Association of Disease-Modifying Treatment and Anti-CD20 Infusion Timing With Humoral Response to 2 SARS-CoV-2 Vaccines in Patients With Multiple Sclerosis

Studies have shown the messenger RNA (mRNA) vaccine against SARS-CoV-2 is safe in multiple sclerosis (MS), but the humoral response to the vaccine was markedly reduced in patients treated with fingolimod and ocrelizumab.[1] We aimed to replicate these findings, test other disease-modifying treatments (DMTs), and investigate whether delaying anti-CD20 infusions can potentiate IgG production following vaccination.

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Methods | We performed a prospective observational cohort study at the Neurocenter of Southern Switzerland. Inclusion criteria were a diagnosis of MS (using the 2017 McDonald criteria); age older than 18 years; and being scheduled for SARS-CoV-2 mRNA vaccine (mRNA-1273 [Moderna] or BNT162b2 [Pfizer]).[2,3] Exclusion criteria were medical treatments influencing response to vaccines other than MS DMTs and a previous symptomatic laboratory-confirmed SARS-CoV-2 infection. Written informed consent was obtained during routine neurological visits and the study was approved by Canton Ticino ethics committee (CETI3863). This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Serum samples were collected at t0 (within 2 weeks prior to first vaccine dose) and t1 (21-35 days after the second dose). Quantification of IgG against SARS-CoV-2 spike receptor-binding domain was performed using a chemiluminescence microparticle immunoassay (Abbott; quantification limits, 21-40 000 AU/mL; cutoff for seropositivity = 50 AU/mL).[4] $CD19^+$ B cells were measured at t0 using fluorescence-activated cell sorting. DMTs, time since last anti-CD20 infusion, and $CD19^+$ B-cell counts were tested for association with log-transformed SARS-CoV-2 IgG using linear models adjusted by age and sex.

Results | We recruited 120 patients between February 25, 2021, and May 11, 2021, in the following treatment groups: anti-CD20 (n = 58: ocrelizumab = 32, rituximab = 25, ofatumumab = 1), sphingosine-1-phosphate receptor (S1P) modulators (n = 9: fingolimod = 7, ozanimod = 2), cladribine (n = 15), teriflunomide (n = 24), and no therapy (n = 14). All individuals received 2 vaccine doses (median [IQR] time between doses = 28 [28-30] days). Median (IQR) time between t0 and first vaccine dose and between second dose and t1 was 0 (0-0) and 26 (21-32) days, respectively.

The **Table** shows demographic and baseline SARS-CoV-2 IgG titers. Four patients had positive results at t0 (cladribine, n = 1; anti-CD20, n = 2; untreated, n = 1) and were excluded from following analyses. The percentage of patients remaining seronegative at t1 was 48.2% in the anti-CD20 group, 33.3% in the S1P modulators group, 7.1% in the cladribine group, 0% in the teriflunomide group, and 0% in the no therapy group (Table). As compared with no therapy, anti-CD20 and S1P modulators were associated with lower SARS-CoV-2 IgG ($\beta = -2.19$, $P < .001$ and $\beta = -1.92$, $P < .001$, respectively), whereas differences were not significant for teriflunomide ($\beta = -0.01$, $P = .98$) and cladribine ($\beta = -0.39$, $P = .44$) (**Figure**, A).

