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Original article

TyPed study: Natalizumab for the treatment of pediatric-onset multiple sclerosis in Portugal

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ABSTRACT

Background: A significant proportion of pediatric-onset multiple sclerosis (POMS) patients do not respond to first-line disease-modifying therapies. Clinical trials showed that natalizumab is effective and safe in adults, but there are limited clinical trial data for children. Natalizumab is currently prescribed off-label for POMS. We aimed to characterize the effectiveness, safety and tolerability of natalizumab in all POMS cases treated in Portugal (from 2007 to 2018).

Methods: Data from clinical records were retrospectively collected for all POMS cases treated with natalizumab in Portugal.

Results: Twenty-one patients were included, 14 (67%) of which were female. The median age at POMS diagnosis was 13 years old. The median duration of treatment with natalizumab was 2 years and 3 months. Median Expanded Disability Status Scale score decreased from 1.5 to 1.0 after 24 months. The Annualized Relapse Rate decreased from 1.31 events/patient/year before treatment with natalizumab to 0 after 12 months of treatment and to 0.04 after 24 months. No gadolinium-enhancing lesions or new or enlarged T2 hyperintense lesions were observed in 8/8 patients (100%) after 12 months, and 4/5 (80%) after 24 months. There was one possible serious adverse event, which did not require dose adjustment. Five patients discontinued treatment due to positive anti-JCV (JC virus) antibody JC serostatus.

Conclusion: Natalizumab may be an effective and safe disease-modifying therapy for POMS. Our results are in line with data published for the adult population, as well as with similar observational studies in pediatric populations in other regions.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease that causes demyelination and degeneration of the central nervous system (CNS). The estimated global prevalence is 33/100,000, but this number varies across different regions of the globe, ranging from

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>100/100,000 in North America and parts of Europe, to <5/100,000 in Southeast Asia and Sub-Saharan Africa (Browne et al., 2014; Leray et al., 2016). In Portugal, the estimated MS prevalence is around 50/100,000 (de Sá et al., 2012; Sá et al., 2006, 2017), which corresponds to over 5000 expected MS patients.

Pediatric-onset MS (POMS) comprises around 5% of all MS cases (McGinley and Rossman, 2017). Current POMS therapies rely upon disease-modifying treatments (DMTs) that include the classical and injectable therapies, such as different formulations of interferon beta (IFN beta) and glatiramer acetate (GA) (Waldman et al., 2016), and some high efficacy drugs: natalizumab and fingolimod, with two more (teriflunomide and dimethyl fumarate) currently under investigation for pediatric populations (Krupp et al., 2019; Yeh and Weinstock-Guttman, 2010). Only fingolimod had specific indication to be used under 18 years of age after the publication of the PARADIGMS study. This clinical trial allowed the direct comparison between fingolimod and intramuscular IFN beta-1a in children aged 10–17 years (Chitnis et al., 2018). Currently, fingolimod is the only approved DMT for POMs.

Relapse recovery is faster (Chitnis et al., 2020), and disability progression is slower in POMS compared to the adult-onset disease. Nevertheless, pediatric patients have a higher relapse rate (Benson et al., 2014; Gorman et al., 2009) and a median age of comparable level of disability 10 years younger than the adult-onset population, due to the early age of disease onset (Renoux et al., 2009). Furthermore, regional brain atrophy in children with POMS carries a high association with cognitive and physical disabilities (Patel et al., 2009). Early treatment of POMS with DMTs may potentially prevent or slow down some of these outcomes (McGinley and Rossman, 2017). The current standard of care for POMS patients includes first-line DMTs (IFN beta and GA) (Waldman et al., 2016), but around 30% of patients are partial- or non-responders to these drugs, and thus require a switch to the so-called second-line DMTs (Yeh et al., 2011).

Natalizumab is an approved second-line DMT for MS. It is a monoclonal antibody against integrin α4β1 that blocks the migration of T- and B-lymphocytes across the blood-brain barrier (Simone and Chitnis, 2016). Tysabri®'s Summary of Product Characteristics states that the safety and efficacy of the drug in children and adolescents up to 18 years have not been established and no recommendation on a posology can be made. However, natalizumab has been shown to have high efficacy in phase III clinical trials for MS. Additionally, in published observational studies reporting off-label use situations, has shown consistent effectiveness in reducing disease activity in POMS patients, including children with aggressive disease onset (Arnal-Garcia et al., 2013; Ghezzi et al., 2015, 2013, 2010; Huppke et al., 2008; Kornek et al., 2013; Yeh and Weinstock-Guttman, 2010), with no relevant adverse effects (AEs) reported up to now (Butzkueven et al., 2014). Nevertheless, the safety and efficacy of Tysabri in children and adolescents up to 18 years have not been established, and no recommendation on a posology can be made.

Since, to date, there are limited clinical trials in which natalizumab has been studied specifically in the POMS population, it is imperative to continuously collect real-world evidence on the clinical profile and outcomes of POMS patients treated with this drug. The present study retrospectively collected data of all POMS cases treated with natalizumab in Portugal (since the drug was introduced in the Portuguese market, in 2007, until November 2018) with the aim of characterizing its effectiveness, safety and tolerability.

2. Material and methods

We performed a retrospective study of POMS patients who began natalizumab treatment when they were aged less than 18 years old. Demographic and clinical data were collected between 12th April and 16th November 2018 from 8 Portuguese sites (who were selected because they reported treating children with natalizumab). All patients and their parents or legal guardian gave their written informed consent to participate in the study, and the Ethics Committees of the sites involved approved the study protocol.

Diagnosis of MS was as defined by the International Pediatric Multiple Sclerosis Study Group (Krupp et al., 2013, 2007) and by the McDonald criteria 2010 (Polman et al., 2011).

Analysed variables were sex, age at diagnosis, age at natalizumab initiation, duration of disease, EDSS (Expanded Disability Status Scale) scores, number of documented relapses, number of gadolinium-enhancing (Gd+) lesions, prior MS treatments (type, number and duration), natalizumab treatment duration and number of infusions, JCV serostatus, number of AEs (adverse events) and SAEs (serious adverse events), discontinuation rates, and number of hospitalizations and/or emergency room visits.

The efficacy analysis included patients with available annualized relapse rate (ARR) data at baseline and at 12 and 24 months post-treatment with natalizumab.

The primary endpoints were change in ARR from the year prior to natalizumab initiation to 12 and 24 months, and the proportion of patients experiencing 12-week confirmed disability worsening at 12 and 24 months from baseline.

Disability worsening was defined as an increase of ≥0.5 points from a baseline EDSS score of ≥6.0, ≥1.0 points from a baseline EDSS score of 1.0 to <6.0, or ≥1.5 points from a baseline EDSS score of 0.0.

Additional endpoints included the proportions of patients who met the following criteria on natalizumab treatment: no gadolinium-enhancing (Gd+) lesions at 12 and 24 months; no new or newly enlarging T2 lesions at 12 and 24 months; No Evidence of Disease Activity (NEDA) at 12 and 24 months, defined as no 12-week confirmed disability worsening, no relapses, no Gd+ lesions, and no new T2 lesions.

Data on adverse and serious adverse events during natalizumab treatment were collected for safety analysis.

Clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 h, and followed by a period of 30 days of stability or improvement. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

Categorical variables were described by their absolute and relative frequencies. Continuous variables were described as median and range (minimum-maximum).

All analyses were performed using JASP 0.8.6.0 software.

3. Results

A total of 21 patients were included in the study (all patients that received natalizumab in Portugal), 14 (67%) of which were female. The median age at MS diagnosis was 13 years old, with 3 patients being diagnosed at 10 years old or less. The median body mass index (BMI) at our evaluation was 21.6 kg/m^2 (range: 16.4–28.4) and only 4 patients were overweight (defined as having a BMI ≥25 kg/m^2). The median duration of disease at natalizumab initiation was 1 year and 2.5 months. Prior to treatment with natalizumab, 57.1% of the patients had taken at least one DMT (N = 12/21). IFN beta-1a was the most frequent treatment prior to natalizumab, and 8 of the 12 pre-treated patients were exposed, at least once, to this drug. Except for two patients, anti-JCV antibodies testing was requested before initiation of treatment with natalizumab (90.5%; N = 19/21). The test was positive in four patients (21%; N = 4/19), and the index value was collected in three cases – the results were 3.52, 3.079 and 0.38. Baseline demographic and clinical features are presented in Table 1.

