Long-term effectiveness of three anti-CGRP monoclonal antibodies in resistant migraine patients: a real-world study

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Abstract

Aim: To assess the long-term effectiveness, clinical predictors, safety, and treatment persistence of three anti-CGRP mAbs (erenumab, galcanezumab, fremanezumab) in RM patients. Methods: A single-center retrospective study was conducted from December 2019 to June 2023 involving 126 RM patients who received anti-CGRP mAbs treatment for at least 6 months. Demographic and clinical data were collected, and assessments were conducted at 6, 12, and 24 months. Effectiveness was evaluated using clinical burden parameters, acute medication usage, and monthly migraine days (MMD). Patients achieving a ≥ 50% reduction in MMD were classified as responders, and baseline parameters and logistic regression between groups were analyzed. Adverse effects and treatment discontinuation were documented. Results: Treatment with anti-CGRP mAbs led to significant reductions in disability, MMD and acute medication usage, with sustained improvements observed up to 24 months. Responders exhibited lower baseline MMD and medication overuse. Medication overuse was identified as a negative predictor of treatment efficacy. Safety profiles were favorable, with few adverse events and minimal treatment discontinuations. Conclusion: Anti-CGRP mAbs prove effective in reducing migraine-related disability and headache frequency in RM patients over a 24-month period with favorable safety profiles. However, controlled studies with larger populations are warranted for further validation.
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What is already known about this subject:

Anti-CGRP mAbs have shown clinical effectiveness and safety in randomized clinical studies.

The majority of real-life studies with anti-CGRP mAbs have collected data up to a 6-month period, with long-term effectiveness studies being scarce.

What this study adds:

Long-term effectiveness and safety of three anti-CGRP mAbs in the clinical practice up to two years.

Anti-CGRP are effective treatments for resistant and chronic migraine patients, reducing migraine-related disability and headache frequency over a 2 year period with a good safety profile.

Introduction

Migraine affects more than one billion people worldwide, making it the sixth most prevalent disease globally. It has an estimated prevalence of approximately 15% in the general population worldwide and 12% in Spain. Moreover, it is the second leading cause of Disability-Adjusted Life Years (DALYs), ranking first in the subgroup of the population under 50 years of age. A significant portion of individuals with High Frequency Episodic Migraine (HFEM) (>8-15 monthly headache days) and Chronic Migraine (CM) (>15 monthly headache days) do not respond well to pharmacological treatments or cannot tolerate them, fitting within the parameters of Resistant Migraine (RM). As per the European Headache Federation (EHF) criteria, these individuals can be classified as RM when they suffer at least 8 days of debilitating headache per month for at least 3 consecutive months without improvement, after at least 3 classes of anti-migraine drugs have been tried and no satisfactory response has been obtained.

Monoclonal antibodies (mAbs) designed to target the calcitonin gene-related peptide (CGRP) or its receptor, known as anti-CGRP mAbs, represent a significant milestone in the field of migraine prevention. Three of them have been authorized by the European Medicines Agency (EMA) — erenumab, galcanezumab, and fremanezumab—for use in preventing episodic migraine (EM) and chronic migraine (CM). In Spain, the Agencia Española del Medicamento y Productos sanitarios (AEMPS; Spanish drug and health products agency) policy for covering the cost of anti-CGRP mAbs includes patients with >8 migraine days per month and previous failure or no tolerability of at least three preventative classes of antimigraine drugs, for at least 3 months, being onabotulinumtoxinA one of them in CM.

The clinical effectiveness of anti-CGRP mAbs has been extensively demonstrated through rigorous 3- to 6-month placebo-controlled randomized clinical trials and extended open-label studies spanning from 9 months to 5 years. These Phase III clinical trials and open-label extensions have revealed that nearly half of the patients treated with anti-CGRP mAbs experience a significant reduction in headache frequency by half. Additionally, they enjoy notable improvements in headache pain intensity, reduced reliance on analgesics, diminished headache-related disability, and an enhanced overall quality of life. These benefits extend to both individuals with episodic and chronic migraine, irrespective of whether they have previously failed preventive treatments or experienced medication overuse.

On the other hand, the majority of real-life studies with anti-CGRP mAbs have collected data up to a 6-month period, with long-term effectiveness studies being scarce and with disparate results in effectiveness predictors such as MIDAS (Migraine Disability Assessment), MMD (Monthly Migraine Days) or age.
The aim of this study is to evaluate the long-term effectiveness, safety, and persistence of three anti-CGRP mAbs in a clinical sample of resistant migraine patients.

Methods

2.1 Study Design

We conducted a single-center, retrospective, real-world observational study on patients with migraine who were treated with anti-CGRP mAbs from December 2019 until June 2023. This study conformed principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines and was approved by the local ethics committee ("Comite Etico de Investigacion Clinica del Hospital Universitario Virgen de la Arrixaca).

