ECRONICON OPEN ACCESS

EC NEUROLOGY
Research Article

Experience on Use of Alemtuzumab in the Treatment of Relapsing -Remitting Multiple Sclerosis in Mexico: A Real-World Multicenter Study

Irene Treviño-Frenk[1,2,3], Luis Enrique Amaya-Sánchez[4,5], Velvet Jaqueline Ruiz-Granados[6], Verónica Rivas-Alonso[5], Luis Enrique Molina-Carrión[6], Miguel Ángel Macías-Islas[7], Juan Manuel Escamilla-Garza[8], Carlos Ferrán Pla -Casamitjana[9], Brenda Bertado-Cortés[4], Mario Alanís-Quiroga[10], Manuel De la Maza-Flores[8], Diana Citlalli López-Hernández[1,3] and José de Jesús Flores-Rivera[2,5]*

[1]Neurology and Psychiatry Department, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

[2]Neurological Center, ABC Medical Center, Mexico City, Mexico

[3]School of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico

[4]Centro Médico Nacional "Siglo XXI", Instituto Mexicano del Seguro Social, Mexico City, Mexico

[5]Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez", Mexico City, Mexico

[6]Centro Médico Nacional "La Raza", Instituto Mexicano del Seguro Social, Mexico City, Mexico

[7]Neuroscience Department, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico

[8]Instituto Tecnológico y de Estudios Superiores de Monterrey, Nuevo León, Mexico

[9]Medica Sur, Mexico City, Mexico

[10]Hospital General Universitario de Torreón, Coahuila, Mexico

***Corresponding Author**: José de Jesús Flores-Rivera, Subdirección de Neurología, Instituto Nacional Neurología y Neurocirugía "Manuel Velasco Suárez", Mexico City, Mexico.

Received: February 07, 2020; **Published:** March 27, 2020

Abstract

Introduction: Multiple sclerosis (MS) is a neuroinflammatory disorder affecting the brain and spinal cord with an autoimmune component. It is the first cause of non-traumatic disability in about 2 million individuals worldwide. Despite several approved disease-modifying therapies (DMT) for the treatment of MS, a high relapsing rate still unresolved. Alemtuzumab is an innovative treatment for relapsing-remitting MS. We aimed to assess the real-world experience of alemtuzumab effectiveness in Mexican medical centers.

Materials and Methods: An observational, retrospective, multicenter, post-marketing study was performed. Data set were collected by a web-based survey. Clinical history, laboratory tests, and imaging scans were collected. The Expanded Disability Status Scale (EDSS) was used to assess disability improvement at 12 and 24 weeks after the treatment onset, before 2nd treatment cycle, and last record. All adverse events experienced along was reported.

Results: A total of 38 cases were recorded, of which 26 (68.4%) were female. The median age was 38.5 years (range 19 - 69). Twenty-two patients (84.2%) were treated with previous DMTs, and 6 (15.8%) started alemtuzumab as the first option. Most participants had an improvement in EDSS after 24 weeks of treatment (24 weeks: 61.3%, before the 2nd cycle: 61.6%, last recorded: 65.8%). The remaining patients had stable EDSS and only one patient had a lower EDSS before their 2nd treatment cycle. An univariate logistic regression analysis showed that, in contrast with relapsing subjects, non-relapsing patients were 3.8 times more likely to have received alemtuzumab (OR 3.81, CI 95% 1.09 - 13.30; p = 0.036).

Conclusion: Alemtuzumab demonstrated its effectiveness and safety for relapsing MS patients in a real-world setting.

Keywords: *Multiple Sclerosis; Alemtuzumab; Neurology; Real-World Evidence*

Abbreviations

MS: Multiple Sclerosis; DMT: Disease-Modifying Therapy; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-Remitting Multiple Sclerosis; NEDA: No Evidence of Disease Activity; IAR: Infusion-Associated Reaction; IFNβ-1a: Interferon β-1a, RWE: Real-World Evidence

Introduction

Multiple sclerosis (MS) is an inflammatory neurodegenerative disorder affecting the brain and spinal cord due to lymphocytic infiltration that causes irreversible autoimmune damage in myelin and axons [1]. It is the first cause of non-traumatic disability in young adults, and according to estimations, it affects more than 2 million individuals worldwide [2]. The estimated prevalence in Mexico is 11 - 20 cases per 100,000 individuals [3]. Approximately, eight percent of MS patients globally experience higher activity and more aggressive disease course. These patients can be categorized as relapsing-remitting multiple sclerosis (RRMS) with active disease [4]. The European Medicines Agency has defined RRMS patients as those with at least two disabling relapses in the first year and at least one gadolinium-enhanced lesion or a significant increase in T2 lesion load [5].

