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ORIGINAL COMMUNICATION

Three-year treatment with anti-CGRP monoclonal antibodies modifies migraine course: the prospective, multicenter I-GRAINE study

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Abstract

Objectives To determine whether extending anti-CGRP mAb treatment beyond 3 years influences migraine course, we analyzed migraine frequency during the first month of treatment discontinuation following three 12-month treatment cycles (Ts).

Methods This multicenter, prospective, real-world study enrolled 212 patients with high-frequency episodic migraine (HFEM) or chronic migraine (CM) who completed three consecutive Ts of subcutaneous anti-CGRP mAbs. Discontinuation periods (D1, D2, D3) were defined as the first month after T1, T2, and T3, respectively. The primary endpoint was the ≥ 50% response rate at D3 compared to D2. Secondary endpoints included changes in monthly migraine days (MMD), monthly headache days (MHD), monthly analgesic intake (MAI), numerical rating scale (NRS), Headache Impact Test-6 (HIT-6), ≥ 50% response rate at D3 versus D1 and D2, and relapse rates to CM or medication overuse.

Results At D3 vs. D2, significant improvements ($p < 0.001$) were observed in the ≥ 50% response rate (77.8% vs. 53.8%), MMD (-2.1 ± 1.7), MHD (-2.9 ± 2.4), MAI (-2.6 ± 2.4), NRS (-0.7 ± 1.3), and HIT-6 (-7.2 ± 5.9), with lower relapse rates to CM (2.3% vs. 18%) and medication overuse (1.3% vs. 10.1%). Compared to D1, D3 demonstrated greater benefits ($p < 0.001$) in MMD (-2.6 ± 1.9), MHD (-5.8 ± 3.3), MAI (-4.9 ± 3.4), NRS (-1 ± 1.6), and HIT− 6 (-9.4 ± 7), alongside higher ≥ 50% response rates (77.8% vs. 25%) and reduced relapses to CM (2.3% vs. 67.7%) and medication overuse (1.3% vs. 34.2%).

Discussion Three years of anti-CGRP mAb treatment revealed a progressive increase in the proportion of ≥ 50% responders (D1: 25%; D2: 53.8%; D3: 77.8%) and substantial reductions in migraine burden, suggesting that prolonged treatment may favorably modify migraine course.

Keywords Migraine · Treatment · Anti-CGRP mAbs · Real world · Discontinuation · Disease modifier

Introduction

Migraine is a highly disabling neurological disorder that, if untreated or poorly managed, can result in a sustained increase in frequency, severity, or both—a phenomenon known as migraine progression [1, 2]. Minimizing the risk of migraine progression requires a multifaceted approach, encompassing optimized acute and preventive treatment strategies [1–3]. Ideally, a preventive migraine treatment should possess disease-modifying properties, targeting underlying neuroplastic changes and delivering long-lasting benefits that extend beyond mere symptom control, even in cases with a stable clinical course. Achieving this goal likely necessitates prolonged treatment durations to address the slow and complex pathophysiological mechanisms underlying migraine progression [2, 4].

Traditional preventive treatments are not regarded as disease-modifying agents, mainly due to their modest overall efficacy and the typically limited duration of use in real-world clinical practice [5]. Monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway represent a significant breakthrough in migraine management. These therapies support long-term use due to their

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remarkable adherence, high efficacy, and excellent tolerability. However, despite these advantages, anti-CGRP mAbs are still not currently regarded as disease-modifying agents. Evidence suggests that discontinuation after one 12-month treatment cycle (T) often leads to an increase in the frequency of migraine attacks, indicating a lack of sustained impact on the underlying disease mechanisms [6–14]. This finding is consistent with the hypothesis that anti-CGRP mAbs initially exert predominantly symptomatic effects (related to their peripheral site of action), while the 'true' preventive migraine effects (related to progressive centripetal trigeminal pathway desensitization) occur only at a later stage. For this reason, the European Headache Federation guidelines recommend extending CGRP-targeting mAb therapy beyond 12–18 months when clinically necessary [15]. Furthermore, it has been suggested that therapy should be discontinued when migraine frequency is reduced to four or fewer days per month, provided that no other clinical factors justify continued treatment [16]. This recommendation reinforces the need for prolonged preventive treatment to achieve a sustained low migraine frequency.

