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Original article

# The recurrence of disease activity after ocrelizumab discontinuation in multiple sclerosis

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ABSTRACT

*Introduction:* Ocrelizumab (OCR) is a highly effective treatment of multiple sclerosis (MS), and B cell repopulation profiles suggest that it might be used as an immune reconstitution therapy. However, data on disease recurrence after stopping treatment with OCR are scarce. Our objective was to evaluate the recurrence of disease activity after OCR discontinuation.

*Methods:* In this multicenter retrospective cohort study, we included MS patients who discontinued OCR, without switching to another treatment, for twelve months or more, after having received at least one full dosage of 600 mg. We defined focal inflammation as the occurrence of a clinical relapse or significant MRI activity (≥3 new T2 lesions or ≥2 contrast-enhancing lesions).

*Results:* We included 53 MS patients; 41 relapsing remitting (RRMS), 5 secondary progressive (SPMS) and 7 primary progressive (PPMS) patients. Median follow-up period after OCR discontinuation was 16 months. We only observed focal inflammation after discontinuation in RRMS patients; 2.4 % (1/41) patients presented with significant MRI activity and matching clinical symptoms, and 7.3 % (3/41) patients presented with a suspected clinical relapse without radiological activity: a total of 9.8 % (4/41) at a median time of 17 months after the last infusion.

*Discussion:* We found focal inflammation after discontinuation of OCR in 4 (9.8 %) of the RRMS patients, of which 1 was radiologically confirmed. Our observations highlight that recurrence of focal inflammation seems low but discontinuation may not be appropriate for everyone. Further larger studies are important to determine the immune reconstitution therapy potential of OCR.

## 1. Introduction

Ocrelizumab (OCR) is a high efficacy therapy in multiple sclerosis (MS) targeting $CD20^{+}$ cells (Hauser et al., 2017; Montalban et al., 2017). It depletes both naïve and memory CD20+ *B* cells, as well as CD20+ *T* cells. Beyond this direct effects on CD20+ cells, it also induces secondary changes in the T cell compartment (Nissimov et al., 2020; Shinoda et al., 2023; Jelcic et al., 2018). Although this depleting effect, especially on memory B cells, is long-lasting, possibly indicating immune reconstitution therapy potential—where the therapy may induce sustained disease control even after discontinuation by 'resetting' the immune system (Baker et al., 2017; Smets et al., 2023; Juto et al., 2020)—the currently approved treatment regimen consists of infusions every 6 months. Family planning or pregnancy, side effects and the risk of adverse effects

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such as infections and neoplasms may prompt discontinuation, but there is no generally accepted protocol to guide a decision to (dis)continue OCR treatment. This continuous dosing strategy requires reevaluation, particularly given the extent and duration of immune depletion (Sellner and Rommer, 2020). Therefore, the objective of this study is to evaluate the potential recurrence of clinical and/or radiological disease activity after discontinuation of OCR.

## 2. Materials and methods

In this retrospective cohort study we included MS patients treated in multiple centers: the MS Center Amsterdam, the Canisius Wilhelmina Hospital, the Rijnstate Hospital and the Erasmus MC in the Netherlands and the University Hospital of Wales in the United Kingdom. Patients provided informed consent for the use of their coded data.

Neurologists in these MS centers screened their patients for compatibility with the following inclusion criteria: (1) relapsing-remitting (RRMS), secondary (SPMS) or primary progressive MS (PPMS) according to the 2017 McDonald criteria (Thompson et al., 2018); (2) $\geq$ two treatment cycles (the initial cycle consisting of two 300 mg doses given two weeks apart, followed by at least one full 600 mg dose administered at least six months later); (3) discontinuation of treatment with OCR without switching to another treatment for $\geq$ 12 months; (4) follow-up data available for $\geq$ 12 months after discontinuation. Follow-up ended upon (re)initiation of OCR treatment or a different disease modifying therapy (DMT). Patients who showed focal inflammation during OCR treatment after the period between start and rebaseline MRI (done 3 - 6 months after start) were excluded.

The primary outcome was the occurrence of focal inflammation after discontinuation. Focal inflammation was defined as the occurrence of a clinical relapse (the appearance, recurrence or aggravation of neurological symptoms for at least 24 h without fever validated by a physician) or significant MRI activity ($\geq$3 new T2 lesions or $\geq$2 contrast-enhancing lesions (CELs)), whichever occurred first. Timing of discontinuation was defined as the date of last OCR infusion.

