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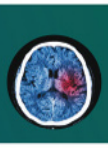

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ORIGINAL ARTICLE

# Predictors of sustained response and effects of the discontinuation of anti-calcitonin gene related peptide antibodies and reinitiation in resistant chronic migraine

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## Abstract

**Background and purpose:** Guidelines for migraine prophylaxis suggest stopping medication after 6–12 months to reevaluate treatment appropriateness. The Italian Medicines Agency set a mandatory regulation to stop anti-calcitonin gene related protein (CGRP) pathway monoclonal antibody (anti-CGRP mAb) treatments for 3 months after 12 months of treatment. Herein, the effects of discontinuation and retreatment of anti-CGRP mAbs in resistant chronic migraine patients are assessed, evaluating predictive factors of sustained response.

**Methods:** This was a monocentric prospective cohort study, enrolling 44 severe (resistant to ≥3 preventive treatments) chronic migraine patients (all with medication-overuse), treated with erenumab (54.5%) or galcanezumab (45.5%) for 12 months, who discontinued treatment for 3 months and then restarted for 1 month.

**Results:** Overall, patients reported an increasing deteriorating trend during the 3 months of discontinuation. Monthly migraine days, number of analgesics, days with at least one analgesic used, a ≥50% response rate (reduction in monthly migraine days), and Migraine Disability Assessment Score and Headache Impact Test 6 total score, remained lower than baseline values, but increased compared to month 12 of treatment. All outcome measures decreased again during the month of retreatment. Patients who did not meet criteria for restarting treatment had a lower Migraine Disability Assessment Score ($p = 0.03$) and Headache Impact Test 6 ($p = 0.01$) score at baseline and better outcome measures during discontinuation compared to patients who restarted treatment.

**Conclusions:** In most patients, the 3-month discontinuation of anti-CGRP mAbs resulted in progressive migraine deterioration that was rapidly reverted by retreatment. However, one-quarter of patients who reported better quality of life indices before treatment showed a sustained benefit during discontinuation and did not need retreatment.

KEYWORDS
CGRP, chronic migraine, discontinuation, erenumab, galcanezumab

  

## INTRODUCTION

Migraine is the third most prevalent and the second most disabling disease worldwide in the age range 20–50 years, with chronic migraine (CM) (≥15 days per month for at least 3 months) affecting 1.4%–2.2% of the general population [1]. A significant proportion of CM patients has an unsatisfactory response to, or does not tolerate, pharmacological treatments, according to the European Headache Federation criteria for resistant migraine [2]. Monoclonal antibodies (mAbs), which block the calcitonin gene related peptide (CGRP) or its receptor (anti-CGRP mAbs), are a new class of prophylactic anti-migraine drugs. Three of them, erenumab, galcanezumab and fremanezumab, have been authorized by the European Medicines Agency for episodic migraine (EM) and CM [3].

Policies for access to novel expensive migraine treatments often include restrictions that may affect disease management [4–6]. The prescription policy of anti-CGRP mAbs of the Italian AIFA grants access to patients with 8 or more monthly migraine days (MMDs) for at least 3 consecutive months; with previous failure, or no tolerability, to at least three preventive classes of antimigraine drugs; and a Migraine Disability Assessment Score (MIDAS) ≥11. To maintain patients in the 1-year reimbursed prescription programme, AIFA requires a ≥50% reduction in the MIDAS score assessed at 3 and 6 months of treatment. AIFA has established that, after 1 year, treatment must be discontinued for a follow-up period of 3 months; if the above-mentioned access criteria are fulfilled again, treatment can be restarted with the same mAb (Figure 1). As of July 2021, AIFA shortened the mandatory 3 months of discontinuation to a single month.

The aim of preventive treatment is to reduce migraine frequency and pain intensity, thus improving quality of life. The interruption of a preventive treatment allows verification of disease improvement, to reassess the need for prophylaxis, or to limit the risk of emergent adverse reactions. Some studies have reported that propranolol, metoprolol, flunarizine and topiramate provide sustained benefits for 6–8 months following their discontinuation [7–9]. Recently, discontinuation after 6–12 months of treatment has been suggested for anti-CGRP mAbs [3]. However, sustained efficacy of anti-CGRP mAbs after discontinuation in clinical trials has been insufficiently investigated [10,11] and predictive factors of sustained response have not yet been identified. Real-world studies, which allow the evaluation of patients generally excluded from most clinical trials (e.g., with several drug class failures), have mainly been focused on erenumab, the first anti-CGRP mAb to receive approval, following varying discontinuation periods from 1 to 4 months [12–14].

Following the AIFA prescription rules, the aim of the study was to assess the effects of 3 months of discontinuation after 12 months of treatment and 1 month of retreatment with erenumab or galcanezumab in resistant CM patients. Potential predictive factors of sustained response were also assessed.