2.2 Patients

The study enrolled participants aged 18 years and older, who met the national guidelines and the European Headache Federation definition criteria for resistant migraine. All patients met the ICHD-3 criteria for either chronic migraine (CM) or high-frequency episodic migraine (HFEM) with ≥8 migraine days per month and previous failure or no tolerability of at least three preventative classes of antimigraine drugs, for at least 3 months, being onabotulinumtoxinA one of them in CM, with or without medication overuse. Following hospital’s clinical guidelines, patients started preventative therapy with erenumab (70 mg monthly, up to 140 mg), galcanezumab (240 mg first dose and 120 mg monthly), or fremanezumab (225 mg monthly) at the Hospital Clinico Universitario Virgen de la Arrixaca. For the purpose of assessing effectiveness, only patients who had been on these treatments for at least 6 months were included in the analysis (Fig. 1). However, all patients were included in the safety and treatment persistence analysis. Ineffectiveness was defined as no reduction in headache frequency, duration or severity.

Clinical variables

We retrospectively collected demographic data (age and sex) and following migraine basal characteristics: presence of aura, medical history, medication overuse and number of prior preventive class failures (antiepileptic drugs, tricyclic antidepressants, beta-blockers, calcium channel blockers, selective serotonin or norepinephrine reuptake inhibitors (SSRI/SNRI) and onabotulinumtoxinA).

Patients completed a questionnaire on baseline and at follow-up visits with, MMD, pain intensity (0–10; numerical rating scale) and monthly acute medication use (defined as Triptans or ergot derivatives; MAM). A migraine day was defined as a calendar day with a headache meeting criterion for migraine (with or without aura) or a day when an acute migraine-specific medication (triptan or ergot) was used. Safety data (adverse effects, AE) and treatment abandon we recorded in every follow-up visit. All data was supervised by a headache specialist, which verified the accuracy and reliability of the completed questionnaire. Migraine-related clinical burden was assessed with MIDAS and Headache Impact Test 6 (HIT-6).

2.4 Assessments

Effectiveness analysis defined responders as those patients with a reduction of ≥50% in frequency (MMD) compared to baseline. Other effectiveness outcomes were reduction from baseline of MIDAS, HIT-6, MMD and MAM intake after 6, 12 and 24 months of treatment. The following baseline characteristics were compared between responders and non-responders at 6 and 12 months: age, sex, MMD, Basal intensity, MAM, prior preventive class failures ≥5, medication overuse, onabotulinumtoxinA inefficacy, MIDAS, HIT-6 and anti-CGRP mAbs treatment (erenumab, galcanezumab or fremanezumab). All patients who received any study treatment were included in the safety study. Persistence of treatment was defined as a non-interrupted treatment sequence based on the treatment posology. Patients were followed from their index date until the first occurrence of the following events: discontinuation of the index therapy (primary outcome of interest) or end of the study period (18 months).

2.5 Statistical analysis

All data was collected in an Excel 2003 database (Microsoft Corporation, Seattle, WA) and analyzed using
SPSS version 28.0 (SPSS Inc., Chicago, IL). Descriptive analysis was conducted using frequency tables and percentages for categorical variables, while continuous variables were summarized using mean and standard deviation (SD). Normality assumption was assessed using the Shapiro-Wilk test. Unpaired t-test or Wilcoxon signed-rank test were computed to compare average scores compared to baseline. Effectiveness analysis included two population sets: patients with at least 6 months of follow-up and patients who completed at least 12 months of treatment with anti-CGRP mAbs (Fig. 1). We assessed statistical significance comparisons among responders and non-responders by Fisher’s exact test for categorical variables and Mann-Whitney U test for the rest of continuous variables. Multivariate logistic regression analysis was carried out. We reported the odds ratios (ORs) and 95% confidence intervals (CIs) for the risk factors associated with responder status at 6 and 12 months; variables included in the equation were significant in previous analysis or had a clinical interest. Persistence of treatment are based on Kaplan-Meier estimates with log-rank tests. A Cox proportional-hazards model with resampled 95% confidence intervals was used to estimate the hazard of drug discontinuation between treatment groups, with erenumab as the reference group. Missing data were excluded, and no data imputation was performed on missing values. All p-values < 0.05 were considered statistically significant.