Several studies have determined that poor prognosis is associated with male gender, late onset of disease, motor and cerebellar symptoms during the onset of disease, a progressive course since the onset, short intervals between attacks, high frequency of early attacks and residual early disability [6]. Regarding the prediction of disability progression in time, it has been recently described that the early onset of the disease is highly associated with a poor prognosis, independently from the initial disease course [7]. Thus, early initiation of disease-modifying therapies (DMT) is pivotal for the adequately control symptoms, prevent severe relapses, improve the patients' QoL, and decrease the associated costs of medical care and monitoring of these patients [8,9]. Although there are about 12 different DMTs for treating MS in the world market, evidence regarding efficacy in more advanced stages of the disease is still limited [8]. Moreover, in many countries, there is limited access to these therapies, especially in Latin American countries where access is a major challenge [10].

Alemtuzumab is a humanized monoclonal antibody that selectively binds CD52. This protein is expressed at the surface of B- and T-lymphocytes in human. Thus, selectively inhibiting these cells and the inflammatory activity in MS [11]. In Mexico, the Federal Commission for the Protection of Healthcare Risk (COFEPRIS) approved this medicine on January 2014. It is prescribed for the treatment of relapsing forms of MS to manage disease activity and limit clinical progression [12]. The efficacy of alemtuzumab has been studied in phase III clinical trials such as CARE-MS I and II. The former was a randomized evaluator-blinded study for comparing alemtuzumab and subcutaneous interferon β-1a (IFNβ-1a) for 2 years. This study showed evidence of lesser relapse rate (0.45 $p < 0.0001$) in the alemtuzumab arm, decrease in gadolinium-enhanced lesions (alemtuzumab 7% vs. IFNβ-1a 19%), and more clinical (74% vs. 56%) and radiological (39% vs. 27%) disease-free patients [13]. In addition, CARE-MS II study included patients with ongoing disease activity with previous DMT. It was compared IFNβ-1a and alemtuzumab in a 2-year follow up. When comparing both interventions, a lesser relapse rate was observed in the alemtuzumab arm (0.51 0.39 - 0.65 $p < 0.001$), and greater percentage of patients with no evidence of disease activity (NEDA, a composite measure defined as absence of relapses, disability worsening, and magnetic resonance imaging activity), clinical or radiological (32% vs. 14%) activity [14]. In the 5-year extension of CARE-MS I, it was reported that 68.5% of patients did not require re-treatment after 2 cycles of alemtuzumab. Additionally, 70% of re-treated patients required one additional cycle, 25.5% required two cycles, and 4.5% required three cycles [15].

In terms of safety, it was reported that alemtuzumab caused an infusion-associated reaction (IAR), the most common adverse event (90% of the study population). Other frequent adverse events were headache, exanthema, fever, and nausea. The most common serious adverse events were hypotension and auricular fibrillation (1%). Also, 67% of patients experienced infections (consisting mostly of nasopharyngitis, urinary tract infections, and herpes simplex virus infections) and 18% of patients showed thyroid alterations (hyperthyroidism 7%, hypothyroidism 5%) [13]. In the 5-year extension, a lower incidence of adverse events was reported than in the core trial (133.6 vs. 705.2 cases-years). It was noted that IAR incidences in patients retreated with alemtuzumab were lower than in the core study. Thyroid disease was the most common autoimmune reaction with a peak incidence on third year. During this period important

drug-related adverse events were also reported: four cases of autoimmune thrombocytopenia, one case of nephropathy and six patients with cancer (two papillary thyroid cancer, one breast cancer, one keratoacanthoma, one lung cancer and one micropapillary thyroid cancer) [15].

Despite controlled scenario achived in randomized clinical trials, real-world evidence (RWE) studies evaluate the impact of a treatment in greater heterogeneity open population. Thus, an RWE study does not control conditions such as therapy adherence, clinical parameters monitoring and follow-up, and so on. For this reason, RWE studies describe a more realistic clinical practice setting where it is possible to capture valuable clinical information about effectiveness and safety [16]. Recently, a pre-marketing RWE study for evaluating the efficacy of alemtuzumab in RRMS Italian patients (n = 40) found that 45% of patients achieved NEDA-3. Furthermore, 75% of the population was relapse-free, 82.5% was free of EDSS worsening and 62.5% had no magnetic resonance imaging (MRI) activity [17].

This study shows real-world evidence on neurologist experiences using alemtuzumab for the treatment of RRMS taking into account the effectiveness and safety parameters. To our best knowledge, this is the first RWE study performed Latin American population.

