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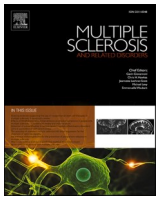

Correspondence

Humoral response to SARS-CoV-2 infection and vaccines against COVID-19 in patients with neuromyelitis optica spectrum disorders: Impact of immunosuppressive treatment

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ABSTRACT

The aim of this study was to evaluate the humoral response to the SARS-CoV-2 infection and vaccination in the NMOSD patients, treated with various immunosuppresants (ISs). Serum IgG against the complete sequence of the receptor binding domain of the spike protein was measured using ELISA SARS-CoV-2 IgG, INEP, Belgrade. Seroconversion occurred in 8/10 patients with COVID-19, and in 5/9 after vaccination. One out of four patients treated with inebilizumab seroconverted (after COVID-19); antibodies were not detected in any of the remaining 3 patients who were vaccinated. Antibodies developed after COVID-19 in 4/5 patients treated with azathioprine and all treated with mycophenolate-mofetil, and after vaccination, in 5/6 patients treated with these ISs. Post-vaccination humoral response was impaired in our NMOSD patients treated with B-cell depleting therapies; seroconversion occurred in almost all patients treated with conventional synthetic disease modifying ISs.

1. Introduction

Patients with neuromyelitis optica spectrum disorder (NMOSD) represent one of the high-risk groups for the potential development of severe COVID-19 infection, being a chronic disabling neurological condition, treated with the immunosuppressants (ISs) (Abboud et al., 2020; Drulovic et al., 2019).

The elicited humoral immunity, after COVID-19 infection and vaccination, is not clearly defined, yet, in the NMOSD patients treated with the various IS (Louapre et al., 2022; Maillart et al., 2020). Until now, in a French case series and a very recent cohort study, performed in a small number of NMOSD patients, it has been shown that SARS-CoV-2 antibody response was decreased after COVID-19 infection in subjects treated with B-cell depleting therapies (Louapre et al., 2022; Maillart et al., 2020).

The aim of this study was to evaluate the humoral response to the SARS-CoV-2 infection and vaccination in our NMOSD patients, treated with various ISs.

2. Methods and materials

Fifty three NMOSD patients who accepted to participate in our previous study (Jovicevic et al., 2022) were contacted by phone, between April 10, 2021 and September 6, 2021, in order to obtain current information regarding COVID-19 and vaccination against SARS-CoV-2. Out of this cohort, 15 patients had COVID-19 and 9 were vaccinated. They have been invited to be serologically tested, and all vaccinated persons and 10/15 with COVID-19 accepted. In one case, in which lethal outcome occurred due to COVID-19, sample was taken from the laboratory biobank. Five patients refused to participate (2 bed-ridden and 3 living distant). Demographic and clinical characteristics were extracted from the Hospital registry. Data related to the diagnosis of the COVID-19 infection and vaccination against SARS-CoV-2 in our patients has been already described (Jovicevic et al., 2022).

The informed consent was waived. The study was approved by the Clinic of Neurology UCCS Institutional Review Board.

The procedure of the detection of IgG class antibodies against SARS-CoV-2 virus in sera samples was performed using ELISA SARS-CoV-2 IgG (INEP, Belgrade, Serbia), as previously described (Drulovic et al., 2021). Briefly, the specificity of the test is based on recombinant SARS-CoV-2 proteins, immobilized on ELISA microtiter plate, including Spike subunit covering the complete sequence of receptor binding domain (RBD).

2.1. Statistical analysis

Statistical analysis includes methods of descriptive statistics. Comparison of values between two groups is performed by using ANOVA. The difference with p-value less than 0.05 is considered as statistically significant.

3. Results

A total of 15 patients with NMOSD were completely evaluated for COVID-19 infection and vaccination against SARS-CoV-2. Nine patients reported vaccination against SARS-CoV-2 between January 28, 2021 and August 27, 2021, and 10 subjects had COVID-19 infection in the same period. Additionally, it has to be emphasized that four of these patients reported vaccination after COVID-19 infection. There were 12 female/3 male patients; mean age was 47.8 ± 14.9 (range, 26–72) years.

Seroconversion was detected in 8/10 patients with COVID-19, and in 5/9 after vaccination. Four of these subjects had both COVID-19 and vaccination.

There was no statistically significant difference in the mean time period between blood sampling and either COVID-19 onset or the date of the last vaccination (4.3 ± 3.1 months, and 3.6 ± 2.0 months, respectively) ($p = 0.577$). For the patients who had both, COVID-19 and were

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vaccinated, we analyzed the data related to the last event.

Administration of ISs was stable in 12 (80%) patients (azathioprine-AZA, $n = 5$, mycophenolate-mofetil- MMF, $n = 3$ and inebilizumab, $n = 4$) for at least one year prior to the study entry, and have not been interrupted during their COVID-19. In the remaining three (20%) patients, ISs were not applied.

