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Original Article / Özgün Araştırma

Evaluation of Demographic, Clinical Characteristics and Side Effects in Multiple Sclerosis Patients Vaccinated Against SARS-CoV-2 Virus

SARS-CoV-2 Virüsüne Karşı Aşılanan Multipl Skleroz Hastalarında Demografik ve Klinik Özelliklerin İncelenmesi ve Yan Etkilerin Değerlendirilmesi

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Abstract

Objective: Our primary objective in our study was to review the side effect of MS patients vaccinated against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus from Istanbul University, Istanbul Faculty of Medicine, Multiple Sclerosis and Myelin Diseases Outpatient Clinic. The secondary objective of our research was to evaluate the demographic, clinical characteristics and disease-modifying therapies of patients who have been infected with coronavirus disease-2019 (COVID-19) and who have been vaccinated against the SARS-CoV-2 virus.

Materials and Methods: A questionnaire was sent via text message or e-mail to patients who were followed up at the Multiple Sclerosis and Myelin Diseases Outpatient Clinic of the Department of Neurology of the Istanbul University, Istanbul Faculty of Medicine. The eligibility criteria were not being in the period of an attack and being volunteered to participate in the study. A questionnaire consisting of a total of 21 questions was answered by the patients and the results of 160 patients were evaluated statistically.

Results: One hundred and seven of the 160 patients were women (67%), and 53 (33%) men. The mean age of the patients was 38 ± 10.9 years. As a majority of the patients, 128 of the patients (80%) were followed up with a diagnosis of relapsing remmitting multiple sclerosis (MS). The rate of COVID-19 infection among the patients was 17% (n = 27). 67.5% (n = 108) of the patients preferred the inactive SARS-CoV-2 vaccine, while 31.8% (n = 51) preferred the BNT162B2 (mRNA) vaccine. Pain at the site of vaccination (20%), fatigue (14%), myalgia (18%), headache (5%) and fever (4%) were side effects. When the side effects after the first dose were compared, the frequency of the side effects of mRNA vaccine was found to be significantly higher (71%) ($P < 0.0001$). Two (1.3%) of the patients after the first dose and 5 (3.8%) after the second dose had an MS attack.

Conclusion: Inactive and mRNA vaccines showed similar side effects with the normal population in patients with MS, and there was no significant difference in the frequency of attacks between vaccines.

Keywords: Multiple sclerosis, SARS-CoV-2, vaccination, side effects

Öz

Amaç: Araştırmamızdaki birincil amacımız, İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Multipl Skleroz ve Miyelin Hastalıkları Polikliniği'nden takipli şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) virüsüne karşı aşılanan multipl skleroz (MS) hastalarında yan etki profilini gözden geçirmektir. Araştırmamızın ikincil amaçları koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu geçiren ve SARS-CoV-2 virüsüne karşı aşılanan hastaların demografik, klinik özelliklerini ve hastalık modifiye edici tedavileri değerlendirmektir.

Gereç ve Yöntem: İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Nöroloji Anabilim Dalı Multipl Skleroz ve Miyelin Hastalıkları Polikliniği'nde takip edilen, 18 yaşını tamamlamış, atak döneminde olmayan ve çalışmaya katılmak için gönüllü olan hastalara kısa mesaj ya da e-posta aracılığıyla anket formu iletildi. Toplam 21 sorudan oluşan anket formu hastalar tarafından cevaplandı ve 160 hastanın sonuçları istatistik açıdan değerlendirildi.

Bulgular: Çalışmamıza katılan MS tanısı ile takipli 160 hastanın 107'si kadın (%67), 53'ü (%33) erkekti. Hastaların ortalama yaşı 38 ± 10,9 idi. Hastaların çoğunluğu olarak 128 hasta (%80) ataklı yineleyici MS tanısı ile takip edildi. Ankete katılan hastaların COVID-19 enfeksiyonu geçirme oranı %17 (n = 27) idi. Hastaların %67,5'si (n = 108) inaktif SARS-CoV-2 aşısını tercih etmekle birlikte, %31,8'i (n = 51) BNT162b2 (mRNA) aşısı tercih etti. Yan etkilerden sırasıyla, aşı bölgesinde ağrı (%20), yorgunluk (%14), kas ağrısı (%18), baş ağrısı (%5) ve ateş (%4) izlendi. Birinci doz sonrası yan etki sıklıkları karşılaştırıldığında, mRNA aşısı olan hastaların yan etki sıklığı (%71), inaktif aşı uygulanan hastaların yan etki sıklığına göre (%40) anlamlı derecede yüksek bulundu ($P < 0,0001$). İlk doz sonrası hastaların 2'si (%1,3) ve ikinci doz sonrası 5'i (%3,8) MS atağı geçirdi. Aşı türleri arasında MS atağı geçirme açısından anlamlı fark bulunmadı.

