Neurología 39 (2024) 383—391

NEUROLOGÍA

www.elsevier.es/neurologia

ORIGINAL ARTICLE

Early beginning of alemtuzumab: Changing the multiple sclerosis treatment paradigm. Interim analysis of the LEMVIDA study

J.E. Meca-Lallana[a,b,*], J.C. Álvarez-Cermeño[c], B. Casanova Estruch[d], G. Izquierdo Ayuso[e], R. Ortiz Castillo[f], A. Rodríguez-Antigüedad[g], C. Calles Hernández[h], en nombre del Grupo de Estudio LEMVIDA

[a] *CSUR Esclerosis Múltiple, Hospital Virgen de la Arrixaca (IMIB-Arrixaca), Murcia, Spain*
[b] *Cátedra de Neuroinmunología Clínica y Esclerosis Múltiple, UCAM-Universidad Católica San Antonio de Murcia, Murcia, Spain*
[c] *Unidad de Esclerosis Múltiple. Instituto de Investigación Ramón y Cajal, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[d] *Unidad de Neuroinmunología Clínica, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[e] *Unidad de Investigación y Tratamiento de la Esclerosis Múltiple, Hospital Vithas Nisa, Sevilla, Spain*
[f] *Unidad de Esclerosis Múltiple, Sanofi, Madrid, Spain*
[g] *Servicio de Neurología, Hospital Universitario Cruces-Osakidetza, Bizkaia, Spain*
[h] *Unidad de Esclerosis Múltiple. Hospital Universitario Son Espases, Palma de Mallorca, Spain*

Received 18 May 2021; accepted 27 June 2021
Available online 26 April 2023

KEYWORDS
Alemtuzumab;
Observational study;
Multiple sclerosis

Abstract
Introduction: LEMVIDA is a real-world prospective study of 3-year follow-up on quality of life of patients with multiple sclerosis (MS) receiving alemtuzumab in Spain.
Methods: This is an interim analysis evaluating the baseline characteristics of patients who started alemtuzumab between October 2016-September 2018. For 3 additional subanalysis patients were categorised by baseline EDSS score; time of alemtuzumab initiation during the recruitment period (cohort 1: October 2016-March 2017, cohort 2: April-September 2017, cohort 3: October 2017-March 2018 and cohort 4: April-September 2018); and the presence of highly active MS criteria.
Results: 161 patients were analysed: 67.1% female, age 38.7 ± 9.4 years, MS duration 8.5 ± 6.0 years, EDSS 3.3 ± 1.7 and number of relapses in the previous 2 years 1.8 ± 1.3. 48.3% of patients presented gadolinium-enhanced (Gd+) lesions (mean: 5.2 ± 6.9) and 63.1% had received prior treatment with fingolimod or natalizumab. Baseline EDSS scores and number of Gd+ lesions were higher in cohort 1 than in cohort 4 (4.1 ± 1.8 vs 3.2 ± 1.7; P = .040 and 10.9 ± 11.9 vs 4.5 ± 5.7; P = .020). The frequency of prior treatment with fingolimod and natalizumab was lower in cohort 4 (60.6%) than in cohort 1 (70.6%) (comparison between groups not analysed).

DOI of refers to article: https://doi.org/10.1016/j.nrl.2021.06.007.
* Corresponding author.
E-mail addresses: pmecal@gmail.com, jmeca@ucam.edu, josee.meca@carm.es (J.E. Meca-Lallana).

https://doi.org/10.1016/j.nrleng.2021.06.006

Conclusions: Unlike phase 3 studies of alemtuzumab, the patients included in LEMVIDA are older, have a longer duration of MS, higher disability and have received previous immunosuppressants. However, throughout the recruitment period, there is a tendency towards an early beginning of treatment with alemtuzumab, probably due to the evidence of higher effectiveness in the early stages of MS.

PALABRAS CLAVE
Alemtuzumab;
Estudio observacional;
Esclerosis múltiple

Inicio temprano de alemtuzumab: cambio en el paradigma de tratamiento en esclerosis múltiple. Análisis intermedio del estudio LEMVIDA

Resumen
Introducción: LEMVIDA es un estudio de práctica clínica, prospectivo de 3 años de seguimiento sobre calidad de vida en pacientes con esclerosis múltiple (EM) tratados con alemtuzumab en España.
Métodos: Análisis intermedio de las características basales de los pacientes que iniciaron alemtuzumab entre octubre de 2016 y septiembre de 2018. Se realizaron tres subanálisis en función de: puntuación EDSS basal; periodo de inicio de alemtuzumab durante el reclutamiento (cohorte1: octubre de 2016 a marzo de 2017, cohorte 2: abril a septiembre de 2017; cohorte 3: octubre de 2017 a marzo de 2018, y cohorte 4: abril a septiembre de 2018); y criterios de EM muy activa.
Resultados: Se analizaron 161 pacientes: 67,1% mujeres, edad 38,7 ± 9,4 años, duración de la EM 8,5 ± 6,0 años, EDSS 3,3 ± 1,7 y número de brotes en los 2 años previos 1,8 ± 1,3. El 48,3% presentaba lesiones realzadas con gadolinio (Gd+) (media: 5,2 ± 6,9) y el 63,1% había recibido tratamiento previo con fingolimod o natalizumab. En el momento basal, la puntuación EDSS y el número de lesiones Gd + fue significativamente superior en la cohorte 1 que en la cohorte 4 (4,1 ± 1,8 vs 3,2 ± 1,7; p = 0,040 y 10,9 ± 11,9 vs 4,5 ± 5,7; p = 0,020). La frecuencia de tratamiento previo con fingolimod y natalizumab fue menor en la cohorte 4 (60,6%) que en la cohorte 1 (70,6%), (comparación entre grupos no analizada).
Conclusiones: A diferencia de los estudios fase 3 de alemtuzumab, los pacientes incluidos en LEMVIDA tienen mayor edad, duración de la EM y discapacidad, y han recibido inmunosupresores previos. Sin embargo, a lo largo del reclutamiento se tiende a adelantar el inicio de alemtuzumab, probablemente debido a la evidencia de una mayor efectividad en etapas tempranas.

