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Original article

SEROLOGICAL RESPONSE TO SARS-COV-2 VACCINES IN PATIENTS WITH MULTIPLE SCLEROSIS IN ARGENTINA

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Abstract

Introduction: The objective was to assess the immunogenicity and effectiveness of vaccines against SARSCoV-2 in multiple sclerosis (MS) patients included in the Argentinean MS registry.

Methods: A prospective cohort study between May and December 2021. The primary outcome was immunogenicity and effectiveness of vaccines during a three-month follow-up. Immunogenicity was evaluated based on detection of total antibodies (Ab) against spike protein and neutralizing Ab in serum 4 weeks after the second vaccine dose. A positive COVID-19 case was defined according to Argentinean Ministry of Health.

Results: 94 patients were included, mean age: 41.7 ± 12.1 years. Eighty (85.1%) had relapsing remitting multiple sclerosis (RRMS); 30 (31.9%) were under fingolimod treatment. The Sputnik V vaccine was the first dose in 33 (35.1%), and AstraZeneca in 61 (64.9%). In 60 (63.8%), the vaccine elicited a specific humoral response. Immunological response according to the vaccination schemes showed no qualitative differences ($p = 0.45$). Stratified analysis according to the MS treatment showed that a significantly smaller number of subjects developed antibodies against spike antigen among those that were on ocrelizumab compared to other groups ($p \leq 0.001$), while a reduced number of patients under ocrelizumab where evaluated ($n = 7$). This was also observed for neutralizing antibodies in the ocrelizumab group ($p < 0.001$). During the three-month follow-up, two individuals were diagnosed with COVID-19.

Conclusion: We found that MS patients that received Sputnik V or AstraZeneca vaccines for SARS-CoV-2 developed a serological response with no differences between the vaccines used.

Key words: multiple sclerosis, COVID-19, vaccines, DMTs, Argentina, serological response

Resumen

Respuesta serológica a vacunas contra SARS-CoV-2 en pacientes con esclerosis múltiple en Argentina

Introducción: El objetivo fue evaluar la inmunogenicidad y efectividad de las vacunas contra el SARS-CoV-2 en pacientes con esclerosis múltiple (EM) incluidos en el registro argentino de EM (RelevarEM, NCT 03375177).

Métodos: Estudio de cohorte prospectivo entre mayo y diciembre 2021. Se evaluó la inmunogenicidad (detección de anticuerpos totales (Ab) contra proteína espiga y anticuerpos neutralizantes en suero) y eficacia (nueva infección por COVID-19) durante seguimiento de tres meses. El momento de detección de anticuerpos fue 4 semanas después de segunda dosis de vacuna. Un caso positivo de COVID-19 se definió de acuerdo con la definición del Ministerio de Salud.

Resultados: Se incluyeron 94 pacientes, edad media de 41.7 ± 12.1 años. Ochenta (85.1%) tenían EM remitente-recurrente; 30 (31.9%) en tratamiento con fingolimod. La vacuna Sputnik V fue usada en 33 (35.1%), mientras que AstraZeneca se administró en 61 (64.9%). En 60 pacientes (63.8 %), la vacuna provocó respuesta humoral específica. La respuesta inmunológica según esquemas de vacunación (Sputnik V, Astra Zeneca o esquemas heterólogos) no mostró diferencias cualitativas ($p = 0.45$). El análisis estratificado según tratamiento recibido para la EM mostró que número significativamente menor de sujetos desarrolló anticuerpos contra el antígeno espiga en los pacientes que recibieron ocrelizumab ($p \leq 0.001$), aunque con un número reducido de pacientes evaluados bajo este tratamiento ($n = 7$). Esto también se observó para anticuerpos neutralizantes en el grupo bajo ocrelizumab ($p < 0.001$). Durante el seguimiento de tres meses, dos personas fueron diagnosticadas con COVID-19.

Conclusión: Encontramos que los pacientes con EM que recibieron vacunas Sputnik V o AstraZeneca para el SARS-CoV-2 desarrollaron respuesta serológica sin diferencias entre las vacunas utilizadas.

