Real-world experience of ocrelizumab in multiple sclerosis patients in Latin America

Experiencia en la vida real con el uso de ocrelizumab en pacientes con esclerosis múltiple en Latinoamérica

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ABSTRACT

Background: Despite the abundance of information concerning ocrelizumab in phase III clinical trials, there is scarce evidence regarding real-world patient profiles. Objective: The aim of this study was to investigate patient profiles, effectiveness and persistence with treatment among patients who used ocrelizumab for treatment of multiple sclerosis in Latin America. Methods: This was a retrospective multicenter study in Argentina, Chile and Mexico. Medical record databases on patients who received ocrelizumab were analyzed. Demographic and clinical variables were described, along with effectiveness outcomes, which included the proportions of patients free from clinical relapses, from disability progression and from new or enlarging T2 or T1 gadolinium-enhancing lesions, on annual magnetic resonance imaging.

Results: A total of 81 patients were included. The most frequent phenotype was relapsing-remitting MS, in 64.2% of the patients. The mean age at study entry was 41.3 ± 12.0 years and 51.8% were women. A total of 38% had had relapse activity during the 12 months before starting on ocrelizumab, with a mean relapse rate of 1.3 ± 0.6 during that period. 75% were free from clinical relapses and 91% were free from gadolinium-enhancing lesions in the relapsing-remitting course. Ocrelizumab discontinuation during the first 12 months was

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the CNS that leads to focal plaques of primary demyelination and diffuse neurodegeneration in the grey and white matter of the brain and spinal cord. In most patients, the disease starts with a relapsing-remitting course (RRMS), which is followed for several years by a secondary progressive phase (SPMS). Patients with primary progressive disease (PPMS) skip the relapsing and remitting stage and start with uninterrupted progression from disease onset.

It has been almost 25 years since the publication of the pivotal trial results for the first disease-modifying therapy (DMT) for RRMS. Currently, the DMTs for MS that have been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) include interferon beta (IFNβ) 1a and 1b, glatiramer acetate (GA), mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab and ocrelizumab.

Ocrelizumab was approved in March 2017 for the treatment of relapsing or primary progressive MS. A phase II trial established 600 mg intravenously every 6 months as the preferred dosing schedule. Two phase III trials evaluated the efficacy of ocrelizumab in patients with RRMS and individual and pooled analyses demonstrated significant reductions in the annualized relapse rate (p < 0.001 pooled), disability progression at 12 weeks (p < 0.001 pooled) and gadolinium-enhancing lesions on magnetic resonance imaging (MRI; p < 0.001). Patients with PPMS were evaluated in a third phase III trial, which showed a significant decrease in both disease progression at 12 weeks (p = 0.03) and the volume of T2-weighted lesions on MRI (p < 0.001). As with other monoclonal antibodies, the adverse effects seen with ocrelizumab were primarily infusion-related reactions and infection. Despite the abundance of information concerning the efficacy and safety of ocrelizumab in phase III clinical trials, there is scarce evidence regarding real-world patient profiles.

The aim of this study was therefore to evaluate patient profiles, effectiveness and persistence with treatment during follow-up, in a retrospective study on patients who were prescribed ocrelizumab for treatment of MS in Latin America (LATAM).

METHODS

We conducted a retrospective multicenter study in Argentina, Chile and Mexico. We reviewed all medical record databases of patients who received ocrelizumab and were followed for at least one year before and after starting treatment. Only patients with a diagnosis of MS defined according to validated criteria were considered for inclusion in the study.

Clinical parameters evaluated at baseline

The demographic and clinical characteristics of the disease were collected at the time when use of ocrelizumab was started. Age and gender data were extracted, along with disease characteristics including the following: age at onset, disease duration since the first relapse (defined as detection of the first sign/symptom that suggested CNS demyelination in the optic nerves, brain stem, spinal cord or other regions and which was not attributable to other diseases), clinical and radiological activity during the year previous to ocrelizumab treatment (clinical activity defined as new...
month and the reasons for discontinuation of treatment with ocrelizumab over the 12 months after inclusion during the follow-up, the proportion of patients discontinuing treatment with ocrelizumab was described in 68% of the patients. The mean age of the patients at study entry was 41.3 ± 12.0 years, and 51.8% of the patients were women. The mean disease duration was 8.4 years, and most of the patients included were employed at the time of study entry (77%). The principal characteristics of the patients included are presented in Table 2. The main reason for starting ocrelizumab among RRMS patients was treatment failure, in 48%, while among PPMS patients the most frequent reason was disease progression (defined as EDSS progression).

