Journal of Neurology (2022) 269:5848–5857
https://doi.org/10.1007/s00415-022-11226-4

ORIGINAL COMMUNICATION

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

Claudia Altamura[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] · Francesca Schiano Di Cola[7] · Florindo d'Onofrio[8] · Cinzia Finocchi[9] · Davide Bertuzzo[10] · Francesco Bono[11] · Angelo Ranieri[12] · Maria Albanese[13] · Roberta Messina[14] · Alberto Doretti[15] · Vittorio Di Piero[6] · Sabina Cevoli[4] · Piero Barbanti[2,16] · Fabrizio Vernieri[1] · For the GARLIT Study Group

Received: 20 March 2022 / Revised: 10 June 2022 / Accepted: 10 June 2022 / Published online: 28 June 2022

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]

✉ Claudia Altamura
c.altamura@policlinicocampus.it

Extended author information available on the last page of the article

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 chronification 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 not 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/emgality-epar-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, rhinorrhoea, 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).

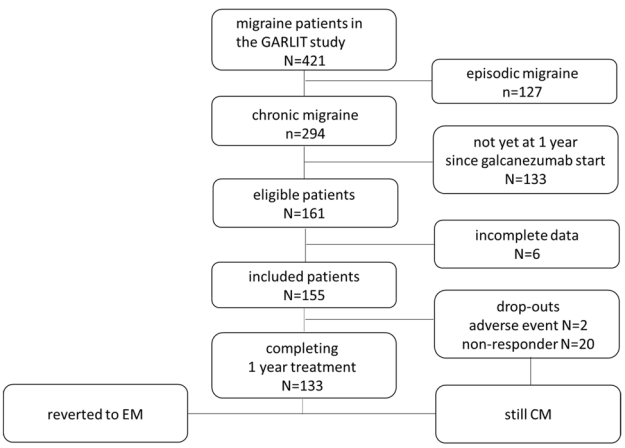

Fig. 1 Study population and design

Table 1 Baseline clinical and demographic characteristics in the whole CM cohort and according to MMDs at the end of the one-year treatment (V12)

	CM cohort ($n=155$)	V12 CM ($n=36$)	V12 EM ($n=119$)	p	V12 CM/HFEM (n = 73)	V12 MFEM/LFEM ($n=82$)	p
Age (years. mean. SD)	46.0 (10.8)	41.5 (12.4)	47.4 (9.9)	**0.004**	46.8 (9.7)	45.3 (11.7)	0.392
Sex (%. *n* Females)	80.0 (124)	80.6 (29)	79.8 (95)	1.000	84.9 (62)	75.6 (62)	0.164
BMI (kg/m^2 mean. SD)	24.62 (4.69)	26.12 (5..23)	24.19 (4.46)	0.**046**	25.04 (4.69)	24.10 (4.44)	0.237
Comorbidities (%)							
Psychiatric	25.1 (39)	41.6 815)	20.2 (24)	0.031	27.3 (20)	23.1 (19)	0.698
Gastrointestinal	20.6 (32)	27.7 (10)	18.4 (22)	0.417	27.4 (20)	14.6 (12)	0.085
Onset age (years. mean. SD)	17.3 (8.6)	13.4 (6.1)	18.5 (8.9)	**0.001**	16.7 (9.1)	17.7 (9.2)	0.424
Disease history (ys. mean. SD)	28.7 (11.4)	28.1 (14.3)	28.9 (10.5)	0.758	29.9 (11.8)	27.5 (11.1)	0.176
Failed preventives (median. min–max)	4 (3–11)	5 (3–10)	4 (3–11)	0.667	5 (3–11)	4 (3–10)	0.622
MMDs (mean. SD)	19.8 (6.1)	23.5 (5.9)	18.7 (5.8)	**< 0.001**	19.7 (6.2)	19.9 (6.1)	0.768
NRS (mean. SD)	7.7 (1.2)	8.2 (1.1)	7.6 (1.2)	**0.014**	7.7 (1.1)	7.7 (1.2)	0.764
Throbbing Pain (%. *n*)	65.1 (101)	75.0 (27)	62.1 (74)	0.084	67.1 (49)	63.4 (52)	0.859
Unilateral pain (%. *n*)	47.1 (73)	27.7 (10)	52.9 (63)	**0.022**	47.9 (35)	46.3 (38)	0.733
Dopaminergic features (%. *n*)	68.3 (106)	69.4 (25)	68.1 (81)	1.000	68.4 (50)	68.2 (56)	1.00
Allodynia (%)	72.9 (113)	69.4 (25)	73.9 (88)	0.669	76.7 (56)	69.5 (57)	0.367
Unilateral cranial autonomic features (%. *n*)	54.1 (84)	52.8 (19)	54.6 (65)	0.821	56.2 (41)	52.4 (43)	0.717
MAMI (mean. SD)	25.8 (29.6)	23.0 (17.0)	18.7 (5.8)	0.184	23.8 (21.3)	27.7 (35.4)	0.429
Triptan responder (%. *n*)	50.9 (79)	33.3 (12)	56.3 (67)	**0.022**	54.8 (40)	47.6 (39)	0.422
Acute medication (%. *n*)							
Triptan	67.1 (104)	55.6 (20)	70.6 (84)	0.107	69.9 (51)	64.6 (53)	0.500
NSAID	54.2 (84)	61.1 (22)	52.1 (62)	0.445	57.5 (42)	51.2 (42)	0.519
Combination drug	20.6 (32)	27.8 (10)	18.5 (22)	0.245	13.7 (10)	26.8 (22)	0.049