The median duration of treatment with natalizumab was 2 years and 3 months, ranging from 1 month to 9 years and 4 months. The number of infusions was the expected for the treatment duration, with a median exposure of 27 infusions (range 1–121).

In the subgroup of 16 patients treated with natalizumab for 12

Table 1
Baseline characteristics of patients.

	N (%)/ Median (range)
Sex:	
Male	7 (33.3%)
Female	14 (66.7%)
Age at diagnosis, years	13.0 (8–17)
Age at natalizumab initiation	14 (9–17)
Duration of disease at natalizumab initiation, months	14.5 (0–67)
EDSS at natalizumab initiation	1.5 (0.0–3.5)
Number of relapses at any point prior to natalizumab initiation	3 (1–9)
ARR in year prior to natalizumab initiation (events/patient/year)	1.325
Anti-JCV serostatus at natalizumab initiation:	
Negative	15 (78.9%)
Positive	4 (21.1%)
Treatments prior to natalizumab*	
IFN beta-1a	12 (57.1%)
IFN beta-1b	3 (14.3%)
GA	3 (14.3%)
Cyclophosphamide	1 (4.8%)
Immunoglobulin	1 (4.8%)
Duration of prior treatment, months	25 (11–65)
Gd^+ lesions	2 (0–56)

ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; GA: glatiramer acetate; Gd^+: gadolinium-enhancing lesions; IFN: interferon; JCV: JC virus; MRI: magnetic resonance imaging; * Treatments prior to natalizumab refer to the total number of treatments ($N = 20$) of the 12 pre-treated patients (several patients were previously exposed to more than one treatment).

months or more, no confirmed disability worsening was observed in the 13 patients for whom there was information available at baseline and at months 12 and/or 24 (Fig. 1). Half of the patients (6 of 12) exhibited a decrease in EDSS score 12 months from baseline, and 60% (6 of 10) exhibited a decrease in EDSS score 24 months from baseline. The mean (standard deviation) EDSS score decreased from 1.66 (0.94) at baseline to 1.42 (0.85) at 12 months and 1.20 (0.86) at 24 months. When comparing mean EDSS values before initiating treatment and during the entire course of treatment with natalizumab, even though there was a variable number of observations per patient, a statistically significant decrease in mean EDSS was observed (1.66 vs 1.39; $t = 2.611$; $p = 0.020$).

No relapses were observed in the first year in this group of patients treated at least for 12 months with natalizumab. There was one case of relapse after 13 months, and another one happened after nearly two years (1 year and 10 months). Mean time to relapse was 35.75 months (range 13–112 months).

The annual relapse rate (ARR) decreased from 1.31 events/patient/year before treatment with natalizumab to 0 after 12 months of treatment and to 0.04 after 24 months.

Among the sixteen patients who completed at least 12 months of treatment, there was MRI information at months 12 and 24 for 8 and 5 patients, respectively. The number of patients without Gd^+ lesions and new or enlarged T2 hyperintense lesions at month 12 was eight (100.0%) and four at month 24 (80.0%).

NEDA-3 was evaluated in the subset of patients with available data for all NEDA parameters ($n = 8$ for 12 months and $n = 4$ for 24 months). The proportion of patients with NEDA-3, i.e., no EDSS progression (12-week sustained), no relapses, no Gd^+ lesions and no new T2 hyperintense lesions was 100.0% ($n = 8$) over 12 months and 75.0% ($n = 4$) over 24 months.

To analyze the safety of natalizumab, we considered all POMS cases treated with natalizumab in Portugal (i.e., all the participants included in the study, described in Table 1). We observed 13 adverse events (AEs) in 6 patients during treatment (Table 2), 8 that were possibly related to natalizumab, 2 that were probably related, and 2 that were unrelated to the treatment. There was no need to change doses or treatment discontinuation in any of the AE and, at the time of the evaluation, all adverse events had resolved except for 1 case of fatigue.

