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Alemtuzumab following natalizumab is more effective in adult-onset than paediatric-onset multiple sclerosis

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Abstract

Background: Paediatric-onset multiple sclerosis (POMS) therapeutic approach derives from of adult-onset multiple sclerosis (AOMS) tailored algorithms.

Objectives: To evaluate in a common clinical scenario the efficacy and safety of alemtuzumab (ALZ) in POMS and AOMS.

Methods: All patients switching from natalizumab (NTZ) to ALZ for safety concerns (high anti-John Cunningham Virus Antibody Index value, anti-JCV Index) were enrolled in this single-centre, retrospective, case-control open-label study.

Results: Ten POMS and 27 AOMS were followed up for 51.3 months. After month 12, we found a lower risk of clinical or radiological relapses among AOMS patients and among patients with older age at ALZ (both $p < 0.05$). Survival analysis revealed an increased risk of relapse in POMS compared with AOMS (logrank $p = 0.00498$) and patients starting ALZ before age 22.75 years than the elder ones (logrank $p = 0.0018$). Survival analysis did not disclose any difference between AOMS and POMS (logrank $p = 0.27$) in terms of progression independent of any relapse activity (PIRA). In addition, no evidence of relapse-associated worsening was observed. Autoimmune events were reported by 5 AOMS and no POMS (29.4% *versus* 0.0%, $p = 0.057$), and survival analysis was not significant (logrank $p = 0.0786$).

Conclusion: ALZ seems more effective in AOMS than in POMS following NTZ. These findings underrate ALZ effectiveness when shifting from NTZ in POMS.

Keywords: alemtuzumab, multiple sclerosis, natalizumab, paediatric-onset multiple sclerosis

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Introduction

Paediatric-onset multiple sclerosis (POMS)[1] is characterized by the rapid accumulation of white and grey matter inflammation and by a higher risk of long-term physical and cognitive disability than adult-onset multiple sclerosis (AOMS).[2] Although POMS aggressive course requires an early and effective therapeutic strategy, current treatments are mainly based on first-line drugs and derive from the application of AOMS therapeutic protocols. Indeed, only two disease-modifying therapies (DMTs), fingolimod and teriflunomide, have been approved for treating POMS,[3,4] but only fingolimod is currently refunded by the Italian Public Health System. Moreover, the efficacy of dimethyl fumarate in POMS has been demonstrated in phase II and III clinical trials, but this DMT has not been approved yet.[5–7] Two further clinical trials are recruiting currently (a phase I, NCT02200718 and a phase III clinical trial, NCT05123703). Finally, injectable treatments[8,9] or natalizumab[10–12] efficacy was observed in observational large case-series studies.[8–12]

Clinical and radiological features of POMS suggest that its immunopathogenic mechanisms

could differ, at least quantitatively, from those of AOMS,[13] thus questioning whether the efficacy and safety of the drugs used to treat AOMS should be uncritically applied to POMS. This is particularly relevant for induction therapies [i.e. alemtuzumab (ALZ), cladribine and autologous hematopoietic stem cell transplantation], whose mechanisms of action imply a marked and possibly long-lasting effect on adaptive immune system (i.e. B- and T-cell receptor repertoire and network).[14]

ALZ, a monoclonal antibody that binds the CD52 on cell surface and almost completely depletes circulating T and B lymphocytes, induces a strong immunosuppression followed by a 'reconstitution phase', which is mostly driven by homeostatic proliferation of T-cells and by *de novo* repopulation of B-cells.[15,16] Moreover, an earlier repopulation of regulatory T-cells have been observed and is thought to further hamper the activation of residual self-reactive lymphocytes.[17] All these effects are supposed to be long lasting and to continue even in the absence of further drug exposure, determining the sustained effect of ALZ on disease activity parameters, as observed in longitudinal studies.[18] On the contrary, the same mechanisms might explain autoimmune events reported in ALZ-treated MS patients,[19,20] which usually appear between months 24 and 48.