Palabras clave: esclerosis múltiple, COVID-19, vacunas, DMTs, Argentina, respuesta serológica

KEY POINTS
Current knowledge

- In multiple sclerosis, most approved vaccines induce robust humoral and cellular immune responses against the SARS-CoV-2.
- However, it is still unknown whether all anti-SARS-CoV-2 vaccines commonly used in Latin America (Sputnik V or AstraZeneca for example) could elicit serological response in multiple sclerosis patients treated with disease-modifying therapies

Contribution of the article to current knowledge

- We provide evidence that multiple sclerosis patients receiving disease modifying treatment that received Sputnik V or AstraZeneca vaccines for SARS-CoV-2 developed a serological response with no differences between the vaccines used.
- Our study contributes to understanding the immunological response to COVID-19 vaccines in multiple sclerosis patients receiving disease modifying drugs where the drug response could be affected.

Different vaccines have been evaluated and used to achieve immunization against COVID-19 in the world[1-4].

In multiple sclerosis (MS), most approved vaccines induce robust humoral and cellular immune responses against the SARS-CoV-2 virus spike protein[1, 5-7]. However, it is still unknown whether all anti-SARS-CoV-2 vaccines commonly used in Latin America like Sputnik V (Gam-COVID-Vac-rAd26/rAd5) and AstraZeneca (AZD1222/ChAdOx1) could elicit serological response in MS patients treated with disease-modifying therapies[3].

RelevarEM is a nationwide, multicenter registry of patients with MS in Argentina[8, 9]. It collects data from daily clinical practice in this population. This approved registry monitors the functional health status of almost 4000 patients in the country[8,9].

The objective of our study was to assess the immunogenicity, effectiveness, and safety

against SARS-CoV-2 vaccines in a subset of MS patients included in RelevarEM.

Materials and methods

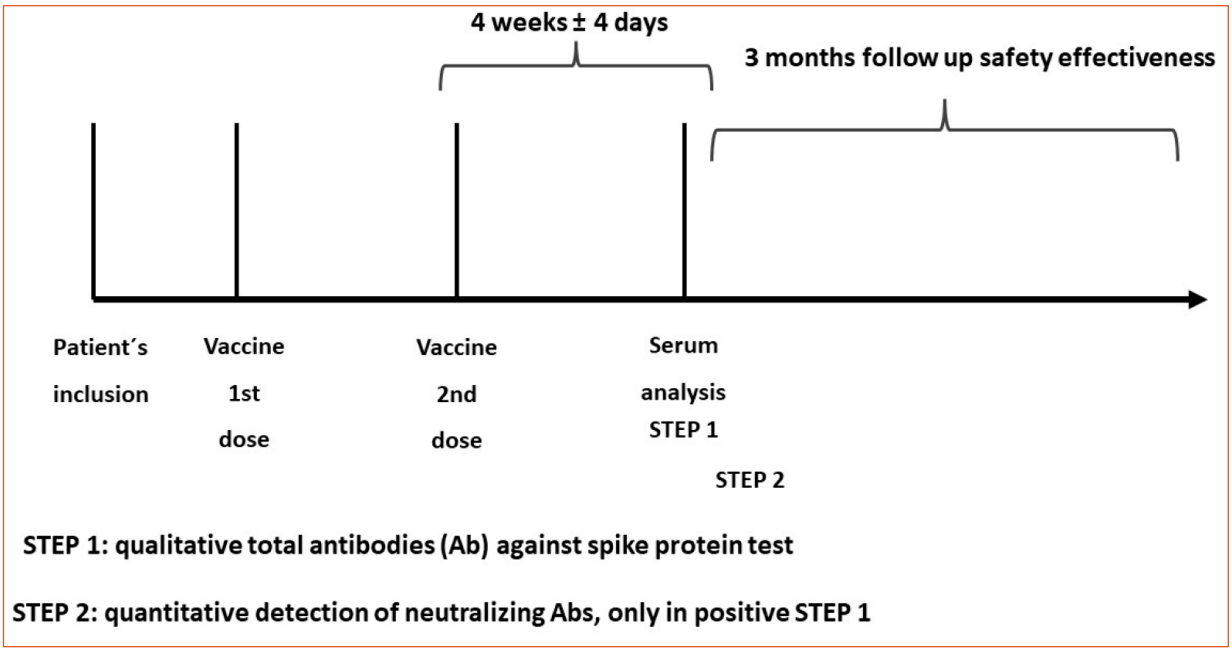
The present investigation was a prospective cohort study that started in May 2021 and finished in December 2021. The study was run on the current MS Argentinean registry, RelevarEM[8, 9]. RelevarEM is a longitudinal, strictly observational multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) registry in Argentina. It is open to all practicing neurologists and MS specialists and their teams across the country. The registry tracks the outcomes of routine clinical practice for MS and NMOSD patients in a web-based platform that allows researchers to register and follow up individuals. The primary objective of the registry was to create an MS physician network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects[8, 9]. Eligible subjects were contacted by their neurologist. Upon patient recruitment, we collected data about demographic and clinical characteristics of participants (age at vaccination, Expanded Disability Status Scale (EDSS) at study entry, ongoing treatment, MS phenotype, and comorbidities); vaccine received as a first and as a second dose, dosing, and intervals; adverse events of vaccination and follow-up time. All patients were actively followed for at least three months since the second COVID-19 vaccine dose (suggested immunization schedule completed).

