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 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.
To control the pandemic, a global effort supported by academic, industrial, and governmental sectors has been focusing on the development of effective vaccines at record speed. This effort has culminated in the recent US Food and Drug Administration (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 [4,5].

Two of the current FDA-approved vaccines include two types of mRNA encoding for the full-length spike protein (mRNA-1273: Moderna TX, Inc., Cambridge, MA, USA) or its receptor-binding domain (BNT162b2; BioNTech-Pfizer, New York, NY, USA). The third vaccine, developed by the Janssen Pharmaceutical Companies of Johnson & Johnson (New Brunswick, NJ, USA), is a viral-vector vaccine that uses a replication-defective adenovirus that 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/AstraZeneca and the Gamaleya National Research Centre for Epidemiology and Microbiology (Russian Federation), respectively, and an inactivated whole SARS-CoV-2 virus vaccine developed by the Wuhan Institute of Biological Products and Sinopharm [4–7].

The approved vaccines have been tested in large-scale phase 3 trials, which recruited both healthy individuals and people with chronic medical conditions [8]. Although the COVID-19 vaccines have not been tested specifically in people with neurological and autoimmune diseases, many expert committees recommend their use in various neurological disorders, including multiple sclerosis (MS) [9–12]. 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. Hence, real-life data on the safety of the COVID-19 vaccine is of utmost importance.

A recent study reported a higher incidence of COVID-19 in an MS cohort compared to the general population [13]. Although most studies do not indicate a more severe course of the disease among MS patients [14,15], some subpopulations, such as patients treated with anti-CD20 therapies, may be at higher risk for severe outcome following COVID-19 infection [16,17]. The importance of effective measures to prevent the disease in this context is therefore understandable.

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 two injections of 30 μg 21 days apart, was reported to be similar to that of other viral vaccines. Adverse events were more common among participants aged <55 years of age compared to those aged >55 years. The most common adverse event was pain at the injection site, reported by 83% of those aged <55 years and by 71% of those aged >55 years after the first dose, and by 78% of those aged <55 years of age and 66% of those aged >55 years 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 [8].

Israel is currently the leading country in the world in the percentage of its population that received both doses of the vaccine [18]. Early efficacy outcomes of the BNT162b2 vaccine in Israel confirm that real-life vaccine efficacy is as good as the data reported from Pfizer’s earlier clinical trials [19].

Given the successful application of the vaccine campaign in Israel, we aimed to report our early safety experience with the BNT162b2 COVID-19 vaccine in a cohort of MS patients.

MATERIALS AND METHODS

This single-center study was conducted using an anonymous questionnaire that was distributed to MS patients from the Neuroimmunology Clinic at the Rabin Medical Center.

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

The second part of the questionnaire was dedicated to the safety profile of the COVID-19 vaccine. In this part, participants were asked if they had received the vaccine (first or both doses), the date of vaccination, and questions on the presence, and type of early reactions (i.e., occurring within the first week from vaccination) 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, additional information regarding the need for specific treatment and the duration of symptoms was requested.

The study data were collected and managed using REDCap, an electronic data capture tool [20,21]. Data analysis was performed between April 17, 2021 and April 22, 2021.

Standard protocol approvals, registrations, and patient consents

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 425 MS patients between March 15, 2021 and April 17, 2021. Patients were informed that completion of the survey was not obligatory. As the data were anonymous, informed consent was not requested.

Statistical analysis

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 nonparametric variables between groups.

Due to the exploratory nature of the study, no adjustment for multiple comparisons was made.

RESULTS

Demographic and disease-related characteristics of the study population

A total of 262 participants (61.6% response rate) completed the questionnaire. The median (range) age was 42 (22–79) years and 199 of the respondents were women (75.9%). Sixty-six participants (25.2%) reported associated comorbidities, including hypertension (32 participants, 12.2%), diabetes mellitus (11 participants, 4.2%) lung diseases (five participants, 2.2%), heart disease (four participants, 1.5%), obesity (37 participants, 14.1%) and malignancy (four participants, 1.5%). A total of 198 participants (75.6%) were treated with disease-modifying therapies (DMTs), and 17 (6.5%) were treated with corticosteroids in the month preceding the first vaccination. Table 1 summarizes the demographic and disease-related characteristics of the study population.

