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SHORT COMMUNICATION

Safety and tolerability of SARS-Cov-2 vaccination in patients with myasthenia gravis: A multicenter experience

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Abstract

Background and purpose: During the COVID-19 pandemic, myasthenia gravis (MG) patients have been identified as subjects at high risk of developing severe COVID-19, and thus were offered vaccination with priority. The lack of direct data on the safety and tolerability of SARS-CoV-2 vaccines in MG have contributed to vaccine hesitancy. To address this issue, the safety and tolerability of SARS-CoV-2 vaccines were assessed in a large cohort of MG patients from two referral centers.

Methods: Patients with confirmed MG diagnosis, consecutively seen between October and December 2021 at two MG centers, were enrolled. Demographics, clinical characteristics, and information regarding SARS-CoV-2 infection/vaccination were extracted from medical reports and/or collected throughout telephonic or in-person interviews.

Results: Ninety-eight (94.2%) of 104 patients included were administered at least two vaccine doses 4 weeks before the interview or earlier, and among them, 63 of 98 (64.2%) have already received the "booster" dose. The most frequently used vaccines were BNT162b2-Pfizer-BioNTech and mRNA-1273-Moderna. Overall, only minor side effects were reported, most commonly local pain and fever. MG worsening after vaccination was observed in eight of 104 (7.7%) cases. The frequency of worsening among muscle-specific tyrosine kinase MG cases (3/9, 33.3%) was significantly higher compared to other serological subgroups. Spontaneous symptom regression was observed in six of eight cases. Twelve of 104 (11.5%) patients had SARS-CoV-2 infection, and none of the SARS-CoV-2-infected MG patients worsened after vaccination.

Conclusions: Our data support the safety and tolerability of mRNA COVID-19 vaccines, which should be strongly recommended in MG patients, who could be at higher risk of complications if exposed to SARS-CoV-2 infection.

KEYWORDS
myasthenia gravis, SARS-COV-2, vaccination

Antonio Farina and Silvia Falso share first authorship.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies (abs) targeting proteins at the motor end plate. Fatigable muscle weakness is its clinical hallmark and can involve ocular, limb, bulbar, and respiratory muscles, the latter resulting in respiratory failure [1]. Immunosuppression is the mainstay of MG therapy, and it is required in the majority of cases to achieve satisfactory symptom control [1]. As a drawback, patients are exposed to a significantly higher risk of infections, which are also well-known triggers of disease exacerbations [2]. For all these reasons, during the COVID-19 pandemic, MG patients have been identified as subjects at high risk of developing severe COVID-19, and thus were offered vaccination with priority. Nevertheless, in patients with autoimmune diseases, there may be concern that the vaccination itself can stimulate the immune system and trigger disease exacerbation [3]. There are no specific guidelines concerning vaccinations in patients with MG, but evidence shows that inactivated vaccines are safe in this population [4]. However, the lack of direct data on the safety and tolerability of SARS-CoV-2 vaccines in MG might contribute to vaccine hesitancy [5]. Therefore, we performed an observational study to investigate safety and risk of disease worsening of SARS-CoV-2 vaccines in a large cohort of consecutive MG patients from two referral centers.

METHODS

We enrolled 114 patients with confirmed MG diagnosis, consecutively seen between October and December 2021 at the Neurology unit of Careggi Hospital of Florence ($n = 62$) and Gemelli Polyclinic Foundation of Rome ($n = 52$). Ten cases were excluded because they had not received vaccination at the time of evaluation. Demographics, clinical characteristics, and information regarding SARS-CoV-2 infection and vaccination were extracted from medical reports and/or collected through telephonic or in-person interviews. MG worsening was defined as the reoccurrence of any symptoms and signs of extraocular, bulbar, respiratory, axial, or limb muscle weakness lasting at least 24 h within the 4 weeks after SARS-CoV-2 infection or vaccination. The severity of MG was evaluated at the time of recruitment according to the Myasthenia Gravis Foundation of America (MGFA) clinical grading [6], and the postintervention status (PIS) classification [7] was used to assess the clinical status at last follow-up after institution of the recorded treatment. Both were assessed by telephonic or in-person evaluation before and after vaccination. Acetylcholine receptor (AChR) and muscle-specific tyrosine kinase (MuSK) abs were tested at diagnosis by standard radioimmunoassay in all patients. Continuous and categorical variables were reported as mean (SD) and proportion (percentage), respectively. Chi-squared test was used to compare categorical variables. All patients provided consent for the use of medical data for research purposes. The study was approved by the ethics committees of both institutions involved.