Introduction

Alemtuzumab, one of the most effective disease-modifying treatments (DMT) for relapsing-remitting multiple sclerosis (RRMS), can be used in either of the 2 main treatment strategies for the disease: induction and escalation. In induction therapy, alemtuzumab is frequently used in the early stages of the disease and constitutes the first step in therapeutic algorithms[1] due to its ability to stabilise or improve neurological function and to reduce disability progression, relapses, and the appearance of new lesions on magnetic resonance imaging (MRI) studies.[2–6] Alemtuzumab also plays an important role in treatment escalation in patients with suboptimal response to a DMT due to persistence of clinical and/or radiological activity.[1] The European Medicines Agency (EMA) summary of product characteristics (SPC) in effect until November 2019 did not provide a clear definition of the ideal candidate or the level of clinical or radiological disease activity for indication of the drug, providing clinicians with some degree of flexibility.[7] In November 2019, after pharmacovigilance authorities reported rare but severe adverse reactions to alemtuzumab, a risk-benefit analysis of its authorised indications was conducted in accordance with Article 20 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council. As a result, indication of the drug was restricted to patients with highly active disease despite treatment with at least one DMT or those with rapidly progressive RRMS, defined as ≥ 2 disabling relapses in a year and ≥ 1 gadolinium-enhancing lesion or a significant increase in T2 lesion load. At present, the most common practice in our setting is escalation therapy with alemtuzumab following lack of response to a previous DMT, although the lack of published studies prevents us from conclusively establishing the best immunosuppressant drug order in highly active MS.

The LEMVIDA study was designed to evaluate self-perceived quality of life in patients with RRMS under treatment with alemtuzumab. The purpose of this interim analysis was to describe the baseline clinical characteristics of these patients in Spain. We consider it important to analyse the way in which alemtuzumab was used in clinical practice in Spain before the implementation of the latest restrictions, to evaluate changes over time in the clinical profile of candidates for alemtuzumab treatment, and to gather safety data.

By the time the SPC for alemtuzumab was modified, patient recruitment had already been completed and most patients had received 2 treatment courses. This article presents the results of an interim analysis of the LEMVIDA study, describing the baseline characteristics of the patients included during the recruitment period and the paradigm shift observed in the indication of alemtuzumab in clinical practice.

Methods

Study design and population

The LEMVIDA study, a Spanish multicentre observational and 3-year prospective study, was ongoing at the time of writing. It included adults with RRMS who started alemtuzumab treatment according to the indications of the SPC, either as a first-line treatment or due to suboptimal response to another DMT. Maximum time from administration of alemtuzumab to inclusion in the study was 8 weeks.

The primary endpoint was quality of life, measured with the 29-item Multiple Sclerosis Impact Scale (MSIS-29). Secondary endpoints included levels of fatigue and depression, cognitive status, bladder dysfunction, disability, relapse rate, radiological findings, and safety data. This interim analysis evaluated all participants of the LEMVIDA study who had completed the baseline visit between October 2016 and September 2018. At the time of analysis, the patients continued to attend follow-up visits every 6 months.

In accordance with the Declaration of Helsinki, the study was approved by the research ethics committee of each participating centre and all patients gave written informed consent.

Assessments and data collection

We analysed the following baseline characteristics: age, sex, time from MS diagnosis to onset of alemtuzumab treatment, time since the last relapse, Expanded Disability Status Scale (EDSS) score at onset of alemtuzumab treatment, number of relapses in the previous 2 years, number and type of previous DMTs, number and location of MRI lesions in the last scan (T2-weighted and gadolinium-enhanced T1-weighted sequences). Relapses were defined as the appearance of new or worsened neurological symptoms attributable to MS, lasting at least 24 hours in the absence of fever, and occurring at least 30 days after the previous episode.

Data analysis

We conducted a descriptive statistical analysis. Quantitative variables are expressed as measures of central tendency and dispersion (mean and standard deviation [SD] or median [Q_1-Q_3]), and qualitative variables as absolute and relative frequencies (number and percentage).

