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Short communication

Adverse events reported by Iranian patients with multiple sclerosis after the first dose of Sinopharm BBIBP-CorV

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ABSTRACT

MS patients were one of the first populations vaccinated in Iran. To date, the most used vaccine brand on Iranian MS patients is Sinopharm COVID-19 vaccine. Here is the first study on the adverse events after the first dose of Sinopharm vaccine on 583 Iranian MS patients. A Google form link was sent to MS patients through social networks, between May 1, 2021 and May 22, 2021. No serious adverse event was reported. At least one complaint (mostly transient) was reported by 350 (60%) of vaccine recipients. Constitutional symptoms (malaise, fatigue, fever, shivering, & generalized body pain) (51%) and headache (9%) were the most reported complaints. We found a relation between gender and prior infection with COVID-19 and reported symptoms (p value less than 0.05). Only five recipients (0.9%) reported MS relapse after vaccination. MS worsening was a minor incident related to fever.

1. Introduction

Evidence suggests that Multiple Sclerosis (MS) prevalence has been rising in Iran in the recent years [1]. Immune system modulation or suppression is the key approach in MS treatment modalities. However, this could predispose the patients to an increased risk of infection [2]. This is the reason that experts in this field have been trying to develop adapted diagnostic, therapeutic, and follow-up protocols through the pandemic [3]. As the vaccines brought rays of hope to end this dark era, MS patients were one of the first populations vaccinated in Iran. To date, the most used vaccine brand on Iranian MS patients is Sinopharm COVID-19 vaccine. As world health organization (WHO) reported: "Sinopharm BBIBP-CorV, is a 2-dose β-propiolactone-inactivated, aluminium hydroxide-adjuvanted vaccine administered on a 0/21–28-day schedule". It was authorized by the National Medical Products Administration of China on December 31, 2020, and by about 45 countries/jurisdictions to be used for adults ≥ 18 years [4]. It seems a safe choice for patients with MS, regarding safety of previous inactivated vaccines on MS patients and also the lack of severe adverse effects of the Sinopharm vaccine in the primary trial phases [5,6]. To our knowledge, there is only one report of vaccination results of MS patients [7], with none on Sinopharm. Here is the first study on the adverse events after the first dose of Sinopharm vaccine on 583 Iranian MS patients.

Methods:

A pilot questionnaire was designed. Following initial revision by two MS patients, the questionnaire was checked by three MS experts. The final Google form link was sent to MS patients through social networks (mainly Telegram®), between May 1, 2021 and May 22, 2021. Each participant was previously registered in the National MS Registry by a unique code. To ensure both the patients' privacy and validity of the data, the responders were asked to enter their code (Supplementary 1). Data on the expanded disability status scale (EDSS), MS type, COVID-19 diagnosis, and the attack were checked by the principal investigator. No other individual access was possible. COVID-19 diagnosis was confirmed by an internist based on either clinical criteria or PCR test results. To differentiate between transient worsening of MS symptoms and a true relapse, full neurologic investigations (history taking, physical exam, imaging) were performed by an MS fellowship.

As the main vaccine for this population was Sinopharm, those patients who got other vaccine types (most of whom were medical staffs) were excluded. The excluded cases have received one of Sputnik V, AstraZeneca, or Bharat Biotech COVAXIN.

1.1. Statistical analysis:

Descriptive statistics was used to evaluate the mean and its standard deviation (SD), or frequency of different basic demographic characteristics of the patients (gender, age (older or

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Table 1
Basic characteristics of MS patients who received Sinopharm vaccine.

Variable	Number (%)
Gender	
Female	449 (78)
Male	130 (22)
Mean age (SD)	36.2 (8.2)
Age ≤ 50 (n, %)	539 (92)
Age > 50 (n, %)	44 (8)
Employment status	
Employed	256 (44)
Unemployed	324 (56)
Mean BMI (SD)	24.6 (4.8)
BMI ≤ 25 (n, %)	347 (59)
BMI > 25 (n, %)	236 (41)
Education	
Illiterate	0
Without academic degree	149 (26)
With academic degree	427 (74)
MS type	
RR	442 (76)
SP	112 (19)
PP	20 (3)
Mean EDSS (SD)	3.0 (1.6)
EDSS ≤ 3 (n, %)	344 (59)
EDSS > 3 (n, %)	239 (41)
MS treatment	
IFN beta-1	137 (23)
GA	36 (6)
Teriflunemide	10 (1.7)
DMF	71 (12)
Fingolimod	86 (15)
Rituximab	185 (32)
Ocrelizumab	4 (1)
Mitoxantron	1 (0.2)
Cyclophosphamide	1 (0.2)
Azathioprine	5 (1)
Prior COVID-19 infection	
Positive	134 (23)
Negative	440 (76)