A total of 38% of the patients included had had relapse activity during the 12 months before starting use of ocrelizumab. During that period, the mean relapse rate was 1.3 ± 0.6. Almost all the relapses in the cohort were treated with corticosteroids (96%). EDSS progression was observed in 49.4% of patients during the previous 12 months, while new T2 MRI lesions were described in 68% of the patients. The activity during the 12 months before use of ocrelizumab was started is described in Table 3.

The study was approved by the local ethics committee of each participating center, and written or oral informed consent was obtained from all participants.

### Statistical analysis
Continuous data were expressed with their means and SD. Categorical data were expressed as percentages. Demographic and clinical variables were described, along with the proportion of the patients who discontinued the treatment with ocrelizumab over the 12 months after inclusion. Persistence was a continuous value defined as the number of days from the date of starting ocrelizumab use to the date of discontinuation of the index treatment. Statistical analyses were performed using the Stata 15 software.

### RESULTS

#### Study population and baseline characteristics
A total of 81 patients met the inclusion criteria and were included (38.3% were from Argentina, 40.7% from Chile and 21% from Mexico) (Table 1). Many of the patients included were part of the compassionate use of ocrelizumab in Latin America. The most frequent phenotype was RRMS, in 64.2% of the patients included (Table 1). The mean age of the patients at study entry was 41.3 ± 12.0 years, and 51.8% of the patients were women. The mean disease duration was 8.4 years, and most of the patients included were employed at the time of study entry (77%). The principal characteristics of the patients included are presented in Table 2. The main reason for starting ocrelizumab among RRMS patients was treatment failure, in 48%, while among PPMS patients the most frequent reason was disease progression (defined as EDSS progression).

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### Table 1. Patient distribution according to country and disease phenotype.

| Country          | Total (n) | RRMS (n) | PPMS (n) |
|------------------|-----------|----------|----------|
| Argentina        | 31 (38.3) | 5 (16.1) | 26 (83.9) |
| Chile            | 33 (40.7) | 30 (90.9) | 3 (9.1)   |
| Mexico           | 17 (21.0) | 17 (100) | 0        |
| Total            | 81 (100)  | 52 (64.2) | 29 (35.8) |

RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis.
**Effectiveness**

Among RRMS patients, during the follow-up, 15% had a relapse, 4% progressed in EDSS and 8% had new gadolinium lesions on follow-up MRI (Table 3). Among PPMS patients, 7% had a relapse, 31% progressed in EDSS and only 2 patients had a new gadolinium lesion on MRI during follow-up (Table 3). Among both RRMS and PPMS patients, there was a reduction in the annualized relapse rate, in comparison with the year before ocrelizumab treatment was started (1.4 ± 0.7 vs. 0.23 ± 0.4; p < 0.001; and 1 ± 0.3 vs. 0.22 ± 0.15; p = 0.01; in RRMS and PPMS respectively) (Table 3).

**Persistence evaluation**

Regarding ocrelizumab administration and persistence during the first year of ocrelizumab treatment, the mean time between the first administration (300 mg) and the second administration (corresponding to the first cycle) was 16 days, while the period between the first and the second cycles was 6.1 months. Ocrelizumab discontinuation during the first 12 months was observed in 3 patients (3.7%). The reasons are described in Table 4. The mean persistence observed at the time of the first-year follow-up was 338 ± 24 days (Figure 1).

