Conversion from chronic to episodic migraine in patients treated with galcanezumab in real life in Italy: the 12-month observational, longitudinal, cohort multicenter GARLIT experience

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Abstract

Objective To investigate in real-life the conversion from chronic migraine (CM) to episodic migraine (EM), specifically to EM with High-Frequency (HFEM: 8–14 monthly migraine days, MMDs), Medium-Frequency (MFEM, 4–7 MMDs), and Low-Frequency EM (LFEM, 0–3 MMDs), and its persistence during 1 year of treatment with galcanezumab.

Methods Consecutive CM patients treated with galcanezumab completing 1 year of observation were enrolled. We collected data on MMDs, pain intensity (Numeric Rating Scale, NRS score), and monthly acute medication intake (MAMI) from baseline (V1) to the 12-month visit (V12).

Results Of the 155 enrolled patients, 116 (around 75%) reverted to EM at every visit and 81 (52.3%) for the entire 1-year treatment. Patients with older onset age (p = 0.010) and fewer baseline MMDs (p = 0.005) reverted more frequently to EM. At V12, 83 participants (53.5%) presented MFEM or LFEM. Patients reverted to MFEM or LFEM for 7 months (25th 1, 75th 11). The medication overuse discontinuation rate at V12 was 82.8% and occurred for 11 months (25th 8, 75th 12). From baseline to V12, the MAMI decreased by 17 symptomatic drugs (p < 0.000001) while the NRS score reduced by almost 2 points (p < 0.000001). A consistent transition to EM for the entire treatment year was observed in 81 (52.3%) patients.

Discussion The 1-year GARLIT experience suggests that more than half of CM patients treated with galcanezumab persistently reverted to EM in real life.

Trial registration ClinicalTrials.gov NCT04803513.

Keywords Calcitonin gene-related peptide · Monoclonal antibodies · Migraine treatment · Real world · Chronic migraine · Conversion

Introduction

Migraine is among the most disabling neurological conditions. In 2019, headache disorders caused disability to 46.6 million people globally. Of those, 88.2% were attributable to migraine, representing the second highest cause of disability worldwide [1, 2]. Migraine distresses people in their productive age, impairing their work performances and social and familial contexts [3]. Moreover, around 8% of patients experience a progressive increase in the frequency of attacks to the point where migraine becomes chronic [4]. Patients with chronic migraine (CM) [5] suffer pain as part of a constellation of symptoms, including non-cephalalgic pain, emotional distress, sleep and gastrointestinal disorders, and other somatic conditions [6, 7]. In addition, CM patients are often forced to consume analgesics to relieve pain, resulting in medication overuse (MO), which worsens patients’ quality of life and is a risk factor for migraine chronification [8].

In this context, calcitonin gene-related peptide (CGRP) targeted therapies revolutionized migraine management [9]. Before their availability, international guidelines [10]
recommended the use of prophylactic medications not specifically developed for migraine treatment and burdened by poor long-term adherence due to their adverse events and often inadequate effectiveness [11].

Randomized controlled trials (RCTs) have consistently demonstrated that monoclonal antibodies (mAbs) specifically designed to target CGRP or its receptor are safe and effective in preventing CM [12]. These results have also been confirmed by real-life studies showing that clinical improvements can be even better in everyday clinical practice than in RCTs [13–16]. However, few studies focused on the efficacy of CGRP targeting mAbs in reverting CM to EM, mainly in the short term [16–18]. Chronic migraine, indeed, is a fluctuating condition: nearly 75% of patients with CM can remit to EM for at least 3 months during 1 year [19]. Migraine chronicification can also be reversible: about 26% of patients with chronic migraine remit within 2 years [20].

Galcanezumab has been available in Italy for migraine prevention since September 2019. Although RCTs demonstrated high efficacy and tolerability of galcanezumab in CM patients [21], a noticeable impact on their highly disabled quality of life is achieved only with sustained response to a preventive treatment.

The present prospective, observational, multicenter study aimed to investigate in real life the persistence of conversion to EM during 1 year of therapy with galcanezumab in CM patients.

Methods

Participants and study design

Galcanezumab for the prevention of high frequency episodic and chronic migraine in Real Life in Italy, i.e., the GARLIT study, is an independent, multicenter, prospective, cohort, real-life study ongoing at 15 headache centers across 8 Italian regions from September 2019. The present study included data from the latest survey on December 6, 2021.

