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COMB157GES01 Study Results Abstract for Public Disclosure

Title

A cross-sectional study to assess the effectiveness and safety of ofatumumab (Kesimpta®) in patients with relapsing multiple sclerosis in the Spanish clinical practice: the CRONOS-MS study.

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NIS Type

NIS with Primary and Secondary Data Collection

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Keywords

Multiple sclerosis; anti-CD20; ofatumumab; real-world

Rationale and background

Ofatumumab (Kesimpta®) is a fully human anti-CD20 monoclonal antibody that received European approval in March 2021 for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease, defined by clinical or imaging features. In November 2022, the Spanish Ministry of Health, Consumption, and Social Welfare confirmed the authorization for ofatumumab inclusion in the pharmaceutical delivery system of the National Health System. This milestone now enables patients with RMS in Spain to access ofatumumab, among other available disease-modifying treatments (DMT), within the clinical practice setting.

Real-world evidence (RWE) of the experience with ofatumumab is limited and no study in patients treated in Spain has been conducted yet. The present study aims to characterize the use of subcutaneous ofatumumab in a real-world setting. Specifically, the investigation will assess the effectiveness, safety, and treatment adherence associated with subcutaneous ofatumumab in individuals with relapsing forms of multiple sclerosis (RMS) within the Spanish healthcare system. Additionally, the study will delve into the patient demographic and experiential aspects, employing patient-reported outcomes (PROs) to gain a comprehensive understanding of the treatment experience in Spain.

Research question and objectives

Primary objective

To determine the effectiveness of ofatumumab in reducing the ARR in patients with RMS in the real-world setting.

Secondary objectives

1. To determine the effectiveness of ofatumumab in reducing the ARR in patients with RMS based on prior DMT (naïve vs previously treated).

2. To determine the effectiveness of ofatumumab in reducing the ARR in patients with RMS based on the efficacy of prior DMT (high-efficacy DMT vs moderate-efficacy DMT).

3. To describe patient characteristics and prior DMTs at baseline (i.e. ofatumumab initiation).

4. To estimate time to first relapse after ofatumumab treatment initiation.

5. To describe the proportion of relapse-free patients during ofatumumab treatment.

6. To assess changes in disability during ofatumumab treatment.

7. To assess radiological activity on MRI scan during ofatumumab treatment.

8. To assess the safety profile of ofatumumab.

9. To examine the adherence to ofatumumab.

10. To estimate the proportion of patients who discontinue ofatumumab during the observation period.

11. To assess work productivity and activity impairment in patients treated with ofatumumab.

12. To evaluate cognitive impairment in patients treated with ofatumumab.

13. To describe fatigue in patients treated with ofatumumab.

14. To describe health-related quality of life (HRQOL) in patients treated with ofatumumab.

15. To assess the change in physician's and patient's perception of patient progress and treatment response to ofatumumab.

16. To evaluate patient satisfaction with ofatumumab.

Study design

This is a non-interventional, cross-sectional, multicentric, and nationwide study, based on primary and secondary data collection.

Setting

The study was conducted on 310 RMS patients at 32 Neurology Departments and MS Units at hospitals in Spain.

Inclusion criteria

1. Aged ≥ 18 years.

2. Written informed consent.

3. Diagnosis of RMS per McDonald Criteria (2017).

4. Ofatumumab treatment in line with the European Kesimpta® summary of product characteristics (SmPC; i.e. adult patients with RMS with active disease defined by clinical or imaging features) during at least 12 months and patients who discontinued ofatumumab after receiving at least one dose with a minimum monitoring of 12 months.

Exclusion criteria

1. Currently participating in a clinical trial.

2. Not able/unlikely to complete with all study activities according to investigator's criteria.

3. Have a contraindication for ofatumumab use, according to the SmPC.

Subjects and study size, including dropouts

Considering the adjusted ARR for ofatumumab (0.12; midpoint confidence intervals 95% CI: 0.09 to 0.14) and teriflunomide (0.22; midpoint confidence intervals 95% CI: 0.18 to 0.26) from the ASCLEPIOS I trial. Patients treated with ofatumumab showed a 56% relative reduction in ARR ($\lambda ofa = 0.111$) compared to those treated before ofatumumab ($\lambda oth = 0.22$), calculated as $\lambda ofa / \lambda oth = 0.5593$. To detect this difference with 90% power and a one-sided alpha level of 0.025 in patients treated with ofatumumab 1-year, and assuming a dispersion parameter of $\kappa = 0.82$, a sample size of 300 participants would be needed. A maximum dropout rate of 3% was expected, therefore, the final sample size should be 310 patients.