## METHODS

All consecutive outpatients treated with anti-CGRP mAbs at the Headache Center of the Careggi University Hospital who signed informed consent and completed 3 months of discontinuation and 1 month of re-initiation after 12 months of treatment were enrolled in the study. All patients discontinued the drug as established by AIFA rules for reimbursed prescription of anti-CGRP mAbs in Italy and did not receive any additional migraine prophylactic medication during this period. The study comprised a 1-month baseline phase, a 12-month treatment phase, a 3-month discontinuation (follow up) phase, and 1-month retreatment with the same anti-CGRP mAb (Figure 1).

Study participants were patients older than 18 years with CM according to ICHD-3 criteria (a mean of ≥15 migraine days per month during the 3 months before treatment), with or without medication-overuse, who started a preventive therapy with erenumab (70 mg monthly, up to 140 mg) or galcanezumab (240 mg first dose and 120 mg monthly) from December 2019 to June 2020. All patients had previous treatment failure for lack of efficacy (no meaningful improvement in the frequency of headaches after the administration of drugs for ≥3 months) or lack of tolerability with ≥3 different classes of migraine-preventive medications. During the treatment and follow-up phases, patients completed a headache diary recording monthly migraine days (MMDs) and acute medications use, in

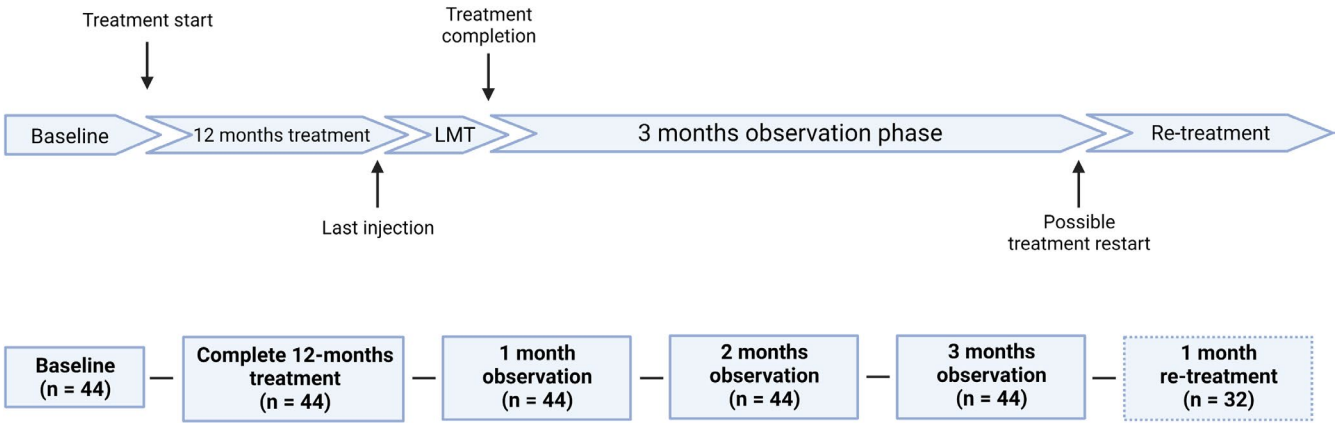


**FIGURE 1** Timeline of the study and patient flowchart. LMT, Last Month Treatment

addition to two questionnaires (MIDAS and Headache Impact Test 6 [HIT-6]).

Demographics, migraine characteristics (pain intensity, presence of aura, disease duration and CM onset), previous failures of ≥3 drug classes, including beta-blockers, tricyclic antidepressants, antiepileptics, and onabotulinumtoxinA (failure with other preventive treatments were recorded), and current concomitant preventive and acute symptomatic treatments (class, absolute number of symptomatic per month and days with at least one symptomatic), were collected at baseline. Migraine-related clinical burden was assessed with MIDAS and HIT-6 questionnaires. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study was approved as part of the *Registro Italiano Cefalee (RICe)* study by the local Ethics committee (Studio RICe, 14591_oss).

### Outcomes

The primary outcome was the absolute change from baseline in MMDs during the follow-up phase (3 months) as compared to baseline and the last month of treatment (12 months). Additional outcomes were response rates (≥50%, ≥75%, and 100% reduction in MMDs) and the absolute change from baseline of both the overall number of acute medications per month and days with at least one acute medication use. Changes from baseline in the MIDAS and HIT-6 scores and the percentage of patients who reported medication overuse during discontinuation were also measured. The percentage of patients that fulfilled criteria for AIFA re-prescription at the end of the 3-month follow-up phase has been reported. Outcome changes compared to baseline, last month of treatment, and the third month of the follow-up phase have also been assessed for 1-month treatment after the follow-up phase. Therefore, a comparative analysis between patients with sustained clinical response after 3 months of discontinuation (*i.e.*, not fulfilled prescription criteria) and patients retreated with mAbs has been carried out by assessing clinical differences at baseline and at several follow-up times.