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**Table 2.** Patient characteristics at baseline.

|                      | Total          | RRMS           | PPMS           |
|----------------------|----------------|----------------|----------------|
| Mean age (years) ± SD| 41.3 ± 12.0    | 37.8 ± 12.0    | 47.4 ± 12.0    |
| Female sex, n (%)    | 42 (51.8)      | 31 (60)        | 11 (38)        |
| Mean EDSS ± SD       | 3.1 ± 1.8      | 2.8 ± 1.9      | 3.6 ± 1.7      |
| Mean disease duration (years) ± SD | 8.4 ± 6.3 | 8.8 ± 7.2 | 7.8 ± 4.3 |
| Working status       |                |                |                |
| Employed             | 63 (77)        | 40 (77)        | 23 (79)        |
| Unemployed           | 18 (23)        | 12 (23)        | 6 (21)         |
| Previous DMT, n (%)  | 62 (76.5)      | 45 (86)        | 17 (58)        |
| Type of previous DMT, n (%) |            |                |                |
| Beta interferon      | 23 (37.0)      | 16 (35.5)      | 7 (41.0)       |
| Glatiramer acetate   | 2 (3.2)        | 2 (4.5)        | 0              |
| Teriflunomide        | 1 (1.6)        | 1 (2.2)        | 0              |
| Fingolimod          | 5 (8.0)        | 2 (4.5)        | 3 (17.7)       |
| Dimethyl fumarate    | 1 (1.6)        | 1 (2.2)        | 0              |
| Natalizumab         | 14 (22.5)      | 11 (24.5)      | 3 (17.7)       |
| Rituximab            | 16 (25.8)      | 12 (26.7)      | 4 (23.5)       |
| Previous 2 or more DMT, n (%) | 41 (50) | 32 (61) | 9 (31) |
| Reason for starting use of ocrelizumab |              |                |                |
| Treatment failure with previous DMT | 20 (25) | 25 (48) | 6 (21) |
| Adverse event with previous DMT | 31 (38) | 14 (27) | 6 (21) |
| Disease progression  | 30 (37)        | 13 (25)        | 17 (58)        |

**Table 3.** Patient characteristics before and after starting treatment with ocrelizumab.

|                      | RRMS |                | PPMS |                |
|----------------------|------|----------------|------|----------------|
|                      | Year before treatment with ocrelizumab | After starting treatment with ocrelizumab | p-value | Year before treatment with ocrelizumab | After starting treatment with ocrelizumab | p-value |
| Relapse activity, n (%) | 32 (62) | 8 (15) | 0.01 | 11 (38) | 2 (7) | 0.37 |
| Mean relapse rate ± SD | 1.4 ± 0.7 | 0.23 ± 0.4 | < 0.001 | 1 ± 0.3 | 0.22 ± 0.15 | 0.01 |
| Steroid treatment for relapse, n (%) | 30 (95) | 3 (37) | 0.001 | 9 (100) | 2 (100) | 0.67 |
| EDSS progression, n (%) | 21 (40.4) | 2 (4) | 0.31 | 19 (65.5) | 9 (31) | 0.09 |
| GAD + MRI activity, n (%) | 30 (58.0) | 4 (8) | 0.06 | 10 (34.5) | 2 (7) | 0.44 |
| T2 MRI activity, n (%) | 41 (78.8) | 18 (35) | 0.001 | 19 (65.5) | 7 (24) | 0.05 |

RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; EDSS: expanded disability status scale; DMT: disease-modifying treatment; SD: standard deviation.
Our study has certain limitations. One important weakness was the low number of patients recruited. Although a greater number of patients could have given a different power to the study, our number permitted the intended analysis. Another limitation was the observational design and the lack of randomization and control group. Lastly, there was only a short follow-up (up to one year).

Our results nevertheless represent the first post-market-studies conducted in Latin America and in its region, on the use of ocrelizumab in a real-world setting. The importance of this study lies in the possibility that it has provided for exploring other conditions beyond the efficacy and safety of specific treatments, in large populations of patients that are not typically included in initial randomized controlled trials, thereby improving our knowledge about a specific treatment in clinical practice.11,12.

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Figure 1. Persistence with ocrelizumab treatment during the study period.