

# mRNA COVID-19 Vaccination Does Not Exacerbate Symptoms or Trigger Neural Antibody Responses in Multiple Sclerosis

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## Abstract

### Background and Objective

In people with multiple sclerosis (pwMS), concern for potential disease exacerbation or triggering of other autoimmune disorders contributes to vaccine hesitancy. We assessed the humoral and T-cell responses to SARS-CoV-2 after mRNA vaccination, changes in disease activity, and development of antibodies against central or peripheral nervous system antigens.

### Methods

This was a prospective 1-year longitudinal observational study of pwMS and a control group of patients with other inflammatory neurologic disorders (OIND) who received an mRNA vaccine. Blood samples were obtained before the first dose (T1), 1 month after the first dose (T2), 1 month after the second dose (T3), and 6 (T4), 9 (T5), and 12 (T6) months after the first dose. Patients were assessed for the immune-specific response, annualized relapse rate (ARR), and antibodies to onconeural, neural surface, glial, ganglioside, and nodo-paranodal antigens.

### Results

Among 454 patients studied, 390 had MS (22 adolescents) and 64 OIND; the mean (SD) age was 44 (14) years; 315 (69%) were female; and 392 (87%) were on disease-modifying therapies. Antibodies to the receptor-binding domain were detected in 367 (86%) patients at T3 and 276 (83%) at T4. After a third dose, only 13 (22%) of 60 seronegative patients seroconverted, and 255 (92%) remained seropositive at T6. Cellular responses were present in 381 (93%) patients at T3 and in 235 (91%) patients at T6 including all those receiving anti-CD20 therapies and in 79% of patients receiving fingolimod. At T3 (429 patients) or T6 (395 patients), none of the patients had developed CNS autoantibodies. Seven patients had neural antibodies that were already present before immunization (3 adult patients with MS had MOG-

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## Glossary

**AEs** = adverse events; **CBA** = cell-based assays; **COVID-19** = coronavirus disease 19; **GBS** = Guillain-Barré syndrome; **IQR** = interquartile range; **MOGAD** = MOG antibody-associated disease; **mRNA** = messenger RNA; **NMOSD** = neuromyelitis optica spectrum disorder; **OIND** = other inflammatory neurologic disorders; **pwMS** = people with MS; **RBD** = receptor-binding domain.

IgG, 2 with MG and 1 with MS had neuronal cell surface antibodies [unknown antigen], and 1 with MS had myelin antibody reactivity [unknown antigen]. Similarly, no antibodies against PNS antigens were identified at T3 (427 patients). ARR was lower in MS and not significantly different in patients with OIND. Although 182 (40%) patients developed SARS-CoV-2 infection, no cases of severe COVID-19 or serious adverse events occurred.

## Discussion

In this study, mRNA COVID-19 vaccination was safe and did not exacerbate the autoimmune disease nor triggered neural autoantibodies or immune-mediated neurologic disorders. The outcome of patients who developed SARS-CoV-2 infection was favorable.

## Introduction

There is evidence that messenger RNA (mRNA) vaccines are safe and provide protection against severe outcome of coronavirus disease 19 (COVID-19).<sup>1</sup> However, one of the main concerns is the potential risk of immune-mediated neurologic complications such as Guillain-Barré syndrome (GBS), transverse myelitis, and Bell palsy.<sup>2</sup> Patients with COVID-19 exhibit an extensive repertoire of autoantibodies including some that are characteristic of systemic autoimmune diseases.<sup>3</sup> Whether humoral autoimmunity against neural tissue and potentially associated neurologic symptoms are also triggered by vaccination is currently unknown. This question is particularly pertinent for patients with underlying chronic neurologic disorders, such as multiple sclerosis (MS), because vaccines could potentially exacerbate the autoimmune disease or trigger other immune-mediated disorders, altogether contributing to vaccine hesitancy.<sup>4</sup>

In MS, mRNA COVID-19 vaccines are safe in the short term but are associated with decreased SARS-CoV-2 humoral responses in patients treated with anti-CD20 therapies and fingolimod.<sup>5,6</sup> In this setting, the benefit of a COVID-19 booster vaccine on the specific immune response against SARS-CoV-2 has yielded controversial results.<sup>7-9</sup>

Although previous studies suggest that disease exacerbation is rare after vaccination, most studies are retrospective<sup>9</sup> or have short follow-up.<sup>10</sup> Moreover, none of these studies provide prospective comprehensive neural antibody assessment. The information provided by the latter may be useful when evaluating the presence of an antibody in a given patient, and this occurs in temporal association with vaccination.<sup>11</sup>

We designed this study at the start of the vaccination campaign in Spain, aiming to determine over 1 year the humoral and T-cell responses against SARS-CoV-2 in people with MS (pwMS) who received mRNA vaccination. We focused on (1) changes in disease activity, (2) development of neural

autoantibodies, (3) frequency and severity of SARS-CoV-2 infections, and (4) adverse vaccine effects.

