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ORIGINAL ARTICLE

Long-term follow up of alemtuzumab-treated patients: a retrospective study in a Belgian tertiary care center

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Abstract

Background Pivotal studies have reported a significant proportion of patients achieving no evidence of disease activity (NEDA) after 2 cycles of treatment with alemtuzumab (ATZ), that can be maintained for several years. Long-term real-world evidence regarding ATZ as well as subsequent treatment trajectories is still scarce.

Objective To analyze the effectiveness and safety of ATZ-treated patients in a tertiary care Belgian center.

Methods A retrospective cohort study including 32 patients treated with ATZ between 2015 and 2021 was performed.

Results 32 patients received 2 ATZ courses with a mean follow-up (FU) duration of 5.6 years (range: 2.25–8.2). 21.75% patients were treatment naïve. 40.5% were previously treated with natalizumab or fingolimod. NEDA-3 was achieved in 61.3–85% of patients, with failure mostly attributed to recurrence of radiological disease activity. During FU, annualized relapse rates remained very low (0.06–0.14), disability improvement occurred in up to 40.5%, whereas disability worsening occurred in up to 13.5%. Retreatment risk was associated with younger age (< 45 years old, Odds Ratio 8.0, $p = 0.02$) and a higher number of previous DMTs (Hazard ratio 2.7, 95%CI 1.3–7.4, $p = 0.02$). Safety in our cohort was consistent with the known profile of ATZ. At the end of FU, 65.6% patients remained untreated after 2 or 3 courses of ATZ, while the remaining switched to anti-CD20 therapy or cladribine.

Conclusion ATZ is a high efficacy therapy for active MS, providing long-term remission in a significant proportion of patients. Retreatment was more frequent in younger patients or patients having failed a higher number of previous DMTs.

Keywords Multiple sclerosis · Alemtuzumab · Real-world evidence · Long-term · Effectiveness · Safety

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, responsible for significant disability in young adults [1]. In the early phases of the disease, inflammatory disease activity, in part mediated by the peripheral immune system, is responsible for clinical relapses and subclinical accumulation of multifocal demyelinating lesions. Phenotypically, most patients experience a relapsing–remitting form of the disease, with phases of progression independent or not from relapses [2]. As disease duration increases, disability progression can increase due to predominant compartmentalized chronic inflammatory processes and axonal degeneration [3].

Current disease-modifying therapies (DMTs) targeting the peripheral immune system are effective against the acute inflammation occurring in early stages of MS. There is, therefore, a window of opportunity to treat the disease early on and limit subsequent disability accumulation, even more so with early high efficacy therapies [4, 5].

Alemtuzumab (ATZ) is a humanized monoclonal antibody directed against the CD52 surface receptor, inducing a rapid depletion of B and T cells followed by progressive repopulation, leading to long-lasting changes in lymphocyte subpopulations [6]. It was the first approved selective immune reconstitution therapy for MS, administered as two courses, with a strict risk management plan due to its adverse event profile. It is classified as a high efficacy therapy indicated for patients with highly active disease failing

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a DMT or patients with rapidly worsening, severe disease, who have had two or more relapses in 1 year [7]. Its efficacy was demonstrated in the CARE-MS I and II phase 3 studies, showing the superiority of ATZ to interferon beta 1a in both naïve and patients failing a previous DMT, respectively [8, 9]. Post-hoc analysis showed that respectively 68 and 58% of patients treated with ATZ reached No Evidence of Disease activity status (NEDA-3) at year 2 [10]. Relapse rates remained low, and a significant proportion of patients were either clinically stable or showed confirmed disability improvement during the 4-year extension of the CARE-MS trials [11]. Real world long-term evidence regarding treatment effectiveness and safety of ATZ in unselected populations is still scarce to support this data. Unlike randomized controlled trials, real-life studies involve larger and more diverse patient populations and thereby can provide a broader understanding of how ATZ performs in routine clinical practice.

This retrospective study of 32 patients treated with at least two courses of ATZ in a tertiary academic center in Belgium aims to present real-world long-term effectiveness and treated with ATZ between 2015 and 2023.

Materials and methods

A retrospective review of MS patients having received ATZ between 2015 and 2021 at the Cliniques Universitaires Saint-Luc, Brussels, Belgium was performed. Baseline demographic data were recorded. Clinical parameters (relapse occurrence and disability status measured by the EDSS score) and radiological features were collected from 1 year prior to starting ATZ treatment until last follow-up visit. Subsequent treatments following the 2 ATZ courses were also recorded, as well as safety data. The study protocol was approved by the University Hospital Ethics Committee (2022/09JUI/237).

Primary objective

The primary objective of the study was to determine the proportion of patients that reached clinical and radiological remission of disease activity (NEDA-3) following 2 ATZ courses at year 2. The proportion of patients maintaining NEDA-3 status was followed. NEDA-3 is defined as no relapse occurrence, no disability worsening, and no radiological disease activity on brain MRI. Radiological disease activity was defined either by the occurrence of a new and/or enlarging T2/FLAIR lesion on brain MRI in comparison with the previous scan or the occurrence of one or more gadolinium-enhancing lesions (GEL). Retreatments by ATZ or switches to another DMT were recorded.

Secondary objectives

The proportion of patients presenting with sustained disability improvement or worsening confirmed over at least 2 evaluations was determined. Disability worsening was defined as one of the following: Expanded Disability Status Score (EDSS) increase by at least 1.5 points if baseline EDSS is 0; increase by 1 point for an EDSS ≥ 1, increase by 0.5 points for an EDSS > 5. In addition, disability worsening was subdivided into relapse-associated or independent from relapse. The reverse was used as definition of sustained disability improvement.