Materials and Methods

Study design

An observational, retrospective, multicenter, post-marketing study was performed. Retrospective data was shared by neurologists from nine Mexican medical centers using a web-based survey. Only Mexican experienced neurologists who have used at least one dose of alemtuzumab in MS diagnosed patients were included in this study. Clinical trainee, residency physicians or neurologists with no experience with alemtuzumab treatment were excluded.

Alemtuzumab was administered as intravenous infusion as described in approved prescribing information for the product. All patients received premedication treatments indicated by their treating neurologist before each alemtuzumab dose.

Participants and outcomes

Twenty neurologists from major Mexican medical centers with proficiency using alemtuzumab in clinics were invited. Most invited neurologists (n = 13, 65%) accepted the invitation.

The study leaders reviewed the survey to verify suitability and understandability of all items before distribution for the participating neurologists. Only patient records with complete information (clinical and radiological data) were included in the study. We confirmed that all medical records met inclusion criteria. Collected data from participating neurologist were stored in a controlled access database and analyzed by the principal investigator and a third-party analyst. Patient consent for the use of this data was not required since data was blinded for the third-party analyst and principal investigator. Third-party analysts had no access to direct patient information. Clinical records were examined by each participating neurologist.

Effectieness data established as EDSS change (after 12 weeks, after 24 weeks, before second cycle, and on last recorded visit) and relapses frequency were collected. Disability improvement were evaluated by disability scoring using the Expanded Disability Status Scale (EDSS). This outcome was defined as decrease of at least 1.0 unit of the EDSS between cutoff times.

Variables

The sample characteristics are presented as the median and range for continuous variables and as frequencies and percentages for categorical variables. Data were classified as demographic, MS classification, disease duration, para-clinical tests for getting diagnosis, early prescribed DMTs, and alemtuzumab therapy follow-up. The alemtuzumab therapy section was further divided in profiling, drug infusions, post-alemtuzumab effectiveness follow-up, and post-alemtuzumab safety follow-up.

Statistical analysis

A comparative analysis among the variables taking into account EDSS changes for each cutoff time period was performed. To determine the statistical significance of discrete variables, chi-squared (χ^2) or Fisher's exact tests were performed. Mann-Whitney U test was

used to calculate p-value of continuous variables.

A univariate logistic regression analysis was run in order to determine the probability for developing an improvement in the EDSS (final vs baseline) among those under alemtuzumab treatment. All statistical tests were performed at the 0.05 level and 95% confidence intervals (CI) were given. All analyses were performed using SPSS statistical software.

Results and Discussion

Baseline demographics and clinical data

A total of 38 cases were recorded, of which 26 (68.4%) were of females. The median age was 38.5 years old (range 19 - 69 years). More than half individuals (57.9%) were living in Mexico City and rest of the population was from further locations (eight states). All patients were diagnosed with MS in accordance with the treating neurologist's reports (Table 1).

Sex, n (%)	
Male	12 (31.6)
Female	26 (68.4)
Median age, (range)	38.5 (19-69)
Residence, n (%)	
Mexico City	22 (57.9)
Non-Mexico City	16 (42.1)
Baseline lesions or relapses, n (%)	
Brain stem	15 (39.5)
Sensory area	10 (26.3)
Motor area	10 (26.3)
Medulla	10 (26.3)
Cerebellum	5 (13.2)
Bowel and bladder function	3 (7.9)
Optic neuritis	8 (21.1)
Poor prognosis lesions, n (%)	28 (73.7)
Number of Gd+ lesions, n (%)	29 (78.4)
Baseline EDSS	3.8
Number of relapses, mean (range)	
On first year of disease progression	1.7 (1-3)
Before first DMT	2.2 (1-10)
Naïve patients, n (%)	6 (15.85)
Number of DMTs before alemtuzumab, %	
1	37.5
2	18.8
3	15.6
≥4	28.1

Table 1: *Baseline demographic and clinical characteristics.*

MS: Multiple Sclerosis; DMT: Disease-Modifying Therapy; Gd+: Gadolinium-Enhanced Imaging.

On clinical characteristics of patients, the most frequently relapses were those that affected the brain stem, sensory system, motor system, medulla, optic neuritis, cerebellum, and bowel and bladder functions. Additionally, twenty eight patients (73.7%) showed lesions relative of poor prognosis, they were affected of posterior fossa (n = 15, 39.5%), sphincter control (n = 3, 10%) or spinal cord (n = 10, 30%) and also were multifocal (n = 10, 26.3%), or required plasmapheresis after the intravenous administration of methylprednisolone bolus regarding severity of the relapse (n = 4, 10.5%). An average of 1.7 relapses (range 1 - 3) were reported for the first year of disease evolution, and 2.2 before initiation of the first DMT (range 1 - 10). Also, oligoclonal bands were observed in 76% of patients who had CSF oligoclonal band screening, . Baseline MRI gadolinium-enhanced lesions (active disease) in 29 patients (78.4%) were identified. Spinal cord lesions were found in 15 of the 23 patients (55.6%) who had a spinal MRI at diagnosis.