RESULTS

Of the final 104 patients included, 49 (47.1%) were women, 62 (59.6%) had late onset MG (median age at disease onset = 57 years, range = 16–86 years), and 21 (20.1%) had ocular MG. The mean disease duration at the time of first vaccine dose was 16 years (SD = 26.6). The majority of patients were ab-positive (92/104, 88.5%), including 83 of 92 (90.2%) with AChR abs and nine of 92 (9.8%) with MuSK abs. Demographic and clinical information of the cohort are shown in Table S1.

SARS-CoV-2 side effects and risk of disease worsening

Ninety-eight of 104 (94.2%) patients were administered at least two vaccine doses 4 weeks before the interview or earlier, and among them, 63 of 98 (64.2%) have already received the "booster" dose (Table 1). In five cases, the vaccine type of the second dose was different from the first, and almost half of the patients (27/63, 42.8%) received a "booster" dose different from the first two doses. The most frequently used vaccines were BNT162b2-Pfizer-BioNTech and mRNA-1273-Moderna (see Table 1 for the frequency breakdown). Six patients, with a previous history of SARS-CoV-2 infection, received only one dose. Overall, only minor side effects were reported (Table 1), most commonly local pain (in 18.3%, 19.4%, and 20.6% of patients after the first, second, and third vaccine dose, respectively) and fever (in 4.8%, 11.2%, and 4.8% of patients after the first, second, and third dose, respectively).

Eighty-four of 104 (80.7%) patients were on immunotherapy at the time of the first dose, with oral corticosteroids being the most common treatment (69/104, 66.3%; Table 1). Steroid and/or immunosuppressant dosage was modified in only 11 of 104 (10.5%) patients during the 3 months prior to the first vaccine dose. The majority of patients (87/104, 83.6%) were in "minimal manifestations" (MM) or better (including MM, pharmacological remission, and complete stable remission) [6] when receiving the first dose. In six patients, the PIS changed at last follow-up compared to the "prevaccination" visit (4/6 patients in MM at time of vaccination reported mild–moderate MG symptoms, whereas in 2/6 PIS changed from MM to pharmacological remission). Only five of 104 (4.8%) patients were treatment-refractory at enrollment.

MG worsening after vaccination was observed in eight of 104 (7.7%) cases (after both the first and second dose, $n = 2$; after the first dose only, $n = 1$; after the second dose only, $n = 1$; after the third dose only, $n = 4$; Table 2). These events were usually mild and occurred mostly after BNT162b2-Pfizer-BioNTech vaccine (7/8 cases). The frequency of worsening among MuSK-MG cases (3/9, 33.3%) was significantly higher compared with AChR-MG (4/83, 4.8%) and seronegative cases (1/12, 8.3%, $p = 0.01$; Table 2). In this subgroup, all patients but one (93.2%) were on immunotherapy at the time of the first vaccine dose. Spontaneous symptom regression was observed in six

