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Safety and humoral response rate of inactivated and mRNA vaccines against SARS-CoV-2 in patients with Multiple Sclerosis

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ABSTRACT

Background: Safety and effectiveness outcomes in Multiple Sclerosis (MS) patients receiving different disease-modifying therapies (DMT) and different types of vaccines against SARS-CoV-2 are limited. Growing evidence coming mainly from Israel, Europe and North America using mRNA and adenoviral vector vaccines has been published.

Objectives: To assess the safety and humoral response of inactivated virus and mRNA vaccines against SARS-CoV-2 in patients with MS.

Methods: Ongoing, multicentric, prospective, observational study performed between February and September 2021. Humoral response (antibodies against spike-1 protein) was determined at least 4 weeks after the complete schedule of anti-SARS-CoV-2 vaccines. Categorical outcome (positive/negative) and total antibody titres were recorded. Adverse events supposedly attributable to vaccination (AESAV) were collected.

Results: 178 patients, 68% women, mean age 39.7 ± 11.2 years, 123 received inactivated (Coronavac-Sinovac), 51 mRNA (Pfizer-BioNtech), and 4 adenoviral vector vaccines (CanSino $n = 2$, Jonhson&Johnson-Jannsen $n = 1$, Oxford-AstraZeneca $n = 1$). Six patients had a history of COVID-19 before vaccination. Overall humoral response was observed in 66.9% (62.6% inactivated vs. 78.4% mRNA, $p = 0.04$). Positive anti-S1-antibodies were observed in 100% of patients with no DMT ($n = 3$), 100% with interferon/glatiramer-acetate ($n = 11$), 100% with teriflunomide/dimethyl-fumarate ($n = 16$), 100% with natalizumab ($n = 10$), 100% with alemtuzumab ($n = 8$), 90% with cladribine ($n = 10$), and 88% with fingolimod ($n = 17$), while 43% of patients receiving antiCD20 ($n = 99$) were positive (38% inactivated vaccine vs. 59% mRNA vaccine, $p = 0.05$). In the multivariate analysis including antiCD20 patients, the predictors for a positive humoral response were receiving the mRNA vaccine (OR 8.11 (1.79–36.8), $p = 0.007$) and a lower number of total infusions (OR 0.44 (0.27–0.74) $p = 0.002$. The most frequent AESAV was local pain (14%), with 4 (2.2%) patients experiencing mild-moderate relapses within 8 weeks of first vaccination compared to 11 relapses (6.2%) within the 8 weeks before vaccination (Chi-squared 3.41, $p = 0.06$).

Discussion: A higher humoral response rate was observed using the mRNA compared to the inactivated vaccine, while patients using antiCD20 had a significantly lower response rate, and patients using antiCD20 and fingolimod had lower antibody titres. In this MS patient cohort, inactivated and mRNA vaccines against SARS-CoV-2 appear to be safe, with no increase in relapse rate. This information may help guidelines including booster shots and types of vaccines in selected populations.

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1. Introduction

Vaccination strategies against SARS-CoV-2 have been implemented worldwide, with different approaches considering available scientific information and local governmental policies.

The most common mechanisms of action include inactivated vaccines (e.g. Sinopharm, Sinovac) in which the target antigen is against the whole virus, producing mostly a humoral immune response (anti-Spike-IgG and anti-Nucleocapsid-IgG), non-replicating viral vector vaccines (e.g. Oxford/Astrazeneca, CanSino, Johnson & Johnson/Janssen), against the Spike-protein with both humoral and cellular immune response, and the novel mRNA vaccines (e.g. Pfizer-BioNTech, Moderna), also against the Spike-protein producing a humoral and cellular immune response (Sharma et al., 2020).

Recommendations from Multiple Sclerosis (MS) expert groups were published and distributed, and to date, safety and effectiveness outcomes in MS patients receiving different disease-modifying therapies (DMT) and different types of vaccines are being published (Achiron et al., 2021a, b, Allen-Philbey et al., 2021; Kelly et al., 2021; Tallantyre et al., 2021Ali et al., 2021 Oct 1), with limited data especially for inactivated vaccines (Ali Sarahian et al., 2021), and prospective multicentric databases are essential for guiding future recommendations.

