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High NEDA and No PIRA in Natalizumab-Treated Patients With Pediatric-Onset Multiple Sclerosis

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Abstract

Background and Objectives

Although pediatric-onset multiple sclerosis (POMS) is characterized by a more rapid accumulation of CNS inflammation than adult-onset MS (AOMS), the therapeutic algorithms applied in POMS are usually based on AOMS therapeutic outcomes. To define a high-efficacy treatment (HET)-based strategy to treat POMS, we designed an observational retrospective study aimed at evaluating the efficacy and safety of natalizumab (NTZ) in naïve POMS and AOMS.

Methods

Starting from 160 patients, we applied a 2:1 (adult:pediatric) matching on propensity scores and obtained 32 patients with NTZ-treated POMS and 64 with AOMS, estimated from a multivariable logistic regression model. All patients were clinically and radiologically followed up every 6 months for a mean period of 46.0 ± 26.9 months.

Results

Following re-baseline at month 6, no difference (log-rank test: $p = 0.924$) in new and enlarging T2 white matter lesions, postcontrast T1 lesions, and relapse rate were observed between POMS and AOMS throughout the study. Progression independent of relapse activity (PIRA) was never observed in POMS, while 9 of 64 patients with AOMS (12.5%) had PIRA events during the follow-up (40.0 ± 25.9 months; log-rank p value 0.0156). JCV seroconversion rate during NTZ infusion did not differ between POMS and AOMS (log-rank test $p = 0.3231$). Finally, no serious adverse event was observed in both POMS and AOMS.

Discussion

The favorable outcomes observed on clinical, especially in PIRA, and radiologic parameters strongly support the use of NTZ as a first-choice HET in POMS.

Introduction

Pediatric-onset multiple sclerosis (POMS) is characterized by a more rapid accumulation of CNS inflammation than adult-onset MS (AOMS). Although POMS reaches disability milestones later than AOMS, they may develop cognitive dysfunction earlier[1,2] and reach permanent physical disability younger.[3-6] Therefore, early and effective treatments are mandatory in POMS. However, the treatments currently available for POMS, namely fingolimod,[7] teriflunomide,[8] and dimethyl fumarate,[9] are considered moderately effective in AOMS, and in all

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Glossary

AOMS = adult-onset MS; **CDW** = clinical disability worsening; **EDSS** = Expanded Disability Status Scale; **HET** = high efficacy treatment; **NTZ** = natalizumab; **PIRA** = progression independent of relapse activity; **POMS** = pediatric-onset multiple sclerosis; **RAW** = relapse-associated worsening; **RCT** = randomized clinical trials.

the randomized clinical trials (RCT) with these drugs in POMS, a persistent inflammatory activity in terms of appearance of new/enlarging T2 WM lesions (n/eT2WML) was observed. Indeed, the n/eT2WML annualized rate was 4.39 in fingolimod,[7] 4.7 per scan in teriflunomide,[8] and 12.4 at week 96 in dimethyl fumarate,[9] suggesting these drugs suppress CNS inflammation only partly in these peculiar patients and calling for more effective treatments. The relevance of timing of HET has been recently underlined by a recent multicenter study that focused on inflammatory disease parameter outcomes (i.e., clinical and radiologic relapse).[10]

Although no RTC has been conducted with natalizumab (NTZ), its efficacy on POMS clinical relapses and conventional MRI parameters has been largely provided.[11,12] In Italy,[13] NTZ has been approved for POMS with an aggressive disease course, defined as at least 2 relapses in the past year and appearance of new lesions on T2-weighted sequences or Gd-enhancing lesions on brain MRI.[14] After the approval of fingolimod for POMS in 2020, NTZ is indicated for the treatment of patients with POMS aged 12–17 years, having active and rapidly evolving MS not responsive to fingolimod, or in the presence of contraindications or persistent side effects because of fingolimod. In a recent Italian MS registry–based study, the risk of PIRA was found to increase progressively with age at disease onset, further pointing out the importance of early treatment to prevent disability. However, as also stated by the authors, no data on the impact of early high-efficacy treatment (HET), such as NTZ, was reported.[15] In line with these findings, a previous study suggested that HET has more chances to slow down disability accumulation in POMS.[4]

Because we recently observed that HET might differently affect patients with AOMS and POMS,[16] we designed a retrospective, single-center study, enrolling propensity-matched patients with NTZ-treated AOMS and POMS, evaluating the efficacy of NTZ on both conventional and unconventional outcomes.

