the underlying condition (in one patient with ataxia with metabotropic glutamate receptor 1 (mGLUR1) antibodies, and in one patient with ataxia and progressive encephalomyelitis with rigidity and myoclonus with GAD65 antibodies, respectively).

In accordance, the incidence of relapses did not increase after vaccination in other neurological autoimmune disorders, even though transient worsening of neurological symptoms may occur without evidence of disease activity (I Lotan et al., 2021; I Lotan et al., 2021).

Although most of our patients showed a favorable response after treatment with immunotherapy, which might suggest an autoimmune nature of the event, the lack of further confirmatory investigations (such as brain magnetic resonance imaging scans or CSF analysis) prevent a definitive discrimination between the occurrence of a transient worsening and a definite immune-mediated relapse.

Our study is limited by the small sample size, the retrospective design, the predominant administration of mRNA-based vaccination, and the lack of evaluation of CNS antibody titers before and after vaccination.

Despite these limits, our data supports the safety of SARS-CoV-2 vaccination in patients with antibody-mediated disorders and may help clinicians to properly inform patients with these rare conditions about the overwhelming benefits of vaccination.

Author contributors

clinical data collection (AD, MG, RI, SoM, VD, AF, MZ, ES, FP, GTM,

Table 1

Demographic, clinical, SARS-CoV-2 infection and vaccination data of included patients (n=66).

Age at vaccination (years)	62 (17-85)
Sex	Male 30 (45.5%)
	Female 36 (55.5%)
Clinical features	Cognitive disturbances 41 (62.1%)
	Altered consciousness 23 (34.8%)
	Psychiatric disturbances 43 (65.2%)
	Focal CNS symptoms 6 (9.1%)
	PNS involvement 13 (19.7%)
	Movement disorders 19 (28.8%)
	Dysautonomia 22 (33.3%)
	Seizures 47 (71.2%)
Disease course	Monophasic 36 (54.5%)
	Relapsing 18 (27.3%)
	Progressive 12 (18.2%)
Paraneoplastic disease	9 (13.6%)
Underlying malignancy	Ovarian teratoma 7 (77.8%)
	Thymoma 2 (22.2%)
Other immunological triggers	Post-vaccination 0
	Post-infectious 3 (4.5%)
Number of flares	1 (1-10)
Disease duration at first vaccine dose (months)	63.3 (2-298)
Time from last relapse at first vaccine dose (months)	38.5 (0-298)
Ongoing immunotherapy at vaccination	None 34 (51.5%)
	Oral steroids 12 (17.9%)
	Intravenous immunoglobulins 3 (4.5%)
	Azathioprine 6 (9.1%)
	Mycophenolate Mofetil 3 (4.5%)
	Rituximab 5 (7.6%)
	Tocilizumab 1 (1.5%)
	Rituximab+oral steroids 1 (1.5%)
	Azathioprine+oral steroids 1 (1.5%)
CASE at vaccination	2 (0-10)
mRS at vaccination	1 (0-4)
Previous history of SARS-CoV-2 infection	7 (10.6%)
SARS-CoV-2 infection severity	Asymptomatic 3 (42.9%)
	Mild symptoms without hospital admission 4 (57.1%)
Flares after SARS-CoV-2 infection	1/7 (14.3%)
Clinical features of post-infectious flares	Worsening of psychiatric disturbances, tremor, and seizure (GAD65)
Time from SARS-CoV-2 infection to flares, days	31
Outcome of SARS-CoV-2-related flares	No improvement 1 (100%)
SARS-CoV-2 vaccine	BNT162b2-Pfizer-BioNTech 55 (83.3%)
	mRNA-1273-Moderna 11 (16.7%)
Number of doses	2 (1-3)*
Side effects at first dose	No side effects 35 (53%)
	Pain at injection site 16 (24.2%)
	Fatigue 3 (4.5%)
	Fever 1 (1.5%)
	Flu-like symptoms 4 (6.1%)
	Headache 1 (1.5%)
	Herpes reactivation 1 (1.5%)
	More than one side effects 2 (3%)
	Relapse 3 (4.5%)
Side effects at second dose	No side effects 37 (63.8%)
	Pain at injection site 9 (15.5%)
	Fatigue 1 (1.7%)
	Fever 3 (5.2%)
	Flu-like symptoms 4 (6.9%)
	More than one side effects 1 (1.5%)
	Relapse 2 (3.4%)
Relapses after SARS-CoV-2 vaccination	5 (7.6%)
Clinical features of post-vaccination relapses	Worsening of ataxia: 1 (mGLUR1)
	Seizures: 2 (both LGI1)
	Seizure + altered mental status: 1 (GAD65)
	Abnormal behavior + movement disorders: 1 (GAD65)
Time from vaccination to relapse, days	7 (2-45)

Table 1 (*continued*)

Outcome of vaccination-related relapses	Worsening 1 (20%)
	Improved 3 (60%)
	Complete recovery 1 (20%)
Follow-up duration (from last vaccine dose), months	7 (1.5-11)

Data are expressed as median (range) and number (percentage), as appropriate. CASE: Clinical Assessment Scale for Autoimmune Encephalitis, mRS: modified Rankin Scale, mGLUR1: metabotropic glutamate receptor 1, GAD65: glutamic acid decarboxylase 65, LGI1: leucine-rich glioma-inactivated protein 1.

* 12 patients received a booster dose of vaccination (data not shown).

RB, LZ, SF, SaM), data generation and interpretation (AD, SaM), drafting the manuscript (AD, SaM, SF), results interpretation (AD, SaM, SF), revising the manuscript for intellectual content (AD, MG, RI, SoM, VD, AF, MZ, ES, FP, GTM, RB, LZ, SF, SaM).

Data availability

Data are available from the corresponding author on reasonable request.

Ethics approval

Approval was obtained from the ethics committee of University Verona (56COVIDCESC).

Consent to participate

Informed consent was acquired.

Declaration of Competing Interest

The authors report no competing interests in relation to this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103827.

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Alessandro Dinoto[a], Matteo Gastaldi[b], Raffaele Iorio[c,d], Sofia Marini[d], Valentina Damato[e], Antonio Farina[e], Marco Zoccarato[f], Elia Sechi[g], Francesca Pinna[h], Giorgia Teresa Maniscalco[i], Ruggero Barnabei[j], Luigi Zuliani[k], Sergio Ferrari[a,#], Sara Mariotto[a,#,*]

[a] *Neurology Unit, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy*

[b] *Neuroimmunology Laboratory, IRCCS Mondino Foundation, Pavia, Italy*

[c] *UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*

[d] *Università Cattolica del Sacro Cuore, Rome, Italy*

[e] *Department of Neurosciences, Drug and Child Health, University of Florence, Florence, Italy*

[f] *UOC Neurologia O.S.A. - Azienda Ospedale Università Di Padova, Padua, Italy*

[g] *Azienda Ospedaliera Universitaria Sassari, Unit of Neurology, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy*

[h] *Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy*

[i] *Neurological Clinic and Stroke Unit, Multiple Sclerosis Center, "A. Cardarelli" Hospital, Naples, Italy*

[j] *Neurology Unit, University of Pavia, Italy*

[k] *Neurology Unit, AULSS8 Berica, Vicenza, Italy*

[*] Corresponding author.

E-mail address: sara.mariotto@gmail.com (S. Mariotto).

[#] These authors equally contributed to the study.