Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Original article

Impact of disease-modifying treatments on humoral response after COVID-19 vaccination: A mirror of the response after SARS-CoV-2 infection

K. Bigaut [a,b,*], L. Kremer [a,b], M. Fleury [a], L. Lanotte [a,b], N. Collongues [a,b], J. de Seze [a,b]

[a] Department of Neurology, hôpitaux universitaires de Strasbourg, 1, avenue Molière, 67200 Strasbourg, France
[b] Clinical Investigation Center, hôpitaux universitaires de Strasbourg, Strasbourg, France

INFO ARTICLE

ABSTRACT

Objective. – To analyze the humoral response after COVID-19 vaccination in patients with multiple sclerosis (MS) according to disease-modifying treatments (DMTs) and in comparison with the humoral response after SARS-CoV-2 infection.

Methods. – We included 28 MS patients with serological results after COVID-19 vaccination (Pfizer-BioNTech or Moderna ARNm) and 61 MS patients with serological results after COVID-19 (COVID-19 group) among patients followed up at the MS Center of Strasbourg, France, between January and April 2021. The primary endpoint was the IgG index according to DMTs (anti-CD20 mAb, sphingosine 1-phosphate receptor [S1PR] modulator and other treatments) and COVID-19 vaccine or COVID-19 groups.

Results. – In the vaccinated MS patients, the median IgG index was lower in patients treated with anti-CD20 mAb and in patients treated with S1PR modulator compared to patients receiving other or no DMTs (4.80 [1.58–28.6], 16.5 [16.3–48.5], 1116 [434–1747] and 1272 [658–1886], respectively, $P < 0.001$). Similar results were found for MS patients after COVID-19.

Conclusions. – Patients with MS and treated with S1PR modulators or anti-CD20 mAb had a reduced humoral response after COVID-19 vaccine.

© 2021 Elsevier Masson SAS. All rights reserved.

1. Introduction

The development of vaccines and the capacity to implement quick and large vaccination campaigns play a key role in COVID-19 pandemic control. The Pfizer-BioNTech (Brooklyn, NY, USA) and Moderna (Cambridge, MA, USA) COVID-19 mRNA vaccines received authorization by the European Medicines Agency in December 2020.

Among patients with multiple sclerosis (MS), those treated with anti-CD20 monoclonal antibodies (mAb) have a higher risk of severe COVID-19 leading to their being vaccinated as a priority [1,2]. However, a reduced humoral response was observed after tetanus, seasonal flu and pneumococcus

vaccinations in this population. Only limited data are available on the immune response after COVID-19 vaccinations in MS patients [3].

The objective of our study was to analyze the humoral response after COVID-19 vaccination in MS patients according to disease-modifying treatments (DMTs) and in comparison with the humoral response after COVID-19.

2. Methods

2.1. Patients

We included 28 MS patients with serological results after COVID-19 vaccination and 61 MS patients with serological results after COVID-19 between January and April 2021 from the MS center of Strasbourg, France.

All 28 vaccinated patients had received 2 doses of Pfizer-BioNTech or Moderna COVID-19 vaccine.

For the 61 MS patients with COVID-19, COVID-19 diagnostic criteria were: positive SARS-CoV-2 PCR on nasopharyngeal swab (40/61, 65.6%); or typical thoracic computed tomography (CT) abnormalities (ground-glass opacities) in epidemic areas (8/61, 13.1%); or anosmia or ageusia of sudden onset in the absence of rhinitis or nasal obstruction (23/61, 37.7%); or COVID-19 typical symptoms (triad of cough, fever and asthenia) in an epidemic zone of COVID-19 (43/61, 70.5%).

Collected data were: age, sex, disease-modifying treatment (DMT) at the time of vaccination or COVID-19 (anti-CD20 mAb, sphingosine 1-phosphate receptor [S1PR] modulator and other treatments) and the time between COVID-19 or COVID-19 vaccination and the serology.