As may be noted, missing data are not presented in the table, so the total count of each category may be less than 583.

younger than 50), employment status, body mass index (BMI) (those with BMI more or less than 25), education level (illiterate, without or with academic degree)). Same approach was used to study prior COVID-19 infection, MS types (relapsing-remitting (RR) versus progressive), EDSS (those with EDSS higher or lower than 3), MS treatment (receiving anti CD20s like rituximab or ocrelizumab versus other drugs), and also different reported side effects. Side effects were grouped into constitutional (malaise, fatigue, fever, shivering, & generalized body pain), headache, injection site reactions, gastrointestinal (GI) (nausea, vomiting, abdominal pain, diarrhea), and respiratory (coughs, dyspnea). Regarding BMI, patients were asked to enter their weight and height, and the final calculation was made by the software. Binary logistic regression methods were adopted to assess the associations between adverse events and basic patients' characteristics. IBM® SPSS® version 26 was employed for analyses.

Table 2
Frequency of different adverse events after the first dose of Sinopharm vaccine.

Variable	Number (%)
At least one constitutional complaint	299 (51)
Fever	99 (17)
Fatigue	146 (25)
Malaise	146 (25)
Generalized body pain	106 (18)
Shivering	13 (2)
At least one gastrointestinal complaint	33 (6)
Nausea	23 (4)
Diarrhea	18 (3)
Abdominal pain	1 (0.2)
At least one respiratory complaint	24 (4)
Cough	16 (3)
Dyspnea	10 (2)
Headache	55 (9)
Injection site reaction	43 (7)

The study protocol was approved at the ethics committee of Tehran University of medical sciences by IRB code of "IR.TUMS.NI.REC.1400.012".

2. Result

Out of 1217 MS patients vaccinated till May 22, 2021, 583 cases who received Sinopharm vaccine filled in the questionnaire. Basic characteristics of the patients are summarized in Table 1. Among the participants, 449 (78%) were female and 324 (56%) were unemployed. Mean age was 36.3 (SD: 8.2) with only 44 (8%) of cases older than 50. All the participants were literate, 149 (26%) of whom did not have any academic degree. BMI was>25 in 236 (41%) cases.

Progressive forms of MS were previously diagnosed in 132 (22%) cases, while 239 (41%) had EDSS scores higher than 3. Moreover, 189 (32%) of participants were on anti CD20s.

Of 134 patients (23%) with history of prior COVID-19 infection, 15 (11%) had been admitted due to the disease.

At least one complaint was reported by 350 (60%) of vaccine recipients. Constitutional complaints were reported by 299 (51%) cases. Headache was the next most-reported symptom (n = 55, 9%). Injection site reactions were seen in 43 (7%) cases. Thirty-three (6%) complained of GI discomfort. Respiratory symptoms were observed in 25 (4%) cases (Table 2). The duration of the symptoms was between some hours to 15 days with mean of 2 (SD:2) days.

Two (0.3%) patients complained of worsened MS symptoms; both were due to post-vaccination fever and improved by fever resolution. Five patients (0.9%) reported MS attacks. All happened within two weeks from the vaccination. Different management strategies were employed based on the attack severity (Table 3).

Constitutional symptoms were significantly more reported by female patients (OR:1.87, 95% CI: 1.24–2.80) (p value: 0.003) and those with prior history of COVID-19 infection (OR:1.49, 95% CI: 1.01–2.21) (p value: 0.05). GI complaints were more common among those with prior infection with COVID-19 (OR:2.26, 95% CI: 1.09 – 4.67) (p value: 0.03) (Table 4). No other association was seen between reported adverse events and basic characteristics (both demographic or MS related ones) (p value > 0.05).

