CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Longitudinal T-Cell Responses After a Third SARS-CoV-2 Vaccination in Patients With Multiple Sclerosis on Ocrelizumab or Fingolimod

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Neurol Neuroimmunol Neuroinflamm 2022;9:e1178. doi:10.1212/NXI.0000000000001178

Abstract

Objectives

To evaluate whether a third vaccination shows an added effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) T-cell responses in patients with multiple sclerosis treated with ocrelizumab or fingolimod.

Methods

This is a substudy of a prospective multicenter study on SARS-CoV-2 vaccination in patients with immune-mediated diseases. Patients with MS treated with ocrelizumab, fingolimod, and no disease-modifying therapies and healthy controls were included. The number of interferon (IFN)-γ secreting SARS-CoV-2–specific T cells at multiple time points before and after 3 SARS-CoV-2 vaccinations were evaluated.

Results

In ocrelizumab-treated patients (N = 24), IFN-γ–producing SARS-CoV-2–specific T-cell responses were induced after 2 vaccinations with median levels comparable to healthy controls (N = 12) and patients with MS without disease-modifying therapies (N = 10). A third vaccination in ocrelizumab-treated patients (N = 8) boosted T-cell responses that had declined after the second vaccination, but did not lead to higher overall T-cell responses as compared to immediately after a second vaccination. In fingolimod-treated patients, no SARS-CoV-2–specific T cells were detected after second (N = 12) and third (N = 9) vaccinations.

Discussion

In ocrelizumab-treated patients with MS, a third SARS-CoV-2 vaccination had no additive effect on the maximal T-cell response but did induce a boost response. In fingolimod-treated patients, no T-cell responses could be detected following both a second and third SARS-CoV-2 vaccination.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by ZONMW (Dutch Organization for Health Research and Development).

Target-to-B! (T2B!) SARS-CoV-2 study group coinvestigators are listed in appendix 2 at the end of the article.

In patients with multiple sclerosis (MS), both ocrelizumab (OCR) and fingolimod (FTY) are associated with decreased humoral responses following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination.[1] Based on the decreased humoral response, patients with MS treated with OCR or FTY are offered a third SARS-CoV-2 vaccination in many countries. Given the poor humoral response, antiviral defense may be more reliant on T cells. The objective of this study was to evaluate longitudinal T-cell responses after second and third SARS-CoV-2 vaccinations in OCR- and FTY-treated patients with MS.

Methods

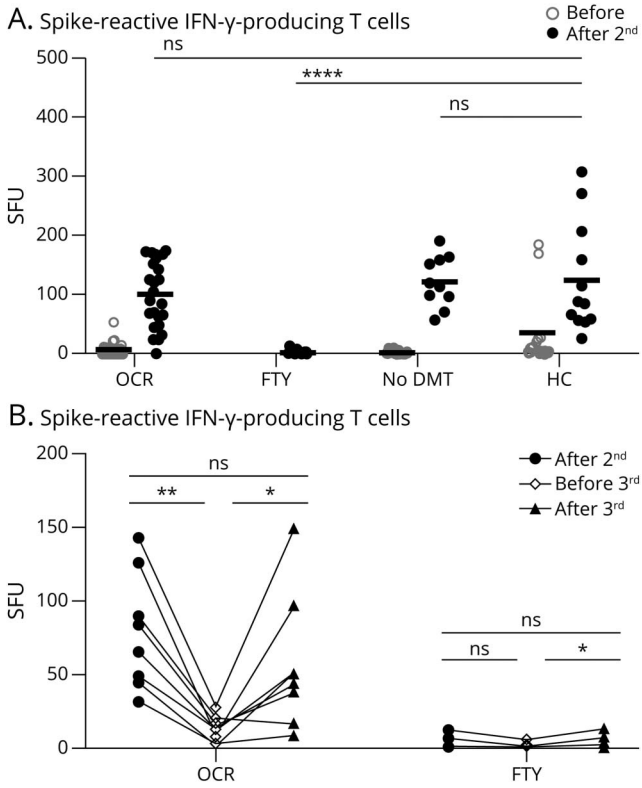
This is a substudy of a prospective multicenter multiarm cohort study on SARS-CoV-2 vaccination in patients with various immune-mediated inflammatory diseases (Target-to-B!). Participants were recruited from February 16, 2021 to August 20, 2021. Participants diagnosed with MS using OCR, FTY, and no disease-modifying therapy (DMT) and healthy controls (HCs) were included. Cryopreserved peripheral blood mononuclear samples, collected before the first vaccination (OCR), after the second vaccination (OCR + FTY), and prior and 1 week after the third