In this study, we focused on a common clinical scenario, in which both AOMS and POMS patients switched from NTZ (a drug available in Italy for treating POMS) to ALZ due to safety concerns (namely, a anti-John Cunningham Virus Antibody Index value, anti-JCV Index >1.5). The evaluation of these two MS groups gave us the opportunity to evaluate the efficacy of ALZ following NTZ in severe forms of MS in different age groups.

Materials and methods

Study population

From September 2015 to August 2020, all patients affected by relapsing-remitting multiple sclerosis (RRMS) and switching from NTZ to ALZ were enrolled in this retrospective, case–control open-label study. Inclusion criteria were (1) diagnosis of RRMS, according to the most recent criteria;[21] (2) NTZ withdrawal due to safety concerns (i.e. anti-JCV Index >1.5); (3) age at ALZ 18 and 55 years old; and (4) follow-up of at least 24 months after the first ALZ infusion. All patients were treated with the same administration protocol for ALZ, as indicated by the Summary of Product Characteristics of European Medical Agency (https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf).

Clinical and radiological follow-up

Clinical and radiological follow-up and disease activity were performed as previously reported.[22] Briefly, all patients were evaluated with a complete neurological examination, which included the Expanded Disability Status Scale (EDSS), and a brain and spinal cord magnetic resonance imaging (MRI) with gadolinium administration every 6 months. A clinical relapse was defined as the occurrence of new symptoms or exacerbation of existing symptoms that lasted for 24 h or longer, in the absence of concurrent illness or fever, and occurring 30 days or more as a previous relapse. The definition of relapse used in this study did not require confirmation by change in EDSS. Radiological disease activity was defined in the presence of any new/enlarging T2-lesion or of any gadolinium-enhancing lesion on post-contrast T1-scans. Clinical disability worsening was defined as an increase in EDSS by 1 step (1.5 steps if baseline EDSS was 0 and 0.5 steps if baseline EDSS was >5.5)[23] confirmed at months 6 and 12. Progression independent of any relapse activity (PIRA) was defined in presence of CDW worsening in absence of any clinical nor radiological inflammatory disease activity, as previously indicated, while relapse-associated worsening (RAW) was indicated in presence of significant and sustained EDSS increase associated with a clinical relapse.[24] EDSS improvement was defined by the reduction of 0.5 points for any EDSS value above 1.0. Baseline and follow-up MRI were performed by 1.5 T or 3.0 T scanners and always included (1) three-dimensional (3D) turbo field echo (TFE, 3D-T1) (This sequence was acquired before and after gadolinium administration.) and (2) 3D-Fluid Attenuated Inversion Recovery (3D-FLAIR). Two experienced observers (M.P. and M.G.), blinded to the patient's identity, assessed all images.

Table 1. Clinical and demographic variables.

	POMS (10 patients)	*p* values	AOMS (17 patients)
Age at MS onset (years)[a]	15.0 ± 2.3	<**0.0001**	28.5 ± 9.2
Sex ratio (F/M)[b]	1.0	0.415	2.4
Number of previous treatment(s)[a]	1 (1–2)	0.158	2 (1–6)
Age at ALZ (years)[a]	19.3 ± 2.0	<**0.0001**	38.2 ± 8.9
EDSS at ALZ[a]	1.5 (1.0–2.0)	**0.010**	2.0 (1.0–3.5)
Disease duration at ALZ (months)[a]	51.7 ± 27.5	*p* = 0.393	115.4 ± 106.9
NTZ-ALZ delay (days)[a]	52.4 ± 37.5	*p* = 0.702	57.2 ± 33.4
BMI at alemtuzumab[a]	21.8 ± 2.4	*p* = 0.31	22.6 ± 3.0
BMI[c] < 18.5	0 (0%)	0.87	0 (0%)
18.5 < BMI[c] < 25	1 (90%)		16 (94.1%)
BMI[c] > 25	1 (10%)		1 (5.9%)

ALZ, alemtuzumab; AOMS, adult-onset multiple sclerosis; BMI, body mass index; EDSS, Expanded Disability Status Scale; NTZ, natalizumab; POMS, paediatric-onset multiple sclerosis.
Results are reported as mean value ± standard deviation or as median (range).
[a]Mann–Whitney *U*-test was applied to test any difference.
[b]Fisher's exact test was applied to test any difference.
[c]Fisher's exact test was applied to test any difference, counting one AOMS and one POMS with BMI <18.5.
Significant *p*-values are in bold.