## Methods

### Participants and Samples

In this prospective observational study, pwMS<sup>12</sup> followed up at 2 Neuroimmunology-MS centers for adults (Hospital Clinic and Hospital Sant Pau de Barcelona) and 1 for adolescents (aged 12–18 years, Hospital Sant Joan de Déu) were invited to participate. Vaccination was performed in accordance with the program established by the Catalan Public Health Care system between April 17, 2021–July 5, 2021 (adults) and June 2, 2021–September 28, 2021 (adolescents). Blood samples were obtained at baseline before the first vaccination dose (T1), 1 month after the first dose (T2), 1 month after the second dose (T3), and 6 (T4), 9 (T5), and 12 (T6) months after the first dose. Participants with other inflammatory neurologic disorders (OIND) of the central or peripheral nervous system served as controls.

Clinical and demographic information was retrieved from electronic medical records of the participants centers. Follow-ups were performed every 3–6 months, with additional visits in case of suspected relapses.<sup>12</sup> Patients were asked to report potential symptoms of SARS-CoV-2 infection,<sup>13</sup> which in all cases required confirmation with antigen tests and/or real-time PCR.

### Procedures

#### Quantification of Antibodies to SARS-CoV-2 by Luminex

IgG antibodies to the receptor-binding domain (RBD) of the spike glycoprotein of SARS-CoV-2 were determined with Luminex. Cutoff values were calculated as the mean plus 2 standard deviations of log<sub>10</sub>-transformed median fluorescence intensities (MFIs) of a donor pool of 47 samples obtained before the COVID-19 pandemic. Antibody synthesis was calculated as the ratio of the raw MFI of a patient

undergoing assessment and the raw MFI from the donor pool; values  $\geq 1$  were considered positive.<sup>14</sup>

### T-Cellular Response (IFN- $\gamma$ ELISpot)

Stimulation was conducted with  $2 \times 10^5$  peripheral blood mononuclear cells and PepTivator SARS-CoV-2 Prot\_S (1  $\mu\text{g}/\text{mL}$ , Miltenyi Biotec). Negative control wells lacked peptides, and positive control ones included anti-CD3-2 mAb. Cells were incubated overnight in precoated anti-IFN- $\gamma$  MSIP white plates and subsequently with horseradish peroxidase-conjugated IFN- $\gamma$  detection antibody; the reactivity was visualized with tetramethylbenzidine. Spots were counted using an automated ELISpot Reader System. To quantify positive peptide-specific responses, spots of the unstimulated wells were subtracted from the peptide-stimulated wells, and the results were expressed as spot-forming units SFU/ $2 \times 10^5$  PBMCs. SARS-CoV-2-specific spots, were defined as stimulated spot numbers  $\geq 6$  SFU/ $2 \times 10^5$  PBMCs, as detailed in eMethods (links.lww.com/NXI/A900).<sup>14</sup>

### Analysis of Antibodies Against Antigens of the CNS

The presence of onconeural, GAD, AK5, neuronal cell surface, and glial antibodies were examined using immunohistochemistry on frozen sections of paraformaldehyde-perfused or postfixed rat brain<sup>15-17</sup> (eMethods, links.lww.com/NXI/A900). Samples showing tissue immunoreactivity were further examined with immunoblot (Euroimmun, Lübeck, Germany) or cell-based assays (CBA) using HEK293 cells transfected with the appropriate plasmids. MOG-IgG were analyzed in all samples by CBA<sup>18</sup> (eMethods).

### Analysis of Antibodies Against Antigens of the PNS

IgG and IgM antibodies against gangliosides GM1, GD1b, and GQ1b were examined with ELISA and confirmed by thin-layer chromatography, as reported<sup>19</sup> (eMethods, links.lww.com/NXI/A900). IgG antibodies to nodo-paranodal antigens (contactin-1, contactin-associated protein 1, neurofascin-155, and nodal NF140/186 neurofascins) were determined with ELISA and confirmed by CBA<sup>20</sup> (eMethods).

### Safety Assessment

Safety included monitoring of soliciting local and systemic adverse events (AEs) for 7 days after each vaccine dose and unsolicited AEs for 1 month after each injection. After this period, only medically attended AEs and serious adverse events were recorded at each scheduled visit until the end of the study.

### Statistical Analysis

Categorical variables were analyzed by the  $\chi^2$  test or Fisher exact test, and continuous variables by means of the *t* test or Mann-Whitney *U* test for independent samples. Comparisons of antibodies and cellular response levels over time were assessed by Wilcoxon signed rank test for paired samples and between groups by the Mann-Whitney *U* test.

The estimate of the risk of nonresponse to the vaccine was assessed by odds ratio (OR) and their 95% CIs of multivariate logistic regression models taking into account the following independent variables: age, smoking habit, type of disease, and therapy. Statistics were performed using SPSS v.25 (Armonk, NY: IBM Corp).

### Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethic Committee of Hospital Clinic of Barcelona (HCB/2021/0036), and written consent was obtained from all participants or the legal representatives in case of adolescents.

### Data Availability

All data are available by request from qualified investigators.

## Results

Four hundred fifty-four patients were recruited, 390 with MS (344 relapsing and 46 progressive; 22 adolescents) and 64 with OIND (22 myasthenia gravis, 18 neuromyelitis optica spectrum disorder (NMOSD)/MOG antibody-associated disease (MOGAD), 9 autoimmune encephalitis, 7 inflammatory neuropathies, 4 GAD antibodies spectrum disorders, and 4 others) (Table 1). 392 of 418 (94%) adult patients were vaccinated with the mRNA-1273 SARS-CoV2 vaccine (Moderna, Cambridge, MA), and all but 1 adolescent with the BNT162b2 mRNA (Pfizer).