We aimed to assess the safety and humoral response rates of anti-SARS-CoV-2 vaccines in patients with MS, with an emphasis on patients receiving inactivated virus and mRNA vaccines.

2. Methods

Multicentric, prospective, observational study including consecutive MS patients (McDonald 2017 criteria) $\geq$ 18 years old, receiving regular clinical care at 4 tertiary MS centres (Hospital Clínico UC, Hospital Dr. Sótero del Río, Clínica Alemana de Santiago, and Clínica Dávila) in Santiago, Chile, who had completed vaccination schedules against SARS-CoV-2 between February and September 2021. The type of vaccine inoculated (inactivated virus (Sinovac-Coronavac), mRNA (Pfizer-BioNtech), adenoviral vector (CanSino, Johnson&Johnson-Jannsen, Oxford-AstraZeneca) was determined according to the availability at each vaccination centre.

This is part of an ongoing observational study including follow-up for at least 1 year of the first dose of anti-SARS-CoV-2 vaccination. Clinical data, MS variables, and the history of COVID-19 before vaccination and DMT use during inoculation was recorded.

Humoral immune response was determined at least 4 weeks after the second dose of either vaccine, by assessing antibodies (IgG and IgM) against spike 1 (S1) and nucleocapsid (N) proteins (ECLIA Cobas, Roche). A categorical result (positive/negative) using the manufacturer cut-off parameters (positive $\geq$0.80 U/mL for anti-S1 and a ratio $\geq$ 1 for anti-N) as well as total antibody levels were recorded.

Although this study used a non-probability sampling based on the convenience of consecutive patients, a low source of bias is expected because of the demographic and clinical characteristics of the cohort.

Routine clinical visits were performed every 3–6 months according to the prespecified protocol (e.g. stable patients using first-line/platform disease-modifying therapies were visited every 6 months, while patients receiving second-line/high efficacy drugs were seen every 3–4 months. Additional visits were arranged when relapses or adverse events were suspected.

A "pre-vaccination" clinical or telematic visit was performed, as all MS patients required a vaccination prescription as a priority group, according to local Ministry of Health guidelines, for assessing the type of preferred vaccine and suggested date of vaccination (e.g. vaccination window of anti-CD20 patients or according to lymphocyte count in cladribine or alemtuzumab patients). Patients were educated on common adverse events and general measures (e.g. Uhthoff's phenomenon, hydration, premedication with acetaminophen or ibuprofen, etc.) and encouraged to report any common or uncommon adverse event supposedly attributable to either vaccine. Also, a telematic visit was performed within 24–48 hrs of vaccination (e.g. telephone call, zoom call, email), keeping close contact until any adverse events were resolved. Furthermore, all Chilean patients had to fill a short questionnaire of adverse events before the second dose of either vaccine. All of this information was documented in the patients' clinical records.

Events supposedly attributable to vaccination (AESAV) were collected, including MS relapses occurring within 8 weeks of the first dose of either vaccine and development of COVID-19 after full vaccination until the last follow-up visit.

For descriptive statistics, results are reported in mean $\pm$ standard deviation for continuous variables, median (range) for ordinal variables and frequencies for categorical variables. Univariate analysis was performed using Chi-Square/Fisher's exact test for categorical variables, and Student's T-test/Mann-Whitney U for continuous variables that were normally/non normally distributed, respectively. A multivariable binary logistic regression for assessing the chance of a positive humoral response in the antiCD20 subgroup was performed. Variables with $p \leq 0.2$ in the univariate analysis were included. Since Ocrelizumab was approved in August 2019 in our country, 22/94 patients currently receiving ocrelizumab, received at least 1 dose of rituximab prior to ocrelizumab treatment. Total doses including rituximab and ocrelizumab have been counted for the univariate/multivariate analysis. Statistical analysis was performed on SPSS 21, considering a p-value $\leq$0.05 as statistically significant.

Patients signed informed consent as part of the ongoing observational MS study database approved by the local Ethics Committee.

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3. Results

Characteristics of included patients are shown in Table 1 and humoral response after vaccination is shown in Table 2.

A positive humoral response (anti-S1-antibodies) was obtained in 100% of patients with no DMT (n = 3), 100% with interferon/

Table 1
Characteristics of included patients.

