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Short Report

Humoral COVID-19 vaccine response in patients with NMOSD/MOGAD during anti-IL-6 receptor therapy compared to other immunotherapies

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Abstract

Background: Data on the humoral vaccine response in patients on anti-interleukin-6 (IL-6) receptor therapy remain scarce.

Objective: The main objective of our study was to investigate the humoral response after vaccination against SARS-CoV-2 in neuromyelitis optica spectrum disorder (NMOSD)/myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) patients treated with anti-IL-6 receptor therapy. Secondarily, we analyzed relapse activity timely associated with vaccination.

Methods: In this retrospective cross-sectional multicenter study, we included 15 healthy controls and 48 adult NMOSD/MOGAD patients without previous COVID-19 infection. SARS-CoV-2 spike protein antibody titers during anti-IL-6 receptor therapy were compared to anti-CD20 antibody therapy, oral immunosuppressants, and to nonimmunosuppressed individuals.

Results: We observed 100% seroconversion in the anti-IL-6 receptor treatment group. Titers of SARS-CoV-2 spike protein antibodies were lower compared to healthy controls (720 vs 2500 binding antibody units (BAU)/mL, $p = 0.004$), but higher than in the anti-CD20 (720 vs 0.4 BAU/mL, $p < 0.001$) and comparable to the oral immunosuppressant group (720 vs 795 BAU/mL, $p = 1.0$). We found no association between mRNA-based vaccines and relapse activity in patients with or without immunotherapy.

Conclusions: Despite being lower than in healthy controls, the humoral vaccine response during anti-IL-6 receptor therapy was evident in all patients and substantially stronger compared to anti-CD20 treatment. No relevant disease activity occurred after mRNA vaccination against SARS-CoV-2.

Keywords: Vaccination, vaccine response, COVID-19, SARS-CoV-2, MOGAD, tocilizumab, satralizumab

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Introduction

Interleukin-6 (IL-6) plays a central role in humoral immunity by regulating B-cell maturation and stimulating immunoglobulin G (IgG) secretion.[1] Confirming its role in antibody-mediated diseases, high efficacy of IL-6 receptor inhibiting (anti-IL6R) monoclonal antibodies satralizumab (SAT) and tocilizumab (TCZ) has been demonstrated in neuromyelitis optica spectrum disorder (NMOSD).[2] Despite the potentially increased risk of infection, data on the humoral vaccine response in patients treated with these therapies remain scarce. Few studies demonstrated a sufficient vaccine immune response to influenza or pneumococcal vaccines during TCZ therapy, but no data on the recently approved SAT are available.[3]

The primary objective of our study was to investigate the effects of IL-6R inhibition on the humoral

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response after vaccination against SARS-CoV-2 in comparison to anti-CD20 therapy and oral immunosuppressants in NMOSD/myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Secondarily, we analyzed the incidence of relapses timely associated with vaccination.

Material and methods

We conducted a retrospective cross-sectional multicenter study in 10 university hospitals. Healthy controls (HC) and patients (⩾18 years) with a diagnosis of NMOSD according to IPND-criteria 2015[4] and MOGAD[5] were included. We investigated SARS-CoV-2 spike protein antibody (spike-ab) titers collected between May 2021 and February 2022 in patients on anti-IL-6R therapy, anti-CD20 antibodies (anti-CD20 monoclonal antibody (mAbs)), oral immunosuppressants (azathioprine (AZA)/mycophenolat mofetil (MMF)) or nonimmunosuppressed individuals. All participants denied a laboratory-confirmed or symptomatic COVID-19 infection before serum sampling. There was no change in therapy regimens prior to vaccination.