TABLE 1 Sars-Cov-2 vaccine safety profile

Characteristic	*n*(%)
Number of doses received	
3 doses	63 (60.6)
2 doses	35 (33.6)
1 dose	6 (5.8)
Type of vaccine received, first dose, *n* = 104	
BNT162b2-Pfizer-BioNTech	74 (71.2)
mRNA-1273-Moderna	29 (27.9)
ChAdOx1-S-AstraZeneca	1 (0.9)
Type of vaccine received, second dose, *n* = 98	
BNT162b2-Pfizer-BioNTech	68 (69.4)
mRNA-1273-Moderna	28 (28.6)
ChAdOx1-S-AstraZeneca	2 (2)
Type of vaccine received, third dose, *n* = 63	
BNT162b2-Pfizer-BioNTech	51 (85)
mRNA-1273-Moderna	12 (20)
Postintervention status at first dose	
Complete stable remission	5 (4.8)
Pharmacological remission	8 (7.7)
Minimal manifestations	74 (71.2)
Improved	13 (12.5)
Unchanged/worsened	4 (3.8)
Immunotherapy at first dose	
Corticosteroids	69 (66.3)
Azathioprine	21 (20.2)
Mycophenolate	15 (14.4)
Intravenous immunoglobulins	4 (3.8)
Rituximab	3 (2.9)
Cyclosporine A	2 (1.9)
Side effects in the 4 weeks after the first dose, *n* = 104	31 (29.8)
Local pain	19 (18.3)
Fever	5 (4.8)
Asthenia	4 (3.8)
Flulike syndrome	3 (2.9)
Headache	3 (2.9)
Rash	2 (1.9)
Two or more	3 (2.9)
Side effects in the 4 weeks after the second dose, *n* = 98	35 (35.7)
Local pain	19 (19.4)
Fever	11 (11.2)
Asthenia	6 (6.1)
Flulike syndrome	6 (6.1)
Headache	3 (3.1)
Rash	1 (1)
Other	4 (4.1)
Two or more	10 (28.6)
Side effects in the 4 weeks after the third dose, *n* = 63	19 (28.3)
Local pain	13 (20.6)
Asthenia	5 (7.9)
Fever	3 (4.8)
Flulike syndrome	1 (1.6)
Headache	1 (1.6)
Other	3 (4.8)
Two or more	5 (7.9)
MG worsening in the 4 weeks after vaccination	8 (7.6)
After first dose	1 (0.9)
After second dose	1 (0.9)
After first and second dose	2 (1.9)
After third dose	4 (3.9)
Mean follow-up after last dose, days	91.2 (SD = 79.0)
Postintervention status at last-follow-up	
Complete stable remission	5 (4.8)
Pharmacological remission	8 (7.7)
Minimal manifestations	71 (68.3)
Improved	15 (14.4)
Unchanged/worsened	5 (4.8)

Abbreviation: MG, myasthenia gravis.

of eight cases. One seronegative MG patient presented with diplopia, limb weakness, and bulbar deficit, which required steroid increase after the second dose of Moderna; one MuSK-MG case presented with bulbar symptoms, which improved only partially after increasing steroids, whereas administration of intravenous immunoglobulins and rituximab led to complete symptom resolution. Overall, the outcome was favorable in all MG worsening cases, with no differences in the MGFA-PIS before vaccination and at last follow-up (Table 2).

SARS-CoV-2 infection

Twelve of 104 (11.5%) patients had SARS-CoV-2 infection, 11 of 12 before and one of 12 after the vaccination. The median follow-up time after the infection was 10.5 months (range = 0.5–21 months). MG worsening during the infection was registered in only one patient (27-year-old male with thymoma-related MG, maximum MGFA = IIIB, treated with corticosteroids), who had mild respiratory distress (peripheral oxygen saturation = 90%) requiring low-flow oxygen without need for hospitalization. This patient received one BNT162b2-Pfizer-BioNTech vaccine 290 days after the infection, without any MG worsening. One other case was infected 130 days after two BNT162b2-Pfizer-BioNTech vaccine doses, again without any MG worsening. Of note, none of the SARS-CoV-2-infected MG patients worsened after vaccination.

TABLE 2 MG worsening after vaccination

Sex/age, years	Type of antibody	Max MGFA	Disease duration at first dose, years	Thymoma/ autoimmune comorbidity	Doses received, *n*	Dose number causing worsening (type)	Immune therapy at first vaccine dose
M, 60	AChR	V	15	No/vitiligo	2	First (Pfizer)	AZA
F, 59	Seronegative	IIIB	18	Yes/no	3	First (Moderna) and second (Moderna)	CS, CyA
F, 34	MuSK	IIB	2	No/no	2	First (Pfizer) and second (Pfizer)	CS
F, 73	AChR	IIIB	7	No/thyroiditis	2	Second (Pfizer)	CS, IVIG every 6 months
F, 83	AChR	I	6	No/no	3	Third (Pfizer)	None
F, 68	AChR	IVB	1	Yes/thyroiditis	3	Third (Pfizer)	CS, AZA
F, 32	MuSK	IIIB	2	No/no	3	Third (Pfizer)	CS, AZA
F, 63	MuSK	IIB	2	No/no	3	Third (Pfizer)	CS

Abbreviations: AChR, acetylcholine receptor; AZA, azathioprine; CS, corticosteroids; CyA, cyclosporine A; F, female; FU, follow-up; I, improved; IVIG, intravenous immunoglobulin; M, male; Max, maximum; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; PIS, postintervention status; RTX, rituximab; U, unimproved.