Statistical analysis

For continuous normally distributed variables, the Student's *t*-test was performed, while for the other continuous variables, the Mann–Whitney *U*-test was performed. For categorical variables, the Fisher's exact test was used. Normality assumption was assessed both graphically (quantiles of normal distribution) as well as using the Shapiro–Wilk normality test. Kaplan–Meier analyses were applied to compare the two MS groups. For Cox regression analysis, sex, baseline EDSS age at MS diagnosis, MS group (POMS *versus* AOMS) and age at first ALZ infusion were evaluated. Log-likelihood of the Cox proportional hazards models and the logrank test results were evaluated to identify an optimal cut-off value for age at ALZ and age at MS diagnosis. EDSS modification was evaluated by means of Friedman's test with Dunn's correction. The significance level was set at 0.05. All the analysis was performed using Stata (v.16.0; Stata Corporation, College Station, TX, USA).

Results

Clinical and demographic variables

Based on age at MS onset, 10 POMS and 17 AOMS patients were recruited. Their clinical and demographic variables are reported in Table 1. After first ALZ infusion, patients were followed up for 51.3 ± 16.9 months. All patients completed a 2-year follow-up; therefore, efficacy data are reported between baseline and month 12, between month 12 and month 24 and between baseline and month 24. Moreover, 23 patients (81.5%) completed a 36-month follow-up. No patient was lost during the follow-up.

ALZ is highly effective in AOMS, but not in POMS, on inflammatory disease parameters

The washout interval between NTZ and ALZ lasted similarly in POMS and AOMS (52.4 ± 37.5 and 57.2 ± 33.4, respectively, $p = 0.702$), and no clinical relapse was observed during this period.

Table 2. Univariate Cox proportional hazards models to evaluate baseline parameters associated with time to first clinical or radiological relapse after the second ALZ infusion.

	Univariate analysis	
	Hazard ratio (95% CI)	***p* value**
Sex		
Female *versus* male	0.52 (0.12; 2.33)	0.394
Age		
Age at alemtuzumab (5 years increase)	0.48 (0.24; 0.97)	**0.040**
AOMS *versus* POMS	0.23 (0.04; 1.16)	0.075
Age at alemtuzumab ⩾22.75 *versus* <22.75	0.08 (0.01; 0.63)	**0.017**
Age at MS (5 years increase)	0.42 (0.17; 1.03)	0.057
Disease duration (5 months increase)	0.96 (0.89; 1.03)	0.245
Baseline EDSS	0.58 (0.14; 2.40)	0.452
Previous treatments	0.66 (0.30; 1.46)	0.360

ALZ, alemtuzumab; AOMS, adult-onset multiple sclerosis; CI, confidence interval; EDSS, Expanded Disability Status Scale; POMS, paediatric-onset multiple sclerosis.
Significant *p*-values are in bold.

All clinical and radiological relapses are illustrated in Figure 1. Between baseline and month 12, only 2 POMS (patients POMS-1, POMS-2) reported a clinical relapse, which in both cases was supported by a radiological reactivation. In addition, one POMS (POMS-8) and two AOMS (AOMS-1 and AOMS-10) presented an asymptomatic radiological reactivation.

Between month 12 and month 24, one POMS (POMS-1) and one AOMS (AOMS-1) reported a clinical relapse with a radiological disease reactivation. No difference in terms of frequency of clinical or radiological relapse was observed within the two groups between baseline and month 12, month 12 and month 24 and baseline and month 24 (Supplementary Table 1).