As an exploratory endpoint, we tried to identify the factors predicting the risk of retreatment after two courses of ATZ.

Finally, adverse effects (infusion reactions, autoimmunity, cancers, and infections) were collected.

Statistical analysis

We performed descriptive statistics of baseline demographics and disease features. Fisher's exact test was used to predict the need for retreatment according to age ($<$ or ≥ 45 years old). Multiple logistic regression analysis was performed to determine the odds ratio for variables associated with retreatment after two courses of ATZ. Cox regression analysis was used to investigate potential explanatory variables associated with a significant hazard ratio for retreatment. The threshold for statistical significance was $p < 0.05$. GraphPad Prism version 10.0.0 was used for all analyses.

Results

Baseline characteristics

A total of 37 patients with relapsing remitting MS received at least 1 dose of ATZ were included in the study. Patient disposition is detailed in Fig. 1. 5 patients were excluded from the study: 1 patient received only one ATZ course and did not pursue the treatment due to $CD4^+$ T cell lymphopenia and disability progression, 1 because she was included in the double blind CAMMS3240 and open label extension studies during which she received a total of 5 courses of ATZ, 1 who refused the to receive the second course of ATZ in the context of the COVID-19 pandemic and 2 who were lost to follow-up.

The cohort consisted of 28 (87.5%) females with a median age at initiation of ATZ of 33 (range 18–54). Mean disease duration was 7.3 years ($\pm$ 7.5). Patients presented

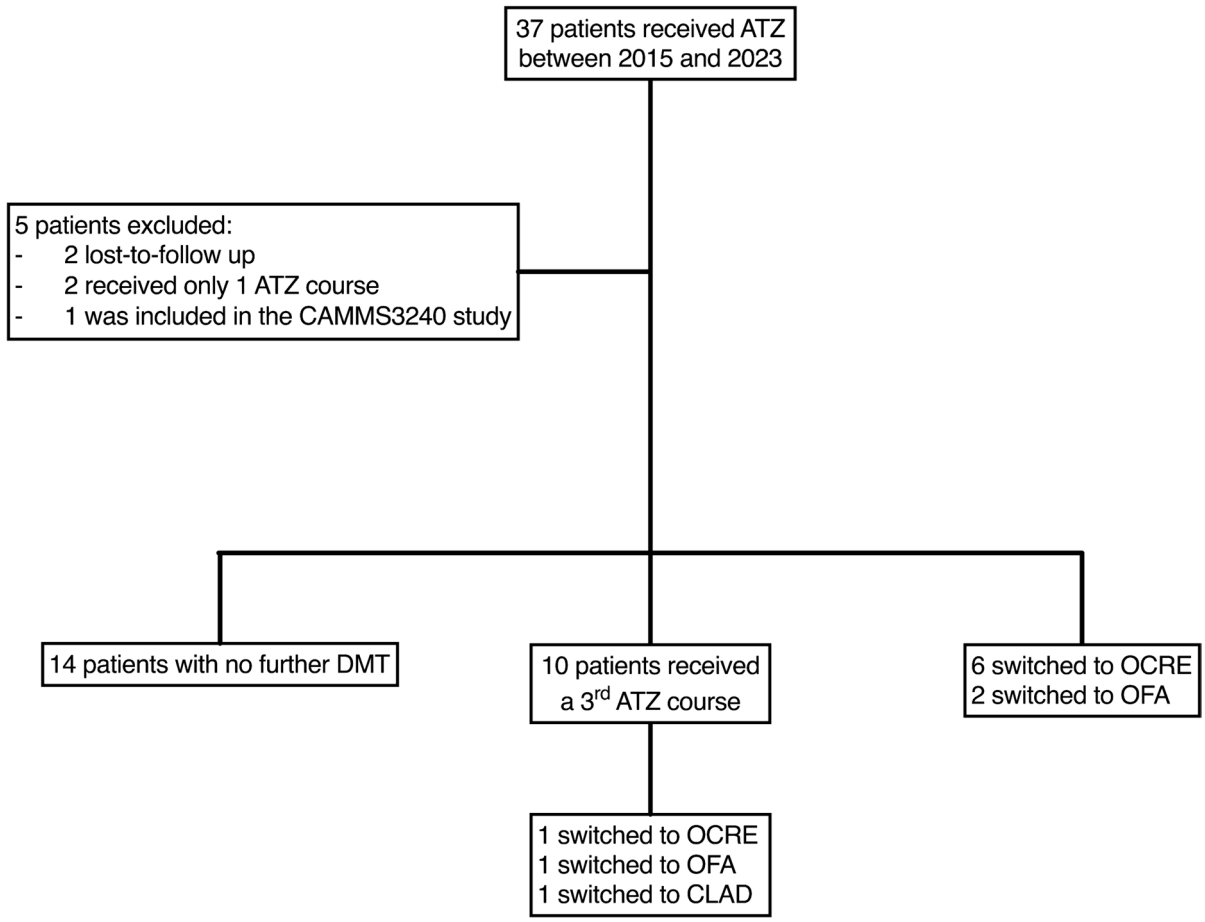


Fig. 1 Patient disposition. *ATZ* alemtuzumab, *OCR*E ocrelizumab, *OFA* ofatumumab, *CLAD* cladribine

a median of 4 (range 2–10) relapses throughout the course of their disease. Disease activity pre-ATZ consisted of a median of 1 relapse (range 0–3) in the year preceding ATZ (Table 1).