Three subanalyses were performed, considering: 1) EDSS score at the initiation of alemtuzumab treatment (0-3, 3.5-4, or $\geq$ 4.5 points); 2) the recruitment period (group 1: October 2016 to March 2017; group 2: April to September 2017; group 3: October 2017 to March 2018; group 4: April to September 2018); and 3) highly active disease, defined as (a) $\geq$ 1 relapse in the previous year despite DMT, and $\geq$ 1 gadolinium-enhancing lesion on T1-weighted sequences or $\geq$ 9 lesions on T2-weighted sequences[8]; or (b) untreated patients presenting $\geq$ 2 relapses in the previous year and $\geq$ 1 gadolinium-enhancing lesion on T1-weighted sequences.[9,10] The second subanalysis evaluated whether the profile of the patients eligible for treatment with alemtuzumab has changed over time due to increased experience with the drug. The subanalysis of patients with highly active MS will help to evaluate whether the EMA's current restrictions on alemtuzumab use have affected the prescription of the drug to patients with highly active MS. Lastly, and although this was not an objective of this interim analysis, we decided to review safety data in view of the safety alert that led the EMA to conduct a risk-benefit evaluation of the drug. This safety analysis included all patients undergoing at least one safety assessment after inclusion in the study.

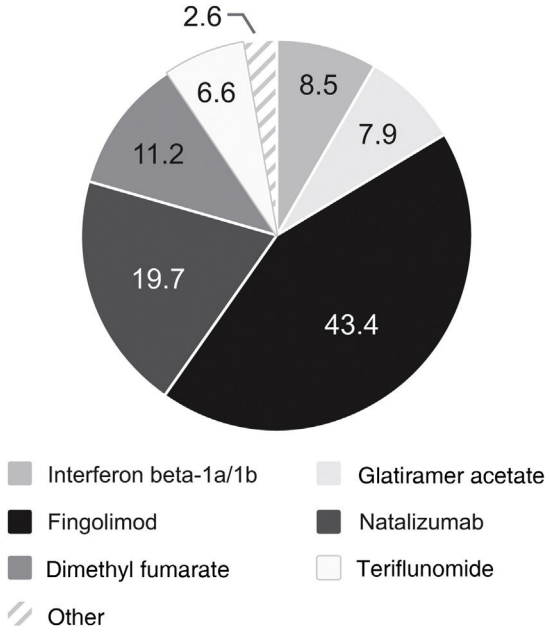

Figure 1 Latest multiple sclerosis treatments administered to patients from the LEMVIDA cohort before alemtuzumab. Other: rituximab (n = 3) and daclizumab (n = 1).

Analyses were based on the available data, meaning that missing data were not imputed; the threshold for statistical significance was set at $P < .05$. Statistical analysis was conducted using SPSS version 22.0 (SPSS Inc.; Chicago, IL, USA).

Results

On 28 September 2018, a total of 167 patients had been included in the study; 2 patients did not meet the selection criteria. Of the 165 evaluable patients, 161 had completed the baseline evaluation and were therefore included in this analysis. Mean age (SD) was 38.7 (9.4) years; 67.1% were women and 94.4% had received DMTs previously. The mean number of previous DMTs was 2.1 (1.1) (Table 1), and the last DMTs received before alemtuzumab were fingolimod and natalizumab, in 43.4% and 19.7% of patients, respectively (Table 1, Fig. 1). At the initiation of alemtuzumab treatment, mean disease duration was 8.5 (6.0) years, mean EDSS score was 3.3 (1.7), and the mean number of relapses in the previous 2 years was 1.8 (1.3) (Table 1). A total of 55.4% of patients presented a baseline EDSS score of 0-3, and 56% had suffered $\geq$ 2 relapses in the previous 2 years. The most recent MRI scan was performed a mean of 3.9 (5.1) months before the start of alemtuzumab treatment, revealing gadolinium-enhancing lesions in 48.3% of the patients; 73% of patients had 10-50 lesions on T2-weighted sequences.

Profile of patients starting treatment with alemtuzumab during the 2-year recruitment period

The percentage of patients starting treatment with alemtuzumab was similar in all 4 semesters of the recruitment period: 21% between October 2016 and March 2017, 21% between April and

Table 1 Baseline characteristics of the LEMVIDA study cohort.

	LEMVIDA cohort (N = 161)
Mean age (SD), years	38.7 (9.4)
Women	108 (67.1%)
Time since diagnosis of MS, years	
Mean (SD)	8.5 (6.0)
Median (Q_1-Q_3)	7.9 (3.6-12.2)
Time since the last relapse, months	
Mean (SD)	13.3 (19.7)
Median (Q_1-Q_3)	6.1 (2.8-12.7)
EDSS score	
Mean (SD)	3.3 (1.7)
Median (Q_1-Q_3)	3.0 (2-4)
EDSS score range	
0	4 (2.5%)
1-1.5	18 (11.2%)
2.0	32 (19.9%)
2.5-3.0	35 (21.8%)
3.5-4.0	34 (21.2%)
4.5-5.5	18 (11.2%)
≥ 6	20 (12.4%)
Relapses in the previous 2 years	
0	24 (14.9%)
1	47 (29.2%)
2	53 (32.9%)
≥ 3	37 (23%)
Mean (SD)	1.8 (1.3)
Median (Q_1-Q_3)	2.0 (1-2)
Gd+ lesions on T1-weighted MRI	
Mean (SD)	5.2 (6.9)*
Median (Q_1-Q_3)	2 (1-7)*
Patients with lesions	70/145 (48.3%)
Lesions on T2-weighted MRI	
≤ 9	9/145 (6.2%)
10-50	106/145 (73.1%)
50-100	27/145 (18.6%)
> 100	3/145 (2.1%)
Previous DMTs	
0	9 (5.6%)
1	31 (19.3%)
2	67 (41.6%)
≥ 3	54 (33.5%)
Mean (SD)	2.1 (1.1)
Median (Q_1-Q_3)	2.0 (1.5-3.0)
Last DMTs before alemtuzumab	
Fingolimod	66 (43.4%)
Natalizumab	30 (19.7%)

DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: standard deviation.
* If the one outlier value of 45 Gd+ T1 lesions is removed, the mean number of lesions is 4.6 (5.0) and the median is 2 (1-6.5).

September 2017, 27% between October 2017 and March 2018, and 30% between April and September 2018.

Significant changes were observed in baseline EDSS score and the number of gadolinium-enhancing T1 lesions (Table 2). Patients in group 1 scored significantly higher on the EDSS than patients in group 4 (4.1 [1.8] vs 3.2 [1.7]; P = .040). The mean number of gadolinium-enhancing T1 lesions was significantly higher in group 1 (patients starting treatment with alemtuzumab sooner after EMA approval in 2015) than in group 4 (10.9 [11.9] vs 4.5 [5.7]; P = .020). The number of relapses was similar between groups (P = .702). However, the percentage of patients starting treatment with alemtuzumab after fingolimod or natalizumab was lower in group 4 (60.6%) than in group 1 (70.6%), although no statistical comparison was performed between groups (Table 2).

Baseline characteristics according to EDSS score at onset of alemtuzumab treatment

A total of 55.4% of patients presented a baseline EDSS score of 0-3, and 23.5% scored ≥ 4.5 (Table 3). Although the patients with higher EDSS scores were older (41.4 [8.2] years for EDSS 3.5-4 and 41.5 [8.9] years for EDSS ≥ 4.5) and presented longer disease duration (9.9 [5.0] years for EDSS 3.5-4 and 10.4 [7.0] years for EDSS ≥ 4.5), no significant differences were observed in the number of relapses between EDSS score groups. The number of gadolinium-enhancing T1 lesions at baseline was significantly different between EDSS groups (Table 3).

Alemtuzumab in patients with highly active multiple sclerosis

A total of 86 patients presented highly active MS. These patients had a mean age of 38 (9.5) years, mean disease duration of 8.2 (5.7) years, a mean of 2.2 (1.1) relapses in the previous 2 years, and a mean of 4.4 (3.0) months since the last relapse. EDSS score at onset of alemtuzumab treatment was 3.5 (1.5), and the mean number of gadolinium-enhancing lesions was 5.7 (7.9).

Patients with highly active MS had received a mean of 2.2 (0.8) DMTs before alemtuzumab (fingolimod and natalizumab in 50% and 11.6% of cases, respectively).

Safety findings

As of 5 December 2019, 148 patients continued in the study, and 147 had received the 2 initial courses of alemtuzumab. Alemtuzumab was discontinued in 17 patients for several reasons, including lack of effectiveness (n = 5), loss to follow-up (n = 5), consent withdrawal (n = 3), decision of the clinician (n = 2), change of treatment (n = 1), and death (n = 1). A total of 33 serious adverse events were reported, 9 of which were considered to be related to alemtuzumab treatment: maculopapular rash (1 case), thrombocytopenia (1), pyrexia (2), fatal haemophagocytic lymphohistiocytosis (1), elevated transaminase levels (1), perfusion-related reaction (1), and lymphocytopenia (1).

Table 4 summarises other adverse events of mild to moderate severity related to alemtuzumab in our cohort, in line with the most recent reports of immune-mediated and cardiovascular reactions. Most cardiac and vascular disorders were reported during alemtuzumab infusion. No cases were reported of haemorrhagic stroke, cervical or cerebral artery dissection, alveolar haemorrhage, or autoimmune hepatitis.

Discussion

The population of the LEMVIDA study, with a mean disease duration of 8 years, a mean EDSS score of 3.3, and a mean of 2 previous

Table 2 Profile of patients starting treatment with alemtuzumab during the 2-year recruitment period.

