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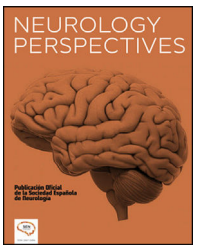

ORIGINAL ARTICLE

Retrospective, multi-centre, open-label study on the use of alemtuzumab for relapsing–remitting multiple sclerosis in clinical practice: A 4-year follow-up

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KEYWORDS
Alemtuzumab;
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Abstract
Introduction: The efficacy and safety of alemtuzumab for patients with relapsing–remitting multiple sclerosis (RRMS) have been demonstrated in clinical trials. However, due to the limitations of these studies, it is important to assess the effects of the drug in clinical practice. The purpose of this study is to describe the effectiveness of alemtuzumab in terms of the number of relapses per year in patients with RRMS in the clinical setting. As secondary objectives, we evaluated its impact on disability and neuroimaging findings, as well as its tolerability and safety following administration.
Methods: We conducted a retrospective, multi-centre, open-label study by reviewing the clinical records of patients receiving alemtuzumab for RRMS treatment.
Results: A total of 32 patients were included at the beginning of the 4-year follow-up period. The mean number of relapses per year remained below 0.35 during follow-up, compared to 1.25 per year before treatment. Disability, as measured with the Expanded Disability Status Scale, improved during the first 2 years, and remained stable thereafter. Neuroimaging revealed a decrease in disease activity. The most frequent adverse effects were infusion-related reactions and infections.
Conclusions: Alemtuzumab has been shown to be effective in clinical practice in reducing the number of relapses per year, improving disability and decreasing disease activity on brain MRI in patients with MS, with adequate tolerability and safety. However, prevention and monitoring strategies continue to be necessary.

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PALABRAS CLAVE
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Estudio abierto retrospectivo multicéntrico sobre la utilización de alemtuzumab en esclerosis múltiple remitente-recurrente en práctica clínica habitual. Seguimiento durante 4 años

Resumen
Introducción: La eficacia y seguridad de Alemtuzumab en pacientes con esclerosis múltiple remitente-recurrente (EMRR) ha sido demostrada en ensayos clínicos. Sin embargo, por las limitaciones de éstos, es importante comprobar cómo se comporta en condiciones de práctica clínica habitual. Nuestro objetivo es describir la efectividad de alemtuzumab medida en número de brotes anuales en práctica clínica en pacientes con EMRR. Como objetivos secundarios valoramos la efectividad en estado de discapacidad y pruebas de neuroimagen, así como la tolerabilidad y seguridad tras su administración.
Método: Hemos realizado un estudio abierto retrospectivo multicéntrico para el cual se han revisado las historias clínicas de pacientes que han recibido tratamiento con alemtuzumab por EMRR.
Resultados: Se incluyeron un total de 32 pacientes al comienzo de los 4 años de seguimiento. La media de brotes anuales se mantuvo por debajo de 0.35 frente a los 1.25 brotes por año antes del tratamiento. La discapacidad medida por la escala EDSS mejoró durante el primer y segundo año, manteniéndose estable posteriormente. Se observó un descenso en la actividad de la enfermedad por pruebas de neuroimagen. Los efectos adversos más frecuentes fueron las reacciones de perfusión y las infecciones.
Conclusiones: Alemtuzumab ha demostrado ser efectivo en práctica clínica en pacientes con esclerosis múltiple en la reducción del número de brotes anuales, la mejora del grado de discapacidad, y la disminución de la actividad en resonancia magnética craneal, con un adecuado perfil de tolerabilidad y seguridad, necesitando medidas de prevención y control.

Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that causes central nervous system demyelination and neurodegeneration. Among the available treatment options, alemtuzumab is a humanised monoclonal IgG1 kappa antibody against the CD52 antigen.[1] The efficacy and safety of alemtuzumab for patients with relapsing–remitting multiple sclerosis (RRMS) have been demonstrated in clinical trials. However, due to the limitations of these studies, it is important to analyse the long-term effects of the drug in clinical practice. The purpose of this study is to describe the effectiveness and safety of alemtuzumab for the treatment of MS in routine clinical practice.