To determine whether prolonged treatment with anti-CGRP mAbs could have disease-modifying effects, specifically designed studies with adequately powered populations are essential. However, indirect evidence can be gleaned from patients undergoing repeated treatment cycles. In this regard, a previous 2-year real-world study demonstrated gradual clinical improvement during a second treatment cycle (T2) with anti-CGRP mAbs, compared to the first (T1), in individuals with high-frequency episodic migraine (HFEM; ≥ 8 migraine days/month) or chronic migraine (CM) [17]. This finding suggests that extended treatment with anti-CGRP mAbs may influence the progression of migraine.

Building on this finding, we conducted a longer (3-year). multicenter, prospective, real-world study to further investigate the potential of anti-CGRP mAbs in modifying the course of migraine.

Methods

This multicenter, prospective real-life study is part of the ongoing Italian Migraine Registry (I-GRAINE). The study received approval from the Institutional Review Board of IRCCS San Raffaele Roma, serving as the coordinating center (RP 19/26), and subsequently from the Ethics Committees of all participating centers. This study was not registered in any public clinical trial registry.

Participants were consecutively recruited from ten headache centers across seven Italian regions (Abruzzo, Campania, Emilia-Romagna, Lazio, Liguria, Lombardy, and Marche), starting on December 14, 2018. Written informed consent was obtained from all participants prior to their inclusion in the study.

The study included patients diagnosed with HFEM or CM who had completed at least three consecutive Ts with erenumab (70 mg or 140 mg), fremanezumab (225 mg), or galcanezumab (120 mg) and achieved a ≥ 50% response rate by week 12 of the first T. All participants had previously failed at least three therapeutic options, including beta-blockers, antiepileptics, and tricyclics (or onabotulinum toxin A in the case of CM). In compliance with the Italian Medicines Agency (AIFA) requirements [18], each T was followed by a minimum 1-month discontinuation period.

We defined D1 as the first month of anti-CGRP mAbs treatment discontinuation following the first T (T1), D2 as the first month of treatment discontinuation following the second T (T2), and D3 as the first month of treatment discontinuation following the third T (T3) (Fig. 1).

Trained neurologists performed in-person interviews utilizing a standardized, semi-structured, web-based

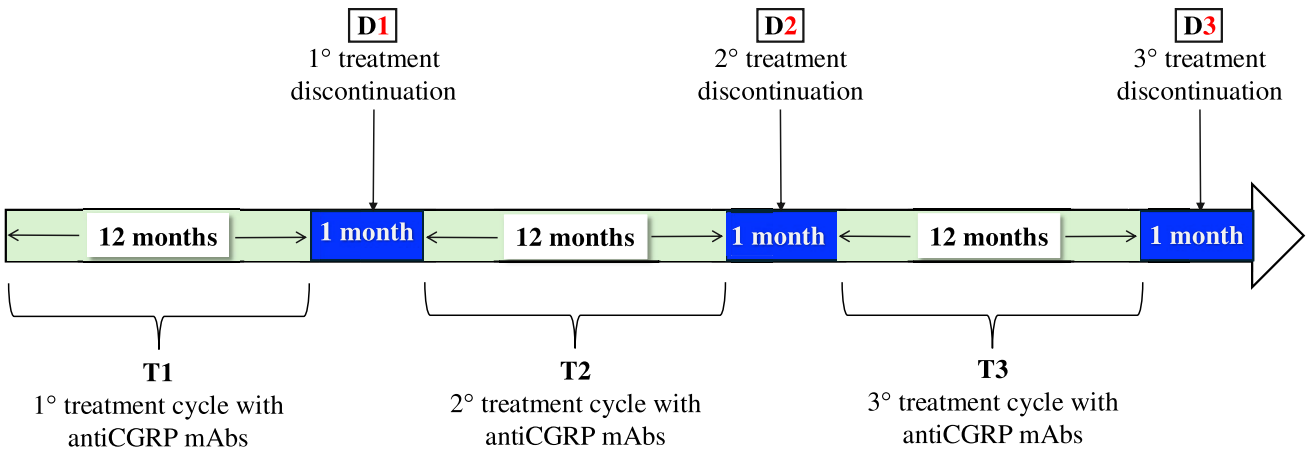

Fig. 1 Flowchart of the study

questionnaire to collect detailed sociodemographic and clinical information [17]. Participants were asked to report the number of monthly migraine days (MMD, for patients with HEM), monthly headache days (MHD, for patients with CM), frequency of monthly analgesic intake (MAI), and pain intensity, which was assessed using the Numerical Rating Scale (NRS). Additionally, migraine-related disability was evaluated using the Headache Impact Test (HIT-6), and any adverse events were recorded by the patients in a paper-based diary throughout the duration of the study.

