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CLINICAL RESEARCH SHORT REPORT

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Safety of mRNA COVID-19 vaccines in patients with well-controlled myasthenia gravis

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Abstract

Introduction/Aims: Data on safety and tolerability of the vaccines against severe acute respiratory virus coronavirus-2 (SARS-CoV-2, or coronavirus disease-2019 [COVID-19]) in patients with myasthenia gravis (MG) are currently limited. In this study we investigated the safety of mRNA-based two-dose vaccination in a cohort of patients with MG.

Methods: This investigation was a prospective observational study of messenger RNA (mRNA)-based vaccines administered to patients with MG with stable disease. Local and systemic reactogenicity after injection was monitored for each dose administered. The patients were categorized and clinically assessed following the recommendations of the Myasthenia Gravis Foundation of America.

Results: Thirty-six males and 55 females (mean age at first vaccine dose, 58.8 years; standard deviation, = 17.1 years) received vaccines. Seventy-two patients (79.1%) were taking one or more immunosuppressant(s). The most frequent adverse effects were injection-site pain, fatigue, myalgia, chills, fever, and headache. Local and systemic reactions were transient; 58.2% of the patients developed one or more reaction(s). There were no anaphylactic reactions. None of the patients had a myasthenic crisis, and two developed a mild deterioration compared with their Quantitative Myasthenia Gravis baseline score. The clinical outcome scores showed no exacerbation of MG symptoms. Patients over 65 years of age developed fewer adverse effects. COVID-19 vaccination did not induce clinical exacerbation in stable patients with MG, regardless of their age, sex, history of myasthenic crisis, or whether they were taking immunosuppressants.

Discussion: Our data are consistent with the mRNA COVID-19 vaccine being well tolerated in patients with well-controlled MG. The findings may contribute to decisions in vaccination campaigns in the future.

KEYWORDS

adverse events, COVID-18, exacerbation, mRNA vaccine, myasthenia gravis, reactogenicity, safety

Abbreviations: AChR, acetylcholine receptor; AChR$^+$, anti-acetylcholine receptor antibody-positive; AE, adverse event; CSR, complete stable remission; E, exacerbation; I, improved; IST, immunosuppressant therapy; IVIg, intravenous immunoglobulin; MC, myasthenic crisis; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; MuSK$^+$, muscle-specific tyrosine kinase antibody-positive; mRNA, messenger RNA; PIS, post-intervention status; PR, pharmacological remission; QMG, Quantitative Myasthenia Gravis; SARS-CoV-2, severe acute respiratory virus coronavirus-2; SAE, serious adverse event; SD, standard deviation; U, unchanged.

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1 | INTRODUCTION

Little is known about the safety of vaccines against severe acute respiratory virus coronavirus-2 (SARS-CoV-2, or coronavirus disease-2019 [COVID-19]) in patients with myasthenia gravis (MG). These patients, and particularly those treated with immunosuppressive therapy (IST), are at high risk for COVID-19–related complications.[1–13]

Vaccination has been demonstrated to be effective in reducing infections and hospitalizations.

In our experience, many patients with MG are concerned about the safety and efficacy of vaccination both in general and for COVID, due to fear of nonmyasthenic side effects and the possible exacerbation of myasthenic symptomatology. Similar hesitancy has been reported among patients with other autoimmune disorders.[14,15] However, this reluctance is not based on evidence, as there have been no prospective, double-blind, randomized studies of the safety of vaccines in patients with MG, except for the influenza and tetanus vaccines.[16–19]

We investigated: (1) reactogenicity (a subset of reactions that occur soon after vaccination)[20] and (2) whether patients with MG have an exacerbation after messenger RNA (mRNA) COVID-19 vaccination.

2 | METHODS

2.1 | Clinical assessment of patients with MG

In this prospective, observational study we examined the safety of the two-dose mRNA-based COVID-19 vaccine (mRNA-1273 [Moderna] or BNT162b2 [Pfizer-BioNTech]) in a cohort of patients with MG monitored at our outpatient neuromuscular clinic. We recorded the dates of the first and second doses, local or systemic reactions, and exacerbation of patients' myasthenic symptoms and the duration compared with prevaccination baseline levels. The patients were followed from the day of vaccination through day 7 after each vaccine dose. Adverse events (AEs) that lasted less than 72 hours were considered transient. The study period was from January 15, 2021 through September 1, 2021.