Methods

Study Population

All patients who started NTZ were enrolled in this retrospective single-center study. Inclusion criteria were (1) diagnosis of MS in line with most recent criteria,[17] especially excluding diagnosis of MOGAD or NMOSD by the absence of anti-MOG and anti-AQ4 antibodies, respectively, and respecting the currently available guidelines and consensus[17-19]; (2) treatment-naïve at NTZ first infusion; (3) available 6-month clinical evaluation (including Expanded Disability Status Scale [EDSS] and Symbol Digit Modalities Test scoring); and (4) available 12-month brain MRI. The obtained cohort was then divided based on age at onset into pediatric-onset and adult-onset MS (POMS and AOMS, respectively) and were propensity-matched.

Clinical and Radiologic Follow-Up

ptAs reported elsewhere,[20] all patients with MS were clinically evaluated at baseline and then every 6 months by a trained neurologist (P.M., P.P., R.F., G.P.), who gave an EDSS score at each visit. Brain MRI was acquired every 6 months and included (1) three-dimensional (3D) turbo field echo (3D-T1) (this sequence was acquired before and after gadolinium administration) and (2) 3D fluid-attenuated inversion recovery. Two experienced observers (P.M., A.D.P.), blinded to the patient's identity, assessed all images.

Clinical and Radiologic Outcomes

Clinical relapse was defined as the occurrence of new symptoms or exacerbation of existing symptoms that lasted for 24 hours or longer, in the absence of concurrent illness or fever, and occurring 30 days or more since a previous relapse. The definition of relapse used in our study did not require confirmation by change in EDSS.[17]

Clinical disability worsening (CDW) 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 >5.0) confirmed after 6 months.[21] Progression independent of any relapse activity (PIRA) was defined as the presence of CDW confirmed after 6 months and in the absence of any clinical nor radiologic inflammatory disease activity, as previously indicated. Relapse-associated worsening (RAW) was indicated by the presence of significant and sustained EDSS increase associated with a clinical relapse.

MRI activity was defined as the presence of contrast-enhancing lesions on T1-weighted images or new/enlarging hyperintense lesions on T2-weighted images (compared with the baseline scan), after checking the fluid-attenuated inversion recovery sequence.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local ethical committee ("Comitato Etico per la Sperimentazione Clinica dell'Azienda Ospedale-Università di Padova", Prot. N. 33n/AO/20).

Statistical Analysis

We applied a 2:1 (adult:pediatric) matching on propensity scores that were estimated from a multivariable logistic regression model including sex, number of relapses and lesions in the 6 months before the treatment start, EDSS score at treatment start, and disease duration from MS symptom onset. Nearest neighbor matching without replacement within a caliper of 0.05 DSs was used. Baseline characteristics were summarized by group, using descriptive statistics, and were compared between patients with AOMS and POMS using the standardized mean difference as calculated according to Cohen d effect size. A Cohen d effect size >0.1 denotes meaningful imbalance in the baseline covariates.[22] To compare length of follow-up between the 2 groups, the Mann-Whitney *U* test was performed; Kaplan-Meier analyses and log-rank test were applied to compare the 2 MS groups in terms of time to first clinical disease activation, to first radiologic activation (new or gadolinium-enhancing white matter lesion), to progression independent of relapse activity (PIRA), and to JCV seroconversion rate (only for the subgroup of patients negative at baseline). The significance level was set at 0.05. All the analyses were performed using Stata (v.16.0; Stata Corporation, College Station, TX) and R (v 4.1.3).

Data Availability

Anonymized data not published within this article will be made available upon reasonable request from any qualified investigator.