The factors associated with an increased risk of disease reactivation after the second infusion were explored using the Cox regression analysis, which showed a predictive value for MS group [AOMS *versus* POMS: hazard ratio (HR) = 0.23; p value = 0.075], age at MS onset (HR = 0.42; p value = 0.057) and age at ALZ (HR = 0.48; p value = 0.040). Due to collinearity issues, it was not possible to perform a multivariable model including all these variables related to age. Age at MS onset and age at ALZ were in fact strictly correlated (Spearman's $r = 0.85$, $p < 0.001$) and both significantly lower in POMS than in AOMS (both $p < 0.001$, Table 2).

Survival analysis revealed an increased risk of relapse in POMS compared with AOMS (logrank $p = 0.0498$) (Figure 2(a)).

For age at ALZ, an optimal cut-off was found based on log-likelihood after the Cox model and logrank test, and it was 22.75 years (log-likelihood = −16.536, logrank test: p value = 0.0018). This cut-off shifted one AOMS to POMS group (AOMS-1) and vice versa (POMS-6). These two new cohorts differ for age at disease onset (15.2 ± 2.6 *versus* 28.4 ± 9.4 years old, $p < 0.0001$) and for EDSS [1.5 (1; 2) *versus* 2 (1; 3.5); p value = 0.048], while did not for disease duration, number of previous treatments, drug-free interval between NTZ and ALZ (Table 3). Survival analysis disclosed that younger patients relapsed earlier compared with the elder ones (logrank $p = 0.0018$) (Figure 2(b)).