All consecutive patients aged 18 or older with a diagnosis of HFEM (8–14 migraine days per month) or CM (1.3 ICHD-3) [5], with the clinical indication to galcanezumab according to the eligibility criteria [22], were considered for enrollment in the GARLIT study. Patients had not been previously involved in any CGRP mAbs trial. The present paper considered only CM patients with 12 months of observation from the start of therapy. Patients were treated with galcanezumab subcutaneous injections as recommended (https://www.ema.europa.eu/en/documents/product-information/emgal_e改革开放_product-information_en.pdf). They received the first loading dose of 240 mg and 120 mg every month afterward. The Italian Medicines Agency allows the reimbursement of CGRP mAbs therapy in migraine patients with at least 8 monthly migraine days and moderate disability (MIDAS score ≥ 11), having a history of an insufficient response to at least three classes of prophylactic treatments (not including calcium-antagonists).

Data collection

Data collection of the GARLIT study is described elsewhere [23]. Patients were assessed at baseline by a headache expert with a face-to-face interview using a semi-structured questionnaire addressing socio-demographic factors, clinical migraine features, previous and current acute and preventive migraine treatments, comorbidities, and concomitant medications. Migraine-related dopaminergic and unilateral cranial autonomic symptoms and allodynia during or between attacks were also investigated. Cranial autonomic symptoms were defined as at least one of the following: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead, facial sweating, miosis, ptosis, and eyelid edema. Dopaminergic symptoms were at least one of the following: yawning, drowsiness, severe nausea (i.e., requiring specific treatment), and vomiting during prodromes, headache stage, and postdromes. Patients were also requested to rate the overall efficacy of triptans in most attacks as none/poor or fair/excellent. Enrolled patients were requested to carefully fill out a daily headache diary reporting monthly migraine days (MMDs) and monthly acute medication intake (number of tablets/month, MAMI) during a run-in month period (baseline) and the 12 months of the study. We calculated the ratio between mean MAMI and MMDs to assess the number of acute medications per attack. Acute medications were classified into triptans, NSAIDs/paracetamol, and combination drugs. All patients were educated on the headache diary use before enrollment in the GARLIT study. Medication overuse was defined in patients taking ≥ 15 NSAIDs or ≥ 10 triptans per month. Based on MMDs, at each time point, patients were classified as CM, HFEM, Medium-Frequency Episodic Migraine (MFEM; 4–7 MMDs), and Low-Frequency Episodic Migraine (LFEM, <4 MMDs). Patients were also asked to rate the pain severity (score 0–10 at the Numerical Rating Scale, NRS) of the monthly most painful attack.

The above-reported variables were recorded at baseline and monthly at every visit (V1 to V12). Telephone/email contacts were allowed when in-office visits were not possible (e.g., isolation/quarantine due to the SARS-CoV-2 pandemic).

Endpoints

The primary endpoint was the conversion rate from CM to EM and, more specifically, to HFEM, MFEM, and LFEM at each time point from V1 to V12. Secondary endpoints
included the rate of MO discontinuation and changes in MAMI and monthly NRS score. We also investigated the predictive factors of MO discontinuation and the conversion to MFEM/LFEM compared to CM/HFEM in the last month of therapy (V12). Finally, we evaluated the use of acute medications during the 12 months of therapy.

**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, and registered at the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and at ClinicalTrials.gov NCT04803513.

**Data availability statement**

Anonymized data will be shared by request from any qualified investigator.

**Statistical analysis**

This is a priori analysis. To achieve a power of 80% and a level of significance 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 with SPSS version 27.0 (SPSS Inc., Chicago, IL, USA). The interval variables between groups were compared with the independent t test (expressed as means with standard deviations [SD]) or Mann–Whitney tests (medians with 25th,75th percentiles). Paired t-test was used to analyze the variable changes over time. Contingency tables (chi-square and two-tailed Fisher’s exact tests) and unadjusted odds ratios (OR) with their 95% confidence intervals (CI) 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 variable (MMDs). We declared data availability of secondary variables (MAMI, NRS), excluding patients with missing values from the analysis. We assessed the percentage of patients with CM, HFEM, MFEM, and LFEM and patients with MO from V1 to V12.

We initially investigated which clinical baseline characteristics were associated with conversion to EM, MFEM/LFEM, and MO discontinuation at V12. These variables (considering only \( p < 0.02 \)) were entered as independent variables in the binary logistic regression (forced entry) to confirm the association with conversion to CM to MFEM or LFEM and MO discontinuation (dependent variables). Bonferroni correction was applied for multiple comparisons.