DMTs before alemtuzumab

Before starting alemtuzumab more than a third of patients (37.5%) received only one DMT. However, almost 30% received more than 3 previous therapies (See table 1). Overall, 32 out of 38 patients (84.2%) had other previous DMT, while 6 patients (15.8%) received alemtuzumab as first option (naïve group). Table 2 showed the therapies previously administered to those patients. It is noteworthy that major DMT prescribed at the beginning was IFNβ, representing a third (38.7%) of all prescriptions in this population. The median time of evolution from MS to the initiation of pharmacotherapy was 5 months (range 0 - 75).

Population with previous DMT, n (%)	
Patients with previous DMT and switched to alemtuzumab	32 (84.2)
Naïve patients	6 (15.8)
Number of Gd+ lesions previous to alemtuzumab, n (%)	21 (55.3)
First DMT after diagnosis, n (%)	
IFNβ	12 (38.7)
Glatiramer acetate	7 (19.4)
Teriflunomide	4 (12.9)
Fingolimod	4 (12.9)
Natalizumab	3 (9.7)
Azathioprine	1 (3.2)
Other (unspecified)	1 (3.2)
Patients with first DMT-associated relapses, n (%)	28 (87.5)
Second DMT after diagnosis, n (%)	
Fingolimod	12 (37.5)
Natalizumab	6 (18.8)
Teriflunomide	6 (18.8)
IFNβ	5 (15.6)
Glatiramer acetate	3 (9.4)
Patients with second DMT- associated relapses, n (%)	24 (85.7)

Table 2: *Previous disease-modifying therapies to alemtuzumab.*
DMT: Disease-Modifying Therapy; Gd+: Gadolinium-Enhanced Imaging; IFNβ: Interferon Beta.

Twenty-eight (87.5%) patients had relapses after first DMT (one relapse occurred in 46.4% of the population). These events produced an early DMT switching to another therapy. The reasons for switching were recorded in only 30 cases: treatment failure (70%), side effects (16.7%), drug intolerance (10%), pregnancy (6.7%), financial reasons (3.3%), and other reasons (6.7%).

Also, table 2 showed second therapy used immediately before switching to alemtuzumab. Twenty-four (%) patients had similar relapses with these new treatments. The reasons for switching to alemtuzumab were recorded only in 28 cases: treatment failure (n = 20, 71.4%), adverse events (n = 3, 10.7%), drug intolerance (n = 3, 10.7%), pregnancy (n = 1, 3.6%) and other reasons (n = 8, 21.4%). Other reasons for switching to alemtuzumab therapy were: JC virus-positive serology, disease progression, continuous urinary tract infections, and radiological activity. Specifically, natalizumab was switched to alemtuzumab due to logistic problems to meet infusion regimen (monthly administration). The median latency time for starting alemtuzumab therapy was 68.5 months (range 4 - 196).

Baseline characteristics of alemtuzumab group

All patients enrolled in this study were treated with alemtuzumab (n = 38). Before treatment onset, these tests were performed for all patients: blood count, blood chemistry, liver function, and routine urine analysis. Only in 37 (97.4%) patients thyroid function tests were performed. Also, laboratory tests for bacterial and virus infections were performed taking into account clinical features of patients. MRI studies showed gadolinium-enhanced lesions in 21 patients (55.3%). Baseline mean EDSS was 3.8 (range 0 - 6.5) previous to alemtuzumab therapy.

Alemtuzumab follow-up: Effectiveness and safety

Retrospective data showed that twenty-four patients (63.2%) completed two treatment cycles, 13 patients received a single cycle so far (34.2%) and only one patient (2.6%) received treatment at third year. It was noticed that 19 patients were followed for more than 2 years and alemtuzumab infusion of 31 patients (81.6%) were administered in hospital facilities. On this time, only 5 patients with flare-up were reported. Furthermore, control MRI was performed in 26 cases (68.4%), as well as 4 cases of gadolinium-enhanced lesions (14.8%) and 3 patients (11.1%) with T2 activity were found.