	Group 1 October 2016-March 2017 (n = 34)	Group 2 April 2017-September 2017 (n = 43)	Group 3 October 2017-March 2018 (n = 50)	Group 4 April 2018-September 2018 (n = 34)	*P*
Mean age (SD), years	37.5 (9.3)	38.6 (8.1)	38.1 (9.7)	41.0 (10.6)	.428
Time from MS diagnosis to the initiation *of alemtuzumab, years*					
Mean (SD)	10.2 (5.6)	7.7 (6.9)	8.3 (5.5)	8.2 (5.7)	.154
Median (Q_1—Q_3)	6.6 (9.4-14.7)	6.9 (2.1-11.7)	8.1 (3.9-12.3)	7.5 (2.7-11.4)	
EDSS score					
Mean (SD)	4.1 (1.8)	3.2 (1.6)	2.9 (1.5)	3.2 (1.7)	.034[§]
Median (Q_1-Q_3)	4.0 (2.5-6)	2.5 (2-4)	3.0 (2-3.6)	3.0 (2-3.5)	
Relapses in the previous 2 years					
Mean (SD)	1.9 (1.5)	1.8 (1.2)	1.8 (1.3)	1.5 (1.2)	.702
Median (Q_1-Q_3)	2 (1-3)	2 (1-2)	2 (1-2)	1 (0.8-2.3)	
Gd+ lesions on T1-weighted MRI					
Mean (SD)	10.9 (11.9)*	3.6 (4.6)	4.0 (4.2)	4.5 (5.7)	.029[§,*]
Median (Q_1-Q_3)	9 (3.3-14.3)*	2 (1-3)	2 (1-6.3)	2 (1-5.5)	
Patients with lesions	12/29 (41.4%)	22/40 (55%)	20/46 (43.5%)	16/30 (53.3%)	.571
Lesions on T2-weighted MRI					
≤ 9	1/31 (3.2%)	3/41 (7.3%)	4/47 (8.5%)	1/26 (3.8%)	.151
10-50	22/31 (71%)	30/41 (73.2%)	30/47 (63.8%)	24/26 (92.3%)	
50-100	6/31 (19.4%)	7/41 (17.1%)	13/47 (27.7%)	1/26 (3.8%)	
> 100	2/31 (6.5%)	1/41 (2.4%)	0 (0%)	0 (0%)	
Previous DMTs					
Mean (SD)	2.3 (0.9)	1.9 (1.1)	2.3 (1.1)	2.1 (1.1)	.344
Median (Q_1-Q_3)	2 (2-3)	2 (1-3)	2 (2-3)	2 (1-3)	
Patients receiving fingolimod or natalizumab	24/34 (70.6%)	27/38 (71.1%)	35/47 (74.5%)	20/33 (60.6%)	

DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: standard deviation.
P-value of the difference between group 1 and group 2: EDSS score, *P* = .020; Gd+ T1 lesions, *P* = .006.
P-value of the difference between group 1 and group 3: EDSS score, *P* = .005; Gd+ T1 lesions, *P* = .012.
P-value of the difference between group 1 and group 4: EDSS score, *P* = .040; Gd+ T1 lesions, *P* = .020.
[§] *P*-value of the difference in the distribution of the variable between groups.
[*] If the one outlier of 45 Gd+ T1 lesions is removed, the mean number of lesions is 7.8 (5.5), the median is 9 (3-9), and the *P*-value of the difference in distribution between groups is not statistically significant (*P* = .067).

DMTs before alemtuzumab, had a worse baseline clinical situation than the patients included in the alemtuzumab clinical programme trials,[2—5] who were younger (34.8 [8.4] years in the CARE-MS II trial[5]) and presented shorter disease duration (4.5 [2.7] years in the CARE-MS II trial[5]), less disability (EDSS score of 2-2.7, depending on the study), and less prior exposure to DMTs (1 DMT in the CARE-MS II trial[5]) (Table 5). Over half of the patients from the LEMVIDA study presented clinical and radiological disease activity despite having received at least 2 DMTs. Therefore, this population would theoretically be expected to have worse prognosis in terms of disability progression[11—13] and greater risk of poor response to alemtuzumab than the population of the phase 3 CARE-MS trials.[2,14—16] In clinical practice, the neurologists participating in the LEMVIDA study usually limit the indication of alemtuzumab to more advanced stages of MS, when other DMTs have failed to control the disease. Although this does not contradict the latest recommendations issued by European experts,[17] it is contrary to the idea of using alemtuzumab to induce early tolerogenic effects in the immune system. Other large prospective cohorts similar to our series, such as those of the German TREAT-MS study[18] (n = 779) and the Canadian MS One-to-One programme[19] (n = 494) (Table 5), reveal the same trend in treatment decisions as the disease progresses. (results not published).

The lack of a clearly defined profile of patients eligible for treatment, of validated biomarkers of treatment response, and even of a clear definition of radiological activity in the indication of alemtuzumab may have had an impact on the selection of the most appropriate timing for indicating the drug. The fact that many patients starting treatment with alemtuzumab have previously received DMTs that were not available during the clinical development of alemtuzumab (eg, fingolimod), and the lack of clinical data in this respect, underscores the importance of performing studies on this patient profile. These ongoing studies,[18,19] together with the LEMVIDA study, will provide valuable information on the real use of alemtuzumab in clinical practice.

Table 3 Patient characteristics according to EDSS score at onset of alemtuzumab treatment.