DISCUSSION

During the current COVID-19 pandemic, clinicians are facing the challenge of balancing risk/benefit in the management of MG patients, especially of the ones under immunosuppressants, with respiratory muscle weakness or with relevant comorbidities. Efficacy and safety of the COVID-19 vaccines were not specifically assessed in MG patients in clinical trials, but, despite a few reports of MG worsening after COVID-19 vaccination [8], the risk of severe complications from COVID-19 in MG patients is generally considered to outweigh that of possible side effects or disease worsening after the vaccine [9,10]. A previous study on the safety of COVID-19 vaccine in MG patients reported no MG worsening in 20 of 22 MG patients who received two doses of the vaccine [11]. Only two patients complained of mild neck weakness after the first dose, which resolved after an increase of pyridostigmine therapy. However, this study was limited by the small number of patients included from a single center, with mostly a mild form of MG (MGFA I-II at maximum disease severity). In our large and representative cohort of MG patients from two referral neurology units, we confirmed that mRNA COVID-19 vaccines are safe in MG patients, including those with previous SARS-CoV-2 infection. In particular, no severe side effects were reported, and the frequency of both local pain and fever, which were the most frequently described in our cohort, is in line with previous studies in healthy individuals [12]. Only eight of 104 (7.7%) patients presented a worsening in MG symptoms within 4 weeks after the vaccine, which, however, was mostly mild and resolved spontaneously in 75% of cases. Moreover, the "booster" dose did not seem to be linked to an increased frequency of side effects or MG worsening. Caution might be warranted in patients with MuSK-MG, who, based on our findings, were more prone to experience MG worsening after COVID-19 vaccination. MuSK-MG subtype harbors defects in both central and peripheral B-cell tolerance checkpoints, and the major role seems to be played by plasmablasts [13]. It can be speculated that trigger factors could stimulate circulating autoreactive B cells and make MuSK-MG patients more susceptible than AChR-MG patients [13]. However, given the small number of patients with MuSK abs included, this result has to be confirmed in further studies. In general, for patients with MG, a case-by-case assessment is recommended, considering age, therapy, and previous response to vaccination. Moreover, this study's results apply to mRNA-based COVID-19 vaccines, given the very limited number of patients who received viral vector-based SARS-CoV-2 vaccines. Our data support the safety and tolerability of COVID-19 vaccination, which should be strongly recommended in MG patients, particularly in those at higher risk of complications when exposed to SARS-CoV-2 infection [14]. Further studies are needed to confirm these findings and to assess the efficacy of SARS-CoV-2 vaccines in MG patients under immunosuppressive therapy.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

MG symptoms at worsening	Vaccine doses after MG worsening	MG symptoms at following doses	Outcome	PIS at first vaccine dose	PIS at last FU
Upper limbs weakness	1 (second, Pfizer)	None	Spontaneous regression after 2 months	MM	MM
Four limbs weakness, bulbar symptoms, diplopia	2 (second, Moderna; third, Pfizer)	Four limbs weakness, bulbar symptoms, diplopia after second dose; none after third dose	Spontaneous regression (first); regression after increasing steroids (second)	MM	MM
Bulbar symptoms	1 (second)	Bulbar symptoms, diplopia	Spontaneous regression (first); regression 1 month after increasing steroids, one IVIG and RTX cycle (second)	MM	MM
Four limbs fatigability	0	–	Spontaneous regression after 2 months	U	U
Diplopia	0	–	Regression 3 weeks after increasing Mestinon	MM	MM
Generalized weakness	0	–	Spontaneous regression after 4 days	MM	MM
Dysphagia, facial muscles weakness	0	–	Spontaneous regression after 7 days	I	I
Ptosis and dysarthria	0	–	Spontaneous regression	MM	MM