bold values indicate statistical significant correlation

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 ($25^{th}8$, $75^{th}12$). 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).

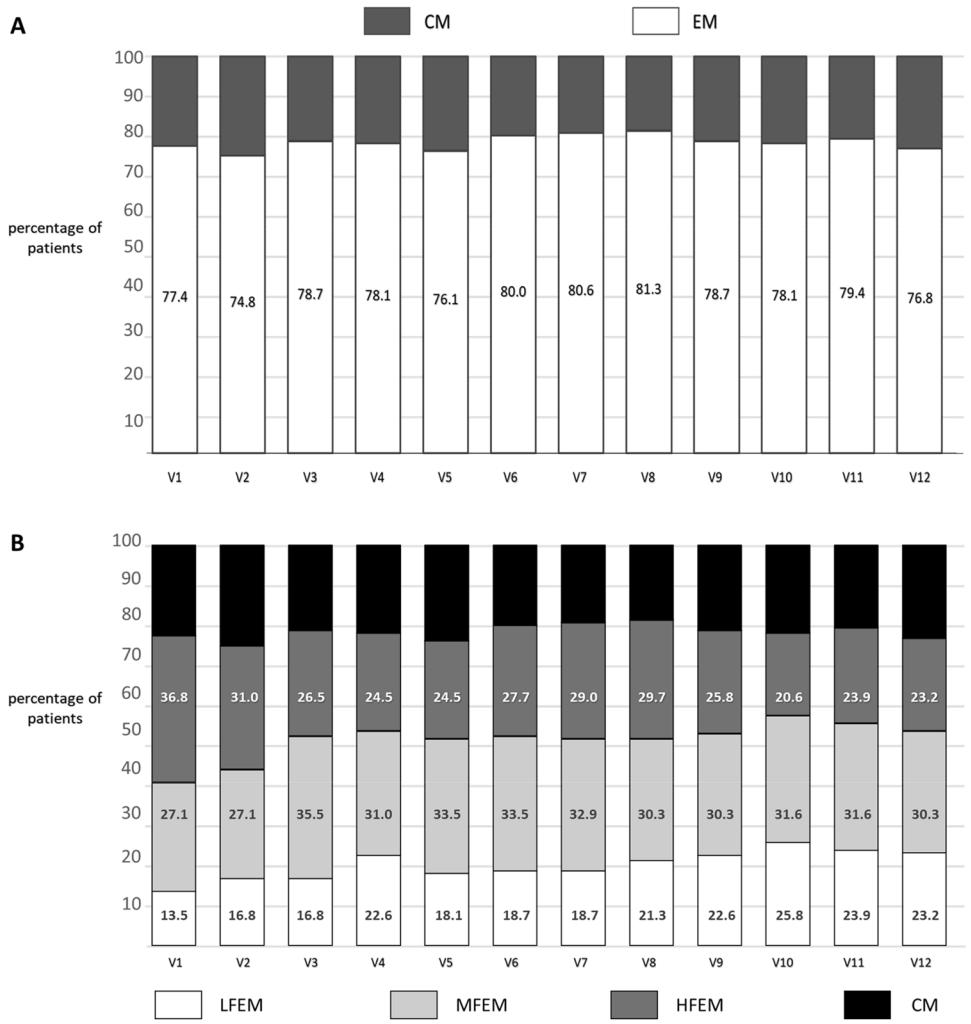

Fig. 2 Percentage of patients reverting to EM (**A**) and to HFEM, MFEM, and LFEM (**B**) from V1 to V12

Table 2 Multivariate logistic regression analysis in predicting the conversion to EM at the end of the one-year treatment (V12)

	B	Standard error	Odds ratio	95% CI		*p*
				Lower	Upper	
Age	− 0.049	0.024	0.952	0.908	0.998	0.041
Female	− 1.148	0.637	0.317	0.091	1.106	0.072
Baseline MMDs	**0.149**	**0.045**	**1.161**	**1.062**	**1.269**	**0.001**
Baseline NRS	0.407	0.215	1.503	0.985	2.292	0.059
Onset Age	**− 0.139**	**0.044**	**0.870**	**0.798**	**0.949**	**0.002**