Lymphocyte counts were included if available at baseline (before first OCR infusion), at last infusion (before administration of last infusion) and $\geq$ 6 months after last OCR infusion. Lymphocyte counts were measured by flow cytometry at the laboratories of each respective center. CD19 was used as the surface marker to identify CD20-expressing B-cells, with calibration performed using beads. The blood biomarkers serum neurofilament light (sNFL) and serum glial fibrillary acidic protein (sGFAP) were included if available at baseline (start OCR), at last infusion (during OCR) and $\geq$ 6 months after last OCR infusion. If multiple samples were available, the sample twelve months after discontinuation was selected. sNfL and sGFAP levels were measured on the Simoa™ HD-X instrument using the N4PE multiplex kit following the instructions (Quanterix, Billerica, USA).

Descriptive data were presented as means with SD for normally distributed data, medians with IQR for non-normally distributed data, or frequencies with percentages. Clinical and radiological characteristics were compared between groups with and without focal inflammation after discontinuation using one-way ANOVA for categorical variables, *t*-test for normally and Mann-Whitney U test for non-normally distributed continuous variables. Statistical analyses were performed with SPSS Statistic software V.28.0 (IBM). A p-value $<0.05$ was considered statistically significant.

Anonymized data will be shared upon reasonable request from any qualified investigator.

## 3. Results

We identified 53 patients, of which 38 were female (71.7 %). At start of OCR treatment, 41 patients had RRMS (77.4 %), 5 had SPMS (9.4 %) and 7 had PPMS (13.2 %). Mean age was 44.4 years. Mean disease duration was 11.2 years. Of the RRMS patients at the start of OCR, 11 patients were defined as SPMS patients at OCR discontinuation. The reasons for discontinuation included side effects ($n$ = 17), no/insufficient effect ($n$ = 8), secondary progression ($n$ = 5), patient preference ($n$ = 13) or pregnancy ($n$ = 10). B cell counts at baseline were available in 33 patients (median B cell count at baseline: 0.217 $\times$ $10^9$/L), for 35 patients at last infusion (median B cell count at last infusion: 0.002 $\times$ $10^9$/L) and for 30 patients after discontinuation (median B cell count at discontinuation: 0.070 $\times$ $10^9$/L). Recurrence of focal inflammation was seen in 4/53 (7.5 %) of the patients in a median follow up duration of 16 months (IQR 13 – 23 months). MRIs were conducted with varying frequency, with a median of 2 MRIs after discontinuation per patient, ranging from 1 to 7 scans, depending on clinical indications and center protocols (Table 1).

Recurrence of focal inflammation was only seen in RRMS patients: significant MRI activity was observed in 1/41 patients (2.4 %), and an additional 3/41 (7.3 %) patients had clinical symptoms suspect for a relapse, without corresponding MRI activity. This resulted in a total of 4 out of 41 patients (9.8 %) experiencing recurrence within a median follow-up duration of 16 months after a mean treatment duration of 21.2 months (Fig. 1). Of the 4 patients with focal inflammation, 1 patient presented with significant MRI activity: one new CEL on MRI brain 31 months after discontinuation, followed by >10 new lesions and >6 CELs on a scan 24 months later (i.e. after total 55 months) with matching clinical symptoms. The patient was then switched to natalizumab. The other 3 patients presented with a clinical relapse without corresponding radiological activity. The clinical presentation of these 3 patients were: dysarthria and dysphagia with stable disease on MRI brain, new motor and sensory symptoms in one leg with stable MRI brain (no MRI spinal cord was performed) and sensory symptoms in both hands with stable MRI brain and cervical cord. One patient started cladribine (Cladribine), one declined treatment and one restarted OCR (Fig. 1 and full case descriptions in appendix 1). Furthermore, there was one patient with 1 new T2 lesion after discontinuation, subsequent scans after this remained stable. According to our definition this patient did not fulfill the criteria of significant MRI activity.

In the group with focal inflammation, reasons for discontinuation varied: personal preference ($n$ = 1), (possible) side effects ($n$ = 2) and pregnancy with prolonged treatment interruption of 21 months ($n$ = 1). Median time to focal inflammation was 17 months after last OCR infusion. B cell counts during OCR treatment were unknown for 1, complete B cell depletion was observed in the others. In 2 patients, B cell repopulation had occurred at the time of focal inflammation. For the other 2 patients, B cells counts were not available at that time.

