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Early safety and tolerability profile of the BNT162b2 COVID-19 vaccine in myasthenia gravis

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Abstract

Although the COVID-19 vaccines are currently recommended for people with myasthenia gravis (MG), there is no data regarding the safety of the vaccines in this population. In order to investigate the real-life safety data of the *BNT162b2* COVID-19 vaccine in people with MG, an anonymous survey was distributed to 142 MG patients. Fifty-six MG patients completed the questionnaire. The median age was 53 years (range 23–83 years); 35 (62.5%) were males, and 25 (44.6%) had associated comorbidities. Thirty-seven participants (66.1%) were treated with immunotherapies. Fifty-five participants (98.2% of the responders) received the *BNT162b2* COVID-19 vaccine. Of these, 32 (58.2%) were < 55 years old, and 23 (41.8%) were > 55 years old. Adverse events were more common in patients younger than 55 years old (46.9% Vs. 17.4%; $p = 0.0428$). Eight participants (14.5%) reported worsening neurological symptoms following the vaccination. Three of those who reported worsening of neurological symptoms (37.5%) required additional treatment. Most events occurred within the first few days after vaccination and resolved within a few weeks. This survey indicates an overall favorable safety and tolerability profile of the *BNT162b2* vaccine in people with MG. Additional prospective, large-scale studies are warranted to confirm these findings.

Keywords: Myasthenia gravis; COVID-19; Vaccine; Safety; Tolerability: Adverse events.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome - coronavirus-2 (SARS-Cov2) [1]. SARS-Cov2 is a single-stranded, positive-sense RNA genome-bearing virus that belongs to the *Coronaviridae* family [2]. COVID-19 was first reported to the World Health Organization (WHO) on December 31, 2019. On March 11, 2020, COVID-19 was declared a global pandemic [3]. The disease is associated with rapid spread and significant morbidity and mortality, making it the most challenging pandemic since the Spanish flu in 1918 [4,5].

To halt the spread of the disease, a global effort of the scientific community, supported by industrial and governmental sectors, has been focusing on the development of effective vaccines. This effort has culminated in the recent FDA approval of three vaccines, while others are approaching the final stages of clinical trials and are expected to be approved in the near future [6,7].

The currently Food and Drug Administration (FDA)-approved vaccines include two types of mRNA encoding for the full-length spike protein (*mRNA-1273, Moderna TX, Inc)* or its' receptor-binding domain (*BNT162b2, BioNTech-Pfizer).* The third vaccine, developed by The Janssen Pharmaceutical Companies of *Johnson & Johnson*, is a viral-vector vaccine that uses a replication-defective adenovirus that

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expresses the full-length spike glycoprotein (Ad26.COV2.S vaccine). Other vaccines currently in use include two viral-vector vaccines developed by researchers at Oxford University and *AstraZeneca* and The Gamaleya National Research center for Epidemiology and Microbiology (Russian Federation) and an inactivated whole SARS-CoV-2 virus vaccine developed by the Wuhan Institute of Biological Products and Sinopharm [6–9].

The approved vaccines have been tested in large-scale phase 3 trials, which recruited both healthy individuals and people with chronic medical conditions [10,11]. Although the COVID-19 vaccines have not been tested specifically in people with neurological and autoimmune diseases, many expert committees, as well as the Centers for Disease Control and Prevention (CDC), recommend their use in various neurological disorders, including multiple sclerosis)MS(and myasthenia gravis(MG) [12,13]. However, the lack of information regarding the safety and efficacy of the vaccines in this specific population is a cause of uncertainty for both patients and physicians.

The COVID-19 vaccination campaign began in Israel in December 2020 using the *BNT162b2 (Pfizer)* vaccine as its sole vaccine. In the clinical trial that led to its approval by the FDA, the safety profile of the vaccine, administered in 2 injections of 30 μg 21 days apart, was reported similar to that of other viral vaccines. Adverse events were more common among participants younger than 55 years of age compared to those older than 55 years of age. The most common adverse event was pain at the injection site, reported by 83% of those younger than 55 years of age and by 71% of those older than 55 years after the first dose, and by 78% of those younger than 55 years of age and 66% of those older than 55 years of age after the second dose. Systemic adverse events were reported less frequently than the local reactions, were more common after the second dose, and included fatigue, headache, fever, and chills [14].

The current study aims to report the early safety and tolerability experience with the *BNT162b2* COVID-19 vaccine in MG patients.

2. Materials and methods

This single-center study was conducted using an anonymous questionnaire that was distributed to all MG patients treated in the Neuroimmunology Clinic at the Rabin Medical Center, for whom an email address was available in our database.