Patients and methods

We conducted a retrospective, multi-centre, open-label study at Hospital Universitario de Ourense and Hospital Ribera Povisa in Galicia, Spain. We reviewed the clinical records of patients treated with alemtuzumab for RRMS. No specific inclusion criteria were established. All included patients had received alemtuzumab at the discretion of the treating neurologist, in line with the indications specified in the drug's summary of product characteristics. In Spain, alemtuzumab is indicated as a disease-modifying treatment for adults with highly active disease who belong to one of the following 2 patient groups[2]: *1)* patients presenting highly active disease despite having received a full and adequate course of at least one disease-modifying treatment; or *2)* patients rapidly progressing to severe RRMS, defined as having 2 or more disabling relapses within a year, as well as one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a recent MRI study.

Alemtuzumab was administered via intravenous infusion, with an initial course of 12 mg/day for 5 consecutive days, followed by a second course, 12 months later, of 12 mg/day for 3 consecutive days. Each day, prior to infusion, patients received methylprednisolone (1000 mg/day on days 1–3, and 500 mg/day on days 4–5), antihistamines, and paracetamol. All patients received oral prophylaxis for herpes virus with aciclovir (200 mg every 12 h) for 4 weeks. Additional 3-day courses of alemtuzumab were administered when deemed necessary due to persistent clinical activity.

All patients underwent clinical assessment, brain MRI, and blood analysis before starting treatment. Participants were required to be at least 18 years old and to have legal capacity, and they all gave written informed consent to the use of their clinical data. We designed a database to collect demographic, clinical, and radiological data during the baseline visit. During annual follow-up visits, data were gathered on relapses, disability as measured with the Expanded Disability Status Scale (EDSS), and number of new gadolinium-enhancing lesions on brain MRI. Lymphocyte

count was monitored every 3 months. Data were also gathered on adverse reactions, distinguishing between reactions occurring during infusion and those occurring over the year following administration, on a yearly basis.

We performed a descriptive analysis of all variables. To compare 2 paired quantitative samples, we used the *t* test for normally distributed data or the non-parametric Wilcoxon signed-rank test for paired data. Statistical analysis of variables was performed using the SPSS software, version 21. The level of statistical significance was set at $P < .05$.

Results

We included 32 patients, 71.9% of whom were women. The first patient was treated in 2015. Mean age (standard deviation) at treatment onset was 40.3 (11.0) years (range, 24–71), and mean disease duration was 12.3 (7.9) years. The main reason for starting alemtuzumab was failure of previous treatments, in 78.1% of patients. The mean number of treatments used before alemtuzumab was 2.1 (range, 0–4), with natalizumab and fingolimod being the most frequent (31.3% each). Alemtuzumab was the first-line treatment in 3 patients (9.4%). In the remaining patients, the reason for switching treatment was an increased risk of progressive multifocal leukoencephalopathy (9.4%) and adverse reactions to the previous treatment (one patient). Five patients (15.6%) received a third course of alemtuzumab, 36–48 months after the first infusion.

Mean EDSS score at baseline was 3.34 (1.59). In the year prior to alemtuzumab onset, our sample had presented a mean of 1.25 (0.67) relapses. A total of 31 patients (96.9%) presented over 30 lesions on T2 MRI sequences, and 15 patients (46.9%) presented gadolinium-enhancing lesions. Mean baseline lymphocyte count was 2135 (1319) cells/μL. A total of 29 patients completed the first year of treatment, 26 completed the second year, 19 completed the third year, and 17 completed the fourth year of follow-up; these patients were therefore included in the statistical analysis.

Alemtuzumab decreased the mean number of relapses per year to 0.23 (0.58; $P < .05$), 0.33 (0.93; P 0.05), 0.18 (0.39; $P < .05$), and 0.20 (0.56; $P < .05$) after the first, second, third, and fourth year of treatment (Fig. 1). Disability as measured with the EDSS improved during the first year (2.6 [1.5]; $P < .05$) and the second year (2.5 [1.5]; $P < .05$), remaining stable during the third and fourth years (2.6 [1.4]; $P > .05$ in both cases) (Fig. 2). Regarding MRI findings, 5 patients (17.2%) presented new T2 lesions during the first year, with a mean of 2 lesions (range, 1–4), while only 2 patients (6.9%) presented gadolinium-enhancing lesions. During the second year, 7 patients (26.9%) presented one new T2 lesion, with no gadolinium-enhancing lesions observed in any patient. During the third year, 3 patients (15.78%) presented new T2 lesions (range, 1–6), and one patient presented gadolinium-enhancing lesions. During the fourth year, 3 patients (17.6%) presented new T2 lesions (range, 1–3), while no patients developed gadolinium-enhancing lesions (Table 1).