The groups without and with focal inflammation showed no statistically significant differences. The patients with emergent focal inflammation were all females, had a lower age at discontinuation (36.5 vs. 42.5 years), a shorter disease duration (6.1 vs. 11.6 years), a shorter OCR treatment duration (15.5 vs. 21.9 months) and a lower expanded disability status scale (EDSS) (3 vs. 3.75) compared to the group with no focal inflammation. The group with focal inflammation was more often previously treated with another second line DMT (75% vs. 45.9 %) and had a higher relapse rate (1.0 vs. 0.42) and more often new T2 lesions and/or CELs (100% vs. 64.9 %) in the year before start of treatment (Table 1).

Of the 34 patients included in the MS Center Amsterdam, sNFL levels were available in 27 and sGFAP levels in 18 patients. During treatment, mean levels of sNFL and sGFAP declined (30.9 vs. 11.2 pg/mL and 78.9 vs 74.4 pg/mL respectively). After discontinuation, levels of sNFL were stable (11.2 vs. 10.9 pg/mL) while sGFAP increased slightly (74.4 vs 88.9 pg/mL), but available data points were limited.

## 4. Discussion

In this real-world cohort of patients that discontinued OCR, we found recurrence of significant MRI activity in 1/41 RRMS patients (2.4 %) and a suspected clinical relapse without any MRI activity in 3/41 RRMS