The primary endpoint was the IgG index according to DMTs in the COVID-19 vaccine or COVID-19 groups.

2.2. SARS-CoV-2 antibody detection

Serum samples were tested using the Abbott or Roche SARS-CoV-2 IgG assay (spike protein). Tests were classified as positive if the index exceeded the threshold defined by the manufacturer (range of the threshold between 0.72 and 1.54 U/ml).

2.3. Standard Protocol Approvals, Registrations, and Patient Consent

This study was approved by local ethics committee. All patients gave written informed consent to be included in the cohort.

2.4. Statistical analysis

Descriptive analyses were performed with results presented as means (standard deviation) and median (interquartile range [IQR]).

Only univariate analyses were done because of the limited size of the population expected for serological response according to COVID-19 vaccine and COVID-19 groups, using a linear regression model adjusted for age, sex, time between the onset of COVID-19 or the first dose of the vaccine and the serology and the DMT group. For this multivariate analysis, as the distribution of residuals did not following a normal distribution, we calculated confidence intervals and p-value by bootstrap (1000 iterations) [4].

Table 1 – Characteristics of the cohort.				
Characteristics	Vaccinated group (n = 28)	COVID-19 group (n = 61)	P-value	Test
Age (years), median [IQR]	53.5 [41.0; 59.2]	47.0 [35.0; 57.0]	0.25	Mann-Whitney
Female, n(%)	23 (82%)	41 (67%)	0.15	χ^2
No. of days between first and second dose of vaccine, median [IQR]	27.0 [25.8; 28.0]	–	–	–
No. of days between of the onset of COVID-19 or first dose of the vaccine and the serology, median [IQR]	45.5 [41.0; 52.0]	116 [76.0; 310]	**<0.001**	Mann-Whitney
IgG index, median [IQR]	145 [15.7; 1034]	36.8 [4.74; 85.0]	**0.019**	Mann-Whitney
Disease-modifying treatment group, n(%)				
No treatment	2 (7.1%)	13 (21%)	**<0.01**	χ^2
Other	12 (43%)	34 (56%)	–	–
S1PR modulator	3 (11%)	9 (15%)	–	–
Anti-CD20 monoclonal antibody	11 (39%)	5 (8.2%)	–	–
Disease-modifying treatment, n(%)				
No treatment	2 (7.1%)	13 (21%)	**<0.01**	Fisher
Glatiramer acetate	0 (0%)	7 (11%)	–	–
Interferon β-1a	1 (3.6%)	2 (3.3%)	–	–
Teriflunomide	3 (11%)	9 (15%)	–	–
Dimethyl fumarate	7 (25%)	6 (9.8%)	–	–
Natalizumab	1 (3.6%)	7 (11%)	–	–
Mycophenolate mofetil	0 (0%)	3 (4.9%)	–	–
S1PR modulator	3 (11%)	9 (15%)	–	–
Anti-CD20 monoclonal antibody	11 (39%)	5 (8.2%)	–	–
IQR: interquartile range; S1PR: sphingosine 1-phosphate receptor. P-value in bold if <0.05.				

Table 2 – IgG index after anti-SARS-CoV-2 vaccination and after COVID-19.

DMT group	Mean (sd)	Median [IQR]	Min	Max	n	P-value	Test
Vaccinated group (n = 28)							
No DMT	1272 (±1737)	1272 [658–1886]	43.8	2500	2	**<0.001**	Kruskal-Wallis
Other DMTs	2965 (±6471)	1116 [434–1747]	209	23383	12	–	–
S1PR modulator	37.7 (±37.0)	16.5 [16.3–48.5]	16.1	80.4	3	–	–
Anti-CD20 mAb	59.2 (±145)	4.80 [1.58–28.6]	0.2	492	11	–	–
COVID-19 group (n = 61)							
No DMT	60.3 (±62.2)	36.8 [8.5–85.0]	0.075	200	13	**0.017**	Kruskal-Wallis
Other DMTs	1022 (±4746)	65.8 [13.3–168]	0.07	27776	34	–	–
S1PR modulator	17.8 (±22.6)	5.0 [0.46–35.0]	0.076	59.0	9	–	–
Anti-CD20 mAb	16.4 (±23.6)	0.25 [0.07–30.1]	0.01	51.6	5	–	–

DMTs: disease-modifying treatments; IQR: interquartile range; mAb: monoclonal antibody; S1PR: sphingosine 1-phosphate receptor; sd: standard deviation. P-value in bold if <0.05.