	EDSS 0-3 (n = 89)	EDSS 3.5-4 (n = 34)	EDSS ≥ 4.5 (n = 38)	*P*
Mean age (SD), years	36.5 (9.6)	41.4 (8.2)	41.5 (8.9)	<.001[§]
Time from MS diagnosis to onset of alemtuzumab, years				
Mean (SD)	7.2 (5.6)	9.9 (5.0)	10.4 (7.0)	.005[§]
Median (Q_1-Q_3)	6.5 (2.2-10.9)	10.1 (6.0-13.5)	8.4 (6.1-13.4)	
Relapses in the previous 2 years				
Mean (SD)	1.7 (1.2)	1.9 (1.1)	1.9 (1.5)	.657
Median (Q_1-Q_3)	2 (1-3)	2 (1-2.3)	2 (1-3)	
Gd+ lesions on T1-weighted MRI				
Mean (SD)	3.5 (3.6)	5.5 (6.3)	10.6 (12.1)*	.038[§,*]
Median (Q_1-Q_3)	2 (1-4)	2 (1-10)	9 (2-14)*	
Patients with lesions	44/83 (53.0%)	13/32 (40.6%)	13/30 (43.3%)	.409
Lesions on T2-weighted MRI				
≤ 9	7/81 (8.6%)	2/33 (6.1%)	0 (0%)	.238
10-50	61/81 (75.3%)	24/33 (72.7%)	21/31 (67.7%)	
50-100	12/81 (14.8%)	7/33 (21.2%)	8/31 (25.8%)	
> 100	1/81 (1.2%)	0 (0%)	2/31 (6.5%)	
Previous DMTs				
Mean (SD)	2.0 (1.1)	2.3 (1.0)	2.4 (1.0)	.180
Median (Q_1-Q_3)	2 (1-3)	2 (2-3)	2 (2-3)	
Patients receiving fingolimod or natalizumab	52/82 (63.4%)	25/33 (75.8%)	29/37 (78.4%)	

DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: standard deviation.
P-value of the difference between groups EDSS 0-3 and EDSS 3.5-4: age, *P* = .001; time to onset of alemtuzumab, *P* = .009; Gd+ T1 lesions, *P* = .421.
P-value of the difference between groups EDSS 0-3 and EDSS ≥ 4.5: age, *P* = .002; time from diagnosis to onset of alemtuzumab, *P* = .011; Gd+ T1 lesions, *P* = .010.
[§] *P*-value of the difference in the distribution of the variable between groups.
[*] If the one outlier of 45 Gd+ T1 lesions is removed, the mean number of lesions is 7.8 (6.6), the median number is 7.5 (2—11), and the *P*-value of the difference in distribution between groups is not statistically significant (*P* = .081).

Table 4 Mild and moderate adverse events.

	Number of AEs	AEs related to alemtuzumab
Cardiac/vascular disorders	19	9 AEs, 8 of which occurred during alemtuzumab infusion: 2 cases of AHT during courses 1 and 2 1 case of hypotension during course 1 3 cases of bradycardia (1 during course 1 and 2 during course 2) 2 cases of tachycardia during courses 1 and 2
Autoimmune hepatitis/hepatic injury/liver enzyme alterations	11	5 AEs 4 cases of elevated transaminase levels 1 case of hepatotoxicity (CMV infection could not be ruled out)
Endocrine disorders/thyroid disorders	32	22 AEs
Thrombocytopenia/low platelet count	9	8 AEs in a patient over the course of immune thrombocytopenic purpura

Safety analysis was performed on the set of patients with at least one safety assessment after inclusion in the study. As eligibility criteria allowed for alemtuzumab to be initiated up to 8 weeks prior to inclusion in the study, we only gathered safety data within the 5 days of the first infusion in 89 patients.
AE: adverse event; AHT: arterial hypertension; CMV: cytomegalovirus.

The patients with EDSS scores ≥ 3.5 at onset of alemtuzumab treatment (44.8%) were older and had longer disease duration and higher numbers of gadolinium-enhancing T1 lesions than those with EDSS scores < 3.5, but similar relapse rates and MRI activity on T2-weighted sequences. These results of the LEMVIDA study show that, in real clinical practice, a substantial number of patients with advanced MS are treated with alemtuzumab. Despite the high percentage of patients with EDSS scores 0-3 (55%), it is lower than the rate reported in the CARE-MS II study (69%). However, the evolution of baseline clinical characteristics of patients treated with

Table 5 Baseline data from the LEMVIDA, CARE-MS II,[5] TREAT-MS,[18] and MS One-to-One studies.[19]

	LEMVIDA (N = 161)	CARE-MS II (N = 426)	TREAT-MS (N = 779)	MS One-to-One (N = 494)
Mean age (SD), years	38.7 (9.4)	34.8 (8.4)	35.8 (9.2)	38.9 (8.7)
Women	108 (67.1%)	281 (66%)	550 (70.6%)	74.3%
Disease duration , *years*				
Mean (SD)	8.5 (6.0)	4.5 (2.7)	7.3 (6.3)	8.0 (6.3)
EDSS score				
Mean (SD)	3.3 (1.7)	2.7 (1.26)	2.9 (1.7)	3.0 (1.7)
Median (Q_1-Q_3)	3.0 (2-4)	2.5 (0-6.5)	2.5 (1.5-4)	3.0 (0.0-8.0)
Relapses in the previous 2 years				
Mean (SD)	1.8 (1.3)	—	2.2 (1.8)	—
Median (Q_1.Q_3)	2.0 (1-2)	2.0 (1.9)	—	—
Gd+ lesions on T1-weighted MRI				
Mean (SD)	5.2 (6.9)	2.28 (6.02)	—	—
Median (Q_1.Q_3)	2 (1-7)	0 (0-72)	—	—
Patients with lesions	70/145 (48.3%)	178/420 (42.4%)	—	—
Previous DMTs				
0	9 (5.6%)	0 (0%)	116 (15%)	0 (0%)
1	31 (19.3%)	299 (70%)	163 (21%)	163 (33%)
2	67 (41.6%)	92 (22%)	241 (31%)	149 (30.2%)
$\geq$ 3	54 (33.5%)	35 (8.2%)	225 (29%)	182 (36.8%)
Mean (SD)	2.1 (1.1)	1 (0.7)	—	—
Median (Q_1.Q_3)	2.0 (1.5-3.0)	1 (1-4)	—	—
Immunosuppressants before alemtuzumab				
Fingolimod	66 (43.4%)	0	168 (21.6%)	161 (32.6%)
Natalizumab	30 (19.7%)	15 (4%)	116 (14.9%)	99 (19.8%)