Table Characteristics of Included Study Subjects

	DMT		No DMT	
	MS			
	OCR (n = 24)	FTY (n = 12)	MS (n = 10)	HC (n = 12)
Age, y, mean (SD)	44 (10.1)	45 (7.8)	53 (13.6)	42 (12.8)
Female sex, n (%)	17 (70)	8 (67)	7 (70)	8 (67)
First and second vaccinations				
Vaccine type				
CX-024414 (Moderna), n (%)	24 (100)	8 (67)	10 (100)	12 (100)
BNT162b2 (Pfizer/BioNtech), n (%)	0 (0)	4 (33)	0 (0)	0 (0)
Seroconversion after the second vaccination, n (%)[a]	3 (13)	3 (25)	10 (100)	12 (100)
Anti-RBD IgG titer, median (IQR)	0.5 (0.1–1.3)	0.1 (0.1–2.1)	273 (248–412)	259 (240–547)
Third vaccination	OCR (n = 8)	FTY (n = 9)		
Vaccine type				
CX-024414 (Moderna), n (%)	8 (100)	9 (100)	NA	NA
Interval between second and third vaccinations in days, median (IQR)	119 (117–119)	95 (87–100)	NA	NA
Interval between the last OCR infusion and the third vaccination in days, median (IQR)	122 (98–144)	NA	NA	NA
Peripheral B- and T-cell counts before the third vaccination				
$CD19^+$ B cells, number/μL, median (IQR)	0.5 (0–3)	15 (13–26)	NA	NA
$CD4^+$ T cells, number/μL, median (IQR)	986 (751–1,100)	24 (24–41)	NA	NA
$CD8^+$ T cells, number/μL, median (IQR)	341 (247–480)	71 (66–85)	NA	NA
Seroconversion after the third vaccination, n (%)[b]	3 (38)	5 (56)	NA	NA
Newly seroconverted, n (%)[c]	1 (17)	2 (33)	NA	NA
Anti-RBD IgG titer, median (IQR)	0.1 (0.1–6.0)	5.5 (1.5–7.6)	NA	NA

Abbreviations: DMT = disease-modifying therapy; FTY = fingolimod; HC = healthy control; Ig = immunoglobulin; IQR = interquartile range; MS = multiple sclerosis; NA = not available; OCR = ocrelizumab; RBD = receptor-binding domain.
Participants received 2 or 3 vaccinations with CX-024414 (Moderna) or BNT162b2 (Pfizer/BioNtech) following the Dutch national vaccination campaign guidelines. Patients previously infected with SARS-CoV-2 (as evidenced by self-reported positive PCR and/or anti-spike or anti-nucleocapsid protein antibodies at baseline and follow-up) were excluded. SARS-CoV-2 antibodies were measured using an in-house developed anti-RBD IgG ELISA. Anti-RBD IgG titers were expressed as arbitrary units (AU) per milliliter. Seroconversion after vaccination was defined as antibodies >4 AU/mL. Eighteen OCR-treated patients were diagnosed with relapsing-remitting MS and 6 with primary progressive MS.
[a] Antibody levels were measured 7–10 days after the second vaccination in the HC, MS–No DMT, and MS-OCR groups vs 28 days after the second vaccination in the MS-FTY group.
[b] Antibody levels were measured 7–10 days after the third vaccination.
[c] Number of individuals with a negative SARS-CoV-2 IgG titer after 2 vaccinations and a positive antibody titer (>4 AU/mL) after the third vaccination.

Figure SARS-CoV-2–Specific T-Cell Responses Do Not Change Following a Third Vaccination Compared With the Response Following a Second SARS-CoV-2 Vaccination in Patients With MS Treated With Ocrelizumab or Fingolimod



Number of spike-specific IFN-γ–producing T cells (A) before vaccination and 1 week after a second vaccination (HC [n = 12], no DMT [n = 10], OCR [n = 24]), or 28 days after the second vaccination (FTY [n = 12]); and (B) after the second vaccination, before the third vaccination, and 1 week after the third vaccination in a selection of OCR-treated patients (n = 8) and FTY-treated patients (n = 9). Results are shown as the average number of spot-forming units (SFU) of S1 and S2 together per 2×10^5 cells after subtracting the SFU of unstimulated wells. Three OCR-treated patients who seroconverted after the second vaccination had an SFU of 83, 48, and 0 (after the second vaccination). Samples not responding to the positive control and samples with too high background were excluded. *$p < 0.05$, **$p < 0.01$, and ****$p < 0.0001$. A Wilcoxon signed-rank test or Mann-Whitney *U* test was performed to compare differences in T-cell responses between paired and unpaired observations, respectively. R version 4.1.0 was used. DMT = disease-modifying therapy; FTY = fingolimod; HC = healthy control; IFN = interferon; MS = multiple sclerosis; OCR = ocrelizumab; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

vaccination (OCR + FTY), were evaluated in an ELIspot for spike-specific interferon (INF-γ) T-cell response. A total of 200,000 cells were stimulated for 16 hours with Spike-1 (S1) or Spike-2 (S2) (JPT-Innovative Peptide-Solutions) peptide pools (1 μg/mL per peptide) in triplicate.