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Sonuç: MS hastalarında inaktif ve mRNA aşıları normal popülasyonla benzer yan etkiler göstermiştir ve aşılar arasında atak geçirme sıklığında anlamlı fark bulunmamıştır.

Anahtar Kelimeler: Multipl skleroz, SARS-CoV-2, aşı, yan etkiler

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is an enveloped single-stranded RNA virus that can infect the cells in various human organs, including the lung epithelium, gastrointestinal tract, heart, kidneys, and central nervous system (CNS) (1). The SARS-CoV-2, which was first detected in China in December 2019 and then spread across the world, caused an ongoing pandemic (1,2). Patients with chronic diseases and those receiving immunotherapy have been identified by the Centers for Disease Control and Prevention as possible high-risk groups for coronavirus disease-2019 (COVID-19) infection (1,3). Further, SARS-CoV-2 caused a devastating pandemic with high morbidity and mortality rates (4). Additionally, COVID-19, one of the deadliest pandemics in history, has caused problems for patients with multiple sclerosis (MS).

MS is an autoimmune, chronic, inflammatory, demyelinating, and neurodegenerative disease of the CNS (5). It is known that MS attacks that are triggered by infections may lead to more prolonged and severe clinical worsening than spontaneous attacks. However, there is concern that immunomodulatory and immunosuppressant treatments that are used to change the course of the disease in MS may increase the risk of COVID-19 infection. Despite reasonable concerns, discontinuation of immunomodulatory treatments is generally not recommended in the literature and guidelines (6,7).

The only way to protect against COVID-19 infection, which does not have a cure, is vaccination. It is not known how immunization against SARS-CoV-2 affects patients with MS or whether the vaccine can trigger the immunological response that can activate the disease. Although the triggering of autoimmune reactions by vaccination is thought to vary according to the type of vaccine and individual genetic susceptibility, it is not fully understood (8). It has been reported that the administration of vaccines, such as vaccines against pneumococcus and influenza in MS, as in other chronic diseases, reduces the risk of mortality and morbidity (9). While live vaccines can moderately increase the risk of MS attacks, inactivated vaccines, such as the influenza vaccine, are known to be safe (10). A guideline on SARS-CoV-2 vaccines has recently been published by the American National Multiple Sclerosis Society (NMSS), which promotes vaccination in patients with MS and emphasizes safety (11). Recommendations for the use of disease-modifying therapies (DMT) and the timing of vaccines are also included in this guide to maximize vaccine efficacy (11). Studies showing that adequate immune responses to inactivated and protein-based vaccines occur in patients with MS using various DMTs found that protein-based and inactivated SARS-CoV-2 vaccines were effective in patients with MS (12). In this article, both the side effects of patients with MS vaccinated against SARS-CoV-2 and those with COVID-19 infection among these patients will be evaluated along with their clinical findings.

Materials and Methods

This study was designed as a cross-sectional descriptive study. A questionnaire form was sent via text message or e-mail to the patients who met the diagnosis criteria for MS, were followed up in the Multiple Sclerosis and Demyelinating Diseases Outpatient Clinic of Istanbul University, Istanbul Medical Faculty and Department of Neurology, were over 18 years of age, were not in the MS attack period, and who had volunteered to participate in the study. The questionnaire consisting of 21 questions was answered by 160 patients.

The study's compliance with the ethical principles was evaluated by the academic committee of the Department of Neurology of Istanbul University, Istanbul Faculty of Medicine and the Ethics Committee of the institution, and their approval was obtained (no: 24.12.2021/23). The patients included in the study answered the questions in the questionnaire after they read the consent form explanation at the beginning of the questionnaire.

In order to collect data, a questionnaire consisting of 21 questions regarding the patients' socio-demographic characteristics, clinical characteristics, and the characteristics of the SARS-CoV-2 vaccine that was administered was given to the patients. The data were collected between December 2021 and March 2022.

Statistical Analysis

The SPSS version 25.0 program was used for the statistical analysis of the findings obtained in the study. The normality distribution of the data used in the comparisons was evaluated using the Kolmogorov–Smirnov test. The mean ± standard deviation values and frequencies were calculated for normally distributed data. The chi-square test was used to compare the categorical data.

