

ARTICLE

Impact of disease-modifying therapies on humoral and cellular immune-responses following SARS-CoV-2 vaccination in MS patients

Susan Trümpelmann¹ | Andreas Schulte-Mecklenbeck¹ | Olga V. Steinberg¹ |
Timo Wirth¹ | Manfred Fobker² | Lisa Lohmann¹ | Jan D. Lünemann¹ |
Heinz Wiendl¹ | Catharina C. Gross¹ | Luisa Klotz¹

¹Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany

²Central Laboratories, University Hospital Münster, Münster, Germany

Correspondence

Catharina C. Gross and Luisa Klotz, Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Albert-Schweitzer-Campus 1A1, 48149 Münster, Germany. Emails: catharina.gross@ukmuenster.de (C. C. G.) and luisa.klotz@ukmuenster.de (L. K.)

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Abstract

The impact of distinct disease-modifying therapies (DMTs) on severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) vaccination efficacy in patients with multiple sclerosis (MS) is still enigmatic. In this prospective comparative study, we investigated humoral and cellular immune-responses in patients with MS receiving interferon beta, natalizumab, and ocrelizumab pre-vaccination and 6 weeks post second SARS-CoV-2 vaccination. Healthy individuals and interferon beta-treated patients generated robust humoral and cellular immune-responses. Although humoral immune responses were diminished in ocrelizumab-treated patients, cellular immune-responses were reduced in natalizumab-treated patients. Thus, both humoral and cellular immune responses should be closely monitored in patients on DMTs. Whereas patients with a poor cellular immune-response may benefit from additional vaccination cycles, patients with a diminished humoral immune-response may benefit from a treatment with SARS-CoV-2 antibodies in case of an infection.

Study Highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

The impact of distinct disease-modifying therapies on severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) vaccination efficacy in patients with multiple sclerosis (MS) is widely enigmatic.

WHAT QUESTION DID THIS STUDY ADDRESS?

We investigated the efficacy of SARS-CoV-2 vaccination on humoral and cellular immune-responses in patients with MS treated with interferon beta, natalizumab, and ocrelizumab.

Susan Trümpelmann, Andreas Schulte-Mecklenbeck, Catharina C. Gross, and Luisa Klotz contributed equally to this work.

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WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Although the SARS-CoV-2 vaccination generated a robust humoral and cellular immune response in both healthy individuals and interferon beta-treated patients, humoral responses are diminished in ocrelizumab-treated patients and cellular immune responses are reduced in natalizumab-treated patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our results may assist individual risk management of patients with MS treated with distinct therapies by suggesting improved exposition prophylaxis and post-exposition treatment with monoclonal SARS-CoV-2 antibodies for ocrelizumab patients and additional vaccination cycles for natalizumab patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) constitutes a substantial risk for patients with multiple sclerosis (MS). Most patients with MS receive distinct disease modifying treatments (DMTs) to prevent disease progression. Such treatments can be classified into three categories based on their mode of action into immune-modulatory, anti-trafficking, as well as immune-cell depleting therapies and might differentially increase the risk associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.¹ As a consequence, patients with MS are prioritized for vaccination in some countries. SARS-CoV-2 vaccination induces immune protection toward COVID-19 in healthy individuals by generating both humoral and cellular immune responses.^{2,3} Previous experience from other vaccinations suggest reduced vaccination efficacy in patients treated with some immune-suppressive MS therapies.^{1,4} Most studies indicate no effect of the prototypic immune-modulating drug interferon beta, which features a pleiotropic mode of action, including alteration of T-cell differentiation,⁵ on the generation of humoral and cellular immune-responses to influenza.^{4,6} In contrast, B-cell depleting therapies, such as ocrelizumab, have been shown to reduce particularly humoral immune-responses to vaccination against tetanus toxoid or influenza.⁷ Furthermore, first studies demonstrate reduced SARS-CoV-2 antibody titers as a consequence of vaccination in patients with MS treated with B-cell depleting therapies.⁸ For anti-trafficking agents, such as natalizumab, which primarily acts by inhibiting central nervous system (CNS) invasion of leukocytes by blocking VLA-4,⁹ some studies indicated a reduced generation of humoral immune-responses to influenza,⁴ whereas others did not find differences in humoral vaccine efficacy against tetanus toxoid or keyhole limpet hemocyanine.⁶