**Results**

Since the first galcanezumab injections, 161 CM patients completed 12 months of observation and were considered in the present study. Six subjects were excluded from the current analysis since the complete data set regarding primary studied variables was unavailable. We finally enrolled 155 patients. Of these, 22 patients (14.2%) dropped out due to lack of effectiveness (20) or adverse events (2) after at least 3 months of therapy; these individuals were included in the analysis as still CM and still MO and considered for the other endpoints for their respective treatment period (Fig. 1).

The MMDs and MAMI were available for all evaluation times. From baseline to V12, monthly NRS was regularly collected for 132 (85.1%) patients. MMDs did not differ between patients with missing or available NRS values (20.5 ± 7.3 vs. 19.7 ± 5.9).

At baseline, patients presented a mean of 19.8 (SD 6.1) MMDs, with an NRS of 7.7 (1.2 SD) and 25.8 (SD 29.6) MAMI; MO was observed in 122 patients (78.2%). Seventy-six (49%) patients were on concomitant preventive therapy. Table 1 summarizes the demographical and clinical profiles of the whole CM cohort at baseline and at the end of the 1-year treatment, classified as V12 CM, V12 EM, V12 CM/HFEM (8 MMDs or more), and V12 MFEM/LFEM (0–7 MMDs).

From baseline to V12, participants reported a decrease in MMDs (around 10 days, 9.6 ± 7.9; \( p < 0.00001 \)), in MAMI (around 17 drugs, 8.2 ± 8.7; \( p < 0.000001 \)), and pain intensity (almost 2 points in NRS score, 5.9 ± 1.79; \( p < 0.000001 \)). At V12, 48 (30.9%) patients were on concomitant preventive medications.

Figure 2 shows the percentage of patients converting to EM during the 12 months of treatment. Around 75% or more of them reverted to EM at each evaluation visit (Fig. 2A).

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Fig. 1 Study population and design
A consistent transition to EM for the entire treatment year was observed in 81 (52.3%) patients, while only 15 (9.7%) patients remained with CM at each evaluation time. Supplemental Fig. 1 (panel A) shows the percentage of patients reverting to CM in at least 1 (90.3%) and up to 12 cumulative months of therapy.

Table 2 reports multivariate logistic regression results having “reversion to EM” at V12 as the dependent variable. After Bonferroni correction, reversion to EM was observed in participants with older onset age (p = 0.010) and less frequent baseline MMDs (p = 0.005).

Return to EM occurred at median for 12 cumulative months (25th 9, 75th 12) and to MFEM or LFEM for 7 cumulative months (25th 1, 75th 11). After the first month of treatment, 63 patients (40.6%) presented less than 8 MMDs (MFEM/LFEM), increasing to 83 (53.5%, Fig. 2B) at V12. However, only 32 (20.6%) improved to MFEM/LFEM consistently from V1 to V12.

Figure 3 illustrates the percentage of patients with MO during the observation period. At baseline, 122 (78.7%) participants presented MO. At V12, 101 out of them (82.8%) had discontinued MO. Patients discontinued MO at median for 11 cumulative months (25th 8, 75th 12). Supplemental Fig. 1 (panel B) shows the percentage of patients discontinuing MO for at least 1 (97.5%) and up to 12 (41.8%) cumulative months of therapy.

Figure 4 displays the variations in MAMI (panel A) and NRS values across evaluation times (panel B). Although the decrease in MAMI intake was principally observed in the first month of therapy, it became more pronounced from V1 to V12 (p = 0.01). The ratio between mean MAMI/MMDs was above 1 at baseline (1.29, i.e., 29% more than one acute medication per migraine day) but consistently lower than 1 (up to 0.80 at V11, i.e., 20% less than one acute medication per migraine day) from V4 to V12 (Fig. 5).

Table 3 summarizes baseline demographical and clinical profiles of patients with baseline MO and compares them according to the presence of MO at the end of the treatment year.

Finally, participants did not substantially modify the class of acute medications used during the year of treatment (Supplemental Fig. 2).
Discussion

Patients with CM face a sort of never-ending migraine attack. From a neurobiological point of view, migraine can be considered an evolutive condition involving different systems that interconnect in a fluctuating balance, producing cycling but sometimes persistent perturbation of neural connectivity homeostasis and even impairment of cognitive performance [24]. From a social point of view, CM imposes constraints in family and work settings and often induces patients to renounce to meaningful opportunities, consequently resulting in high levels of frustration.

