



Brief report

[Translated article] Alemtuzumab in relapsing–remitting multiple sclerosis in clinical practice: Annual NEDA-3 follow-up for up to 4 years



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A B S T R A C T

Objective: The effectiveness of alemtuzumab in patients with relapsing–remitting multiple sclerosis (RRMS) have been demonstrated in clinical trials. The primary endpoint was to describe the annual effectiveness of alemtuzumab over a 4-year period, according to the different parameters of the NEDA-3 concept (no evidence of disease activity) in clinical practice.

Methods: A retrospective, observational multicentric open study of patients with RRMS treated with alemtuzumab between 2015 and 2024. Effectiveness was assessed according to different parameters of the NEDA-3 concept (absence of relapses, stability in disability status according to the EDSS scale, and absence of new lesions and/or contrast enhancement in brain magnetic resonance imaging) with annual follow-up for up to four years.

Results: A cohort of 32 patients (71.9% women, mean age 40.3 ± 11 years) were included. The proportion of patients achieving NEDA-3 was 51.7% (15/29) in the first year, 56.2% (12/26) in the second year, 47.4% (9/19) in the third year, and 47.1% (8/17) in the fourth year. At the end of the study, 82% of patients remained relapse-free, 59% had stable disability according to the EDSS scale, and over 47% were free of radiological activity.

Conclusions: Alemtuzumab has proven to be effective, over 4 years, in clinical practice in patients with RRMS according to the different parameters of the NEDA-3 concept.

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Alemtuzumab en esclerosis múltiple remitente-recurrente en práctica clínica: seguimiento anual de NEDA-3 hasta 4 años

R E S U M E N

Objetivo: la eficacia y seguridad de alemtuzumab en pacientes con esclerosis múltiple remitente-recurrente (EMRR) ha sido demostrada en ensayos clínicos. El objetivo de este estudio es describir la efectividad de alemtuzumab de forma anual durante 4 años según los diferentes parámetros del concepto NEDA-3 (*No evidence of disease activity*) en vida real.

Método: estudio abierto, observacional, retrospectivo y multicéntrico de pacientes con EMRR que recibieron tratamiento con alemtuzumab entre 2015 y 2024. Se evaluó la efectividad según los diferentes parámetros del concepto NEDA-3 (ausencia de brotes, estabilidad en el estado de discapacidad según la escala EDSS y ausencia de lesiones nuevas y captación de contraste en las imágenes de la resonancia magnética) con un seguimiento anual de hasta 4 años.

Resultados: se incluyeron 32 pacientes (71,9% mujeres), con una edad media de $40,3 \pm 11$ años. El porcentaje de pacientes que alcanzó NEDA-3 fue del 51,7% (15 de 29) en el primer año; 46,2% (12 de 26) en el segundo; 47,4% (9 de 19) en el tercero y 47,1% (8 de 17) en el cuarto. Al finalizar el estudio, el 82% de los pacientes permanecían libres de brotes, el 59% presentaba una discapacidad estable y el 47% no mostraba actividad radiológica.

Palabras clave:

Alemtuzumab

Esclerosis múltiple

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Conclusiones: alemtuzumab ha demostrado ser efectivo, durante 4 años, en vida real en pacientes con EMRR según los diferentes parámetros del concepto NEDA-3.

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Introduction

Multiple sclerosis is an inflammatory, demyelinating immune-mediated disease that causes neurodegeneration of the central nervous system. The treatments available include alemtuzumab, a humanized IgG1 kappa monoclonal antibody that selectively targets the CD52 antigen.¹ In Spain, this antibody has been approved as a disease-modifying therapy for relapsing–remitting multiple sclerosis (RRMS) in adults with very active disease that meet the following criteria: (i) very active disease following completion of an adequate cycle with a disease-modifying therapy; and (ii) rapid progression to severe RRMS, defined as the occurrence of two or more disabling relapses in the last year, and the presence of one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI), or with a significant increase in T2 lesion load compared to a previous MRI study.

The concept of ‘no evidence of active disease’ (NEDA-3) emerged with the advent of natalizumab. NEDA-3 is a composite assessment based on three variables: no clinical relapses, no disability progression, and no new or enlarging lesions on brain MRI.¹ The efficacy and safety of alemtuzumab in RRMS have been largely demonstrated in clinical trials (CTs). However, gaining a deeper understanding of its long-term effects in clinical practice is essential. The purpose of this study was to determine the yearly real-world effectiveness of alemtuzumab in RRMS patients to a maximum follow-up of four years, according to the different NEDA-3 parameters.