The primary endpoint was the ≥ 50% response rates at D3 compared to D2. Secondary endpoints encompassed a) change in MMD for HFEM and MHD for CM at D3 compared to D2; b) change in MAI, NRS, and HIT-6 scores at D3 compared to D2; c) variation in MMD, MHD, MAI, NRS, and HIT-6 scores at D3 compared to D1; d) ≥ 50% response rates at D3 compared to D1; e) proportion of patients relapsing from episodic migraine to CM and from no-medication overuse to medication overuse at D3 compared to D2; f) proportion of patients relapsing from episodic migraine to CM and from no-medication overuse to medication overuse at D3 compared to D1. We also assessed changes in MMD, MHD, MAI, NRS, and HIT-6 scores at T1 (weeks 45–48) vs. baseline, D1 vs. T1 (weeks 45–48), T2 (weeks 45–48) vs. T1 (weeks 45–48), T2 (weeks 45–48) vs. D1, D2 vs. T2 (weeks 45–48), D2 vs. D1, T3 (weeks 45–48) vs D2, T3 (weeks 45–48) vs. T2 (weeks 45–48), T3 (weeks 45–48) vs. T1 (weeks 45–48), and D3 vs. T3 (weeks 45–48).

We excluded individuals with major cardio-cerebrovascular conditions or clinically significant medical comorbidities (e.g., malignancies, hepatic diseases, drug or alcohol abuse, psychosis, etc.), those previously treated with anti-CGRP mAbs or subjects who had received onabotulinum toxin A within the past three months.

Statistical methods

Descriptive statistics were calculated using frequencies and percentages for qualitative variables, and means with standard deviations (SD) for quantitative variables. Univariate analysis was performed to compare HFEM and CM patients on host factors and clinical parameters. Continuous variables were compared using the t test and ANOVA for normally distributed data, and the Mann–Whitney and Kruskal–Wallis tests were used for non-normally distributed data. The Kolmogorov–Smirnov test was applied to verify the normality of the quantitative variables' distributions. The Chi-square test was used to compare categorical variables, and Fisher's exact test was applied for dichotomous variables when expected frequencies did not meet the assumption of the Chi-square test. Comparisons of mean changes in MMD, MHD, monthly analgesic medications, NRS, and HIT-6 between baseline, T1, T2, and T3, and D1, D2, and D3 were conducted using the t test for paired samples or the Wilcoxon signed-rank test. Differences in the number of monthly headache days during follow-up were also analyzed by stratifying the sample into erenumab and galcanezumab/fremanezumab patients, using the Wilcoxon signed-rank test for paired samples. A p value < 0.05 was considered significant. All statistical analyses were performed using SPSS version 14.0.