| TABLE 1 Demographic and disease-related characteristics of the survey participants |
|-----------------------------------------------|
| Characteristic                                      | Value |
| Women, n (%)                                         | 199 (75.9) |
| Median (range) age, years                            | 42 (22–79) |
| Age <55 years, n (%)                                 | 196 (74.8) |
| Associated comorbidities, n (%)                     | 66 (25.2)* |
| Hypertension                                         | 32 (12.2) |
| Diabetes mellitus                                    | 11 (4.2) |
| Lung disease                                         | 5 (1.9) |
| Heart disease                                        | 4 (1.5) |
| Obesity                                              | 37 (14.1) |
| Malignancy                                           | 4 (1.5) |
| Treated with DMTs, n (%)                             | 198 (75.6) |
| Natalizumab                                          | 14 (7.1) |
| Ocrelizumab                                          | 39 (19.6) |
| Dimethyl fumarate                                    | 49 (24.7) |
| Teriflunomide                                        | 19 (9.6) |
| Fingolimod                                           | 26 (13.1) |
| Cladribine                                           | 4 (2) |
| Glatiramer acetate                                   | 27 (13.6) |
| Interferon beta 1a (Avonex)                          | 5 (2.5) |
| Interferon beta 1a (Plegridy)                        | 3 (1.5) |
| Interferon beta 1a (Rebif)                           | 9 (4.5) |
| Interferon beta 1b (Betaferon)                       | 3 (1.5) |
| Treated with corticosteroids in the past month before vaccination, n (%) | 17 (6.5) |

*Some participants reported more than one associated comorbidity.

Safety profile of the COVID vaccine: Early adverse events

A total of 239 participants (91.2% of the responders) had received the vaccine. Eighteen (7.5%) had received only one dose, and 221 (92.5%) had received both doses.

The reason for receiving just one dose of the vaccine was a prior diagnosis of COVID-19 in seven participants (38.9%) and personal or medical concern because of side effects after the first dose in 11 participants (61.1%). The mean time from the second shot to data analysis was 43.3 ± 18.1 days (median 39 days, range 27–103 days).

A total of 136 participants (56.9%) reported early adverse events following the COVID vaccine. Of those participants who had received just the first dose of the vaccine, 12 (66.7%) experienced adverse events. Of those who had received both doses of the vaccine, 122 (55.2%) reported adverse events; 13 participants (10.6%) reported adverse events only after the first dose, 59 (48.4%) reported adverse events only after the second dose, and 51 (41.8%) reported adverse events after both doses. The most common adverse event was pain at the injection site, reported by 111 participants (46.4%), followed by fatigue, muscle pain, headache, and dizziness (Table 2).

Of those who were vaccinated, 182 (76.1%) were aged <55 years, and 57 (23.9%) were aged >55 years. A total of 95 participants aged <55 years (52.2%) and 23 participants aged >55 years (40.3%) reported adverse events (p = 0.1517).

Of those participants who had received the vaccine, 179 (75.8%) were treated with DMTs. Of these, 100 participants (55.9%) reported adverse events. Among 57 participants who had received the vaccine and were not treated with DMTs, 36 (63.2%) reported adverse events (p = 0.0683). One hundred and twenty-seven participants treated with DMTs (70.9%) were aged <55 years, and 52 (29.1%) were aged >55 years. Sixty-nine participants in the younger age group (54.3%) and 23 participants in the older age group (44.2%) reported adverse events (p = 0.0356).

No association between type of DMT and frequency and type of adverse events was detected. The rate of adverse events is summarized in Table 2.

Safety profile of the COVID vaccine: Worsening of neurological symptoms

Thirty-six participants (15.1%) reported new or worsening neurological symptoms following the vaccination. Five participants received just one dose, and 31 received both doses of the vaccine. The median age was 41 years (mean age 41.6 ± 13.3 years). Twenty-nine were women (80.5%), and 28 (77.8%) were treated with DMTs. Eight participants (22.2%) had associated
comorbidities (two had hypertension, one had diabetes mellitus, one had lung disease, three were obese, and one had obesity and hypertension). Of those who had received just the first dose of the vaccine, three (60%) experienced new or worsening neurological symptoms. Of those who had received both doses of the vaccine, three participants (9.7%) reported new or worsening neurological symptoms only after the first dose, 18 (58.1%) reported new or worsening neurological symptoms only after the second dose, and 10 (32.3%) reported new or worsening neurological symptoms after both doses of the vaccine.

The most common new or worsening neurological symptoms included sensory disturbances (i.e., numbness, tingling, and itching sensations, $n = 21$), muscle weakness ($n = 17$), pain ($n = 13$), and gait instability ($n = 12$). Other symptoms included walking difficulty ($n = 9$), visual symptoms ($n = 6$), and sphincteric problems ($n = 5$; Table 3).