Among the 7 patients who had no relapse before being treated with ATZ, 3 were JCV-positive, treated with natalizumab (NTZ) until their pregnancy and ATZ was initiated post-pregnancy. 1 patient was switched from NTZ for convenience, 1 patient was JCV-positive and had previously failed fingolimod therapy; 1 patient was switched due to JCV seroconversion while on NTZ and 1 patient had recurrent radiological disease activity and refused continuous immunotherapy. In the year prior to starting ATZ patients had a median of 7 (range 0–30) new T2/FLAIR lesions and 5 (range 0–30) GEL. Median EDSS at ATZ initiation was 3 (range 0–6). Seventy eight percent of patients ($n = 25$) had received a median of two previous DMTs (range 0–6), of which 40.5% were considered high efficacy (natalizumab or fingolimod). Seven (21.75%) patients were treatment naïve. DMTs used prior to ATZ are shown in Fig. 2.

Effectiveness outcomes: clinical and radiological follow-up

Mean/median duration of follow-up upon initiation of ATZ was 67 months (5.6 years) with a range of 27 to 98 months (Table 2). During this period 14 patients did not present recurrence of clinical and/or radiological disease activity and were therefore not retreated (Fig. 1). 10 patients received a third ATZ course at a median of 24 months (range 12–38 months) following the second course. Of those patients, three presented recurrence of radiological disease activity and initiated anti-CD20 treatment or cladribine. 8 patients did not receive a third course of ATZ and started instead treatment with an anti-CD20 monoclonal antibody. The median delay between starting anti-CD20 therapy after ATZ (either 2 or 3 courses) was 21 months (range 11–40).

a. Relapses

Mean annualized relapse rate in the year preceding initiation of ATZ was 1.1 (±0.8) and fell to 0.06 (±0.25) at year

Table 1 Baseline characteristics of ATZ-treated patients

Females n/N (%)	28/32 (87.5%)
Age (years)	
Mean ± SD	34 ± 10
Median (range)	33 (18–54)
Disease duration (years)	
Mean ± SD	7.3 ± 7.5
Median (range)	6 (0–26)
Baseline EDSS	
Median (range)	3 (0–6)
Total number of relapses since disease onset[1]	
Mean ± SD	4 ± 2
Median (range)	4 (2–10)
Number of relapses in the year preceding ATZ[2]	
Mean ± SD	1 ± 1
Median (range)	1 (0–3)
Number of new GEL on brain MRI prior to ATZ[3]	
Mean ± SD	5 ± 6
Median (range)	3 (0–30)
Number of new FLAIR/T2 lesions on brain MRI prior to ATZ[3]	
Mean ± SD	7 ± 7
Median (range)	5 (0–30)
Presence of spinal cord lesions on MRI n/N (%)	27/28 (96.4%)
Number of prior DMTs	
Mean ± SD	2 ± 2
Median (range)	2 (0–6)
DMT-naïve prior to ATZ n (%)	7 (21.9%)
High-efficacy DMT as last treatment prior to ATZ n/N (%)[4]	13/25 (52%)

n/N number of patients/total, SD: standard deviation, EDSS expanded disability status score, ATZ alemtuzumab, GEL gadolinium-enhancing lesion, MRI magnetic resonance imaging, DMT disease-modifying treatment, High-efficacy DMT: = fingolimod (n = 8/12), natalizumab (n = 5/12). [1] n = 26; [2] 7 patients with no relapse before ATZ; [3] n = 27; [4] excluding DMT-naïve patients prior to ATZ

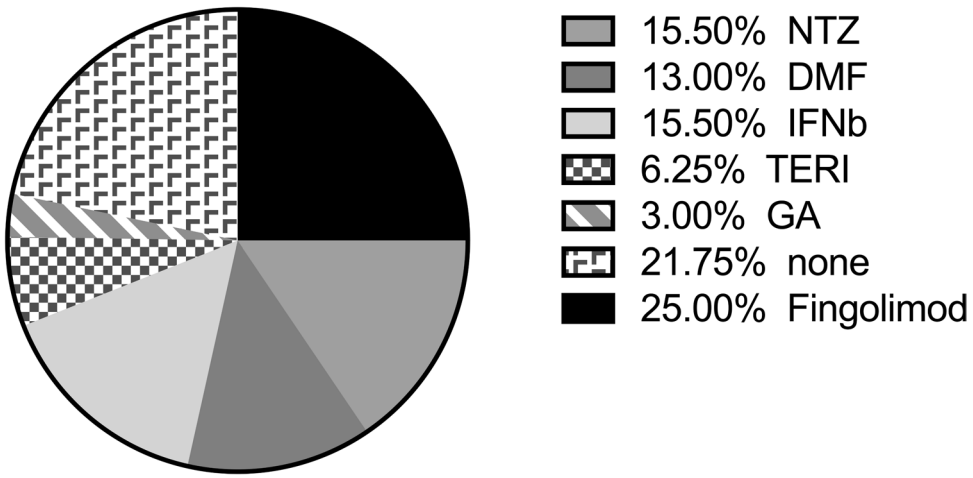


Fig. 2 Disease-modifying treatments pre-alemtuzumab. % of patients under a given DMT is indicated in the legend. DMT: disease-modifying treatment

1, 0.09 (± 0.3) at year 2, 0.13 at year 3 (± 0.35) and 0.14 at year 4 (± 0.35) (Fig. 3). No relapses occurred at year 5 through 7, with a caveat of the small number of patients having reached this follow-up duration. The proportion of relapsing patients was reduced from 77 to 7% at years 1 and 2 following treatment with ATZ, 14% at years 3 and 4. No relapses occurred at years 5 through 7.