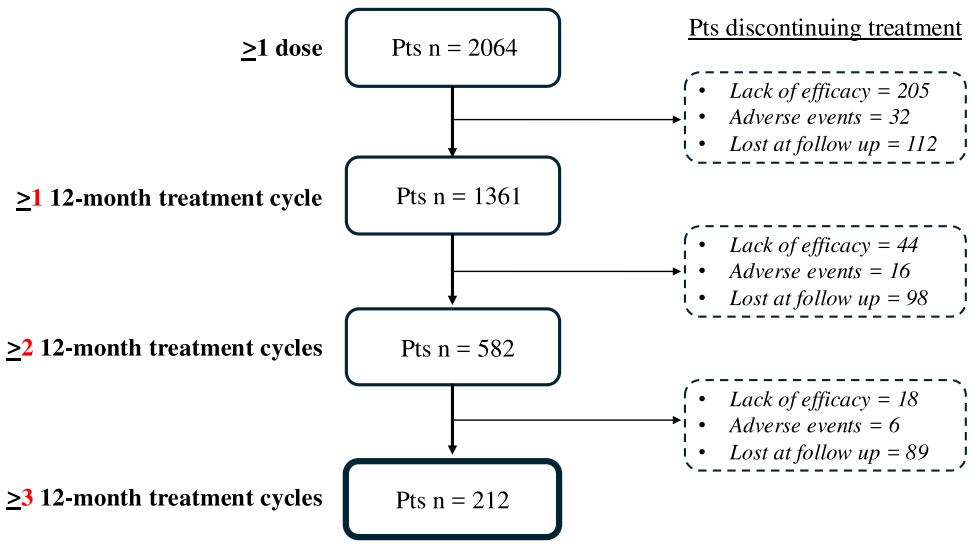

Fig. 2 Patients' disposition

Results

As of 27 June 2024, a total of 2064 subject with migraine had received at least one dose of anti-CGRP mAbs (Fig. 2). Among these, 212 participants who completed three Ts were included in the statistical analysis (HFEM/CM: 63/149; F/M: 163/49; mean age: 48.1 ± 11.5 years; treatment distribution: erenumab, 154; galcanezumab, 34; fremanezumab, 24) (Table 1). Individuals with CM were younger ($p = 0.022$), and had higher MAI ($p < 0.001$) and more frequent psychiatric comorbidities ($p < 0.007$) compared to those with HFEM. Twenty-two patients (10.4%) transitioned from erenumab to either galcanezumab ($n = 10$) or fremanezumab ($n = 12$). Specifically, 2 patients switched during T1 (1 to fremanezumab and 1 to galcanezumab), 7 during T2 (4 to fremanezumab and 3 to galcanezumab), and 16 during T3 (9 to fremanezumab and 7 to galcanezumab). The reasons for switching included constipation in one case and a subjective perception of reduced efficacy over time with the initial mAb. Subjects receiving anti-CGRP mAbs targeting the ligand (galcanezumab or fremanezumab) had higher NRS scores ($p = 0.001$) and lower number of prior treatment failures ($p = 0.020$) compared to those receiving erenumab or shifting from erenumab to galcanezumab or fremanezumab (Supplementary Table 1). Early in the study, AIFA revised its guidelines—following the recommendation of the Italian Neurological Society—reducing the mandatory treatment discontinuation period from at least three months to at least one month. The mean duration of treatment discontinuation between the different Ts was 1.9 months at D1 (range 1–3), 1.5 months at D2 (range 1–4), and 1.2 months at D3 (range 1–4).

Table 1 Baseline demographic and clinical characteristics of migraine patients, stratified by diagnosis

	Number N (%) or mean ± SD			*p* value
	All patients	HFEM	CM	
	N = 212 (100)	*N* = 63 (29.7)	*N* = 149 (70.3)	
Age, yrs	48.1 ± 11.5	50.1 ± 9.7	46.9 ± 12	0.022
Females	163 (76.9)	51 (80.9)	112 (75.2)	0.361
BMI	22.9 ± 2.8	23.2 ± 2.8	22.8 ± 2.8	0.417
Age onset	17.1 ± 7.4	17.8 ± 7.1	16.8 ± 7.5	0.354
MMD at baseline	10.9 ± 3.8	10.9 ± 3.8	–	–
MHD at baseline	20.6 ± 5.8	–	20.6 ± 5.8	–
MAI	18.8 ± 10	10.1 ± 3.7	22.1 ± 10	< 0.001
Medication overuse	143 (67.4)	–	143 (95.9)	-
Medication overuse duration, yrs	6.3 ± 7	–	6.3 ± 7	-
NRS score	7.9 ± 1	8 ± 1	7.8 ± 1	0.188
Unilateral pain	120 (56.6)	35 (55.6)	85 (57)	0.841
UAS	127 (59.9)	37(58.7)	90 (60.4)	0.820
Ictal allodynia	120 (56.6)	39 (61.9)	81(54.4)	0.820
Dopaminergic symptoms	96 (45.3)	31(49.2)	65(43.6)	0.630
HIT-6 score	67.4 ± 6.8	66.7 ± 6.6	67.7 ± 7	0.349
Patients using concomitant migraine prophylaxis	106 (50)	31 (49.2)	75(50.3)	0.826
Prior treatment failures, *n*	4.4 ± 1.7	4.4 ± 1.8	4.5 ± 1.6	0.655
Pts with ≥ 1 comorbidity	101 (47.6)	27(42.9)	74(49.7)	0.364
Pts with psychiatric comorbidities	53 (25)	8 (12.7)	45(30.2)	0.007
Pts using concomitant medications	56 (26.4)	15 (23.8)	41 (27.5)	0.576
Erenumab	154 (72.6)	39 (61.9)	115 (77.1)	0.158
Galcanezumab	34 (16)	14 (22.2)	20 (13.4)	
Fremanezumab	24 (11.3)	10 (15.8)	14 (9.3)	