In the first part of the questionnaire, participants were asked general demographic and disease-related questions, including age, gender, disease duration, use of disease-modifying therapies, recent treatment with corticosteroids, and associated comorbidities.

The second part of the questionnaire was dedicated to the safety and tolerability profile of the COVID-19 vaccine. In this part, participants were asked if they received the vaccine (first or both doses), date of vaccination, presence and type of adverse reactions to the vaccine (pain/redness/swelling at the injection site, generalized muscle pain, headache, dizziness, fever, chills, fatigue, or other), and presence, type and timing of new or worsening neurological symptoms following the vaccination. In case of worsening neurological symptoms after the vaccination, participants were asked about additional information regarding the need for specific treatment and the duration of symptoms.

The study data was collected and managed using REDCap, an electronic data capture tool [15,16]. Data analysis was performed between July 6, 2021 and July 12, 2021.

The study was approved by the Rabin Medical Center institutional review board (study approval number 0061–21-RMC). An invitation email with a link to the survey was distributed to 142 MG patients between June 8, 2021 and July 5, 2021. Patients were informed that completion of the survey was not obligatory. Informed consent was not requested.

Statistical analysis was performed using GraphPad Prism version 9.1.2 (GraphPad Software, San Diego, CA, USA). Descriptive statistics are presented as total counts and percentages, median and range. Fisher's exact test was used for comparison of non-parametric variables between groups.

3. Results

3.1. Demographic and disease-related characteristics of the study population

Fifty-six participants (39.4% response rate) completed the questionnaire. The median age was 53 years (range 23–83 years); 35 were males (62.5%). The median disease duration was 8.8 years (mean 8.79 $\pm$ 5.66 years). Twenty-five participants (44.6%) reported associated comorbidities:16 (28.6%) had hypertension; 11(19.6%) had obesity; 9 (16.1%)-diabetes mellitus; 5 (8.9%)- lung diseases; 2 (3.6%)-heart diseases; and 3 (5.4%)- malignancy. Thirty-seven participants (66.1%) were treated with immunotherapies. Table 1 summarizes the demographic and disease-related characteristics of the study population.

3.2. Safety profile of the COVID vaccine- immediate adverse events

Fifty-five participants (98.2% of the responders) received the vaccine. Fifty-one participants (92.7%) received two doses, and 4 (7.3%) received one dose. Among those who received one dose, 3 participants (75%) were previously diagnosed with COVID-19 and were therefore advised to obtain just one dose, and 1 (25%) did not receive the second dose because of personal or medical concern due to side effects after the first dose. The mean time from the second shot to data analysis was 108.73 $\pm$ 47.03 days (median 127 days, range 5–168 days).

Nineteen participants (34%) reported immediate adverse events following the COVID vaccine. Four participants (21.1%) reported immediate adverse events only after the first dose, 6 participants (31.6%) reported immediate adverse events only after the second dose, and 9 (47.4%) reported

Table 1
Demographic and disease-related characteristics of the survey participants.

	Number of participants
Males (%)	35 (62.5%)
Age (median; range)	53; range 23–83
Age < 55 years old	32 (58.2%)
Associated comorbidities	25 (44.6%)*
Hypertension	16 (28.6%)
Diabetes mellitus	9 (16.1%)
Lung disease	5 (8.9%)
Heart disease	2 (3.6%)
Obesity	11 (19.6%)
Malignancy	3 (5.4%)
Treated with immunotherapy	37 (66.1%)%)**
Oral corticosteroids	28 (50%)
Azathioprine	4 (8.9%)
Mycophenolate Mofetil	3 (5.3%)
Methotrexate	2 (3.6%)
Rituximab	9 (16.1%)
IVIG	6 (10.7%)
PLEX	2 (3.6%)
Eculizumab	1 (1.8%)

IVIG= Intravenous immunoglobulins (given every 3–4 weeks).
PLEX= plasma exchange (given every 3–4 weeks).
* Some participants reported more than 1 associated comorbidity.
** Some participants reported more than 1 immunotherapy.

immediate adverse events after both doses. The most common immediate adverse event was pain at the injection site, reported by 9 participants (47.4%), followed by fatigue, headache, muscle pain, and dizziness (Table 2).

Thirty-two participants who received the vaccine (58.2%) were < 55 years old, and 23 (41.8%) were > 55 years old. Fifteen participants <55 years of age (46.9%) and 4 participants > 55 years (17.4%) reported immediate adverse events ($p=0.0428$). Adverse events were more common in patients younger than 55 (46.9% Vs. 17.4%; $p=0.0428$).