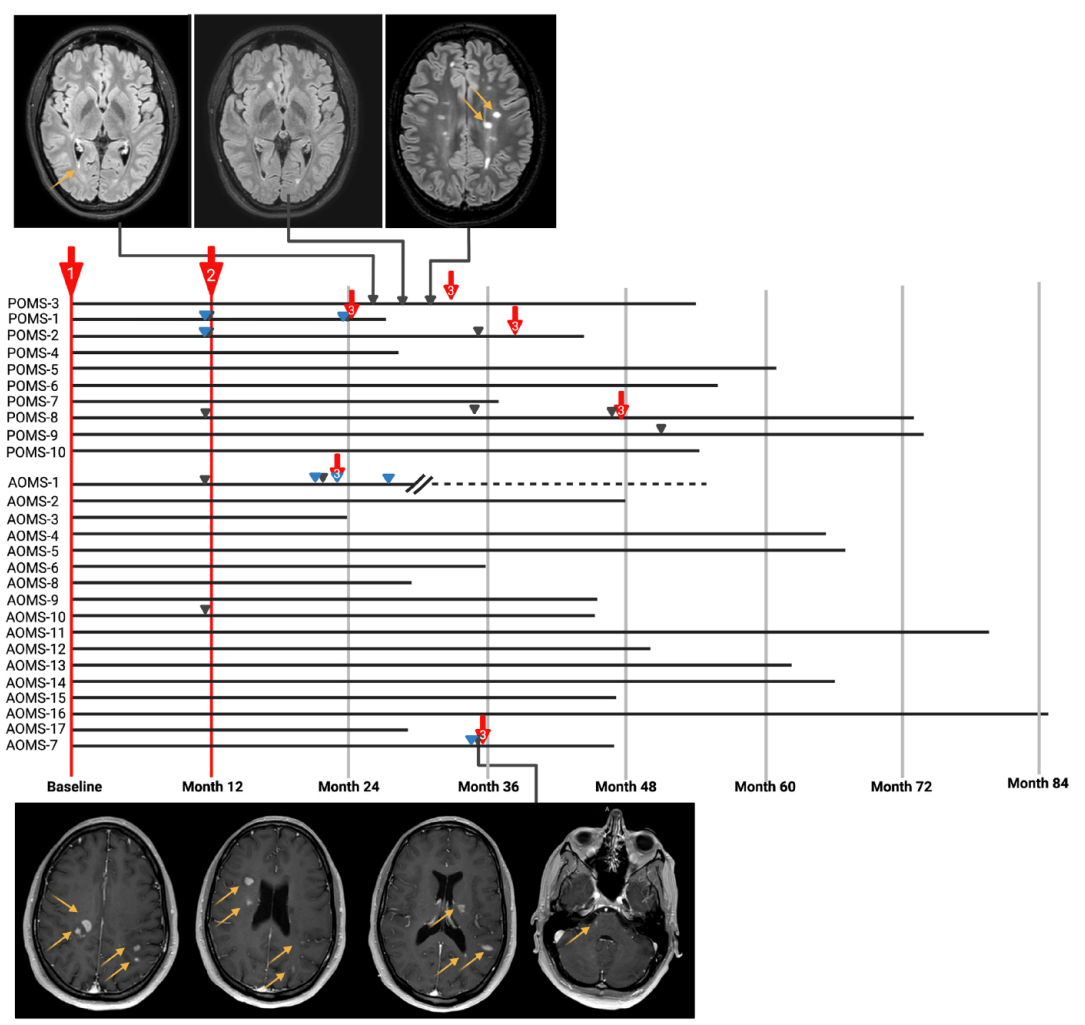

Figure 1. Disease reactivation in POMS and AOMS cohorts.
Disease course in our cohort. Red arrows indicate alemtuzumab administrations (the white number inside the arrowhead indicates the cycle). Grey and blue arrow heads indicate radiological and clinical reactivation, respectively. MRI on the top: three FLAIR sequences from three different MRI scans illustrating new gadolinium-enhancing (yellow arrow) or not (white arrow) lesions in a POMS patient. MRI on the bottom: gadolinium-enhancing lesions (yellow arrow) in an AOMS patient. Between the first two cycles of alemtuzumab (between baseline and month 12), two POMS patients presented a clinical relapse (both associated with a radiological disease reactivation). Moreover, one additional POMS and two AOMS experienced a radiological disease reactivation. After the second course of alemtuzumab at month 12, only one AOMS experienced a clinical and radiological disease reactivation during the following 12 months (between months 12 and 24). This patient had already had a radiological disease activity between the two courses.

ALZ effect on clinical disability

Despite clinical and radiological activity, EDSS values did not worsen in any POMS during the entire observation, while in AOMS group, two patients had a significant worsening (+1.0 EDSS point confirmed after 6 and 12 months). Survival analysis did not disclose any difference between AOMS and POMS (logrank $p = 0.27$) in terms of PIRA. In addition, no evidence of relapse-associated worsening was observed.

A significant EDSS improvement was observed and confirmed at 12 months in three POMS (30%) and three AOMS (17.7%, $p = 0.64$); survival analysis did not disclose any difference between these two groups (logrank $p = 0.58$).

Safety data

No POMS patient reported severe infusion-associated reaction (IARs), severe infections in the