A total of 25 patients (78.81%) presented infusion-related reactions during the first course of alemtuzumab, with erythema being the most frequent (59.4%), followed by fever and rash (18.8% each) and pruritus (9.4%). Only one patient (3.1%) experienced a severe reaction, consisting of disseminated erythema, which developed on the third day of administration, requiring treatment discontinuation and hospitalisation for 10 days. During the second course, infusion-related reactions were observed in 53.84% of the total sample (n = 16); the most frequent was rash (23.07%), followed by erythema (19.23%), fever (19.23%), headache (11.53%), and pruritus (11.53%). No severe adverse reactions were reported. Among the 4 patients (16.6%) completing the

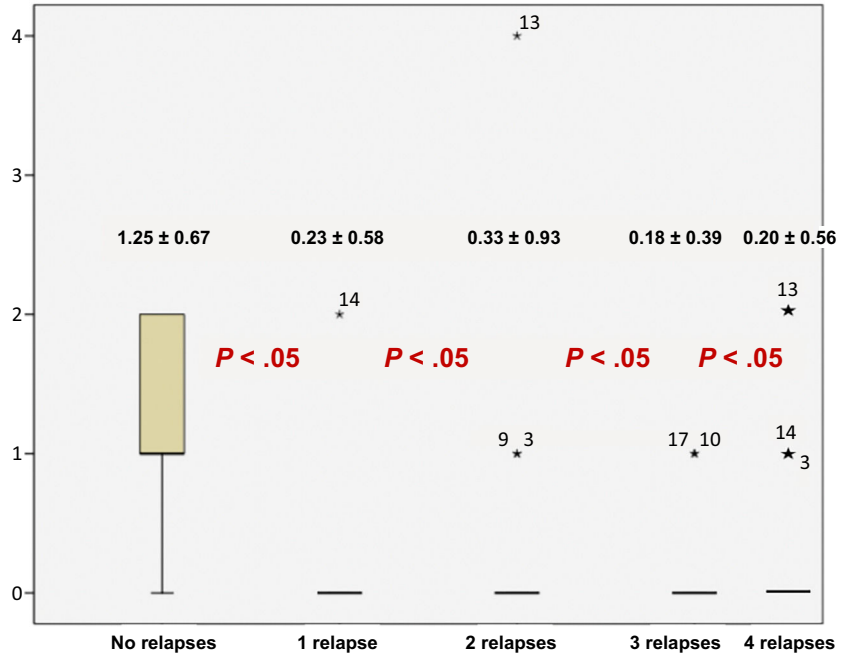

Figure 1 Annualised relapse rate during follow-up in a cohort of patients treated with alemtuzumab.