Results

Of the 160 patients with MS who participated in the study and followed up, 107 (67%) were female and 53 (33%) were male. The mean age of the patients was 38.0 ± 10.9 years. According to the course of the disease, 128 patients (80%) had relapsing MS (RRMS), eight patients (5%) had secondary progressive MS, eight patients (5%) had primary progressive MS, 10 patients (6.3%) had single-attack MS, and six patients (3.8%) had clinical isolated syndrome. Regarding DMT, 73 (45.6%) were receiving fingolimod, 31 (19%) ocrelizumab, 23 (14.4%) teriflunomide, seven (4.4%) IFN beta-1a, six (3.8%) natalizumab, and three (1.9%) alemtuzumab. There were 15 (9%) patients who did not receive DMT. Thirty-one (19.3%) patients were receiving first-line treatment, and 111 (69.3%) were receiving second-line treatment. The demographic and clinical characteristics of the patients who participated in the survey study are summarized in Table 1.

The rate of COVID-19 infection of the patients who participated in the survey was 17% (n = 27) (Table 1). Of the patients, 66.7% (n = 18) were female, and one patient was over 55 years of age. Further, three patients (11%) used cortisone in the last month before the disease. Of the patients, 89% (n = 24) were not hospitalized, and three patients (11%) were hospitalized. Two of the hospitalized patients were receiving fingolimod and teriflunomide, and one patient was being followed up without

treatment. No patient was followed in the intensive care unit. Patients had a COVID-19 infection before they were vaccinated.

Although 67.5% (n = 108) of the patients who participated in the study preferred an inactivated SARS-CoV-2 vaccine, 31.8% preferred (n = 51) an mRNA vaccine, and 0.7% (n = 1) preferred a viral vector (adeno-associated virus) vaccine. Anaphylaxis was not observed in any of the patients after the first or second dose. There was no hospitalization due to SARS-CoV-2 vaccine side effects. When the side-effect profiles were examined, after the first dose in patients who were given the inactivated SARS-CoV-2 vaccine, fatigue (20%), pain at the vaccination site (13%), myalgia (7.4%), headache (3.7%), fever (2.8%), and nausea/vomiting (0.9%) were observed (Figure 1). After the second dose, fatigue (17.6%), pain at the injection site (10.2%), myalgia (10.2%), and headache (11.1%) were observed (Figure 2).

Table 1. Clinical and demographic findings of patients with multiple sclerosis vaccinated against SARS-CoV-2

	Number	%
Total	160	
Gender (F/M)		
Female	107	67
Male	53	33
Age (mean ± SD)	38 (± 10.9)	
Disease course		
Single-attack MS	10	6.3
CIS	6	3.8
RRMS	128	80
PPMS	8	5
SPMS	8	5
Disease-modifying therapies		
IFN beta-1a	7	4.4
Teriflunomide	23	14.4
Dimethyl fumarate	1	0.6
Fingolimod	73	45.6
Ocrelizumab	31	19.4
Natalizumab	6	3.8
Cladribine	1	0.6
Without medication	15	9.4
COVID-19 infection		
Yes	27	17
No	133	83
Vaccination		
Inactive (Sinovac)	108	67.5
mRNA (BioNTech)	51	31.8
AAV-vector (AstraZeneca)	1	0.7

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, F: Female, M: Male, SD: Standard deviation, MS: Multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis, PPMS: Primary progressive multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, AAV-vector: Adeno-associated virus vector, CIS: Clinical isolated syndrome

After the first dose of the mRNA SARS-CoV-2 vaccine, pain at the vaccination site (35.3%), myalgia (19.6%), fatigue (11.8%), headache (7.8%), and fever (%) 5.9) were observed (Figure 1). Side effects were observed at a higher rate after the second dose. Muscle pain (35.3%), pain at the injection site (33.3%), fatigue (33.3%), headache (25.5%), fever (21.6%), and nausea/vomiting (2%) were also observed (Figure 2).

For the patients receiving second-line treatment, pain at the injection site (19.8%), fatigue (14.7%), myalgia (10.3%), headache (5.2%), fever (1.7%), and rash (0.9%) were observed. No COVID-19 infection was observed after vaccination. There was no statistically significant difference between the frequency of the side effects of the patients who received first- and second-line treatments ($P > 0.05$).