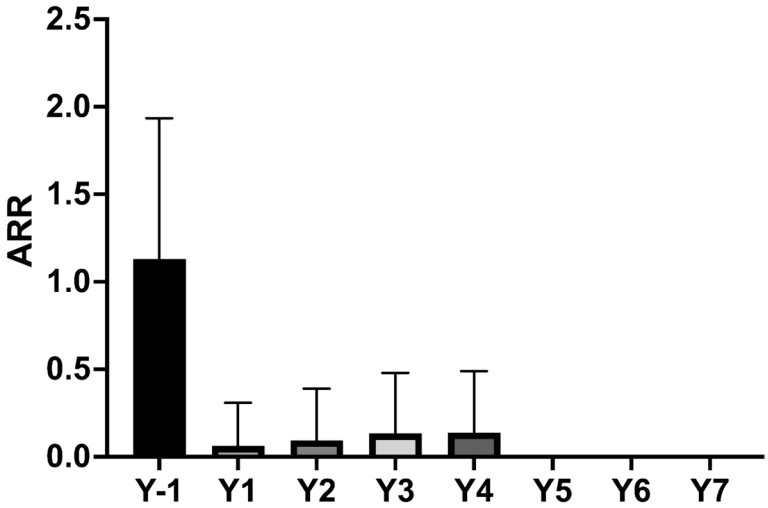
Table 2 Outcomes after a 2-year course of alemtuzumab

Follow-up duration (months)	
Mean ± SD	67.3 ± 18
Median (range)	67 (27–98)
Timing of 3rd ATZ course after year 2 ($n = 9$) in months	
Mean ± SD	21.2 ± 9.3
Median (range)	24 (12–38)
Timing of anti-CD20 initiation after last ATZ course ($n = 9$) in months	
Mean ± SD	22.4 ± 7.6
Median (range)	21 (11–40)
Proportion of patients with NEDA-3 at Y3 after 2 courses of ATZ[b]	61.30%
Duration of follow-up after a third ATZ course ($n = 6$)[a]	
Mean ± SD	35.7 ± 15.3
Median (range)	41 (5–50)
Duration of follow-up after starting anti-CD20 treatment ($n = 7$)[2]	
Mean ± SD	35.6 ± 13.1
Median (range)	42 (7–49)
Total number of patient-years of follow-up (n)	162
Total number of patient-years free of treatment n (%)	74 (45.7%)

ASD standard deviation, *ATZ* alemtuzumab, *OCRE* ocrelizumab, *NEDA* No Evidence of Disease Activity,

[a]Excluding patients who shifted to another treatment due to recurrence of disease activity ($n = 3$) and one patient with no follow-up

[b]After 2 ATZ courses, excluding one patient with no follow-up



	Y-1	Y1	Y2	Y3	Y4	Y5	Y6	Y7
Mean ARR ± SD	1.1 ±0.8	0.06 ±0.25	0.09 ±0.3	0.13 ±0.35	0.14 ±0.35	0	0	0
Proportion of patients with a relapse n/N	24/31	2/32	3/32	4/30	4/29	0/22	0/15	0/10
%	77	7	7	14	14			

Fig. 3 Mean Annualized relapse rate during the year before initiating ATZ**.** (Y-1) through year 7 post-ATZ. Data is presented as mean ± SD. *ATZ* alemtuzumab, *ARR* annualized relapse rate, *SD* standard deviation

b. Radiological disease activity

During years 1 throughout 5 following the start of ATZ, between 67.7 and 95% of patients were devoid of new T2/FLAIR or GEL on yearly brain MRI (Fig. 4). Of note, these proportions were comparable when excluding patients who received a third ATZ course or initiated another DMT (data not shown). The only patient with 8 years of follow-up, remained clinically stable but showed one new GEL lesion on his brain MRI at year 8 (data not shown).