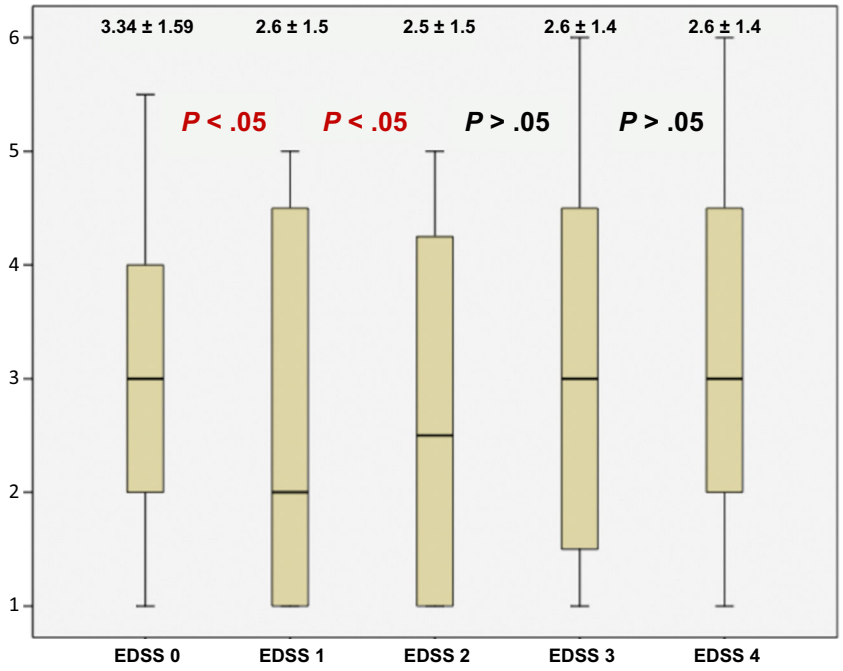

Figure 2 Annual Expanded Disability Status Scale scores during follow-up in a cohort of patients treated with alemtuzumab.

third course of alemtuzumab during the third year of follow-up, only one presented an infusion-related reaction, which was very mild. The remaining patient who received a third course, during the fourth year of follow-up, had been asymptomatic for 3 years, and did not present any infusion-related reactions.

During the first treatment course, the most frequent adverse reaction was urinary tract infection, in 3 patients (9.3%). Two patients (6.2%) presented elevated blood pressure and one patient (3.1%) presented a seizure in the context of urinary tract infection. Over the following 12 months, 17 patients (53.1%) developed adverse reactions, most commonly urinary tract infections (7 patients; 21.9%) and herpes zoster (3 patients; 9.3%). Only one patient (3.1%) experienced a severe adverse reaction (pulmonary embolism). During the second treatment course, only one patient (3.8%) experienced an adverse reaction, consisting of asymptomatic elevation of transaminase levels (AST: 307; ALT: 768; GGT: 37). During follow-up, 2 patients (8.3%) presented urinary tract infection, and another 2 patients (8.3%) presented worsening of spasticity. Two cases were considered severe: one patient presented an epileptic seizure and the other experienced worsening of spasticity requiring hospital admission. No adverse reactions were reported during the third treatment course, completed by 5 patients. During follow-up, the most frequent adverse reactions were thyroid disorders, occurring in 7 patients (36.8%): 4 patients (21%) presented thyroiditis, with one requiring radioactive iodine therapy, and the remaining 3 (15.7%) presented hypothyroidism. Additionally, 2 patients experienced severe adverse reactions: one died from urosepsis and the other developed prostate cancer. During the fourth year of follow-up, hypothyroidism was the most frequent complication (2 patients; 6.8%). Two patients presented severe adverse reactions: herpes zoster ophthalmicus in one and deep vein thrombosis with pulmonary embolism in the other.

Severe lymphocytopenia (< 200 lymphocytes/μL) was detected in 8 patients (25%) during the first month after the initial course of alemtuzumab, in 4 (15.3%) during the first month after the second course, and in one patient (5.2%) during the first month after the third course. No cases of severe lymphocytopenia were observed during the remaining follow-up period.

Discussion

This retrospective, multi-centre, real-world study analyses clinical outcomes and adverse reactions to alemtuzumab for

Table 1 Annual brain MRI study: number of patients with new lesions, number of new lesions per patient, and number of patients with gadolinium-enhancing lesions.

Year	1	2	3	4
MRI	n = 29	n = 16	n = 12	n = 11
New lesions	5 patients (17.2%)	7 patients (43.8%)	3 (35%)	3 (27.2%)
No. lesions	1–4	1	1–6	1–3
GD+ lesions	2 patients	0	1 patient	0

RRMS. We included 32 patients treated at 2 centres. Several open-label studies with up to 5 years of follow-up have been published, with some including over 200 patients.[3–6] In Spain, a study conducted at Hospital de Cabueñes in Gijón included 23 patients.[7] Furthermore, data are available from extension studies.[8,9] We believe that our results are representative of routine clinical practice, as we included patients from 2 general hospitals with a variety of previous treatments and follow-up periods of up to 4 years.