DMT: disease-modifying treatment; EDSS: Expanded Disability Status Scale; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging; MS: multiple sclerosis; SD: standard deviation.

alemtuzumab in the LEMVIDA study reveals a change in this trend: in more recent years, treatment was started at earlier stages of the disease and in patients with lower levels of disability and disease activity, probably due to greater experience with the drug and the greater effectiveness observed when it is used at earlier stages. The patients starting alemtuzumab in 2016 presented an EDSS score nearly one point higher than that of patients starting alemtuzumab in 2018 (4.1 vs 3.2), and twice as many gadolinium-enhancing lesions (10.9 vs 4.5). The relapse rate and number of previous DMTs were similar, although the proportion of patients switching to alemtuzumab from such selective immunosuppressants as fingolimod and natalizumab was smaller in the second group (70.6% vs 60.6%). This suggests a shift in neurological clinical practice over the 2-year recruitment period, revealing a trend towards treatment onset at earlier stages and lower levels of disability, rather than prescribing the drug as a third-line treatment after natalizumab or fingolimod, indicated for patients with highly active MS or rapidly evolving severe disease.[20,21]

Conclusions

This article publishes baseline data from a large cohort of patients with RRMS treated with alemtuzumab in real practice in Spain. Although the population included in the LEMVIDA study was mainly characterised by longer disease duration and greater disability, our data also reveal a trend toward early prescription of alemtuzumab to previously treated patients. These results are published after the procedure conducted to re-evaluate the risk-benefit balance of alemtuzumab, in accordance with Article 20 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council; therefore, it is important to communicate any safety findings observed in populations with different characteristics from those specified for the new indication. We hope that the final results of the LEMVIDA study will help to determine the most suitable patient profile for indication of alemtuzumab, and better characterise the safety profile of the drug. In the meantime, this interim analysis found no unexpected safety concerns associated with alemtuzumab.

The interpretation of our results may be limited by the observational nature of this study. Furthermore, the situation reflected by our results may change as new information about the drug comes to light.

Author contributions

CAC, BCS, GIA, ROC, and ARA participated in study conception and design. JEML, BCS, ARA, and CCH participated in data collection. JEML and ROC drafted the manuscript. All authors participated in data analysis and interpretation, critically reviewed the manuscript, and approved the final version.

Funding

The LEMVIDA study was funded by Sanofi.

Conflicts of interest

JEML has received grants, lecture honoraria, and consultancy fees from Almirall, Biogen, Celgene, Genzyme, Merck, Novartis, Roche, and Teva. JCAC has received consultancy fees from Sanofi. BCS declares that the Clinical Immunology Unit has received funding from Sanofi, Roche, Novartis, Merck, Biogen Idec, Teva, Almirall, Celgene, Mylan, and Bayer, as well as fees from Sanofi, Roche, Novartis, Merck, and Celgene for participating in meetings and congresses. GIA has received lecture honoraria and consultancy fees from Bayer, Biogen Idec, Novartis, Sanofi, Merck Serono, Almirall, Roche, Actelion, Celgene, and Teva. ROC is an employee of Sanofi and may hold stocks and/or stock options from Sanofi. ARA has received lecture honoraria and consultancy fees from Biogen, Sanofi, Merck, Novartis, Roche, and Teva. CCH has received lecture honoraria and consultancy fees from Merck, Sanofi, Teva, Novartis, and Biogen Idec.