The primary outcome of the study was to measure the immunogenicity of anti-SARS-CoV-2 vaccines. Secondary outcomes included measuring the immunogenicity of anti-SARS-CoV-2 vaccines stratified by vaccines used and ongoing MS treatments and finally to measure the effectiveness (COVID-19 cases in post-vaccination MS patients) of vaccines in all the MS patients included during 3 months after their vaccination. Clinical and demographic data were obtained from treating neurologists. Information was collected by communication between physician and patient to find out whether infection had occurred in the 3-month follow-up period. If that was the case, specific information regarding the infection was requested from the treating physician (date, symptoms, need for hospitalization, assisted ventilation, treatment, and evolution). Physician contact was made proactively every 30 days during the 3-month period after vaccine schedule completion[10]. Immunogenicity was evaluated based on the detection of total antibodies (Ab) against spike protein and neutralizing Ab in serum[11]. The moment of detection was 4 weeks after the second dose of the vaccine, and this process was applied both for viral vector-based vaccines (Sputnik V, AstraZeneca, CanSino and Janssen), mRNA-based vaccines (Moderna and Pfizer), inactivated vaccines (SinoVac, SinoPharm and Bharat) and vaccines based on recombinant protein nanoparticles (Novavax). All patients included in the study underwent a laboratory test 4 weeks after the second vaccination for quantitative and qualitative detection of neutralizing antibodies, anti-spike antigen antibodies, and total antibodies. The test was conducted at the *Instituto de Investigaciones Biomédicas en Retrovirus y SIDA*, UBA-CONICET (INBIRS) of the University of Buenos Aires Faculty of Medicine, a laboratory accredited in Argentina to perform the test[12]. A positive COVID-19 case was defined according to the criteria established by the Ministry of Health in Argentina: a detectable SARS-CoV-2 specific response by PCR or positive antigen test or a close contact with a COVID-19 case and compatible symptoms. Safety data for the first three months after the first dose of the vaccine, adverse events related to vaccination (local and/or systemic reactions), as well as clinical activity of the disease (relapses) occurring in the first three months after the first vaccination were evaluated. These data were collected by communication between treating physician and patient. The contact was made proactively every 30 days during the 3-month period after vaccine schedule completion.

As for the main objective of the study (immunogenicity), total IgG antibodies against spike protein and RBD were tested 4 weeks after the second dose in fully vaccinated individuals (STEP 1). Qualitative (positive or negative) results were obtained (Fig. 1). Total IgG antibodies were qualitatively measured by COVIDAR ELISA (Laboratorio Lemos, Argentina). If antibodies were detected in STEP 1, neutralizing antibody titer was determined as described below (STEP 2).