New or neurological symptoms occurred within the first 24 h after vaccination in 22 participants (61.1%), 10 participants (27.8%) reported the occurrence of new or worsening neurological symptoms within a few days to 1 week after the vaccination, two participants (5.5%) reported the onset of new or worsening neurological symptoms 10 days after vaccination, and two participants (5.5%) reported the onset of symptoms 1 month after vaccination.

Twenty-eight participants who reported new or worsening neurological symptoms (77.8%) did not require any additional medication to treat their symptoms. Six participants (16.7%) required simple analgesics, one participant (2.8%) received benzodiazepines, and one (2.8%) was treated with corticosteroids.

| TABLE 2  Frequency and type of adverse events among the survey participants |
|---------------------------------------------------------------|
| Local pain/redness/swelling at the injection site | Headache | Dizziness | Muscle pain | Fatigue | Fever | Chills |
| Number of responders (%)a | 111 (46.4) | 88 (36.8) | 31 (12.6) | 88 (36.8) | 91 (38.1) | 38 (15.9) | 70 (29.7) |
| Number of responders aged <55 years (%)b | 67 (60.4) | 59 (67.1) | 22 (71) | 67 (76.1) | 45 (49.5) | 33 (86.8) | 55 (78.6) |
| Responders aged <55 years, n (%) | | | | | | | |
| First dose | 18 (26.9) | 6 (10.2) | 6 (27.3) | 10 (14.9) | 10 (22.2) | 2 (6.1) | 8 (14.5) |
| Second dose | 25 (37.3) | 33 (56) | 12 (54.5) | 41 (61.2) | 24 (53.3) | 26 (78.8) | 33 (60) |
| Both doses | 24 (35.8) | 20 (33.9) | 4 (18.2) | 16 (23.9) | 11 (24.4) | 5 (15.2) | 14 (25.5) |
| Number of responders aged >55 years (%) | 44 (39.6) | 29 (32.9) | 9 (29) | 21 (23.9) | 46 (50.5) | 5 (13.2) | 15 (21.4) |
| Responders aged >55 years, n (%) | | | | | | | |
| First dose | 6 (13.6) | 4 (13.8) | 2 (22.2) | 6 (28.6) | 10 (21.7) | 2 (40) | 2 (13.3) |
| Second dose | 20 (45.5) | 10 (34.5) | 2 (22.2) | 6 (28.6) | 20 (43.5) | 3 (60) | 10 (66.7) |
| Both doses | 18 (40.9) | 15 (51.7) | 5 (55.6) | 9 (42.9) | 16 (34.8) | 0 (0%) | 3 (20) |
| Number of responders treated with DMTs (%) | 58 (52.3) | 48 (54.5) | 15 (48.4) | 45 (51.1) | 53 (58.2) | 25 (65.8) | 38 (54.3) |
| Responders treated with DMTs, n (%) | | | | | | | |
| First dose | 20 (34.5) | 8 (16.7) | 4 (26.7) | 12 (26.7) | 8 (15.1) | 2 (8) | 12 (31.6) |
| Second dose | 22 (37.9) | 32 (66.7) | 6 (40) | 22 (48.9) | 30 (56.6) | 18 (72) | 17 (44.7) |
| Both doses | 16 (27.6) | 8 (16.7) | 5 (33.3) | 11 (24.4) | 15 (28.3) | 5 (20) | 9 (23.7) |
| Number of responders not treated with DMTs (%) | 53 (47.7) | 40 (45.5) | 16 (51.6) | 43 (48.9) | 38 (41.8) | 13 (34.2) | 32 (45.7) |
| Responders not treated with DMTs, n (%) | | | | | | | |
| First dose | 12 (22.6) | 15 (37.5) | 4 (25) | 8 (18.6) | 9 (23.7) | 2 (15.4) | 6 (18.8) |
| Second dose | 31 (58.5) | 14 (35) | 10 (62.5) | 26 (58.1) | 20 (52.6) | 6 (46.2) | 19 (59.4) |
| Both doses | 10 (18.9) | 11 (27.5) | 2 (12.5) | 9 (20.9) | 9 (23.7) | 5 (38.5) | 7 (21.9) |

*aOut of the total number of responders who were vaccinated.