### Statistical analysis

This is an explorative analysis, and although the sample size was not based on any statistical consideration, it was considered in line with previous studies on the topic [10–14]. Demographic and baseline characteristics were summarized descriptively, namely mean ± standard deviation [SD] or median interquartile range [IQR] for continuous variables and number (percentage) for categorical data. Normality assumption was assessed using the Shapiro-Wilk test. For independent variables, the Mann–Whitney *U* test for continuous variables and the two-tailed Pearson chi-squared test or the Fisher's test for categorical variables were applied, as appropriate. Wilcoxon signed-rank test was calculated to study effectiveness variables pre-post changes in quantitative variables. An exact McNemar's test was run for categorical dependent variables. A *p*-value <0.05 was considered significant for all variables. Bonferroni correction was applied for multiple comparisons. All data were analyzed using SPSS software version 26.0 (IBM Corp. SPSS Statistics).

## RESULTS

### Baseline characteristics

Forty-four patients (79.5% females, mean age 47.1 ± 12.8 years) with CM (4.5% with aura [2/44]) and medication overuse were followed up for 3 months after treatment discontinuation of an anti-CGRP mAb (Figure 1). Baseline migraine characteristics of participants are reported in Table 1. Overall, 54.5% of patients (24/44) were treated with erenumab and 45.5% (20/44) with galcanezumab. The mean (±SD) headache pain intensity on a 0–10 scale (numeric rating scale [NRS] scale) was 7.4 ± 1.1 points. The mean number of acute medications per month was 36.6 ± 23.7, and days with at least one analgesic use per month 22.1 ± 6.7. Patients presented a high MIDAS (116.4 ± 75.8) and HIT-6 total score (68.5 ± 4.8) at baseline.

Overall, 32/44 (72.7%) patients fulfilled the *AIFA* criteria to restart treatment at the end of the mandatory discontinuation period (MMDs ≥8 and MIDAS score ≥11). All patients completed a 1-month follow-up of retreatment (baseline characteristic in Table 1). During the discontinuation, no patients dropped-out or received any migraine prophylactic medications.

### Discontinuation phase

In the overall population, during the entire discontinuation phase, MMDs were significantly lower than at baseline (mean ± SD; 10.4 ± 7.8 at month-12 of treatment and 15.0 ± 8.4 at month-3 of discontinuation [$p < 0.0001$]) (Figure 2). The trend of the MMDs in the follow-up phase compared to month-12 of treatment showed a significant increase in MMDs at month-2 ($p = 0.003$) and month-3 ($p < 0.001$), but not at month-1 ($p = 0.48$) (Figure S1; Tables S1 and S2).

HIT-6 total score, although progressively increasing over time after treatment discontinuation, remained lower than baseline at each month of discontinuation ($p < 0.0001$). At both month-12 of treatment and month-3 of discontinuation, MIDAS was lower than baseline ($p < 0.0001$). HIT-6 total score showed a significant increase at month-2 and month-3, but not at 1 month after discontinuation, compared to month-12 of treatment ($p = 0.004$ and $p < 0.0001$, respectively). MIDAS score was also considerably lower ($p < 0.0001$) at month-3 of discontinuation as compared to month-12 of treatment (Figure 2; Tables S1 and S2).

The number of analgesics and days with at least one analgesic used, which remained lower than baseline during the 3-months of discontinuation ($p < 0.0001$), were higher ($p < 0.001$) at month-2 and month-3, but not at month-1, after discontinuation, as