### Humoral Response Prevacination and Postvaccination

At T1, 74/325 (23%) patients were RBD antibody seropositive, and seropositivity increased to 326/402 (81%) at T2 and 367/428 (86%) at T3. No differences were found between adults and adolescents with MS or between patients with MS and OIND. Seronegative patients included 51 (14%) with MS (representing 44% of those receiving anti-CD20 and 36% of those receiving fingolimod) and 10 (18%) with OIND (representing 46% of those treated with rituximab) (Table 2). RBD antibody levels were not different between adults and adolescents with MS (9.1 [4.2] vs 9.4 [5.3]) and increased by a factor of 2.94 in cases that were seropositive before vaccination (3.7 [2] vs 10.8 [3.8];  $p < 0.0001$ ).

At T4, 276 (83%) patients who had received 2 doses remained seropositive. The mean antibody titer decreased by a factor of 2.13 ( $p < 0.0001$ ) (Table 2; Figure 1). Seronegative patients included 50 (17%) patients with MS (representing 51% of those treated with anti-CD20 and 60% of those treated with fingolimod) and 6 (17%) with OIND (representing 33% of rituximab-treated patients) (Table 2). Overall, at T5, 51 (98%) patients and at T6, 44 (96%) patients who had received 2 vaccination doses were still seropositive (data not shown).

**Table 1** Baseline Demographic and Clinical Characteristics of the Cohort

	Total (n = 454)	MS (n = 390)	OIND (n = 64)
Age, y, mean (SD)	44.1 (14.1)	44.5 (12.6)	41.6 (21)
Female sex, n (%)	315 (69)	284 (72.8)	31 (48)
<b>Disease phenotype, n (%)</b>			
Relapsing MS	344 (75.8)	344 (88)	—
Progressive MS	46 (10)	46 (11.8)	—
Myasthenia gravis	22 (4.8)	—	22 (34.3)
NMOSD/MOGAD	18 (3.9)	—	18 (28)
Autoimmune encephalitis	9 (1.9)	—	9 (14)
Inflammatory neuropathy	7 (1.5)	—	7 (10.9)
GAD antibody spectrum disorder	4 (0.9)	—	4 (6.2)
Other OIND <sup>a</sup>	4 (0.9)	—	4 (6.2)
Disease duration, mo, median (IQR)	119.7 (54.8–204.8)	131.0 (59.4–210.5)	66.0 (34.0–139.2)
EDSS score, median (range)		2.0 (0–7.5)	—
Annualized relapse rate, prior year, median (range)	0 (0–3)	0 (0–3)	—
<b>Treatment, n (%)</b>			
None	61 (13.4)	50 (12.8)	11 (17.2)
Interferon $\beta$	38 (8.4)	38 (9.8)	0
Glatiramer acetate	36 (7.9)	36 (9.2)	0
Teriflunomide	35 (7.7)	35 (9.0)	0
Dimethyl fumarate	70 (15.5)	70 (18)	0
Natalizumab	21 (4.6)	21 (5.4)	0
Fingolimod	47 (10.4)	47 (12.1)	0
Cladribine	7 (1.5)	7 (1.8)	0
Ocrelizumab	35 (7.7)	35 (9.0)	0
Rituximab	59 (13.1)	40 (10.3)	19 (29.7)
Ofatumumab	6 (1.3)	6 (1.5)	0
Alemtuzumab	2 (0.4)	2 (0.5)	0
Other immunosuppressor (IS) <sup>b</sup>	14 (3.1)	1 (0.2)	13 (20.3)
Corticosteroids	12 (2.6)	0	12 (18.7)
Double IS <sup>c</sup>	9 (2.0)	0	9 (14.1)
Clinical trial	2 (0.4)	2 (0)	0 (0)

Abbreviation: EDSS = Expanded Disability Status Scale; GAD = glutamic acid decarboxylase; IQR = interquartile range; MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; OIND = other inflammatory neurologic disorder.

<sup>a</sup> Longitudinal extensive myelitis; cerebellar ataxia; atypical clinical isolated syndrome; Aicardi Goutieres

<sup>b</sup> Intravenous (IV) immunoglobulins (5); azathioprine (4); mycophenolate mofetil (2); tocilizumab (1); eculizumab (1); receptor of autologous hematopoietic stem cell transplantation (1).

<sup>c</sup> Rituximab+prednisone (4); rituximab+prednisone+mycophenolate mofetil (1) azathioprine+prednisone (1); IV immunoglobulins+prednisone (1); mycophenolate mofetil+prednisone (2).