In our sample, the mean age at onset of alemtuzumab treatment was 40.3 years, with a mean disease duration of 12.3 years. Therefore, our patients were older than those included in the CARE-MS I (33 years) and CARE-MS II trials (34.8 years), but had a similar age to those included in other real-world studies, which typically report a mean age of approximately 38 years.[6,7,10–13] Likewise, mean disease duration in our sample is similar to those reported in the literature, at around 11 years.[3] The high percentage of women (71.9%) in our sample stands in contrast with those observed in clinical trials (64%–65%), but is in line with other real-world studies (74%–82%).[4–7] The main reason for starting alemtuzumab was treatment failure, with a mean of 2.1 previous treatments, most frequently natalizumab and fingolimod. However, the efficacy of alemtuzumab in MS is based on evidence from 3 multi-centre, randomised clinical trials in which interferon beta 1a was used as an active control.[10–12] The phase III CARE-MS II trial[12] included patients previously treated with interferon beta or glatiramer acetate who had shown inadequate response. Regarding effectiveness, our results are consistent with those reported in clinical trials. The phase II trial demonstrated a 74% decrease in the annualised relapse rate (ARR), which remained at 0.18 and 0.26 after 2 years of follow-up in the CARE-MS I and CARE-MS II trials, respectively.[10–12] To understand the effects of alemtuzumab in our study, it should be noted that both interferon beta and glatiramer acetate have shown considerable efficacy against placebo in the treatment of MS, and are considered first-line treatments, whereas the most frequently used drugs in our sample are considered second-line therapies, with higher efficacy but also greater risk of adverse reactions.[13] Compared to open-label studies, the ARR in our study was also very similar, with a decrease in the total number of relapses of up to 96%.[3,4,6,14] Notably, in the study conducted in Gijón, no relapses were observed during the first 6 months; the first relapse occurred 8 months after the first course, with 13% of patients subsequently presenting relapses after the second course of alemtuzumab.[7] Finally, extension studies have observed significant decreases in the ARR, with a mean of 0.16 relapses per year after 13 years of follow-up.[15,16]

On the other hand, compared to clinical trials[10,11] where all included patients were treatment-naïve, only 3 patients in our sample (9.4%) started alemtuzumab as a first-line therapy, a rate similar to that reported in the Danish MS registry.[3] Furthermore, nearly 10% of patients started alemtuzumab as an alternative to natalizumab due to the risk of progressive multifocal leukoencephalopathy. This indication is not considered in clinical trials but constitutes a common alternative in real practice. Five patients (15.6%) completed a third course of alemtuzumab between 36 and 48 weeks after the first infusion. This rate is higher than those reported in other studies with shorter follow-up periods, where only 8% of patients require additional treatment courses.[4,6] However, in extension studies of up to 12 years, between 42% and 65% of patients received more than 2 courses.[8,9,15,17,18] Some evidence suggests that presenting more than one relapse in the year prior to alemtuzumab initiation doubles the likelihood of requiring additional treatment courses.[19]

Regarding disability as measured with the EDSS, the mean baseline score in our sample was 3.34 (1.59), considerably higher than those reported in clinical trials, at a mean of 2.[10,11] Furthermore, our results confirm the decrease in disability scores observed in extension studies with follow-up periods of 2–11 years,[8,9,12,20] as well as in other open-label studies,[3,4,7,14,15,19,22–24] which report stability or improvement of disability in 47%–60% of patients.

Our neuroimaging findings are superior to those reported in the phase III trials in terms of the frequency of new T2 lesions and the number of gadolinium-enhancing lesions,[11,12] and are in line with findings from extension studies, with up to 69% of patients presenting no radiological activity.[19,25,26] These favourable differences may be attributed to the real-world nature of our study, where radiological follow-up studies were not protocolised for all patients, but rather were performed at the discretion of the treating physician. In other open-label studies[4,6,14,21] with follow-up periods between 2 and 3 years, only 21% of patients presented new T2 or gadolinium-enhancing lesions.