Patients' inclusion criteria were: (1) male or female outpatients over 18 years of age, with documented diagnosis of MG; (2) on stable therapy for MG for at least 180 days before the first vaccination; and (3) requesting information about the mass anti-COVID vaccination program by our health authorities (HA). No exclusion criteria were applied (except a history of severe allergic reaction) following guidelines from our HA. We collected the following data: sex; age at first vaccination dose; age at onset of MG; duration of MG; Myasthenia Gravis Foundation of America (MGFA)[21] class at diagnosis; history of thymoma; previous myasthenic crisis (MC); Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Activities of Daily Living (MG-ADL) scores[21] at the time of vaccine; postintervention status (PIS)[21]; and patients' doses of pyridostigmine, corticosteroids, and other immunosuppressants.[21–23] Examinations were performed after the

TABLE 1 Demographic and clinical characteristics at first dose of vaccine

Sex (M/F)	36/55
Female (%)	(60.4)
Age at clinical onset (mean ± SD), years	44.41 ± 20.97
Age at first vaccine dose (mean ± SD), years	58.84 ± 17.05
Disease duration (mean ± SD), years	14.43 ± 10.18
Thymectomy, n (%)	49 (53.8)
Thymoma, n (%)	16 (17.6)
Non-thymoma, n (%)	33 (36.3)
Serological status	
AChR$^+$	78
MuSK$^+$	5
Seronegative	8
MGFA class at diagnosis	
I	13
II	38
III	29
IV	11
PIS	
CSR	11
PR	22
MM-1	13
MM-2	2
MM-3	32
I	7
U	4
History of crisis or severe exacerbation, n (%)	38 (41.8)
Treatment	
Pyridostigmine Mean daily dose, mg (range)	42 (46.2) 157.5 (15-300)
IST, n (%)	72 (79.1)
Prednisone, n (%) Mean daily dose, mg (range)	28 (30.8) 8.3 (2.5-40)
Azathioprine, n (%) Mean daily dose, mg (range)	5 (5.5) 60 (50-100)
Mycophenolate, n (%) Mean daily dose, mg (range)	5 (5.5) 1,100 (500-2,000)
Tacrolimus, n (%) Mean daily dose, mg (range)	58 (63.7) 3.5 (1-6)
IVIg, n (%)	9 (9.9)
No treatment	11 (12.1)
QMG score prevaccination	6.12 ± 3.95
MG-ADL prevaccination	2.2 ± 2.2

Abbreviations: AChR$^+$, anti-acetylcholinesterase antibody-positive; CSR, complete stable remission; F, female; I, Improved; IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; M, male, MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MM-1, patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy; MM-2, patient has received only low-dose cholinesterase inhibitors (pyridostigmine 120 mg/day) for at least 1 year; MM-3, patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year; MuSK$^+$, muscle-specific kinase antibody-positive; PIS, postintervention status; PR, pharmacological remission; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; U, unchanged.

same time interval since the most recent dose of pyridostigmine to prevent variations in the total QMG scores.

The BNT162b2 mRNA vaccine was administered with two 30-μg intramuscular doses, whereas the mRNA-1273 vaccine was administered with two 100-μg intramuscular doses, according to the manufacturer's instructions.

Three keywords ("COVID19 vaccine," "myasthenia gravis," and "myasthenia gravis crisis") were used in our search of the Vaccine Adverse Event Reporting System (VAERS) database.

The study protocol was approved by a local institutional review board. All patients provided informed consent.

2.2 | Statistical analysis

The analysis was performed with R statistical software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), using descriptive analysis tools and frequency tables. The data are expressed as the mean and standard deviation for quantitative variables. The results for the categorical variables are expressed as both absolute values and percentages (proportions). The Fisher exact test was used to compare proportions and the one-proportion *Z* test was used to compare an observed sample proportion to a population one. Logistic regression was used to investigate the influence of variables selected based on their expected relevance on adverse effects. The final selection was made with two methods: the stepwise method by the Akaike Information Criterion (AIC) and the Least Absolute Selection and Shrinkage Operator (LASSO) method. The significance level was set at 0.05.

3 | RESULTS

3.1 | Patients' characteristics

The entire cohort of 91 patients received one of the two approved mRNA-based COVID-19 vaccines. Two men, 23 and 79 years of age, respectively, only received one vaccine dose, because they had been infected with COVID at 62 and 183 days before being vaccinated, respectively, according to the recommendations of our HA. PIS varied widely among patients. Eight patients were well controlled with pyridostigmine alone. Most patients were taking an IST, and 22 of 72 required more than one. Fewer than 1 in 10 received maintenance intravenous immunoglobulin (IVIg) (Table 1).