Disability improvement was measured by a one-point decrease in EDSS. In this context, we calculated the difference between the initial EDSS and each cutoff time measured: 12 weeks, 24 weeks, at the beginning of 2nd cycle and the last recorded value. Baseline EDSS was 3.8. EDSS at 12 weeks and 24 weeks after starting the therapy was 3.1 (range 0 - 7) and 2.9 (range 0 - 7), respectively. In the other hand, the value of same parameter before 2nd cycle of alemtuzumab was 3.0 (range 0 - 7). Finally, last recorded EDSS for this study was 2.6 (range 0 - 7).

Also, we calculated the percentage of unchanged or improved EDSS in comparison with initial value. For instance, a decrease of 1.0 unit at least on this parameter was considered as a change (better or worse). We found an improved change on 65.8% of patients (baseline vs. last) and stable value in 34.2% (Figure 1).

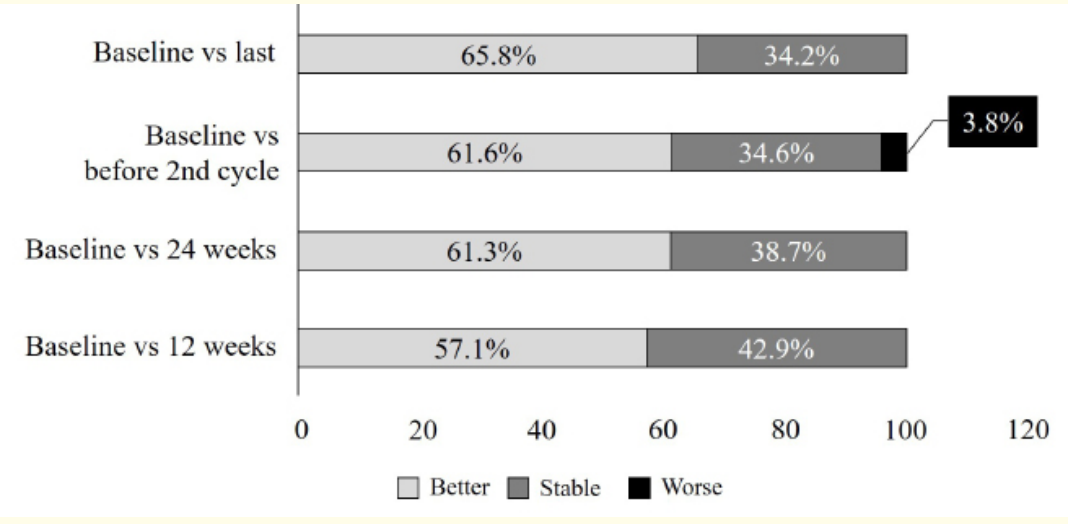

Figure 1: *EDSS calculated for each time lapse during alemtuzumab treatment.*

The univariate logistic regression analysis showed that it is 3.8 times more likely that patients achieve an improvement in EDSS in comparison with stable disease (OR 3.81, CI 95% 1.09 - 13.30; p = 0.036).

Adverse events reported included AIRs (n = 28, 73.7%), of which most were rash (72.4%), pruritus (48.3%), headache (41.4%), pyrexia (27.6%), nausea or vomiting (24.1%), cytopenia (3.4%) and others related (24.1%). Furthermore, nine patients had thyroid disorders: four patients with autoimmune thyroiditis (10.5%) and 5 with subclinical hypothyroidism (13.1%), representing 23% of the study population (Table 3).

Adverse event	%
IARs	73.7
Exanthema	74.2
Rash	48.3
Headache	41.4
Pyrexia/Fever	27.6
Nausea/Vomiting	24.1
Cytopenias	3.4
Other AEs (thyroid disorders)	24.1
Autoimmune thyroiditis	10.5
Subclinical hypothyroidism	13.1

Table 3: *Adverse events reported in patients treated with alemtuzumab.*
AE: Adverse Event; IAR: Infusion-Associated Reaction.

After alemtuzumab treatment, three patients (7.9%) eventually received a different DMT. These therapy switches were due to adverse events (two individuals), cognitive impairment (one individual) and relapses (one individual).

Final Remarks and Discussion

This RWE study has shown the effectiveness and safety of alemtuzumab for treating Mexican RRMS patients based on clinical experience. Since there are scarce data in real-world setting for this therapy, evidence revealed in this study will be very valuable for evidence-based decision making in clinics and it will enrich the existing knowledge on alemtuzumab effectiveness gained from early pivotal randomized clinical trials.

First at all, it may be noticed that median age is slightly higher in our study than CARE-MS I and II trials [13,14]. In this context, an epidemiological study performed in a Northern-Mexico population (n = 38) reported a median age of 40.3 years for disease diagnosis, which is quite similar to reported in this study. Also, most of population (82%) had a progressive relapsing MS diagnosis [3]. This suggested that this group lacked an adequate disease control, possibly due to use of DMTs that constantly failed [5]. As observed in results section of this study, the relapse frequency in spite of administration of several DMTs was high (> 80% of cases). For this reason, there is a need to identify effective and safe interventions for treating these cases. Another fact that match with our results is the proportion of female cases as described for other clinical studies (global or local setting) [3,4,14].