**Table 1**
Patient characteristics at discontinuation OCR.

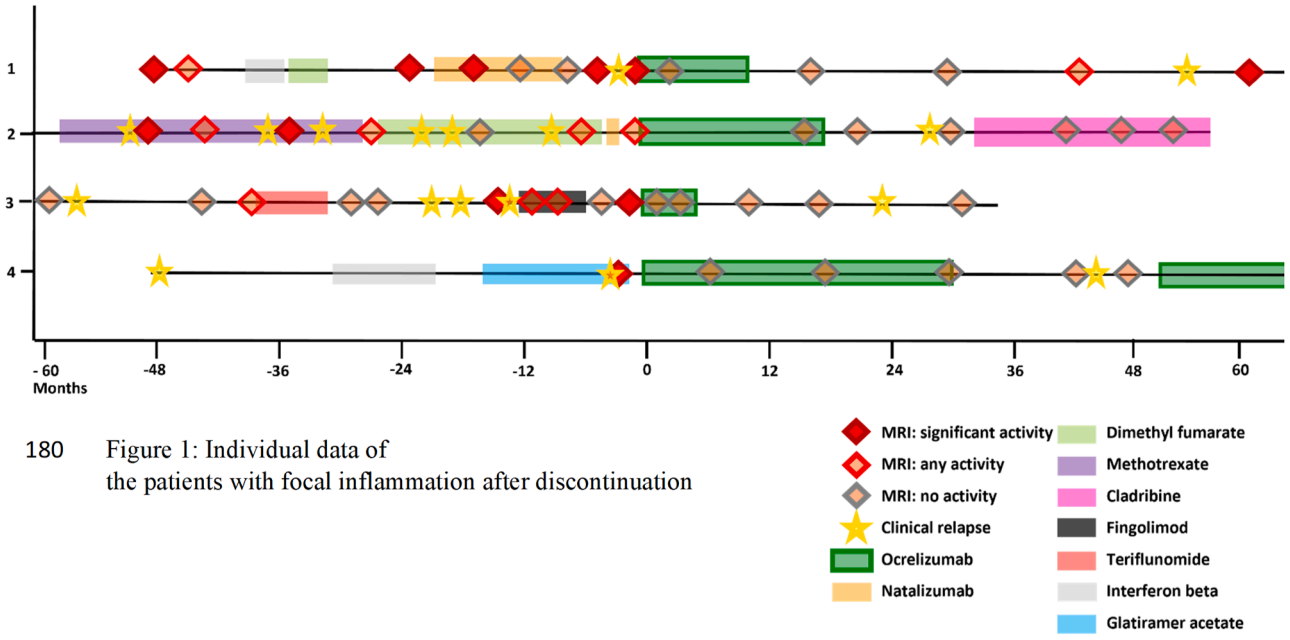
| | | All patients (N = 53) | RRMS patients subset (n = 41) | No focal inflammation after discontinuation (n = 37) | Focal inflammation after discontinuation (n = 4) | *p* value |
|---|---|---|---|---|---|---|
| **Age, years** | | 44.4 ± 11.5 | 41.9 ± 11.2 | 42.5 ± 11.5 | 36.5 ± 5.1 | NS |
| **Sex, female** | | 38 (71.7) | 34 (82.9) | 30 (81.1) | 4 (100) | NS |
| **MS type at OCR start** | RRMS | 41 (77.4) | 41 (100.0) | 37 (100.0) | 4 (100) | - |
| | SPMS | 5 (9.4) | 0 (0) | 0 (0) | 0 (0) | |
| | PPMS | 7 (13.2) | 0 (0) | 0 (0) | 0 (0) | |
| **MS type at OCR discontinuation** | RRMS | 30 (56.6) | 30 (73.2) | 26 (70.3) | 4 (100) | NS |
| | SPMS | 16 (30.2) | 11 (26.8) | 11 (29.7) | 0 (0) | |
| | PPMS | 7 (13.2) | 0 (0) | 0 (0) | 0 (0) | |
| **Disease duration, years** | | 11.2 ± 6.7 | 11.1 ± 6.2 | 11.6 ± 6.3 | 6.1 ± 1.4 | NS |
| **Previous use of DMT before OCR** | No DMT | 13 (24.5) | 8 (19.5) | 8 (21.6) | 0 (0) | NS |
| | Fist-line DMT | 17 (32.1) | 13 (31.7) | 12 (32.4) | 1 (25) | |
| | Both first and second-line DMT | 23 (43.4) | 20 (48.8) | 17 (45.9) | 3 (75) | |
| **Number of DMT before OCR** | | 1.7 ± 1.4 | 1.9 ± 1.3 | 1.8 ± 1.4 | 2.5 ± 0.58 | NS |
| **Last DMT before OCR** | None | 13 (24.5) | 8 (19.5) | 8 (21.6) | 0 (0) | NS |
| | Interferon beta | 5 (9.4) | 3 (7.3) | 3 (8.1) | 0 (0) | |
| | Dimethyl fumarate | 10 (18.9) | 9 (22.0) | 9 (24.3) | 0 (0) | |
| | Glatiramere acetate | 4 (7.5) | 3 (7.3) | 2 (5.4) | 1 (25) | |
| | Fingolimod | 8 (15.1) | 6 (14.6) | 5 (13.5) | 1 (25) | |
| | Natalizumab | 11 (20.8) | 11 (26.8) | 9 (24.3) | 2 (50) | |
| | Alemtuzumab | 1 (1.9) | 1 (2.4) | 1 (2.7) | 0 (0) | |
| | Daclizumab | 1 (1.9) | 0 (0) | 0 (0) | 0 (0) | |
| **EDSS** | | 5.25 (3 – 6.88) | 3.5 (3 – 6.5) | 3.75 (3 – 6.5) | 3 (2.5 – 3) | NS |
| **OCR treatment duration, months** | | 20.9 ± 12.5 | 21.2 ± 13.0 | 21.9 ± 13.1 | 15.5 ± 11.1 | NS |
| **Reason for discontinuation** | Side effects | 17 (32.1) | 15 (36.6) | 13 (35.1) | 2 (50) | NS |
| | No/insufficient effect | 8 (15.1) | 1 (2.4) | 1 (2.7) | 0 (0) | |
| | Secondary progression | 5 (9.4) | 3 (7.3) | 3 (8.1) | 0 (0) | |
| | Patient preference | 13 (24.5) | 12 (29.3) | 11 (29.7) | 1 (25) | |
| | Pregnancy | 10 (18.9) | 10 (24.4) | 9 (24.3) | 1 (25) | |
| **Restarted DMT (after >12 months)** | None | 31 (58.5) | 20 (48.8) | 18 (48.6) | 2 (50) | NS |
| | OCR | 13 (24.5) | 12 (29.3) | 11 (29.7) | 1 (25) | |
| | Planned to restart OCR | 4 (7.5) | 4 (9.8) | 4 (10.8) | 0 (0) | |
| | Cladribine | 3 (5.7) | 3 (7.3) | 2 (5.4) | 1 (25) | |
| | Dimethyl fumarate | 2 (3.8) | 2 (4.9) | 2 (5.4) | 0 (0) | |
| **Relapse rate year before start** | | 0.47 ± 0.63 | 0.48 ± 0.64 | 0.42 ± 0.65 | 1 ± 0 | NS |
| **New T2 and/or CELS year before start** | | 37 (69.8) | 28 (68.3) | 24 (64.9) | 4 (100) | NS |
| **Follow-up duration, months** | | 16 (13 – 23) | 16 (13 – 21) | 15 (13 – 20.5) | 19 (14 – 28.5) | NS |
| **B cell count (cells x $10^9$/L)** | at start OCR | 0.217 (0.218 – (0.392) | 0.283 (0.142 – 0.439) | 0.306 (0.158 – 0.477) | 0.135 (0.127 – 0.135) | NS |
| | at last infusion OCR | 0.002 (0.0 – 0.013) | 0.002 (0.0 – 0.14) | 0.002 (0.0 – 0.13) | 0.019 (0.002 – 0.018) | |
| | after discontinuation OCR | 0.070 (0.017 – 0.148) | 0.077 (0.022 – 0.144) | 0.064 (0.018 – 0.144) | 0.136 (0.078 – 0.136) | |
| **sNFL (pg/ml)** | at start OCR | 30.9 ± 36.5 (n 16) | 32.7 ± 40.3 (n 13) | 35.9 ± 43.2 (n 11) | 14.8 ± 6.0 (n 2) | NS |
| | during OCR | 11.2 ± 6.5 (n 26) | 9.4 ± 5.2 (n 20) | 9.2 ± 5.5 (n 18) | 11.3 ± 0.8 (n 2) | |
| | after discontinuation OCR | 10.9 ± 7.9 (n 18) | 8.6 ± 4.4 (n 14) | 8.9 ± 4.7 (n 12) | 7.1 ± 1.2 (n 2) | |
| **sGFAP (pg/ml)** | at start OCR | 78.9 ± 42.2 (n 15) | 80.2 ± 44.6 (n 13) | 85.4 ± 45.7 (n 11) | 51.9 ± 32.5 (n 2) | NS |
| | during OCR | 74.4 ± 35.8 (n 17) | 67.9 ± 33.7 (n 14) | 68.7 ± 35.7 (n 12) | 62.7 ± 26.2 (n 2) | |
| | after discontinuation OCR | 88.9 ± 57.4 (n 2) | 88.9 ± 57.4 (n 2) | 88.9 ± 57.4 (n 2) | - (n 0) | |