**TABLE 1** Patients demographic and clinical features at baseline

| | All population ($n = 44$) | Re-treatment after discontinuation ($n = 32$) | Sustained response after discontinuation ($n = 12$) | $p$ value[b] |
|---|---|---|---|---|
| Demographics | | | | |
| Age [years], mean ± SD | 47.1 ± 12.8 | 46.0 ± 13.1 | 50.0 ± 12.1 | 0.25 |
| Sex female, *n* (%) | 35 (79.5) | 27 (84.4) | 8 (66.7) | 0.22 |
| Migraine features | | | | |
| Monthly migraine days, mean ± SD | 23.5 ± 5.8 | 23.6 ± 6.2 | 23.4 ± 4.9 | 0.87 |
| Aura, *n* (%) | 2 (4.5) | 2 (6.3) | 0 | 1.00 |
| Migraine duration [years], mean ± SD | 32.4 ± 12.8 | 32.6 ± 13.5 | 32.2 ± 11.6 | 0.76 |
| Chronicization duration [years], mean ± SD | 16.9 ± 11.3 | 18.5 ± 11.7 | 12.9 ± 9.5 | 0.15 |
| NRS score, mean ± SD | 7.4 ± 1.1 | 7.7 ± 0.9 | 6.8 ± 1.3 | 0.07 |
| Concomitant preventive treatment, mean (SD) | 0.2 (0.4) | 0.2 (0.5) | 0.2 (0.3) | 0.90 |
| Prior preventive classes failures, mean ± SD | 4.4 ± 0.7 | 4.6 ± 0.6 | 4.2 ± 1.0 | 0.13 |
| Medication overuse, *n* (%) | 44 (100) | 32 (100) | 12 (100) | 1.00 |
| Days with at least one analgesic use, mean ± SD | 22.1 ± 6.7 | 21.7 ± 7.3 | 23.2 ± 5.2 | 0.56 |
| Analgesics number, mean ± SD | 36.6 ± 23.7 | 37.6 ± 25.5 | 34.1 ± 19.0 | 0.76 |
| Migraine-related clinical burden | | | | |
| Disability (MIDAS), mean ± SD | 116.4 ± 75.8 | 130.9 ± 76.7 | 77.75 ± 60.2 | **0.03** |
| Headache-related impact (HIT-6), mean ± SD | 68.5 ± 4.8 | 69.4 ± 4.9 | 66.17 ± 4.2 | **0.01** |
| Prior preventive class failures[a] | | | | |
| 4 classes | 12 (27.3) | 9 (28.1) | 3 (25.0) | 0.68 |
| 5 classes | 25 (56.8) | 21 (65.6) | 5 (41.6) | |
| Drug classes | | | | |
| Beta-blockers | 40 (90.9) | 31 (96.9) | 9 (75.0) | 0.06 |
| Tricyclic antidepressant | 42 (95.5) | 31 (96.9) | 11 (91.7) | 0.47 |
| Calcium channel blockers | 41 (93.2) | 30 (93.8) | 11 (91.7) | 1.00 |
| Antiepileptic drugs | 41 (93.2) | 29 (90.6) | 12 (100) | 0.55 |
| SSRI/SNRI | 3 (6.8) | 2 (6.3) | 1 (8.3) | 1.00 |
| OnabotulinumtoxinA | 30 (68.2) | 24 (75.0) | 6 (50.0) | 0.15 |

Abbreviations: HIT-6, Headache Impact Test *6*; MIDAS, Migraine Disability Assessment; SNRI, serotonin-norepinephrine reuptake inhibitor Percentages are expressed on column total; SSRI, selective serotonin reuptake inhibitors. Values in bold are statistically significant.

[a]All patients have at least 3 prior preventive class failures.

[b]$p$ value calculated between re-treatment and sustained response populations after 3 months discontinuation of treatment.

compared to month-12 of treatment (Figure S2; Tables S1 and S2). During the 3 months of discontinuation, the percentage of patients with medication-overuse, although remaining lower than baseline ($p < 0.0001$), progressively increased (13/44, 29.5% at month 1; 20/44, 45.5% at month 2 and 27/44 and 61.4% at month-3). However, only the increase at month-3 was statistically higher ($p = 0.003$) than the percentage observed at month-12 of treatment (Tables S1 and S2). Patients with a ≥50% response rate (reduction in MMDs) decreased from 61.4% in month-12 of treatment to 38.6% during month-3 of discontinuation ($p = 0.006$) (Figure 3a; Table S3).

## Sustained response during discontinuation

Next, a subgroup analysis was performed of the patients who, after the 3 months of discontinuation, met the criteria set by *AIFA* for anti-CGRP mAb retreatment (restarters, 32/44 [72.7%]), and those who, having a sustained clinical response during discontinuation, did not meet such criteria (not-restarters, 12/44 [27.3%]). Five patients were treated with erenumab (41.7%) and 7 with galcanezumab (58.3%). Patients who restarted treatment showed significantly higher MIDAS ($p = 0.03$) and HIT-6 ($p = 0.01$)