A total of 394 patients received a third dose, 175.2 (56) days (median [IQR], 162.5 [131.5–217]) after the second dose. Table 2 includes information of the patients assessed before

and 4 weeks after the third dose. Among 60 (34%) patients who were seronegative, 13 (22%) seroconverted (representing 13% of the seronegative patients treated with anti-CD20

**Table 2** Humoral Immune Response According to the Disease and Therapy

	<b>T3 n = 428</b>	<b>T4 n = 332</b>	<b>Pre-3 n = 175</b>	<b>Post-3 n = 175</b>	<b>T6 n = 276</b>
<b>Multiple sclerosis</b>					
<b>RBD antibody positive, N (%)</b>	322 (86.3)	246 (83)	92 (64.3)	108 (71.3)	232 (91.7)
<b>RBD antibody titer, mean (SD)</b>	9.4 (5.2)	4.4 (2.8)	3.9 (3.2)	5.1 (3.8)	7.9 (4.0)
<b>No. of patients positive (%)</b>					
<b>Anti-CD20</b>	41 (56)	26 (49)	22 (39)	26 (46.4)	24 (68.6)
<b>Fingolimod</b>	30 (63.8)	12 (40)	7 (33.3)	10 (47.6)	32 (78)
<b>Injectables</b>	71 (100)	63 (97)	4 (100)	4 (100)	48 (98)
<b>Other oral</b>	107 (99)	84 (99)	39 (100)	39 (100)	84 (100)
<b>Natalizumab</b>	21 (100)	14 (100)	10 (100)	10 (100)	13 (100)
<b>Untreated</b>	47 (97.9)	40 (95)	7 (70)	10 (100)	27 (100)
<b>Other inflammatory neurologic disorder</b>					
<b>RBD antibody positive, N (%)</b>	45 (81.8)	30 (83.3)	23 (71.8)	25 (89.6)	23 (100)
<b>RBD antibody titer, mean (SD)</b>	8.7 (5.1)	4.1 (2.5)	3.6 (2.9)	5.9 (3.7)	8.3 (3.0)
<b>No. of patients positive (%)</b>					
<b>Rituximab</b>	7 (53.8)	4 (66.6)	6 (54.5)	7 (63.6)	1 (100)
<b>Corticosteroids</b>	11 (91.6)	9 (90)	6 (85.7)	7 (100)	8 (100)
<b>Double IS</b>	7 (77.7)	4 (66.6)	4 (66.6)	5 (83.3)	4 (100)
<b>Other IS</b>	12 (92.3)	7 (87.5)	6 (85.7)	6 (85.7)	9 (100)
<b>Untreated</b>	8 (100)	6 (100)	1 (100)	1 (100)	1 (100)

Patients with 2 doses: (T3) 1 month after the second vaccination dose; (T4) 6 months after the first dose; and (Pre-3) before the third dose (185 [58] days after the first dose). Patients with 3 doses: (Post-3) after the third dose (4 weeks); and (T6) 12 months after the first dose (177 [49.7] days after the third dose); RBD: receptor-binding domain; injectables: interferon  $\beta$  (38)+ acetate glatiramer (35); other oral: teriflunomide (35)+dimethyl fumarate (70)+cladribine (7); double IS: rituximab+prednisone (4); rituximab+prednisone+mycophenolate mofetil (1); azathioprine+prednisone (1); IV immunoglobulins+prednisone (1); mycophenolate mofetil+prednisone 2); Other IS: IV (IV) immunoglobulins (5); azathioprine (4); mycophenolate mofetil (2); tocilizumab (1); eculizumab (1); receptor of autologous hematopoietic stem cell transplantation.

and 21% of those seronegative treated with fingolimod). The mean RBD antibody levels increased by a factor of 1.4 ( $p < 0.0001$ ) for all cases assessed and 20.9 for those patients who seroconverted ( $p < 0.001$ ) (Table 2; Figure 1).

At T6, 177 (49.7) days (median [IQR], 183 [132–206]) after the third dose, 255 (92%) patients were seropositive. Seronegative patients included 21 (8%) of 253 with MS (representing 31% of those treated with anti-CD20 and 22% of those treated with fingolimod) (Table 2). The proportion of seropositive patients, 115/126 (91%), was similar after excluding those who had breakthrough COVID-19. Overall, the mean RBD antibody levels increased by a factor of 1.14 ( $p = 0.013$ ) and by 1.24 in those who had SARS-CoV-2 infection (post-third dose 6.2 [3.6] vs 7.7 [4.1];  $p = 0.003$ ) (Figure 1). At each time point, patients treated with anti-CD20 or fingolimod had significantly lower RBD antibody levels than the rest of patients, including treated and untreated cases (Figure 1).