3.2 | Reactogenicity

None of our patients developed acute allergic reactions or serious adverse events (SAEs). More than half of the patients developed at least one reaction. Local and systemic reactions were transient (Table 2). There were no significant differences in reactogenicity between mRNA-1273 or BNT162b2. The proportion of patients under 65 years of age with at least one AE was 69.4%, whereas in those over 65 years of age it was 45.2% (95% confidence interval [CI], 0.14-0.93; $P = .032$). We found no significant differences when comparing the proportions of patients with reactions in the groups (1) treated with steroids (n = 28) and (2) not treated with steroids (n = 63) (95% CI, 0.28-2.06; $P = .647$). A comparison of patients on (1) low doses of steroids (n = 23) and (2) high doses (≥15 mg/day) of steroids

TABLE 2 Local and systemic reactions after messenger RNA–based COVID-19 vaccinations in MG patients

	MG cohort, n (%)		CDC Atlanta, n (%)[27]		*P* value (95% CI)	
	Dose 1 (n = 91),	Dose 2 (n = 89)	Dose 1 (n = 3,643,918)	Dose 2 (n = 1,920,872)	Dose 1	Dose 2
Nothing	45 (49.5%)	49 (55.1%)	NR	NR		
Any injection site reaction	37 (40.7%)	27 (30.3%)	2,550,710 (70.0%)	1,443,899 (75.2%)	<0.001 (−0.40, −0.19)	<0.001 (−0.55, −0.35)
Fatigue	9 (9.9%)	12 (13.5%)	1,127,638 (30.9%)	1,034,462 (53.9%)	<0.001, (−0.28, −0.14)	<0.001 (−0.48, −0.33)
Headache	10 (11.0%)	5 (5.6%)	943,607 (25.9%)	897,005 (46.7%)	0.0018 (−0.22, −0.08)	<0.001 (−0.46, −0.36)
Myalgia	1 (1.1%)	3 (3.4%)	705,100 (19.4%)	845,314 (44.0%)	<0.001 (−0.21, −0.16)	<0.001 (−0.45, −0.36)
Chills	1 (1.1%)	1 (1.1%)	321,009 (8.8%)	600,354 (31.3%)	0.0159 (−0.10, −0.05)	<0.001 (−0.33, −0.27)
Fever ≤38°C	3 (3.3%)	5 (5.6%)	314,676 (8.6%)	566,112 (29.5%)	0.1038 (−0.10, −0.01)	<0.001 (−0.29, −0.19)
Diarrhea	0 (0.0%)	1 (1.1%)	189,878 (5.2%)	133,877 (7.0%)	0.0454 (−0.06, −0.05)	0.0503 (−0.09, −0.03)
Abdominal pain	0 (0.0%)	2 (2.2%)	111,044 (3.0%)	117,494 (6.1%)	0.1657 (−0.04, −0.02)	0.1929 (−0.08, −0.002)
Rhinorrhea	1 (1.1%)	0 (0.0%)	NR	NR		
Flu-like symptoms	1 (1.1%)	1 (1.1%)	NR	NR		
Lethargy	2 (2.2%)	2 (2.2%)	NR	NR		
Double vision	1 (1.1%)	1 (1.1%)	NR	NR		

Abbreviations: MG, myasthenia gravis; NR, not reported.

Note: Flu-like symptoms are a group of symptoms similar to those caused by the influenza virus. These include fever, chills, headache, muscle or body aches, cough, sore throat, runny nose, fatigue, nausea, vomiting, and diarrhea.

TABLE 3 Logistic regression with no interactions on the adverse effects of vaccination

						95% CI for OR	
	Estimate	SE	*z* value	Pr(>|*z*|)	OR	Lower (2.5%)	Upper (97.5%)
(Intercept)	3.0629	1.2109	2.5293	0.0114	21.3885	2.1998	267.11
Sex (male)	−0.4296	0.5803	−0.7403	0.4591	0.6508	0.1969	1.9627
Age at vaccination	−0.0386	0.0165	−2.3418	0.0192	0.9622	0.9296	0.9923
Disease duration	0.0007	0.0241	0.0276	0.9780	1.0007	0.9545	1.0506
Thymoma (yes)	−0.2101	0.6328	−0.3320	0.7399	0.8105	0.2294	2.8335
Myasthenic crisis (yes)	0.3074	0.5510	0.5579	0.5769	1.3599	0.4607	4.0835
Prednisone	−0.0675	0.0505	−1.3362	0.1815	0.9347	0.8365	1.0279
Corticosteroid-sparing IST	−0.7960	0.6183	−1.2874	0.1980	0.4511	0.1285	1.4904
IVIg (yes)	−0.7401	0.8218	−0.9005	0.3678	0.4771	0.0919	2.4750
Baseline QMG	0.0886	0.0793	1.1171	0.2640	1.0927	0.939	1.2855

Abbreviations: CI, confidence interval; estimate, estimate of the regression beta coefficients; IST, immunosuppressant therapy; IVIg, intravenous immunoglobulin; OR, odds ratio; Pr(>|*z*|), *P* value corresponding to the *z* statistic; QMG, quantitative myasthenia gravis; SE, standard error of the coefficient estimates; *z* value, *z* statistic.