Methods

An open, observational, retrospective, multicentric study involved patients who received alemtuzumab between 2015 and 2024. The sample consisted of adult patients with RRMS and full legal capacity to sign the informed consent form. Exclusion criteria were not established to ensure cohort representativity and assess treatment effectiveness in real-world clinical practice conditions. Hence, eligible cases were sequentially analyzed.

Demographic, clinical and radiological data were extracted from electronic medical records (IANUS[®]) and prescribing systems (SILICON[®] and PEA). The primary efficacy endpoint was NEDA-3, as assessed annually based on the number of patients who completed every year of treatment, for a maximum follow-up of four years. Relapse was defined as a new neurological manifestation lasting over a minimum of 24 h that could be related either to the appearance of one or more demyelinating lesions or to the exacerbation of existing symptoms that had remained stable or absent in the last month. Disability was assessed using the *Expanded Disability Status Scale* (EDSS). Stable brain MRI was established based on the absence of new or gadolinium-enhancing lesions on T2-weighted sequences. Prior to treatment initiation, the totality of patients underwent a clinical evaluation and MRI examination.

A regimen of alemtuzumab was administered intravenously, starting with an initial cycle of 12 mg/day for 5 consecutive days, followed by a second cycle (at 12 months) of 12 mg/day for three consecutive days. In case of persistent clinical activity, two additional three-day cycles could be administered 12 months after the last infusion. The premedication scheme included methylprednisolone (1000 mg at days 1–3 and 500 mg at days 4–5), antihistamines and paracetamol. In addition, patients received oral prophylaxis with acyclovir against the herpes virus (200 mg/BID) for 4 weeks.

The study was approved by the Research Ethics Committee of Galicia, Spain (code 2023/519), on 25/04/2024. This study was conducted in accordance with the principles of the Declaration of Helsinki and all applicable regulations on human rights and biomedicine. Compliance with the Spanish Organic Law 3/2018 on Data Protection was ensured to guarantee patient anonymity and confidentiality.

Descriptive statistics were applied to the totality of variables using the SPSS software package version 21. Qualitative variables were expressed in terms of absolute and relative frequencies. Parametric continuous variables were presented as mean \pm standard deviation, whereas non-parametric continuous variables were described as median and interquartile range.

Results

A total of 32 patients (71.9% women), with a mean age of 40.3 \pm 11 years, were included. Table 1 describes the baseline characteristics of the study population. Patients had experienced a mean of 1.25 \pm 0.67 relapses in the last year, had an EDSS of 3.34 \pm 1.59, and 96.9% exhibited over 30 lesions on MRI T2 sequences.

Alemtuzumab was the first-line treatment in three patients (9.4%) and second- or later-line treatment in 29 patients (90.6%). Patients had received a median of 2.1 (range 0–4) previous treatments, with natalizumab and fingolimod being the most common treatments (31.3%, respectively). The reasons for switching to alemtuzumab included therapeutic failure of previous treatment (78.1%); risk of progressive multifocal leukoencephalopathy (9.4%); and adverse events caused by the previous treatment (3.1%).

Overall, 29 patients completed the first year of follow-up, 26 the second, 19 the third, and 17 completed the fourth year. Drop-outs were attributable to a death, three toxicity-related treatment discontinuations, and insufficient follow-up in 11 patients. Administering a third cycle of alemtuzumab was necessary in 15.6% of patients.

Fig. 1 details the patients who achieved NEDA-3 status, amounting to a total of eight patients (47.1%) after the fourth year of follow-up. Table 2 describes changes in NEDA-3 variables. During the first year of

Table 1
Characteristics of patients prior to initiation of alemtuzumab.

Baseline Characteristics	Value
Age at initiation of alemtuzumab (years) mean \pm SD	40.3 \pm 11.0
Women, n (%)	23 (71.9)
Time from diagnosis to initiation of alemtuzumab (years) mean \pm SD	12.3 \pm 7.9
EDSS (Mean \pm SD)	3.34 \pm 1.59
Number of relapses the previous year (Mean \pm SD)	1.25 \pm 0.67
Previous treatments, n (%)	
None (naïve)	3 (9.4)
Natalizumab	10 (31.3)
Fingolimod	10 (31.3)
Cladribine	3 (9.4)
Dimethyl fumarate	3 (9.4)
Glatiramer	1 (3.1)
Ocrelizumab	1 (3.1)
Teriflunomide	1 (3.1)
Number of previous lines (median, IQR)	2.1 (0–4)
Gd-enhancing lesions, n (%)	15 (46.9)
Lesions on T2, n (%):	
0–30	1 (3.1)
>30	31 (96.9)

SD: Standard Deviation; EDSS: Expanded Disability Status Scale; Gd: gadolinium.