Determination of neutralizing antibodies (STEP 2) was performed by ELISA in samples with detectable anti-SARS-CoV-2 antibodies (positive STEP 1). Briefly, serial two-fold dilutions were incubated with 200 SARS-CoV-2 plaque-forming units (PFU) for 1 hour at room temperature, in triplicates. The mixture was then added to 80% confluent Vero-E6 cell monolayers in 96-well plates and incubated at 37 °C for 1 hour. Then, cells were washed and culture medium containing 2% FBS was added. After 72 hours, plates were fixed with 4% paraformaldehyde for 20 minutes at room temperature and stained using a 0.5% crystal violet dye solution in acetone and methanol. The neutralization titer was calculated as the reciprocal of the highest plasma dilution that showed 80% inhibition of the cytopathic effect.

Figure 1 | Flow diagram of the study



A specific form was developed to collect data for the research project. The form was added to the RelevarEM registry as a vaccination supplementary form to follow every patient.

Analysis was conducted for both vaccination schedules and treatment strategies used in the patients included in the study.

Sample

All MS-diagnosed patients included in RelevarEM who received any approved SARS-CoV-2 vaccine were invited to participate in the study. To reduce the probability of selection bias, we sought to include all professionals in Argentina who oversaw healthcare of MS patients in Argentina and were active members of RelevarEM.

Each center submitted the project for approval following the local regulations in force.

An institutional ethics committee approved the center registration or declared its exemption of approval, as well as the informed consent (IC).

Statistical analysis

Baseline characteristics of the cohort were reported in percentages for categorical data and in median and range or mean ± SD standard deviation for continuous data. Only participants with a complete vaccination schedule (at least two doses) and a minimum three-month follow-up period were included in the analysis. In order to compare categorical variables, chi-squared test or Fisher's exact test were used. T-test was performed for continuous variables with normal distribution, and Wilcoxon or Kruskal-Wallis tests were used for variables of non-normal distribution, according to the variance homogeneity between groups. Linear correlation between continuous variables was calculated by the Spearman method. All tests were two-sided, with a 0.05 alpha risk. Statistical analysis was performed using R Studio, version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 94 patients were included during the study period. The mean age at study entry was 41.7 ± 12.1 years. Most individuals were relapsing-remitting MS patients (RRMS) (n = 80, 85.1%). The majority were female (n = 63, 67%) and the median Expanded Disability Status Scale (EDSS) was 2 (SD 1.3, range 1-6.5). The most frequently used treatment was fingolimod, observed in 30 (31.9%) patients. Patients had a low comorbidity score (Charlson score index 0.08, SD 0.32). Ten patients (10.6%) were infected with COVID-19 prior to study inclusion from May 2020 to June 2021. In those patients, infection was confirmed by PCR testing. Among previously infected patients, only 1 (0.01%) was hospitalized (Table 1). All patients included were fully

vaccinated. In 33 patients (35.1%), Sputnik V vaccine was used as the first dose, while 61 patients (64.9%) received AstraZeneca in the same instance (Table 1). As for the second dose received, in 32 patients (34%), the vaccine administered was Sputnik V and 62 (66%) were given AstraZeneca (Table 1). No other vaccines were administered to the sample of patients despite other vaccines were available in Argentina at the time of the study. We analyzed patients with homologous (Sputnik V-Sputnik V or AstraZeneca-AstraZeneca) or heterologous (Sputnik V-AstraZeneca or AstraZeneca-Sputnik V) vaccination schedules. Ninety-two-point five percent of patients completed a homologous schedule (Table 1). Clinical and demographics variables are shown in Table 1.

Serological response

We analyzed the humoral immunogenicity in terms of presence of antibodies (STEP 1) and functionality (STEP 2) as described in the statistical plan. Detection of total antibodies against