Note: Variables entered in step 1 include: sex, age, duration of disease, thymoma, myasthenic crisis, prednisone, corticosteroid-sparing IST, IVIg, and baseline QMG. Two variable selection methods were applied: the stepwise Akaike Information Criterion (AIC) and Least Absolute Selection and Shrinkage Operator (LASSO) with the optimal parameter. Both methods demonstrate that age is the only statistically important variable.

(n = 5) showed no significant differences (95% CI, 0.12-13.53; $P = 1$). We also observed no significant differences when investigating the effect of corticosteroid-sparing immunosuppressive therapy on reactions to vaccines, or for AEs in the 9 patients taking IVIg (95% CI, 0.18-4.81; $P = 1$). Other variables, such as thymectomy, MGFA class when diagnosed, PIS, history of crisis, baseline QMG, MG-ADL, type of antibodies associated with myasthenia, and disease duration, were not factors in reactogenicity. Age was the only statistically significant risk factor in the univariate analysis (see Table S1). Age was also the only statistically significant variable in the multivariate analysis (Table 3).

None of the patients had MC. We observed no changes in functional status, except in two patients. Diplopia lasted 4 days in the first patient, whereas in the second there was reduced endurance in the lower limbs lasting 2 weeks. It was not necessary to change the treatment of the patient who developed diplopia (QMG baseline score was 9 and MG-ADL baseline score was 3, which rose to 11 and 5, respectively, after vaccination due only to the ocular items). In the second patient, with worsening strength in the lower limbs, we increased the prednisone dose (QMG baseline score 4 and MG-ADL baseline score 1, which rose to 7 and 6, respectively, after vaccination).

4 | DISCUSSION

We found that mRNA vaccination was safe in a population of patients with MG with stable disease based on the MGFA classification and a stable medication regimen in the previous 6 months. Thirty-eight (41.7%) of the patients developed no AE, and a variety of mostly transient local and general AEs were reported in the remaining patients. The AEs were mild. Age was the only risk factor for AEs. The cases reported in the VAERS and a single-center case series of 22 patients using inactivated virus vaccines addressed the side effects of the COVID vaccination among myasthenic patients.[24,25] At the time of this writing, the VAERS website had recorded 75 exacerbations, 17 myasthenic crises, and 115 instances of new-onset MG after COVID vaccination.[26] The incidence of reactogenicity in our cohort was significantly lower than in a V-safe survey (V-safe provides personalized and confidential health check-ins via text messages and web surveys) that enrolled 3,643,918 healthy volunteers.[27] Unlike our study, events in VAERS are not limited to 7 days of follow-up, which may account for the differing frequencies of AEs in our cohort compared with the VAERS reports. Other possible explanations for the differences in AE frequencies are differences in cohort size and age, comorbidities, concurrent medications, patient self-reporting to VAERS without a physician's oversight, and a lack of comprehensive information about MGFA class and immune status.

No myasthenic crisis was noted in the time frame of the study, but two patients had worse QMG and MG-ADL scores after vaccination. The changes observed in the functional scales for myasthenia in our cohort are far below threshold for clinical relevance according to most QMG assessment studies.[28,29]

Several types of COVID-19 vaccines have been approved for emergency use with availability varying depending on the country.[30–34] Reports show that the effectiveness of these vaccines can be reduced by immunosuppressant agents, especially those with B-cell–depleting therapies, but this was not evaluated in the current study.[35–37] The information available for other autoimmune diseases suggests that IST does not influence reactogenicity, but it does reduce immunogenicity after vaccination.[38] To date, mRNA vaccines have not been associated with risk of infection. The US Centers for Disease Control and Prevention has recommended mRNA vaccines as heterologous boosters due to the loss

of effectiveness by COVID vaccines in both normal and immunocompromised patients in the United States.[30]

The main limitations of this study are: (1) its relatively small sample size; (2) only short-term reactivity was studied, while the possible long-term negative effects of vaccination were not monitored; and (3) its lack of information regarding patients with MG whose decision to receive the vaccination or otherwise was overseen by their primary health-care physician. In conclusion, our results suggest that mRNA COVID vaccines do not induce clinical exacerbations of MG, and have high levels of safety in stable patients with MG.

CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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