bold values indicate statistical significant correlation

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

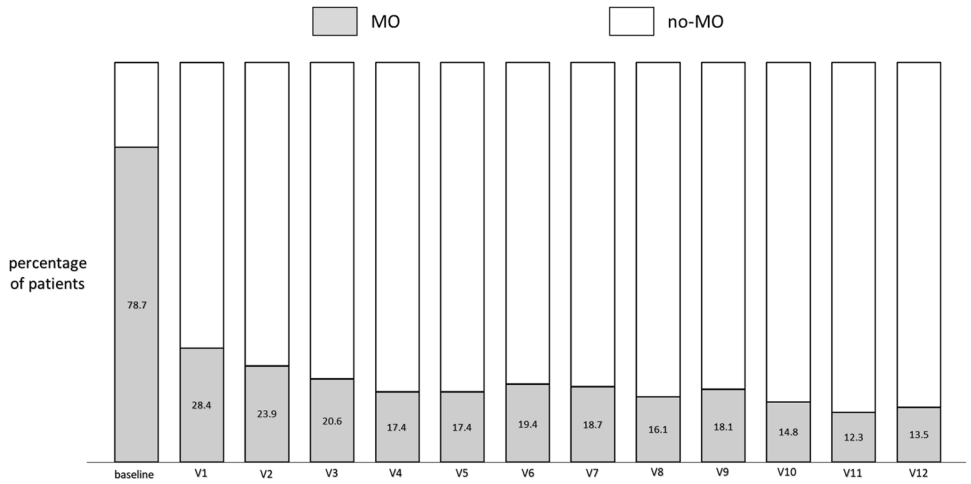

Fig. 3 Percentage of patients with medication overuse (MO) from V1 to V12

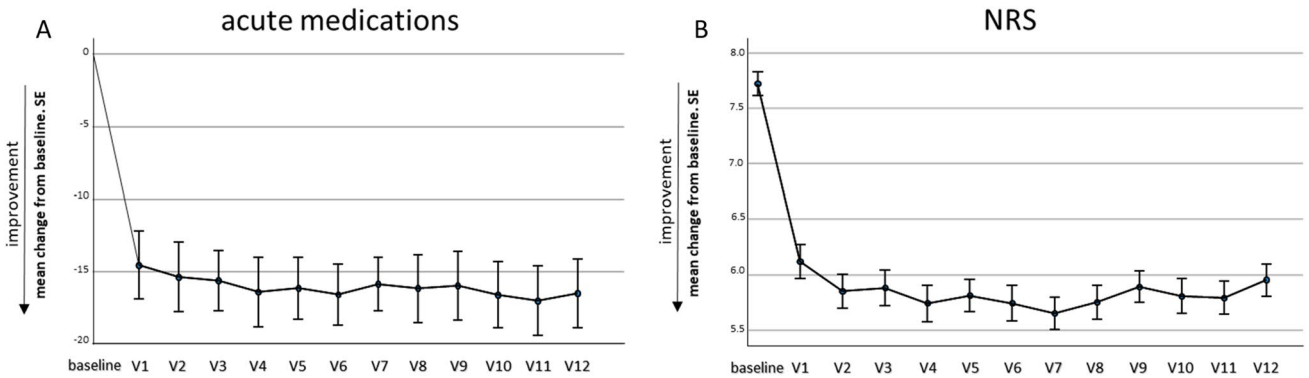

Fig. 4 Mean changes in the MAMI (panel **A**) and NRS score (panel **B**) from baseline to V12. *SE* standard error

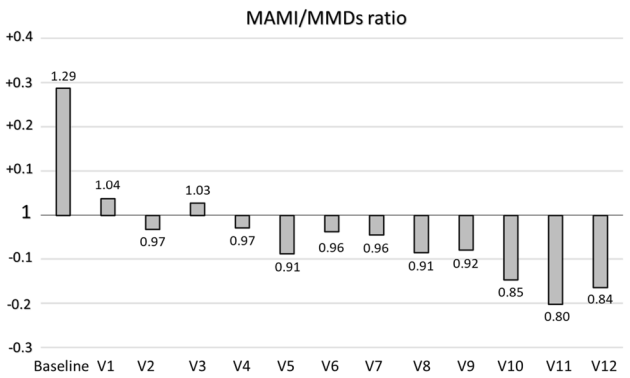

Fig. 5 Ratio between the mean MAMI and MMDs from baseline to V12. A ratio of 1 corresponds to the intake of one acute medication for each migraine day

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

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)

	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/m^2 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

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

[25], as one could a priori hypothesize. The decrease in MAMI intake was mainly observed in the first month of therapy (by 14.5 drugs) but became more pronounced at V12 (around 17, Fig. 4 panel A). Similarly, pain intensity was eased already in the first month of therapy (Fig. 4 panel B). However, less severe attacks did not influence acute medication choices, except for a reduction in combination therapies by around a quarter (Supplemental Fig. 1). A possible interpretation is that a fall in migraine frequency and less intense pain leads to an immediate decrease in MAMI and a further decline over the months when patients become more and more capable of coping with migraine attacks, as discussed above. This change in attacks' management is well depicted by the almost progressive reduction in MAMI/MMDs ratio (Fig. 5).

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 comprehensive economic evaluation comparing the CGRP 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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11226-4.

Acknowledgements 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, Renata Rao: Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, Luigi d'Onofrio, Daniele Spitalieri: Neurology Unit, San Giuseppe Moscati Hospital, Avellino, Marco Aguggia: 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, Bruno Colombo: Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, Massimo Filippi, Stefano Messina: Department of Neurology, Stroke Unit and Laboratory of Neuroscience, Italian Auxological Institute, Scientific Institute for Research and Health Care, Milan, Italy., Gianluca Demirtzidis. We would like to thank Marcel Bach Pages for revising the content of this manuscript.