Demographic and clinical variables	$N = 178$
Sex female n(%)	121(68)
Age mean±SD years	39.7 ± 11.2
Disease Duration mean±SD years	7.4 ± 6.5
Phenotype RRMS/CIS vs. SPMS/PPMS n(%)	152(85) vs. 26(15)
EDSS median(range)	2.0(0–7.5)
COVID-19 before the first dose of vaccine n(%)	6(3.3)
Disease-Modifying Therapy	*n(%)*
No therapy	3(1.7)
IFN/GA	11(6.2)
TER/DMF	16(9)
FTY	17(9.6)
CLAD	10(5.6)
NTZ	10(5.6)
OCR/RTX	99(55.6)
ALEM	8(4.5)
Other	4(2.3)
Type of COVID-19 vaccine	*n(%)*
Inactivated SARS-CoV-2 (Sinovac-Coronavac)	123(69.1)
mRNA (Pfizer-BioNTech)	51(28.7)
Ad5-nCoV (CanSino)	2(1.1)
Ad26.COV2.S (Johnson & Johnson-Jannsen)	1(0.6)
ChAdOx1-S (Oxford-AstraZeneca)	1(0.6)

MS multiple sclerosis; RRMS relapsing-remitting multiple sclerosis; CIS clinically isolated syndrome; SPMS secondary progressive multiple sclerosis; PPMS primary progressive multiple sclerosis; EDSS expanded disability status scale; DMT disease-modifying therapy, IFN interferon beta, GA glatiramer acetate, TER teriflunomide, DMF dimethyl fumarate; FTY fingolimod; NTZ natalizumab; CLAD cladribine; OCR ocrelizumab; RTX rituximab; ALEM alemtuzumab; Other: BTKI phase III trial, azathioprine.

Table 2
Humoral response after SARS-CoV-2 vaccine.

Overall humoral response	% Positive (n/total)
anti-S1 antibodies*	66.9 (119/178)
anti-N**	22.1(36/124)
According to the type of vaccine (positive anti-S1)	*% Positive (n/total)*
Inactivated virus	62.6 (77/123)
mRNA	78.4 (40/51)
Adenovirus vector	50 (2/4)
*Six patients had COVID-19 before vaccination, with no serology available prior to the inoculation.4 patients had a positive anti-S1 after vaccination (1 Inactivated Vaccine-FTY, 1 mRNA Vaccine -NTZ, 1mRNA Vaccine -OCR, 1 Inactivated Vaccine -OCR). 2 patients were negative (1 mRNA Vaccine -OCR, 1 Inactivated Vaccine-OCR).**31/36 received the inactivated vaccine, 5/36 received the mRNA vaccine, 1 patient with symptomatic COVID-19 before vaccination under treatment with NTZ, and 4 with a possible asymptomatic infection explaining the positive anti-N antibodies (1=IFN, 1=CLAD, 2=OCR)	
Mean anti-S1 antibodies titre according to DMT	U/mL±SD
No therapy	871±1171
IFN/GA	595±1016
TER/DMF	922±1127
FTY*	228±403
CLAD**	562±845
NTZ	485±738
OCR/RTX	236±529
ALEM***	1267±1351

*Median lymphocytes count 590/uL (240–1582) **Median time since last CLAD dose was 6 months (1–9) and median lymphocyte count was 1330/uL (850–2425) ***Median time since last ALEM infusion was 16 months (3–48) and median lymphocyte count was 1535/uL (760–2800). DMT disease-modifying therapy, IFN interferon beta, GA glatiramer acetate, TER teriflunomide, DMF dimethyl fumarate; FTY fingolimod; NTZ natalizumab; CLAD cladribine; OCR ocrelizumab; RTX rituximab; ALEM alemtuzumab;.

glatiramer-acetate ($n = 11$), 100% with teriflunomide/dimethyl-fumarate ($n = 16$), 100% with natalizumab ($n = 10$) and 100% with alemtuzumab ($n = 8$), 90% with cladribine ($n = 10$), 88% with fingolimod ($n = 17$), and 43% with ocrelizumab/rituximab ($n = 99$).

In the whole cohort, a higher humoral response rate was observed with the mRNA vaccine compared to the inactivated vaccine (78.4% vs. 62.6%, $p = 0.04$).

3.1. AntiCD20 subgroup analysis

Of the 99 patients using antiCD20 monoclonal-antibodies (OCR $n = 94$, RTX $n = 5$), 38% (26/69) had a positive humoral response with the inactivated vaccine, 59% (16/27) with the mRNA vaccine ($p = 0.05$), and 33% (1/3) with the adenoviral vector vaccines.

Mean anti-S1 antibodies levels were significantly lower in the antiCD20 subgroup compared to the other DMT (236±529 vs. 687±958 u/mL, $p = 0.002$).

Mean time from the last antiCD20 infusion to the first dose of either vaccine was 166±92 days with a median of 3 infusions before vaccination (range 1–8).

Patients with positive humoral response had a longer time since the last infusion (195±91 vs. 147±88 days, $p = 0.028$) and fewer total infusions prior to vaccination (mean 2.0 ± 1.1 vs. 3.6 ± 1.7, $p<0.001$).

In the multivariate analysis, the predictors for a positive humoral response were receiving the mRNA vaccine (OR 8.11 (1.79–36.8), $p = 0.007$) and number of total infusions (OR 0.44 (0.27–0.74) $p = 0.002$ (Table 3)).

3.2. Safety

Adverse events supposedly attributable to vaccination, MS relapses and SARS-CoV-2 infection after full vaccination are shown in Table 4.

Most adverse events were considered mild and included local pain (14%), myalgia (4%), headache (4%), and mild fever (2%). Four patients presented with relapses during 8 weeks from the first vaccine dose. Two patients were participating in a BTKi phase III trial and presented with optic neuritis 2 and 3 weeks after the second dose of the inactivated vaccine. Both patients required intravenous methylprednisolone. As these patients presented with relapses during their randomization period and had recently started their blinded therapy, there is no certainty about the therapeutic effect of the treatment during vaccination and relapse. One patient was receiving rituximab since 2018 and had a mild sensory myelitis with a new lesion in the thoracic spinal cord 2 weeks after the first dose of the inactivated vaccine, with complete symptom resolution after oral steroids, and one patient had recently received rituximab in March 2021 prior to vaccination, with a mild optic neuritis 2 weeks after the first dose of the inactivated vaccine, also with resolution after oral prednisone.

Table 3
Binary logistic regression for a positive humoral response in antiCD20 patients.

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95%CI)	p	OR (95%CI)	p
Age (years)	0.99 (0.95–1.02)	0.39		
Sex (male)	0.99 (0.43–2.25)	0.98		
Disease Duration (years)	0.95 (0.89–1.01)	0.08	0.99 (0.91–1.07)	0.76
EDSS	0.97 (0.78–1.20)	0.76		
Type of Vaccine (mRNA)	2.41 (0.97–5.97)	0.06	8.11 (1.79–36.8)	0.007
Days since last infusion	1.01 (1.00–1.01)	0.03	1.01 (0.99–1.01)	0.07
Number of total infusions	0.43 (0.29–0.65)	<0.001	0.44 (0.27–0.74)	0.002

In the whole cohort, the mean annualized relapse rate was 0.36±0.59 the year before vaccination. No statistically significant difference was observed comparing the relapse rate within the 8 weeks before vaccination (11 relapses, 6.2%) and the 8 weeks after vaccination (4 relapses, 2.2%) (Chi-squared 3.41, $p = 0.06$).

4. Discussion

In this MS patient cohort, inactivated and mRNA vaccines against SARS-CoV-2 appear to be safe, with a 2% of reported relapses during the 8 weeks following vaccination. No increase in the relapse rate compared with the 8 weeks prior the vaccine was observed.

In the whole sample, higher humoral response rates were observed using the mRNA compared to the inactivated vaccine, which is in line with a recent large sentinel surveillance study including over 56,000 individuals reporting that positive humoral responses were 77.3% after the second dose of the inactivated vaccine compared to 96.5% after the second dose of the mRNA vaccine (Saure et al. 2021), and the reported clinical effectiveness of the inactivated vaccine in over 10 million people in Chile, with adjusted vaccine effectiveness of 65.9% in the prevention of COVID-19 (Jara et al., 2021).

In patients using antiCD20, the lowest humoral response rate was observed, and anti-S1 antibody positivity was associated with fewer total infusions and receiving the mRNA vaccine. In recent studies including only mRNA vaccines, MS patients treated with antiCD20 made lower positive serology rates (Sormani et al., 2021) and had lower S1-binding antibodies titres, and this result was associated with time since the last antiCD20 infusion (Disanto et al., 2021), while patients developed T cell responses similar to healthy controls (Apostolidis et al., 2021, Brill et al., 2021). Using mRNA and adenoviral vector vaccines, the use of antiCD20 and fingolimod was also associated with lower seroconversion, and those patients receiving the mRNA vaccine had a significant greater IgG response compared to the adenoviral vector vaccine (Tallantyre et al., 2021).

How this information translates to the clinical effectiveness of anti-

Table 4
Adverse Events Supposedly Attributable to vaccines and COVID-19 after full vaccination.

				%(*n*)	
no AESAV				74%(132)	
local pain				14%(25)	
myalgia				4%(7)	
headache				4%(6)	
mild fever				2%(4)	
MS relapse				2%(4)	
Relapses within 8 weeks of first dose of either vaccine					
Sex, age	*Phenotype and EDSS*	*DMT*	*Timing and Vaccine Type*	*Topography and severity*	*Treatment*
Woman, 32 yo	RRMS, EDSS 2.0	Rituximab	2 weeks after the first dose of Inactivated virus vaccine	Optic Neuritis, mild	Oral steroids
Woman, 47 yo	RRMS, EDSS 2.0	Rituximab	2 weeks after the first dose of Inactivated virus vaccine	Dorsal Myelitis, mild	Oral steroids
Woman, 53 yo	RRMS, EDSS 3.0	Btki phase III trial	3 weeks after the second dose of Inactivated virus vaccine	Optic Neuritis, moderate	IV steroids
Woman, 42 yo	RRMS, EDSS 1.0	Btki phase III trial	2 weeks after the second dose of Inactivated virus vaccine	Optic Neuritis, moderate	IV steroids
COVID-19 After full vaccination					
Sex, age, DMT	*Phenotype and EDSS*	*Vaccine type*	*Humoral response*	*COVID-19 outcomes*	
Woman, 45 yo Ocrelizumab	RRMS, EDSS 2.0	Inactivated virus	positive S1 (low titre 2.2 U/mL)	required hospitalization for oxygen therapy, fully recovered	
Woman, 32 yo, Rituximab	RRMS, EDSS2.0	Inactivated virus	negative S1	required hospitalization and 1 day of non-invasive mechanical ventilation, fully recovered	

*Pooled AESAV from all vaccines collected within 8 weeks after the first inoculation. DMT disease-modifying therapy, RRMS relapsing-remitting MS, EDSS expanded disability status scale, IV intravenous.

SARS-CoV-2 vaccines in preventing COVID-19 in patients receiving antiCD20 monoclonal antibodies, and the utility of booster vaccines and selection of the best available vaccine in these high-risk patients is still a fundamental matter of research.

Since August 11th, our country has included MS patients as a priority for mRNA booster vaccination, with a second booster vaccine during the first trimester of 2022.

The main limitations of the present study are the small sample size, not having serological status before vaccination, and the short follow-up period after completed vaccination schedule, precluding an interpretation of the impact of humoral response on the clinical efficacy of either vaccine. Larger multicentric prospective studies with longer follow-up evaluating the safety and effectiveness of anti-SARS-CoV-2 vaccines in preventing COVID-19 in MS patients are still needed.

This information may help vaccination guidelines, including booster shots and preferring mRNA vaccines, if available, in selected populations.

CRediT authorship contribution statement

Ethel Ciampi: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Reinaldo Uribe-San-Martin:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Bernardita Soler:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Lorena García:** Investigation, Validation, Writing – review & editing. **Jorge Guzman:** Investigation, Validation, Writing – review & editing. **Carolina Pelayo:** Investigation, Validation, Writing – review & editing. **Lukas Jürgensen:** Investigation, Validation, Writing – review & editing. **Ignacio Guzman:** Investigation, Validation, Writing – review & editing. **Francisco Vera:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Lorna Galleguillos:** Investigation, Validation, Writing – review & editing. **Claudia Cárcamo:** Conceptualization, Investigation, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

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