It should be observed that the patients enrolled in our study had a baseline active disease (68%) in spite of DMTs for controlling disease. Furthermore, it is important to mention that high percentage of patients had poor prognosis relapses (73.7%). In such scenario, it was possible to determine the effectiveness of alemtuzumab taking into account previous therapy failure as CARE-MS II assessed. Although real-world setting is characterized by non-controlled conditions is helpful to establish the intervention's robustness in realistic conditions [14].

In the other hands, IFNβ and glatiramer acetate were the therapeutic options most frequently used by neurologists who participated in the study and match with reported in CARE-MS II [14]. This finding confirms that in spite of time elapsed since alemtuzumab launch, these DMTs are still the first choice in clinical MS management [13]. Recently, Prosperini., *et al.* reported the results of the RWE study of alemtuzumab in Italian population and found that IFNβs and glatiramer acetate are part of the DMTs administered to this population. However, they are not considered last option before alemtuzumab [17]. The high relapse rate observed for these DMTs (previous to alemtuzumab) is closely associated to therapy failure (70%) and reveals a lack of control on disease progression. A similar observation was reported in Italian population where it was found that 65% (26/40) of patients showed disease progression [17].

A recent study on impact of DMTs in quality of life (QoL) revealed that therapy switching due to adverse events improves health-related QoL. Although no clinical outcome was considered for the assessment of QoL, fewer patients were switched to another DMT after alemtuzumab in comparison with traditional DMTs [18]. For this reason, a group of Latin American MS experts recommended the use of alemtuzumab as first option in patients with active disease [19]. Our results showed that only 15.8% received alemtuzumab as the first choice for treating the disease.

Most patients (71%) had suboptimal disease control before alemtuzumab administration. Despite treatment with other DMTs after relapse or adverse event triggering, administration of alemtuzumab was delayed (6.1 years). This choice could potentially increase the risk of unfavorable MS activity and progression. Our study showed that 28.1% of patients had ≥ 4 different DMTs (See table 1). Another indirect factor that perhaps limited alemtuzumab prescription as therapeutic option was the relatively recent marketing approval for Mexico [10].

Interestingly, when neurologists switched from first DMT to a second DMT (different than alemtuzumab) this did not significantly modify relapse rate: Thus, 85.7% of patients with at least one relapse and switched to different DMT remained with relapses (See table 2). This suggests poor disease control which is associated with QoL decrease and increase of healthcare-related expenses [10].

Previous studies have mentioned that patients with poor prognostic factors and aggressive MS should be evaluated for receiving alemtuzumab at any time during the course of MS [19]. This study included patients with high EDSS of 6.5 more than mild EDSS values. Our results showed that almost all patients stabilized or improved their EDSS after alemtuzumab treatment. Only one patient was worsened (before 2nd cycle). However, this patient improved later and, for this reason was not considered as treatment failure. Interestingly, Prosperini., *et al.* reported a similar result in Italian patients, where before the 2nd cycle of alemtuzumab there was an increase in EDSS associated with a mild worsening of disease symptoms during this period [17]. Interestingly, association between disease baseline activity (relapse) and probability for stabilizing or improving after alemtuzumab suggested that improvement and a higher disease activity are associated.

It is interesting that EDSS change from baseline values of current study had large differences with CARE-MS I and CARE-MS II studies (two years and 5 years, respectively). Considering a population with previous DMT treatment and 5-years follow up (CARE-MS II), alemtuzumab showed more patients with stable EDSS (51.7%) than improved (24.9%) or worsened (23.4%) EDSS [14]. In contrast, the effectiveness of our study (non-controlled conditions) defined as negative change in EDSS was observed in each of time period. Thus, we observed a large percentage of improved EDSS (> 60%) than stable or worsened EDSS in Mexican population. However, there was no statistical significance associated with the treatment duration. It should be noted that our results are limited to patients with a least two treatment cycles (63%). On the other hand, safety of alemtuzumab was similar to evidences reported in CARE-MS II for patients with two treatment cycles, whose IARs decreased over time (3 - 5 cycles) [14].