Luisa Fofi, Renata Rao, Luigi d'Onofrio, Daniele Spitalieri, Marco Aguggia, Fabio Bombardieri, Bruno Colombo, Massimo Filippi, Stefano Messina, Gianluca Demirtzidis

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

Conflicts of interest Maria Albanese received honoraria or travel grants from Novartis, Teva, Merck Serono; Claudia Altamura received travel grants and honoraria from Novartis, Eli Lilly, Lusofarmaco, Laborest, Allergan, Almirall; Cinzia Aurilia received travel grants and honoraria from FB-Health, Lusofarmaco, Almirall, Eli-Lilly Novartis and Teva; Piero Barbanti received travel grants, honoraria for advisory boards, speaker panels or clinical investigation studies from Alder, Allergan, Angelini, Bayer, ElectroCore, Eli-Lilly, GSK, Lusofarmaco, MSD, Novartis, Stx-Med, Teva, Visufarma, Zambon; Francesco Bono received honoraria as a speaker or for participating in advisory boards from Teva, Novartis, Ipsen; Sabina Cevoli received travel grants, honoraria for advisory boards, speaker panels or clinical investigation studies from Novartis, Teva, Lilly, Allergan, Ibsa, Amgen and Lundbeck; Vittorio Di Piero received grants and honoraria by Bayer, Biogen, Lilly, TEVA and Novartis; Florindo d'Onofrio received grants and honoraria from Lilly, Teva, Novartis, Neopharmed; Alberto Doretti received grants and honoraria from Novartis, Eli Lilly; Gabriella Egeo received travel grants and honoraria from Eli-Lilly, Novartis, New Penta and Ecupharma; Valentina Favoni received honoraria as speaker or for participating in advisory boards from Ely-Lilly, Novartis and Teva; Cinzia Finocchi received grants and honoraria from Novartis, Eli Lilly, AIM group; Carlo Lovati received grants from Novartis and Lilly. Florindo d'Onofrio received grants and honoraria from Lilly, Teva, Novartis, Neopharmed; Ilaria Maestrini received honoraria from Eli Lilly. Roberta Messina received honoraria as speaker from Novartis, Eli Lilly, and Teva. Armando Perrotta travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan, Eli-Lilly, Novartis, and Teva; Angelo Ranieri received speaker honoraria from Teva, Lilly; Fabrizio Vernieri received travel grants, honoraria for advisory boards, speaker panels, or clinical investigation studies from Allergan, Amgen, Angelini, Eli-Lilly, Lundbeck, Novartis, and Teva; Nicoletta Brunelli, Marilena Marcosano and Francesca Schiano Di Cola, Davide Bertuzzo have nothing to disclose.

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.