The GARLIT is a large, multicenter, prospective, real-life study performed on galcanezumab. We have described the conversion rate to EM and MO discontinuation in the short term (3 months) and their prognostic factors [25]. The present analysis investigated these endpoints in the long...
term, i.e., 1 year. Around 75% or more of patients experienced remission to EM from V1 to V12 (Fig. 1A), and more than half of them (52.3%) consistently for the whole treatment year. These findings should also be appraised in light of a cohort of people with a very long disease history and multiple preventive treatment failures. Although a direct comparison is not possible, the conversion rate to EM observed as early as the first month of therapy in our cohort (77.4%) seems higher than previously described in RCTs with fremanezumab [18] and erenumab [26] (around 50%) and slightly higher than the rate reported in two real-life studies on the use of erenumab which increased at later time points (64–68%) [16, 17].

Our previous short-term analysis [25] observed lower BMI, unilateral pain, good response to triptans, and MO as positive predictive factors of rapid conversion to EM. Although we also found a trend for the above variables in the long term (Table 1), regression analysis did not confirm these findings (Table 2). Still, this analysis highlighted an older onset age and fewer monthly migraine attacks at baseline as positive predictive factors for good outcomes.

While it is not unexpected that more frequent attacks are less likely to decline to an episodic frequency, the association between younger onset age and worse outcomes deserves careful consideration. Interestingly, a study investigating genetic and clinical conditions predicting erenumab therapy outcomes reported an association...
of younger onset age and a variant of the receptor activity modifying protein 1 with a less prominent response [27]. CM is often pictured as the result of inadequate therapeutic management. However, the GARLIT participants had been treated according to best clinical practice for a long time before enrollment [10]. It can be speculated that constitutional characteristics (genetic or epigenetic) influence the lifetime course of migraine and possibly impact the response to pharmacological treatments [24, 28]. These considerations suggest that the earlier the migraine onset, the more favorable the outcome if adequate pharmacological and non-pharmacological treatments are offered early [29].

Nevertheless, a cross-sectional analysis of a large pool of patients from the American Registry for Migraine Research demonstrated that using a 15-headache day/month cut-off to distinguish EM from CM does not accurately capture the burden of illness nor reflect the treatment needs [30]. The authors proposed reconsidering the concept of CM, including also attack frequency ranging from 8 to 14.

In the GARLIT population, the percentage of participants with MMDs below 8 increased from V0 (40.6%) to V12 (53.5%). This benefit was obtained for a median of 7 months, and in 32 patients (20.6%), for the entire duration of the 12-month therapy. None of the evaluated baseline characteristics, not even baseline MMDs, seemed to predict the conversion to MFEM or LFEM.

Can the chronic migraine brain unlearn pain? Although mAbs targeting the CGRP pathway cannot meaningfully cross the blood–brain barrier, few studies observed a central functional restoration of the pain network in the short term [31, 32] as a possible effect of a peripheral modulation of sensory input. Other factors may help transform a very disabling condition such as CM into a manageable episodic disorder. We envision that some patients, perceiving persisting a long-term benefit, might be capable of reverting the migraine-driven vicious circles affecting different aspects of life, e.g., lifestyle and psychosocial situations. Once the frequency of migraine attacks decreases, patients are more likely to lead a healthier lifestyle and be less impacted by the fear of pain and psychosocial stress [33]. This indirect advantage exerted by mAb targeting the CGRP pathway is also supported by the no-return to the baseline condition after 3 months of suspension [34].

Along the same lines, 82.8% of patients with MO at baseline had discontinued it after 12 months of treatment. The percentage of participants with MO gradually decreased from V1 to V12 (Fig. 3). MO discontinuation was not influenced by baseline characteristics, not even by the baseline number of acute medications as observed in the short term.

### Table 3
Baseline clinical and demographic characteristics in patients with MO at baseline (first column) and compared (second and third column) according to MO presence at the end of the one-year treatment (V12)