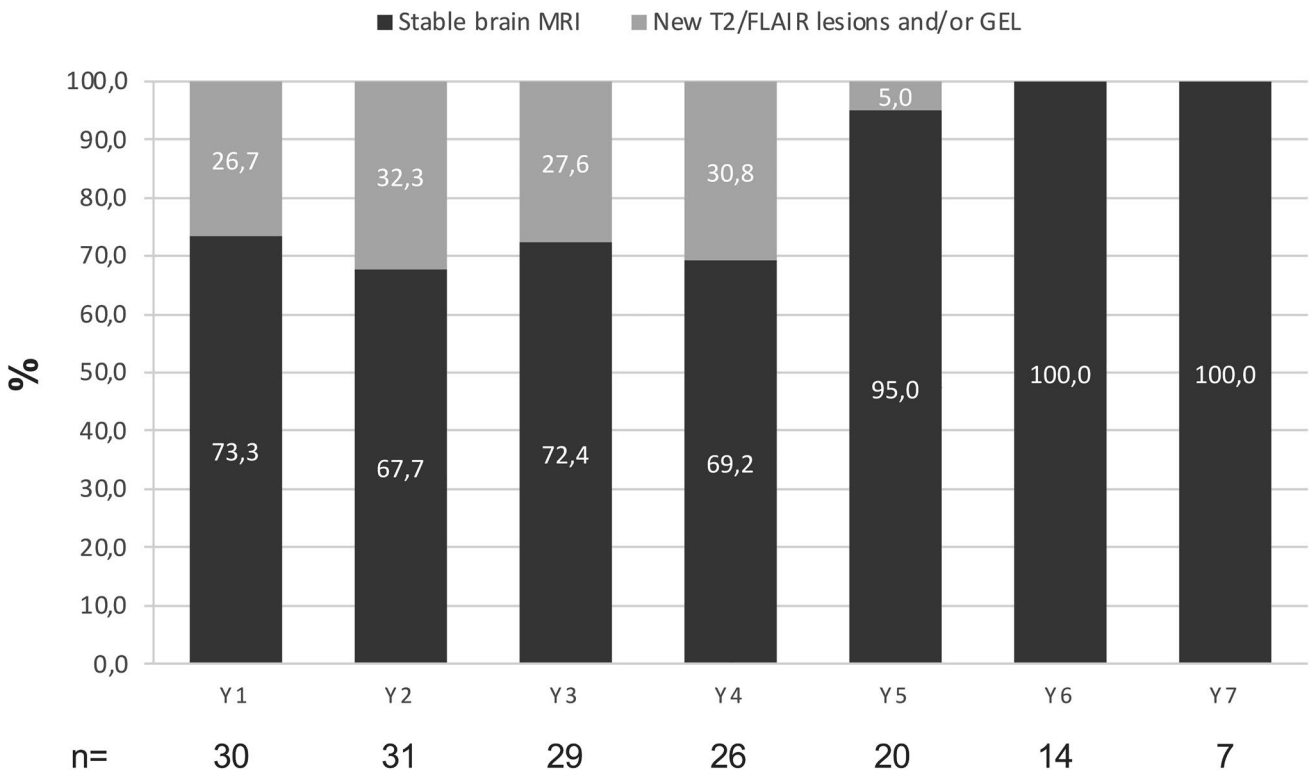


Fig. 4 Proportion (%) of patients with stable MRI vs. patients with new T2/FLAIR lesions and/or gadolinium-enhancing lesions (GEL) throughout years 1 to 7, independently of treatment status. Number of patients for whom data is available is indicated

c. Disability

During the follow-up period, the EDSS score remained stable in 50% ($n=32$) of patients. Sustained disability improvement occurred in 31.25% ($n=10$) patients. On the contrary, 12.5% of patients ($n=4$) experienced progression independent of relapse activity as defined per protocol and 6.25% patients ($n=2$) experienced relapse-associated worsening at the end of the follow-period. Yearly proportions of patients experiencing disability stability, improvement or worsening is present in Fig. 5a. Individual disability trajectories are illustrated in Fig. 5b, c.

d. NEDA-3

The proportion of patients reaching NEDA-3 status is outlined in Fig. 6, independently of treatment status. Between years 1 and 5 of follow-up, 61.3–85% of patients were considered in remission. Failure to reach NEDA-3 was mostly due to radiological recurrence of inflammatory disease activity, mostly isolated (5–23.33% between years 1 and 5), but sometimes with occurrence of a relapse (3.45–9.68%). Disability worsening alone was only responsible in 3.2–10% of the patients for failure to reach NEDA-3 status.

Regarding patients receiving either a third course of ATZ ($n=9$) or switching to anti-CD20 ($n=7$), with at least 6 months of follow-up, NEDA-3 was maintained for a median duration of respectively 24 and 32 months (Mann–Whitney test non-significant) (Table 2). However, 3/9 patients presented again with radiological disease activity between 21 and 23 months after their third course of ATZ, whereas no patients on anti-CD20 until last follow-up presented with recurrences of disease activity. The number of patients with NEDA-3 according to treatment status, for which follow-up is available, is detailed in Table 3.

Factors influencing the risk of retreatment

Odds ratio for retreatment if < 45 years old was 8.00 (Fisher's exact test, $p=0.02$). Using multiple logistic regression analysis, higher age was also associated with slightly lower odds of retreatment (OR 0.85, 95%CI 0.72–0.95, $p=0.015$) as shown in Table 4. A higher number of previous DMT was associated with a higher likelihood of retreatment (HR 2.7, 95%CI 1.3–7.4, $p=0.02$) as shown in Table 5.

