Caspian Journal of Internal Medicine 2025 (Winter); 16(1): 126-131
DOI: 10.22088/cjim.16.1.126

Original Article

De-escalation of anti-CD20 monoclonal antibodies to low-moderate efficacy disease-modifying treatments (DMTs) in patients with relapse-remitting multiple sclerosis: An initial Iranian experience

Sepideh Paybast (MD) [1]
Nasim Rezaeimanesh [2]
Abdorreza Naser Moghadasi (MD) [3, 4*]

1. Department of Neurology, Imam Hossein Educational Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Multiple Sclerosis Research Center, Neuroscience Institute; Tehran University of Medical Sciences, Tehran, Iran
3. Multiple Sclerosis Research Center, Neuroscience Institute; Tehran University of Medical Sciences, Tehran, Iran
4. Sina MS Research Center, Sina Hospital, Tehran University of Medical Sciences, Hasan Abad Sq., Tehran, Iran

*** Correspondence:**
Abdorreza Naser Moghadasi, Multiple Sclerosis Research Center, Neuroscience Institute; Tehran University of Medical Sciences, Tehran, Iran

E-mail:
abdorrezamoghadasi@gmail.com
Tel: +98 2166348571

Received: 12 Sep 2023
Revised: 15 Jan 2024
Accepted: 23 Jan 2024
Published: 19 Oct 2024

Abstract

Background: Anti-CD20 are among the high-efficacy DMTs commonly used in treating multiple sclerosis (MS). Long-term safety data on anti-CD20s are limited. There is convincing evidence of hypogammaglobulinemia in the long-term use of anti-CD20s, raising the likelihood of infection. Accordingly, there is an unmet need for de-escalation therapy in stable patients to reduce adverse events. Herein we aimed to describe our experience with ten relapse-remitting MS (RRMS) patients who were switched from anti-CD20s to the low-moderate efficacy DMTs.

Methods: This cohort study was conducted between January 2020 and February 2023 at the MS Research Center of Sina Hospital, Tehran, Iran, to identify the characteristics of RRMS patients who were switched from anti-CD20s to low-moderate efficacy DMTs within 12 months of the last anti-CD20 infusion. Patients were then followed up to 18 months after de-escalation.

Results: All patients were females, with a mean age of 39.3±2.53-year-old and a mean disease duration of 9.7±1.39 years. After a mean of 2.95±0.44 years of treatment with anti-CD20s, patients were de-escalated to INF-β1a (n=5), dimethyl fumarate (DMF) (n=3), fingolimod (n=1), and teriflunomide (n=1). The main reason for anti-CD20 discontinuation was an infectious concern. Within 18 months of follow-up, no patient developed clinical or MRI activity. Additionally, we did not find evidence of disability progression in any patients (P=0.13).

Conclusion: The present study is a real-world experience of de-escalating anti-CD20s to low-moderate efficacy DMTs, which suggests that at short-term follow-up, de-escalating anti-CD20s appeared to be effective and safe in RRMS patients.

Keywords: Anti-CD20, B cell depleting monoclonal antibody, De-escalation, Relapse remitting multiple sclerosis, RRMS.

Citation:
Paybast S, Rezaeimanesh N, Naser Moghadasi A. De-escalation of anti-CD20 monoclonal antibodies to low-moderate efficacy disease-modifying treatments (DMTs) in patients with relapse-remitting multiple sclerosis: An initial Iranian experience. Caspian J Intern Med 2025; 16(1): 126-131.

Multiple sclerosis (MS) is known as the most prevalent autoimmune-mediated neurodegenerative disorder of the central nervous system (CNS), with various symptoms and uncertain course. In 80 – 90% of patients, the disease starts with a relapsing-remitting (RRMS) phenotype, which, for the majority, shifts to a secondary progressive (SPMS) form within 20 – 25 years after onset (1, 2). The advent of disease-modifying therapies (DMTs) has significantly improved the management of disease activity and slowed the progression of disability in MS patients. While the traditional treatment in RRMS starts with moderate-efficacy DMTs and subsequently escalates to higher-efficacy DMTs when there is evidence of breakthrough activity, there is an increasing interest in considering the use of high-efficacy treatments at an earlier stage in the management of MS (3, 4).