Results

3.1 Participants’ demographics and baseline parameters

A total of 126 patients were treated with anti-CGRP mAbs from November 2019 until June 2023, of which 101 underwent at least 6 months of treatment (Fig. 1). As shown in Table 1, 46 were treated with erenumab, 41 with galcanezumab and 14 with fremanezumab, being 85% female and mean age was 47.9 +- 11.0 years. The mean monthly migraine days was 18.3 +- 7.0, with a mean pain intensity in a 1-10 scale of 8.6 +- 1.0, where 14.1% of patients experienced aura and patients needed a mean of 16.2 +- 6.8 days of MAM intake. 47% of the participants overused medication and 90% of them had experienced five or more preventive class failures, of which all of them failed with antiepileptic drugs, 97% with tricyclic antidepressants, 99% with beta-blockers, 96% with calcium channel blockers, 65% with SSRI/SNRI and 85% with onabotulinumtoxinA, total or partially. To assess migraine-clinical burden, MIDAS disability and Headache-related impact (HIT-6) was measured, with a mean of 133.0 +- 87.8 and 70.1 +- 5.6 respectively, evidencing the severe status of this patients.

Baseline parameters were similar among patients classified by the three anti-CGRP mAbs treatments, except for differences on the number of triptans or ergot derivatives use and calcium channel blockers inefficacy, which showed statistical significance among groups (p=0.04 and p=0.023, respectively).

3.2 Treatment Effectiveness Analysis

Overall, the migraine-related clinical burden parameters measured (HIT-6 and MIDAS) were markedly attenuated at any time measured (Fig.2).

The mean MIDAS at 6 months was 48.3 +- 70.7 (-84.7 from baseline; p<0.001), 28.0 +- 26.7 at 12 months (-93.0 from baseline p<0.01) and 39.7 +- 32.4 at 24 months (-105.0 from baseline; p<0.001) and 39.7 +- 32.4 at 24 months (-93.0 from baseline p<0.01). As for HIT-6, the mean at 6 months was 59.0 +- 8.2 (-11.0 from baseline; p<0.001), 60.8 +- 7.2 at 12 months (-9.3 from baseline; p<0.001) and 65.2 +- 7.4 at 24 months (-4.9 from baseline; p=0.066).

Our data also point to a significant reduction (p<0.001 at all measured times) of MMD (Fig. 3), starting at baseline with 18.36 +- 7.02 and moving to 8.15 +- 8.07 at 6 months, 6.1 +- 5.6 at 12 months and 6.4 +- 4.4 at 24 months. A similar trend follows MAM intake, which drop drastically from baseline (16.2 +- 6.76), being 6.4 +- 6.4, 5.4 +- 5.7 and 4.7 +- 3.77 at 6, 12 and 24 months respectively (p<0.001 in all cases).

Subsequently, patients were classified as responders (>50% reduction in frequency of MMD) or non-responders (<50% reduction in frequency of MMD) and the baseline characteristics of these patients were compared at 6 and 12 months of treatment (Table 2). At 6 months, responders suffered less baseline MMD (17.0 +- 6.7 vs 20.9 +- 6.9; p=0.030), took less acute medication per month (14.5 +- 5.6 vs 18.6
+8.4; p=0.026) and had less medication overuse (33% vs 78.6%; p<0.001). This trend was repeated at 12 months, where responders suffered less baseline MMD (17.4 +- 6.7 vs 22.1 +- 6.2; p=0.014), took less acute medication (16.0 +- 5.8 vs 20.4 +- 6.9; p=0.05) and had a lower percentage of medication overuse (34.2 vs 62.5%; p=0.038). Meanwhile, age, sex, baseline intensity, MIDAS, HIT and or whether they were on treatment with erenumab, galcanezumab or fremanezumab was similar between the groups studied.

3.3 Clinical Predictors of Response

Multivariate analyses were conducted to evaluate the clinical factors that could predict a response of [?] 50% in patients with either 6 or 12 months of follow-up (Table 3). These models accounted for 36% and 23% of the variance, explaining responder status at 6 and 12 months, respectively (as measured by Nagelkerke R²). At 6 months, baseline MMD was associated with a higher response rate (OR 0.805, 95% C.I 0.6-0.9; p=0.043) as well as medication overuse (OR 0.181, 95% C.I 0.0-0.7; p=0.016). There were no significant associations found between variables and responders at the 12-month follow-up.

3.4 Safety Analysis

During the study period, 19 patients reported at least one AE (15%), although no serious adverse effects were reported. The most frequent adverse effect was constipation (8.7%), followed by injection site erythema (3.9%), hypotension (1.6%) and myalgia (1.6%). Only one patient abandoned treatment due to AE.

3.5 Persistence Analysis

In total, 21 out of 126 (16%) patients discontinued treatment during the 18 months of the persistence study, 18 due to ineffectiveness, 2 due to pregnancy and 1 due to AEs. Survival curves based on Kaplan Meier estimates are shown in Fig.4. The probability of remaining on treatment across time was similar between erenumab (16.6 +- 0.4) and galcanezumab (16.7 +- 0.5) compared to fremanezumab (14.3 +- 1.4), which persistence was lower than the other mAbs, although it did not reach statistical significance (p=0.010). Hazard Ratio to estimate the hazard of drug discontinuation was higher for fremanezumab (HR 2.77, 95 CI % 0.91-8.44; p=0.073) compared to galcanezumab (HR 0.98, 95 CI % 0.36-2.62; p=0.962), with erenumab as the reference group.