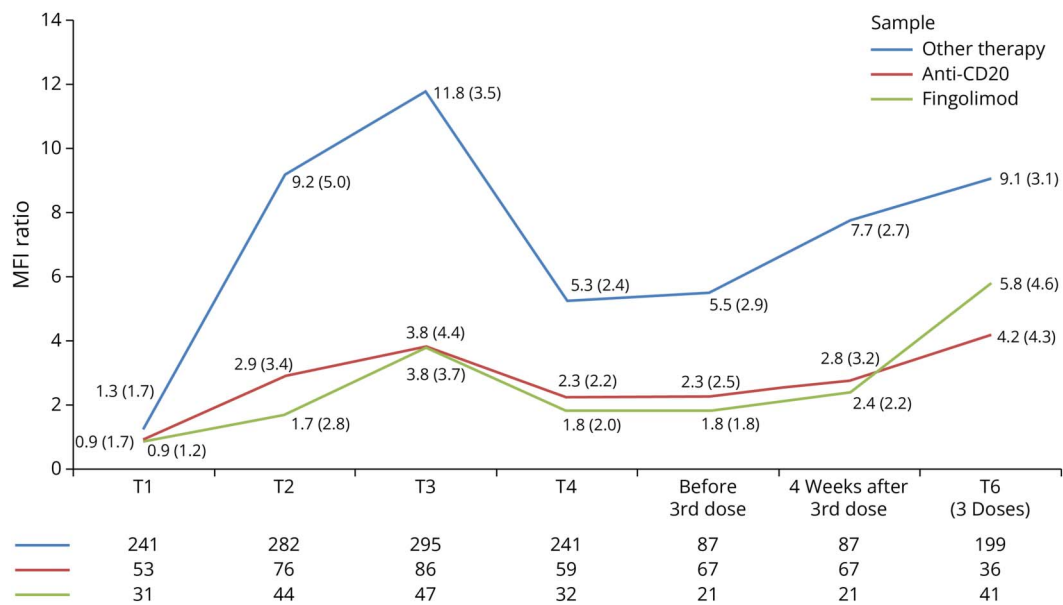
### T-Cellular Response

At T3, 381 (93%) patients developed cellular responses (80% had both humoral and cellular responses) (eFigure 1, links. [lww.com/NXI/A900](http://lww.com/NXI/A900)). The frequency was not different between pwMS and those with OIND or between adults and adolescents with MS. ELISpots for the S protein showed a higher mean value in adults compared with that in adolescents with MS (46 vs 22;  $p < 0.0001$ ) and a lower mean value in patients treated with fingolimod compared with those treated with anti-CD20 or other therapies (24 [30] vs 54 [79] or 46 [43];  $p < 0.009$ ). Cellular responses were detected in 82 (98%) patients on anti-CD20 therapies and 33 (75%) on fingolimod. Seven of the 23 (30%) RBD seropositive patients without cellular response and 4 of the 6 patients without any response were on fingolimod (eFigure1).

At 179 (69) days (median [IQR], 168 [159–199]) after the first dose, T-cell responses remained positive in 77 of 85 (91%) patients who were assessed before receiving the third



**Figure 1** Longitudinal Dynamics of Antibodies Against SARS-CoV-2 Receptor-Binding Domain According to the Type of Treatment



(T1) before vaccination; (T2) 1 month after the first dose; (T3) 1 month after the second dose, (T4) 6 months after the first dose, and (T6) 12 months after the first dose. Receptor-binding domain antibody levels are expressed as mean (SD) of the median fluorescence intensity ratio. Patients treated with anti-CD20 or fingolimod had significantly lower levels of receptor-binding domain antibodies than those treated with other therapies across different time points (compared by general lineal model adjusted by age). Other therapy includes untreated patients and those treated with other therapy than anti-CD20 and fingolimod (as detailed in Table 1). The number of patients with receptor-binding domain antibodies before vaccination (at T1) included 61 in the group treated with other therapies (blue), 8 in the group anti-CD20 (red), and 5 in the group fingolimod (light green).

dose; however, the levels were lower compared with that of T3 (56.46 vs 43.8;  $p = 0.046$ ). Four weeks after the third dose, the levels increased from 36.02 to 59.35;  $p < 0.001$  and all 6 negative anti-CD20 patients became positive.

At T6, T-cell responses remained positive in 34 (89.5%) of 38 patients who received 2 doses and in 235 (91%) of 259 patients who received 3 doses (84% had both humoral and cellular responses). Cellular responses were observed in all patients on anti-CD20 therapy and 27 of 34 (79%) patients on fingolimod. Six of 23 (26%) RBD antibody seropositive patients without cellular responses and the only 1 without any response were on fingolimod (eFigure 2, [links.lww.com/NXI/A900](https://links.lww.com/NXI/A900)).

### Factors Associated With Humoral and T-cell Responses

Treatment with anti-CD20 therapy or fingolimod were independent predictors of RBD antibody seronegativity after 2 or 3 vaccine doses, whereas treatment with fingolimod along with lymphocyte count  $<500$  cells/mm<sup>3</sup> was the only independent predictor of absent cellular responses (Table 3).

### Clinical Disease Activity and Development of Neural Antibodies After Vaccination

At T6, after 1 year of follow-up and compared with the year before vaccination, we did not observe an increase in clinical activity for any of the diseases studied. Thus, the annualized relapse rate (ARR) for MS was 0.09 vs 0.19 ( $p < 0.0001$ ) and

for NMOSD/MOGAD 0.65 vs 0.35 ( $p = 0.096$ ), and no significant changes were observed in the Expanded Disability Status Scale score; the mean exacerbation for myasthenia gravis was 0 (1) vs 0.57 (0.7) ( $p = 0.53$ ).

At T3, no new CNS neural antibodies were identified in any of the 429 patients tested nor in the 395 patients tested at T6. Overall, MOG-IgG antibodies were detected in 3 adult patients with typical MS (titer 1:320, 1:320; 1:160; eTable 1, [links.lww.com/NXI/A900](https://links.lww.com/NXI/A900)), neuronal surface antibodies against unknown antigens (confirmed by live hippocampal neuronal cultures) in 2 patients with myasthenia gravis and 1 with MS, and brain myelin immunostaining (negative for MOG-IgG with CBA) in 1 patient with MS<sup>18</sup>; however, all these antibodies were already present in samples collected at T1 and remained positive at T6. MOG antibodies were also found in stored samples obtained during first presentation 6 and 8 years before vaccination in 2 of the 3 positive patients. Similarly, no new PNS antibody reactivity was observed in any of the 427 patients tested at T3.