 Publisher: Babol University of Medical Sciences

CD20 B-cell-depleting therapies are among the high-efficacy DMTs frequently employed in treating MS. They have been shown to significantly decrease the radiological and clinical activity in RRMS with potential benefits even in progressive MS. They cause selective depletion of B-cell through different antibody-cell and complement-mediated mechanisms. While, long-term treatment with anti-CD20s appears to be relatively well tolerated, convincing evidence discloses that with long-term treatment, many patients develop hypogammaglobulinemia and neutropenia, which again increase the risk of infection. Additionally, evidence from large comparative studies on cancer is still lacking (5, 6). Given the possible increased risk of infection with long-term use of anti-CD20s, primarily identified during the COVID-19 pandemic, in line with sporadic reports on malignancies in anti-CD20-treated MS, there has been particular interest in de-escalating anti-CD20s over time (5-7). The initial effort arose during the COVID-19 pandemic when several observational studies were published to investigate the effect of extended or personalized dosing of anti-CD20s on RRMS patients. They proposed that the extended interval dosing (EID) of anti-CD20s infusion could be a potential risk mitigation strategy to reduce the susceptibility to COVID-19 infection.

While the impact of the de-escalation of anti-CD20s on their effectiveness remains to be demonstrated in well-designed trials, the current data favor the reduced risk of anti-CD20s adverse events while maintaining drug efficacy without disease progression or recurrence (8-12). It should be noted that data on de-escalating anti-CD20s to low-moderate efficacy DMTs is scarce, and there is no guideline to demonstrate when and how we could think of de-escalation. To our knowledge, there is only a report on ten patients switching from anti-CD20s to dimethyl fumarate (DMF), which revealed two clinical or radiological activities in the first six months of DMF initiation (13). Considering the paucity of data on anti-CD20s de-escalation in the literature, herein we aimed to describe our experience with ten RRMS patients who switched from either rituximab or ocrelizumab to the low-moderate efficacy DMTs.

Methods

Study design: This investigation was a retrospective, single-center cohort study, which was conducted from January 2020 to February 2023 at the MS Research Center of Sina Hospital, Tehran, Iran, to examine the outcome of RRMS patients who deescalated from either rituximab or ocrelizumab to the low-moderate efficacy DMTs. This study was reviewed and approved by the local Institutional Review Board. Moreover, written informed consents were taken from all participants, according to the Declaration of Helsinki.

Study population: RRMS patients with definite diagnosis based on the latest McDonald's criteria which had been treated with anti-CD20s for at least one year and switched to lower efficacy DMTs were included. Patients who discontinued treatment due to pregnancy, patients who had clinical or radiological activity on anti-CD20s, patients aged below 18 years old, patients who could not undergo an MRI examination,and those who declined to participate were excluded from the study.

Study measures: First, a researcher-made questionnaire including demographic and MS characteristics consisting of age, gender, disease duration, the reason for anti-CD20 de-escalation, the DMT class before and after anti-CD20 treatment, the annual relapse rate (ARR) before and during anti-CD20, and the neurological status based on the Expanded Disability Status Scale (EDSS) were filled. Then, the patients were followed from anti-CD20 discontinuation up to at least 18 months after the new DMT initiation. During the follow-up, clinical and MRI activity, disability progression, and adverse events were evaluated at each clinic assessment. Clinical activity was defined as an acute monophasic clinical episode with objective findings typical of MS, lasting at least 24 hours without infection or fever (12). A new or enlarged T2-weighted or T1-weighted gadolinium-enhancing lesion was defined as MRI activity. A progression was defined for a rise of 1.5 points if baseline EDSS was equal to 0, 1 point if the baseline EDSS range from 0 to 5, and 0.5 points if the baseline EDSS was equal to or greater than 5.0 (14).

Statistical analysis: Descriptive statistical analysis was conducted. Non-parametric distributed quantitative variables were presented as median(s) and interquartile range(s) (IQR). Qualitative data were introduced as frequency and percentage(s).