Immunoglobulin G antibodies against SARS-CoV-2 spike protein (Spike-abs) were analyzed with the Elecsys anti–SARS-CoV-2S enzyme immunoassay and SARS-CoV-2 total antibody assay (Siemens) 4 to 26 weeks after the second vaccine dose. Titers are indicated in binding antibody units (BAU)/mL according to the WHO International Standard (NIBSC Code 20/136) for transferability of results. The cutoff value for seropositivity was set at 0.8 BAU/mL. Demographic, disease-specific, vaccination, and laboratory data were collected for further analysis. Mild lymphopenia was defined as lymphocyte counts $<1500/\mu L$[6] and IgG deficiency below 700 mg/dL. Relapses were classified as temporally associated if they occurred up to 4 weeks after vaccination.

Statistical analysis

Statistical analyses were conducted using SPSS software version 26 (IBM Corp., Armonk, USA). Regression analysis was performed to predict spike-ab titers based on age, time interval between the second vaccine and spike-ab investigation, previous anti-CD20 therapy, last available prevaccination lymphocyte count, and IgG serum level. Continuous variables were compared by nonparametric statistical tests (Mann–Whitney U/Kruskal–Wallis test, significance threshold $p < 0.05$).

Results

Patient characteristics

Thirty patients with NMOSD (25 AQP4-IgG$^+$, 5 AQP4-IgG$^-$/MOG-IgG$^-$), 18 with MOGAD, and 15 HC were included (Table 1). They were mostly vaccinated with BNT162b2/Comirnaty® ($n=50$, 79%), followed by a combination of Comirnaty® and ChAdOx1/Vaxzevria® ($n=10$, 16%) or mRNA-1273/Spikevax® ($n=3$, 5%). Thirty-nine of 48 patients (81%) received immunotherapy, including rituximab ($n=17$, 44%), anti-IL6R therapy ($n=13$, 33%, 4 SAT/9 TCZ), and oral immunosuppressants ($n=9$, 23%, 6 AZA/3 MMF).

Effect of different immunotherapies on spike-ab titers

Seropositivity rate was 100% in patients on anti-IL-6R therapy, oral immunosuppressants, and those without immunotherapy. Only 41% of patients treated with anti-CD20 mAbs were seropositive (Table 1).

Patients on anti-IL-6R inhibitors had significantly lower spike-ab titers than HC (720 vs 2500 BAU/mL, $p=0.004$). Vaccine response in this group was significantly stronger compared to anti-CD20 mAbs (720 vs 0.4 BAU/mL, $p<0.001$), and similar to oral immunosuppressants (720 vs 795 BAU/mL, $p=1.0$) (Figure 1(a)).

Univariate regression analysis revealed age ($F(1,61)=11.9$, $p=0.001$, $R^2=0.15$) and time interval between the second vaccine and spike-ab investigation ($F(1,61)=4.03$, $p=0.049$, $R^2=0.047$) as two potential predictors of humoral response. Only age remained significant in a multivariate analysis. Both factors were comparable among all treatment groups (Table 1).

Factors influencing vaccine response on anti-IL6R therapy

To explore the broad spike-ab range during anti-IL-6R therapy, subgroup analysis was performed (Figure 1(b)). Mild lymphopenia (7/13 patients, 3 SAT/4 TCZ) was associated with lower antibody titers (609 vs 2117 BAU/mL, $p=0.058$), without reaching the significance level. Neither previous treatment with Rituximab (RTX) (7/13, median 833 days before vaccination, 746 vs 456 BAU/mL, $p=0.667$), nor IgG deficiency (735 vs 502 BAU/mL, $p=0.575$) influenced the humoral immune response.

Table 1. Clinical characteristics, seropositivity rate, and humoral vaccine response in patients and healthy controls.

	NMOSD/MOGAD				HC ($n=15$)
	Anti-IL6R ($n=13$)[a]	Anti-CD20 ($n=17$)[b]	Oral IT ($n=9$)[b]	No IT ($n=9$)	
Female sex, *n* (%)	12 (93)	16 (94)	5 (56)	7 (78)	11 (73)
Age, years, median (range)	48 (23–62)	49 (29–68)	42 (32–72)	34 (20–63)	33 (22–67)
AQP4-IgG+/-IgG-/MOG-IgG+	8/0/5	12/3/2	2/2/5	3/0/6	–
Disease duration, years, median (range)	9 (3–42)	10 (2–40)	19 (15–33)	10 (1–22)	–
Duration of treatment, months, median (range)	29 (10–139)	56 (10–172)	40 (21–181)	–	–
Vaccination type					
Comirnaty, *n* (%)	12 (92)	15 (88)	7 (78)	6 (67)	10 (67)
Comirnaty/Vaxzevria, *n* (%)	0	1 (6)	1 (11)	3 (33)	5 (33)
Spikevax, *n* (%)	1 (8)	1 (6)	1 (11)	0	0
Spike-ab seropositivity, *n* (%)	13/13 (100)	7/17 (41)	9/9 (100)	9/9 (100)	15/15 (100)
Spike-ab titer, BAU/mL, median (range)	720 (102–2500)	0.4 (0–213)	795 (250–2500)	2500 (181–2500)	2500 (809–2500)
Time btw. 2nd vaccination and spike-ab, days, median (range)	72 (22–154)	67 (28–174)	77 (48–138)	91 (39–169)	76 (34–165)
Lymphopenia, *n* (%)	7/13 (54)	7/16 (44)	2/9 (22)	1/6 (17)	–
IgG deficiency, *n* (%)	6/12 (50)	3/15 (20)	0/6	0/4	–
Pretreatment with RTX, *n* (%)	7/13 (54)	–	0/8	1/7 (14)	–
Time between last anti-CD20 and first vaccination, days (range)	833 (317–4357)	136 (76–289)	–	508	–

anti-IL6R: IL-6 receptor inhibiting monoclonal antibodies; HC: healthy controls; IT: immunotherapy; MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD: Neuromyelitis optica spectrum disorder; RTX: rituximab; spike-ab: Immunoglobulin G antibody against SARS-CoV-2 spike protein.
[a]Three of 13 patients are treated with concomitant steroid therapy.
[b]One patient from the group is treated with concomitant steroid therapy.

Relapse activity after vaccination

Only one MOGAD patient with recurrent optic neuritis (13 in 4 years, current treatment TCZ/prednisolone) experienced another attack 1 week after the first Comirnaty® vaccination. One week prior to vaccination prednisolone dose was tapered (from 12.5 to 10 mg). No further relapses were observed after both vaccinations in the other 47 patients, including 11 without immunotherapy (6 MOGAD, 5 AQP4-IgG$^+$-NMOSD).

Discussion

We observed seroconversion in all patients on anti-IL6R therapy; however, spike-ab titers were significantly lower than in HC. These findings are in line with rheumatological studies, demonstrating sufficient antibody response rate to influenza/pneumococcal and SARS-CoV-2 vaccinations during TCZ treatment.[3,7]

Anti-IL-6R-treated patients had a significantly better humoral immune response than those on RTX, the most frequent long-term therapy for NMOSD/MOGAD in Germany. For anti-CD20 mAbs, lower spike-ab titers were already documented in multiple sclerosis (MS).[8] Even though IL-6 is an important driver of B-cell maturation and antibody production and TCZ/SAT can result in significant functional changes in these cells, no B-cell depletion itself occurs in contrast to RTX.[1]

We observed a broad range of spike-ab titers in the anti-IL-6R therapy group. Previous anti-CD20 treatment seems to have no significant influence on the spike-ab titers. As previously reported lymphocyte count influences the humoral COVID-19 vaccine response in MS[9]; similarly, we observed a trend to lower absolute spike-ab titers in patients with mild lymphopenia not reaching the significance level probably due to a small sample size.

Vaccination led to no relevant disease exacerbation, besides one patient with a very actively relapsing MOGAD and simultaneous prednisolone tapering. Previously relapse activity has been described mostly after Vaxzevria® vector-vaccination in MS and MOGAD[10]; however, most patients in our study received mRNA-based vaccines.