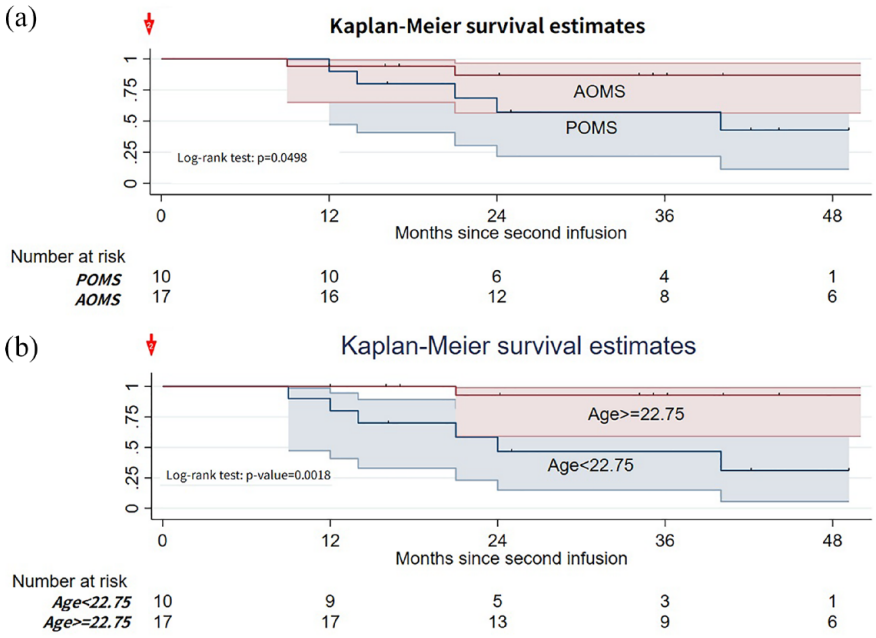

Figure 2. Kaplan–Meier survival estimates and 95% CI for the time to first clinical or radiological relapse after induction phase in POMS and AOMS cohorts and based on age at alemtuzumab (cut-off 22.75 years). Bars indicate censoring. (a) Survival analysis disclosed a higher risk of disease reactivation in POMS compared with AOMS (logrank test: $p = 0.0498$). (b) Survival analysis showed that the risk of disease reactivation associated with age at alemtuzumab (logrank test: $p = 0.0018$).

Table 3. Classifying MS patients based on age at alemtuzumab.

	Age <22.75 years (10 patients)	*p* values	Age ⩾22.75 years (17 patients)
Age at MS onset (years)[a]	15.2 ± 2.6	<**0.001**	28.4 ± 9.4
Sex ratio (F/M)[b]	1.5	1.000	1.8
Number of previous treatment(s)[a]	1 (1–2)	0.158	2 (1–6)
Age at ALZ (years)[a]	19.1 ± 1.3	<**0.001**	38.3 ± 8.6
EDSS at ALZ[a]	1.5 (1.0–2.0)	**0.048**	2.0 (1.0–3.5)
Disease duration at ALZ (months)[a]	46.2 ± 22.4	0.218	118.6 ± 105.4
NTZ-ALZ delay (days)[a]	54.3 ± 37.3	0.911	56.1 ± 33.7

ALZ, alemtuzumab; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NTZ, natalizumab.
Results are reported as mean value ± standard deviation or as median (range).
[a]Mann–Whitney *U*-test was applied to test any difference.
[b]Fisher's exact test was applied to test any difference.
Significant *p*-values are in bold.

6 months after ALZ infusion or autoimmune adverse events during the follow-up.

No AOMS patient reported severe IARs or severe infections in the 6 months after ALZ infusion. Nine AOMS (52.9%) developed an autoimmune thyroiditis; five patients already had a subclinical thyroiditis [i.e. positive for antithyroglobulin or antithyroid peroxidase antibody with normal thyroid-stimulating hormone (TSH) value and no

clinical symptom] at baseline. One AOMS patient developed an autoimmune encephalitis (anti-$GABA_AR$) 23 months after first ALZ infusion. Globally, autoimmune events were reported by five AOMS and no POMS (29.4% *versus* 0.0%, $p = 0.057$), and survival analysis revealed a non-significant higher risk of autoimmunity in AOMS (logrank $p = 0.0764$).

Discussion

POMS constitutes a rare group of patients, whose therapeutic approach is debated and mainly tailored based on adult-onset MS therapies. As the effect of NTZ on POMS has been largely described,[10,11] it constitutes in our country an optimal therapeutic approach before 18 years. As a proportion of POMS present a high JCV Index, in every-day clinical practice, the therapeutic shift from natalizumab at age 18 years is common. ALZ has been considered an effective treatment in AOMS, also after natalizumab,[25–29] and therefore few POMS were shifted to ALZ due to safety concerns. In line with previous reports,[30] we observed that the frequency of disease reactivation in POMS treated with ALZ following NTZ was a rare event during the induction and early reconstitution phase (i.e. in the next 24 months after ALZ administration). The positive impact of ALZ progressively decreased in POMS and in younger patients, however. This finding was an unexpected finding and raised some food for thought.