| Characteristic                      | Baseline MO (n = 122) | V12 MO (n = 21) | V12 non-MO (n = 101) | p     |
|------------------------------------|-----------------------|----------------|----------------------|-------|
| Age (years. mean. SD)              | 48.8 (9.6)            | 48.4 (9.4)     | 43.9 (10.3)          | 0.051 |
| Sex (%. n females)                 | 77.9 (95)             | 71.4 (15)      | 79.2 (80)            | 0.563 |
| BMI (kg/m². mean. SD)              | 23.94 (4.40)          | 24.29 (4.2)    | 24.25 (4.5)          | 0.970 |
| Comorbidities (%)                  |                       |                |                      |       |
| Psychiatric                        | 23.8 (29)             | 23.8 (5)       | 23.7 (24)            | 0.775 |
| Gastrointestinal                   | 20.5 (25)             | 28.6 (6)       | 18.8 (19)            | 0.215 |
| Disease history (ys. mean. SD)     | 30.9 (10.8)           | 26.4 (10.8)    | 30.8 (11.1)          | 0.100 |
| Onset age (years. mean. SD)        | 17.6 (8.7)            | 17.6 (9.0)     | 17.5 (7.1)           | 0.221 |
| Failed preventives (median. min–max) | 5 (3–11)             | 4 (3–10)      | 5 (3–11)            | 0.642 |
| MO history (years. mean. SD)       | 6.6 (11.3)            | 5.7 (7.9)      | 6.1 (11.5)           | 0.887 |
| MMDs (mean. SD)                    | 19.9 (5.5)            | 19.5 (6.3)     | 20.7 (5.6)           | 0.392 |
| NRS (mean. SD)                     | 7.8 (1.1)             | 7.7 (1.3)      | 7.7 (1.1)           | 0.850 |
| Throbbing Pain (%. n)              | 66.4 (81)             | 80.9 (17)      | 63.4 (64)            | 0.288 |
| Unilateral pain (%. n)             | 49.2 (60)             | 38.1 (8)       | 51.4 (52)           | 0.316 |
| Dopaminergic features (%. n)       | 68.0 (83)             | 66.7 (14)      | 68.3 (69)           | 1.00  |
| Allodynia (%)                      | 74.6 (91)             | 71.4 (15)      | 75.2 (76)           | 0.784 |
| Unilateral cranial autonomic features (%. n) | 54.9 (67) | 52.4 (11) | 55.4 (56) | 0.804 |
| MAMI (mean. SD)                    | 30.3 (36.7)           | 41.7 (65.7)    | 27.3 (18.6)          | 0.332 |
| Triptan responder (%. n)           | 52.5 (64)             | 52.4 (11)      | 52.5 (53)           | 1.00  |
| Acute medication (%. n)            |                       |                |                      |       |
| Triptan                            | 68.9 (84)             | 61.9 (13)      | 70.3 (71)            | 0.449 |
| NSAID                              | 23.0 (28)             | 52.4 (11)      | 55.4 (56)           | 0.814 |
| Combination drug                   | 54.9 (67)             | 33.3 (7)       | 20.8 (21)            | 0.255 |
increase this benefit and impact the migraine course in the treatment regimens, if economically sustainable, further whether multidisciplinary approaches and more extended throughout the months of therapy and tended to improve the ment year. This shift and MO discontinuation were persistent cohort around half of them became EM for the entire treat-

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tion of concomitant therapy on the outcome at the end of quality of life measures, i.e., psychosocial the changes in these aspects to guide regulatory drug agencies.

One may wonder if a further extended treatment regimen beyond 1 year would additionally help patients with HFEM shift to MFEM o LFEM. The open-label extension of RCTs demonstrated the tolerability and efficacy of CRGP pathway targeted mAbs in the long term [35]. However, the high cost of the mAb primarily limits their wide and prolonged use. Preliminary economics evaluations predicted that erenumab is also likely to reduce migraine-related direct and indirect costs compared to standard care [36]. Hence, a comprehen-

sive economic evaluation comparing the CRGP pathway targeted mAb to standard care is thus necessary to clarify these aspects to guide regulatory drug agencies.

Our study has some limitations. Mainly, we did not assess the changes in quality of life measures, i.e., psychosocial scales, everyday habits, and demographic characteristics (e.g., BMI). These evaluations would have helped clarify the relative contribution of these aspects to the shift from chronic to episodic migraine. Moreover, we should consider that patients with migraine may experience cyclic oscillation between chronic and episodic frequency of attacks [19]. A more extended observation period is necessary to confirm the efficacy of mAbs targeting the CGRP in persistently reverting CM to an episodic condition. Similarly, up to 30% of patients in our cohort had not discontinued previous preventive medications. Therefore, we cannot exclude the influence of concomitant therapy on the outcome at the end of the galcanezumab treatment year.

In summary, the long-term GARLIT experience suggests that around three-quarters of patients treated with galcanezumab can revert from CM to EM in real life, and in our cohort around half of them became EM for the entire treatment year. This shift and MO discontinuation were persistent throughout the months of therapy and tended to improve over time. Future studies are necessary to understand whether multidisciplinary approaches and more extended treatment regimens, if economically sustainable, further increase this benefit and impact the migraine course in the longer term.

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Declarations

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Ethical approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. 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, and registered at the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and at ClinicalTrials.gov NCT04803513.

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