AUTHOR CONTRIBUTIONS

Antonio Farina: Conceptualization (equal), data curation (equal), formal analysis (equal), validation (equal), visualization (equal), writing–original draft (equal). **Silvia Falso:** Data curation (equal), formal analysis (equal), investigation (equal), validation (equal), visualization (equal), writing–original draft (equal). **Sara Cornacchini:** Data curation (supporting), formal analysis (supporting), investigation (supporting), validation (supporting). **Gregorio Spagni:** Data curation (supporting), methodology (supporting), validation (supporting), writing–review & editing (supporting). **Gabriele Monte:** Investigation (supporting), validation (supporting), visualization (supporting). **Alice Mariottini:** Methodology (supporting), project administration (supporting), supervision (supporting), writing–review & editing (supporting). **Luca Massacesi:** Funding acquisition (equal), resources (equal), software (equal), writing–review & editing (supporting). **Alessandro Barilaro:** Data curation (supporting), investigation (supporting), validation (supporting), writing–review & editing (supporting). **Amelia Evoli:** Funding acquisition (equal), resources (equal), software (equal), supervision (supporting), writing–review & editing (supporting). **Valentina Damato:** Conceptualization (lead), data curation (lead), investigation (lead), methodology (lead), project administration (lead), supervision (lead), validation (lead), visualization (lead), writing–original draft (lead), writing–review & editing (lead).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Evoli A, Spagni G, Monte G, Damato V. Heterogeneity in myasthenia gravis: considerations for disease management. *Expert Rev Clin Immu*. 2021;17:1-11. doi:10.1080/1744666x.2021.1936500
2. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. *J Neurol*. 2018;265(6):1251-1258. doi:10.1007/s00415-018-8751-9
3. Westra J, Rondaan C, vanAssen S, Bijl M. Vaccination of patients with autoimmune inflammatory rheumatic diseases. *Nat Rev Rheumatol*. 2015;11(3):135-145. doi:10.1038/nrrheum.2014.206
4. Strijbos E, Tannemaat MR, Alleman I, et al. A prospective, double-blind, randomized, placebo-controlled study on the efficacy and safety of influenza vaccination in myasthenia gravis. *Vaccine*. 2019;37(7):919-925. doi:10.1016/j.vaccine.2019.01.007
5. Zhou Q, Zhou R, Yang H, Yang H. To be or not to be vaccinated: that is a question in myasthenia gravis. *Front Immunol*. 2021;12:733418. doi:10.3389/fimmu.2021.733418
6. Jaretzki A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. *Neurology*. 2000;55(1):16-23. doi:10.1212/wnl.55.1.16
7. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87(4):419-425. doi:10.1212/wnl.0000000000002790
8. Singh S, Govindarajan R. COVID-19 and generalized myasthenia gravis exacerbation: a case report. *Clin Neurol Neurosur*. 2020;196:106045. doi:10.1016/j.clineuro.2020.106045

9. Group IMW, Jacob S, Muppidi S, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci*. 2020;412:116803. Doi: 10.1016/j.jns.2020.116803
10. Živković SA, Gruener G, Narayanaswami P. Committee the AQ and PS. Doctor—Should I get the COVID-19 vaccine? Infection and immunization in individuals with neuromuscular disorders. *Muscle Nerve*. 2021;63(3):294-303. doi:10.1002/mus.27179
11. Ruan Z, Tang Y, Li C, et al. COVID-19 vaccination in patients with myasthenia gravis: a single-center case series. *Nato Adv Sci Inst Se*. 2021;9(10):1112. doi:10.3390/vaccines9101112
12. Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis*. 2021;21(7):939-949. doi:10.1016/s1473-3099(21)00224-3
13. Stathopoulos P, Kumar A, Heiden JAV, Pascual-Goñi E, Nowak RJ, O'Connor KC. Mechanisms underlying B cell immune dysregulation and autoantibody production in MuSK myasthenia gravis. *Ann N Y Acad Sci*. 2018;1412(1):154-165. doi:10.1111/nyas.13535
14. Jakubíková M, Týblová M, Tesař A, et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival. *Eur J Neurol*. 2021;28(10):3418-3425.

SUPPORTING INFORMATION

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