Table 1 | Baseline characteristics of included patients

	n = 94
Mean age at study entry (SD)	41.7 (12.1)
Mean disease duration, years (IQR)	6 (4-11)
RRMS, n (%)	80 (85.1)
SPMS, n (%)	14 (14.9)
Female gender, n (%)	63 (67)
Median EDSS, (IQR)	2 (2-3)
Previous treatments received	
Interferon beta, n (%)	9 (9.6)
Glatiramer acetate, n (%)	2 (2.1)
Teriflunomide, n (%)	6 (6.4)
Fingolimod, n (%)	30 (31.9)
DMF, n (%)	12 (12.8)
Natalizumab, n (%)	12 (12.8)
Alemtuzumab, n (%)	7 (7.4)
Ocrelizumab, n (%)	7 (7.4)
Rituximab, n (%)	1 (1.1)
Cladribine, n (%)	8 (8.5)
Median Charlson comorbidity index score (IQR)	0 (0-0)
Previous COVID-19 infection, n (%)	10 (10.6)
Previous hospitalization due to COVID-19 infection, n (%)	1 (1.1)
Assisted ventilation due to COVID-19 hospitalization previous vaccination, n (%)	0
First vaccine dose received	
Sputnik V, n (%)	33 (35.1)
AstraZeneca, n (%)	61 (64.9)
Second vaccine dose received	
Sputnik V, n (%)	32 (34)
AstraZeneca, n (%)	62 (66)
Mean time (days) between first and second vaccine doses, (SD)	32 (6)
Homologous vaccine schedule, n (%)	87 (92.5)
Heterologous vaccine schedule, n (%)	7 (7.5)
Mean time between (days) first and second vaccine doses, (SD)	32 (6)

RRMS: relapsing remitting multiple sclerosis; SPMS; secondary progressive multiple sclerosis; DMT: disease modifying treatment; DMF: dimethyl fumarate

RBD and spike protein was performed in all individuals. We found that 60 participants (63.8%) were able to develop a specific humoral response after vaccination, while a negative result was obtained in 34 patients (36.2%) after two vaccine doses (Table 2). In all participants with a positive response in STEP 1, neutralizing antibodies were quantified (STEP 2). We stratified immunological response according to the vaccination schedules that individuals received, as follows: Sputnik V or AstraZeneca homologous schedules (both doses of the same vaccines), and heterologous schedules. We observed no differences in qualitative response between vaccines or combination received (Sputnik V and AstraZeneca, p = 0.87, Table 2). We also stratified the analysis for MS treatment groups. Despite the low number of patients in each group, a significantly low number of subjects developed antibodies against spike antigen in the group of patients treated with ocrelizumab, and a lower number of subjects developed antibodies in the group receiving fingolimod compared to other group of treatments (Table 3).

During the three-month follow-up, two individuals were diagnosed with COVID-19 by PCR testing. One patient was receiving fingolimod and the other was on ocrelizumab treatment. None of them required hospitalization or oxygen supply.

No MS relapses during the three-month follow-up were reported in patients after the complete vaccination schedule.

Safety data were obtained from 90 patients. A total of 18 (20%) reported adverse events after vaccination. Most common events were fatigue (33.3%), fever (33.3%) and injection site reaction (33.3%). There were no significant differences in the frequency of adverse events between both vaccines (Table 4).

Discussion

This is the first study in Argentina and one of the few in the Latin American region to evaluate the immunogenicity, effectiveness, and safety against SARS-CoV-2 vaccines in a subset of patients with MS.

Several findings must be highlighted. Much information about Pfizer and Moderna vaccines has been gathered[1, 5-7, 10, 11], and this study provides a comprehensive overview of COVID-19 vaccine use in MS patients in the Latin America region. Individuals with heterologous vaccination schedule were included in the study. This

Table 2 | Serological response according to vaccines and treatments received

Variable	Positive ELISA (n = 60)	Negative ELISA (n = 34)	p value
Mean age (SD)	42 (12)	39 (10)	0.24
Female gender, n (%)	19 (32)	9 (32)	0.77
Mean disease duration, years (IQR)	6 (5-9.5)	6 (4-11)	0.35
Median EDSS (IQR)	2 (1-3)	2 (2-3)	0.43
Previous COVID-19 infection, n (%)	6 (50)	6 (50)	0.45
Vaccine, n (%)			0.87
Sputnik V	21 (35)	39 (65)	
AstraZeneca	11 (32)	22 (65)	
DMT, n (%)*			0.0004
Interferon beta (n:9)	8 (89)	1 (11)	
Teriflunomide (n:6)	3 (50)	3 (50)	
Fingolimod (n:30)	25 (83)	5 (17)	
DMF (n:12)	10 (83)	2 (17)	
Natalizumab (n:12)	7 (58)	5 (42)	
Ocrelizumab (n:7)	0	7 (100)	
Cladribine (n:8)	4 (50)	5 (62)	
Others (n:5)	3 (60)	4 (80)	