Variables and data sources

Primary variable

Reductions in the ARR during ofatumumab treatment compared to baseline (i.e. 12 months preceding the initiation of ofatumumab).

Secondary variables

1. Reductions in the ARR during ofatumumab treatment compared to baseline (i.e. 12 months preceding the initiation of ofatumumab, if available) in naïve vs previously treated patients.
2. Reductions in the ARR during ofatumumab treatment compared to baseline (i.e. 12 months preceding the initiation of ofatumumab, if available) in previously treated with high-efficacy DMT vs previously treated with moderate-efficacy DMT.
3. Patient characteristics at baseline (i.e. ofatumumab initiation):
    - Demographics:
        - Age, gender, ethnicity, education, working status, type of job, physical activity, smoking status, and alcohol consumption
    - Anthropometrics:
        - Body mass index (BMI)
    - Clinical characteristics:
        - Type of MS (relapsing-remitting MS [RRMS], active secondary progressive MS [SPMS])
        - Time (years) since MS diagnosis
        - Number of relapses in the last 24 and 12 months before the start of ofatumumab treatment
        - Expanded Disability Status Scale (EDSS) score (last EDSS conducted at any point within 6 months before ofatumumab initiation; the EDSS must have been assessed with no concurrent relapses and at least 30 days after the onset of last relapse)
        - Symbol Digit Modalities Test (SDMT) score (last SDMT conducted at any point within 6 months before ofatumumab initiation), if available
        - Radiological disease activity status:
            - Presence (yes/no) and number of Gd+-T1 lesions within the 6 months before ofatumumab initiation
            - Presence (yes/no) and number of new/enlarged T2 lesions within the 6 months before ofatumumab initiation, if available.
    - Prior DMTs:
        - Presence: yes/no
        - If previously treated, name (i.e. active ingredient) and date of initiation and end of each prior DMT

- Reason for switching from the prior DMT to ofatumumab (poor effectiveness, presence of adverse events, poor adherence, patient's wish, mode of administration, other)
- Number of DMT changes before starting ofatumumab
- Time (years) treated with the prior DMT
- Time (months/days) elapsed between the last administration of prior DMT and ofatumumab initiation

- Comorbid medical conditions, including hypertension, cardiac disease, diabetes mellitus, uveitis, and others
- Administered concomitant symptomatic treatment of MS, such as corticoids, potassium channel blockers (fampridine), antidepressants, and others

4. Number of days from ofatumumab treatment initiation to first relapse.
5. Proportion of relapse-free patients 12 months after ofatumumab treatment initiation.
6. Change in EDSS score after 6 months (±2 months) and after 12 months (±2 months) of ofatumumab treatment initiation compared to the EDSS before ofatumumab treatment initiation.
7. Radiological disease activity on the cranial MRI conducted after 6 months (±2 months) and after 12 months (±2 months) of ofatumumab initiation compared to baseline MRI, if available:
   - Presence (yes/no) and number of Gd+T1 lesions
   - Presence (yes/no) and number of new and/or enlarging T2 hyperintense lesions
8. Percentage of participants reporting AEs and serious AEs (SAEs) after the first injection of ofatumumab and during this treatment:
   - Percentage of participants reporting any AEs
   - Percentage of participants reporting injection site reactions (ISR), type of ISR (systemic, local), premedication use, and ISR resolution (spontaneous, use of treatments)
   - Percentage of patients with SAEs
   - Percentage of patients with AEs leading to temporal or permanent discontinuation
   - Number of pregnancies and pregnancy outcome
9. Proportion of participants with non-adherence, defined as skipping at least one dose during initial dosing (i.e. missing one weekly injections, defined as not receiving the dose within the established 7 and 14 days after the prior dose) or during maintenance dosing (missing one monthly injection, defined as not receiving the dose within the established month after the prior dose) as per SmPC.
10. Proportion of patients who discontinue ofatumumab during the observation period, reasons (such as lack of effectiveness [relapses, radiological activity], AEs, tolerability, patient decision, other), timepoint (e.g. between dose x and dose y) for temporal or permanent discontinuation, posterior DMT for permanent discontinuation and timepoint or restarting ofatumumab for temporal discontinuation.
11. Scores on the Work Productivity and Activity Impairment (WPAI) questionnaire at the study visit.