3.   Results

We included 28 MS patients in the COVID-19 vaccine group and 61 MS patients in the COVID-19 group.

3.1.   Descriptive analysis

The descriptive analysis is summarized in Table 1. The proportion of patients treated with anti-CD20 mAb was higher in the COVID-19 vaccine group (11 patients [39%]) than in the COVID-19 group (5 patients [8.2%]; $P < 0.01$). Patients treated with anti-CD20 mAb were more often vaccinated than other patients, due to the recommendations of the French National Authority for Health prioritizing this population at a higher risk of severe COVID-19 [1,5]. The delay between the onset of COVID-19 and serology was greater than the delay between the first dose of the vaccine and serology, due to the unavailability of serology during the first wave of the outbreak.

3.2.   Humoral response after COVID-19 vaccination and COVID-19

In vaccinated MS patients, the median IgG index was lower in patients treated with anti-CD20 mAb and in patients treated with S1PR modulator compared to patients receiving other or no DMT (4.80 [1.58–28.6], 16.5 [16.3–48.5], 1116 [434–1747] and 1272 [658–1886], respectively, $P < 0.001$), indicating a weaker humoral response to vaccination (Table 2). A similar result was found for MS patients after COVID-19 (Table 2).

In the multivariate analysis, no differences were found between the IgG index in MS patients after COVID-19 vaccination and MS patients after COVID-19 (coefficient = 649 [−2622; 3918], $P = 0.58$).

3.3.   Sensitivity analysis

Among the 11 patients treated with anti-CD20 mAb, patients vaccinated in 4 months from the last infusion had a weak humoral response (Fig. 1). After 4 months, 2/3 patients developed a humoral response and the patient with a low IgG index had anti-CD20 mAb infusion between vaccination and the serology (37 days after the first dose of vaccine and 15 days before the serology) probably influencing the result.
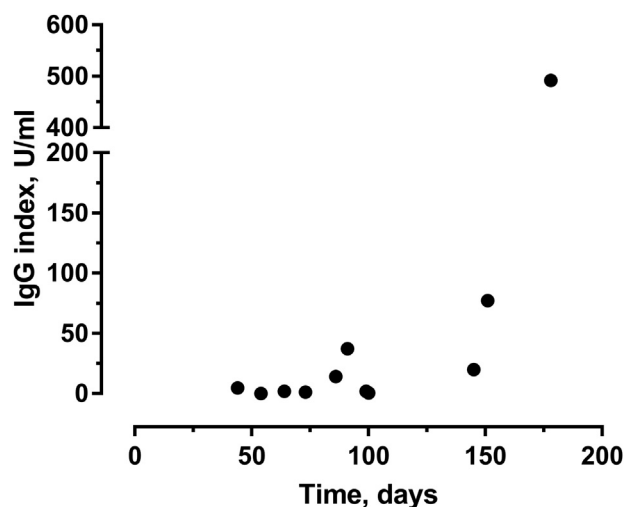

Fig. 1 – IgG index according to the time between the last infusion of anti-CD20 mAb and the first dose of COVID-19 vaccine.

4.   Discussion

Our study showed a reduced humoral response after COVID-19 vaccine in MS patients treated with anti-CD20 mAb or S1PR modulator compared to other patients. These results mirrored the humoral response in MS patients after COVID-19.