### SARS-CoV-2 Infection Postvaccination

The frequency was analyzed in 2 periods: the first period was from April 17, 2021, to December 15, 2021, and a second in which the Omicron variant became predominant in Spain (>50%) was from December 16, 2021, to July 5, 2022. Of the 182 SARS-CoV-2 infections in 180/454 (40%) patients, 14 were in the first and 168 in the second period (patients with 1

**Table 3** Factors Associated With Humoral and Cellular Responses

Dependent variable	Independent variables	OR	95% CI	p Value	R <sup>2</sup>
Absent serologic response after 2 vaccination doses	Anti-CD20	50.0	17.0 to 143	<0.0001	0.43
	Fingolimod Other therapy	38.5 Reference	12.0 to 125	<0.0001	
	Age at vaccination, type of disease, smoking habit, lymphocytes/mm <sup>3</sup> ≤ or >500			NS	
Absent cellular response after 2 doses	Fingolimod and lymphocytes/mm <sup>3</sup> ≤ 500	14.9	5.4 to 40	<0.0001	0.16
	Other therapy and >500 lymphocyte counts	Reference		NS	
	Age at vaccination, type of therapy, type of disease, smoking habit lymphocytes/mm <sup>3</sup> ≤ or >500			NS	
Absent cellular or serologic response after 2 doses	Fingolimod and lymphocytes/mm <sup>3</sup> ≤ 500	90	10.6 to 1.000	<0.0001	0.34
	Other therapy and >500 lymphocytes/mm <sup>3</sup>	Reference		NS	
	Age at vaccination, type of therapy, type of disease, smoking habit, lymphocytes/mm <sup>3</sup> ≤ or >500			NS	
Absent serologic response after 3 doses	Anti-CD20	55.6	6.5 to 500	<0.0001	0.40
	Fingolimod Other therapy	43.5 Reference	5.1 to 333	0.001	
	Age at vaccination, type of disease, smoking habit, lymphocytes/mm <sup>3</sup> ≤ or >500			NS	
Absent cellular response after 3 doses	Anti-CD20	NS	NS	NS	0.10
	Fingolimod Other therapy	3.1 Reference	1.18 to 8.5	0.023	
	Age at vaccination, type of disease, smoking habit, lymphocytes/mm <sup>3</sup> ≤ or >500			NS	
Absent cellular or serologic response after 3 doses	Anti-CD20	4.0	1.6 to 8.9	0.03	0.14
	Fingolimod Other therapy	6.6 Reference	2.9 to 14.9	0.001	
	Age at vaccination, type of disease, smoking habit, lymphocytes/mm <sup>3</sup> ≤ or >500			NS	

Abbreviation: NS = nonsignificant.

Other treatment: no fingolimod and no anti-CD20 therapy. Lymphocytes/mm<sup>3</sup>: before first or third vaccine dose.

dose: 4, with 2 doses: 56, and with 3 doses: 122). There were no significant differences in the percentage of patients with breakthrough COVID-19 according to therapy (eTable 2, [links.lww.com/NXI/A900](https://links.lww.com/NXI/A900)). Although 7 (3.8%) patients treated with anti-CD20 therapy were hospitalized, all had mild COVID symptoms, and none required admission to ICU.

### Safety

Overall, after the first vaccine dose, the most frequent side effects were pain at the injection site (87%) and fatigue (36%) (Figure 2A; eTable 3, [links.lww.com/NXI/A900](https://links.lww.com/NXI/A900)) and fever (91%) and pain at the injection site (60%) in adolescents (eTable 4). The comparison of adverse events between adults and adolescents is shown in Figure 2B and summarized in eTable 4. No severe adverse events were identified.