12. Scores on the SDMT at the study visit.
13. Scores on the Modified Fatigue Impact Scale-5 (MFIS-5) at the study visit.
14. Scores on the EuroQol-5 dimension (EQ-5D)-5L at study the visit.
15. Scores on the Patients' Global Impression of Change (PGIC) scale completed by patients and the Clinical Global Impressions (CGI) scale completed by physicians.

Scores on the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

The study will use primary and secondary data collection. Primary data collection includes information collected using PRO, clinical-reported outcomes (ClinRO), scales or tests and the interview during the study visit. Secondary data collection includes existing data from electronic medical records (EMR) or paper-based medical records, collected as part of the routine follow-up of patients with RMS in the clinical practice.

Statistical methods

Frequency tables will be performed for categorical variables, whereas continuous variables will be described by the mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum of each variable. The number of non-evaluable outcomes and missing data will also be provided.

A statistical analysis plan (SAP) describing the proposed statistical analysis in detail will be developed as a separate document once the study protocol has been approved.

Relative reduction in ARR of patients treated with ofatumumab will be calculated using a generalized linear model for a negative binomial distribution, considering the previous ARR as an adjustment variable. Other adjustment variables may be defined in the SAP.

Kaplan-Meier analyses will be provided for time to first relapse. The median and the 95% CI as well as the number of events and patients censored will be provided.

An interim analysis will be conducted when 30% of the study sample has been included in the study for the primary objective and some secondary objectives.

Sensitivity analysis for the study objectives considering participants who have discontinued ofatumumab within 12 months after the first dose will be conducted.

Results

Patient profile

This study evaluated a real-world population of 310 patients with MS (98.71% RRMS, 1.29% secondary progressive), with a mean age of 42.15 years and a higher proportion of females (68.39%). Almost all patients (96.77%) were Caucasian. More than half of patients (57.74%) presented comorbidities.

Mean time since MS diagnosis was 8.36 years with a median of 5.0 years. In the 24 and 12 months before starting ofatumumab, most patients (84.84% and 90.65%, respectively) had zero or one relapse, with a mean of 0.74 and 0.66 relapses, respectively.

In the 6 months prior to starting treatment with ofatumumab mean EDSS was 2.10 and mean SDMT was 48.90.

At baseline, 25.48% of patients presented gadolinium-enhancing T1 lesions (mean: 3.14; median 2.0), and 85.16% exhibited T2 lesions, with 38.26% showing more than 20 lesions.

Effectiveness of ofatumumab

The ARR was reduced >90% in patients with MS 12 months after treatment with ofatumumab (0.66 vs 0.06, $p < 0.0001$), regardless of their treatment status (previously treated or naïve). Considering the

efficacy of prior DMT, patients previously treated with moderate-efficacy DMTs had a higher ARR reduction compared with those who had received high-efficacy DMTs (93.3% vs 83.3%).

After ofatumumab treatment (mean exposition time: 426.81 days), <7% of patients relapsed, with a median time to relapse of 100 days (mean exposition time: 139.95 days).

On the other hand, the proportion of patients with gadolinium-enhancing T1 lesions decreased from 25.48% at baseline to 0.00% at 12 months after treatment initiation. In addition, new or enlarged T2 lesions after 12 months were observed in only 6.13% of patients.

EDSS remained stable after one year treatment with ofatumumab.

Adherence and discontinuation

All the initial doses (week 0, 1 and 2) were received by almost all patients included in the study (99.03%) and 98.71% of patients received all subsequent monthly doses. Based on this, 97.74% of the patients were considered adherent.

Only eight (2.58%) patients discontinued treatment; the main reason for discontinuation was lack of effectiveness (37.50%). Only one patient discontinued due to adverse events.

PROs, ClinRO, scales and tests

The use of WPAI showed that patients in our study reported a mean of 32.65% of activity impairment due to their health status. In addition, and considering only those patients currently employed, the mean percentage of general incapacity for work due to health was 23.07%. In this sense, these patients reported missing a mean of approximately 3 working hours in the past seven days and actually working a mean of approximately 32 hours.

After treatment with ofatumumab, the mean score for the SDMT was 48.94, showing no change from the score obtained in the 6 months prior to starting treatment with ofatumumab (48.90).