Patients treated with anti-CD20 mAb or S1PR modulator had a reduced humoral response to pneumococcal or seasonal influenza vaccines [6,7]. Achiron et al. showed similar results after COVID-19 vaccination with only 22.7% of serological positivity in patients treated with ocrelizumab (10/44) and 3.8% with fingolimod (1/26) compared to 100% in patients treated with cladribine (23/23) or without DMT (32/32) [3]. Thus, these patients could be at risk of infection with SARS-CoV-2 even after vaccination. However, only one patient, treated with ocrelizumab, was reported to have vaccine failure. This patient developed COVID-19 symptoms 19 days after receiving the second dose of Pfizer-BioNTech COVID-19 vaccine and serological assay was negative for IgG to the spike protein. This apparent low frequency of vaccine failure in

patients treated with anti-CD20 mAb could be explained by preservation of a cellular response to vaccination [8].

Although the size of the population is very small and so, interpretation should be taken with caution, a time from the last infusion of anti-CD20 mAb higher than 4 months seems to play a role in the humoral response after vaccination probably linking to the beginning of B-cells repopulation which around of 6 months [9]. Thus, to increase the humoral response after COVID-19 vaccination, the first dose may be delayed to up to 4 months from the last infusion of anti-CD20 mAb and the next infusion need to be potentially delayed of 1 month after the second dose. However, the risk of rebound of disease activity must be considered on a case-by-case basis.

Our study has some limitations. First, the small size of the cohort limited the power of the study, especially for a comparison between the various DMTs. Second, the comparison of humoral response after COVID-19 vaccine and COVID-19 was limited by the large variation in the delay between the onset of COVID-19 or the first dose of COVID-19 vaccine and the serology.

In conclusion, the humoral response after COVID-19 vaccination was lower in MS patients treated with S1PR modulator or anti-CD20 mAb. In France, based on previous results of humoral response after vaccination, patients treated with anti-CD20 mAb receive three doses of COVID-19 vaccine but data is needed on the effectiveness of this recommendation. Our results need to be confirmed in a larger study, such as the COV-POPART cohort (NCT04824651) evaluating immune response to COVID-19 vaccines in specific populations, including MS patients.

Disclosure of interest

Acknowledgments

REFERENCES

[1] Sormani MP, De Rossi N, Schiavetti I, Carmisciano L, Cordioli C, Moiola L, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann Neurol 2021. http://dx.doi.org/10.1002/ana.26028.

[2] Louapre C, Collongues N, Stankoff B, Giannesini C, Papeix C, Bensa C, et al. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol 2020. http://dx.doi.org/10.1001/jamaneurol.2020.2581.

[3] Achiron A, Mandel M, Dreyer-Alster S, Harari G, Magalashvili D, Sonis P, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord 2021;14. http://dx.doi.org/10.1177/17562864211012835 [17562864211012836].

[4] Medistica. pvalue.io, a graphic user interface to the R statistical analysis software for scientific medical publications. Available on: https://www.pvalue.io 2020.

[5] Haute Autorité de Santé. La stratégie vaccinale et la liste des publics prioritaires. Ministère des Solidarités et de la Santé; 2021 [https://solidarites-sante.gouv.fr/grands-dossiers/vaccin-covid-19/publics-prioritaires-vaccin-covid-19 (accessed April 26, 2021)].

[6] Bar-Or A, Calkwood JC, Chognot C, Evershed J, Fox EJ, Herman A, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology 2020;95:e1999–2008. http://dx.doi.org/10.1212/WNL.0000000000010380.

[7] Kappos L, Mehling M, Arroyo R, Izquierdo G, Selmaj K, Curovic-Perisic V, et al. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. Neurology 2015;84:872–9. http://dx.doi.org/10.1212/WNL.0000000000001302.

[8] Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 2020;586:594–9. http://dx.doi.org/10.1038/s41586-020-2814-7.

[9] Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676–88. http://dx.doi.org/10.1056/NEJMoa0706383.