Results

Ten patients were enrolled in the present study. All patients were females, with a mean±SD age and disease duration of 39.3±2.53-year-old and 9.7±1.39 years, respectively. No patient reported underlying comorbidity at MS diagnosis. Four patients (40%) with highly active MS were treated with rituximab from the beginning, and six patients were escalated to anti-CD20 due to breakthrough disease activity. Interferon beta (INF-β) and glatiramer acetate (GA) were the most commonly used DMTs before

anti-CD20 initiation, with a mean duration of 4.25±0.56 years. As shown in table 1, the ARR before anti-CD20 initiation was estimated to be 2.8± 0.38, dramatically dropping to zero during treatment with anti-CD20. The mean age at anti-CD20 initiation was 33.85±8.43 years. More ever, the mean EDSS at the time of anti-CD20 initiation and discontinuation was 3.15± 0.94 and 2.85±1.08, respectively. Nine patients were treated with rituximab for a mean of 3.9±0.44 years. They received a single 1-gram dose of rituximab in a regular maintenance interval of six months, with an average of eight rituximab doses. The patient treated with ocrelizumab received anti-CD20 for two years with a cumulative dose of 2400 mg.

Based on the results, the reasons for anti-CD20 de-escalation included the occurrence of severe COVID-19 associated with secondary hypogammaglobinemia (n=1), the safety concern related to anti-CD20s in the COVID-19 pandemic (n=6), acute abdominal pain and peritonitis (n=1), thyroid cancer (n=1), and the development of ulcerative colitis (n=1). The majority of patients (n=5) de-escalated to INF-β 1a subcutaneous (SC), followed by DMF (n=3), fingolimod (n=1), and teriflunomide (n=1). Our patients' DMT profile is summarized in figures 1 and 2.

The patient with thyroid cancer underwent tumor resection with chemoradiotherapy, and the one with ulcerative colitis received sulfasalazine (500 mg twice a day) with fingolimod. Over a mean follow-up of 1.7±0.2 years, no patient experienced clinical or MRI activity. Moreover, no evidence of progression was identified. At the last visit, the mean EDSS was estimated to be 2.85±1.22, which was not significantly different from the EDSS at discontinuation (P=0.13). No patient discontinued their DMT nor developed adverse events. Those who developed an autoimmune disease and cancer on anti-CD20 were stable in terms of both conditions after anti-CD20 de-escalation.

Table 1. Baseline demographic and MS characteristics of patients who underwent anti-CD20 de-escalation

Case	Age (year)	Sex	Disease duration (year)	Mean ARR in the year before anti-CD20 initiation	Anti-CD20 type	ARR on anti-CD20	Duration of anti-CD20 usage (year)	EDSS at anti-CD20 initiation	EDSS at anti-CD20 de-escalation	CD19 level at anti-CD20 de-escalation	Reason for de-escalation
1	35	F	12	3	RTX	0	2	4	2.5	0	COVID-19 concern
2	41	F	10	2	RTX	0	1	2.5	2	0.1	COVID-19 concern
3	56	F	16	5	RTX	0	1.5	4.5	4	0.35	Peritonitis
4	33	F	8	2	RTX	0	2	3	3	1.1	Thyroid cancer
5	33	F	5	1	RTX	0	1	2	1.5	0	Severe COVID-19 and SHG
6	28	F	3	2	RTX	0	1.5	2	2	0	COVID-19 concern
7	44	F	17	4	OCR	0	2	4.5	5	0.2	Ulcerative colitis
8	37	F	8	3	RTX	0	2	3	3	0.3	COVID-19 concern
9	40	F	8	2	RTX	0	3	2.5	2	1.3	COVID-19 concern
10	46	F	10	4	RTX	0	1	3.5	3.5	0	COVID-19 concern

MS: multiple sclerosis, DMT: disease-modifying treatment, ARR: annual relapse rate, EDDS: Expanded Disability Status Scale, F: female, RTX: rituximab, OCR: ocrelizumab, SHG: secondary hypogammaglobulinemia.