Although the impact of DMTs on the humoral vaccination response has been well studied in MS, their impact on cellular vaccination response remains enigmatic. To

obtain clinical guidelines for patients with MS, we studied the effects of prototypic DMTs—namely the immune modulatory interferon beta, the anti-trafficking agent natalizumab, and the B-cell depleting therapy ocrelizumab on both humoral and cellular antigen-specific immune responses to SARS-CoV-2 vaccination.

METHODS

Forty-one patients with MS treated with interferon beta ($n = 13$), natalizumab ($n = 9$), or ocrelizumab ($n = 19$) and 30 healthy individuals were recruited at the Department of Neurology of the University Clinic in Münster between February and December 2021 (Figure S1A, Table 1). EDTA-blood and serum samples were withdrawn prior to the first SARS-CoV-2 vaccination and 6 weeks following the second vaccination. Peripheral blood mononuclear cells (PBMC) were isolated using Lymphoprep density gradients and cryo-conserved.¹⁰ Serum was aliquoted and frozen at -80°C . Antibody titers were determined in serum by SARS-CoV-2 S1/RBD IgG Ab ELISA (IBL International) and titers above 11 units/ml were considered as a positive result, as recommended by the manufacturer. T-cell responses were investigated in thawed PBMC. For proliferation analysis, PBMC were stained with eFluor670 (ThermoFisher) following the manufacturer's instructions and 2×10^6 cells/ml were incubated in RPMI/10% fetal bovine serum (FBS) +5 $\mu\text{g/ml}$ recombinant SARS-CoV-2 spike protein (Miltenyi Biotech) for 5 days. After 2 days 125 U/ml IL-2 (Invitrogen) were added. Proliferation was determined by flow cytometry (Cytotflex, Beckman Coulter) in CD4 and CD8 memory T cells (ZombieNIR⁻CD45⁺FSC^{low}SSC^{low}CD3⁺CD56⁻CD4^{+/-}CD8^{+/-}CD45RO⁺ and CD45RO⁻CD27⁻) by eFluor670 dilution. Cytokine production was analyzed in overnight rested PBMC following incubation in RPMI/10% FBS +10 $\mu\text{g/ml}$ SARS-CoV-2 protein/1 $\mu\text{g/ml}$ CD28.2 (BD Biosciences) for 6 h. After 2 h, 10 $\mu\text{g/ml}$

TABLE 1 Patient demographics

	HD	INF- β	NAT	OCR
<i>n</i>	30	13	9	19
Median age, years (25%–75%)	40 (30–53)	42 (32–54)	37 (31–44)	48 (31–57)
Females	19/30 (63.33%)	10/13 (76.92%)	9/9 (100.0%)	8/19 (42.11%)
Median disease duration, years (25%–75%)	NA	9.71 (5.92–10.80)	8.86 (4.80–12.30)	12.76 (4.21–19.28)
Median treatment duration, years (25%–75%)	NA	8.16 (5.33–9.81)	5.03 (1.86–9.12)	2.92 (1.63–3.72)
Median last treatment cycle, days (25%–75%)	NA	Continuous	Continuous	182.0 (168.0–226.0)
Previous SARS-CoV-2 infection	0/30 (0%)	0/13 (0%)	0/9 (0%)	0/19 (0%)
Vaccine				
BNT162b2 (Pfizer-BioNTech)	4/30 (16.13%)	10/13 (76.92%)	8/9 (88.89%)	16/19 (84.21%)
mRNA-1273 (Moderna)	25/30 (83.33%)	1/13 (7.69%)	0/9 (0%)	3/19 (15.79%)
AZD1222 (AstraZeneca)	1/30 (3.33%)	0/13 (0%)	0/9 (0%)	0/19 (0%)
AZD1222 (AstraZeneca) + BNT162b2 (Pfizer-BioNTech)	0/30 (0%)	0/13 (0%)	1/9 (11.11%)	0/19 (0%)
AZD1222 (AstraZeneca) + mRNA-1273 (Moderna)	0/30 (0%)	2/13 (15.38%)	0/9 (0%)	0/19 (0%)

Abbreviations: HD, healthy donors; INF- β , interferon beta; NA, not applicable; NAT, natalizumab; OCR, ocrelizumab.

ml Brefeldin A (ThermoFisher) was added. Cells were stained for flow cytometry using lineage defining antibodies prior to intracellular staining of cytokines using Fix + Perm solution (ThermoFisher) according to the manufacturer's instructions.

Statistical analyses of resulting data were performed with GraphPad Prism V6 using Wilcoxon matched-pairs signed-rank test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

This study was performed according to the Declaration of Helsinki following approval of the local ethics committee under 2010-182-f-S. All participants signed informed consent.

Data will be available upon request from the corresponding authors.

RESULTS

To investigate the effect of distinct DMTs on humoral immune response to SARS-CoV-2 vaccination, SARS-CoV-2 spike antibodies were determined in serum of healthy individuals and patients with MS treated with distinct DMTs prior vaccination and 6 weeks following the second vaccination (Figure S1A, Table 1). None of the participants had previous clinical signs or symptoms of COVID-19 as supported by negative baseline antibody titers (Table 1, Figure 1a). Healthy individuals, and interferon beta and natalizumab-treated patients generated comparable amounts of SARS-CoV-2 spike protein antibodies, whereas antibodies were only detected in three of 19 ocrelizumab-treated patients investigated for antibody

titers (Figure 1a). One ocrelizumab patient with partly recovered B cell frequencies (pre-vac.: 0.04%/lymphocytes, post-vac.: 4.46%/lymphocytes) 6 weeks following second vaccination generated an antibody titer comparable to healthy individuals (Figure 1a, black box). These data indicate that B-cell depleting ocrelizumab diminishes humoral immune responses to vaccination against SARS-CoV-2, whereas it is sustained under interferon beta and natalizumab therapy. Because anti-viral vaccination effects are not limited to humoral responses, we determined the impact of distinct DMTs on T-cell proliferation and cytokine production in response to SARS-CoV-2 spike protein *ex vivo* (Figure S1A). Following vaccination, interferon beta and ocrelizumab-treated patients exhibited enhanced T-cell responses to spike proteins compared to prior vaccination, including proliferation of CD8 and CD4 memory T cells as well as TNF- α and IL-2 production by CD4 memory T-cells (Figure 1b). T-cell proliferation and cytokine production were comparable between interferon beta-treated patients and healthy controls, whereas cytokine production by CD4 memory T-cells was enhanced in ocrelizumab-treated patients (Figure 1b). In contrast, CD8 and CD4 memory T-cell responses were diminished in patients treated with natalizumab, pointing toward an impaired cellular immune-response in these patients.

DISCUSSION

Our data exemplify that distinct immune-modulatory therapies have an impact on generating a full vaccination

Humoral response

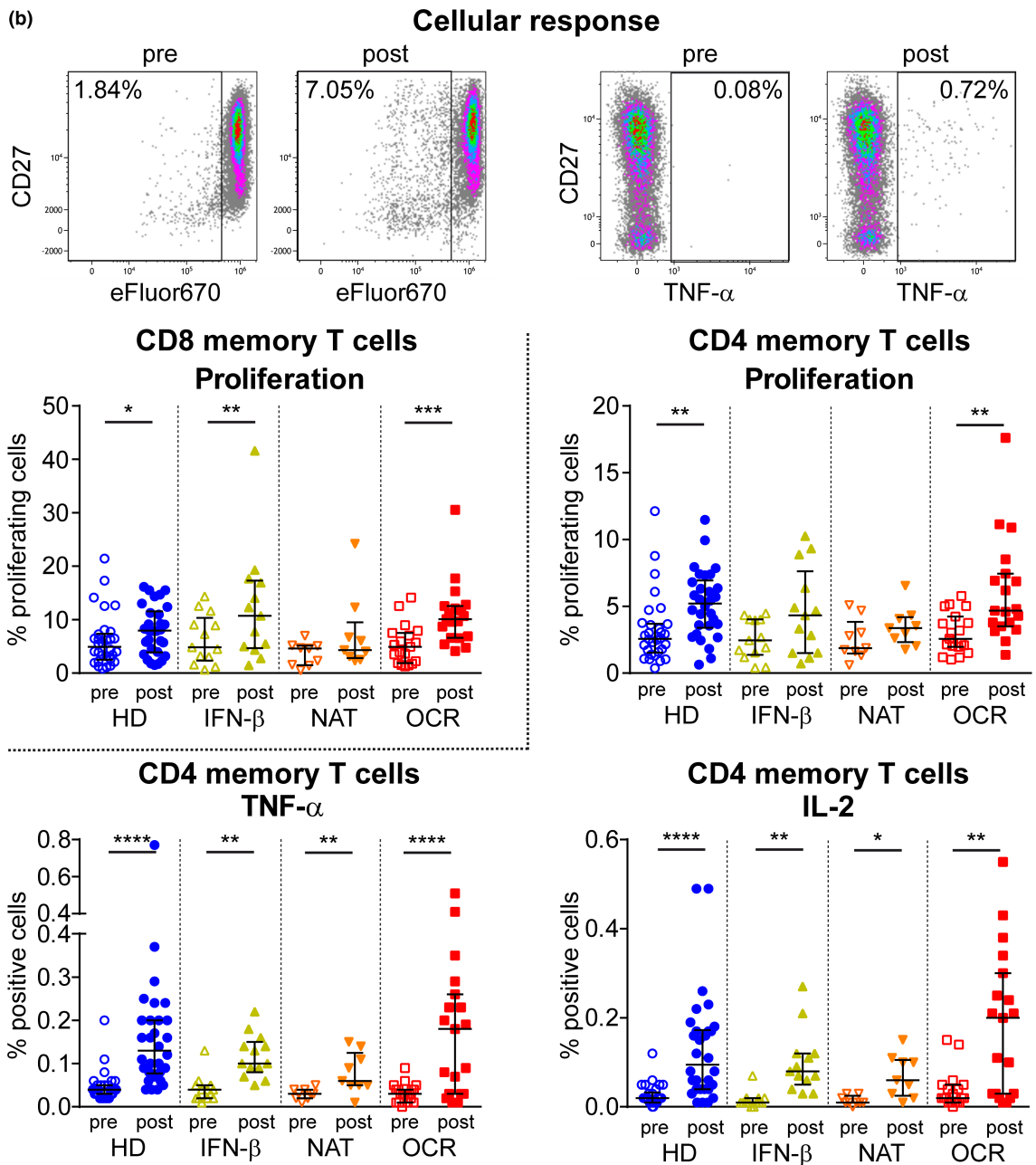
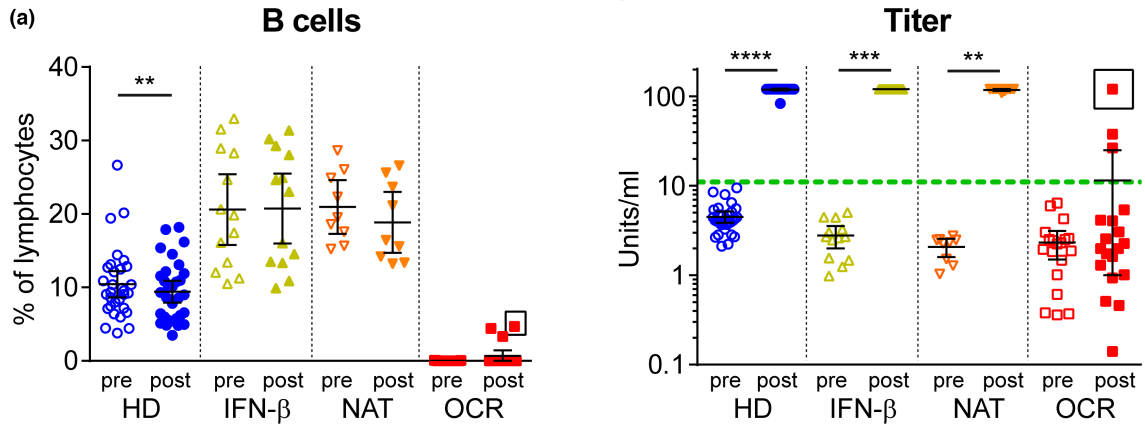


FIGURE 1 Humoral and cellular immune responses to SARS-CoV-2 proteins in patients with MS under disease-modifying therapy upon vaccination. (a) Humoral immune responses. Left: Proportion of B cells (CD19⁺CD20⁺) within lymphocytes (CD45⁺FSC^{low}SSC^{low}Zombie⁻) quantified by flow cytometry of PBMC isolated prior first (open symbols) and 6 weeks after second vaccination (closed symbols) from 30 healthy donors (HD, blue) and 41 patients with MS under therapy with interferon beta (IFN- β , green, $n = 13$), natalizumab (NAT, orange, $n = 9$), or ocrelizumab (OCR, red, $n = 19$). Right: SARS-CoV-2 spike protein antibody titers in the serum of 30 HD and 41 patients with MS (13 IFN- β , 9 NAT, and 19 OCR). The green line indicates the threshold for positive Ab evaluation. (b) Cellular immune responses investigated in PBMC from 30 HD and 41 patients with MS (13 IFN- β , 9 NAT, 19 OCR). Reactivity of CD4 memory T cells and CD8 memory T cells in response to SARS-CoV-2 spike protein in vitro. Top: Representative dot plots for proliferation and TNF- α production of CD4 memory T cells. Center: Proliferation of CD8 and CD4 memory T cells; bottom: TNF- α and IL-2 production of CD4 memory T cells. Error bars indicate the median with interquartile range. Statistical analyses were performed with GraphPad Prism V6 using Wilcoxon matched-pairs signed-rank test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. HD, healthy donors; MS, multiple sclerosis; PBMC, peripheral blood mononuclear cell; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2

response to SARS-CoV-2 with some therapies predominantly affecting the humoral (i.e., the B-cell depleting therapy ocrelizumab) and others the cellular immunity (i.e., the trafficking agent natalizumab; Figure S1B). In line with previous observations regarding influenza vaccination,^{4,11–15} interferon beta does not impair humoral and cellular responses toward SARS-CoV-2 vaccination. In contrast, we observed diminished humoral immune responses in ocrelizumab-treated patients, proposing that B-cell depleting therapies prevent development of protective antibody levels, whereas cellular immune-responses were not impaired. Our results confirm earlier observations⁸ of a larger cohort; thus, validating the sensitivity of the applied methods. Notably, the cellular immune response was enhanced in these patients compared with healthy individuals. So far, it remains enigmatic whether a robust cellular vaccination response is sufficient to prevent severe disease courses in case of a COVID-19 infection. Thus, additional safety measures should be considered to prevent virus exposition. In case of COVID-19 infection, ocrelizumab-treated patients may benefit from treatment with anti-SARS-CoV-2 monoclonal antibodies like bamlanivimab,¹⁶ etesevimab, casirivimab,¹⁷ imdevimab, or sotrovimab.¹⁸

In contrast to interferon beta and ocrelizumab, the effect of natalizumab on vaccination efficacy in general has yet to be resolved. Whereas some studies report maintained development of protective antibody titers against recall (tetanus toxoid) and neoantigens (keyhole limpet hemocyanin),¹⁹ others find reduced humoral responses toward influenza vaccination.^{4,14,15,20} Here, we clearly demonstrated that natalizumab treatment of patients with MS has no impact on humoral immune response to SARS-CoV-2 vaccination, whereas it diminishes cellular immune responses. The blockade of VLA-4 by natalizumab primarily inhibits extravasation of leukocytes into the CNS. Less well-known effects of VLA-4 blockade include alterations in T-cell activation by interferences with T-cell/antigen-presenting cell interaction, as well as increase T-cell suppression by regulatory lymphocyte subsets, which may contribute to the observed reduced T-cell proliferation compared to healthy controls and other

DMTs in natalizumab-treated patients with MS. For example, preclinical infection models revealed reduced IL-12p40 mRNA levels in dendritic cells as well as reduced T-cell activation, including cytokine production as a consequence of blockade of VLA-4/VCAM-1 interaction.²¹ Furthermore, VLA-4 blockade directly affects T-cell/APC interaction by altering the formation of the immunological synapse²² and respective knock-out experiments showed a skewing of T-cell differentiation toward regulatory subsets.²³ VLA-4 is involved in antigen-dependent stimulation of T cells by modulating SLP-76 phosphorylation.²⁴ In addition, natalizumab therapy results in an increase of NK cells in the blood, which are known to suppress antigen-activated T cells.¹⁰ In summary, VLA-4 blockade affects T-cell activation directly by interfering with antigen-presentation and costimulation as well as indirectly by strengthening regulatory lymphocytes, thus providing possible explanations for the reduced efficacy of SARS-CoV-2 vaccination on cellular immune responses in natalizumab-treated patients with MS. Although natalizumab-treated patients benefit from SARS-CoV-2 vaccinations by developing protective antibody titers, their long-term protection by T-cell mediated immunity may be impaired. Thus, these patients may benefit from additional vaccination cycles to boost cellular immunity.

We are well-aware of the shortcomings of this study. Due to the limited sample size further studies are warranted to confirm these data in a larger cohort and to elucidate long-term vaccination efficacy. Furthermore, longitudinal studies could elucidate the efficacy of additional vaccination cycles on humoral and cellular immune responses.

In summary, our results emphasize the requirement to monitor both humoral and cellular immune responses to assess vaccination efficacy. Thereby, we were able to derive clinical guidelines to optimize risk management of patients with MS treated with distinct immune-modulating, anti-trafficking, and immune-cell depleting therapies by improved exposition prophylaxis and post-exposition treatment with monoclonal SARS-CoV-2 antibodies for ocrelizumab-treated patients and additional vaccination cycles for natalizumab-treated patients.

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CONFLICT OF INTEREST

H.W. received honoraria for acting as a member of Scientific Advisory Boards for Biogen, Evgen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma, and Sanofi-Aventis and receives speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche, Gemeinnützige Hertie-Stiftung, Merck Serono, Novartis, Roche Pharma, Genzyme, Teva, and WebMD Global. He is also a paid consultant for Abbvie, Actelion, Biogen, IGES, Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, and the Swiss Multiple Sclerosis Society. His research is funded by Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, and Sanofi-Genzyme. C.C.G. received speaker honoraria from Mylan and DIU Dresden International University GmbH, and travel expenses for attending meetings from Biogen, Euroimmun, Mylan, and Novartis Pharma. She received research funding from the German Research Foundation, the European Union, the IZKF Münster, Biogen, Roche, and Novartis. L.K. received compensation for serving on Scientific Advisory Boards for Alexion, Genzyme, Janssen, Merck Serono, Novartis, and Roche. She received speaker honoraria and travel support from Bayer, Biogen, Genzyme, Grifols, Merck Serono, Novartis, Roche, Santhera, and Teva. She receives research support from the German Research Foundation, the IZKF Münster, IMF Münster, Biogen, Novartis, and Merck Serono. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.S.M., O.V.S., C.C.G., and L.K. wrote the manuscript. H.W., C.C.G., and L.K. designed the research. S.T., T.W., M.F., and L.L. performed the research. S.T., A.S.M., O.V.S., and J.D.L. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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