*bOut of the total number of responders who reported the specific adverse event.
Sixteen participants (44.4%) reported that new or worsening neurological symptoms resolved within 3 days, in seven participants (19.4%) the symptoms resolved within 1 week, in seven participants (19.4%) the duration of symptoms was between 1 and 2 weeks, and in six participants (16.7%) the duration of symptoms was longer than 1 month. One participant (2.8%) reported the persistence of new or worsening symptoms, consisting of muscle pain and walking difficulty, at the time of filling out the questionnaire. The latter participant was treated with corticosteroids for suspected myelitis without improvement. Cervical and thoracic MRI did not demonstrate a new spinal cord lesion.

**DISCUSSION**

A massive COVID-19 vaccination strategy is currently being implemented in many countries around the world. While the use of the vaccines is recommended to people with MS, the fact that MS patients were not included in the clinical trials poses uncertainties regarding the safety and efficacy of the vaccines for both patients and their treating neurologists. Herein, we report our early experience regarding the safety of the BNT162b2 vaccine in a selective cohort of MS patients.

The spectrum of adverse events reported in our study is comparable to that reported in Pfizer's phase 3 clinical trial [8]. 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, adverse events among MS patients were more frequent in the younger age group (<55 years) compared to older individuals (>55 years). 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. While the median age of the participants in our survey was relatively young, the fact that the majority of the participants younger than 55 years were treated with DMTs may explain the overall lower rate of adverse events observed. The occurrence of new or worsening neurological symptoms following the vaccine was reported by 15.1% of the participants in our survey. The most common symptom was sensory disturbances, and only approximately one-fifth (22.2%) of those who reported new or worsening neurological symptoms required medical treatment. Medical treatment was mostly symptomatic, and only one participant (2.8%) received corticosteroids. This relatively low rate of new or worsening neurological symptoms 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 MS relapse [28,29].

Vaccine hesitancy refers to a broad range of factors causing low vaccination uptake. Among these factors, confidence in the safety and effectiveness of the vaccine plays an important role [30]. Vaccine hesitancy regarding the pneumococcal vaccine and, more recently, the COVID-19 vaccines has been reported in a significant proportion of MS patients [31–33]. The data reported in the present study, which are in line with another early safety report on the BNT162b2 vaccine in MS [34], may help to address the safety concerns related to the vaccine in this population.

The limitations of this study are mostly related to the relatively small number of responders. Also, the nonresponding rate of approximately 40% may bias the results, as the rate of adverse events and new or worsening neurological symptoms among those who did not respond may be different than that reported by the responders.

In conclusion, the safety profile of the BNT162b2 vaccine in people with MS is similar to that reported in the general population. The overall rate of adverse events may be lower in MS patients treated with DMTs. The rate of new or worsening neurological symptoms is relatively low; most events are of mild severity, do not require

**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 (number of participants; %) |
|---------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------|
| Muscle weakness                       | 5 (13.9)                               | 10 (27.8)                              | 2 (5.6)                                | 17 (47.3)                        |
| Walking difficulty                    | 3 (8.3)                                | 6 (16.7)                               | 0                                      | 9 (25)                           |
| Gait instability                      | 3 (8.3)                                | 8 (22.2)                               | 1 (2.8)                                | 12 (33.3)                        |
| Visual problems                      | 2 (5.6)                                | 2 (5.6)                                | 2 (5.6)                                | 6 (16.8)                         |
| Pain                                  | 4 (11.1)                               | 6 (16.7)                               | 3 (8.3)                                | 13 (36.1)                        |
| Sensory disturbances                 | 7 (19.4)                               | 8 (22.2)                               | 6 (16.7)                               | 21 (58.3)                        |
| Sphincteric problems                 | 2 (5.6)                                | 2 (5.6)                                | 1 (2.8)                                | 5 (13.9)                         |
specific treatment, and resolve within a few days. These data should be further validated in additional prospective, large-scale studies.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest. The authors do not have any specific agreements with the vaccine manufacturer for data delivery or similar.

AUTHOR CONTRIBUTIONS
Itay Lotan: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (lead); Writing – original draft (lead); Writing – review and editing (equal). Adi Wilf-Yarkoni: Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Writing – original draft (equal); Writing – review and editing (equal). Yitzhak Friedman: Resources (equal); Writing – original draft; Writing – review and editing (equal). Hadas Stiebel-Kalish: Conceptualization (equal); Investigation (equal); Methodology (equal); Resources (equal); Writing – original draft (equal); Writing – review and editing (equal). Israel Steiner: Conceptualization; Methodology (equal); Writing – original draft (equal); Writing – review and editing (equal). Mark Andrew Hellmann: Conceptualization (equal); Methodology (equal); Project administration (equal); Resources (equal); Writing – original draft (equal); Writing – review and editing (equal).

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

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