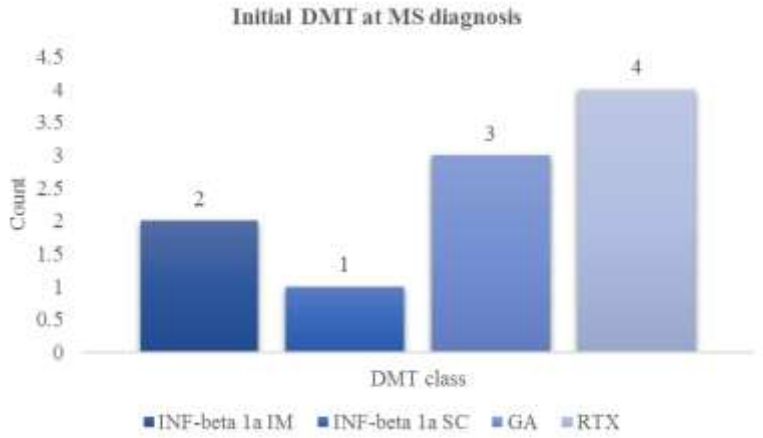

Figure 1. The the DMT frequency among relapse-remitting MS at diagnosis. DMT: disease-modifying treatment, MS: multiple sclerosis, INF: interferon, IM: intramuscular, SC: subcutaneous, GA: glatiramer acetate, RTX: rituximab

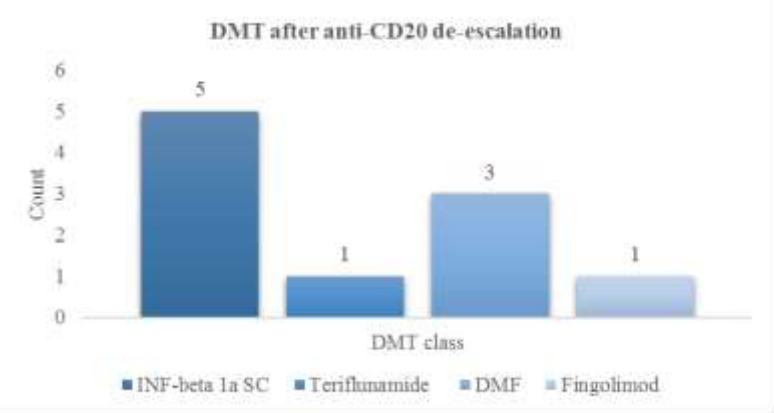

Figure 2. Frequency of chosen DMT after anti-CD20 de-escalation in relapse-remitting MS patients. DMT: disease-modifying treatment, MS: multiple sclerosis, INF: interferon, SC: subcutaneous, DMF: dimethyl fumarate

Discussion

In this retrospective observational study, we evaluated in this retrospective observational study, we evaluated the efficacy of de-escalation of anti-CD20s to low-moderate efficacy DMTs in RRMS. Our results demonstrated that after a mean of 2.95±0.44 years of treatment with anti-CD20s, de-escalating to low-moderate efficacy DMTs appeared safe and effective in RRMS patients at an 18-month follow-up. The main reasons for de-escalation were infectious concerns followed by autoimmunity and malignancy on anti-CD20s which highlights the importance of immunosuppression in the long-term use of anti-CD20s.

Most MS patients are diagnosed with RRMS, which can progress into SPMS. Notably, disability progression is partly related to new focal inflammatory demyelinating lesions. In contrast, progression independent of relapse activity (PIRA) from the biological onset of MS is considered the main culprit for disability accumulation in progressive forms of MS (1, 2). Over the past 25 years, more than a dozen DMTs have been approved for MS to reduce disease activity and disability accumulation. A fast development of MS therapeutics is going on, with numerous investigative therapies currently in different stages of clinical trials. Many real-world studies favor the early initiation of high-efficacy DMTs, particularly in MS patients with poor prognostic factors. While the high-efficacy DMTs prioritize efficacy, their main limitation is an unfavorable risk/benefit ratio in long-term use (3, 4, 15, 16). Anti-CD20 antibodies such as rituximab proved highly efficacious yet remained an off-label treatment in MS until its humanized surrogate, ocrelizumab, was approved in 2018 (3, 4).