Results

Study Population

From 160 patients (38 with POMS, 122 with AOMS), propensity matching defined 2 cohorts composed of 32 patients with POMS and 64 with AOMS, whose clinical and demographic variables are summarized in the Table. Mean follow-up was 46.0 ± 26.9 months in patients with POMS (range 9–136) and 40.0 ± 25.9 months in those with AOMS (range 1–109, $p = 0.33$).

Patients With NTZ-Treated POMS Did Not Develop PIRA During the Follow-Up

The effect of NTZ on conventional MRI (i.e., n/eT2WML and postcontrast T1 lesions) parameters was evaluated by survival analysis, which did not disclose difference between AOMS and POMS (log-rank test: $p = 0.924$, Figure 1A). Since only 1 AOMS presented a clinical relapse, with no RAW, these graphs are not shown. Radiologic reactivation occurred more frequently during the first 6 months of NTZ treatment in both groups (5/8 POMS, 62.5%; 10/18 AOMS, 55.6%). However, after the re-baseline in month 6, no difference was observed afterward ($p = 0.943$). In addition, NEDA-3 at month 24 was observed in 91% of patients with POMS and in 84% of those with AOMS. Of interest, PIRA was never observed in patients with POMS during the follow-up while 9 patients with AOMS (12.5%) had at least 1 PIRA event during the follow-up (log-rank p value 0.0156) (Figure 1B). In these patients, a PIRA event occurred 2.4 ± 0.8 years after disease onset and 1.7 ± 1.0 years after first natalizumab infusion.

Safety of Natalizumab in POMS

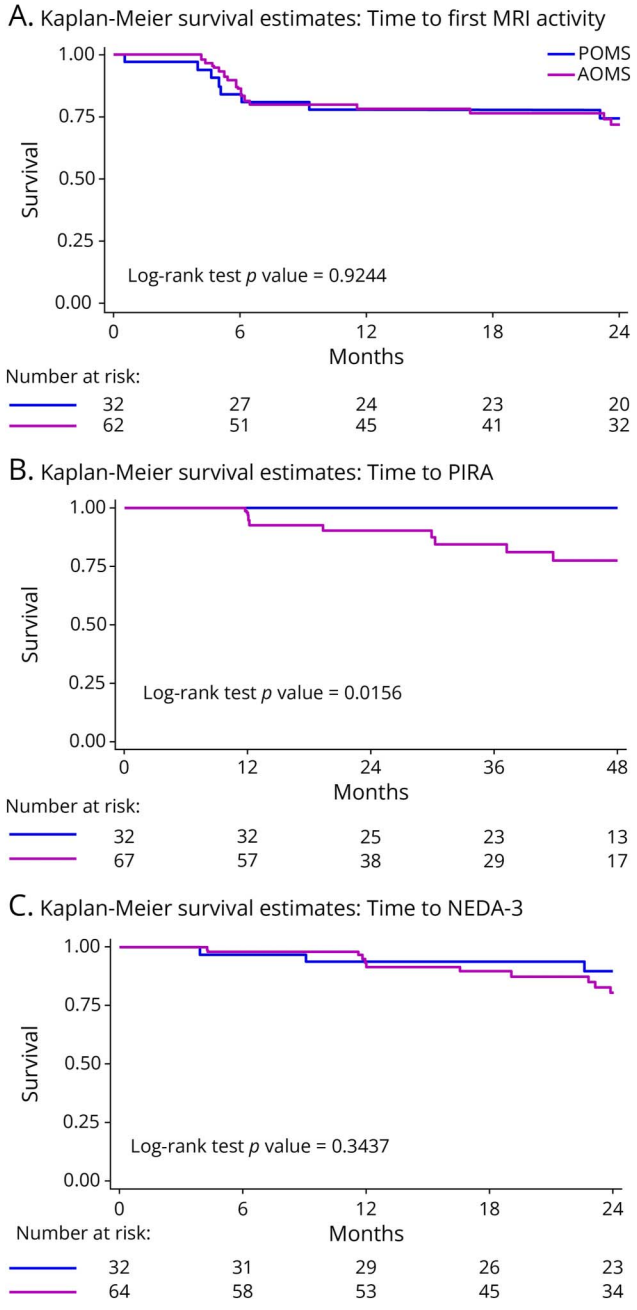
A highly positive JCV Index (>1.5) was the cause of NTZ discontinuation in 13 patients with POMS, who switched to a different treatment (6 to alemtuzumab, 4 to ofatumumab, 2 to fingolimod, 1 to ozanimod) as soon as they reached the age of 18, when for others HET could be administrated in line with the rules stated by the Italian Agency for Medicines (AIFA). There was no other reason of discontinuation in POMS. In AOMS, 1 patient discontinued NTZ because of the appearance of anti-NTZ Ab, 2 because of iatrogenic hepatitis (2.8%), and 5 for a high JCV Index (switching treatments were ocrelizumab 1, ofatumumab 1, dimethyl fumarate 1, fingolimod 1, alemtuzumab 1). At baseline, 8 patients with POMS (28.1%) and 8 patients