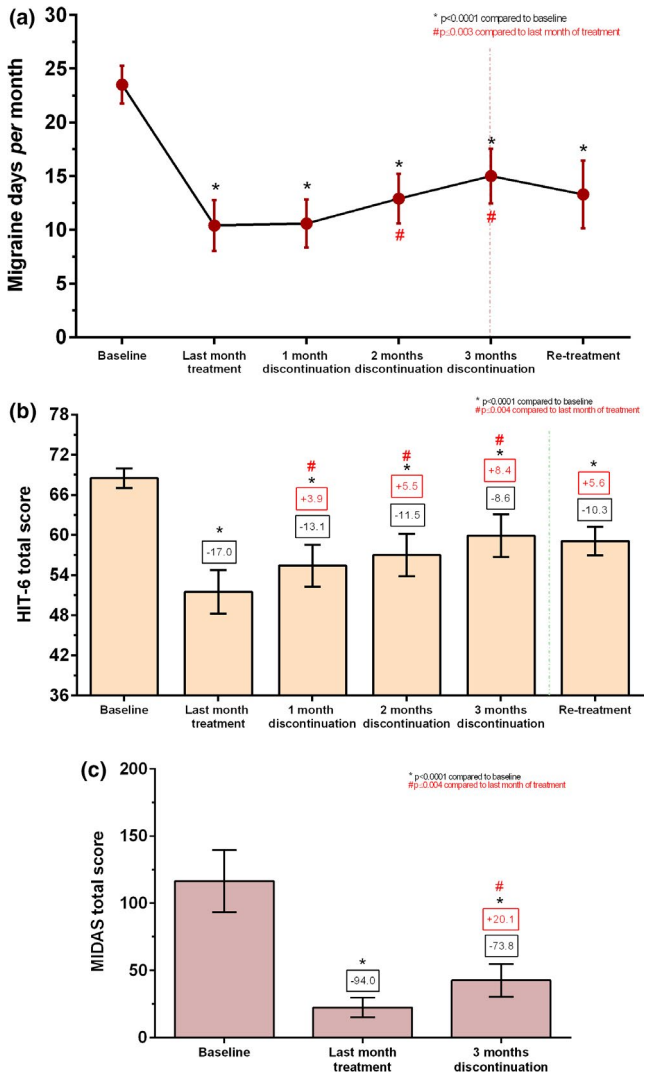


**FIGURE 2** Overall population. (a) Monthly Migraine Days (MMDs) frequency during the study, (b) the Headache Impact Test 6 (HIT-6) questionnaire total score, and (c) Migraine Disability Assessment (MIDAS). Error bars represent 95% confidence intervals. Mean reduction compared to baseline reported in black square and mean reduction compared to last month of treatment in red square

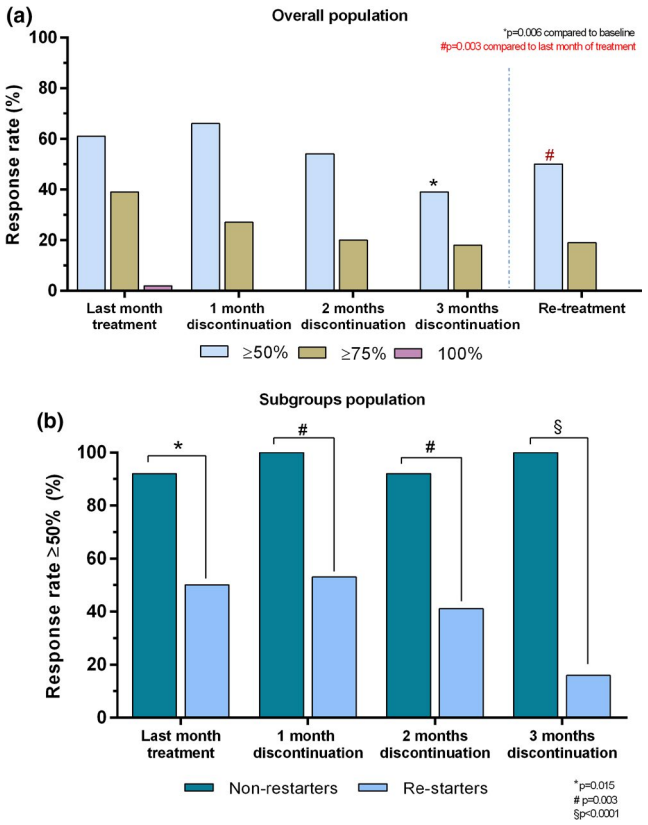


**FIGURE 3** Response rate *per* month based on MMDs during treatment discontinuation and retreatment in (a) the overall population and (b) subgroups population. (Restarters were those patients who met the criteria set by AIFA to restart treatment, whereas not-restarters were those patients who, showing a sustained response, did not)

total scores at baseline as compared to the 12 patients who did not restart, whereas other baseline variables, including MMDs ($p = 0.87$) and medication overuse ($p = 1.00$), did not differ between the two groups (Table 1). Significant differences of MIDAS ($p < 0.001$) and HIT-6 ($p \leq 0.03$) total scores between restarters and not-restarters were observed at month-12 of treatment and throughout the discontinuation phase (Figure 4). Furthermore, MMDs ($p \leq 0.001$), number of analgesics ($p \leq 0.002$) and days with at least one analgesic used ($p \leq 0.008$), and responder rates ≥50% ($p \leq 0.003$), were different between restarters and not-restarters (Figures 3b and 4, Figures S1–S3) at each month of discontinuation. Not-restarters did not show medication overuse at month-12 of treatment ($p = 0.002$) and at month-3 of discontinuation ($p < 0.0001$), whereas only one patient reported medication overuse at month-1 ($p = 0.07$) and month-2 ($p = 0.003$) of discontinuation (Table S1).