Mean values are displayed with ± standard deviation. Median values are displayed with (interquartile range). Frequencies are displayed with (percentages). Values were calculated using one-way ANOVA for categorical variables and *t*-test and Mann-Whitney U test for normally and non-normally distributed continuous variables, respectively. Disease duration was calculated until the end of our follow up period. Cumulative DMT exposure was calculated by dividing the years on previous DMTs by disease duration at the start of OCR treatment. RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis: DMT, disease-modifying therapies; EDSS, expanded disability status scale; CEL, contrast-enhancing lesions; sNFL, serum neurofilament light; sGFAP, serum glial fibrillary acidic protein; NS, not significant.

patients (7.3 %), resulting in a total of 4 patients (9.8 %). No inflammatory activity was seen in progressive forms of MS in this cohort.

Of the four cases with (suspected) disease activity, only one showed both clinical symptoms and corresponding MRI activity. In one case, MRI activity could have been missed due to the absence of a spinal cord MRI. The other two cases could have been pseudo-relapses, though this could not be confirmed retrospectively. Addressing this could have halved the proportion of focal inflammation cases. Additionally, using more stringent criteria, such as requiring a measurable increase in EDSS or using classification separating relapses with active MRI and acute clinical events with stable MRI, as recent data suggest (Gavoille et al., 2024; Alvarez et al., 2024), might have resulted in a lower proportion of disease recurrence. Nonetheless, we chose to adhere to the conventional definition to ensure alignment with established research. On the other hand, the retrospective nature of this cohort, combined with the current medical practice of continuing OCR every six months without an exit strategy, introduces a bias towards including patients with milder disease courses, which makes the observed percentage of disease recurrence in this highly selected population even more significant..