DMT: disease modifying treatment; DMF: dimethyl fumarate; EDSS: expanded disability status scale

Table 3 | Proportions of patients with serological response (antibodies against spike antigen) according to vaccines and disease-modifying therapies

DMT	Sputnik V n (%)	AstraZeneca n (%)
Interferon beta	1/2 (50)	7/7 (100)
Teriflunomide	2/2 (100)	1/4 (25)
Fingolimod	7/9 (78)	18/21 (86)
DMF	3/3 (100)	7/8 (87)
Natalizumab	4/6 (67)	3/6 (50)
Ocrelizumab	0/3 (0)	0/4 (0)
Cladribine	1/2 (50)	3/6 (50)
Others	3/5 (60)	0/5 (0)

DMT: disease modifying treatment; DMF: dimethyl fumarate

Table 4 | Post-vaccination safety and effectiveness in included patients

	n = 90
Post-vaccine COVID-19 infection, *n* (%)	2 (2.2)
Mean time between first dose vaccine and infection (days) (SD)	48 (15)
General adverse events, *n* (%)	18 (20)
Fatigue, *n* (%)	6/18 (33.3)
Fever	6/18 (33.3)
Injection site pain	6/18 (33.3)
Headache	2/18 (11.1)
Chills	1/18 (5.5)

strategy was implemented in Argentina to solve a problem of vaccine availability and the limited data about safety, efficacy, and immunogenicity of COVID-19 vaccines. It is important to note that, despite the low number of patients included, there are more cases under investigation. A considerable number of patients (almost 64%) developed total antibodies (Ab) against spike protein after COVID-19 vaccination. It should be mentioned that, due to availability of vaccines in Argentina between June and September 2021, a heterologous scheme of vaccination (the possibility to combine doses of vaccines, i.e., Sputnik V and AstraZeneca and Sputnik V and Moderna or Pfizer) was available. This allowed us to analyze a small number of patients. However, the overall immunological response was lower than that observed in clinical trials of both vaccines in general population (98.2% and 99% for Sputnik V and AstraZeneca, respectively)[13,14]. In Argentina, no previous studies were carried out in MS patients to evaluate vaccine response, but some data exist regarding the response to Sputnik V and AstraZeneca in general population. A study evaluated SARS-CoV-2-specific antibody responses after Sputnik V vaccination in healthcare workers in Argentina, measuring IgG anti-spike titers and neutralizing capacity after one and two vaccine doses in a cohort of naive or previously infected volunteers[12]. Around 21 days after receiving the first dose of the vaccine, 94% of naive participants developed spike-specific IgG antibodies. A single Sputnik V dose elicited higher antibody levels and virus-neutralizing capacity in previously infected individuals than in naive patients who received the full two-dose schedule[12]. As observed in previous studies, patients receiving anti-CD20 therapy (ocrelizumab and rituximab) had the lowest qualitative and quantitative response against COVID-19 vaccine[5, 10], while a reduced number of patients under ocrelizumab where evaluated in our study (n = 7).

We only observed two infections during the follow-up period and those infections were not severe. No relapses were described during the three-month follow-up after the complete vaccination schedule.

Our study has many limitations that should be mentioned. Probably, the most relevant limitation is the modest number of patients included and the observational design implemented. However, many considerations were done to avoid information bias, for instance, the way of analyzing the serological response and the strict clinical follow-up. Another limitation of the study is the absence of analysis on the cellular response to vaccines as well as the exclusion of other vaccines used in Argentina (Moderna and Pfizer). However, one of the objectives was to assess the response to vaccines in MS patients that had not been evaluated before.

In conclusion, we found that MS patients that received Sputnik V or AstraZeneca vaccines for SARS-CoV-2 developed a serological response, with no differences between the vaccines used. Only two cases of COVID-19 were identified during the 3-month follow-up.

Our study contributes to understanding the immunological response to COVID-19 vaccines in MS patients receiving disease modifying

drugs (DMDs) where the drug response could be affected[1-4, 10-13]. Despite increasing evidence is being collected and the evidence-practice gap is narrowing, much remains to be done to elucidate the immune response to other vaccines and other factors like the ones considered in our study.

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