### Discussion

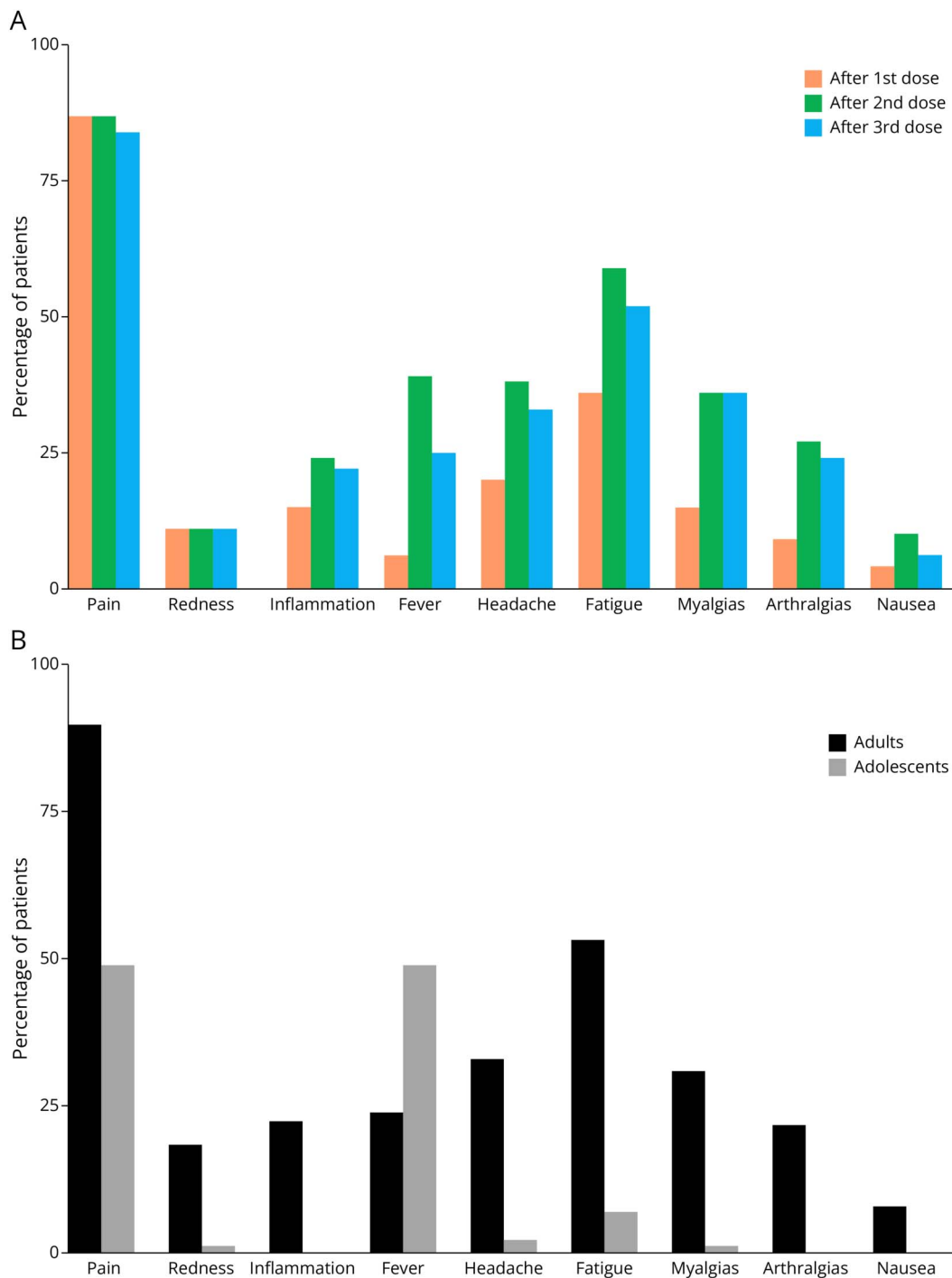
In this prospective 1-year longitudinal study on pwMS and patients with OIND, we found that mRNA COVID-19 vaccination did not exacerbate the autoimmune disease nor triggered neural autoantibodies or new autoimmune disorders. Moreover, we observed a high level of immunogenicity against SARS-CoV-2 after 2 vaccine doses, and a durable (>6 months) humoral and T-cell response after the third dose that

was associated with an improved outcome of SARS-CoV-2 infection, and a high safety profile.

The study confirmed that after the first 2 vaccination doses, most patients (>80%) developed a humoral immune response that persisted for at least 6 months albeit with declining titers of RBD antibodies,<sup>5,21</sup> but humoral responses were not attained in 40%–50% of patients receiving anti-CD20<sup>22-24</sup> or fingolimod therapies,<sup>6,23</sup> and both treatments were the main predictors of persistent seronegativity. However, most patients (>90%) developed a cellular response, although the frequency (75%) and the titer were lower in fingolimod-treated patients, and fingolimod treatment along with lymphocyte count <500 cells/mm<sup>3</sup> was the only predictor of absent cellular response.<sup>23</sup>

Similar to some,<sup>6,23,24</sup> but not all studies,<sup>5,9,22,25</sup> we found no association between a negative antibody response and total lymphocyte count or B-cell count or the time interval between the last anti-CD20 infusion and vaccination. The latter is probably because almost all patients were vaccinated a few days before the new scheduled infusion. However, the frequency of cellular response in patients treated with anti-CD20 or fingolimod was high, particularly for those on anti-CD20 therapies. Compared with other DMTs, fingolimod-treated patients showed the lowest levels of

**Figure 2** Frequency of Local and Systemic Side Effects



(A) Overall frequency of the cohort after each vaccine dose. (B) Frequencies of adult and adolescent patients with multiple sclerosis. Data after plotting the 3 surveys (after first, second, and third vaccine dose).

cellular responses; it was the drug most frequently administered in cases of humoral but no cellular responses or cases without any response (humoral or cellular). Five (35%) of the SARS-CoV-2 infections that occurred in the first 6 months of the study, including 1 reinfection, affected patients treated with fingolimod. Given that 2 of these patients had both, humoral and cellular, responses positive, and the

other 2 had only a positive cellular or antibody response, the role of the antibody response in protecting from breakthrough infection seems also important.