Table Clinical and Demographic Variables Before and After Matching on Propensity Scores

	Before propensity score matching			After propensity score matching		
	AOMS	POMS		AOMS	POMS	
	121	34	Cohen d	64	32	Cohen d
Sex, number of males (%)	44 (36.4)	12 (35.3)	0.022	23 (35.9)	12 (37.5)	0.032
EDSS score at NTZ initiation, median (IQR)	2.0 (1.0–2.50)	1.25 (1.0–1.88)	0.627	1.5 (1.0–2.0)	1.5 (1.0–2.0)	0.010
Months since MS disease onset, median (IQR)	7.0 (3.35–29.26)	3.93 (2.61–6.95)	0.630	4.65 (2.70–8.10)	4.01 (2.71–7.36)	0.043
Relapse 6 mo before NTZ initiation, median (IQR)[a]	0.0 (0.00–0.17)	0.0 (0.00–0.17)	0.271	0.0 (0.00–0.00)	0.0 (0.00–0.04)	0.063
Lesions 6 mo before NTZ initiation, median (IQR)[b]	0.17 (0.00–0.50)	0.33 (0.00–0.51)	0.013	0.17 (0.00–0.50)	0.35 (0.00–0.55)	0.077

Abbreviations: AOMS = adult-onset multiple sclerosis; EDSS = Expanded Disability Status Scale; IQR = interquartile range; NTZ = natalizumab; POMS = pediatric-onset multiple sclerosis.
Patients were matched without replacement in a variable 2:1 (adult:pediatric) ratio, using nearest neighbor matching within a caliper of 0.05 SDs of the propensity score. Cohen d values >0.10 were considered clinically meaningful.
[a] Number of relapses occurred in the previous 6 mo.
[b] Number of new/enlarging or gadolinium-enhancing lesions in the previous 6 mo.

Figure 1 Survival Analysis of Radiologic Disease Activity (A), Progression Independent of Relapse Activity (B), and NEDA-3 (C)



Survival analysis disclosed no difference between POMS and AOMS in radiologic disease activity (A). On the other hand, the risk of PIRA was increased in AOMS compared with POMS (log-rank *p* value: 0.0156) (B). Finally, NEDA-3 condition did not differ between the 2 groups (C). AOMS = adult-onset multiple sclerosis; PIRA = progression independent of relapse activity; POMS = pediatric-onset multiple sclerosis.

with AOMS (12.5%) had detectable anti-JCV antibodies. Of interest, the seroconversion rate during NTZ was 13 of 38 patients with POMS and 5 of 64 patients with AOMS (log-rank test $p = 0.3231$) (eFigure 1). Finally, no progressive multifocal leukoencephalopathy (PML) nor other serious adverse events occurred in either group during the follow-up period.

