Neurol Ther
https://doi.org/10.1007/s40120-025-00754-6

ORIGINAL RESEARCH

Disease Course in Patients Switched from Natalizumab to Alemtuzumab: An Italian Multicenter, Prospective, Observational Study

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Received: December 19, 2024 / Accepted: April 14, 2025

ABSTRACT

Introduction: Natalizumab is a highly efficacious therapy (HET) for patients with relapsing remitting multiple sclerosis (RRMS). Its prolonged use is limited by the risk of progressive multifocal leukoencephalopathy (PML) in patients positive for anti-JCV antibodies. Aims of this work were to evaluate clinical and radiological efficacy at 6 and 12 months after alemtuzumab infusion in patients switching from natalizumab and the safety of this exit strategy.
Methods: This real-world, prospective, multicentric, observational study was conducted in three Italian MS centers and included a total of 35 patients with RRMS. Natalizumab treatment occurred from October 2010 to April 2021, whereas switch to alemtuzumab occurred from February 2018 to January 2023. Median washout period between the two drugs was 2 months. Patients underwent brain MRI before alemtuzumab start and then 6 and 12 months after the first alemtuzumab cycle.
Results: No clinical relapse occurred during the washout period, nor between the first and second alemtuzumab infusion. Radiological activity was present in 4/35 (11%) and 2/35 (6%) patients, respectively, at 6 and 12 months after the first alemtuzumab administration. Expanded Disability Status Scale (EDSS) increase developed in 4/35 (11%) and 5/35 patients (14%), respectively, at 6 and 12 months. No PML occurred, nor any serious adverse event. For patients in center 1 (17 patients), follow-up continued for a median of 3.5 years; NEDA-3 (No Evidence of Disease Activity) was present in 14/17 patients (82%) at the end of follow-up. Autoimmunity occurred in 23% of patients.
Conclusions: Alemtuzumab is a valid exit strategy after natalizumab interruption.

Prior Presentation: Ectrims 2024; Copenaghen 18–20 September; ePoster Number P1752.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-025-00754-6.

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Published online: 21 May 2025

Keywords: Multiple sclerosis; Patients' management; Exit strategy; Safety

Key Summary Points

Why carry out this study?

Natalizumab is extremely efficacious in controlling inflammatory activity in MS.

The risk of PML requires an exit strategy in JCV+ patients. The study aimed to evaluate efficacy and safety of alemtuzumab in patients who stopped natalizumab.

What was learned from the study?

Natalizumab withdrawal needs a switch to a highly efficacious therapy, to avoid rebound risk. The use of alemtuzumab was an efficacious and safe treatment option.

INTRODUCTION

Natalizumab (NTZ) is a humanized recombinant monoclonal antibody that binds to the α4 chain of the integrin very late activation antigen (VLA)-4 [1, 2]. It is a high-efficacy therapy (HET) in relapsing remitting multiple sclerosis (RRMS) [3, 4]. In patients with RRMS NTZ treatment is recommended to continue indefinitely without treatment interruptions. Therefore, its therapeutic potential is limited by the risk of progressive multifocal leukoencephalopathy (PML), a viral infection of the brain mediated by JC (John Cunningham) virus [5]. Patients previously treated with immunosuppressive drugs, positive for JCV antibodies, and exposed to natalizumab for more than 2 years have the highest risk of developing PML [6]. For this reason, there is a need to switch treatment to maintain disease control while minimizing PML risk. It is well known that NTZ cessation is associated with rebound disease activity [7–10] that peaks around month 4–7 after NTZ interruption [11]. To avoid rebound effects many therapeutic strategies have been adopted. The switch to fingolimod (FTY) showed superior efficacy compared to beta-interferon and glatiramer acetate in previous studies [12]. A study by Alping and coauthors [13] showed the superiority of rituximab versus fingolimod in controlling disease activity after NTZ cessation; but rituximab is restricted to off-label use in RRMS. With the US Food and Drug Administration (FDA) approval of ocrelizumab in 2017 a new exit strategy from NTZ became available; the use of anti-CD20 monoclonal antibodies (CD20mAb) grew owing to their efficacy and favorable safety profile including rare de novo and carryover PML [14]. However, chronic use of B-depleting drugs can lead to hypogammaglobulinemia, which increases infectious risk together with aging and immunosenescence [15]. A valid option for active RRMS is alemtuzumab (ALEM), a monoclonal anti-CD52 antibody, whose efficacy has been widely demonstrated in clinical trials as well as in the real world [4, 16–18].