Thirty-seven participants who received the vaccine (67.3%) were treated with immunotherapies. Fifteen participants treated with immunotherapies (40.5%) reported adverse events, compared to 6 participants not treated with immunotherapies (33.3%; $p=0.7691$). Twenty-one participants treated with immunotherapies were younger than 55 years of age (56.8%), and 16 (43.2%) were older than 55. Twelve participants in the young-age group (57.1%) and 3 participants in the old-age group (18.8%) reported immediate adverse events ($p=0.0409$).

The rate of immediate adverse events is summarized in Table 2.

3.3. Safety profile of the COVID vaccine- worsening of neurological symptoms

Eight (14.5%) participants reported new or worsening neurological symptoms following the vaccination. The median age was 49 years (mean age 48.4 ± 9.6 years). Seven (87.5%) were males, and 7 (87.5%) were treated with immunotherapies (four- corticosteroids, two-azathioprine, one-rituximab). Three participants (27.5%) had associated comorbidities (one- hypertension, one- lung disease, and one-heart disease). New or worsening neurological symptoms occurred after the first dose in 4 (50%) participants, after the second dose in 2 (25%) participants, and after both doses in 2 (25%) participants.

The most common new or worsening neurological symptoms included general muscle weakness ($n=7$), gait difficulty ($n=5$), dysphagia ($n=4$), and dyspnea ($n=4$). Other symptoms included dysarthria ($n=2$), ptosis ($n=1$), and diplopia ($n=1$) (Table 3).

Three participants reported the occurrence of new or worsening neurological symptoms within a few hours after the vaccine; in 4 participants, new or worsening neurological symptoms developed after 1–4 days, and in 1 participant, new or worsening neurological symptoms developed after one week.

Five participants who reported new or worsening neurological symptoms (62.5%) didn't require any additional medication to treat their symptoms. The other 3 participants (37.5%), who received chronic low-dose oral corticosteroids, were treated only with higher doses of corticosteroids.

Three participants (37.5%) reported that new or worsening neurological symptoms resolved within a few days to 1 week; in 2 participants (19.4%), the symptoms resolved within 2–3 weeks; in 1 participant (19.4%), the duration of symptoms was up to 1 month; and in 1, the duration of symptoms was longer than 1 month. One participant, who completed the questionnaire four weeks after the onset of new or worsening neurological symptoms, reported the persistency of symptoms, consisting of dysarthria, dysphagia, dyspnea, and general muscle weakness.

4. Discussion

To the best of our knowledge, this is the first study reporting safety and tolerability data of any COVID-19 vaccine in MG patients.

Viral infections are a known trigger of disease exacerbation in MG [17,18]. Likewise, during the past year, several cases of MG exacerbation have been reported following COVID-19 infection [19,20]. In a Brazilian observational study of 15 consecutive MG patients admitted due to COVID-19, 87% required admission in intensive care unit, and 73% required mechanical intubation [21]. Moreover, MG patients with COVID-19 may experience disease exacerbation following some of the COVID-19 treatments, like hydroxychloroquine and azithromycin [22–24].

While vaccines are aimed to provide immunity against specific pathogens, there is a concern regarding the potential triggering of unwanted immune response following vaccination. This may trigger an autoimmune disease or cause a clinical worsening in people with clinically stable disease. Therefore, the risks and benefits of vaccination should be considered for each vaccine separately. In general, the risk of vaccination-triggered MG exacerbation with other vaccines is deemed low and is outweighed by the benefit of preventing the infection [25]. However, this risk and the rate of adverse

Table 2
Frequency and type of immediate adverse events among the survey participants.