–: not computable

HFEM high-frequency episodic migraine, *CM* chronic migraine, *BMI* Body Mass Index, *MHD* monthly headache days, *MMD* monthly migraine days, *MAI* monthly analgesic intake, *NRS* Numeric Rating Scale, *UAS* unilateral cranial autonomic symptoms, *Dopaminergic symptoms*: presence during prodromes, headache stage or postdromes of have at least one of the following symptoms: yawning, somnolence, nausea, vomiting, mood changes, fatigue or diuresis, *HIT-6* Headache Impact Test-6

The three Ts with anti-CGRP mAbs resulted in a progressive and significant improvement in all primary and secondary outcomes across the various time points. Importantly, when stratified by treatment type, no significant differences were observed among patients treated exclusively with erenumab, those treated exclusively with galcanezumab or fremanezumab, and those who initially received erenumab and later switched to galcanezumab or fremanezumab.

Primary endpoint (Table 2, Fig. 3; Supplementary Figs. 1, 2):

A significantly higher ≥ 50% response rate was observed at D3 compared to D2 (77.8% vs. 53.8%; $p < 0.001$).

Secondary endpoints (Table 3, Figs. 3, 4, 5; Supplementary Figs. 3, 4):

At D3, a statistically significant reduction ($p < 0.001$) was observed in MMD (− 2.1 ± 1.7), MHD (− 2.9 ± 2.4), MAI (− 2.6 ± 2.4), NRS (− 0.7 ± 1.3), and HIT-6 scores (− 7.2 ± 5.9) compared to D2. Additionally, a smaller proportion of patients relapsed from episodic migraine to CM (2.3% vs. 18%) and from non-medication overuse to medication overuse (1.3% vs. 10.1%) within the same time interval.

Further, at D3, a significantly ($p < 0.001$) greater improvement was noted in MMD (− 2.6 ± 1.9), MHD (− 5.8 ± 3.3), MAI (− 4.9 ± 3.4), NRS (− 1 ± 1.6), and HIT-6 scores (− 9.4 ± 7), along with higher ≥ 50% response rate (77.8% vs. 25%), compared to D1. A lower proportion of patients also experienced a relapse from episodic migraine to CM (2.3% vs. 67.7%) and from no-medication overuse to medication overuse (1.3% vs. 34.2%).

Changes in MMD, MHD, MAI, NRS, and HIT-6 scores at various time points, including T1 (weeks 45–48) vs.

Table 2 Comparison of ≥ 50% response rates from baseline across different 12-month treatment cycles with anti-CGRP mAbs (T1, T2, T3) and discontinuation time points (D1, D2, D3)

Comparison	≥50% response rate	*p* value
T2 vs T1	94.8% vs 92.9%	< 0.001
D2 vs D1	53.8% vs 25%	< 0.001
T3 vs T2	96.2% vs 94.8%	< 0.001
D3 vs D2	**77.8% vs. 53.8%**	**< 0.001**
D3 vs D1	77.8% vs 25%	< 0.001
T3 vs T1	96.2% vs 92.9%	< 0.001

T1 first 12-month treatment cycle with anti-CGRP mAbs, *T2* second 12-month treatment cycle with anti-CGRP mAbs, *T3* third 12-month treatment cycle with anti-CGRP mAbs, *D1* first month of treatment discontinuation after T1, *D2* first month of treatment discontinuation after T2, *D3* first month of treatment discontinuation after T3