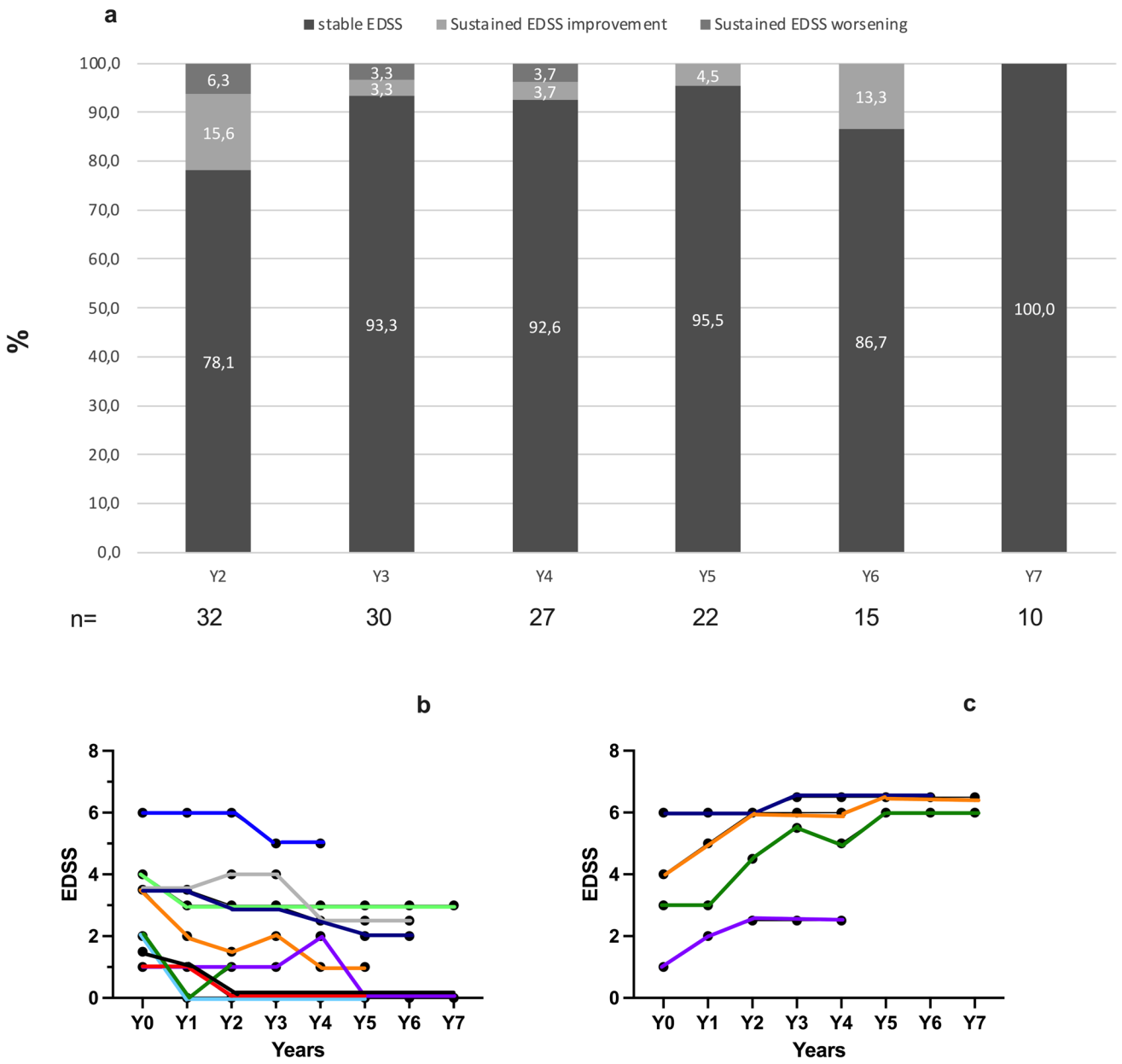


Fig. 5 **(a)** Proportion of patients with stable or sustained disability improvement (DI) or worsening (DW) from year 1 (Y2) to year 7 (Y7) of follow-up after starting alemtuzumab, independently of treatment status. Number of patients (*n*) for whom data is available is indicated below the graph. Individual patient trajectories for patients with sustained DI ($n=10$) (**b**) and DW ($n=4$) (**c**). Of note, patients ($n=2$) with relapse-associated worsening at the end of follow-up were not plotted

Safety outcomes

The most common adverse events were infusion-related, appearing in 17 (54.8%) of patients, followed by thyroid disease in 11 (34.4%) patients (Table 6). No cardio-vascular event occurred following ATZ administration. Of these, 7 (63.6%) developed Basedow's disease, 4 (27.4%) Hashimoto thyroiditis and one (9%) patient presented with De Quervain thyroiditis. Mean time to thyroid events was 30 months (±20) following the first course of ATZ. A case of Listeriosis occurred in a 44-year-old female patient during the month following the first cycle of ATZ. Two patients (6.25%) developed malignancy: 1 basal cell carcinoma occurring 5 years after starting ATZ, and 1 breast ductal carcinoma in situ (DCIS) 4.5 years after the first course of ATZ.

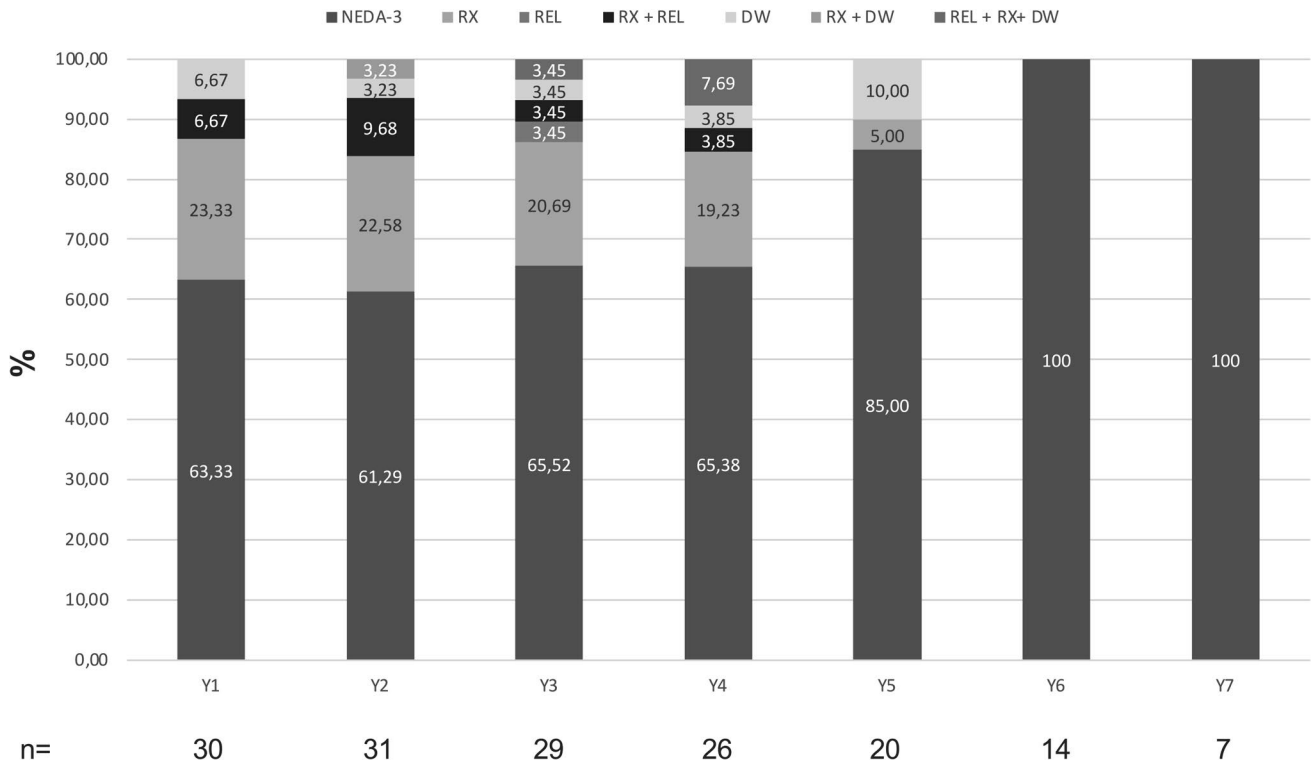


Fig. 6 Proportion of patients divided according to the components of the NEDA-3 score, independently of treatment status. *NEDA* no evidence of disease activity, *RX* radiological disease activity, *REL* relapse, *DW* disability worsening

Table 3 Number and proportion of patients with NEDA-3 according to follow-up duration, subdivided according to treatment status

		Y3	Y4	Y5	Y6	Y7
Total number of patients with available FU		29	26	20	14	7
Total number of patients with NEDA-3		19	17	17	14	7
NEDA-3 ATZ2		17	10[a]	7[a]	6[a]	4[a]
NEDA-3 ATZ3	Y2	1	0	–	–	–
	Y3	NA	4	2	2[a]	–
	Y4	NA	NA	2	2	1[a]
NEDA-3 Anti-CD20	Y2	1	1	1	1	–
	Y3	NA	2	2	1[a]	–
	Y4	NA	NA	3	2[a]	2[a]

FU follow-up, *Y* year, *NEDA-3* no evidence of disease activity, *ATZ2* two courses of ATZ years 1 and 2, *ATZ3* third course of ATZ, *NA* not applicable,– no available follow-up, [a] for which follow-up is available

Discussion

Alemtuzumab is classified as a high efficacy DMT for relapsing MS, with a unique mechanism of action and treatment regimen. The change in the composition and activity of the immune system following profound depletion by the anti-CD52 monoclonal antibody ATZ induces remission of the disease, free of treatment in a significant proportion of patients for a certain duration. Data regarding the long-term real-life use of ATZ remains however scarce. Real-world evidence reporting the use of ATZ for treating highly active MS can offer valuable insights into the drug's long-term effectiveness and safety in a clinical setting, thereby complementing the data from short-term randomized controlled trial. Real-life studies also help identify potential rare adverse events that may not have been captured in phase III clinical trials. Finally, real-life studies provide valuable evidence that can guide treatment decisions and inform clinical guidelines, ultimately improving patient care for individuals with MS.

Table 4 Multiple logistic regression for 'retreatment' after 2 ATZ courses

Variable	OR	95% CI	p-value
Age (in years)	0,85	0,72–0,95	**0,015**
Gender	0,35	0,0085–7,1	0,51
Disease duration (yrs)	0,77	0,46–1,0	0,18
n° of relapses in the year before ATZ	1,1	0,22–6,5	0,87
Baseline EDSS	0,86	0,40–1,7	0,66
n° of DMTs before ATZ	3,5	1,1–24	0,10

Bold indicates statistical significance at the p<0.05 level

ATZ alemtuzumab *OR* odds ratio

Table 5 Cox regression for time to retreatment after 2 ATZ courses

Variable	HR	95% CI	*p* value
Age (in years)	1,0	0,92–1,1	0,69
Gender	0,47	0,093–2,6	0,36
Disease duration (yrs)	0,73	0,48–1,0	0,08
n° of relapses in the year before ATZ	0,27	0,038–0,97	0,09
Baseline EDSS	0,72	0,43–1,1	0,14
n° of DMTs before ATZ	2,7	1,3–7,4	**0,02**

Bold indicates statistical significance at the p<0.05 level

ATZ alemtuzumab, *HR* hazard ratio

Table 6 Adverse events reported in patients having received at least 2 courses of ATZ

Adverse events		n/N (%)
Infusion related adverse events *N* = 14/32 (43.75%)	Cutaneous rash	9/12 (64.3)
	Headaches	3/12 (21.4)
	Dyspnea	2/12 (14.3)
Thyroid disease *N* = 11/32 (34.4%)	Grave's disease	7/11 (63.6)
	Hashimoto's thyroiditis	3/11 (27.4)
	De Quervain thyroiditis	1/11 (9)
Infections *N* = 3/32 (9.4%)	Herpes simplex virus/ Herpes zoster virus	2/3 (66.7)
	Listeriosis	1/3 (33.3)
Malignancy		2/32 (6.25)

In our cohort, patients had highly active MS with both at least 1 relapse and a median of 7 (range 0–30) new T2/FLAIR lesions and 5 (range 0–30) GEL prior to starting ATZ, consistent with other published cohorts [12, 13]. Contrary to the pivotal phase III CARE-MS 2 trial, real-life treatment switches include oral DMTs and switches from natalizumab, mainly for JC virus seroconversion. In 3/5 JCV seropositive NTZ-treated patients, ATZ was initiated post-pregnancy, without recurrence of disease activity. No rebound was observed in patients switching from fingolimod ($n = 8$).

Following treatment with ATZ, we report a 90–95% reduction in clinical relapses, 69–73% of patients free of radiological disease activity and 78–100% with stable disability level during years 1 to 4. This translates into an overall NEDA-3 proportion of 63–65%, as reported in the TOPAZ study for patients with highly active disease and is remarkably consistent with the real-life effectiveness reported in other cohorts [14–17]. Consequently, 14/32 (43.75%) patients remained treatment-free after 2 ATZ courses, with a median follow-up duration of 51 months (range 30–86). In the CARE-MS I and II extension studies, 63% and 50% of patients respectively did not receive additional treatment throughout year 6 [11].