While generally well tolerated, anti-CD20s have some safety concerns that must be considered. In controlled treatment intervals of the pivotal phase 3 trials, the most prevalent adverse events related to ocrelizumab were

infusion-related reactions and infections, aligning with the active comparator group. While the longer-term infectious safety remains unknown, the evidence suggests that long-term anti-CD20 therapy leads to hypogammaglobulinemia. A reduced serum immunoglobulins level, particularly IgG levels, is associated with an elevated risk of serious infection (5, 6, 17). It seems that since these antibodies deplete B cells, which play a role in the immune response, patients may be at an increased risk of infections, particularly respiratory tract infections (18). In line with these assumptions, In the face of the COVID-19 pandemic, several studies have suggested that MS patients treated with anti-CD20s were at higher risk for severe COVID-19 outcomes than those under other treatments. The COVID-19 pandemic has also heightened the attention on how anti-CD20s might reduce the efficacy of COVID-19 vaccines (19, 20). On the other hand, in the OPERA 1 and OPERA 2 clinical trials, the adverse events of particular interest were malignancy, driven mainly by a higher rate of breast cancer (5-7, 17). In light of safety concerns associated with anti-CD20s, there has been an emergent interest in the de-escalation approach in stable patients, mainly elderly patients, which may consist of extended intervals, reduced dosing, or potentially transition to a less potent DMT (8). Many studies evaluating large cohorts of MS patients have consistently revealed that extended interval dosing (EID) between two infusions of rituximab or reduced dosing of rituximab in MS is associated with a low risk of disease activity (9).

It has been proposed that stable MS patients undergoing anti-CD20 therapy should transition to extended interval dosing due to its association with a reduced risk of disease activity (8). A recent prospective cohort of 718 rituximab-treated RRMS patients exposed to EID revealed 24 clinical and radiological relapses. Of these, 20 occurred within eight months since the previous infusion and four with intervals over eight months. The results highlighted that relapse risk remains low with the EID regimen (21). Although the data on ocrelizumab is expanding, available studies are limited to small case series with short-term follow-ups, which have also shown conflicting results. Accordingly, an Italian multicenter study found that while standard dosing or EID did not affect the confirmed disability progression, EID appeared to be associated with a higher risk of MRI activity (11). In addition, exceptional circumstances, such as the incidence of autoimmune disease, malignancy or persistent severe hypogammaglobulinemia on anti-CD20, make the continuation of therapy impossible. The need for correct decision-making has yet to be met in this context.

There is substantial evidence of long-term benefits and an absence of rebound disease activity after the prolonged extension or discontinuation of rituximab (8). Conversely, there is only one abstract report on ten patients switching from rituximab to DMF (13). Based on the results, our patients' demographic and MS characteristics were almost comparable. However, the main reason for rituximab discontinuation was insurance issues in their case series compared to infectious concerns in ours. In addition, all their patients were switched to DMF, which was associated with clinical stability in eight patients during the first six months. We assume this difference might be due to several factors: (1) in our study, one patient was switched to fingolimod, which is more potent than other first-line DMTs, (2) four patients were treated with anti-CD20 from the beginning, where their immune system might be differently regulated. At this juncture, more evidence-based guidelines must be used to determine when and how to de-escalate anti-CD20s. Observational studies in reduced or extended interval dosing of anti-CD20s have gained insights into real-world effectiveness. Similarly, our preliminary case series suggest that, after a period of disease stability of about three years in our experience, anti-CD20s could be efficiently de-escalated to low-moderate high-efficacy DMTs. However, there were several limitations in our study. First, the sample size was small. Second, we observed patients for 18 months and did not investigate the long-term outcomes. Third, we did not examine the cognitive aspects that might be purely affected without overt clinical activity or progression. Extensive randomized studies in long-term follow-up are needed to confirm our results. The present study is a real-world experience of de-escalating anti-CD20s to low-moderate efficacy DMTs. Ten patients de-escalated to low-moderate efficacy DMTs were clinically and radiological stable at 18 months follow-up.

Acknowledgments

None.

Funding: This study was granted by Tehran University of medical sciences under the grant number: 1400-3-233-56038.

Ethics approval: The study protocol was reviewed and approved by the Ethics Committee of the Tehran University of Medical Sciences by the ethics number: IR.TUMS.NI.REC.1400.069.

Conflict of Interests: The authors declare no conflict of interest.

Authors' contribution: A.N.M: Hypothesis, supervision, data collection, drafting the manuscript and approving the final format of the manuscript; S.P: Data collection, analysis, drafting the manuscript and approving the final format of the manuscript; N.R: Drafting the manuscript and approving the final format of the manuscript.