Infusion-related reactions constitute the most frequent adverse reaction to alemtuzumab.[27] In our study, their frequency decreased during the first, second, and third courses of treatment, as has been observed by the European Medicines Agency.[2] Erythema, rash, fever, and pruritus were the most frequent adverse reactions after each treatment course, and were mild or moderate in all cases. However, to prevent these reactions, paracetamol, corticosteroids, and antihistamines may be administered over the course of treatment. Furthermore, physicians administering alemtuzumab should remain vigilant for these reactions.[2] All patients gave written informed consent for use of the drug and were aware of said risk. Compared with our cohort, infusion-related reactions were more frequent in the phase III clinical trials, occurring in up to 90.1% of patients.[28] These differences may be explained by the stricter monitoring in clinical trials. In other open-label studies, infusion-related reactions have been reported with variable frequency, typically of mild-to-moderate intensity, and mainly occurring during the first course.[4,6,7,14] Only one patient (3.1%) in our study developed a severe infusion-related reaction, presenting with a disseminated erythematous reaction, occurring during the first treatment course and requiring hospitalisation and discontinuation of the drug. In the CARE-MS trials, severe infusion-related reactions were reported in up to 3.1% of the patients. In a study conducted in Italy,[24] one patient presented severe rash and pruritus requiring several doses of corticosteroids and antihistamines, resembling the case reported in our study. Finally, in a study conducted in the United States, 2 patients required hospitalisation due to cytokine release syndrome.[21]

In our sample, infections constituted the most frequent adverse event, mainly urinary tract infection and herpes virus infection, which rarely present associated

complications. Similarly, most of the infections reported in clinical trials were mild to moderate, affecting 67%–77% of patients; although this frequency is much higher than in our study, it decreased over time.[15] In other open-label studies, the frequency of infections was similar to that observed in our cohort.[5–7,21] Regarding herpes zoster, the summary of product characteristics recommends prophylactic aciclovir for one month following administration of alemtuzumab to reduce the risk.[2] Notably, none of our patients developed *Listeria* meningitis, one of the most severe adverse reactions described in the literature.[29]

Autoimmune disorders, particularly autoimmune thyroid disorders, may also appear following treatment with alemtuzumab.[6,11,12] Their incidence peaks at 24–36 months after treatment initiation in 11%–33% of patients[3,4,7–9] [3,4,7–9,21,24,30]; this rate is consistent with our findings. In the TOPAZ extension study, with up to 9 years of follow-up, 46.3% of patients presented thyroid disorders, with 6.4% being classified as severe.[16] Most cases are linked to Graves disease (71.6%), with up to 16.4% of patients presenting a fluctuating course, transitioning from hypothyroidism to hyperthyroidism or vice versa.[31] Thyroid function should therefore be monitored every 3 months, for up to 5 years post-treatment.[2,32] Interestingly, autoimmune thyroid disorders have not been observed in patients treated with alemtuzumab for chronic B-cell leukaemia, suggesting that this phenomenon is associated with MS.[33] On the other hand, none of our patients presented other autoimmune adverse reactions described in clinical trials or open-label studies.[4,10–12,16,24,34]

Regarding the risk of neoplasia, only one case of prostate cancer was reported in our cohort. Although several types of cancer have been reported in clinical trials, no significant differences were observed between patients receiving and not receiving alemtuzumab.[11,12]

Finally, other rare but severe adverse events were reported during the pharmacovigilance period, leading to the reassessment of marketing authorisation for alemtuzumab in 2019. These include cardiovascular events, autoimmune disorders, or liver injury, none of which were observed in our sample. Although one patient presented transient elevation of transaminase levels during the first treatment course, this may have been due to the concurrent use of antibiotics for urinary tract infection and paracetamol for fever, rather than representing an autoimmune drug reaction. Furthermore, a systematic review of liver injury secondary to alemtuzumab found insufficient evidence to support a causal association.[27,35–39] Lastly, the cases of pulmonary embolism and deep vein thrombosis observed in our sample are more probably associated with immobility, given these patients' severe disability, rather than with the use of alemtuzumab.

Regarding lymphocyte counts at one month of treatment, the CARE-MS I and CARE-MS II trials reported a rapid, marked decrease in CD4+ T cell counts in 95.3% of patients, as well as CD8+ T cell depletion in 85.4% and 83.7% of patients, respectively.[40] Furthermore, after one year of treatment, lymphocyte count remained low in 46%–70% of patients, with reconstitution (ie, lymphocyte counts >400 cells/μL) occurring at approximately 35 months.[41]

In conclusion, alemtuzumab has been demonstrated to be effective in reducing the ARR, controlling disability progression as measured with the EDSS, and stabilising disease progression on neuroimaging. It also presents a good safety profile and is supported by an effective protocol for detecting and managing adverse reactions.

Ethical considerations

The study was approved by the drug research ethics committee of the region of Galicia (CEIm-G).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2025.100192.

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