References

1. Stovner LJ, Nichols E, Steiner TJ et al (2018) Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 17:954–976. https://doi.org/10.1016/S1474-4422(18)30322-3
2. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z, Lifting the Burden: the Global Campaign against Headache (2020) Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 21(1):137. https://doi.org/10.1186/s10194-020-01208-0
3. Ashina M, Katsarava Z, Do TP et al (2021) Migraine: epidemiology and systems of care. Lancet 397:1485–1495. https://doi.org/10.1016/S0140-6736(20)32160-7
4. Buse DC, Fanning KM, Reed ML et al (2019) Life with migraine: effects on relationships, career, and finances from the chronic migraine epidemiology and outcomes (CaMEO) study. Headache 59:1286–1299. https://doi.org/10.1111/head.13613
5. Headache Classification Committee of the International Headache Society (IHS) (2018) The international classification of headache disordersition, 3rd edition. Cephalalgia 38:1–211. https://doi.org/10.1177/0333102417738202
6. Altamura C, Corbelli I, de Tommaso M et al (2021) Pathophysiological bases of comorbidity in migraine. Front Hum Neurosci 15:640574. https://doi.org/10.3389/fnhum.2021.640574
7. Ferrari MD, Goadsby PJ, Burstein R et al (2022) Migraine. Nat Rev Dis Prim 8:2. https://doi.org/10.1038/s41572-021-00328-4
8. Schwedt TJ, Hentz JG, Sahai-Srivastava S et al (2021) Headache characteristics and burden from chronic migraine with medication overuse headache: cross-sectional observations from the Medication Overuse Treatment Strategy trial. Headache J Head Face Pain 61:351–362. https://doi.org/10.1111/head.14056
9. Edvinsson L, Haanes KA, Warfvinge K, DiN K (2018) CGRP as the target of new migraine therapies: successful translation from bench to clinic. Nat Rev Neurol 14:338–350. https://doi.org/10.1038/s41582-018-0003-1
10. Evers S, Áfra J, Frese A et al (2009) EFNS guideline on the drug treatment of migraine: revised report of an EFNS task force. Eur J Neurol 16:968–981. https://doi.org/10.1111/j.1468-1331.2009.02748.x
11. Hepp Z, Dodick DW, Varon SF et al (2017) Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. Cephalalgia 37:470–485. https://doi.org/10.1177/0333102416678382
12. Soni P, Chawla E (2021) Efficacy and safety of anti-calcitonin gene-related peptide monoclonal antibodies for treatment of chronic migraine: a systematic review and network meta-analysis. Clin Neurol Neurosurg 209:106893. https://doi.org/10.1016/j.clineuro.2021.106893
13. Barbanti P, Aurilia C, Cevoli S et al (2021) Long-term (48 weeks) effectiveness, safety, and tolerability of erenumab in the prevention of high-frequency episodic and chronic migraine in a real world: Results of the EARLY 2 study. Headache J Head Face Pain 61:1351–1363. https://doi.org/10.1111/head.14194
14. Caronna E, Gallardo VJ, Alpuente A et al (2021) Anti-CGRP monoclonal antibodies in chronic migraine with medication overuse: real-life effectiveness and predictors of response at 6 months. J Headache Pain 22:120. https://doi.org/10.1186/s10194-021-01328-1