## Re-initiation phase

In the month of retreatment, patients showed a significant reduction in MMDs (−5.5 ± 8.0) compared to month-3 of discontinuation ($p = 0.001$), but not month-12 of treatment ($p = 0.40$). The number of analgesics, days with at least one analgesic used, and HIT-6 total score, were lower as compared to month-3 of discontinuation ($p = 0.0001$, $p < 0.001$ and $p < 0.001$, respectively), whereas no change was shown in comparison to month-12 of treatment, except for the HIT-6 total score (Table 2; Figure 2 and Figure S2). The percentage of patients with medication-overuse was reduced compared to month-3 of discontinuation ($p = 0.004$) (Table 2) A relevant percentage of restarters showed a resolution of medication overuse (50% at month-12 of treatment and 15.6% at month-3 of discontinuation) (Table S1). In the month of retreatment, the percentage of responders ≥50% significantly increased to 50.0% ($p = 0.003$, compared to discontinuation month 3) (Figure 3; Table S3). Only one patient reported two adverse reactions in the first month of

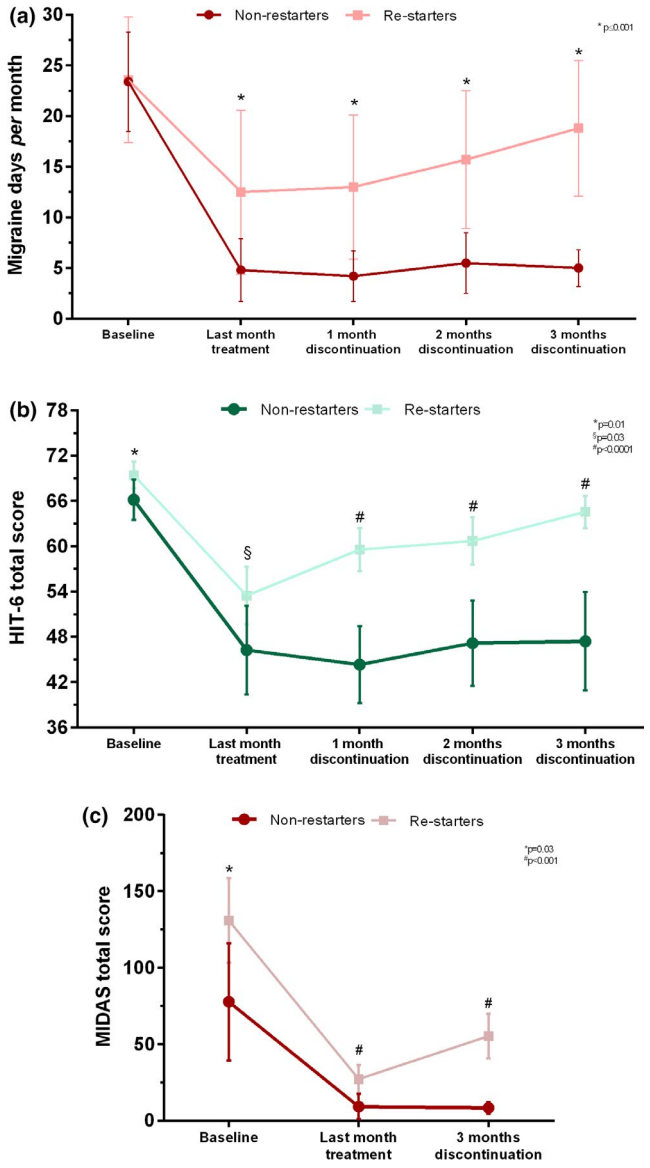


**FIGURE 4** Not-restarters and restarters groups. (a) Monthly Migraine Days (MMDs) frequency during the study, (b) the Headache Impact Test 6 (HIT-6) questionnaire total score, and (c) Migraine Disability Assessment (MIDAS). Error bars represent 95% confidence intervals. (Restarters were those patients who met the criteria set by AIFA to restart treatment, whereas not-restarters were those patients who, showing a sustained response, did not)

retreatment, and in particular, pain and erythema in the injection site.