The presence of neurological symptoms lasting longer than 24 hours was accepted as an MS attack. After the first dose of the vaccine, two patients, one (0.9%) of whom received the inactive vaccine and one (0.9%) of whom received the mRNA vaccine,

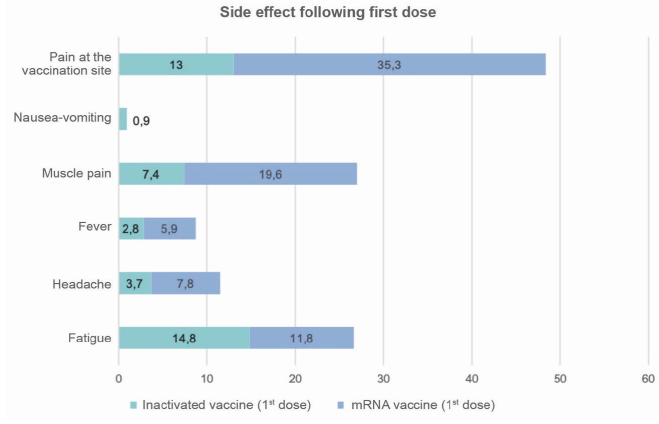

Figure 1. Side effects after the first dose of the vaccination in patients with MS receiving the SARS-CoV-2 vaccine

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, MS: Multiple sclerosis

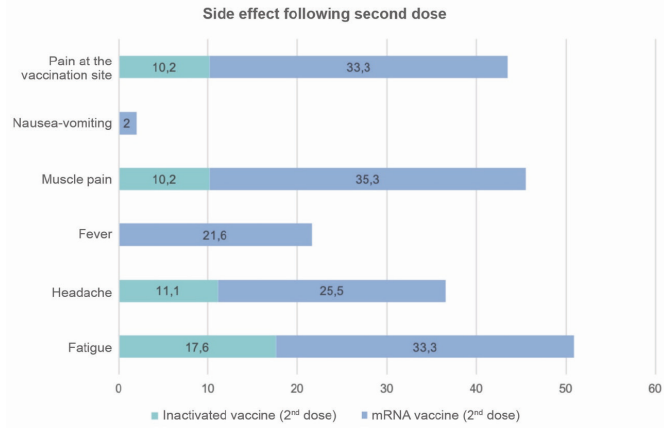

Figure 2. Side effects after the second dose of the vaccination in patients with MS receiving the SARS-CoV-2 vaccine

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, MS: Multiple sclerosis

developed an MS attack. Five patients (3.1%) had an MS attack after the second dose. Although three (2.8%) of the patients had an attack following the inactivated vaccine and two (3.9%) following the mRNA vaccine, no significant difference was found between the vaccine types ($P > 0.8$).

At least one side effect developed in 50% of patients after the first dose of the SARS-CoV-2 vaccine and in 47% of patients after the second dose. When the frequency of the side effects was compared after the first dose, it was found to be significantly higher effects in patients who had the mRNA vaccine (71%) than in the patients who received the inactivated vaccine (40%) ($P < 0.0001$). It was also found to be significantly higher in patients who had the mRNA vaccine after the second dose (73%) ($P < 0.0001$).

Discussion

Despite concerns about vaccines and diseases that affect the immune system, the American Academy of Neurology 2019 guidelines emphasized that there is no clear evidence that vaccination increases the risk of MS activity (13). While the safety of inactivated and protein-based vaccines in patients with MS can be deduced from studies on non-SARS-CoV-2 vaccines with similar properties, the novelties of mRNA, DNA, and viral vector vaccines against SARS-CoV-2 make it difficult to predict their safety in MS. However, inactivated and mRNA SARS-CoV-2 vaccines have been administered to many patients with MS in Türkiye and around the world. Based on safety data from clinical studies, no serious MS-related problems have been reported with inactivated or mRNA vaccines, except for rare cases of facial palsy (14,15).

In this study, the side-effect profiles and their frequencies in the SARS-CoV-2 vaccines were evaluated. The findings showed that patients with MS had a similar side-effect profile and frequency with the side effects reported in the general population after inactive and mRNA vaccination against SARS-CoV-2 (15). Kelly et al. (13) emphasized that inactivated SARS-CoV-2 vaccines were probably safe and effective in patients with MS. Anaphylaxis was not observed after the first or second dose among the patients in this study who received an inactivated or mRNA SARS-CoV-2 vaccine, and no adverse events required hospitalization.

In this study, at least one side effect developed in 50% of the patients after the first dose of SARS-CoV-2 vaccine and in 47% of the patients after the second dose.