Primary endpoint is highlighted in bold

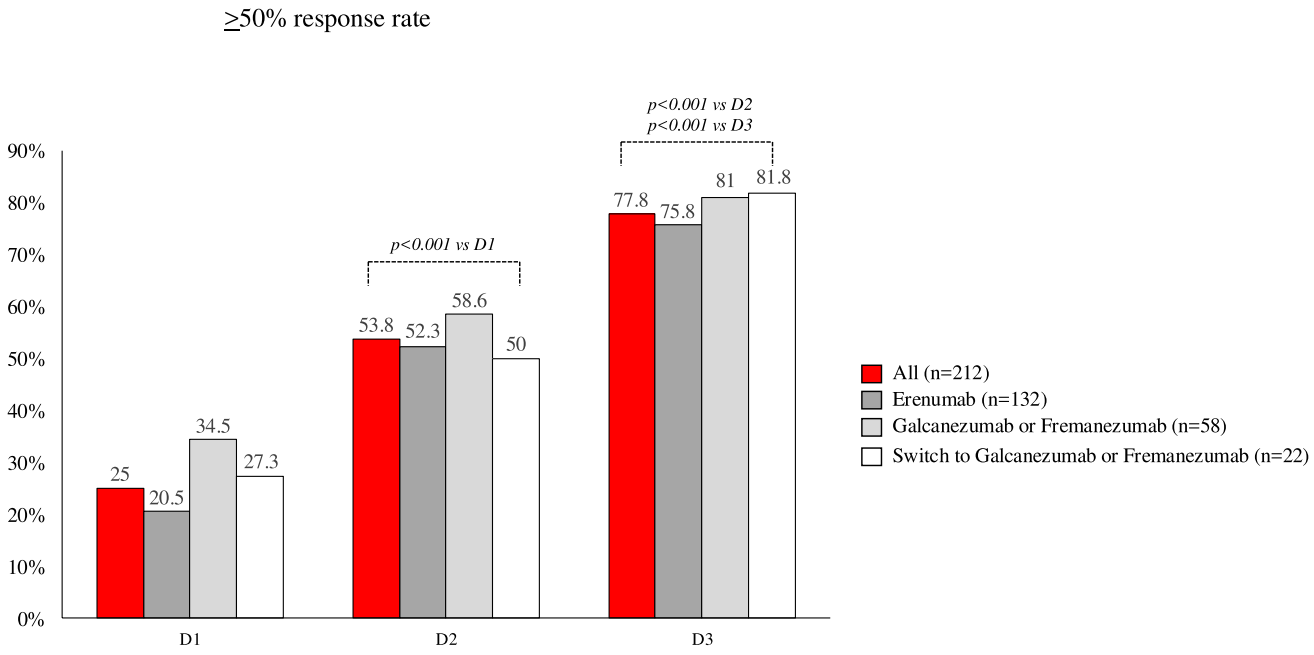

Fig. 3 Proportion of patients with a ≥ 50%, reduction in monthly migraine days following treatment with anti-CGRP mAbs across the entire migraine population. *D1*: first month of treatment discontinuation after the first anti-CGRP treatment cycle; *D2*: first month of treatment discontinuation after the second anti-CGRP treatment cycle; *D3*: first month of treatment discontinuation after the second anti-CGRP treatment cycle; *All*: all patients treated with anti-CGRP mAbs; *Erenumab*: patients treated with erenumab across the three treatment cycles; *Galcanezumab or Fremanezumab*: patients treated with Galcanezumab or Fremanezumab across the three treatment cycles; *Switch to Galcanezumab or Fremanezumab*: patients who switched from Erenumab to Galcanezumab or Fremanezumab at any time across the three treatment cycles

Table 3 Variation in selected migraine outcomes across 12-month treatment cycles with anti-CGRP mAbs (T1, T2, T3) and discontinuation time points (D1, D2, D3)