## DISCUSSION

Discontinuation of anti-CGRP mAbs was associated with a time-dependent and progressive increase in MMDs, analgesics use, and a deterioration of patient quality of life that started the first month after drug withdrawal. Thus, 3 months of discontinuation were associated in most patients with a variable but significant increase in all migraine-relevant outcome measures as compared to month-12 of treatment. One-month retreatment after discontinuation led to the decrease of MMDs and analgesics use, with values comparable to the last month of treatment. However, subgroup analysis showed a small but consistent group of patients with sustained clinical response during the discontinuation phase and who did not restart treatment.

Follow-up analyses have been performed for some randomized clinical trials (RCTs) with erenumab and galcanezumab to assess discontinuation on migraine. The follow-up of two RCTs with galcanezumab (EVOLVE-1 and -2 trials) showed a minimal worsening after a 4-month discontinuation, and migraine frequency still significantly lower compared to baseline, in patients with EM [11]. Another study with follow-up data of two RCTs (NCT02174861 and REGAIN [NCT02614261]) suggests that, although with a small increase in MMDs over time, the effect of anti-CGRP mAbs persists up to 3 months compared to baseline after the discontinuation of a prolonged treatment (12-month treatment with erenumab and 9-month treatment with galcanezumab) [10]. Real-world observational studies have shown that MMDs and other migraine-related outcomes returned close to baseline values after 4 months of discontinuation. After 12 months of treatment, MMDs increased in almost all patients (with EM or CM) within 3 months of discontinuation, with half reaching higher or similar frequency compared to baseline [13]. Another study reported, after 4 months of discontinuation, a progressive increase in migraine frequency, with most patients returning to baseline values [14]. In a short 4-week observational study, discontinuation was associated with a rapid increase in all outcome measures as compared to the last 4 weeks of treatment, which, however, remained lower than baseline [12].

Our results are in line with studies showing a progressive increase in MMDs and other migraine-related measures over time, starting from the first month of discontinuation. Notably, at month-3 after discontinuation, MMDs and other migraine-relevant outcome measures, although higher than those at month-12 of treatment (indicating a clear deteriorating trend), were still significantly lower than baseline. The difference in results from various studies [12–14], including the present one, could be due to diverse duration of treatments before discontinuation (ranging from 8 to 12 months), different baseline values in severity of disease, and presence or not of medication overuse. Importantly, in the present study, all patients presented medication overuse at baseline (100.0%) that was remarkably attenuated at month-12 of treatment (36.4%), and the value at month-3 of discontinuation (61.4%) did not reach the initial values.

Erenumab and galcanezumab have similar elimination half-life times of about 28–27 days [15]. Thus, 3 months after discontinuation, plasma levels are at about 12.5% of peak concentration. The hypothesis that the corresponding low plasma concentration retains a residual beneficial effect cannot be rejected. However, erenumab 21 mg [16] and galcanezumab 50 mg [15,17], which reduced CGRP plasma concentration by about 39%, failed to show efficacy in EM. Thus, on one hand, it is unlikely that after discontinuation

**TABLE 2** Headache variables and changes during 1 month treatment re-started compared to baseline, last month of treatment and the third month of the observational phase

| **1 month after re-treatment ($n = 32$)** | | | |
|---|---|---|---|
| Monthly migraine days | 13.3 ± 8.7 | | |
| *p* value vs baseline | **<0.0001** | Change compared to *baseline* | −10.2 ± 8.3 |
| *p* value vs last month of treatment | 0.40 | Change compared to *last month of treatment* | +0.7 ± 4.8 |
| *p* value vs last month discontinuation | **0.001** | Change compared to *last month observational period* | −5.5 ± 8.0 |
| Days with at least one analgesic used | 11.0 ± 6.2 | | |
| *p* value vs baseline | **<0.0001** | Change compared to *baseline* | −10.8 ± 7.9 |
| *p* value vs last month of treatment | 0.83 | Change compared to *last month of treatment* | −0.1 ± 3.9 |
| *p* value vs last month discontinuation | **<0.001** | Change compared to *last month observational period* | −5.3 ± 7.7 |
| Number of analgesics used | 10.9 ± 7.8 | | |
| *p* value vs baseline | **<0.0001** | Change compared to *baseline* | −22.1 ± 17.8 |
| *p* value vs last month of treatment | 0.74 | Change compared to *last month of treatment* | +0.3 ± 4.8 |
| *p* value vs last month discontinuation | **0.0001** | Change compared to *last month observational period* | −9.7 ± 16.1 |
| Medication overuse, *n* (%) | 15 (46.9) | | |
| *p* value vs baseline | **<0.0001** | Change compared to *baseline* | −53.1% |
| *p* value vs last month of treatment | 1.00 | Change compared to *last month of treatment* | +10.5% |
| *p* value vs last month discontinuation | **0.004** | Change compared to *last month observational period* | −14.5% |
| Headache-related impact (HIT-6) | 59.1 ± 5.9 | | |
| *p* value vs baseline | **<0.0001** | Change compared to *baseline* | −10.3 ± 6.4 |
| *p* value vs last month of treatment | **0.005** | Change compared to *last month of treatment* | +5.6 ± 10.3 |
| *p* value vs last month discontinuation | **<0.001** | Change compared to *last month observational period* | −5.4 ± 6.7 |

*Note:* All values are reported as mean ± SD as otherwise specified.