The most frequently reported side effects following the mRNA SARS-CoV-2 vaccination in the general population were pain at the injection site (83%), fatigue (59%), and headache (52%), all of which occurred following the second dose of the vaccine and mostly in young people (15). Achiron et al. (15) reported that the frequencies of patients with any side effects following mRNA vaccination in patients with MS were 29.7% after the first dose and 40.2% after the second dose. In this study, following the first dose of the mRNA SARS-CoV-2 vaccine in patients with MS, pain at the injection site (35.3%) and myalgia (19.6%) were the most frequently observed, whereas following the second dose, muscle pain (35.3%) and pain at the injection site (33.3%) were the most common. Although side effects were observed at a higher rate following the second dose, they were lower than in the general population and in patients with MS reported in the literature.

In the phase-3 safety and efficacy data of inactivated SARS-CoV-2 vaccine in Türkiye, fatigue (8.2%) and pain at the injection site (2.4%) were the most common side effects (16,17). The most common side effects were fatigue (20%) and pain at injection site (13%) following the first dose in patients who received the inactivated SARS-CoV-2 vaccine and participated in the survey. Following the second dose, fatigue (17.6%) and pain at the injection site (10.2%) were the most common side effects.

In the literature, demyelinating events in inactivated and mRNA SARS-CoV-2 vaccines are rare and have been reported mainly with viral vector vaccines (17). Live attenuated vaccines should be avoided as much as possible in patients with MS who are receiving immunomodulatory or immunosuppressive therapy. Weakened but partially protective vaccine responses developed in patients with MS receiving sphingosine-1-phosphate modulators and B-cell therapies (12). Other DMTs are not expected to significantly affect the efficacy of SARS-CoV-2 vaccines (12).

In this study, two (1.3%) of the patients had an MS attack following the first dose of vaccination, and five (3.1%) of the patients had an MS attack following the second dose within a month after the vaccination. There was no significant difference between the vaccine types among the patients who had an attack. In the study by Achiron et al. (15), in which they reported the safety and side effects after an mRNA vaccination, eight patients (2.1% of 388 vaccinated patients with RRMS) developed an MS attack within 10–19 days following the first dose of the vaccine, and five patients (1.6% of 306 vaccinated patients with RRMS) developed an MS attack within 14–21 days following the second dose of vaccine. An MS attack was observed in 306 patients (14).

Coyle et al. (18) reviewed the vaccine recommendations for patients with MS and emphasized that patients should be vaccinated, especially with the recommendations of the American Multiple Sclerosis Society, and that the vaccine was unlikely to trigger an MS attack or worsen chronic symptoms. Even if side effects temporarily exacerbate MS symptoms, it is recommended to still administer both doses of the vaccine (18).

While patients with MS were assumed to be at higher risk for COVID-19 infection due to the use of immunosuppressive or immunomodulatory agents, a meta-analysis of 12 studies showed that the prevalence in patients with MS was 4%, which is not a high rate (19). The hospitalization rate was reported to be 10%, and the mortality rate was 4% (19). In another study, the rate of hospitalization in patients with MS with a COVID-19 infection was reported to be 17% (20). Although most patients with RRMS were outpatients, the hospitalization rate was found to be higher in patients with progressive MS (20). Those who received B-cell therapies as DMT were associated with higher disease severity (20). In this study, the rate of hospitalization was 11%, which is similar to the literature. There was no significant difference between the hospitalization rate and DMTs used by the patients. A recent retrospective study found no difference in the use of DMT between patients with MS with a mild COVID-19 infection and patients with a severe COVID-19 infection (21).

Study Limitations

One of the limitations of this study was that only patients with a certain level of education who could use the internet or telephone could participate in the survey. Another limitation was that since the hospital was a reference center, the patient population mainly

consisted of patients using second-line treatments. This was also one of the positive aspects of the study, which provided an opportunity to answer questions about the side-effect profiles of patients using second-line therapy.

Conclusion

Data on the safety of SARS-CoV-2 vaccines in patients with MS are limited. This study found that the frequency of attacks did not differ between vaccines in patients with MS and that their side-effect profiles were safe. More studies are needed to investigate the effect of DMTs on vaccines.

Ethics

Ethics Committee Approval: The study's compliance with the ethical principles was evaluated by the academic committee of the Department of Neurology of Istanbul University, Istanbul Faculty of Medicine and the Ethics Committee of the institution, and their approval was obtained (no: 24.12.2021/23).

Informed Consent: The patients included in the study answered the questions in the questionnaire after they read the consent form explanation at the beginning of the questionnaire.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.E., Ö.K., G.Y.Y., Design: M.E., Ö.K., G.Y.Y., Data Collection or Processing: Ö.K., G.Y.Y., T.G., M.K., M.E., Analysis or Interpretation: Ö.K., G.Y.Y., T.G., M.K., M.E., Literature Search: Ö.K., G.Y.Y., Writing: Ö.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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