The only SAE was severe pneumonia which occurred during treatment with natalizumab, with possible relation to the drug. This event required treatment for one month and no natalizumab dose adjustments were necessary.

At the time of evaluation, five patients had discontinued natalizumab treatment (23.8%), all due to JCV+ serostatus. Three of these five patients had already JCV+ serostatus at the beginning of natalizumab therapy, with antibody index of 3.52, 3.079 and 0.84. The other two patients were negative when they started natalizumab and became positive during the course of treatment.

Table 2
Adverse events.

	Number of events
Serious Adverse events	
Pneumonia	1
Adverse events	
Headache	2
Tonsillitis	2
Arthralgia	1
Erysipelas	1
Fatigue	1
Gastroenteritis	1
Left palpebral edema	1
Respiratory infection	1
Urinary infection	1
Lipothymia	1

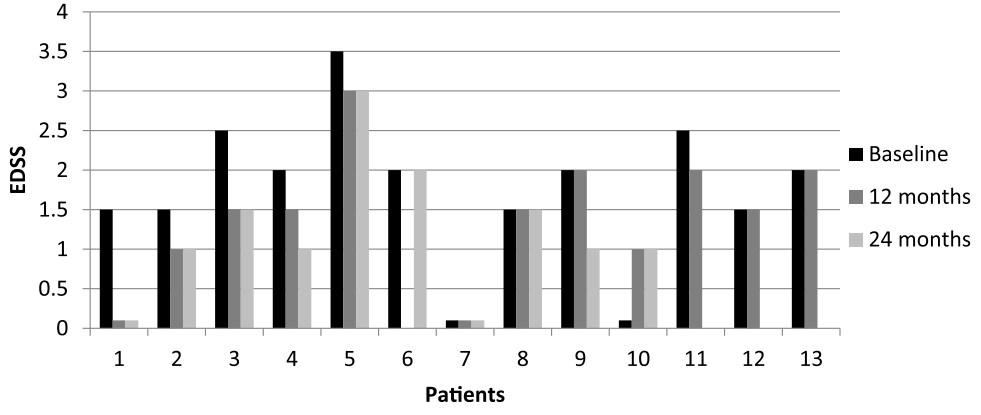

Fig. 1. Changes in EDSS over time.

4. Discussion

This retrospective study shows that natalizumab treatment reduced disease activity in patients with POMS, with no concomitant relevant AEs, consistent with other published observational studies (Arnal-Garcia et al., 2013; Butzkueven et al., 2014; Ghezzi et al., 2015, 2013, 2010; Huppke et al., 2008; Kornek et al., 2013; Yeh and Weinstock-Guttman, 2010).

Compared to adult-onset MS, patients with POMS have higher rates of inflammatory demyelination early in the disease (Pfeifenbring et al., 2015). Despite this, most current guidelines, including the Portuguese General Health Directorate one(PORTUGAL. Direção-Geral da Saúde, 2015), continue to endorse the use of low-efficacy DMTs as first-line in the pediatric population, with progressive stepwise therapy escalation (McGinley and Rossman, 2017). Some authors argue that given the specific characteristics of MS in the pediatric population, the use of high-efficacy DMTs early in the disease might improve the outcomes of POMS (McGinley and Rossman, 2017).

Even though natalizumab's high-efficacy and safety profile would make it a particularly suitable DMT for POMS, many clinicians are still reluctant to use it during periods of growth and development (Simone and Chitnis, 2016), perhaps due to the lack of randomized clinical trials. In fact, second-line DMTs, except for fingolimod, are used off-label in children (Jeong et al., 2019), and to address this issue, the International Pediatric MS Study Group has recommended the inclusion of children in clinical trials for emerging MS therapies (Chitnis et al., 2012). Until clinical trial data are available, the assessment of safety and efficacy of DMTs in the treatment of POMS continues to rely on off-label post--marketing studies, except fingolimod, as it was demonstrated in the PARADIGMS study (Chitnis et al., 2018).

The largest published retrospective observational study to date on natalizumab as a therapy for POMS came from an Italian study with over 100 patients (Ghezzi et al., 2015) where, during a mean treatment duration of 34.2 ± 18.3 months, the ARR significantly decreased more than 95% (from 2.3 in the year prior to natalizumab to 0.1 at the time of the last natalizumab infusion) and mean EDSS decreased around 30% (from 2.6 ± 1.3 at natalizumab initiation to 1.8 ± 1.2 at the time of the last visit). Our study similarly shows improvements, with ARR decreasing more than 95% (from 1.31 to 0.04 events/patient/year after 24 months) and EDSS improving more than 30% (from 1.5 to 1.0 after 24 months). The age of the patients at diagnosis and at the initiation of natalizumab treatment were similar in both studies and, despite the difference in disease status at the beginning of treatment, with worst EDSS values and ARR in the Italian study, similar degrees of improvement were achieved (Ghezzi et al., 2015). A smaller retrospective study, similar to ours, done in the Spanish POMS population and which included 9 patients, saw a dramatic reduction of both ARR (from 3 to 0) and EDSS (from 3.0 to 1.0) (Arnal-Garcia et al., 2013). A prospective study on the use of natalizumab in pediatric patients in Kuwait also corroborates these findings, with significant improvements of both ARR and EDSS (Alroughani et al., 2017).

No relevant AEs related to natalizumab were described in the present study or in the studies mentioned above (Alroughani et al., 2017; Arnal-Garcia et al., 2013; Ghezzi et al., 2015), thus reinforcing the conclusion that natalizumab appears safe for use in the pediatric population. The main risk concern associated with natalizumab treatment is progressive multifocal leukoencephalopathy (PML), and the presence of anti–JCV antibodies in serum is one of the risk factors for the development of PML (Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould et al., 2005; Van Assche et al., 2005). In the current study, 23.8% of patients ($n = 5$) discontinued treatment due to positive anti-JCV serostatus. It should be noted that 2 of them were negative at treatment beginning and seroconverted during the time they were exposed to the drug. In children, a high conversion rate may be theoretically expected, due to the frequent contact with different microbial agents (namely viruses), for which immunity is thus acquired (childhood is a phase of life in which there is a large immune growth, with memory acquisition for multiple infectious agents). Despite carrying the greatest risk for PML among all DMTs, natalizumab's high efficacy makes it nonetheless superior to other DMTs in models of long-term morbidity and mortality (Bargiela et al., 2017). It is thus important to manage the risk of PML by frequent serologic testing for anti–JCV antibodies and MRI screening. It has been suggested that extending the interval between natalizumab infusions may reduce PML risk (Ryerson et al., 2019). However, the benefit-risk profile of this strategy is still to be confirmed due to the lack of efficacy data.

Since the last consensus statements concerning guidelines for treatment on POMS published in 2012, five clinical trials with 4 different drugs in pediatric MS were initiated. The 2019 updated recommendations from the International Pediatric Multiple Sclerosis Study Group reviewed the new evidence concerning the use of MS therapeutic agents in POMS, including the use of DMTs. They agreed that there is a need to develop more studies of MS treatments in POMS regarding dose, alternate drugs and safety information in children (Waubant et al., 2019).

There are clinical trials underway that are evaluating the efficacy and safety of the more recently available drugs (such as teriflunomide, alemtuzumab and dimethyl fumarate - ClinicalTrials.gov Identifiers NCT02201108, NCT03368664 and NCT02283853, respectively) in the pediatric population. The information that may result from these clinical trials and from observational studies like ours will be essential in assessing whether the therapeutic escalation strategy continues to make sense in children and adolescents, or whether, given the high inflammatory burden of the disease, initiation of treatment with a potentially more effective drug would be more useful (thus defining an intervention closer to therapeutic induction). As a form of the disease with little epidemiological expression, collecting real-world data, over time, as in the present study, will be an important research strategy to add scientific knowledge in POMS. Moreover, all the information gathered worldwide so far highlights the high efficacy of natalizumab with few adverse effects in this particular setting. This, coupled with the recent formal approval for fingolimod use in POMS, may contribute to the revision of many of the current therapeutic conceptualization schemes in pediatric populations.