The most frequent adverse events reported in CARE-MS II were dose-dependent IARs (headache, rash, nausea, and fever). However, it was determined that only 3% had IARs [13]. Our results also show a high percentage of patients with IARs, quite similar to the reported value in the 5-year follow-up study CARE-MS II after second cycle (90.3%) and Prosperini., *et al.* study (95%, 38/40) [14,17]. Other common adverse event is infections (most frequent were Herpes zoster and urinary tract infection) with an incidence of 21% (8/38) in our population, very similar to reported in pivotal studies [14]. Also, severe leukopenia and myocardial infarction were recorded, possibly

due to cardiac ischemia promoting effect of corticoids administered during treatment or another likely proinflammatory cardiovascular process [20].

Moreover, our study found that 9 patients had thyroid disorders [4 patients with autoimmune thyroiditis (10.5%) and 5 with subclinical hypothyroidism (13.1%)], representing 23% of the study population. These results are similar to those observed in the 5-year extension CARE-MS II study, which reported a 16.5% peak of thyroid disorders (that diminished to 3.3% at the end of the study), and to those observed in the 5-year CARE-MS I study, that had a 16.7% incidence in the third year [15]. Finally, our findings matched with those observed by Prosperini., *et al.* regarding the incidence of thyroid dysfunctions (20%, 8/40) and herpes virus opportunistic infections (17.5%, 7/40) [17].

Additionally, a subject had polyarthritis 4 months after starting a first cycle with alemtuzumab; this case is still under study, and seronegative rheumatoid arthritis is suspected. The patient has an important familial record of this disease. Until now we have not found reports describing rheumatoid arthritis as an adverse event of alemtuzumab. However, we have not ruled it out as a premature secondary autoimmunity. It should be also stated that three patients received a different DMT after administering alemtuzumab due to adverse events or relapses. In only one case it was administered due to disability progression with radiological activity in T2 and atrophy.

Recently, European Medicine Agency restricted alemtuzumab due of new reports on immune-associated conditions and the presence of heart and blood vessels disorders, including fatal cases, when alemtuzumab was used. For this instance, a detailed review is ongoing in order to clarify this situation. Despite the above report, COFEPRIS have not determined whether this situation is applicable for Mexico. Nowadays, there is not any immunological or cardiovascular similar threats reported for the Mexican population. For this reason, this pharmacovigilance alert did not affect the progress of this study at all.

Our study does not consider MS-associated comorbidities. As extensively known, diabetes mellitus, cardiovascular diseases and obesity are highly prevalent conditions in Mexico and they are associated with MS pathophysiology [21,22]. It has been described that MS is associated with diabetes, hypertension, cardiopathies and chronic lung diseases. A retrospective case and controls study using administrative data of a large Canadian population found that in a population with diagnosed MS the presence of comorbidities is associated with an increase in mortality risk [23].

For this study major limitations include the retrospective, observational nature of this study, which introduces unknown selection and other treatment biases but are a necessary component of performing a study with high external validity (informing on actual treatment conditions, as opposed to the highly-controlled environment of an RCT). Finally, the sample size of this study is relatively small and the length of follow-up is rather short, which limits the extent of rare adverse events that could be observed and its generalizability to the entire Mexican population with MS.

Conclusion

This real-world evidence study of alemtuzumab in RRMS patients contributes to the knowledge on effectiveness and safety of this intervention in non-controlled and realistic setting of clinical practice. The limited population sample could be a factor which generate uncertainty but is supported by heterogeneity of population evaluated. Alemtuzumab safety would be limited to IARs and immunosuppression-associated infections. For this reason, it is recommended to use this DMT into hospital facilities with constant medical supervision. Our major finding is that higher disease activity is associated with a greater probability of response with alemtuzumab.

Acknowledgements

The authors would like to thank Juan Carlos Sánchez-Salgado from Guzsel Publicidad, S.A. de C.V. for his contribution in writing and editing of this manuscript. This service was supported by Sanofi Mexico, S.A. de C.V.

Conflict of Interest

The authors state the following potential conflicts of interests regarding the research, authorship and/or publication of this article: ITF has been a consultant and/or speaker for Sanofi, TEVA, Novartis, Roche, Stendhal and Merck. She has been also researcher in clini-

cal trials funded by Sanofi and Roche. MAMI has been an advisor for Sanofi-Genzyme. CFPC is a Roche/Genentech employee. JJFR has been medical writer and advisory board member for Sanofi. LEAS, VJRG, VRA, LEMC, JMEG, BBC, MAQ, MDMF, and DCLH have nothing to disclose.

Funding

The authors received financial support from Sanofi Mexico S.A. de C.V. for the research required for this project.