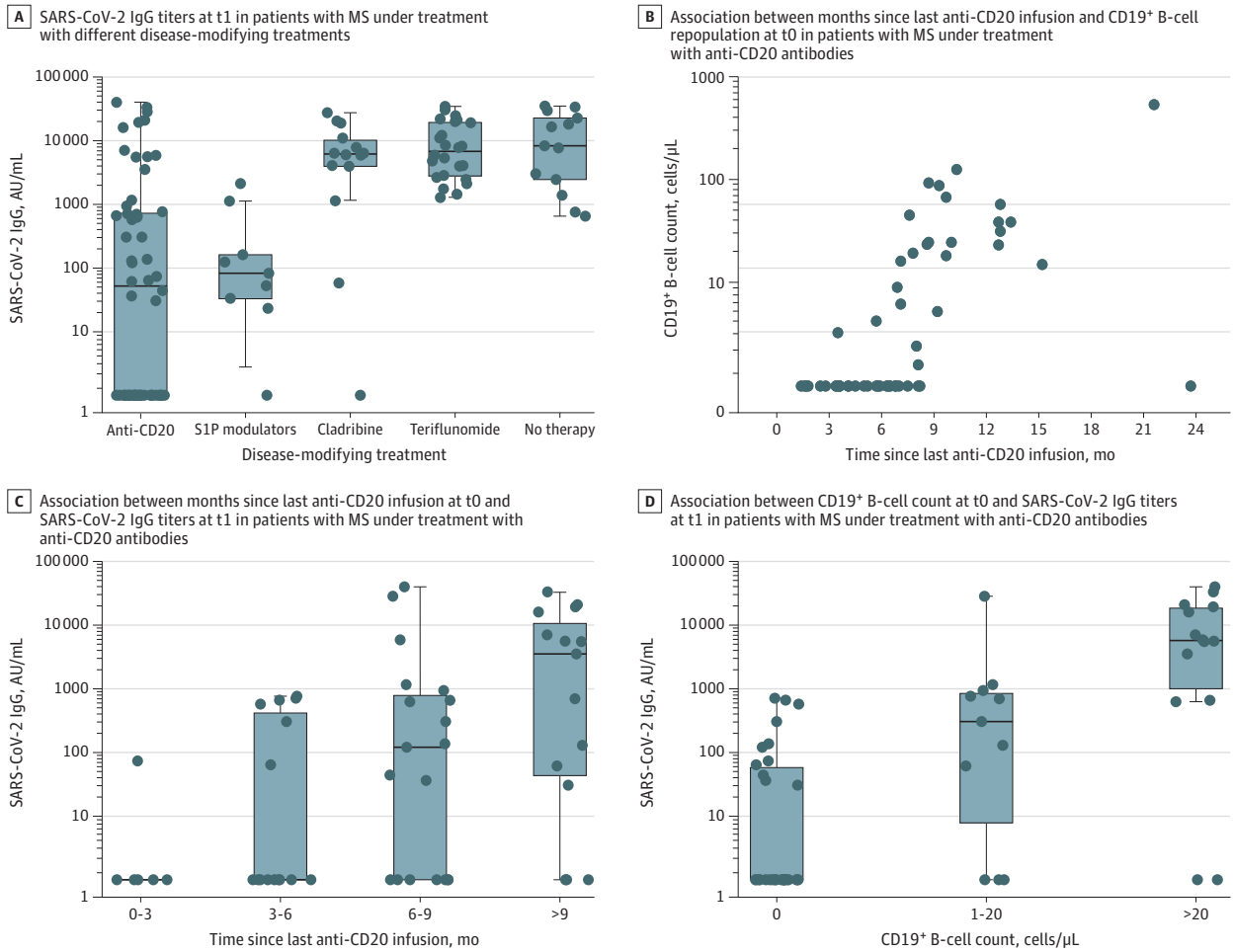
Table. Baseline Demographic Characteristics and SARS-CoV-2 IgG Serostatus at t0 and t1 of Patients With MS Included in the Study (Overall and Stratified by DMT)[a]

	No. (%)					
Variables	All patients	Anti-CD20	S1P modulators	Cladribine	Teriflunomide	No therapy
No.	120	58	9	15	24	14
Age, y, median (IQR)	55.0 (46.4-61.0)	56.0 (49.1-60.8)	52.5 (49.8-57.0)	51.0 (41.2-59.7)	55.7 (45.5-66.6)	51.8 (44.8-59.0)
Sex						
Female	74 (61.7)	39 (67.2)	5 (55.5)	7 (46.7)	13 (54.2)	10 (71.4)
Male	46 (38.3)	19 (32.8)	4 (44.5)	8 (53.3)	11 (45.8)	4 (28.6)
SARS-CoV-2 IgG status						
At t0						
Negative	116 (96.7)	56 (96.5)	9 (100.0)	14 (93.3)	24 (100.0)	13 (92.9)
Positive	4 (3.3)	2 (3.5)	0	1 (6.7)	0	1 (7.1)
At t1						
Negative	31 (26.7)	27 (48.2)	3 (33.3)	1 (7.1)	0	0
Positive	85 (73.3)	29 (51.8)	6 (66.7)	13 (92.9)	24 (100)	13 (100)
SARS-CoV-2 IgG at t1, AU/mL						
Median (IQR)	1218 (32-7798)	52 (0-724)	82 (32-160)	6175 (3982-10 194)	6853 (2791-19 322)	8309 (2451-22 685)
Geometric, mean (SD)	382.2 (43.1)	44.5 (45.3)	81.6 (9.4)	2745.5 (15.4)	6817.4 (2.8)	6876.2 (4.3)

Abbreviations: DMT, disease-modifying treatment; MS, multiple sclerosis; S1P, sphingosine-1-phosphate receptor; t0, within 2 weeks prior to first vaccine dose; t1, 21-35 days after the second dose.

[a] The analysis of SARS-CoV-2 IgG at t1 is restricted to those patients who were seronegative at t0.

Figure. SARS-CoV-2 IgG by Disease-Modifying Treatments and Association With CD19⁺ B-Cell Counts and Months Since Anti-CD20 Therapy



A, SARS-CoV-2 IgG titers at t1 (21-35 days after the second dose) in patients with multiple sclerosis (MS) under treatment with anti-CD20 antibodies, sphingosine-1-phosphate receptor (S1P) modulators, cladribine, teriflunomide, and no therapy. B, Association between months since last anti-CD20 infusion and CD19⁺ B-cell repopulation at t0 (within 2 weeks prior to first vaccine dose) in patients with MS under treatment with anti-CD20 antibodies. C, Association between months since last anti-CD20 infusion at t0 and SARS-CoV-2 IgG titers at t1 in patients with MS under treatment with anti-CD20 antibodies (3-6 vs 0-3 months: β = 0.78, P = .27; 6-9 vs 0-3 months: β = 1.50, P = .03; >9 vs 0-3 months: β = 2.45, P = .001). D, Association between CD19⁺ B-cell count at t0 and SARS-CoV-2 IgG titers at t1 in patients with MS under treatment with anti-CD20 antibodies (1-20 vs 0: β = 1.25, P = .007; >20 vs 0: β = 2.54, P < .001).