So far, there are no reports on a significant risk of PML in alemtuzumab-treated patients with MS. In the present study we conducted a real-world multicenter prospective analysis on efficacy and safety in patients with RRMS switched from NTZ to ALEM.

The primary aim of this study was to evaluate clinical and radiological efficacy at 6 and 12 months after alemtuzumab infusion in patients switching from natalizumab; the secondary endpoint was to evaluate the safety of this sequential therapeutic strategy.

PATIENTS AND METHODS

This real-world, multicentric, observational, prospective study was conducted in three Italian MS centers: center 1 (the promoter center) contributed 18 patients; centers 2 and 3 contributed 15 and 2 patients, respectively, so data from these two centers were analyzed together and named as center 2.

Inclusion criteria were age ≥ 18 years, diagnosis of RRMS according to 2017 revised McDonald criteria [19], previous treatment with natalizumab, ability to perform contrast-enhancement brain MRI; exclusion criteria were pregnancy or breastfeeding and any clinically significant or

unstable medical condition that in the opinion of the MS clinician would have precluded safe and complete study participation.

The study was approved by Ethical Committee of the promoter center (Ethical Approval 121/2017) and by the Ethics Committees of University Hospital of Padova and ASST Papa Giovanni XXIII of Bergamo. It was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and each patient gave informed written consent.

Data from 35 subjects with RRMS were prospectively collected. Clinical and demographic characteristics of these patients are described in Table 1.

Natalizumab treatment occurred from October 2010 to April 2021, whereas switch to alemtuzumab occurred from February 2018 to January 2023. Patients were clinically stable during natalizumab treatment and EDSS at alemtuzumab start was the same as at natalizumab stop.

Reasons for natalizumab interruption were PML risk in 29 patients (82.9%), increase in transaminases in 2 patients (5.7%), radiological activity in 3 patients (8.6%), and patient decision in 1 case (2.8%). When the switch was due to JCV positivity, the index value, duration of natalizumab exposure, and the patient's perception of PML risk were taken into account.

Patients underwent contrast-enhanced brain MRI after the last natalizumab infusion and just before the first alemtuzumab cycle to rule out early signs of PML. MRI was performed by radiologists with particular experience in the field of MS. The protocol used axial T2-weighted scans, coronal flair-weighted scans, DWI sequences, and a post-contrast T1-weighted scan aiming at looking for early signs of PML.

As JCV is not constantly detected in PML-affected patients, lumbar puncture is not routinary performed in JCV+ patients before any therapeutic switch [20, 21], so it was not carried out in the study population.

Contrast-enhanced brain MRI was repeated 6 and 12 months after the first alemtuzumab cycle.

Clinical evaluation occurred every 6 months; laboratory data collection occurred monthly. In the promoter center a longer follow-up was available for longitudinal observational data in 17 patients.

Antiviral prophylactic therapy with acyclovir 200 mg BID was used for the first month after alemtuzumab infusion; furthermore, food prophylaxis was indicated for listeriosis risk the

Table 1 Patients' clinical and demographic characteristics

	Total	Center 1	Center 2
Number	35	18	17
Female/male	27/8	13/5	14/3
Median age at disease onset, years (range)	28 (11–60)	28.5 (13–60)	20 (11–51)
EDSS at NTZ start, median	2.0 (1–3)	2.0 (1–3)	2.0 (1–3)
No. NTZ infusions, median	19 (3–86)	16.5 (10–86)	22 (3–71)
Median washout period, months	2 (1–5)	2 (1–3)	1 (1–5)
Median age at ALM start, years (range)	32 (18–62)	33 (20–62)	31 (18–52)
EDSS 6 months, median	1.5 (0–3.5)	1.75	1.75
EDSS 12 months, median	1.5 (0–3.5)	1.5	1.5

ALM alemtuzumab, *EDSS* Expanded Disability Status Scale, *NTZ* natalizumab

month before and the month following drug infusion.