Bibliography

1. Compston Alastair and Alasdair Coles. "Multiple Sclerosis". *Lancet* 372.9648 (2008): 1502-1517.
2. Reich Daniel S., *et al*. "Multiple Sclerosis". *The New England Journal of Medicine* 378.2 (2018): 169-180.
3. De la Maza M and G Arrambide. "Prevalencia de Esclerosis Múltiple En El Municipio de San Pedro Garza García, Nuevo León". *Medicina Interna de México* 3.9 (2006): 7-10.
4. Dubey Divyanshu., *et al*. "Intractable and Highly Active Relapsing Multiple Sclerosis - Role of Alemtuzumab". *Neuropsychiatric Disease and Treatment* 11 (2015): 2405-2414.
5. Freedman Mark S and Carolina A. Rush. "Severe, Highly Active, or Aggressive Multiple Sclerosis". *Continuum* 22.3 (2016): 761-784.
6. Bergamaschi Roberto. "Prognostic Factors in Multiple Sclerosis". *International Review of Neurobiology* 79 (2007): 423-447.
7. Guillemin Francis., *et al*. "Older Age at Multiple Sclerosis Onset Is an Independent Factor of Poor Prognosis: A Population-Based Cohort Study". *Neuroepidemiology* 48.3-4 (2017): 179-187.
8. Cerqueira João J., *et al*. "Time Matters in Multiple Sclerosis: Can Early Treatment and Long-Term Follow-up Ensure Everyone Benefits from the Latest Advances in Multiple Sclerosis?" *Journal of Neurology, Neurosurgery, and Psychiatry* 89.8 (2018): 844-850.
9. Curkendall Suellen M., *et al*. "Potential Health Care Cost Savings Associated with Early Treatment of Multiple Sclerosis Using Disease-Modifying Therapy". *Clinical Therapeutics* 33.7 (2011): 914-925.
10. Skromne-Eisenberg Eli., *et al*. "Disease-Modifying Therapies in Multiple Sclerosis in Latin America". *Multiple Sclerosis Journal - Experimental, Translational and Clinical* 3.3 (2017): 2055217317723369.
11. Berger T. "Immunological Processes Related to Cognitive Impairment in MS". *Acta Neurologica Scandinavica* 134.200 (2016): 34-38.
12. Ziemssen Tjalf and Katja Thomas. "Alemtuzumab in the Long-Term Treatment of Relapsing-Remitting Multiple Sclerosis: An Update on the Clinical Trial Evidence and Data from the Real World". *Therapeutic Advances in Neurological Disorders* 10.10 (2017): 343-359.
13. Cohen Jeffrey A., *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* 380.9856 (2012): 1819-1828.
14. Coles Alasdair J., *et al*. "Alemtuzumab CARE-MS II 5-Year Follow-up: Efficacy and Safety Findings". *Neurology* 89.11 (2017): 1117-1126.
15. Havrdova Eva., *et al*. "Alemtuzumab CARE-MS I 5-Year Follow-up: Durable Efficacy in the Absence of Continuous MS Therapy". *Neurology* 89.11 (2017): 1107-1116.
16. Ziemssen T., *et al*. "[Real-world evidence: Benefits and limitations in multiple sclerosis research]". *Der Nervenarzt* 88.10 (2017): 1153-1158.
17. Prosperini Luca., *et al*. "No Evidence of Disease Activity (NEDA-3) and Disability Improvement after Alemtuzumab Treatment for Multiple Sclerosis: A 36-Month Real-World Study". *Journal of Neurology* 265.12 (2018): 2851-2860.

18. Jongen Peter Joseph. "Health-Related Quality of Life in Patients with Multiple Sclerosis: Impact of Disease-Modifying Drugs". *CNS Drugs* 31.7 (2017): 585-602.

19. Gracia Fernando., *et al*. "Esclerosis Múltiple En América Central y El Caribe: Estado Actual y Recomendaciones Clínicas". *Revista Mexicana de Neurociencia* 18.2 (2017): 76-88.

20. Kabata Tamon., *et al*. "Vascular Endothelial Growth Factor in Rabbits during Development of Corticosteroid-Induced Osteonecrosis: A Controlled Experiment". *The Journal of Rheumatology* 35.12 (2008): 2383-2390.

21. Meza Rafael., *et al*. "Burden of Type 2 Diabetes in Mexico: Past, Current and Future Prevalence and Incidence Rates". *Preventive Medicine* 81 (2015): 445-450.

22. Rtveladze Ketevan., *et al*. "Obesity Prevalence in Mexico: Impact on Health and Economic Burden". *Public Health Nutrition* 17.1 (2014): 233-239.

23. Marrie Ruth Ann., *et al*. "Effect of Comorbidity on Mortality in Multiple Sclerosis". *Neurology* 85.3 (2015): 240-247.

Volume 12 Issue 4 April 2020