Previous data on OCR discontinuation are limited. The first completed randomized-controlled trial of therapy discontinuation in MS only included two patients on OCR in the discontinue group and was therefore inconclusive concerning this debate (Corboy et al., 2023). A recent registry-based cohort did not show a significant increase in risk of relapse or time reduction to first focal MRI activity after discontinuation, but only included three OCR patients in the discontinuation group and therefore grouped rituximab and OCR together as anti-CD20 therapies, leading to a comparable size ($n = 58$) to our cohort (Jouvenot et al., 2024). Another register-based cohort that included patients that interrupted treatment with rituximab, showed no signs of disease reactivation in the patients that interrupted rituximab for >12 months (Juto et al., 2020). In a retrospective study, no patients showed a relapse after discontinuation of anti-CD20 therapy, but only included nine patients on rituximab and none on OCR (Chappuis et al., 2023). In studies with




180 Figure 1: Individual data of the patients with focal inflammation after discontinuation

**Fig. 1.** Individual data of the patients with focal inflammation after discontinuation.

extended intervals between infusions follow-up is generally short and the results vary: while no clinical relapses have been observed with extended dosing schedules, some MRI activity has been reported (Zanghi et al., 2022; van Lierop et al., 2022). Low rates of disease activity have been seen 12–18 months after last infusion suggesting the potential of use of ocrelizumab as immune-reconstitution therapy (Baker et al., 2020), which is supported by the stable NfL values we found after discontinuation. However, our number of disease recurrence, and the numbers from these other studies, are low compared to other treatment classified as immune-reconstitution therapy. After treatment with cladribine (Cladribine), 25 % of the patients showed clinical relapses in a period of 2 years untreated (Giovannoni et al., 2018). Data on the long-term efficacy of stem cell transplantation is are limited, a cohort of 174 RRMS patients showed evidence of disease activity in 27 % of the patients within a 5-year follow-up period after treatment (Silfverberg et al., 2024).

The group of RRMS patients without focal inflammation was slightly older than the group with focal inflammation, although not significant, most likely due to our small sample size. This is in line with previous studies showing an association between higher age at DMT discontinuation and a lower risk of relapses during follow-up (Jouvenot et al., 2024; Coerver et al., 2023; Yano et al., 2019).

Our study has some limitations related to the observational design and small sample size, which could have led to a selection bias. Given the difficulties in identifying this patient cohort, we chose broad inclusion criteria. This resulted in a diverse group, including progressive patients, pregnant patients and patients who restarted OCR treatment. Also, the timing of follow-up differed between all patients, with not all data available at similar time points and some missing data, such as EDSS at the end of the follow-up period. Therefore, we were unable to draw conclusions on the amount of progression after discontinuation. This is important in relation to the possibility that if even no apparent focal inflammation is observed after discontinuation, there may still be a higher risk of disability progression with lower OCR exposure (Hauser et al., 2023). In our data collection, we defined SPMS as clinical deterioration independent of relapses for ≥1 year after an initial relapsing-remitting course. However, this classification may have introduced variability and inconsistency in identifying SPMS, as clinical disease course definitions are increasingly viewed as a continuum (Kuhlmann et al., 2023).

In conclusion, our findings highlight that recurrence of focal inflammation after OCR discontinuation is scarce but not absent. Hence, discontinuing OCR may not be appropriate for everyone and stresses the importance of larger studies to determine the immune reconstitution therapy potential of OCR.

## Author statement

The principal author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; the principal author had full access to all of the data; and has the right to publish any and all data separate and apart from any sponsor.

## Data availability statement

Anonymized data will be shared upon reasonable request from any qualified investigator.

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## CRediT authorship contribution statement

**E. Coerver:** Writing – review & editing, Validation, Project administration, Investigation, Conceptualization. **L. Schoof:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **L. Hogenboom:** Writing – review & editing, Visualization, Methodology, Conceptualization. **M. Wessels:** Writing – review & editing, Data curation, Conceptualization. **P. van Ruyven:** Investigation, Data curation. **A. van Samkar:** Writing – review & editing, Data curation. **J. Mostert:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Z. van Kempen:** Writing – review & editing, Supervision. **B.W. van Oosten:** Writing – review & editing, Supervision, Conceptualization. **B.H. Wokke:** Writing – review & editing, Conceptualization. **E. Tallantyre:** Writing – review & editing, Data curation, Conceptualization. **KM. Myhr:** Writing – review & editing. **O. Torkildsen:** Writing – review & editing, Validation. **J. Killestein:** Writing – review & editing, Supervision, Methodology,

Conceptualization. **I. Smets:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization. **E. Strijbis:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

## Declaration of competing interest

E. Coerver reports no disclosures.
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O. Torkildsen received speaker honoraria from Biogen, Merck, Sanofi, Teva, Gilead, Janssen and Novartis; and has participated in clinical trials organized by Biogen, Merck, Sanofi, Novartis, and Roche.

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## Supplementary materials

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