15. Belvís R, Irimia P, Pozo-Rosich P et al (2021) MAB-MIG: registry of the spanish neurological society of erenumab for migraine prevention. J Headache Pain 22:74. https://doi.org/10.1186/s10194-021-01267-x
16. Pensato U, Baraldi C, Favoni V et al (2022) Real-life assessment of erenumab in refractory chronic migraine with medication overuse headache. Neurol Sci 43:1273–1280. https://doi.org/10.1007/s10072-021-05426-5
17. Ornello R, Casalena A, Frattale I et al (2020) Conversion from chronic to episodic migraine in patients treated with erenumab: real-life data from an Italian region. J Headache Pain 21:102. https://doi.org/10.1186/s10194-020-01171-w
18. Lipton RB, Cohen JM, Bibeau K et al (2020) Reversion from chronic migraine to episodic migraine in patients treated with fremanezumab: post hoc analysis from HALO CM study. Headache 60:2444–2453. https://doi.org/10.1111/head.13997
19. Serrano D, Lipton RB, Scher AI et al (2017) Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. J Headache Pain 18:101. https://doi.org/10.1186/s10194-017-0787-1
20. May A, Schulte LH (2016) Chronic migraine: Risk factors, mechanisms and treatment. Nat Rev Neurol 12:455–464
21. Detke HC, Goadsby PJ, Wang S et al (2018) Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 91:E2211–E2221. https://doi.org/10.1212/WNL.0000000000006640
22. Sacco S, Bendtsen L, Ashina M et al (2019) European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain 20:6. https://doi.org/10.1186/s10194-018-0955-y
23. Vernieri F, Altamura C, Brunelli N et al (2021) Galcanezumab for the prevention of high frequency episodic and chronic migraine in real life in Italy: a multicenter prospective cohort study (the GARLIT study). J Headache Pain 22:35. https://doi.org/10.1186/s10194-021-01247-1
24. Andreou AP, Edvinsson L (2019) Mechanisms of migraine as a chronic evolutive condition. J Headache Pain 20:117. https://doi.org/10.1186/s10194-019-1066-0
25. Vernieri F, Altamura C, Brunelli N et al (2022) Rapid response to galcanezumab and predictive factors in chronic migraine patients: a 3-month observational, longitudinal, cohort, multicenter, Italian real-life study. Eur J Neurol 29:1198–1208. https://doi.org/10.1111/ene.15197
26. Lipton RB, Tepper SJ, Silberstein SD et al (2021) Reversion from chronic migraine to episodic migraine following treatment with erenumab: results of a post-hoc analysis of a randomized, 12-week, double-blind study and a 52-week, open-label extension. Cephalalgia 41:6–16. https://doi.org/10.1177/0333102420973994
27. Zecca C, Cargnin S, Schankin C et al (2022) Clinic and genetic predictors in response to erenumab. Eur J Neurol 29:1209–1217. https://doi.org/10.1111/ene.15236
28. Gerring ZF, McRae AF, Montgomery GW, Nyholt DR (2018) Genome-wide DNA methylation profiling in whole blood reveals epigenetic signatures associated with migraine. BMC Genom 19:69. https://doi.org/10.1186/s12864-018-4450-2
29. Charles JA, Peterlin BL, Rapoport AM et al (2009) Favorable outcome of early treatment of new onset child and adolescent migraine-implications for disease modification. J Headache Pain 10:227–233