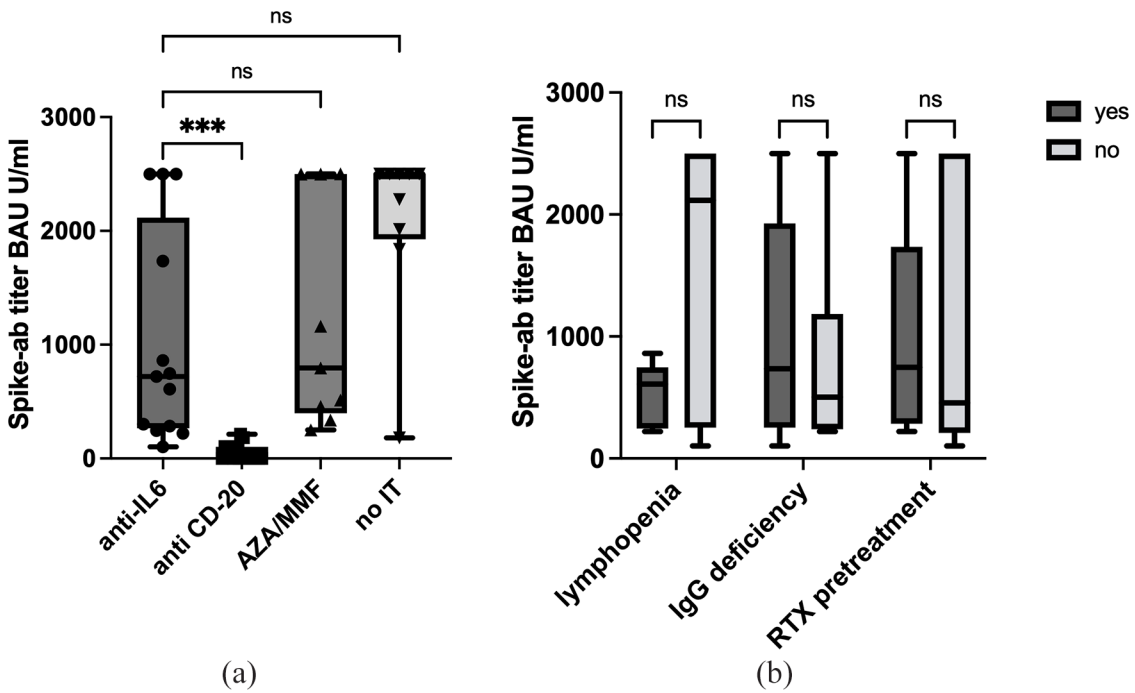

Figure 1. Boxplots showing SARS-CoV2 spike protein-specific antibodies (BAU/mL) in NMOSD/MOGAD patients separated for all immunosuppressants, anti-IL-6 $n=13$, anti-CD20 $n=17$, AZA/MMF $n=9$, no IT $n=9$ (a) and for anti-IL6 therapy alone (b), according to possible influencing factors, lymphopenia $n=7$, IgG deficiency $n=6$, RTX pretreatment $n=7$. Data were analyzed with a Kruskal–Wallis test.
AZA: azathioprin; IT: immunotherapy; MMF: mycophenolat-mofetil; ns: not significant; RTX: rituximab.
***$p<0.001$.

The main limitations of our study are the observational nature, resulting in heterogeneous patient groups and vaccine types. We studied neither the T-cell immune response nor the COVID-19 infection rate postvaccination.

In conclusion, despite being lower than in HC, humoral vaccine response with anti-IL6R therapy was evident in all patients and substantially stronger compared to anti-CD20 treatment. An mRNA vaccination against SARS-CoV-2 seems not to be associated with increased disease activity in NMOSD/MOGAD.

Declaration of conflicting interests

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Ethics

The local ethics committees of each participating NEMOS center approved this study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

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