The mean total score obtained in the MFIS-5 questionnaire evaluating patients' fatigue was 8.53 points.

The overall patients' HRQoL, evaluated with the EQ-5D-5L questionnaire, was good, scoring a mean of 72.28/100 points. In line with this result, the score for each dimension was low (≤2.00 points).

According to physician's and patient's evaluation of patient's perception of patient progress and treatment response to ofatumumab, at least half of the patients improved in some degree after treatment with ofatumumab.

The minimum score for each domain of TSQM-9 questionnaire was 72/100.

Safety

A total of 197 (63.55%) patients reported adverse events (AEs). The total number of AEs was 550, of which 267 (48.55%) were considered unrelated to ofatumumab. Most patients (76.65%) presented 1-3 AEs, with a mean number of 2.79 AEs per patient.

Most AEs recorded were mild (92.55%) and only 7 serious AEs (1.27%) were reported in 5 patients; 3 patients reported 1 SAE, and 2 patients reported 2 SAEs, resulting in a mean (SD) of 1.40 (0.55) SAE per patient.

Only 3 patients (0.97%) with AEs discontinued the treatment.

The most common AE was the systemic reaction related to the injection (28.91%), reported in 30.00% of patients.

Exploratory analysis: prediction of response to ofatumumab and depletion of B cells after ofatumumab treatment

An older patient's age (OR: 1.037) and a higher number of relapses in the previous 12 months (OR: 1.683) were considered risk factors for EDSS worsening after 12 months. Similarly, the number of relapses in the previous 12 months (OR: 2.311) was found to be a risk factors for new or enlarged T2

lesions after 6 months. In addition, male sex (OR: 3.356) was found to be a risk factors for new or enlarged T2 lesions after 12 months.

Regarding B cell depletion, patients in our study showed a statistically significant decrease in blood B-cell count from 166.78 cells/µL at baseline to 0.99 cells/µL after ofatumumab treatment initiation ($p < 0.0001$:

Discussion

The CRONOS study provides an overview of the use of ofatumumab for the treatment of MS in routine clinical practice in Spain.

Overall, sociodemographic and clinical characteristics of patients included in our study are similar to those included in the ASCLEPIOS clinical trials and in real-world studies and thus, is representative of patients with MS.

Treatment with ofatumumab was effective in reducing ARR after 12 months regardless of treatment status and the efficacy of previous treatments received. In addition, only a small proportion of patients relapsed, and radiological and MRI activity were reduced, as previously reported.

Regarding quality of life, patients in our study presented an overall good HRQoL and were not likely to be affected by fatigue. Patients improved after treatment with ofatumumab and were satisfied with the treatment. Data in the literature on this regard are limited.

Treatment with ofatumumab resulted in the expected adverse events based on previous clinical trials and real-world studies. Despite this, ofatumumab represents a safe therapeutic option for patients with MS.

Conclusion

The CRONOS study provides an overview of the current situation of the patients with MS treated with ofatumumab in routine clinical practice in Spanish hospitals as well as real-world evidence supporting the effectiveness and safety of ofatumumab in patients with MS.

Patients with MS in our study experienced significant improvements in ARR and disease activity 12 months after treatment with ofatumumab, regardless of their previous treatment received. In addition, patients had a good overall quality of life, showing some degree of improvement and high satisfaction with the treatment.

Overall, the results of our study confirm the beneficial effects of ofatumumab observed in both clinical trials and real-world studies, showing that ofatumumab is an effective and safe treatment option for patients with MS in a real-world setting.

1 List of abbreviations

Abbreviations	Explanation
AE	Adverse event
ARR	Annualized relapse rate
BMI	Body mass index
CGI	Clinical Global Impressions
DMT	Disease-modifying treatments
EDSS	Expanded Disability Status Scale
EMR	Electronic medical record
EQ-5D	EuroQol-5 dimension
Gd+	Gadolinium-enhancing
HRQoL	Health-related quality of life
IQR	Interquartile range
ISR	Injection site reactions
MFIS	Modified Fatigue Impact Scale
MS	Multiple sclerosis
NIS	Non-Interventional Study
PGIC	Patients' Global Impression of Change
PRO	Patient-reported outcome
RMS	Relapsing multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SmPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
WPAI	Work Productivity and Activity Impairment