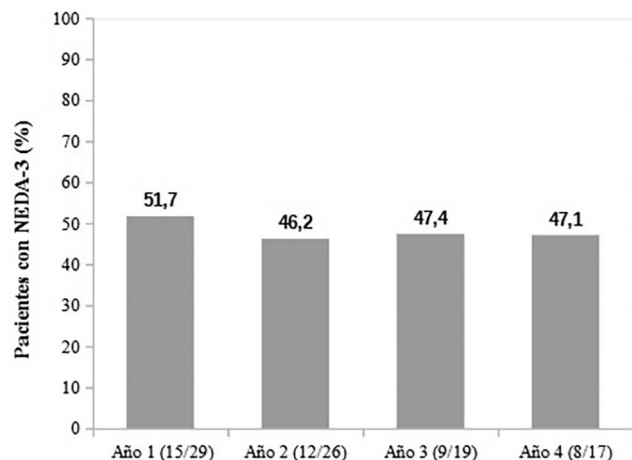


Figure 1. Annual percentage of patients achieving NEDA-3 (No evidence of disease activity). The number of patients that fulfilled the NEDA-3 criteria over the total of evaluable patients per year is shown between brackets.

treatment, 90% of patients did not experience any relapse; 100% remained stable or their disability improved, and 83% exhibited a non-active disease on MRI examination. After the fourth year, 82% remained relapse-free; 59% had a stable EDSS, and 47% exhibited no MRI activity.

Discussion

A study was conducted to assess the effectiveness of alemtuzumab in 32 patients with RRMS based on the clinical and radiological NEDA-3 criteria, which were fulfilled by 47.1% (8/17) of patients. There are previous studies in the literature involving a maximum of three years of follow-up and more than 200 patients.^{2–5} This study presents the limitations inherent to retrospective studies, added to a small sample size. However, the cohort is relevant to our national context, being comparable to that of other case series reported in Spain, such as that of Hospital of Cabueñes, Gijón ($n = 23$),⁶ and a multicentric case series study carried out in five hospitals in Madrid ($n = 115$).⁷ Additionally, data are available from two five-year extension clinical trials.^{8,9}

In relation to the baseline characteristics of the sample, our patients were older age (40.3 years) than participants in the CARE-MS I-II clinical trials (33–34.8 years),^{10,11} albeit comparable to reported in a clinical practice study (38 years).⁶ The estimated disease duration in our study (12.3 years) is comparable to that reported in other case series.⁴ The percentage of female patients was higher in our study (71.9%) than in the clinical trials (64–65%), but similar to other real-world studies (71–82%).^{3–7} The main reason for starting alemtuzumab therapy was failure of previous treatment, with a median of two previous treatments, being natalizumab and fingolimod being the most common therapies. It is worth noting that the patients in the clinical trials were treatment-naïve or had been unresponsive to first-line treatment with interferon beta-1a or glatiramer acetate.^{10–12}

A progressive loss of follow-up was observed, with the sample having decreased virtually by a half ($n = 17$) at year 4 with respect to the

initial sample, which may constitute a selection bias. However, the decrease in sample size was mainly due to inadequate follow-up duration to allow full assessment of treatment response ($n = 11$), rather than to treatment failure ($n = 2$) or toxicity ($n = 1$, severe infusion reaction). A patient died from urinary tract sepsis.

After a four-year follow-up, 47.1% achieved NEDA-3 status, exceeding 29.2% (14/48) reported in a two-center study conducted in Slovenia and Croatia, but falling behind 75% (6/8) documented by a Spanish five-year case series study.^{7,13} MRI activity was the main factor that hindered NEDA-3 fulfillment, albeit a high proportion of patients exhibited no clinical symptoms despite evidence of radiological activity.

