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RESEARCH SUBMISSION

Effectiveness and tolerability of galcanezumab for migraine prevention in patients ≥65 years: A real-life multicenter study

Julia Peris-Subiza MD[1] | Víctor Obach MD[2] | Daniel Guisado-Alonso MD, PhD[1] | Fernando Velasco Juanes MD, PhD[3] | Rocío Álvarez Escudero MD[4] | María Martín Bujanda MD[5] | Sonsoles Aranceta MD[6] | Aintzine Ruisánchez MD[7] | Natalia Roncero MD[8] | Ane Mínguez-Olaondo MD, PhD[9,10,11,12] | Amaya Echeverria MD[13] | Alba López-Bravo MD[14] | Ángel Luis Guerrero-Peral MD, PhD[15,16] | David García-Azorín MD, PhD[16,17] | Elisa Cuadrado-Godia MD, PhD[1,18] | Galca-Only Study Group

Correspondence
Daniel Guisado-Alonso, Neurology Department, Department of Medicine and Life Sciences, Hospital del Mar Barcelona, Universitat Pompeu Fabra (UPF), Pg. Marítim de la Barceloneta 25, Barcelona 08003, Spain.
Email: dguisadoalonso@hmar.cat

Abstract

Background: Patients with migraine aged ≥65 years old are underrepresented in clinical trials. This study compares effectiveness, excellent response, and tolerability of galcanezumab in patients ≥65 years and those younger than 65 years, specifically assessing age as a predictor of response.

Methods: This real-life, multicenter cohort study included patients with chronic or high-frequency episodic migraine who did not respond to more than or equal to three preventive drugs, treated with galcanezumab, and followed for 12 months from 12 Spanish hospitals, between November 2019 and January 2022. Effectiveness was defined as ≥50% reduction in monthly headache days (MHD), and excellent response as ≥75% reduction at 6 months. Tolerability was based on the percentage of patients discontinuing due to adverse events.

Results: We included 1055 patients (934 patients <65 years, 121 patients ≥65 years). Older patients had higher baseline MHD [25 (interquartile range [IQR]

Abbreviations: aOR, adjusted odds ratio; CGRP, calcitonin gene-related peptide; CI, confidence interval; CM, chronic migraine; HFEM, high-frequency episodic migraine; IQR, interquartile range; mAb, monoclonal antibody; MHD, monthly headache days; MMD, monthly migraine days.

David García-Azorín and Elisa Cuadrado-Godia are equal contribution as last author.

Galca-Only Study Group: Neus Fabregat (Headache Unit, Neurology Department, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain), Marta Ruibal (Neurology Department, Hospital Universitario de Donostia, San Sebastian, Spain), Izaro Kortazar Zubizarreta (Neurology Department, Osakidetza Basque Health Service, Araba University Hospital, Bioaraba, Vitoria-Gasteiz, Spain), Nuria Riesco (Neurology Department, Hospital Universitario Central de Asturias, Oviedo, Spain), Lucia González-Fernández (Neurology Department, Hospital Universitario Central de Asturias, Oviedo, Spain), Paula Manera (Faculty of Health and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain), Agustín Oterino Duran (Neurology Department, Hospital Universitario Central de Asturias, Oviedo, Spain), Yésica González-Osorio (Headache Unit, Neurology Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain), Santiago Fernández-Fernández (Headache Unit, Neurology Department, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain), Juan Carlos García-Moncó (Neurology Department, Hospital Universitario de Basurto, Bilbao, Spain), Isabel Fernández-Pérez (Neurology Department, Department of Medicine and Life Sciences, Hospital del Mar Barcelona, Universitat Pompeu Fabra (UPF), Barcelona, Spain), Joan Jiménez-Balado (Neurology Department, Department of Medicine and Life Sciences, Hospital del Mar Barcelona, Universitat Pompeu Fabra (UPF), Barcelona, Spain).

For affiliations refer to page 948.

15–30) vs. 20 (14–30), $p = 0.045$], but lower HIT-6 scores [67 (IQR 63–72) vs. 69 (66–73), $p < 0.001$]. Effectiveness was similar across age groups at 3 (57.0% vs. 48.8%, $p = 0.090$), 6 (57.0% vs. 51.8%, $p = 0.281$), and 12 months (52.1% vs. 51.4%, $p = 0.889$). However, excellent response was more frequent in the ≥65 years group at 3 months (32.2% vs. 23.1%, $p = 0.028$) and 6 months (33.9% vs. 23.5%, $p = 0.012$), with a non-significant difference at 12 months (33.1% vs. 25.4%, $p = 0.071$). Tolerability was comparable within age groups (5.8% discontinuation due to adverse effects in patients ≥65 years vs. 6.7% in patients <65 years; $p = 0.837$). Age was independently associated with effectiveness (adjusted odds ratio [aOR]: 1.02; 95% confidence interval [CI]: 1.004–1.03) and excellent response (aOR: 1.02; 95% CI: 1.01–1.04). A statistically significant association was found in the logistic regression model for excellent response when age was dichotomized at 65 years, with increasing age linked to a higher likelihood of an excellent treatment response (aOR: 1.79; 95% CI: 1.13–2.82, $p = 0.012$).

Conclusions: Galcanezumab is as effective and well-tolerated in patients aged ≥65 years as in younger patients but older patients showed a higher rate of excellent response. Age is associated with a better response to galcanezumab.

Plain Language Summary

This study shows that galcanezumab is equally effective and well-tolerated in patients aged 65 and older as in younger patients, with a higher proportion of excellent responders in older patients. Despite having more baseline headache days, older patients responded well to the treatment, with age being linked to better outcomes. These results suggest that galcanezumab is an excellent option for migraine prevention in older adults.

KEYWORDS

calcitonin gene-related peptide, effectiveness, excellent response, migraine prevention, monoclonal antibodies, real-world study

BACKGROUND

Migraine reaches its peak incidence and prevalence between the ages of 20 and 34, but its impact extends across all age groups. In the absence of a curative treatment, it often becomes a chronic condition, highlighting the need for ongoing surveillance and effective management strategies throughout life.[1,2]

However, migraine in people over 65 years of age has been less studied and most of the current treatments have not been tested in this group of age,[3–5] especially due to the concern of a higher risk of side effects, mainly at a cardiovascular level. In addition to age limitations, patients in routine clinical practice do not meet the stricter criteria of clinical trials. Therefore, it is imperative to investigate drug performance in real-world settings.

Galcanezumab is a monoclonal antibody (mAb) that selectively binds to calcitonin gene-related peptide (CGRP), blocking its physiologic activity.[6] Its efficacy and safety for the prevention of episodic and chronic migraine has been proven in various clinical trials (EVOLVE-1, EVOLVE-2, REGAIN) in the population aged between 18 and 65 years.[3–5] The later CONQUER trial for more refractory cases included patients up to 75 years, although the number of participants between 65 and 75 years was very limited ($n = 13$).[7] Other recent studies have incorporated patients aged 65 years or older treated with anti-CGRP mAbs[8–11]; however, a comparison with younger patients is currently lacking.

To tackle this problem, we investigated the effectiveness and tolerability of galcanezumab among patients aged 65 years or older with high-frequency episodic migraine (HFEM) and chronic migraine (CM) over 3, 6, and 12 months in a real-world setting and compared the outcomes with those of younger patients. We wanted to analyze if age was a predictor of good response.

We hypothesized that among patients with CM or HFEM who have not responded to multiple preventive treatments, galcanezumab would be equally effective and well-tolerated in patients aged ≥65 years compared to those <65 years, and that increasing age would not be associated with a different likelihood of achieving an excellent treatment response.

METHODS

Study setting and design

A prospective multicentric cohort study was conducted from November 15, 2019, to January 31, 2022, within 12 Spanish public university hospitals, the Galca-only consortium. The aim of the consortium was to evaluate the performance of galcanezumab in the real-world scenario, as this was the only mAb available in those centers. The study received approval from the ethics committees of Hospital Clinic of Barcelona Ethics Committee (HCB/2021/1327) and from all participating institutions. Additionally, all enrolled patients provided written informed consent prior to their participation in the study. No statistical power calculation was conducted prior to the study, and the sample size was determined by the available data from the participating centers. The global results of the study have been published previously.[11]

Patient selection

Participants in the study had to meet specific inclusion criteria, including a diagnosis of migraine following the International Classification of Headache Disorders, 3rd version.[12] According to the reimbursement criteria established by the Spanish Ministry of Health, patients were required to be older than 17 years, have a diagnosis of HFEM (8 or more migraine days) or CM (15 monthly headache days with 8 or more fulfilling diagnostic criteria for migraine days) in the preceding three months, and to have experienced poor response with at least three preventive drugs in HFEM, or two oral preventive treatments and onabotulinumtoxinA in CM. Patients previously treated with anti-CGRP mAbs were excluded. A flowchart depicting the inclusion and exclusion criteria and treatment retention rate is shown in Figure S1.

Galcanezumab was administered in a loading dose of 240 mg, followed by a monthly dose of 120 mg.

Data collection

During the baseline visit prior to treatment initiation, the following demographic and clinical variables were collected: age, sex, prior history of psychiatric disorders (depressive syndrome or anxiety), other chronic painful syndromes including fibromyalgia, type of migraine (HFEM or CM), monthly headache days (MHD) within the previous 3 months, baseline Headache Impact Test (HIT-6) score,[13] prior number of preventive treatments, and concomitant use of migraine preventive drugs including onabotulinumtoxinA. The headache scales used were selected based on those common to all centers. Cardiovascular risk factors of the patients ≥65 years old were collected retrospectively for this substudy.

Patients were monitored at least at 3 months (8–12 weeks), 6 months (20–24 weeks), and 12 months (44–48 weeks). Throughout the follow-up, patients gathered the information using headache diaries. The number of MHD and occurrence and frequency of side effects leading to treatment discontinuation were assessed.

Outcomes and measures

The main objective was to evaluate the effectiveness, excellent response, and tolerability of galcanezumab at 3, 6, and 12 months, comparing the results between patients <65 and ≥65 years.

Effectiveness was evaluated by the 50% and 75% responder rates, defined as the percentage of patients achieving a reduction of ≥50% in the number of MHD. Excellent response[14] was defined as the reduction of ≥75% in MHD, at 3, 6 and 12 months, in the preceding month, with respect to the baseline. Patients experiencing an excellent response are also referred to as super-responders in the literature. The response rate was calculated through intention-to-treat analyses. We define daily headache as MHD ≥ 30. Tolerability was determined based on the percentage of patients withdrawing the treatment due to adverse events. Missing data are included in each table.

As a secondary objective, we analyzed the factors associated with effectiveness and excellent response at 6 months, with age as the main variable of interest.

Bias and confounders

The study cohort consisted of consecutive, unselected patients, helping to reduce selection bias. The outcomes of interest were not present at baseline. Although some participants discontinued treatment or were lost to follow-up, all enrolled patients were included in the 12-month intention-to-treat analysis using conservative assumptions to handle missing data. Specifically, in the case of time-evolving variables, the last observation carried forward method was applied. Patients who discontinued the study due to lack of efficacy or adverse events were considered non-responders at all time points following discontinuation. This approach helped mitigate potential bias due to treatment discontinuation or dropout. Follow-up data were collected using headache diaries, minimizing subjective recall bias. Potential confounders were addressed in the statistical analysis.[11]

Statistical analysis

Continuous variables were reported as means and standard deviations or medians and interquartile range (IQR) according to the type and distribution of each variable. Categorical variables were expressed as counts and percentages.

Bivariate comparisons between demographics and clinical variables and the outcomes of interest (effectiveness, tolerability, and excellent response) were performed using the Mann–Whitney *U* test

TABLE 1 Comparison of baseline characteristics between patients <65 years and ≥65 years.

Parameter	Total $n=1055$	<65 years $n=934$ (88.5%)	≥65 years $n=121$ (11.5%)	p-Value
Age, median (IQR)	50 (42–58)	48 (41–55)	68 (66–72)	**<0.001**
Sex (female), *n* (%)	875 (82.9)	777 (83.2)	98 (81.0)	0.545
Type of migraine (chronic), *n* (%)	806 (76.4)	712 (76.2)	94 (77.7)	0.723
Psychiatric comorbidity, *n* (%)	346 (32.8)	311 (33.3)	35 (28.9)	0.335
Chronic non-cephalic pain, *n* (%)	206 (19.5)	180 (19.3)	26 (21.5)	0.563
Fibromyalgia, *n* (%)	101 (9.6)	91 (9.7)	10 (8.3)	0.603
Baseline MHD, median (IQR)	20 (14–30)	20 (14–30)	25 (15–30)	**0.045**
Daily headache at baseline, *n* (%)	348 (33.0)	294 (31.5)	54 (44.6)	**0.004**
Baseline MMD, median (IQR)	16 (12–29)	16 (12–28)	20 (12–30)	0.288
Baseline HIT-6, median (IQR)*	69 (66–72)	69 (66–73)	66.5 (63–72)	**<0.001**
No. of previous oral preventive treatments, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.884
Prior or concomitant botulinum toxin, *n* (%)**	770 (87.5)	684 (87.6)	86 (86.9)	0.840

Note: Missing information for *18, **175 patients. Bold values indicate statistical significance at $p<0.05$.
Abbreviations: IQR, interquartile range; MHD, monthly headache days; MMD, monthly migraine days.

TABLE 2 Cardiovascular risk factors of the elderly population.

Cardiovascular risk factors	$n=98$[a] (%)
Female	78 (79.6)
Arterial hypertension	31 (31.6)
Diabetes mellitus	6 (6.1)
Dyslipidemia	41 (41.8)
Tobacco smoker	25 (25.5)
Ischemic cardiopathy	1 (1.0)
Peripheral arteriopathy	3 (3.1)
Stroke	2 (2.0)

[a]Missing information for 23 patients aged ≥65 years, all from Hospital Universitario de Navarra.

for ordinal or non-normally distributed variables (as assessed by the Shapiro–Wilk test). For categorical variables, either the χ^2 test or Fisher's exact test was used, as appropriate.

Thereafter, we performed multivariable logistic regression analyses to assess the association with effectiveness and excellent response at 6 months. Variables with a p-value <0.1 in the bivariate analysis were included in the model to identify those independently associated with effectiveness or excellent response. We reported the adjusted odds ratios (aORs) for variables that reached statistical significance. Age was introduced as a continuous variable (Model 1) or dichotomized variable (Model 2). All statistical assumptions were checked and met, including: (1) absence of concerning collinearity (variance inflation factors <5); (2) linear association between numerical predictors and log-odds of response; (3) absence of influential cases (Cook's distance).

Statistical significance for all the analyses was set at 0.05 (two-sided). All the analyses were performed using Stata version 15 (StataCorp LLC, College Station, TX, USA) and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) in the RStudio 2023.06.1 environment (Posit PBC, Boston, MA, USA).

RESULTS

Study sample

A total of 1055 patients were included. The vast majority ($n=875$, 82.9%) were females, with CM ($n=806$, 76.4%). Baseline characteristics are summarized in Table 1. Concerning age, median age was 50 years (IQR 42–58); 121 patients (11.5%) were ≥65 years and the maximum age was 85. Patients ≥65 years had a higher number of baseline MHD [25 (IQR 15–30) vs. 20 (14–30), $p=0.045$] and a higher percentage had daily headache [54 (44.6%) vs. 294 (31.5%), $p=0.004$]; however, baseline HIT-6 score was lower in this group of patients [67 (IQR 63–72) vs. 69 (66–73), $p<0.001$]. There were no significant differences in other baseline characteristics. Cardiovascular risk factors of the patients aged ≥65 years are described in Table 2.

Primary outcome: Responder rates

During follow-up, a greater reduction in MHD was observed in the ≥65 years subgroup (Figure 1). Regarding effectiveness, there were no significant differences between patients over and under 65 years at 3 months (57.0% vs. 48.8%, $p=0.090$), 6 months (57.0% vs. 51.8%, $p=0.281$), or 12 months (52.1% vs. 51.4%, $p=0.889$), as shown in Table 3 and Figures 2 and 3. However, excellent response was more frequent in the ≥65 years subgroup at 3 months (32.2% vs. 23.1%, $p=0.028$) and 6 months (33.9% vs. 23.5%, $p=0.012$), with a non-significant difference at 12 months (33.1% vs. 25.4%, $p=0.071$).

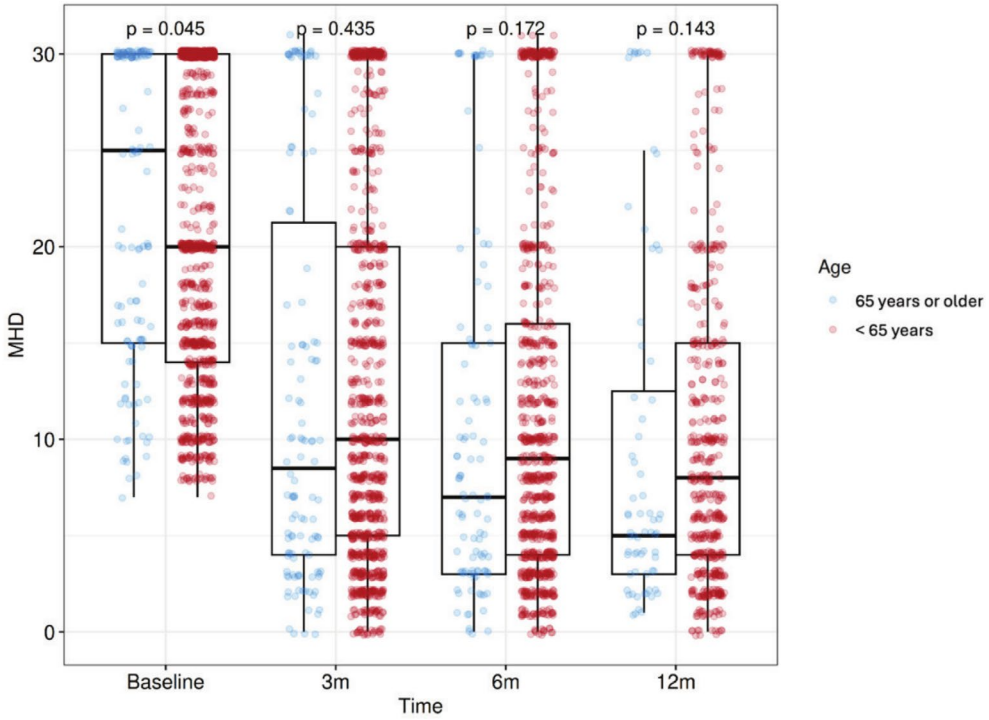

FIGURE 1 Reduction of monthly headache days in patients <65 years versus ≥65 years. On the vertical axis, the monthly headache days (MHD); on the horizontal axis, the time in months at the moment of follow-up. In red, the group <65 years; in blue, the group ≥65 years. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Effectiveness and excellent response[a] in patients <65 years versus ≥65 years at different time points during evolution.

Parameter	Total *n* = 1055	<65 years *n* = 934 (88.5%)	≥65 years *n* = 121 (11.5%)	*p*-Value
3 months				
Days of reduction of MHD, median (IQR)	7 (1–13)	7 (1–13)	8 (0–15)	0.280
50% MHD reduction, *n* (%)	525 (49.8)	456 (48.8)	69 (57.0)	0.090
75% MHD reduction, *n* (%)	255 (24.1)	216 (23.1)	39 (32.2)	**0.028**
6 months				
Days of reduction of MHD, median (IQR)	8 (0–14)	7 (0–14)	9 (0–15)	0.128
50% MHD reduction, *n* (%)	553 (52.4)	484 (51.8)	69 (57.0)	0.281
75% MHD reduction, *n* (%)	260 (24.6)	219 (23.5)	41 (33.9)	**0.012**
12 months				
Days of reduction of MHD, median (IQR)	7 (0–14)	7 (0–14)	8 (0–15)	0.638
50% MHD reduction, *n* (%)	543 (51.5)	480 (51.4)	63 (52.1)	0.889
75% MHD reduction, *n* (%)	277 (26.3)	237 (25.4)	40 (33.1)	0.071

Abbreviations: IQR, interquartile range; MHD, monthly headache days; MMD, monthly migraine days.

[a]Effectiveness was defined as ≥50% reduction in monthly headache days, and excellent response as ≥75% reduction in monthly headache days.

Bold values indicate statistical significance at $p < 0.05$.

Primary outcome: Tolerability

In terms of tolerability, galcanezumab was well tolerated, with no significant differences observed in the incidence of drug withdrawal attributable to adverse effects over the 12-month follow-up period within age groups (5.8% in patients ≥65 years vs. 6.7% in patients <65 years; $p = 0.837$). A comprehensive compilation of adverse events leading to treatment discontinuation in each age group can be found in Table S1, with no significant differences observed between the two age groups. The table reports the total number of adverse events, not the number of patients affected, as some individuals experienced more than one event.

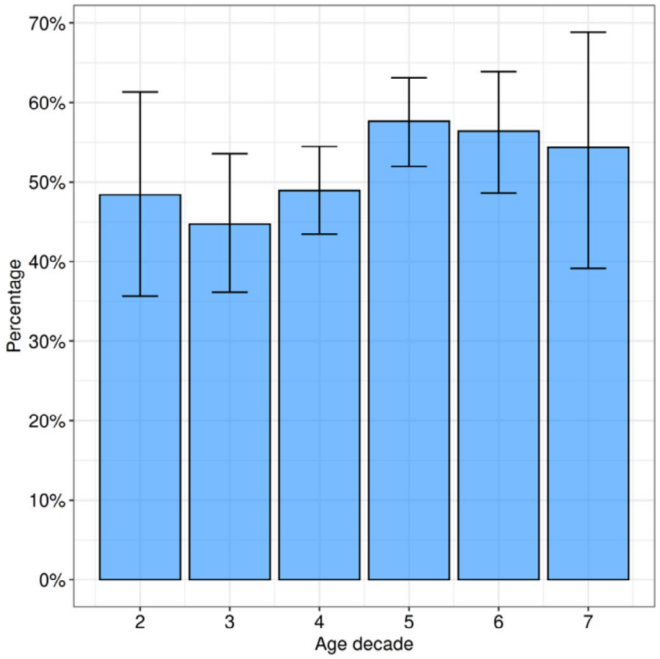

FIGURE 2 Effectiveness[a] of galcanezumab across different age decades. On the vertical axis, effectiveness of galcanezumab at 6 months; on the horizontal axis, the different age decades. [a]Effectiveness was defined as ≥50% reduction in monthly headache days. [Color figure can be viewed at wileyonlinelibrary.com]

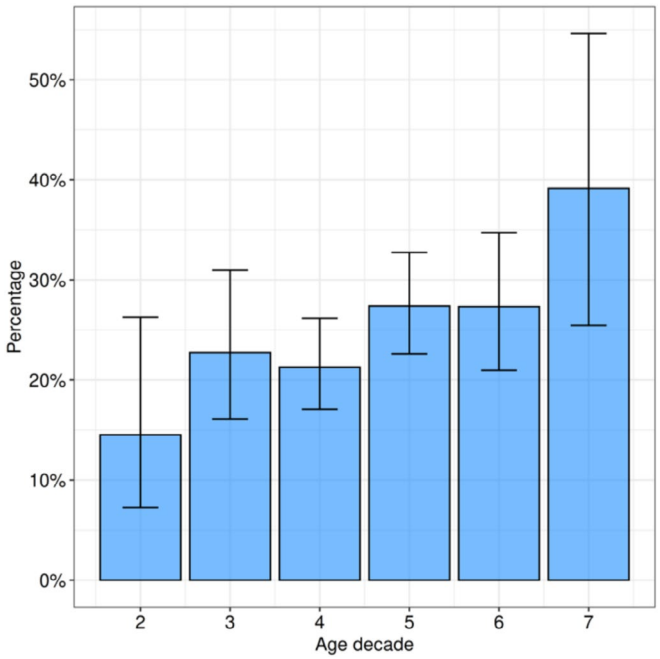

FIGURE 3 Excellent response[a] of galcanezumab across different age decades. On the vertical axis, excellent response of galcanezumab at 6 months; on the horizontal axis, the different age decades. [a]Excellent response as ≥75% reduction in monthly headache days. [Color figure can be viewed at wileyonlinelibrary.com]

Treatment discontinuation due to lack of efficacy occurred in 60 patients (5.7%) at month 3, 181 patients (17.1%) at month 6, and 223 patients (21.1%) at month 12. Additionally, 9 patients (0.9%) discontinued galcanezumab for other reasons, such as a desire to become pregnant or relocation.[11]

Secondary outcome: Response predictors

Regarding the secondary objective, analysis of factors associated with excellent response at 6 months, age, absence of psychiatric comorbidity, fibromyalgia or other chronic non-cephalic pain,

TABLE 4 Bivariate analysis of predictors of effectiveness[a] of galcanezumab at 6 months of follow-up.

Parameter	Total $n=1055$	No 50% MHD reduction, $n=502$ (47.6%)	50% MHD reduction, $n=553$ (52.4%)	p-Value
Age, median (IQR)	50 (42–58)	48 (42–57)	51 (43–58)	**0.008**
≥65 years, *n* (%)	121 (11.5)	52 (10.4)	69 (12.5)	0.281
Sex (female), *n* (%)	875 (82.9)	415 (82.7)	460 (83.2)	0.825
Type of migraine (chronic), *n* (%)	806 (76.4)	416 (82.9)	390 (70.5)	**0.001**
Psychiatric comorbidity, *n* (%)	346 (32.8)	193 (38.5)	153 (27.7)	**<0.001**
Chronic non-cephalic pain, *n* (%)	206 (19.5)	118 (23.5)	88 (15.9)	**0.002**
Fibromyalgia, *n* (%)	101 (9.6)	61 (12.2)	40 (7.2)	**0.007**
Baseline MHD, median (IQR)	20 (14–30)	25 (15–30)	20 (12–30)	**<0.001**
Daily headache at baseline, *n* (%)	348 (33.0)	202 (40.2)	146 (26.4)	**<0.001**
Baseline HIT-6, median (IQR)*	69 (66–72)	70 (66–74)	68 (65–72)	**<0.001**
No. of previous oral preventive treatments, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.833
Prior or concomitant botulinum toxin, *n* (%)**	770 (87.5)	379 (91.8)	391 (83.7)	**<0.001**

Note: Missing information for *18, **175 patients. Bold values indicate statistical significance at $p<0.05$.

Abbreviations: IQR, interquartile range; MHD, monthly headache days.

[a]Effectiveness was defined as ≥50% reduction in monthly headache days.

TABLE 5 Multivariable logistic regression analysis of predictors of effectiveness[a] of galcanezumab at 6 months of follow-up.

Parameter	aOR	95% CI	p-Value
Model 1			
Age	1.02	1.004–1.03	**0.008**
Psychiatric comorbidity	0.64	0.48–0.86	**0.003**
Model 2			
≥65 years versus <65 years	1.35	0.87–2.12	0.178
Psychiatric comorbidity	0.64	0.48–0.86	**0.003**

Note: Model 1: age as a continuous variable. Model 2: age as a dichotomized variable (≥65 years vs. <65 years). Models were additionally adjusted for a set of predictors which do not reach statistical significance. Specifically, we adjusted for: type of migraine, chronic non-cephalic pain, fibromyalgia, baseline monthly headache days, daily headache at baseline, baseline HIT-6, and prior or concomitant botulinum toxin. Bold values indicate statistical significance at $p<0.05$.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]Effectiveness was defined as ≥50% reduction in monthly headache days.

absence of chronic migraine, a lower baseline HIT-6 score, and prior or concomitant onabotulinumtoxinA treatment were statistically associated with effectiveness at 6 months in the bivariate analysis (Table 4). In the multivariable analysis, only age as a continuous variable (aOR: 1.02; 95% CI: 1.004–1.03, $p=0.008$) and psychiatric comorbidity (aOR: 0.64; 95% CI: 0.48–0.86, $p=0.003$) were independently associated with effectiveness (Table 5, Model 1). However, when age was introduced as a dichotomized variable (<65 vs. ≥65 years) the association was no longer maintained (Table 5, Model 2).

The same analysis was repeated for excellent response at 6 months. Again, age, absence of psychiatric comorbidity, absence of fibromyalgia, absence of chronic migraine, daily headache at baseline, and prior or concomitant onabotulinumtoxinA treatment were associated with an excellent response (Table 6). In the multivariable analysis, age as a continuous variable (aOR: 1.02; 95% CI: 1.01–1.04, $p<0.001$), psychiatric comorbidity (aOR: 0.68; 95% CI: 0.49–0.96, $p=0.026$), fibromyalgia (aOR: 0.49; 95% CI: 0.26–0.92, $p=0.026$), and daily headache at baseline (aOR: 0.47; 95% CI: 0.26–0.85, $p=0.012$) remained statistically significant, associated with excellent response at 6 months (Table 7, Model 1). In the second model, where the age variable was dichotomized, the results were equivalent (Table 7, Model 2).

Finally, we performed stratification analysis to study the interaction between age and sex and main comorbidities shown in Table 1. We found that age association with effectiveness and excellent response was maintained in males and females (Figure S2). However, the effect of age was attenuated in patients with psychiatric conditions (Figure S3).

DISCUSSION

In this real-world study, we analyzed the effectiveness and tolerability of galcanezumab in patients aged 65 years and older, a group underrepresented in pivotal clinical trials. Our study, conducted across multiple real-world healthcare centers, found that the effectiveness and tolerability of galcanezumab are similar across all age groups; however, older patients exhibited a higher proportion of excellent responses. Moreover, increasing age was identified as an independent factor associated with a better response to treatment.

TABLE 6 Bivariate analysis of predictors of excellent response[a] of galcanezumab at 6 months of follow-up.

Parameter	Total $n = 1055$	No 75% MHD reduction, $n = 795$ (75.4%)	75% MHD reduction, $n = 260$ (24.6%)	p-Value
Age, median (IQR)	50 (42–58)	49 (42–58)	51.5 (43.5–59.5)	**0.004**
≥65 years, *n* (%)	121 (11.5)	80 (10.1)	41 (15.8)	**0.012**
Sex (female), *n* (%)	875 (82.9)	666 (83.8)	209 (80.4)	0.207
Type of migraine (chronic), *n* (%)	806 (76.4)	625 (78.6)	181 (69.6)	**0.003**
Psychiatric comorbidity, *n* (%)	346 (32.8)	278 (35.0)	68 (26.2)	**0.009**
Chronic non-cephalic pain, *n* (%)	206 (19.5)	164 (20.6)	42 (16.1)	0.120
Fibromyalgia, *n* (%)	101 (9.6)	89 (11.0)	12 (5.0)	**0.006**
Baseline MHD, median (IQR)	20 (14–30)	20 (15–30)	20 (12.5–30)	**0.002**
Daily headache at baseline, *n* (%)	348 (33.0)	282 (35.5)	66 (25.4)	**0.003**
Baseline HIT-6, median (IQR)*	69 (66–72)	69 (66–72)	68 (66–72)	0.488
No. of previous oral preventive treatments, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.833
Prior or concomitant botulinum toxin, *n* (%)**	770 (87.5)	586 (89.2)	184 (82.5)	**0.009**

Note: Missing information for *18, **175 patients. Bold values indicate statistical significance at $p < 0.05$.

Abbreviations: IQR, interquartile range; MHD, monthly headache days.

[a]Excellent response as ≥75% reduction in monthly headache days.

TABLE 7 Multivariable logistic regression analysis of predictors of excellent response[a] of galcanezumab at 6 months of follow-up.

Parameter	aOR	95% CI	p-Value
Model 1			
Age	1.02	1.01–1.04	**<0.001**
Psychiatric comorbidity	0.68	0.49–0.96	**0.026**
Fibromyalgia	0.49	0.26–0.92	**0.026**
Daily headache at baseline	0.47	0.26–0.85	**0.012**
Model 2			
≥65 years versus <65 years	1.79	1.13–2.82	**0.012**
Psychiatric comorbidity	0.68	0.49–0.95	**0.025**
Fibromyalgia	0.51	0.27–0.95	**0.033**
Daily headache at baseline	0.49	0.27–0.89	**0.018**

Note: Model 1: age as a continuous variable. Model 2: age as a dichotomized variable (≥65 years vs. <65 years). Models were additionally adjusted for a set of predictors which do not reach statistical significance. Specifically, we adjusted for: type of migraine, chronic non-cephalic pain, baseline monthly headache day, and prior or concomitant botulinum toxin. Bold values indicate statistical significance at $p < 0.05$.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]Excellent response as ≥75% reduction in monthly headache days.

Regarding effectiveness, we did not observe significant differences in the ≥50% reduction of MHD in older patients compared to <65 years. In both groups, effectiveness rates at 3, 6, and 12 months ranged between 51% and 57%, closely aligning with previously reported outcomes in other real-world studies[15] and randomized control trials.[10,16–18] However, a higher proportion of older patients achieved an excellent response, at least within the first 6 months. At 12 months, this difference was no longer significant due to an increase in the excellent response in the younger group. To our knowledge, these results have not been previously reported, since most of the real-world evidence studies have not specifically evaluated this outcome in older adults.[15] This finding is particularly relevant considering that our cohort of people ≥65 years was very refractory with a high proportion of CM, daily headache at baseline, and elevated median MHD, even higher than in younger patients. This is consistent with previous studies showing that, although the overall prevalence of migraine decreases after the age of 60, CM is common, reflecting low remission rates for CM compared to episodic migraine throughout the natural course of the disease.[19,20]

Tolerability was also similar in both age groups, a relevant finding given the constant concern about cardiovascular risk when anti-CGRP drugs are administered in older people. As shown in Table 2, our sample of patients ≥65 years old had cardiovascular risk factors. Even so, no cardiovascular events (including stroke or myocardial infarction) occurred during the study. Our results agree with previous real-world studies that analyzed effectiveness and safety in patients ≥65 years old treated with different anti-CGRP mAbs.[9,10,21] Moreover, managing migraine in this population involves specific challenges, including drug interactions with comorbid treatment and polypharmacy. In regard with this, galcanezumab and other anti-CGRP mAbs have shown little or no interaction with other drugs.[22] This finding, added to the favorable effectiveness and tolerability profile already evidenced, makes galcanezumab an excellent choice for the preventive treatment of migraine in people age ≥65 years.

Finally, we examined whether age was associated with the treatment response. We analyzed the 6-month time point as this is the follow-up time used in most of the randomized controlled trials.[3–5,7,17]

Increasing age was associated with a better treatment response at 6 months. Specifically, the odds of achieving a good response increased by 2% for each additional year of age, or 20% for each new decade. However, this effect is modest, and real-world prospective randomized studies are still needed for confirmation. It is important to note that the data reflect an intention-to-treat approach, which helps ensure that success rates are not artificially inflated. When we dichotomized age at 65 years, the association was only observed for the excellent response, reinforcing the consistency of age as a predictor for this specific outcome. Age was also independently associated with effectiveness and excellent response in the biggest European real-world study of mAbs for migraine prevention.[14] Although this association deserves future investigations, we believe that it can likely be attributed to a complex interplay of multiple factors. Younger individuals with migraine may contend with a higher number of triggering factors which can initiate a migraine attack, like hormonal factors, stress or lack of sleep, given the heightened demands associated with familiar, social, and occupational responsibilities during this life stage.[11,23] Consequently, these multifaceted demands could potentially diminish the treatment's overall efficacy in this demographic group. Nevertheless, the interpretation of this results must be cautioned, and further randomized clinical trials and real-world evidence studies including other populations should confirm our findings.

The other factors associated with response to galcanezumab treatment in our study were psychiatric comorbidity, fibromyalgia, and daily headache at baseline. These negative factors have been reported in other real worlds studies,[15] especially the unfavorable effect of depression that has been associated with higher CGRP levels and a lack of decrease of these levels after erenumab treatment.[24] In our study, although age and psychiatric comorbidities were independently associated with treatment response, the effect of age was attenuated by the presence of psychiatric diseases. The detrimental effect of psychiatric diseases, especially anxiety and depression,[14] have been previously described, although the association is not fully understood. Several mechanisms of comorbidity have been discussed in literature, such as psychiatric disorders causing migraine; migraine causing psychiatric syndromes (e.g., pain leading to anticipatory anxiety); and common etiology of both syndromes (e.g., shared genetic factors concerning neurotransmitters).[25]

Our study has several limitations. Although we include a large multicenter cohort, the number of cases older than 65 years was relatively low. This could prevent us for finding other important associations with clinical variables and outcomes. Moreover, relevant data such as proportion of migraine with aura was not included in the study. These data could have enhanced our interpretation of our results since aura symptoms are more prevalent in patients ≥65 years old and might be associated with CGRP levels and treatment response.[26,27] Another limitation is that we gathered cardiovascular risk factors for older patients, but these data are not available for younger patients. Also, older patients are more likely to be treated with other medications which are also used for migraine prevention. Although we do not believe these medications played a major role in our results, considering the demonstrated refractoriness of migraine to three preventive treatments prior to the indication of galcanezumab, their inclusion would have been valuable. Psychiatric comorbidities were registered as a unique variable, and it could have been more informative to differentiate anxiety and depression from the other conditions. Besides the limitations already mentioned, the study may be subject to residual confounding, as other comorbidities, such as vascular risk factors, were not included in the logistic regression and could potentially influence or predict outcomes. Selection bias and confounding should also be considered, especially given the relatively low number of patients aged ≥65 years and the retrospective collection of cardiovascular risk factors. Nevertheless, further studies with different populations, different mAbs, and analysis of other comorbidities are needed to confirm the favorable profile of anti-CGRP mAbs in patients aged ≥65 years and find out the most relevant predictors for treatment response to tailor a more personalized medicine.

CONCLUSIONS

In patients aged 65 years and older, treatment with galcanezumab for migraine prevention is as effective and well-tolerated as it is in younger patients. Moreover, a higher percentage of older patients achieved an excellent response to this treatment. Overall, older age appears to be associated with a more favorable response to galcanezumab. Given these findings, future studies should further explore the relationship between age and the effectiveness of anti-CGRP medications, and future trials should not exclude older patients with migraine.

AUTHOR CONTRIBUTIONS

Study concept and design: Elisa Cuadrado-Godia, Daniel Guisado-Alonso, David García-Azorín, Víctor Obach. Acquisition of data: Julia Peris-Subiza, Víctor Obach, Daniel Guisado-Alonso, Fernando Velasco Juanes, Rocío Álvarez Escudero, María Martín Bujanda, Sonsoles Aranceta, Aintzine Ruisánchez, Natalia Roncero, Ane Mínguez-Olaondo, Amaya Echeverria, Alba López-Bravo, Ángel Luis Guerrero-Peral, David García-Azorín, Elisa Cuadrado-Godia. Analysis and interpretation of data: Julia Peris-Subiza, Daniel Guisado-Alonso, Elisa Cuadrado-Godia. Drafting of the manuscript: Julia Peris-Subiza, Daniel Guisado-Alonso, Elisa Cuadrado-Godia. Revising it for intellectual content: Julia Peris-Subiza, Víctor Obach, Daniel Guisado-Alonso, Fernando Velasco Juanes, Rocío Álvarez Escudero, María Martín Bujanda, Sonsoles Aranceta, Aintzine Ruisánchez, Natalia Roncero, Ane Mínguez-Olaondo, Amaya Echeverria, Alba López-Bravo, Ángel Luis Guerrero-Peral, David García-Azorín, Elisa Cuadrado-Godia. Final approval of the completed manuscript: Julia Peris-Subiza, Víctor Obach, Daniel Guisado-Alonso, Fernando Velasco Juanes, Rocío Álvarez Escudero, María Martín Bujanda, Sonsoles Aranceta, Aintzine Ruisánchez, Natalia Roncero, Ane Mínguez-Olaondo, Amaya Echeverria, Alba López-Bravo, Ángel Luis Guerrero-Peral, David García-Azorín, Elisa Cuadrado-Godia.

AFFILIATIONS

[1]Neurology Department, Department of Medicine and Life Sciences, Hospital del Mar Barcelona, Universitat Pompeu Fabra (UPF), Barcelona, Spain
[2]Headache Unit, Neurology Department, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain
[3]Neurology Department, Hospital Universitario Cruces, Bilbao, Spain
[4]Neurology Department, Hospital Universitario Central de Asturias, Oviedo, Spain
[5]Neurology Department, Hospital Universitario de Navarra, Navarra, Spain
[6]Neurology Department, Hospital Parc Taulí, Barcelona, Spain
[7]Neurology Department, Hospital Universitario de Galdakao-Usansolo, Bilbao, Spain
[8]Neurology Department, Hospital Universitario de Basurto, Bilbao, Spain
[9]Neurology Department, Hospital Universitario de Donostia, San Sebastian, Spain
[10]Faculty of Health Sciences, University of Deusto, San Sebastian, Spain
[11]Neuroscience Area, Bioguipuzkoa Health Institute, Donostia, Spain
[12]Athenea Neuroclinics, Donostia, Spain
[13]Neurology Department, Osakidetza Basque Health Service, Araba University Hospital, Bioaraba, Vitoria-Gasteiz, Spain
[14]Headache Unit, Neurology Department, Hospital Reina Sofía Tudela de Navarra, Tudela, Spain
[15]Headache Unit, Neurology Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
[16]Department of Medicine, University of Valladolid, Valladolid, Spain
[17]Headache Unit, Neurology Department, Hospital Universitario Río Hortega de Valladolid, Valladolid, Spain
[18]Faculty of Health and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain

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CONFLICT OF INTEREST STATEMENT

Within the past 24 months, **Víctor Obach** has received speaker/travel grants/ clinical trials from Teva, Abbvie, Eli Lilly, Lundbeck, Pfizer, and Biohaven. **Ángel Luis Guerrero-Peral** has received research funding from the Regional Health Administration (Gerencia Regional de Salud SACYL) in Castilla y Leon, Spain, and speaker/travel grants/ clinical trials from Teva, Abbvie, Amgen, Eli Lilly, Lundbeck, Novartis, Pfizer, and Biohaven. **Daniel Guisado-Alonso** has received speaker/ travel grants/ clinical trials from Teva, Abbvie and Eli Lilly. **Julia Peris-Subiza, Fernando Velasco Juanes, Rocío Álvarez Escudero, María Martín Bujanda, Sonsoles Aranceta, Aintzine Ruisánchez, Natalia Roncero, Ane Mínguez-Olaondo, Amaya Echeverria, and Alba López-Bravo,** report no competing interests. **David García-Azorín** has received research funding from the Regional Health Administration (Gerencia Regional de Salud SACYL) in Castilla y Leon, Spain. Speaker/travel grants/ clinical trials from Teva, Abbvie, Amgen, Eli Lilly, Lundbeck, Novartis, Pfizer and Biohaven. **Elisa Cuadrado-Godia** has received speaker/ travel grants/ clinical trials from Teva, Abbvie, Eli Lilly, Lundbeck and Pfizer.

ORCID

Julia Peris-Subiza https://orcid.org/0009-0002-4393-5861
Víctor Obach https://orcid.org/0000-0002-0518-1053
Daniel Guisado-Alonso https://orcid.org/0000-0002-5799-3184
Fernando Velasco Juanes https://orcid.org/0009-0006-1246-6061
Alba López-Bravo https://orcid.org/0000-0002-2465-2316
David García-Azorín https://orcid.org/0000-0002-3132-1064
Elisa Cuadrado-Godia https://orcid.org/0000-0002-9147-875X

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