One out of four patients treated with inebilizumab, seroconverted after COVID-19; antibodies were not detected in none of the three vaccinated. In 4/5 patients treated with AZA and all treated with MMF, antibodies had been developed after COVID-19, and after vaccination, in 5/6 patients treated with these ISs.

Nine patients received vaccines against SARS-CoV-2: 7 inactivated Sinopharm vaccine, one mRNA-vaccine Pfizer-BioNTech, and one viral vector vaccine Sputnik V. Five patients (55.6%) developed seroconversion after vaccination; one immunized with Pfizer-BioNTech and one with Sputnik V (both treated with AZA), and the remaining three, after Sinopharm vaccine (two treated with AZA and one with MMF). Four patients, immunized with Sinopharm, who did not develop antibodies against SARS-CoV-2 were treated with inebilizumab ($n = 3$) and AZA ($n = 1$).

4. Discussion

This is one of the first case series studies, demonstrating the possibility to develop humoral response to SARS-CoV-2 in NMOSD patients, with and without maintenance ISs, after COVID-19 infection and/or vaccination. In our study, seroconversion occurred in 8/10 NMOSD patients after COVID-19, and in 5/9 after vaccination. One out of four patients, treated with inebilizumab, seroconverted after COVID-19 and antibodies were not detected in none of the remaining 3 patents who were vaccinated. In 4/5 patients treated with AZA and all treated with MMF, antibodies developed after COVID-19, and, after vaccination, in 5/6 patients treated with these ISs. Thus, it was demonstrated that in our NMOSD patients treated with B-cell depleting therapies post-vaccination humoral response was impaired. Additionally, in almost all patients treated with conventional synthetic disease modifying ISs, seroconversion occurred after COVID-19 and vaccination.

Recently published studies demonstrated results related to the development of antibody response under conventional ISs and B-cell depleting therapies which are in line with our findings (Maillart et al., 2020; Loupre et al., 2022; Sieiro Santos et al., 2022). In the first reported case with NMOSD, who developed COVID-19 under B-cell depleting therapy (ofatumumab), SARS-CoV-2 serology was negative (Maillart et al., 2020). Additionally, it has been shown that all five patients with MS/NMOSD affected by COVID-19 and treated with B-cell-depleting therapies had negative SARS-CoV-2 serology (Maillart et al., 2020). More recently, in the French cohort study, out of four NMOSD patients, two were treated with rituximab, one with ofatumumab, and one with MMF. Patient with MMF had positive SARS-CoV-2 serology, and in the total cohort that comprise persons with MS and NMOSD, seroconversion rate for patients treated with anti-CD20 was low, 47.6% (Loupre et al., 2022). It has been already demonstrated that patients with MS, treated with B-cell depleting therapies, generate lower antibody response rate, following vaccination (Achiron et al., 2021; Sormani et al., 2021). On the other hand, it has to be emphasized that recently, new B-cell depleting therapy, inebilizumab, a humanized anti-CD19 monoclonal antibody, was approved for the treatment of NMOSD (Cree et al., 2019).

Findings from the observational study conducted to characterize the immune response to mRNA SARS-CoV-2 vaccines in patients with immune-mediated rheumatic diseases (IMRDs), and to assess the impact of ISs and biological therapies in the elicited immune response, has just been reported (Sieiro Santos et al., 2022). In line with our findings, it has been demonstrated that in patients with IMRDs, monotherapy with MMF and AZA did not significantly affect seroconversion rates. On the other hand, rituximab showed impaired humoral responses (31% responders), but cellular responses were often preserved.

In conclusion, post-vaccination humoral response was impaired in our NMOSD patients treated with B-cell depleting therapies. After COVID-19 and vaccination, seroconversion occurred in almost all patients treated with conventional synthetic disease modifying ISs. Keeping in mind the importance of cellular immune response after immunization, our data regarding the development of humoral immune response after various types of vaccines against SARS-CoV-2, may be still potentially useful in future considerations of vaccination strategies for NMOSD patients, especially those treated with B-cell depleting therapies.

Declaration of Competing Interest

Vanja Jovicevic has no conflict of interest. Jovana Ivanovic has no conflict of interest. Nikola Momcilovic has no conflict of interest. Marko Andabaka has no conflict of interest. Olivera Tamas has been an speaker for Medis, Merck, Teva, Hemofarm, Novartis and Roche. Nikola Veselinovic has been an speaker for Medis, Merck, Teva, Hemofarm, Novartis and Roche. Danica Cujic has no conflict of interest. Marija Gnjatovic has no conflict of interest. Sarlota Mesaros has been an advisor or speaker for Medis, Merck, Teva, Hemofarm, Sanofi, and Roche. Tatjana Pekmezovic has been an advisor or speaker for Sanofi-Genzyme, Medis, Hemofarm, Merck, Teva, Janssen, and Roche. Jelena Drulovic has been an advisor or speaker for Bayer HealthCare, Sanofi-Genzyme, Medis, Merck, Teva, Novartis, Biogen, Hemofarm, Janssen, and Roche.

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