Given the evidence for low-dose rituximab in MS[5] and following the example of neuromyelitis optica, we regularly measure CD19⁺ B and CD19⁺ CD27⁺ memory B cells (at least every 3 months) and schedule ocrelizumab and rituximab infusions in stable patients only in case of CD19⁺ CD27⁺ repopulation (≥1 cell/uL). Median (IQR) time between last anti-CD20 infusion and first vaccine dose was 7.1 (4.3-9.3) months, with 19 (34.5%) and 15 (27.3%) patients receiving the first dose at 6 to 9 and more than 9 months after last anti-CD20 infusion, respectively. CD19⁺ B cells started to repopulate at 6 months after last infusion (Figure, B). There was a progressive increase in SARS-CoV-2 IgG with time since last anti-CD20 infusion (Figure, C) and CD19⁺ B-cell count (Figure, D). Associations were similar when analyzing rituximab and ocrelizumab separately (not shown). No patients had relapses while waiting for vaccination.

Discussion | In this study, the humoral response against SARS-CoV-2 at 1 month after vaccination was appropriate under treatment with cladribine and teriflunomide and diminished/absent under treatment with anti-CD20 therapies and S1P modulators. Delaying anti-CD20 infusions by 3 to 6 months before vaccination could, however, increase the probability of developing appropriate humoral responses, especially in selected clinically and radiologically stable patients. Limitations of the study include the short follow-up (only 1 month after vaccination), the relatively small sample size (especially of S1P modulators and cladribine groups), and the lack of data on additional DMTs. Future studies should aim at investigating antibody dynamics over time, if and how T cell–mediated responses[6] after vaccination are influenced by DMTs, and whether these biological measures actually reflect vaccine efficacy in terms of preventing severe SARS-CoV-2 infection.

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Visual Neglect After an Isolated Lesion of the Superior Colliculus

Based on electrophysiological data from nonhuman primates and other species, models of visual attention predict that, in humans, the midbrain superior colliculus (SC) represents the last downstream structure of a large fronto-subcortical attentional network.[1] This view is partly supported by human case studies showing that visuospatial inattention, often referred to as *visual neglect*, can occur after extensive brain lesions affecting, among others, the SC.[1] Here, we show the rare case of a patient with a small lesion solely confined to the SC, confirming the models' prediction and demonstrating that, in humans, an isolated SC lesion may result in contralesional visual neglect.

The SC receives retinal input predominantly from the contralateral visual hemifield, striate cortex, prefrontal cortex, frontal eye field, and parietal cortex.[1] It processes visual input and controls the orientation of head and eye movements in response to visual stimuli. Experiments in animals have shown that the SC is also implicated in attentional mechanisms. For instance, inactivation of the SC in monkeys or cats results in neglect-like signs to targets presented in the contralateral visual field.[1] However, a review of the PubMed database revealed that, to date, no direct evidence exists to show that an isolated lesion of the SC produces contralateral visual neglect in humans.

Methods | A woman in her 40s presented with a small abscess confined to the right SC (**Figure 1**).[2] She was otherwise healthy. Because the data measured were part of a routine clinical examination and not a study, institutional board review approval did not apply. The patient gave explicit written consent for the use of her clinical data for research purposes and publication. The data of the 15 healthy control individuals were acquired as part of another study on free visual exploration, which was approved by the Ethics Committee Nordwest and Zentralschweiz, Switzerland.

The unilateral involvement of the SC enabled us to observe an asymmetry in visual attention deployment, directly demonstrating the role of this structure in the latter. Our experimental protocol used a free visual exploration paradigm,[3] quantifying visual attention deployment in the left and right hemispace by means of the horizontal distribution of visual fixations. We predicted that the mean number of fixations and the cumulative fixation duration would be decreased within the left contralesional and increased within the right ipsilesional hemispace. In addition, as previous data showed an ipsilesional bias in early attentional orientation in neglect,[3] we also tested the hypothesis that the first saccade would be less frequently directed toward the contralesional left hemispace. 2-sided *P* values were statistically significant at $P < .05$. Analyses were done using Singlims.[4]

Results | Three months after diagnosis and medical treatment, the analysis of the free visual exploration behavior revealed a mean gaze position of 2.143° visual angle, above the cutoff of 1.333°, indicating neglect.[3] Statistical analyses[4] (**Figure 2**), comparing the patient's oculomotor data against those derived from