The association with MS group (POMS *versus* AOMS) and age at ALZ observed in survival analysis might suggest that the high rate of inflammatory waves characterizing the early MS phase, especially POMS, are likely not fully suppressed by pulsed immunosuppression and require additional cycles of ALZ to reshape adaptive immunity, especially when shifting from NTZ, which is known to potentially expand circulating self-reactive B- and T-cells.[31] The absence of autoimmune adverse events further suggests that in POMS, ALZ fails on both MS-specific and MS-unrelated immunological mechanisms, as it conversely does in adults. It, however, has to be pointed out that, despite radiological reactivation, the EDSS score did not increased during the follow-up and no POMS presented RAW or PIRA.

In addition, the association with age at diagnosis with a cut-off elder than the conventional definition of POMS could be explained considering that MS biological onset precedes the clinical onset by months/years. Therefore, it may be possible that a subgroup of AOMS have a biological onset in paediatric age, thus questioning the correct identification of POMS cases. Indeed, in our series, one AOMS-1 patient had clinical onset at 18.8 years, with biological onset possibly during adolescence.

Finally, part of the difference between POMS and AOMS derives from the high efficacy of ALZ (especially when excluding patient AOMS-1): indeed, just one patient (AOMS-7) had a clinical relapse with a severe radiological reactivation, which means that 94% of AOMS completed a median follow-up of 45 months (mean follow-up of 48.9 ± 17.3 months) achieving the NEDA (no evidence of disease activity) condition. These efficacies on MS-related mechanisms are counterbalanced by a higher risk of autoimmune events. These data are in line with long-term studies on ALZ in AOMS.[27,28,32–34]

Although in this study we present data on the largest available cohort of POMS treated with ALZ following NTZ, we are aware of our study limitations, such as the limited number of patients and the retrospective design of the study. The short follow-up is also a limitation in the evaluation of PIRA and in weighting the impact of disease reactivation (clinical and radiological) on long-term disability. Finally, our PIRA definition is completely based on EDSS, as already reported in the literature,[24] but lacks putative relevant information from other relevant tests (such as 9-hole peg-test and time 25-foot walk). Thus, our results need to be handled with caution and to be confirmed by multicentre, longitudinal, phase IV studies, as already performed in AOMS.[35]

In conclusion, our preliminary data suggest that ALZ following NTZ is highly effective in AOMS and less effective in POMS. Additional studies are needed to clarify whether ALZ (or more broadly, induction therapies) might be an effective therapeutic approach for POMS, especially when shifting from NTZ, and if an additional course should be always administered in young patients, especially in POMS. The observation that in an identical clinical scenario (i.e. shifting

from NTZ) ALZ is differently effective in two subcohorts of MS patients may help pave the road for personalized therapy.

Declarations

Ethics approval and consent to participate

The study was approved by the 'Comitato Etico per la Sperimentazione Clinica dell'Azienda Ospedaliera di Padova' (Prot n 33n/AO/20), and all patients gave written informed consent.

Consent for publication

Not applicable.

Author contributions

Marco Puthenparampil: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft.

Marta Gaggiola: Data curation; Formal analysis; Methodology; Writing – review & editing.

Alessandro Miscioscia: Conceptualization; Methodology; Writing – review & editing.

Valentina Annamaria Mauceri: Data curation; Writing – original draft.

Federica De Napoli: Data curation; Writing – review & editing.

Giovanni Zanotelli: Data curation; Writing – review & editing.

Mariagiulia Anglani: Supervision; Writing – review & editing.

Margherita Nosadini: Conceptualization; Writing – review & editing.

Stefano Sartori: Conceptualization; Writing – review & editing.

Paola Perini: Conceptualization; Writing – review & editing.

Francesca Rinaldi: Conceptualization; Writing – review & editing.

Paolo Gallo: Conceptualization; Funding acquisition; Writing – review & editing.

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Competing interests

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Availability of data and materials

Anonymized data is available upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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