Finally, as described in the CARE-MS extension studies, we observed a significant proportion of patients with sustained disability improvement (31.25%) throughout the observation period, with only 12.5% of patients having sustained disability worsening, independent of relapses [11, 18, 19]. This was also reported in the post-hoc studies of the CARE-MS trials, where 43% of patients ($n = 511$) showed confirmed disability improvement and 34% confirmed disability worsening at any time during the 9-year follow-up period [20].

Interestingly, most patients failed NEDA because of recurrence of subclinical disease activity on MRI (19–22%) between years 2 and 4, again in line with the results of the TOPAZ study, reporting 65–72% of patients free of radiological disease activity up to year 7 of follow-up [14]. Most retreatment decisions were based on this criterion, with patients either receiving a third course of ATZ or switching to anti-CD20 treatment. In our cohort, a third course of ATZ was administered at a median of 24 months (range 14–37). 6 patients for whom follow-up is available (median 41 months; range: 5–50) remain treatment-free. 3/10 presented with recurrence of radiological disease activity leading to reinitiating DMT between 21 and 23 months after the third ATZ course. 8 patients switched to anti-CD20 treatment at a median of 20 months (range 14–37) after the second ATZ course. 7 patients for whom follow-up (median: 42 months; range: 7–49) is available remained on this treatment and were free of disease activity.

Logistic regression showed that the odds ratio for retreatment after 2 ATZ courses was higher if patients were younger, possibly due to higher age-related inflammatory activity. In particular, if patients were < 45 years old, the odds ratio for retreatment was 8 (Fisher's exact test, $p = 0.02$). Using cox regression analysis, the time to retreatment was shorter if the patient had a higher number of treatments pre-ATZ (Hazard ratio of 2.67, 95%CI 1.25–7.41; $p = 0.02$). In the same line, results from the Danish MS cohort treated with ATZ, showed that each

additional DMT prior to ATZ increased the odds of retreatment by 44% [13]. In this study, an additional factor linked to risk of retreatment was the number of relapses prior to ATZ.

Overall, out of a total 162 patient-years of treatment, in our cohort 74 (45.7%) patients-years were without DMT, which has pharmaco-economic implications, in a context of budgetary constraint and need for demonstrating cost-effectiveness of expensive immunotherapies for MS [21, 22].

Infusion-related reactions were the most common adverse event reported, in 43.75% of patients, mostly as cutaneous reactions. Thyroid disease was the most common secondary autoimmune event, occurring in 34.4% of patients having received at least two courses of ATZ. In the finish cohort of ATZ-treated patient, thyroid event occurred in 26.4% of cases and in the CARE-MS studies in 35.3% of cases [23, 24]. 7/11 cases occurred between years 2 and 4 of treatment (mean time to onset 30 months ± 20), in agreement with the peak of incidence described in the extension of the CARE-MS studies. Most patients presented Grave's disease (63.6%) a slightly higher proportion than reported by Dayan et al.

Infectious complications were rare, in line with the known safety profile of ATZ. The occurrence of a case of Listeria Monocytogenes septicemia shortly after the first ATZ course, prompted us to prescribe antibiotic prophylaxis for the next patients, in addition to the recommended dietary measures [25].

Two cases of neoplasia were diagnosed during follow-up (1 case of ductal carcinoma in situ and 1 case of basal cell carcinoma in a 48- and 53-year-old female respectively). The incidence of these cancer types has risen over the last decades due an increase in global population, aging and to more systematic breast or skin screening [26, 27]. No conclusion can, therefore, be inferred regarding an increased rate of cancer or a trend in the incidence of a particular cancer type in alemtuzumab-treated patients, nor from our small cohort (32 cases) and nor from the long-term follow-up of patients in the clinical trials.

Retrospective studies in a small cohort of patients face several limitations. Firstly, the small sample size reduces the statistical power and generalizability of the findings. The outcomes observed in a limited number of patients may not accurately represent the broader population. Secondly, the retrospective nature of the study can introduce bias and does not allow to establish causal relationships due to the absence of randomization and control group. Confounding variables and selection bias can further impact the internal validity of the study. Therefore, while retrospective studies can provide valuable insights, it is essential to interpret the findings cautiously and consider the limitations inherent in the design and sample size. Despite these limitations, the effectiveness and safety data provided in this study are in line with the known profile of ATZ.

In conclusion, we hereby provide, albeit in a small cohort, real-world long-term data regarding treatment trajectories in MS patients treated with ATZ, including the administration of a third treatment course (31.2%) or the switch to anti-CD20 therapy (34.4% of patients). Remarkably, 43.75% of patients received only 2 courses of ATZ and achieved long-term remission according to the components of NEDA-3. An additional 21.8% achieved remission with a third ATZ course. With a median follow-up of 67 months, most patients remain clinically stable or some experience sustained disability improvement, in line with long-term data from the MS-BASE registry demonstrating that treatment with ATZ or other high efficacy therapies reduces the risk of transition to secondary progressive MS [5]. In our cohort, retreatment was more frequent in younger patients or patients having failed a higher number of previous DMTs, highlighting the need to treat with high efficacy disease-modifying therapies very active inflammatory disease before failure of several lines of treatment in order to induce long-term remission and prevent disability progression.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Andreea Florea and Vincent van Pesch. The first draft of the manuscript was written by Andreea Florea and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon request. Data are located in controlled access data storage at the Cliniques Universitaires Saint-Luc.

Declarations

Conflict of interests Prof. van Pesch received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall, Novartis Pharma, and Alexion. Prof. El Sankari and Dr. Florea have no relevant financial or non-financial interests to disclose.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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