References

1. Oh J. Diagnosis of Multiple Sclerosis. Continuum (Minneap Minn) 2022; 28: 1006-24.
2. Ward M, Goldman MD. Epidemiology and pathophysiology of multiple sclerosis. Continuum (Minneap Minn) 2022; 28: 988-1005.
3. Simpson A, Mowry EM, Newsome SD. Early Aggressive treatment approaches for multiple sclerosis. Curr Treat Options Neurol 2021; 23: 19.
4. Śladowska K, Kawalec P, Holko P, Osiecka O. Comparative safety of high-efficacy disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. Neurol Sci 2022; 43: 5479-5500.
5. Krajnc N, Bsteh G, Berger T, Mares J, Hartung HP. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: an overview with emphasis on pregnancy, vaccination, and risk management. Neurotherapeutics 2022; 19: 753-773.
6. Vikse J, Jonsdottir K, Kvaløy JT, Wildhagen K, Omdal R. Tolerability and safety of long-term rituximab treatment in systemic inflammatory and autoimmune diseases. Rheumatol Int 2019; 39: 1083-90.
7. Ineichen BV, Moridi T, Granberg T, Piehl F. Rituximab treatment for multiple sclerosis. Mult Scler 2020; 26: 137-52.
8. Rolfes L, Meuth SG. Stable multiple sclerosis patients on anti-CD20 therapy should go on extended interval dosing-"Yes". Mult Scler 2022; 28: 691-3.
9. van Kempen ZL, Toorop AA, Sellebjerg F, Giovannoni G, Killestein J. Extended dosing of monoclonal antibodies in multiple sclerosis. Mult Scler 2022; 28: 2001-9.
10. Sahi NK, Abidi SMA, Salim O, et al. Clinical impact of Ocrelizumab extended interval dosing during the COVID-19 pandemic and associations with CD19+ B-cell repopulation. Mult Scler Relat Disord 2021; 56: 103287.
11. Zanghì A, Avolio C, Signoriello E, et al. Is it time for Ocrelizumab extended interval dosing in relapsing remitting MS? Evidence from an Italian multicenter experience during the COVID-19 pandemic. Neurotherapeutics 2022; 19: 1535-45.
12. Rolfes L, Pawlitzki M, Pfeuffer S, et al. Ocrelizumab extended interval dosing in multiple sclerosis in times of COVID-19. Neurol Neuroimmunol Neuroinflamm 2021; 8; e1035.
13. Vollmer B, Riddle E, Mendoza J, Alvarez E. Retrospective evaluation of De-escalation from anti-CD20 therapies to Fumarates as a treatment approach (P3-4.003). Neurology 2022; 98.
14. Healy BC, Glanz BI, Swallow E, et al. Confirmed disability progression provides limited predictive information regarding future disease progression in multiple sclerosis. Mult Scler J Exp Transl Clin 2021; 7: 2055217321999070.
15. Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease‐modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol 2022; 269: 5382-94.
16. Bourre B, Casez O, Ciron J, et al. Paradigm shifts in multiple sclerosis management: Implications for daily clinical practice. Rev Neurol (Paris) 2023; 179: 256-264
17. Gabelić T, Barun B, Adamec I, Krbot Skorić M, Habek M. Product review on MAbs (alemtuzumab and ocrelizumab) for the treatment of multiple sclerosis. Hum Vaccin Immunother 2021; 17: 4345-62.
18. Margoni M, Preziosa P, Filippi M, Rocca MA. Anti-CD20 therapies for multiple sclerosis: current status and future perspectives. J Neurol 2022; 269: 1316-34
19. Schiavetti I, Ponzano M, Signori A, et al. Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: A systematic review and meta-analysis. Mult Scler Relat Disord 2022; 57: 103358.
20. Etemadifar M, Nouri H, Pitzalis M, et al. Multiple sclerosis disease-modifying therapies and COVID-19 vaccines: a practical review and meta-analysis. J Neurol Neurosurg Psychiatry 2022; 93: 986-94.
21. Cucuzza CS, Longinetti E, Ruffin N, et al. Sustained low relapse rate with highly variable B-cell repopulation dynamics with extended rituximab dosing intervals in multiple sclerosis. Neurol Neuroimmunol Neuroinflamm 2023; 10: e200056.