Table 3
Clinical characteristics of the patients with MS relapse after vaccination with Sinopharm COVID-19 vaccine.

Case Number	Age (years old)	Gender	MS duration (years)	MS type	DMD	EDSS	Prior history of COVID-19	Symptoms of the attack	Symptoms duration (days)	Management of the attack
1	50	Female	18	RRMS	Fingolimod	6	Negative	Ataxia	6	Dexamethasone IM 8 mg daily for 3 days
2	41	Female	10	PPMS	Ocrelizumab	6	Positive	Severe ataxia	7	IVMP 1 g daily for 5 days
3	43	Female	21	SPMS	Fingolimod	5	Negative	Paresis of left lower extremity	2	No intervention
4	46	Male	4	RRMS	IFN-beta 1a	1.5	Negative	Paraparesis and urinary incontinency	8	IVMP 1 g daily for 5 days
5	48	Female	15	RRMS	Rituximab	4	Negative	Paresthesia and paresis of right lower extremity	9	IVMP 1 g daily for 5 days

DMD: disease-modifying drug, RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis,

Table 4
Multiple regression outputs for significant associations between adverse effects after the first dose of Sinopharm vaccine and basic patient characteristics.

		B	OR (95% CI)
Constitutional symptoms	Gender (Female)	0.63	1.87 (1.24–2.80)
	Prior history of COVID-19 infection	0.40	1.49 (1.01–2.21)
Gastointestinal symptoms	Prior history of COVID-19 infection	0.80	2.26 (1.09 – 4.67)

B: beta coefficient, OR: odds ratio, CI: confidence interval.

3. Discussion

As far as the authors of the present study are concerned, this is the first study of reported adverse events after the first dose of Sinopharm COVID-19 vaccine on MS population. No serious adverse event was found. The prevalence of at least one adverse reaction was found to be more in our study (60%) compared to the phase two trial of the vaccine (29%) [6]. It is also more than adverse events reported after COVID-19 BNT162b2 vaccine (30% after the first dose) [7]. A recent study in United Arab Emirates (UAE) also showed higher prevalence of at least one post-vaccination symptom [8]. Similar to the results of previous studies [68], side effects were mostly transient in our cases.

The most notable symptoms were of constitutional type, followed by injection site reactions, which is in line with the previous studies [6–8]. In the phase two trial of the vaccine, fever was the most common post inoculation systemic adverse event of the Sinopharm vaccine [6]. Fatigue and malaise were more common among our population. This may be explained by high prevalence of fatigue among MS patients as general [9] and particularly among Iranian MS patients [10]. Saeed et al. also reported fatigue as a more reported symptom after vaccination in UAE participants [8]. However, no such distribution was reported after COVID-19 BNT162b2 vaccine [7]. They found a minor association between adverse events and young age, lower EDSS, and immunomodulatory drugs [7]. We found a relation between gender and prior infection with COVID-19 and reported symptoms. The latter association may be explained by enhanced immune response after the second exposure to the viral antigens [11]. Regarding gender differences, other observational evidences also suggests higher prevalence of symptoms like lethargy, fatigue, and back pain in female participants [8,12]. Previous studies indicate a greater response to the viral vaccine, followed by more reported adverse events due to the greater inflammatory reaction, in female patients [13,14]. Hormonal and environmental factors are considered as underlying factors [15].

No hypothesis could be addressed to the observed relationship between the post-vaccination GI symptoms and previous COVID-19 infection, so further investigation is encouraged.

Only five recipients (0.9%) reported MS relapse after vaccination. This is close to the acute relapse risk reported in relation to COVID-19 BNT162b2 vaccine (2.1% after the first and 1.6% after the second dose) [7]. MS worsening was a minor incident related to fever, similar to what was found in relation to COVID-19 BNT162b2 vaccine [7].

As confirmed MS diagnosis was a necessity in this step of national vaccination protocol, those with clinically isolated syndrome (CIS) or radiologically isolated syndrome (RIS) were not included in our surveillance.

This primary report involved a limited number of patients in a short duration of follow-up. Further studies with more patients and with longer follow up periods are encouraged.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.09.030.

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