Values in bold are statistically significant, Bonferroni correction for multiple comparisons. Percentages are expressed on column total.

Abbreviations: HIT-6, Headache Impact Test 6; MIDAS, Migraine Disability Assessment.

and 3 half-lives the mAbs maintain a protective action; on the other hand, it is unclear if long-term treatments (>12 months) have a disease modifying effect in migraine. Some oral migraine prophylactics with an alleged mode of action in the CNS, such as flunarizine, propranolol, and topiramate, have shown a prolonged (from 6 to 8 months) reduction in MMDs after treatment cessation [7–9]. Further detailed investigation is required to assess whether presumably peripherally acting treatments, such as anti-CGRP mAbs, may retain some beneficial effect months after their discontinuation. It is worth noting that in our (72.7%) and other (91.5% and 78.1%) [12,14] studies, most patients restarted therapy at the end of the withdrawal phase, underlining increased disability after anti-CGRP mAb discontinuation.

Interestingly, the subgroup of patients (approximately 1/4 of the total) who showed a sustained clinical response during the discontinuation period (not-restarters), and therefore did not meet the criteria for restarting treatment, whilst reporting similar MMDs and medication-overuse as restarters, reported lower MIDAS and HIT-6 scores at baseline. Therefore, a less severe migraine as quantified by a relatively lesser disability, and not by the number of MMDs, could be considered a predictive factor for a more beneficial and sustained response to anti-CGRP mAbs. Notably, not-restarters showed a superior and persistent reduction in MMDs, number of analgesics and days with at least one analgesic used, and disability questionnaire total scores at the last month of treatment and throughout the entire period of discontinuation. It should be noted that not-restarters were no longer medication-overusers at the end of both month-12 of treatment and month-3 of discontinuation. However, of the 32 restarters, medication overuse resolved at month-12 of treatment in half, and about 15% remained non-medication-overusers at month-3 of discontinuation. These findings suggest that resolution of medication-overuse does not seem to distinguish the two populations of restarters and not-restarters.

A limitation of the present study to assess discontinuation is the sample size, which, although one of the largest reported so far, remains insufficient to draw firm conclusions. Another limitation of this prospective, observational study is that the impact of discontinuation should be controlled with a placebo group, to assess the nocebo effect, due to the negative expectations inherent to non-controlled trials associated with the discontinuation of an effective treatment.

## CONCLUSIONS

Our results suggest that anti-CGRP mAbs maintain some degree of protection up to 3 months after treatment discontinuation

against CM compared to baseline, but not compared to the last month of treatment. In fact, a deterioration trend can be observed in all outcomes starting from the first month after discontinuation. Although our present and other [10–14] results do not support the view that anti-CGRP mAb are disease-modifying drugs, the variable nature of migraine burden [1] justifies an interruption period. Interruption is also justified by the presence of a subgroup (about 25%) of patients who showed a sustained beneficial effect after anti-CGRP mAbs discontinuation, which was predicted by lower MIDAS and HIT-6 scores before starting the treatment. Further, sufficiently powered observational real-world studies, as well as randomized placebo-controlled trials, are necessary to determine the effects of long-term treatments with anti-CGRP mAbs, and of their discontinuation and restart, and to identify reliable predictors for patients who need continuous therapy.

## CONFLICT OF INTEREST

P.G: received personal fees from Allergan, Eli Lilly, Novartis, Amgen, TEVA; Grants from Amgen, TEVA, Eli-Lilly, Allergan, Chiesi; Scientific Advisory Board, Endosome Therapeutics; Founding scientist of FloNext srl, Spinoff of the University of Florence. F.D.C received personal fees from TEVA, Eli Lilly, Novartis. Other authors have no conflicting interests.

## AUTHOR CONTRIBUTIONS

**Luigi Francesco Iannone:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Davide Fattori:** Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Software (equal); Validation (equal); Visualization (equal); Writing – review & editing (equal). **Silvia Benemei:** Investigation (equal); Methodology (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Alberto Chiarugi:** Investigation (equal); Methodology (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **P Geppetti:** Conceptualization (lead); Data curation (lead); Formal analysis (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead). **Francesco De Cesaris:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

## ETHICAL APPROVAL

The study was approved as a part of the *Registro Italiano Cefalee (RICe)* study by the local Ethics committee (Studio RICe, 14591_oss).

## DATA AVAILABILITY STATEMENT

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

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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