Statistical Analysis

Sample size was calculated referring to RESTORE study [22]; in that study it was estimated that among patients who were stable on natalizumab (no Gd+ lesions) switching from natalizumab to other therapies (IFN, GA, methylprednisolone), 48% presented MRI activity in the first 6 months of the new therapy. To verify a reduction of this proportion to 24% if patients started alemtuzumab with a 90% power at a 5% confidence level, 35 patients were needed.

Clinical and radiological endopoints were monitored and described for all patients for 12 months (see supplementary material); for patients of the promoter center a median follow-up of 3.5 years was available.

RESULTS

Patients' clinical and demographic characteristics are described in Table 1. Median number of NTZ infusion was 19 (3–86); median washout period from the last NTZ infusion to ALEM start was 2 months (range 1–5): in this period, no clinical relapse was observed. EDSS at alemtuzumab start was the same as at natalizumab stop. During the short washout period, patients were stable both clinically and radiologically.

Brain MRI performed just before starting alemtuzumab was negative for any sign suggestive of PML.

Clinical and Radiological Outcome at 6 Months

No patient had clinical relapses in the first 6 months after ALEM infusion. Out of 35 patients, 31 have stable brain MRI (no new/enlarging lesions, no enhancing lesions), whereas 4 patients had radiological activity (presence of new lesions in 3 patients and evidence of both enhancing and new lesions in 1 patient), without clinical signs of reactivation. In 31 out of 35 patients EDSS was stable or decreased compared to EDSS at alemtuzumab start; in the other 4 patients EDSS increased by 0.5 or 1 point in 3 and 1 patients, respectively.

Clinical and Radiological Outcome at 12 Months

Data at 12 months refer to clinical and radiological status just before the second ALEM cycle. No clinical relapse occurred between the first and second cycle of alemtuzumab. Out of 35 patients, 33 had stable brain MRI (neither new or enlarging lesions nor enhancing lesions compared to brain MRI performed 6 months after ALEM cycle), whereas 2 patients showed radiological activity (new and enhancing lesions), without clinical relapse; in one of the two patients, radiological activity was already present at 6 months. In 30 out of 35 patients EDSS was stable or decreased compared to EDSS at alemtuzumab start; in the other 5 patients an increase of 0.5 or 1 point occurred (in 4 and in 1 patient, respectively). Figure 1 shows median EDSS at NTZ start and then 6 and 12 months after the first ALEM cycle.

NEDA-3 (No Evidence of Disease Activity) status was present in 28/35 patients (80%) at the time of the second ALEM cycle (Fig. 2).

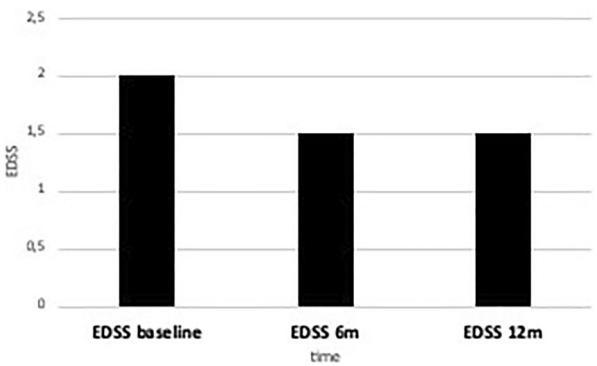

Fig. 1 EDSS at natalizumab start, 6 and 12 months after the first ALEM cycle

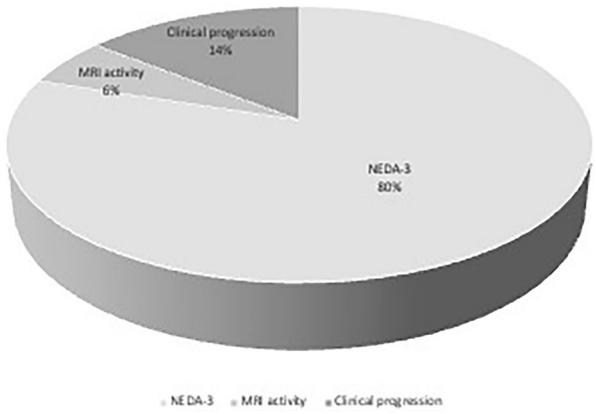

Fig. 2 NEDA-3 and EDA status 12 months after the first ALEM cycle

Table 2 Longitudinally followed-up patients in NEDA-3 status in the years following the second alemtuzumab cycle

No. of NEDA-3 patients/total no. of patients					
1st–2nd year	2nd–3rd year	3rd–4th year	4th–5th year	5th–6th year	> 6 years
14/17	14/14	9/9	7/7	6/6	3/3

Longitudinal Observational Data

For the promoter center (center 1) patients' longitudinal evaluation was available in 17 out of 18 patients; one patient was lost at follow-up. Median follow-up after alemtuzumab start was 3.5 years (range 1.4–6.4 years). In this group of patients, clinical assessment and brain MRI with the same protocol and with the same instrument were performed every 6 months.

NEDA-3 status was present in 14 out of 17 patients (82%) at the end of follow-up; loss of NEDA-3 was due to radiological activity in all three cases and occurred in the first year after the second cycle (Table 2).

Therapeutic decision after NEDA-3 loss was natalizumab resuming (1 patient), alemtuzumab third cycle (1 patient) and autologous stem cell transplantation (AHSCT, 1 patient). It is of interest that in the first case, natalizumab was able to control the disease, as before alemtuzumab start; in the second case the patient did not respond to the third alemtuzumab cycle, nor to the following disease-modifying therapy (anti-CD20 monoclonal antibody); in the third case the patient underwent AHSCT but had radiological and clinical reactivation 18 months after the procedure.

Safety

No serious adverse event occurred in the 12 months after alemtuzumab start. Three patients in center 1 did not complete the second cycle of alemtuzumab; more specifically, one patient developed reduction in platelets count and received 1 day instead of 3 days of drug infusion, and two patients developed an increase in transaminases and received 2 days instead of 3 days of drug administration. No specific treatment was required, and side effects resolved spontaneously. Data about secondary autoimmunity were available for the 17 longitudinally followed patients in center 1; 4 out of the 17 patients developed thyroid autoimmunity. More specifically, thyroid autoimmunity consisted of Basedow disease (1 patient), hyperthyroidism (2 patients), and reactivation of preexistent thyroiditis (1 patient); globally thyroid complications occurred in 23.5% of subjects. No patient developed PML.

DISCUSSION

This prospective, observational, multicenter real-world study on patients switching from NTZ to ALEM aimed to evaluate both the efficacy and safety of this exit therapeutic strategy.

It is well known that disease activity returns 3 to 6 months after NTZ discontinuation if no other drug is started. No guidelines exist about how to manage patients who stop NTZ.

The use of NTZ extended-interval dosing (EID) was only recently introduced as a treatment option to limit, but not to avoid, PML risk. Literature data report similar effectiveness of NTZ with EID at a dosing interval of 6 weeks versus standard interval dosing (SID) [23–26].

A recent review by Brown et al. [27] showed that CD20mAb are a suitable transitional option for patients who discontinue NTZ, with very low rates of carryover PML (0.6%) and low rates of clinical relapse. Another study by Bigaut et al. [28] showed the superiority of ocrelizumab compared to fingolimod after NTZ cessation.