	Local painat the injectionsite	Rednessat the injection site	Swellingat the injection site	Headache	Dizziness	Musclepain	Fatigue	Fever	Chills
Number of responders (%)*	20 (36.4%)	7 (12.7%)	8 (14.5%)	12 (21.8%)	4 (7.3%)	13 (23.6%)	19 (34.5%)	4 (7.3%)	5 (9.1%)
Number of responders <55 years old (%)**	15 (75%)	5 (71.4%)	6 (75%)	9 (75%)	4 (100%)	10 (77%)	15 (78.9%)	2 (50%)	4 (80%)
First dose	7 (46.7%)	2 (40%)	2 (33.3%)	5 (55.6%)	1 (25%)	4 (40%)	6 (40%)	0	1 (25%)
Second dose	8 (53.3%)	3 (60%)	4 (66.7%)	4 (44.4%)	3 (75%)	6 (60%)	9 (60%)	2 (100%)	3 (75%)
Number of responders >55 years old (%)	5 (25%)	2 (28.6%)	2 (25%)	3 (25%)	0	3 (23%)	4 (21.1%)	2 (50%)	1 (20%)
First dose	2 (40%)	1 (50%)	1 (50%)	1 (33.3%)	0	1 (33.3%)	1 (25%)	1 (50%)	0
Second dose	3 (60%)	1 (50%)	1 (50%)	2 (66.7%)	0	2 (66.7%)	3 (75%)	1 (50%)	1 (100%)
Number of responders treated with immunotherapies (%)**	15 (75%)	7 (100%)	8 (100%)	11 (91.6%)	3 (75%)	10 (77%)	11 (57.9%)	2 (50%)	4 (80%)
One dose	7 (46.7%)	3 (42.9%)	3 (37.5%)	5 (45.4%)	1 (33.3%)	4 (40%)	5 (45.4%)	1 (50%)	1 (25%)
Two doses	8 (53.3%)	4 (57.1%)	5 (62.5%)	6 (54.6%)	2 (66.7%)	6 (60%)	6 (54.6%)	1 (50%)	3 (75%)
Number of responders not treated with immunotherapies (%)	5 (25%)	0	0	1 (8.4%)	1 (25%)	3 (23%)	8 (42.1%)	2 (50%)	1 (20%)
One dose	2 (40%)	0	0	1 (100%)	1 (100%)	1 (33.3%)	3 (37.5%)	0	0
Two doses	3 (60%)	0	0	0	0	2 (66.7%)	5 (62.5%)	2 (100%)	1 (100%)

* Out of the total number of responders; some participants reported more than one adverse event.
** Out of responders who reported the specific adverse event.

Table 3
New or worsening neurological symptoms.

New or worsening neurological symptoms	First dose (number of participants;%)	Second dose (number of participants;%)	Both doses (number of participants;%)	Total
Ptosis	1 (100%)	0	0	1
Diplopia	1 (100%)	0	0	1
Weakness in mastication	0	0	1 (100%)	1
Dysphagia	1 (25%)	2 (50%)	1 (25%)	4
Dysarthria	2 (100%)	0	0	2
Dyspnea	4 (100%)	0	0	4
Muscle weakness	3 (42.9%)	2 (28.6%)	2 (28.6%)	7
Gait difficulty	3 (60%)	1 (20%)	1 (20%)	5

events associated with the COVID-19 vaccines in people with MG are currently unknown.

The spectrum of immediate adverse events reported in our study is comparable to that reported in Pfizer's phase 3 clinical trial[14]. As seen in the general population, local reactions (i.e., pain, redness, and swelling at the injection site) were the most common adverse events. Also in line with what was reported in the general population, immediate adverse events among MG patients were more frequent in the young-age group (< 55 years old) compared to older individuals (>55 years old). A possible explanation for this observation may be related to the more vigorous immune response mounted by younger individuals. In fact, the occurrence of adverse events following vaccination is thought to be mediated by immunological responses, therefore reflecting the activity of the immune system [26,27]. As the immune system tends to gradually deteriorate with age [28,29], older people often experience less pronounced side effects after vaccination [30,31]. However, the overall rate of adverse events among our survey responders is lower than that reported in the general population [14]. A possible explanation for this observation may be related to the fact that most of the participants in our survey were treated with DMTs, many of which have an immunosuppressive effect. If the rate of adverse events is indeed related to the activity of the immune system, people who are treated with immunosuppressive medications, as were most of the participants in our survey, may develop fewer adverse events following vaccination.

The occurrence of new or worsening neurological symptoms following the vaccine was reported by 14.5% of the participants in our survey. Medical treatment, consisting of an increased dose of oral corticosteroids, was needed in 3 cases (37.5%). This relatively low rate of clinical worsening following the COVID-19 vaccine, as well as its' overall mild severity, is in line with prior data on other (non- live-attenuated) vaccines that were not related to an increased risk of MG exacerbation [32–36].

The limitations of this study are mostly related to the relatively small number of responders. Also, the response rate

to the survey was relatively low. This may bias the results, as the rate of adverse events and new or worsening neurological symptoms among those who did not respond may differ from that reported by the responders. Nevertheless, given the lack of safety data of the COVID-19 vaccines in MG, the information presented here may be helpful for clinicians facing patients' concerns regarding the vaccination.

5. Conclusions

The safety profile of the *BNT162b2* vaccine in people with MG is similar to that reported in the general population. The overall rate of immediate adverse events may be lower in MG patients treated with immunotherapies. The rate of worsening neurological symptoms is relatively low. These data should be validated in additional prospective, large-scale studies.

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Data statement

Anonymized data presented in this report will be made available to bona fide investigators upon request to the corresponding author.

Declaration of Competing Interest

none.

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