Discussion

In this retrospective study on a RM population, we have studied parameters such as safety, persistence, and effectiveness of the treatment, being one of the few studies to provide long-term information in a real-world setting. The preventive treatments erenumab, galcanezumab and fremanezumab have been shown to have a good safety profile and to be effective in patients with resistant migraine in the long term (24 months), coinciding with the results observed in clinical trials.

In the baseline characteristics of the patients, we can observe that they are severe patients, which more than 90% of patients having failed [?] 5 previous treatments, doubling the minimum migraine days to require treatment ([?]8 days, mean 18.3 +- 7.0) and very high mean values of clinical-related burden (MIDAS and HIT).

The MIDAS questionnaire was developed to measure headache-associated disability, and in a recent study, it was proposed as a better model to assess disability than MMD. In our study we were able to observe a reduction of 64%, 79% and 70% at 6, 12 and 24 months, respectively, data that are similar to those obtained in other studies at 6 and 12 months, although other studies have reported smaller differences at 3 or 6 months, possibly because the baseline MIDAS in those studies were substantially lower. With respect to the HIT-6 questionnaire, it was also reduced at all times measured with respect to the baseline level, as previously observed at [?]12 months.

Previous real-world studies had reported a decrease in MMD from 1-12 months. Our data also indicate a significant reduction in MMD that is maintained for up to 24 months. Moreover, responders ([?] 50% response) had lower baseline MMD than non-responders at 6 and 12 months, and in the multivariate analysis, MMD was a negative predictor of response at 6 months. Our results are consistent with previous findings,
and therefore this could suggest the robustness of the association and serve as a reliable predictor value for estimating treatment response.

Medication overuse affects 50% of the migraine population and current recommendations to resolve this situation are based on patient education, reduction of overused medication and concomitant treatment with preventive medications. Our data show that there was a >50% reduction in MAM from 6-24 months, and responders at 6 months had a lower basal MAM intake. On the other hand, there was a higher percentage of medication overuse in non-responders, and it acted as an important negative predictor of treatment effectiveness. In a recent study, it was observed that those patients treated with anti-CGRP mAbs together with other traditional pharmacological treatments for migraine experienced a greater reduction in the frequency of headaches and use of symptomatic medication compared to patients with conventional treatment alone. Thus, this could suggest that this treatment may be more effective than other conventional treatments in reducing medication overuse, although the likelihood of the treatment being effective in these individuals is lower than in other migraine patients. In any case, specific studies are needed to reach firm conclusions regarding this aspect.

Regarding treatment persistence, we had to limit the study to 18 months for the treatments to be comparable, as fremanezumab was authorized by the AEMPS later than the previous ones. We observed that, among the three drugs studied, fremanezumab seemed to have lower persistence, although it was not statistically significant, and the sample size was small.

One of the major limitations when conducting this type of study is to be able to evaluate the specific role of this treatment, as these patients take other preventive and concomitant medication, which may overestimate the real effectiveness of the drugs. Moreover, being an observational study, it allows us to establish an association between known and observed factors, but not causality. Another limitation we encountered was the lack of data we found, which prevented us from performing some analyses that would have provided more insight into the subject. However, the data provided by this study allow us to approximate the efficacy in the real population and to complete the long-term safety profile.

Conclusions

We have observed in a real-world study with RM patients that the anti-CGRP mAbs studied are effective, not only in reducing the disability associated with migraine but also in reducing acute medication usage, with a very good safety profile, showing that these effects are maintained for up to two years. However, controlled studies with a larger population are needed to further confirm the results observed in this study.

Declarations

Funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The data collected and analyzed for the current study are available from the corresponding author on reasonable request.

Conflict of interest

None to declare.

Bibliography

Figure Captions:

Figure 1. Flow diagram of the study. Abbreviations: Anti-CGRP mAbs, Monoclonal antibodies designed to target the calcitonin gene-related peptide or its receptor; AE: adverse effects.
Figure 2. a) MIDAS and HIT questionary scores at baseline and follow-ups and b) Monthly migraine days (MMD) and monthly acute medication (MAM) days at baseline and follow-ups. Number in square represents mean reduction compared to baseline for each follow-up. Error bars represent standard error of the mean (SEM). *p < 0.05, **p < 0.01, ***p < 0.001 vs. baseline. Abbreviations: MIDAS, Migraine Disability Assessment; HIT-6, Headache Impact Test; M, months.

Figure 3. Persistence of erenumab, galcanezumab and fremanezumab based on Kaplan-Meier estimates.

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