Some concerns arise about long-term safety of chronic immunosuppressive treatment; it is known that hypogammaglobulinemia is a potential long-term complication of anti-CD20 therapy [15] and that the risk of infections is thought to be increased with hypogammaglobulinemia, particularly when sustained for a prolonged period [29].

A recent study by Zeineddine and colleagues [30] reported the superior effectiveness of anti-CD20 drugs and alemtuzumab compared with fingolimod in stable patients switching from NTZ because of JCV antibody positivity. In this retrospective work, of 321 patients with stable RRMS treated with NTZ for at least 6 months, 255 switched to rituximab/ocrelizumab, 52 to fingolimod, and only 14 to alemtuzumab.

Another large observational cohort study showed that ocrelizumab use was associated with the lowest annualized relapse rate and the longest time to first relapse after NTZ cessation compared to fingolimod and dimethyl fumarate [31].

In a recent Italian study [32] ALEM was used as an exit strategy from NTZ in a population of 17 patients with adult-onset MS and 10 patients with pediatric-onset MS for safety concerns (high anti-JCV index), showing its effectiveness especially in the adult-onset patients.

A retrospective review of patients with MS having received ALEM between 2015 and 2021 in Belgium [33] analyzed 37 subjects, 5 of whom were JCV+ patients previously treated with NTZ; no disease activity was observed in this group.

In the present study we prospectively collected data from three Italian Centers on 35 patients, switching from NTZ to ALEM, mainly because of safety concerns (PML risk in 83% of cases).

In the washout period no patient experienced clinical or radiological disease activity.

In the first year after NTZ interruption no clinical relapse was observed; after the first ALEM cycle radiological activity was detected in four and two patients at 6 and 12 months, respectively. No serious adverse event occurred, no PML developed.

Long-term efficacy of alemtuzumab was confirmed by longitudinal follow-up of patients enrolled in the promoter center. Globally, we observed NEDA-3 status in 14 out of 17 patients (82%). Loss of NEDA-3 was due to the appearance of radiological activity in the first year after the second ALEM cycle. Patients not responding to alemtuzumab did not respond to other depletive treatment or to AHSCT.

No serious adverse events were observed. Two out of 17 patients did not complete the second cycle as a result of reduction in platelet count (1 patient) and increase in transaminases (2 patients); no specific treatment was necessary and alterations reverted spontaneously. Despite the failure to complete the second cycle, the two patients showed absence of disease activity at the end of follow-up.

Thyroid autoimmunity developed in 23% of patients, in accordance with the literature [34, 35].

This study has a small number of patients and that represents a limitation. However, we think the paper provides relevant data for everyday clinical practice about the management of stable NTZ-treated JCV+ patients.

CONCLUSIONS

Our study showed that the use of ALEM as exit strategy was safe and efficacious; our results are confirmed in smaller study populations. These data may help neurologists to better manage JCV+ NTZ-treated patients in their routine clinical practice.

ACKNOWLEDGEMENTS

We thank Dr Chiara Sciolla for support in data collection. We thank the participants for their involvement in the study.

Author Contributions. Simona Malucchi contributed in selection and follow-up of patients and in writing. Paola Perini, Francesca

Rinaldi, Marta Radaelli and Maria Malentacchi selected and followed up patients. Antonio Bertolotto planned the study. Alessia Di Sapio contributed in the writing and in the overall control of the whole study. All authors contributed to the article and approved the submitted version.

Funding. This investigator-initiated study was funded by Sanofi. The Journal's Rapid Service Fees were funded by the authors.

Data Availability. Data relative to radiological and clinical results for each patient are published as supplementary material. The datasets generated and analyzed during the current study are available from the corresponding author.

Declarations

Conflict of Interest. Simona Malucchi, Paola Perini, Francesca Rinaldi, Marta Radaelli, Maria Malentacchi, Antonio Bertolotto and Alessia di Sapiodeclare state that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval. The study was approved by Ethical Committee of the promoter center (Ethical Approval 121/2017) and by the Ethics Committees of University Hospital of Padova and ASST Papa Giovanni XXIII of Bergamo. It was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and each patient gave informed written consent.

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