30. Ishii R, Schwedt TJ, Dumkrieger G et al (2021) Chronic versus episodic migraine: the 15-day threshold does not adequately reflect substantial differences in disability across the full spectrum of headache frequency. Headache J Head Face Pain 61:992–1003. https://doi.org/10.1111/HEAD.14154
31. Ziegeler C, Mehnert J, Asmussen K, May A (2020) Central effects of erenumab in migraine patients: an event-related functional imaging study. Neurology 95:e2794–e2802. https://doi.org/10.1212/WNL.0000000000010740
32. Thiele A, Klehr L, Strauß S et al (2021) Preventive treatment with CGRP monoclonal antibodies restores brain stem habituation deficits and excitability to painful stimuli in migraine: results from a prospective case-control study. J Headache Pain 22:149. https://doi.org/10.1186/s10194-021-01364-x
33. Yin JH, Lin YK, Yang CP et al (2021) Prevalence and association of lifestyle and medical-, psychiatric-, and pain-related comorbidities in patients with migraine: A cross-sectional study. Headache 61:715–726. https://doi.org/10.1111/head.14106
34. Vernieri F, Brunelli N, Messina R et al (2021) Discontinuing monoclonal antibodies targeting CGRP pathway after one-year treatment: an observational longitudinal cohort study. J Headache Pain 22:154. https://doi.org/10.1186/s10194-021-01363-y
35. Ashina M, Goadsby PJ, Reuter U et al (2019) Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia 39:1455–1464. https://doi.org/10.1177/0333102419854082
36. Mahon R, Lang A, Vo P et al (2021) Cost-effectiveness of erenumab for the preventive treatment of migraine in patients with prior treatment failures in Sweden. Pharmacoeconomics 39:357–372. https://doi.org/10.1007/S40273-020-00996-2

Authors and Affiliations

Claudia Altamura[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] · Francesca Schiano Di Cola[7] · Florindo d'Onofrio[8] · Cinzia Finocchi[9] · Davide Bertuzzo[10] · Francesco Bono[11] · Angelo Ranieri[12] · Maria Albanese[13] · Roberta Messina[14] · Alberto Doretti[15] · Vittorio Di Piero[6] · Sabina Cevoli[4] · Piero Barbanti[2,16] · Fabrizio Vernieri[1] · For the GARLIT Study Group

1 Headache and Neurosonology Unit, Neurology, Fondazione Policlinico Campus Bio-Medico, Via Alvaro del Portillo, 200, 00128 Rome, Italy

2 Headache and Pain Unit, IRCCS San Raffaele, Rome, Italy

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

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

5 IRCCS NEUROMED, Pozzilli, IS, 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 Neurology Unit, San Giuseppe Moscati Hospital, Avellino, Italy

9 IRCCS Ospedale Policlinico San Martino, Genoa, Italy

10 Neurology and Stroke Unit, Asti Hospital, Asti, Italy

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

12 Neurology and Stroke Unit, AORN A.Cardarelli, Naples, Italy

13 Headache Center, Neurology Unit, Tor Vergata University Hospital, Rome, Italy

14 Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

15 Department of Neurology, Stroke Unit and Laboratory of Neuroscience, Italian Auxological Institute, Scientific Institute for Research and Health Care, Milan, Italy

16 San Raffaele University, Rome, Italy