Discussion

POMS poses a primary challenge compared with AOMS, namely the more rapid accumulation of CNS inflammation[23] that may trigger neurodegenerative mechanisms responsible for long-term disability accumulation. Increasing evidence indicates that the early administration of HET in POMS can significantly affect both short and long-term clinical and quality-of-life outcomes. The relevance of an appropriate therapeutic approach has been underlined by longitudinal data that demonstrated a significant reduction (between 50 and 70%) of the risk of persistent disability in patients with POMS.[4] On the other hand, the rate of n/eT2WML observed under moderate-efficacy therapies,[24,25] also in head-to-head RCT,[7-9] strongly stresses the relevance of HET since disease onset. Therefore, the early use of HET has been highly recommended in POMS.[26]

To evaluate the effects of a HET administrated early in POMS, in our retrospective, single-center study, we enrolled 160 naïve patients with MS who initiated NTZ as first-line therapy. The inclusion of AOMS as a control cohort allowed us to weigh the efficacy of NTZ in POMS. After propensity matching for demographic and clinical variables, the study population was finally composed of 64 patients with AOMS and 32 with POMS.

Evaluation of inflammatory disease parameters (i.e., clinical relapses, radiologic activity) by means of survival analysis did not reveal difference between POMS and AOMS, indicating an excellent response to NTZ in both groups (after a re-baseline at month 6, NEDA-3 at month 24 was observed in 92.0% of patients with POMS and in 85.7% of patients with AOMS). These findings strongly confirm previous reports.[11,12,27] Noteworthy, while PIRA events were observed in 12.5% of patients with NTZ-treated AOMS, no PIRA event was observed in those with POMS, suggesting a favorable impact on disease progression in this population. These findings constitute a major argument in favor of the early HET initiation in POMS.

To what extent the lack of PIRA events in patients with NTZ-treated POMS is driven by the almost complete suppression of inflammation needs to be carefully weighted. Because POMS and AOMS were matched for disease duration, our data seem to suggest a major role of age in neurodegeneration. However, POMS constitutes the group of patients with MS having the shortest interval between the biological and clinical onset of the disease, and the longer the subclinical period, the higher is the risk of developing neurodegenerative phenomena.

In line with our findings, because clinical disability (and thus EDSS) worsening in POMS is almost exclusively a RAW, the administration of HET is strongly recommended[21-24] to prevent RAW accrual[4] and subclinically evolving neurodegeneration.

The safety profile of NTZ in POMS was largely favorable, with discontinuation exclusively driven by JCV Index positivity. Of note, the rate of JCV Index positivity seroconversion did not differ significantly between POMS and AOMS. Because the great majority of JCV-positive patients with AOMS were not treated with NTZ, we preferred to report the rate rather than the percentage that would have been misleading.

Despite the relatively limited sample size, the absence of any serious adverse event confirms the safety of NTZ also in the pediatric population, at least in JCV-negative patients.

We are aware of the limitations of our study. First, the retrospective design calls for longitudinal prospective data collection that are actually in due course. Although our cohort of patients with NTZ-treated POMS is one of the largest single-center cohort available and a standardized patient management protocol was applied to both POMS and AOMS, our data should be confirmed by a multicenter study including a higher number of patients. Finally, PIRA merits to be evaluated in a longer follow-up that is also in due course.

In conclusion, our study provides valuable insights into the efficacy and safety of NTZ in POMS. The favorable outcomes observed in clinical and radiologic parameters support the use of NTZ as a first-choice treatment option in POMS.

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Disclosure

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Alessandro Miscioscia, MD	Department of Neurosciences; Padua Neuroscience Centre, University of Padua, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Margherita Nosadini, MD, PhD	Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua; Neuroimmunology Group, Paediatric Research Institute "Città della Speranza", Padua, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Alessandro Di Paola, MD	Neuroradiology Unit, University Hospital of Padua, Italy	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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Continued

Appendix *(continued)*

Name	Location	Contribution
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Paolo Gallo, MD, PhD	Department of Neurosciences, University of Padua; Multiple Sclerosis Centre, and Day Hospital and Centre for Advanced Neurological Therapies Unit, University Hospital of Padua, Italy	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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