In our study, improved results were obtained in terms of relapse control, as compared to pivotal trials. Overall, 77% (292/376) and 78% (86/112) of patients remained relapse-free in the CAMMS223 and CARE-MS I study at 3 and 2 years, respectively. However, this cohort consisted of treatment-naïve patients.^{10,12} It is noteworthy that, among patients previously treated with interferon beta-1a or glatiramer acetate, relapse control decreased to 65% (278/426).¹¹ In our study, despite the fact that nearly all patients had received previous high-efficacy therapies, the proportion of patients who remained relapse-free at the end of each year exceeded 80%. Therefore, it is reasonable to infer that the clinical impact of the treatment may be even greater. Similar data were obtained in CARE-MS I and II at 5-year follow-up, with 85% (276/325) and 88% (281/319) of patients having not experienced relapse, respectively.^{8,9} However, in the 13-year follow-up TOPAZ study, the percentage of patients free of relapse decreased to 43.5%.¹⁴ Similar data were obtained in another Spanish real-world study, where 86.8% [33/38] of patients remained free of relapse at 4 years.⁷ In a Danish study, 74% (155/209) and 75% (157/209) of patients remained relapse-free the first and second year, respectively,² with comparable results documented in two Italian studies.^{3,5} Another Italian case series study reported an even higher efficacy in relapse control (90.5% - 32/35) at 36 months.¹⁵

In our study, sustained disability stability was achieved in a smaller proportion of patients (59% at 4 years), as compared to the 5-year extension studies, in which prevention of disability progression was reported in 76.6% (245/325) and 82.2% (263/320) of patients, respectively.^{8,9} These findings are consistent with those reported in other clinical practice studies, where EDSS remained stable in 81–85% of patients at 2–3 years of follow-up.^{2–5}

In our study, 47% of patients exhibited stable MRI at 4 years, which falls behind 68% (221/325) and 70% (223/319) reported in the 5-year CARE-MS I and II extension studies, respectively.^{8,9} Additionally, our rates were also lower than those reported in other 3–5-year case series, being 70% (7/10) and 85.7% (30/35), respectively.^{7,15} Our results are comparable to those of an Italian study involving 90 patients, of whom almost half developed new lesions between the first and second cycle of alemtuzumab.³ Nevertheless, it is worth noting that almost the totality of patients in the Italian study had very active disease and had received a previous natalizumab scheme.⁵

In conclusion, alemtuzumab has been demonstrated to be effective in fulfilling the NEDA-3 goal for four years.

Contribution to the scientific literature

The concept of ‘no evidence of active disease’ (NEDA-3) emerged with the advent of natalizumab (no relapse, no brain MR activity, no progression of disability). This ambitious therapeutic goal has been used for the last decade in a variety of clinical trials as a measure to assess the efficacy of study treatments. The present study provides real-world evidence of the efficacy of alemtuzumab for disease control as a function of the three NEDA-3 variables.

Clinical practice findings contribute to a better understanding of the real-life effects of a medication, far from the optimal conditions of clinical trials. The results of this series provide long-term data, as it is a four-year clinical trial. These findings offer another decision-making support

Table 2
Changes in NEDA-3 variables over time.

NEDA-3 parameters	Year 1 ($n = 29$)	Year 2 ($n = 26$)	Year 3 ($n = 19$)	Year 4 ($n = 17$)
Number of relapses, n (%)	26/29 (90)	20/26 (77)	15/19 (79)	14/17 (82)
Stable EDSS, n (%)	29/29 (100)	16/26 (61.5)	14/19 (74)	10/17 (59)
Stable MRI, n (%)	24/29 (83)	12/26 (46)	9/19 (47)	8/17 (47)

EDSS: Expanded Disability Disease Scale; NEDA-3: no evidence of disease activity; MRI: magnetic resonance imaging.

tool that may guide the development of therapeutic algorithms or approaches. Further and larger studies are needed to confirm the results obtained in this study.

CRedit authorship contribution statement

Leticia Herrero-Poch: Writing – original draft, Data curation. **Maria Susana Fortes-González:** Writing – original draft, Conceptualization. **Antonio Pato-Pato:** Data curation, Conceptualization. **Pablo Gaveiras-Araújo:** Data curation, Conceptualization. **Martín Lorenzo-García:** Supervision, Formal analysis. **Daniel Apolinar García-Estévez:** Supervision, Formal analysis. **Jose Ramón Lorenzo-González:** Supervision, Formal analysis.

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Conflict of interest

The authors declare no conflict of interest.

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