Standard Protocol Approvals, Registrations, and Patient Consents

The ethics committee of the Amsterdam UMC, location AMC (2020.194), approved the study, and participants provided written informed consent. Dutch Trial register, ID: NL8900.

Data Availability

Data sets used during this study are available from the corresponding author on reasonable request.

Results

Baseline information of patients with MS treated with OCR (n = 24), FTY (n = 12), and no DMT (n = 10) and healthy controls (n = 12) is summarized in Table. T-cell responses against SARS-CoV-2 S-proteins were significantly induced in OCR-treated patients after 2 vaccinations and were comparable to those in HCs and patients with MS without DMT (Figure, A). In contrast, no T-cell responses were detectable in FTY-treated patients following 2 vaccinations.

T-cell responses in patients with MS treated with OCR (n = 8) or FTY (n = 9) were compared after the second vaccination with directly before the third vaccination and a week after the third vaccination (Figure, B). A third vaccination upregulated SARS-CoV-2–specific T cells in OCR-treated patients but not to a higher extent than directly after the second vaccination (in 6 of 8 patients T-cell response were slightly lower after the third vaccination). In contrast, the third vaccination did not yield significant SARS-CoV-2–specific T-cell responses in FTY-treated patients. Although a very limited significant increase in SFU after the third vaccination was observed, the SFU was still in range of the baseline response of HCs and MS without DMT (Figure, A vs Figure, B).

Discussion

In this study, SARS-CoV-2 T-cell responses following the second vaccination were found to be comparable in OCR-treated patients with MS, patients with MS without DMT, and HCs. We established that a third vaccination induces a recall of SARS-CoV-2 T cells in OCR-treated patients but does not further increase circulating SARS-CoV-2 T-cell numbers compared with after the second vaccination. This is in agreement with recent studies describing a T-cell recall after the third vaccination,[2,3] which was similar compared with the second vaccination for both OCR-treated patients and healthy controls.[2] T-cell responses induced by the vaccine have been demonstrated to be only minorly compromised to variants of concerns, including Omicron, both in healthy controls[4] as in OCR-treated patients.[3]

In FTY-treated patients, we observed no detectable T-cell response against SARS-CoV-2 following 2 vaccinations. This is in line with previous findings that showed IFN-γ T-cell responses in only 14.3% of FTY-treated patients after 2 vaccinations.[1] In our study, T-cell responses remained absent also after 3 vaccinations. This is in contrast to previous findings in other vaccination settings, like influenza, where vaccination of FTY-treated patients induced normal T-cell responses.[5] Also, recall responses to tetanus vaccination were normal in a placebo-controlled study involving FTY-treated healthy volunteers, although responses to a novel antigen were affected.[6] Together, these data may indicate

that FTY therapy affects vaccination responses to novel (neo)antigens, like SARS-CoV-2, but that recall responses to antigens exposed to before the start of FTY treatment are less affected. Despite the impaired humoral and cellular immune responses following SARS-CoV-2 vaccination in FTY-treated patients, the risk of severe COVID-19 in these patients seems similar to the general population,[7] introducing a clinical/immunologic paradox. FTY is associated with only moderate increased risk of infectious diseases, despite the FTY-induced lymphopenia.[8] A possible explanation could be that although circulatory T cells are severely reduced, the number and function of T cells in lymphoid tissue and mucosal tissues, like the lung, might not be affected.

In conclusion, in OCR-treated patients with MS, the third SARS-CoV-2 vaccination does not have an additive effect on the maximal T-cell response but does induce a booster response. In FTY-treated patients, both after a second and third SARS-CoV-2 vaccination, no SARS-CoV-2–specific T-cell responses are detected in the peripheral blood.

Acknowledgment

The authors thank the cryobiology facility of Sanquin Amsterdam for PBMC isolation.

Study Funding

The Netherlands Organisation for Health Research and Development (ZONMW), grant number: 10430012010009.

Disclosure

J. Killestein reported speaking and consulting relationships with Biogen, Genzyme, Merck, Novartis, Roche, Sanofi, and TEVA. Amsterdam UMC, location VUmc, MS Center Amsterdam, has received financial support for research activities from Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi, and TEVA. C.E. van de Sandt has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement (#792532). F. Eftimov, G.J. Wolbink, S.M. van Ham, and T.W. Kuijpers reported a grant from ZonMW for COVID research in patients with autoimmune diseases (ZonMW grants: 10430012010009, 10430022010020, and 10430072010007). The T2B collaboration project is financed by the PPP Allowance made available by Top Sector Life Sciences & Health to Samenwerkende Gezondheidsfondsen (SGF) under project number LSHM18055-SGF to stimulate public-private partnerships and cofinancing by health foundations that are part of the SGF. All other authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* January 18, 2022. Accepted in final form March 30, 2022. Submitted and externally peer reviewed. The handling editor was Scott S. Zamvil, MD, PhD, FAAN.

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Neurol Neuroimmunol Neuroinflamm 2022;9;
DOI 10.1212/NXI.0000000000001178