After a third dose, only 22% of the seronegative patients seroconverted, but the frequency for patients on anti-CD20 therapy or fingolimod was very low (13% and 21%, respectively)<sup>7,26</sup>;



however, the booster led to a specific and durable cellular response, for at least 6 months, in all patients treated with anti-CD20 therapy, similar to the experience of a previous study.<sup>8</sup> The booster also increased the cellular response in patients treated with fingolimod (80%) and reduced the proportion of patients without any response, which is different from previous studies.<sup>6,27</sup> No significant differences were seen between patients on ocrelizumab or rituximab. Of note, the humoral responses still remain quantitatively impaired after a fourth dose in patients treated with ocrelizumab.<sup>9,28</sup>

In spite of the high frequency of both humoral and cellular responses in most DMT groups (i.e., between 86% and 100%) and the lower frequencies of responses in the anti-CD20 and fingolimod groups (70% and 59%, respectively), 37% of patients developed COVID-19 during the Omicron period, with a comparable percentage of infections across all therapies. This clinical-immunologic dissociation was also observed in a study that determined the effect of different DMTs on the development of humoral and cellular responses against SARS-CoV-2 infection.<sup>29</sup> All patients in our study who required hospitalization for breakthrough COVID-19 during the second semester were on anti-CD20 therapy, although the percentage of infections in this group was not significantly different from that of untreated patients (39% vs 35%). Altogether, these findings suggest that cellular responses play an important role in providing protection against severe disease; it is known that in anti-CD20-treated patients, the cytotoxic CD8<sup>+</sup> T-cell response against the Omicron variant is reduced.<sup>8</sup>

The overall rate of infection in our study (40%) was higher than that reported in a smaller series (20%)<sup>26</sup> or a large Italian cohort of patients (7.7%),<sup>30</sup> but in these studies, the ascertainment of infection was only based on PCR results. Yet, in all studies, the outcome was good and the frequency of hospitalization was low (3.1%–8%).<sup>26,30,31</sup>

The finding that mRNA COVID-19 vaccination did not exacerbate the activity of the underlying autoimmune disease in our study, although the high frequency of breakthrough COVID-19 and that infections are well-known causes of clinical exacerbation and pseudorelapses, is in line with that of a recent study that included more than 1,200 patients with different immune-mediated inflammatory diseases.<sup>32</sup>

GBS and CNS demyelination have been the most frequently described autoimmune neurologic complications of COVID-19 vaccination, although they are very rare (<1 per 1,000,000 doses of vaccine administered).<sup>33</sup> In some patients, the occurrence of GBS has been linked to mRNA vaccines, but this is more frequently reported with viral vector-based vaccines, usually 6–8 weeks after the first dose.<sup>33–35</sup> However, the presence of ganglioside antibodies was underreported in these studies, and the prevalence of these antibodies is unknown in this setting. In our study, we did not detect ganglioside antibodies in any of the 427 patients tested 8 weeks after the first

dose, but it must be taken into account that most of the patients had been vaccinated with an mRNA vaccine.

Regarding CNS demyelination, there are case reports or small (<30 cases) series describing postvaccination transverse myelitis,<sup>36</sup> acute disseminated encephalomyelitis,<sup>37,38</sup> optic neuritis,<sup>39,40</sup> NMOSD,<sup>41</sup> or MOGAD.<sup>42,43</sup> Similar to GBS, most patients with MOGAD received the ChAdOx1 nCoV-19 vaccine within the previous 6 weeks (6–42 days). In this study, we tested more than 400 patients 8 weeks after the first dose and 1 year later, and none developed new neuronal or glial autoantibodies. Of importance, if it were not because we had archived serum samples obtained before vaccination, a few patients would have been characterized with neural antibodies induced by vaccines<sup>11</sup>; however, the archived samples already had the indicated antibodies. Therefore, the finding in our study of patients harboring unexpected antibodies for the underlying disease before vaccination supports the concept that their detection in temporal association with vaccination is not enough to prove causality.

Several considerations and limitations should be noted. The initial planned design for this prospective study included 2 vaccine doses and 1-year follow-up, but it had to be later adapted according to the course of the pandemic; therefore: (1) prolonged longitudinal dynamics of the immune response associated with 2 doses ended with a small sample size because most patients received additional doses; (2) this forced us to limit the number of studies of humoral and cellular responses related to the third dose (which includes the 4 weeks preceding and the 4 weeks after this dose); therefore, we prioritized the group whose information seemed most relevant, which included approximately 50% of patients treated with anti-CD20 and fingolimod; (3) there was a variable loss of patients at different time points; however, among 454 patients initially recruited, 322 (71%) to 428 (94%) had the immune responses assessed at each of the indicated time points, and all patients underwent clinical follow-up for 1 year, but unfortunately, MRI scans were not included in the study; and (4) the information provided refers to mRNA vaccines, mainly mRNA-1273 SARS-CoV2; therefore, we cannot generalize the findings to other COVID-19 vaccines. However, the inclusion of OIND allows us to generalize the findings to neuroinflammatory disorders other than MS.

Overall, the current findings show that mRNA COVID-19 vaccination does not exacerbate disease activity or trigger a neural autoantibody response, and associates with durable (>6 months) humoral and T-cell responses after the third dose. In the study, the outcome of patients who developed SARS-CoV-2 infection was favorable.

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## Appendix (continued)

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