Acknowledgements

The authors wish to thank the members of the LEMVIDA study group, who attended the patients participating in the study: L. Forero (H. Puerta del Mar), E. Agüera (H. Reina Sofía), E. Durán Ferreras (C. H. de Huelva), A. Alonso (H. R. U de Málaga), S. Eichau (H. Virgen Macarena), M. González Platas (H. U. de Gran Canaria Doctor Negrín), M. J. Sedano Tous (H. Marqués de Valdecilla), N. Téllez (H. C. de Valladolid), A. B. Caminero Rodríguez (H. Nuestra Señora de Sonsoles), D. Pérez (H. El Bierzo), S. Martínez Yelamos (H. de Bellvitge), A. Saiz (H. Clìnic), J. Batlle (H. Sant Pau i Santa Tecla), G. Martín (H. Virgen de la Cinta), L. Ramió Torrentà (H. Dr. Josep Trueta), J. Sotoca (H. Mutua de Terrassa), E. Jiménez (H. San Pedro de Alcántara), A. Rodríguez Regal (C. H de Pontevedra), J. M. Prieto (H. C. U. de Santiago), J. R. Lorenzo (H. Povisa), E. Álvarez (H. Álvaro Cunqueiro), M. A. Llaneza (H. Arquitecto Marcide), A. López Real (H. U. A Coruña), A. Candeliere (H. Rafael Méndez), T. Ayuso (C. H. Navarra), A. Álvarez de Arcaya (H. Txagorritxu), A. Belenguer (H. G. de Castellón), F. Gascón Jiménez (H. C. de Valencia), and L. Berenguer (H. Marina Baixa).

The authors also wish to thank Isabel Caballero of Dynamic Science S.L. for her assistance in drafting this manuscript. This study received financial support from Sanofi.

References

1. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc. 2014;89:225—40, http://dx.doi.org/10.1016/j.mayocp.2013.11.002.
2. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung H-P, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380:1819—28, http://dx.doi.org/10.1016/S0140-6736(12)61769-3.
3. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359:1786—801, http://dx.doi.org/10.1056/NEJMoa0802670.
4. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology. 2012;78:1069—78, http://dx.doi.org/10.1212/WNL.0b013e31824e8ee7.
5. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012;380:1829—39, http://dx.doi.org/10.1016/S0140-6736(12)61768-1.
6. Fox EJ, Sullivan HC, Gazda SK, Mayer L, O'Donnell L, Melia K, et al. A single-arm, open-label study of alemtuzumab in treatment-refractory patients with multiple sclerosis. Eur J Neurol. 2012;19:307—11, http://dx.doi.org/10.1111/j.1468-1331.2011.03507.x.
7. EMA. Lemtrada (alemtuzumab): EU summary of product characteristics. [online]. [Accessed 25 March 2019]. Available at: https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf.
8. Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, Agoropoulou C, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012;11:420—8, http://dx.doi.org/10.1016/S1474-4422(12)70056-X.
9. Hutchinson M, Kappos L, Calabresi PA, Confavreux C, Giovannoni G, Galetta SL, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. J Neurol. 2009;256:405—15, http://dx.doi.org/10.1007/s00415-009-0093-1.
10. Krieger S, Singer B, Freedman M, Lycke J, Berkovich R, Margolin D. Treatment-naive patients with highly active RRMS demonstrated durable efficacy with alemtuzumab over 5 years (S51.003). Neurology. 2016;86 16 Supplement. S51.003.
11. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. Eur J Neurol. 2009;16:1202—9, http://dx.doi.org/10.1111/j.1468-1331.2009.02708.x.
12. Rio J, Nos C, Tintore M, Téllez N, Galán I, Pelayo R, et al. Defining the response to interferon-beta in relapsing-remitting multiple sclerosis patients. Ann Neurol. 2006;59:344—52, http://dx.doi.org/10.1002/ana.20740.
13. Rudick RA, Polman CH. Current approaches to the identification and management of breakthrough disease in patients with multiple sclerosis. Lancet Neurol. 2009;8:545—59, http://dx.doi.org/10.1016/S1474-4422(09)70082-1.
14. Coles AJ, Cohen JA, Fox EJ, Giovannoni G, Hartung H-P, Hardova E, et al. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. Neurology. 2017;89:1117—26, http://dx.doi.org/10.1212/WNL.0000000000004354.
15. Havrdova E, Arnold DL, Cohen JA, Hartung H-P, Fox EJ, Giovannoni G, et al. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. Neurology. 2017;89:1107—16, http://dx.doi.org/10.1212/WNL.0000000000004313.
16. Menge T, Stuve O, Kieseier BC, Hartung HP. Alemtuzumab: the advantages and challenges of a novel therapy in MS. Neurology. 2014;83:87—97, http://dx.doi.org/10.1212/WNL.0000000000000540.
17. Berger T, Elovaara I, Fredrikson S, McGuigan C, Moiola L, Myhr K-M, et al. Alemtuzumab use in clinical practice: recommendations from European multiple sclerosis experts. CNS drugs. 2017;31:33—50, http://dx.doi.org/10.1007/s40263-016-0394-8.

18. Akgün K, White R, Kern R, Engelmann U, Haase R, Guikema B, et al. Real-world effectiveness of alemtuzumab in relapsing-remitting MS patients in Germany: interim results of the TREAT-MS study (P3.2-057). Neurology. 2019;92 15 Supplement.
19. Smith A, Hashemi L, Poole E, Gehchan A. services real-world evidence of patients treated with alemtuzumab in Canada. In: 7th Joint ECTRIMS-ACTRIMS Meeting; 2017. 2017.
20. EMA. Gilenya (fingolimod): EU summary of product characteristics. [online]. [Accessed 25 March 2019]. Available at: https://www.ema.europa.eu/en/documents/product-information/gilenya-epar-product-information_en.pdf.
21. EMA. Tysabri (natalizumab): EU summary of product characteristics [online]. [Accessed 25 March 2019]. Available at: https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf.