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ORIGINAL ARTICLE

Maintenance of response and predictive factors of 1-year GalcanezumAb treatment in real-life migraine patients in Italy: The multicenter prospective cohort GARLIT study

Fabrizio Vernieri[1] | Nicoletta Brunelli[1] | Marilena Marcosano[1] | Cinzia Aurilia[2] | Gabriella Egeo[2] | Carlo Lovati[3] | Valentina Favoni[4] | Armando Perrotta[5] | Ilaria Maestrini[6] | Renata Rao[7] | Luigi d'Onofrio[1] | Cinzia Finocchi[8] | Marco Aguggia[9] | Francesco Bono[10] | Angelo Ranieri[11] | Maria Albanese[12,13] | Vittorio Di Piero[6] | Sabina Cevoli[4] | Claudia Altamura[1] | Piero Barbanti[2,14] | for the GARLIT Study Group

[1]Headache and Neurosonology Unit, Neurology, Fondazione Policlinico Campus Bio-Medico, Rome, Italy

[2]Headache and Pain Unit, IRCCS San Raffaele Pisana, Rome, Italy

[3]Neurology Unit, Headache Center, University Hospital L. Sacco, Milan, Italy

[4]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

[5]IRCCS NEUROMED, Pozzilli, Isernia, Italy

[6]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

[7]Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[8]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[9]Neurology and Stroke Unit, Asti Hospital, Asti, Italy

[10]Neurology Unit, Center for Headache and Intracranial Pressure Disorders, A.O.U. Mater Domini, Catanzaro, Italy

[11]Neurology and Stroke Unit, AORN A. Cardarelli, Naples, Italy

[12]Neurology Unit, Headache Center, Tor Vergata University Hospital, Rome, Italy

[13]Department of Systems Medicine, Tor Vergata University, Rome, Italy

[14]San Raffaele University, Rome, Italy

Correspondence
Fabrizio Vernieri, Headache and Neurosonology Unit, Neurology, Fondazione Policlinico Campus Bio-Medico di Roma, Via Alvaro del Portillo, 200, 00128 Rome, Italy.
Email: f.vernieri@policlinicocampus.it

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Campus Bio-Medico University.

Abstract

Background and Purpose: To evaluate the 1-year effectiveness and tolerability of galcanezumab in real life and the prognostic indicators of persistent response.

Methods: High-frequency episodic migraine (HFEM) and chronic migraine (CM) patients treated with galcanezumab who completed a 1-year observation were enrolled. The primary outcomes assessed during the 12 months (V1–V12) were the change in monthly migraine days (MMDs) from baseline and the response rates ≥50% in MMDs (MMD ≥50% RR). The secondary outcomes were changes in pain intensity (numerical rating scale [NRS]) and in monthly acute medication intake (MAMI).

Results: We enrolled 191 patients (77.5% CM). Twenty-three patients (12%) dropped out, two for nonserious adverse events. At least 40% of patients took add-on standard

For the GARLIT Study Group, refer Appendix.

Claudia Altamura and Piero Barbanti contributed equally to the article.

preventives from baseline to V12. At V12, MMDs were reduced by 6.0 days in HFEM and by 11.9 days in CM patients (both $p < 0.00001$); NRS and MAMI were also decreased in both groups ($p < 0.00001$). One-hundred eight (56.5%) patients presented MMD ≥50% RR for 9 cumulative months (interquartile range=8): we defined this value as the cutoff for a persistent response. Persistent responders were less likely to have a higher body mass index (BMI) ($p = 0.007$) but more frequently had a good response to triptans ($p = 0.005$) and MMD ≥50% RR at V1 ($p < 0.0000001$). Patients without a persistent response were on add-on therapy for longer periods of time ($p < 0.001$).

Conclusions: Galcanezumab was effective and well-tolerated in the 1-year term, with most patients presenting MMD ≥50% RR for at least 9 months. Triptan response, lower BMI, and MMD ≥50% RR in the first month emerged as predictive factors for a persistent response.

KEYWORDS
CGRP, galcanezumab, migraine, monoclonal antibodies, real life

INTRODUCTION

The evidence from studies evaluating monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway (mAbs anti-CGRP) has been transforming migraine prevention strategies. Randomized controlled trials (RCTs) demonstrated that the mAbs anti-CGRP receptor (i.e., erenumab [1, 2]), and mAbs targeting the CGRP ligand (i.e., galcanezumab [3–5], fremanezumab [6, 7], and eptinezumab [8]) are effective and safe in the prevention of episodic and chronic migraine (CM). Open-label extension studies have also demonstrated their clinical benefit and tolerability in the long term [9, 10]. Real-life studies showed that clinical improvements could be even better in everyday clinical practice than in RCTs [11–14]. However, several drug regulatory agencies have imposed limitations on their use due to their high costs. In this context, optimizing the use of mAbs anti-CGRP would allow treating those patients with a good and persistent response and avoid prolonged ineffective treatment in subjects who will not eventually benefit.

There are still other questions that would help optimize everyday clinical practice, which remain unanswered and are not explored in RCTs, such as the maintenance of good response in real life [10, 15], the concomitant use of other preventive therapies [16], the predictive factors of outcome [11, 15, 17, 18], and finally, when mAbs anti-CGRP should be considered ineffective [19, 20].

Galcanezumab has been available in Italy for the preventive treatment of high-frequency episodic migraine (HFEM) (8–14 migraine days per month) and CM patients since September 2019.

Galcanezumab in Real Life Migraine Patients in Italy (GARLIT) is an independent, observational, prospective, multicenter study ongoing since November 2019 at 16 Italian headache centers. Two previous GARLIT experiences [15, 18] reported the 3- and 6-month effectiveness and tolerability of galcanezumab in HFEM and CM patients in a real-life setting. The present study aimed to investigate the effectiveness and tolerability of galcanezumab in real-life CM and HFEM patients after 1 year of treatment. We also explored the maintenance of response, the possible predictors of a good outcome, and the clinical aspects related to the use of concomitant preventives.

METHODS

Participants and study design

The GARLIT study is an independent, multicenter, prospective, cohort, real-life study ongoing at 16 Italian headache centers from September 2019, with the latest data survey on 30 November 2021.

All consecutive patients aged 18 years or older with a diagnosis of HFEM (8–14 migraine days per month) or CM (1.3 International Classification of Headache Disorders (ICHD-3)) [21], with indication to galcanezumab treatment according to eligibility criteria [22, 23], were considered for enrolment. The present article considered only patients completing the 12-month treatment observation. Patients received galcanezumab subcutaneous injection with the first loading dose of 240 mg followed by a monthly 120 mg injection, as recommended [24].

Data collection

Data collection for the GARLIT studies has been described previously [18]. Patients were assessed at baseline by a headache expert with a face-to-face interview using a questionnaire addressing sociodemographic factors, comorbidities, clinical migraine features, including migraine-related dopaminergic and unilateral cranial autonomic symptoms [25] and allodynia during or between attacks [26]. Dopaminergic features included at least one following symptoms: yawning, somnolence, severe nausea (i.e., requiring specific treatment) and vomiting during prodromes, headache stage, or postdromes; unilateral cranial autonomic symptoms were defined as at

least one of the following symptoms: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and/or eyelid edema.

Previous and current acute and preventive migraine treatments and concomitant medications were investigated. Triptan users were classified as good responders if they were headache free within 2 h after treating at least two out of three migraine attacks with one triptan [17]. Participants' weight and height were also collected. Enrolled patients were requested to carefully fill out a daily headache diary during a run-in month period (baseline) and the entire duration of the study (from V1 to V12) including the monthly migraine days (MMDs) and monthly acute medication intake (MAMI). Medication overuse (MO) was defined as the intake of ≥15 Non-steroidal anti-inflammatory drugs (NSAIDs) or ≥10 triptans per month. We considered medication overuse headache (MOH) in CM patients according to the ICHD-3 definition [21]. Patients were also asked to rate pain severity (score 0–10 on the numerical rating scale [NRS]) of the monthly most painful attack and fill out migraine disability questionnaires (Headache Impact Test [HIT-6] [27], monthly, and the Migraine Disability Assessing [MIDAS] questionnaire [28], quarterly).

The above-reported variables and any adverse events (AEs) were recorded at baseline and monthly at every in-office visit (V1–V12). Telephone/email contacts were allowed when in-office visits were not possible (e.g., isolation/quarantine due to the SARS-CoV-2 pandemic). All AEs were reported and classified as gastrointestinal (e.g., nausea, constipation), cutaneous (e.g., injection-site reactions: rash/erythema, pruritus, urticaria, edema/induration), arthralgia/flu like, Raynaud phenomenon, dizziness, and other (<1% of patients: i.e., drowsiness, alopecia, anxiety).

End points

The primary end point was the change in MMDs during the 12 months of treatment compared to baseline. We assessed the response rates (RRs) as the percentual reduction in MMDs from V1 to V12 compared to the baseline. We summed the cumulative months with at least a 50% reduction in MMD (MMD ≥50% RR) and defined as persistent responders those patients achieving MMD ≥50% RR in cumulative months equal to or higher than the median value observed in the whole cohort. We also investigated the predictive factors of a persistent response. Moreover, the frequency of MMD ≥50%, ≥75%, and 100% RR was calculated at V1, V3, V6, and V12. Secondary end points included the changes in monthly MAMI, NRS score, and quarterly changes in HIT-6 and MIDAS scores. Finally, we evaluated the use of add-on preventive therapies to galcanezumab along the treatment year.

Standard protocol approvals, registrations, and patient consents

All patients provided written informed consent. The study was approved by the Campus Bio-Medico University Ethical Committee n. 30/20, mutually recognized by the other local ethical committees, registered at the Italian Medicines Agency (Agenzia Italiana del Farmaco), and ClinicalTrials.gov NCT04803513.

Statistical analysis

This is an a priori analysis. To achieve a power of 80% and a significance level of 5% (two-sided), for detecting an effect size of 0.25 between paired variables, we calculated a sample size of at least 128 subjects. Statistical analyses were performed using SPSS version 27.0 (IBM). The interval variables between groups were compared with independent *t* tests (expressed as means with standard deviations) or Mann-Whitney tests (medians with interquartile range). A paired *t* test was used to analyze the variable changes over time. Contingency tables (χ^2 and two-tailed Fisher exact tests) and unadjusted odds ratios with their 95% confidence intervals (CIs) were run to compare frequencies between groups. All tests were bilateral. Statistical significance was set as a two-tailed $p < 0.05$. We included only subjects with complete information regarding the primary studied variables (MMDs). We declared data availability and ran the analysis only in patients with usable data for the secondary variables (MAMI, NRS, HIT-6, MIDAS).

We initially investigated which clinical baseline characteristics were associated with a persistent response (considering $p < 0.01$). These variables (independent variables) were entered in binary logistic regression (forced entry) to confirm the association to the persistent response (dependent variable). Bonferroni correction was applied for multiple comparisons.

RESULTS

To date, 414 patients have been enrolled in the GARLIT study at 16 participating centers. As of 30 November 2021, 198 patients completed 12 months of observation since the first galcanezumab injections at 12 centers, and were considered in the present study. Seven subjects were excluded from the current analysis due to an incomplete data set of primary variables. Hence, a total of 191 patients (153 female [80.1%], 46.6 ± 10.5 years, minimun–maximum = 18–80 years) were finally enrolled. Of these, 23 patients (12.0%) dropped out at least after 3 months of therapy due to lack of effectiveness or AEs; these patients were included in the analysis as nonresponders and considered for the other end points for the treatment period.

At baseline, 148 (77.5%) patients were affected by CM, 43 (22.5%) by HFEM, and 128 subjects (67.0%) also presented MO.

Table 1 summarizes baseline demographical and clinical profiles of CM and HFEM patients. The reported psychiatric comorbidity in all participants was an anxiety disorder and/or minor depression; in one HFEM patient, it was associated with a personality disorder. Gastroesophageal reflux disease was the most often complaint of gastrointestinal comorbidities (27), sometimes associated with hiatal

TABLE 1 Baseline demographic and clinical profiles in HFEM and CM patients

Profile	HFEM, *n* = 43	CM, *n* = 148	*p*
Age, years, mean (SD)	47.4 (10.8)	46.4 (10.5)	0.594
Sex, female, % (*n*)	81.4 (35)	79.7 (118)	1.000
BMI, kg/m^2, mean (SD)	23.55 (2.92)	24.59 (4.61)	0.324
Comorbidities (%)			
Psychiatric	18.6 (8)	24.3 (36)	0.536
Gastrointestinal	11.6 (5)	21.6 (32)	0.160
Vascular	0 (0)	5.4 (8)	0.200
Hormonal	13.9 (6)	12.8 (19)	1.000
Diabetes	0 (0)	1.4 (2)	1.000
Hypertension	13.9 (6)	13.5 (20)	1.000
Cancer	18.6 (8)	1.4 (2)	<0.001
Immuno-rheumatologic	2.3 (1)	6.8 (10)	0.687
MO, % (*n*)	21.4 (9)	80.4 (119)	<0.001
Disease history, mean (SD)	29.2 (14.6)	29.0 (11.2)	0.948
Failed preventives, median (minimum–maximum)	4 (3–12)	5 (3–11)	0.040
NRS, mean (SD)	7.6 (1.3)	7.7 (1.2)	0.646
MMDs, mean (SD)	11.4 (3.4)	19.8 (6.2)	<0.001
MAMI, mean (SD)	15.0 (10.4)	25.8 (28.7)	<0.001
HIT-6, mean (SD)	64.6 (7.1)	66.9 (6.6)	0.047
MIDAS, mean (SD)	49.4 (39.7)	76.9 (47.8)	0.003
Throbbing pain (%, *n*)	41.8 (18)	58.1 (86)	0.076
Unilateral pain (%, *n*)	58.2 (25)	48.6 (72)	0.221
Dopaminergic features (%)	58.1 (25)	66.2 (98)	0.435
Allodynia (%)	44.2 (19)	73.6 (109)	<0.001
Unilateral cranial autonomic features, % (*n*)	41.9 (18)	56.0 (83)	0.057
Triptan responder, % (*n*)	79.1 (34)	52.7 (78)	0.003
Add-on preventive therapy, % (*n*)	48.8 (21)	52.5 (78)	0.730
Antiepileptic	18.6 (8)	22.3 (33)	0.678
Amitriptyline	18.6 (8)	25.7 (38)	0.536
β-Blockers	25.6 (11)	14.9 (22)	0.112
OnabotulinumtoxinA	0	3.4 (5)	0.589
Calcium channel blockers	0	6.1 (9)	0.212
Candesartan	0	3.4 (5)	0.589
Other, antidepressants, neuroleptics	4.7 (2)	19.6 (29)	0.018

Abbreviations: BMI, body mass index; CM, chronic migraine; HFEM, high-frequency episodic migraine; HIT-6, Headache Impact Test; MAMI, monthly acute medication; MIDAS, Migraine Disability Assessment Scale; MMDs, monthly migraine days; MO, medication overuse; NRS, Numeric Rating Scale.

hernia (five); two patients were affected by irritable bowel syndrome. Gastrointestinal comorbidities were not specified in eight patients.

The MMDs and MAMI data were fully available for the evaluation times. From baseline to V12, NRS score was regularly collected in 32 HFEM (74.4%) and 102 CM (69.9%) patients; quarterly HIT-6 scores were available for 25 HFEM (58.1%) and 66 CM (44.6%) patients, and quarterly MIDAS scores for 20 HFEM (46.5%) and 58 CM (39.2%) patients.

Figure 1 displays MMD (left panel) and MAMI (right panel) variations along evaluation times in HFEM and CM patients. The main changes were observed in the first month of therapy. Figure 2 shows the percentage of patients achieving an MMD ≥50% RR for the first time during the observation period. Of note, 57.6% of patients

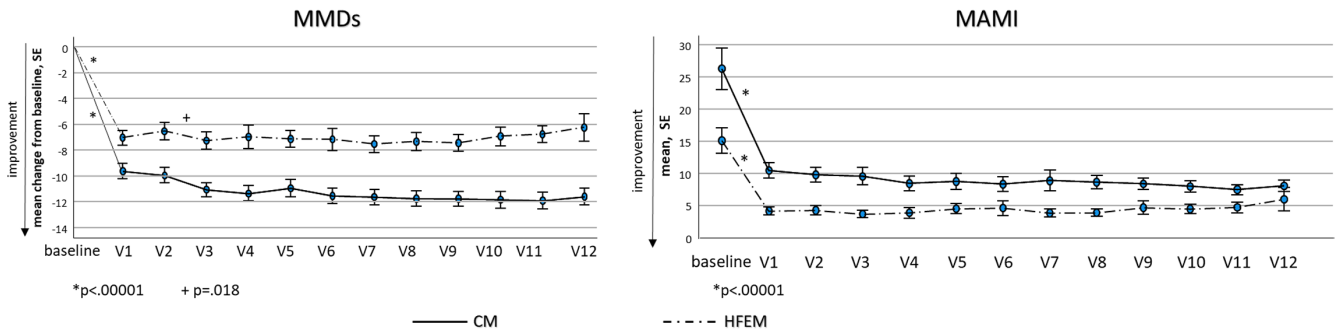

FIGURE 1 (Left) Mean monthly migraine days (MMDs) changes from baseline to V12 in high-frequency episodic migraine (HFEM, dashed line) and chronic migraine (CM, solid line) patients. (Right) Monthly acute medication intake (MAMI) changes from baseline to V12 in HFEM (dashed line) and CM (solid line) patients. The levels of significance indicate the results of paired *t* tests for MMDs and MAMI along the evaluation times.

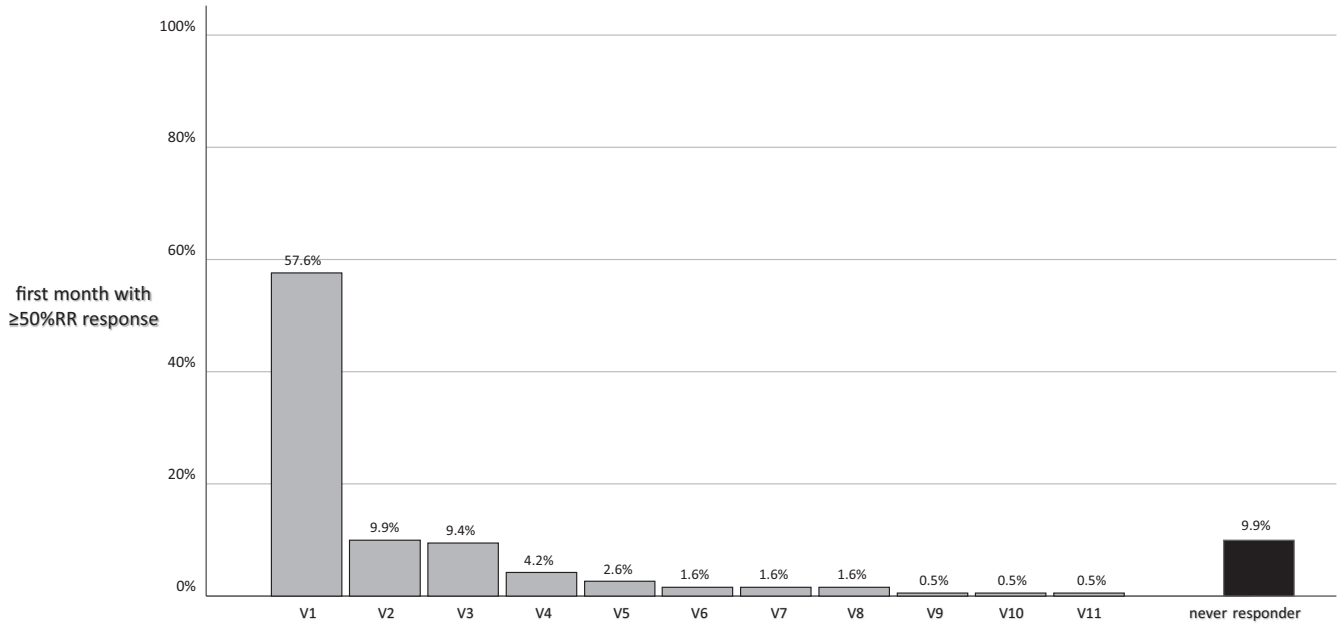

FIGURE 2 Frequency of patients achieving monthly migraine day 50% response rate (RR) for the first time during the observation period.

started responding during the first month of treatment, 76.9% within the first trimester, whereas 9.9% of patients never presented a 50% MMD reduction.

Episodic migraine

Patients reported a significant decrease (consistently for all the variables $p < 0.00001$) from baseline to V12 in MMDs (from 11.5 ± 3.5 to 5.5 ± 5.5), in MAMI (from 15.4 ± 10.9 to 6.4 ± 10.1), in NRS (from 7.6 ± 1.2 to 5.6 ± 1.8), in HIT-6 score (from 64.7 ± 8.0 to 52.4 ± 8.3), and in MIDAS score (from 49.1 ± 40.1 to 11.5 ± 12.3).

We observed an MMD ≥50% RR in 65.1% of patients at V1, 69.8% at V3, 76.7% at V6, and 73.8% at V12. The MMD ≥75% RR was achieved in 34.9% of cases at V1, 39.5% at V3, 30.2% at V6, and 37.2% at V12. Three patients achieved MMD ≥100% RR at V1 (7.0%), five patients at V3 (11.6%), four at V6 (9.3%), and one at V12 (2.3%) (Figure 3, left panel).

Chronic migraine

Patients reported a relevant decrease from baseline to V12 (consistently for all the variables $p < 0.00001$) in MMDs (from 19.3 ± 5.8 to 7.4 ± 5.9), in MAMI (from 26.2 ± 31.6 to 7.8 ± 8.4), in NRS (from 7.6 ± 1.2 to 5.7 ± 1.6), in HIT-6 score (from 67.1 ± 6.7 to 53.4 ± 9.3), and in MIDAS score (from 78.4 ± 53.8 to 20.8 ± 29.8).

We observed an MMD ≥50% RR in 55.4% of patients at V1, 64.9% at V3, 61.5% at V6, and 60.5% at V12. The MMD ≥75% RR was achieved in 24.3% of cases at V1, 31.1% at V3, 35.1% at V6, and 38.1% at V12. Two patients achieved MMD 100% RR at V1 (1.4%), five patients at V3 (3.4%), seven at V6 (4.7%), and five at V12 (3.4%) (Figure 3, right panel).

As a median, patients (56.5%) responded for nine cumulative months (25th, four; 75th, 12). We defined this value (9 cumulative months with MMD ≥50% RR) as the cutoff for a persistent response in our sample. The percentage of patients achieving MMD ≥50% RR

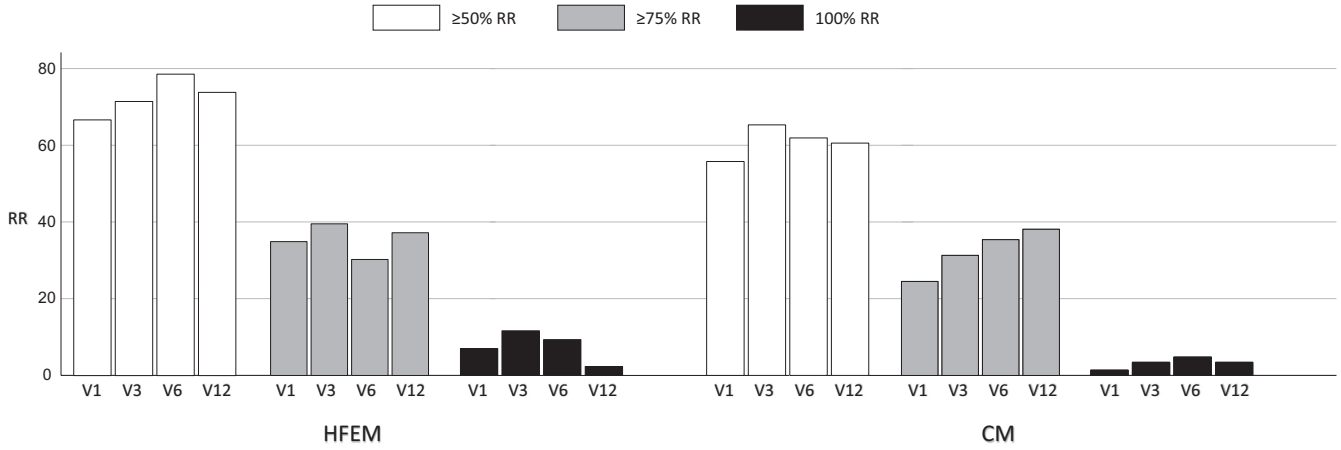

FIGURE 3 Percentage of high-frequency episodic migraine (HFEM) (left) and chronic migraine (CM) (right) patients achieving 50%, 75%, and 100% response rate (RR) at V1, V3, V6, and V12.

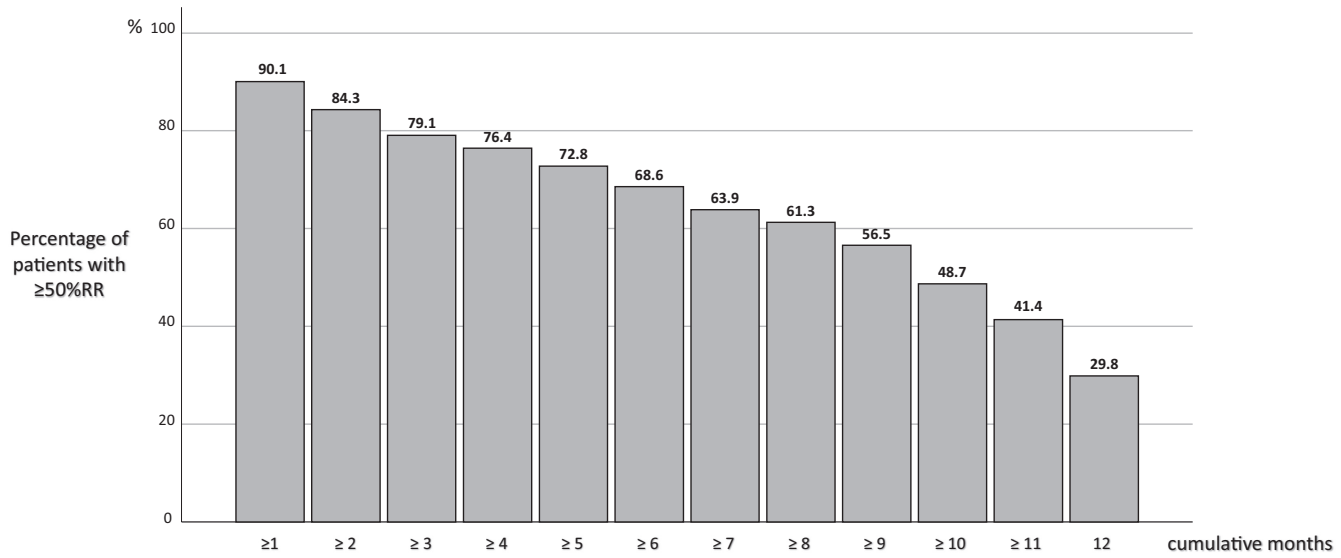

FIGURE 4 Percentage of patients achieving monthly migraine day 50% response rate (RR) in at least 1 month up to 12 cumulative months of therapy.

in at least 1 month was 90.1%, whereas 29.8% of patients responded for the whole year of therapy (Figure 4).

At baseline, 99 patients (51.8%) took at least one add-on standard preventive drug and 43 (22.5%) at least two. These percentages tended to decrease during the treatment period (Figure 5).

Table 2 summarizes baseline demographical and clinical characteristics in patients who achieved a persistent versus nonpersistent response. In the CM group, the prevalence of MOH was not different in persistent responders (57.1%) compared with nonpersistent responders (42.9%, $p = 0.096$). A higher body mass index (BMI), psychiatric and gastrointestinal comorbidity, poor response to triptans, and longer period on add-on preventive therapy were associated with a nonpersistent response. Because we considered the prolonged use of add-on preventive therapy as a consequence of an unsatisfactory response to galcanezumab rather than a possible determinant, we did not include it in the regression analysis.

Table 3 displays binary logistic regression having persistent response as the dependent variable. After Bonferroni correction, lower BMI ($p = 0.042$) and good response to triptans ($p = 0.030$) resulted in positive factors associated with a persistent response.

Interestingly, an MMD ≥50% RR in the first month of treatment is also largely associated with a persistent response ($p < 0.0000001$, 95% CI=6.132–24.274). Out of the 108 persistent responders, 88 (81.5%) achieved 50% ≥ RR at V1, whereas for the nonpersistent responders, 61 out of 83 (73.5%) did not achieve ≥50% RR at V1.

Patients completing 1 year of treatment were 168 (88.0%), and only nine patients (4.7%) discontinued galcanezumab before 6 months of therapy. Of the 23 patients (12.0%) who did not complete the 12-month treatment, 20 discontinued galcanezumab due to inefficacy, two due to nonsevere AEs (one case of urticaria, and one case of severe constipation), and one due to technical difficulties to receive the drug.

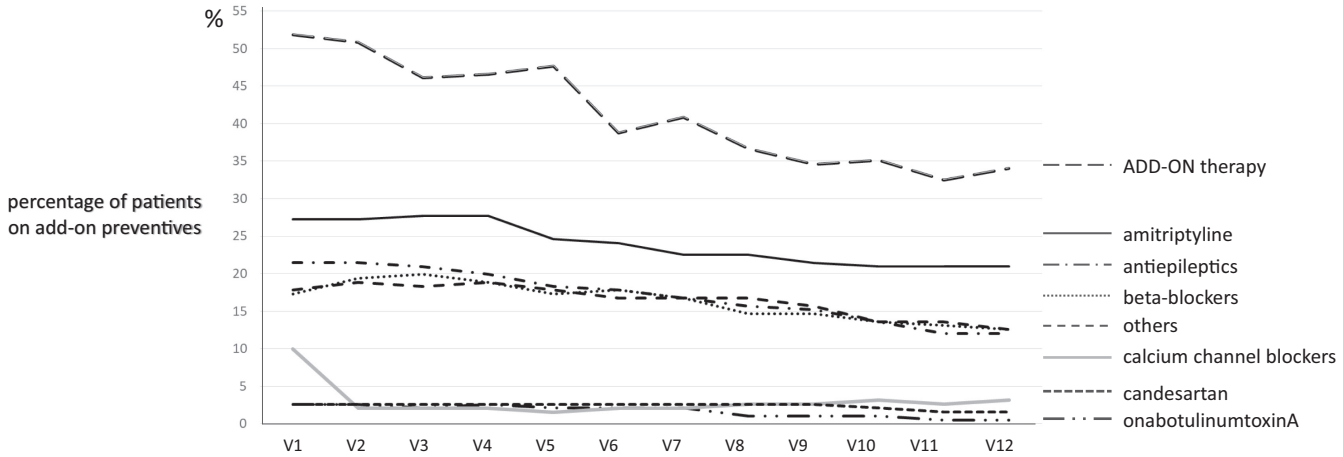

FIGURE 5 Percentage of patients receiving add-on standard therapies along the year of treatment.

The most common events were constipation and injection-site reactions (>2% of patients). Other events, including dizziness, arthralgia/flu-like symptoms, and the Raynaud phenomenon, were reported in <2% of patients throughout the study.

DISCUSSION

The GARLIT is a large multicenter, prospective, real-life cohort study performed on galcanezumab. The present observation describes the 12-month treatment effectiveness, safety, and tolerability of this monoclonal antibody-targeting CGRP.

As observed after 3 and 6 months of treatment [15, 18], here we confirm a large decrease in MMDs, number of acute medications, and pain intensity score in HFEM and CM patients treated with galcanezumab for 12 months. Moreover, disability scores, HIT-6 scores and MIDAS scores, significantly improved, along with the 1-year observation.

This study also aimed to investigate the persistence of those benefits and possible predictors of good outcome to be used in clinical practice.

An RR of 50% or higher for MMDs is considered as the primary measure to evaluate the efficacy of preventive treatments. However, the maintenance of the response for a long observation period is equally, if not more, important. More than half of our cohort achieved at least a 50% reduction in migraine attacks frequency with respect to baseline for three-quarters of the study observation period. Of note, about 30% of patients presented an MMD ≥50% RR in each of the 12 months of treatment. We have previously reported that an MMD ≥50% RR during the entire 6 months of therapy was observed in about 40% of cases [18]. The response in our real-life experience appeared to be more sustained than that observed in RCTs. The analyses of the data in the galcanezumab 120-mg dose arm from EVOLVE-1, EVOLVE-2, and REGAIN studies reported that 19.0% of episodic patients responded for 6 consecutive months and 16.8% of CM patients for 3 consecutive months [10, 29]. Also, after 1 year of treatment, the persistence of response to galcanezumab in real life seems higher than in RCTs.

In the present study, we also observed that a higher BMI negatively influenced the outcome, whereas a good response to triptans was a positive factor associated with a persistent response.

We described the detrimental effect of being overweight in the previous analyses of the GARLIT study regarding the consistent response in the first 3 months of therapy [15] and after 6 months [18]. A population pharmacokinetic (PK) analysis of galcanezumab, using data pooled from seven clinical studies, showed that patient body weight has a modest effect on apparent clearance (CL/F), with median galcanezumab concentrations being lower in the heaviest patients than in the lightest patients. However, this outcome was determined not to be clinically relevant in the context of model-estimated random variability. Galcanezumab dosing adjusted for body weight is not currently warranted in adults [30]. Of note, the mean BMI of patients enrolled in EVOLVE-1 [3], REGAIN [5], and CONQUER [31] RCTs was above 25, which is the cutoff value to define overweight, supporting the evidence that galcanezumab can be also effective in overweight patients. Mechanisms beyond PK probably take place to lessen this benefit.

Obesity is one of the comorbid conditions associated with CM [32]. Higher levels of trigeminal CGRP have been reported in obese individuals compared with normal-weight subjects [33]. Interictal CGRP levels in peripheral blood rise with increasing migraine frequency as a result of repeated activation of the trigeminovascular system. This may trigger more frequent episodes and eventually lead to CM. In this scenario, overweight patients might require a multitargeted approach or longer treatment time with strict weight control. Alternatively, the activation of other pain mediators could be hypothesized. The adipose tissue secretes proinflammatory cytokines and adipocytokines implicated in migraine pathophysiology. Moreover, some neuroendocrine mediators, such as orexin, modulate nociception, and metabolism [34]. A detrimental effect of a higher BMI has also been observed in post hoc analyses of eptinezumab RCTs [35]. Hence, a similar evaluation or ad hoc designed trials should be

TABLE 2 Baseline demographical and clinical characteristics in patients with persistent compared with the nonpersistent response

	Persistent response $n = 108$	Nonpersistent response $n = 83$	p
Age, years, mean (SD)	48.1 (9.8)	44.7 (11.1)	0.023
Sex, female, % (*n*)	83.3 (90)	75.9 (63)	0.208
BMI, kg/m^2, mean (SD)	23.21 (3.16)	26.07 (5.21)	<0.001
Comorbidities (%)			
Psychiatric	15.7 (17)	33.7 (28)	0.006
Gastrointestinal	11.1 (12)	28.9 (24)	0.004
Vascular	5.5 (6)	1.2 (1)	0.243
Hormonal	12.0 (13)	13.2 (11)	0.817
Diabetes	0	2.4 (2)	0.165
Hypertension	11.1 (12)	15.6 (13)	0.360
Cancer	5.5 (6)	2.4 (2)	0.475
Immuno-rheumatologic	3.7 (4)	7.2 (6)	0.488
MO, % (*n*)	68.5 (74)	65.1 (54)	0.640
Disease history, mean (SD)	29.2 (11.5)	28.8 (12.5)	0.837
Failed preventives, median (25th, 75th)	4 (3, 6)	4 (3, 6)	0.797
NRS, mean (SD)	7.7 (1.1)	7.7 (1.3)	0.792
MMDs, mean (SD)	17.7 (6.3)	18.2 (7.2)	0.572
MAMI, mean (SD)	23.1 (18.1)	23.6 (33.9)	0.901
HIT-6, mean (SD)	67.4 (6.9)	65.1 (6.9)	0.020
MIDAS, mean (SD)	73.6 (48.3)	67.9 (48.1)	0.463
Throbbing pain, % (*n*)	53.7 (58)	57.8 (48)	0.642
Unilateral pain, % (*n*)	56.4 (61)	43.3 (36)	0.123
Dopaminergic features, % (*n*)	64.8 (70)	62.7 (52)	0.863
Allodynia, % (*n*)	69.4 (75)	63.9 (53)	0.441
Unilateral cranial autonomic features, % (*n*)	53.7 (58)	50.6 (42)	0.867
Triptan responder, % (*n*)	70.4 (76)	43.4 (83)	<0.001
Months in add-on preventive therapy, median (25th, 75th)	2 (0, 8)	11 (1, 12)	<0.001

Abbreviations: BMI, body mass index; HIT-6, Headache Impact Test; MAMI, monthly acute medication; MIDAS, Migraine Disability Assessment Scale; MMDs, monthly migraine days; MO, medication overuse; NRS, numeric rating scale.

TABLE 3 Binary logistic regression analysis on persistent response

						95% CI	
	B	SE	Wald	*p*	Odds ratio	Lower	Upper
Age	0.033	0.019	2.882	0.090	1.034	0.995	1.074
Female	0.417	0.486	0.735	0.391	1.517	0.585	3.935
BMI	−0.160	0.060	7.150	0.007	0.852	0.758	0.958
Psychiatric comorbidity	−0.559	0.491	1.293	0.256	0.572	0.218	1.498
Gastrointestinal comorbidity	−1.032	0.552	3.494	0.062	0.356	0.121	1.051
Triptan responder	1.114	0.399	7.786	0.005	3.045	1.393	6.658

Abbreviations: BMI, body mass index; CI, confidence interval.

performed for the available mAbs anti-CGRP to confirm the real-life findings and investigate if there is an mAb-specific effect.

The good response to triptans resulted significantly as associated with persistent MMD ≥50% RR. Sumatriptan was demonstrated to reduce the release of vasoactive peptides, including substance P and CGRP [36, 37]. This finding suggested that triptans indirectly share a common pathway with mAb targeting the CGRP. In this light, a positive response to triptans might also be a marker of favorable response to mAbs anti-CGRP pathway. This observation confirmed previous findings from the GARLIT [15] study and one real-life study evaluating erenumab [17] and may be clinically useful to optimize prevention strategies in migraine patients.

In the present study, the number of past preventives failures [15, 18] and unilateral pain [18], which emerged in the 3- and 6-month studies as predictors of outcome, were not associated with a persistent response in the whole year of treatment. This suggests that other more relevant components have a greater impact moving forward with the months of therapy.

The main effect on reduction in MMDs, as well as in any of the other efficacy measures, was observed as early as the first month of therapy. This finding was not unexpected, because RCTs and real-world evidence have previously documented the early response to galcanezumab and the other mAbs anti-CGRP. In RCTs, galcanezumab efficacy was observed as early as the first day after injection [38]. Moreover, we found that reaching MMD ≥50% RR in the first month of treatment is strongly associated with a persistent response. More than 80% of persistent responders achieved MMD ≥50% RR at V1, whereas about 70% of nonpersistent responders did not. This observation is of paramount importance from a clinical point of view, because we may speculate that late-onset benefit is less likely in the absence of an early response.

We did not observe any treatment-related cardiovascular or cerebrovascular AEs, in line with the observation of a preserved cerebral and systemic hemodynamics in patients treated with mAbs [39]. The discontinuation rate of 12% (23 out of the 191 enrolled patients) was lower than that observed in the galcanezumab RCTs and much smaller than that reported in patients treated with standard oral migraine preventives [40]. Only two patients ceased treatment because of AEs (one case of urticaria, and one case of severe constipation), whereas one patient discontinued galcanezumab for lack of effectiveness.

Numerous clinical questions remain unanswered around mAbs targeting the CGRP pathway for migraine prevention. One of these is whether a combination of a monoclonal antibody with the standard-of-care therapy may be more effective than mAbs alone, and if so, in which patients. In our sample, 51.8% of patients took standard preventives at baseline. The percentage of patients in combination treatment tended to progressively decrease over the 12 months of therapy, but it was still prescribed, especially in patients with a less consistent response. Future studies are necessary to specifically address the possible benefit of combination therapy by adding the central effect of standard preventives to the peripheral inhibition of CGRP by mAbs.

In conclusion, our real-life study over 12 months demonstrated early and sustained effectiveness and tolerability of galcanezumab in hard-to-treat HFEM or CM patients who had previously not responded adequately to at least three preventive treatments.

In the search for clinical predictors of good outcome, we found a positive association with good response to triptans and a negative association with overweight. Moreover, the response in the first month of therapy strongly reflects the following course. However, further studies evaluating other mAbs targeting the CGRP pathway are necessary to continue to identify prognostic factors that could allow optimization of migraine management and cost reduction.

Although with some drawbacks compared to RCTs, real-life studies better represent migraine patients we treat in our everyday clinical practice and may deliver helpful suggestions for better management practices with the new treatments transforming migraine prevention.

AUTHOR CONTRIBUTIONS

Claudia Altamura: Data analysis and interpretation, drafting the manuscript for intellectual content. **Piero Barbanti and Sabina Cevoli:** Conceptualization of the study. **Vittorio Di Piero:** Revising the manuscript for intellectual content. **Fabrizio Vernieri:** Design and conceptualization of the study, drafting the manuscript for intellectual content. **Nicoletta Brunelli, Marilena Marcosano, Cinzia Aurilia, Gabriella Egeo, Carlo Lovati, Valentina Favoni, Armando Perrotta, Ilaria Maestrini, Renata Rao, Luigi d'Onofrio, Cinzia Finocchi, Marco Aguggia, Francesco Bono, Angelo Ranieri, and Maria Albanese:** Major role in the acquisition of data.

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CONFLICT OF INTEREST

M.Ag. received grants from Novartis and Lilly. M.Al. received honoraria or travel grants from Novartis, Teva, Merck Serono, Almirall, and Biogen. C.Al. received grants and honoraria from Lusofarmaco, Laborest, Abbvie, Novartis, and Eli Lilly. C.Au. received travel grants and honoraria from FB-Health, Lusofarmaco, Almirall, Eli-Lilly, Novartis, and Teva. P.B. received travel grants, honoraria for advisory boards, speaker panels or clinical investigation studies from Alder, Allergan, Angelini, Assosalute, Bayer, ElectroCore, Eli-Lilly, GSK, Lundbeck, Lusofarmaco, 1MED, MSD, New Penta, Noema Pharma, Novartis, Stx-Med, Teva, Visufarma, and Zambon. F.B. received honoraria as a speaker or for participating in advisory boards from Teva, Novartis, and Ipsen. S.C. received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Novartis, Teva, Lilly, Allergan, Ibsa, Amgen, and Lundbeck. V.D.P. received grants and honoraria by Bayer, Biogen, Lilly, TEVA,

and Novartis. G.E. received travel grants and honoraria from Eli-Lilly, Novartis, New Penta, and Ecupharma. V.F. has received honoraria as speaker or for participating in advisory boards from Ely-Lilly. C.F. received travel grants, honoraria Lilly, TEVA, and Aim Group. C.L. received grants from Novartis and Lilly. I.M. received honoraria from Eli Lilly. A.P. received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan, Eli-Lilly, Novartis, and Teva. A.R. received speaker honoraria from Teva and Lilly. R.R. received honoraria for speaker panels from Teva, Lilly, and Novartis. F.V. received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan-Abbvie, Amgen, Angelini, Eli-Lilly, Lundbeck, Novartis, and Teva. N.B., L.d.O., and M.M. have no competing interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TRIAL REGISTRATION

ClinicalTrials.gov NCT0480351.

ORCID

Fabrizio Vernieri https://orcid.org/0000-0002-9594-9336
Valentina Favoni https://orcid.org/0000-0001-5335-2438
Francesco Bono https://orcid.org/0000-0002-4650-6635
Maria Albanese https://orcid.org/0000-0002-5113-2017
Vittorio Di Piero https://orcid.org/0000-0002-2631-7562
Claudia Altamura https://orcid.org/0000-0002-5934-5535
Piero Barbanti https://orcid.org/0000-0002-5670-3755

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APPENDIX A

The GARLIT Study Group

Carmelina Maria Costa (Headache and Neurosonology Unit, Neurology, Fondazione Policlinico Campus Bio-Medico, Rome, Italy), Luisa Fofi (Headache and Pain Unit, IRCCS San Raffaele Pisana, Rome, Italy), Francesca Schiano Di Cola (Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy), Florindo d'Onofrio (Neurology Unit, San Giuseppe Moscati Hospital, Avellino), Davide Bertuzzo (Neurology and Stroke Unit, Asti Hospital, Asti, Italy), Fabio Bombardieri (Center for Headache and Intracranial Pressure Disorders, Neurology Unit, A.O.U. Mater Domini, Catanzaro, Italy), Roberta Messina Messina (Neurology, Neurorehabilitation and Neurophysiology Units, IRCCS Ospedale San Raffaele and University 'Vita e Salute', Milan, Italy), Bruno Colombo (Neurology, Neurorehabilitation and Neurophysiology Units, IRCCS Ospedale San Raffaele and University 'Vita e Salute', Milan, Italy), Massimo Filippi (Neurology, Neurorehabilitation and Neurophysiology Units, IRCCS Ospedale San Raffaele and University 'Vita e Salute', Milan, Italy), Alberto Doretti (Istituto Auxologico Italiano, IRCCS, Department of Neurology-Stroke Unit and Laboratory of Neuroscience - Milan, Italy), Gianluca Demirtzidis (Istituto Auxologico Italiano, IRCCS, Department of Neurology-Stroke Unit and Laboratory of Neuroscience - Milan, Italy), Stefano Messina (Istituto Auxologico Italiano, IRCCS, Department of Neurology-Stroke Unit and Laboratory of Neuroscience - Milan, Italy).