This study had limitations inherent to its retrospective nature. Collection of clinical data was not performed systematically, leading to low numbers of patients that could be analysed for all the desired endpoints. Future studies of natalizumab in POMS in Portugal should ideally be prospective in nature and include standardised timings for clinical data collection, such as MRIs, EDSS and JCV serostatus.

5. Conclusion

The present study is the first to analyze the use of natalizumab for the treatment of POMS in the Portuguese population. Our findings suggest the effectiveness and safety of natalizumab in the pediatric population.

CRediT authorship contribution statement

Filipe Palavra: Conceptualization, Methodology, Investigation, Writing – original draft. **Sónia Figueiroa:** Investigation, Writing – review & editing. **Ana Sofia Correia:** Investigation, Writing – review & editing. **Fernando Tapadinhas:** Investigation, Writing – review & editing. **João Cerqueira:** Investigation, Writing – review & editing. **Rui Pedro Guerreiro:** Investigation, Writing – review & editing, Investigation, Writing – review & editing. **João de Sá:** . **Maria José Sá:** Investigation, Writing – review & editing. **Sofia Almeida:** Resources. **Patrícia Mota:** Resources. **Lívia Sousa:** Supervision.

Declaration of Competing Interest

Filipe Palavra: Participates as investigator in clinical trials and observational studies sponsored by Biogen, Novartis, Merck, Roche,

Sanofi-Genzyme and Teva. Received clinical research funding from Biogen and Merck. Received personal compensation for participating on advisory boards from Novartis, Biogen, Teva, Sanofi-Genzyme, Merck, Bayer and Roche and for participating as a speaker at meetings and teaching courses sponsored by Biogen, Novartis, Merck, Teva and Sanofi-Genzyme.

Sónia Figueiroa: Participates as investigator in clinical trials and observational studies sponsored by Biogen. Received clinical research funding from Biogen. Received personal compensation for participating on advisory boards from Merck.

Ana Sofia Correia: Participates as investigator in clinical trials and observational studies sponsored by Biogen, Novartis and Sanofi-Genzyme. Received an educational sponsorship from Merck Serono. Received personal compensation for participating on advisory boards from Novartis, Biogen, Sanofi-Genzyme, Merck and Roche and for participating as a speaker at meetings and teaching courses sponsored by Biogen, Novartis and Merck.

Fernando Tapadinhas: Has no conflicts of interest to disclose.

João Cerqueira: Participates as investigator in clinical trials and observational studies sponsored by Biogen, Novartis, Merck, Roche, Celgene and J&J. Received research funding from Biogen. Received personal compensation for participating on advisory boards from Novartis, Biogen, Teva, Sanofi-Genzyme, Merck, Bayer and Roche and for participating as a speaker at meetings and teaching courses sponsored by Roche, Biogen, Novartis, Merck, Teva and Sanofi-Genzyme.

Rui Pedro Guerreiro: Participates as investigator in clinical trials and observational studies sponsored by Biogen, Novartis, Merck and Sanofi-Genzyme. Received personal compensation for participating on advisory boards from Novartis, Biogen, Sanofi-Genzyme, Merck and Bayer and for participating as a speaker at meetings and teaching courses sponsored by Biogen, Novartis and Merck.

João de Sá: Participates as a speaker at meetings and teaching courses sponsored by Biogen, Sanofi-Genzyme, Novartis, Merck and Roche.

Maria José Sá: Participates as investigator in clinical trials and observational studies sponsored by Biogen, Novartis, Merck, Roche, Sanofi-Genzyme and Teva. Received personal compensation for participating on advisory boards from Bayer, Biogen, Novartis, Teva, Sanofi-Genzyme, Merck and Roche and for participating as a speaker at meetings and teaching courses.

Sofia Almeida: Employee of and hold stock and/or stock options in Biogen.

Patrícia Mota: Employee of and hold stock and/or stock options in Biogen.

Lívia Sousa: Participates as investigator in clinical trials and observational studies sponsored by Biogen, Novartis, Merck, Roche, Sanofi-Genzyme and Teva. Received personal compensation for participating on advisory boards from Bayer, Biogen, Novartis, Teva, Sanofi-Genzyme, Merck and Roche and for participating as a speaker at meetings and teaching courses.

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