Comparison	Parameter	Change (Mean ± SD)	*p* value
T1 (weeks 45–48) vs baseline	MMD	− 7.3 ± 4.1	< 0.001
	MHD	− 15.2 ± 6.1	< 0.001
	MAI	− 13.7 ± 8.4	< 0.001
	NRS	− 3.4 ± 1.6	< 0.001
	HIT-6	− 17.2 ± 10.2	< 0.001
D1 vs T1 (weeks 45–48)	MMD	+ 5.3 ± 2.2	< 0.001
	MHD	+ 7.7 ± 3.1	< 0.001
	MAI	+ 6.7 ± 4.1	< 0.001
	NRS	+ 2.4 ± 1.1	< 0.001
	HIT-6	+ 10.9 ± 6.6	< 0.001
T2 (weeks 45–48) vs T1 (weeks 45–48)	MMD	− 0.5 ± 1.4	0.011
	MHD	− 0.3 ± 2.4	0.077
	MAI	− 1 ± 3.3	< 0.001
	NRS	− 0.03 ± 1.6	0.072
	HIT-6	− 1 ± 6.7	0.028
T2 (weeks 45–48) vs D1	MMD	− 5.3 ± 1.9	< 0.001
	MHD	− 5.1 ± 3.0	< 0.001
	MAI	− 7.7 ± 3.7	< 0.001
	NRS	− 2.4 ± 1.7	< 0.001
	HIT-6	− 11.9 ± 6.8	< 0.001
D2 vs T2 (weeks 45–48)	MMD	+ 5.0 ± 2.5	< 0.001
	MHD	+ 5.2 ± 2.7	< 0.001
	MAI	+ 5.4 ± 3.1	< 0.001
	NRS	+ 2.1 ± 1.9	< 0.001
	HIT-6	+ 9.9 ± 6.9	< 0.001
D2 vs D1	MMD	− 0.5 ± 1.7	0.034
	MHD	− 2.9 ± 3.6	< 0.001
	MAI	− 2.3 ± 3.7	< 0.001
	NRS	− 0.3 ± 1.4	0.004
	HIT-6	− 2.1 ± 6.2	< 0.001
T3 (weeks 45–48) vs D2	MMD	− 5.8 ± 1.8	< 0.001
	MHD	− 5.8 ± 2.7	< 0.001
	MAI	− 5.6 ± 2.7	< 0.001
	NRS	− 2.3 ± 1.8	< 0.001
	HIT-6	− 7.2 ± 5.9	< 0.001
T3 (weeks 45–48) vs T2 (weeks 45–48)	MMD	− 0.4 ± 1	0.001
	MHD	− 0.7 ± 1.6	< 0.001
	MAI	− 0.2 ± 1.8	0.049
	NRS	− 0.2 ± 1.1	0.307
	HIT-6	− 1.6 ± 3.7	< 0.001
T3 (weeks 45–48) vs T1 (weeks 45–48)	MMD	− 1 ± 1.5	< 0.001
	MHD	− 1 ± 2.5	< 0.001
	MAI	− 1.2 ± 3.5	< 0.001
	NRS	− 0.2 ± 1.6	0.404
	HIT-6	− 2.6 ± 6.9	< 0.001
D3 vs T3 (weeks 45–48)	MMD	+ 3.2 ± 1.9	< 0.001
	MHD	+ 3.1 ± 2	< 0.001
	MAI	+ 3.1 ± 2.1	< 0.001
	NRS	+ 1.5 ± 1.9	< 0.001
	HIT-6	+ 4.2 ± 5.6	< 0.001

Table 3 (continued)

Comparison	Parameter	Change (Mean ± SD)	*p* value
D3 vs D1	MMD	− 2.6 ± 1.9	< 0.001
	MHD	− 5.8 ± 3.3	< 0.001
	MAI	− 4.9 ± 3.4	< 0.001
	NRS	− 1 ± 1.6	< 0.001
	HIT-6	− 9.4 ± 7	< 0.001
D3 vs D2	MMD	− 2.1 ± 1.7	< 0.001
	MHD	− 2.9 ± 2.4	< 0.001
	MAI	− 2.6 ± 2.4	< 0.001
	NRS	− 0.7 ± 1.3	< 0.001
	HIT-6	− 7.2 ± 5.9	< 0.001

T1 first 12-month treatment cycle with anti-CGRP mAbs, *T2* second 12-month treatment cycle with anti-CGRP mAbs, *T3* third 12-month treatment cycle with anti-CGRP mAbs, *D1* first month of treatment discontinuation after T1, *D2* first month of treatment discontinuation after T2, *D3* first month of treatment discontinuation after T3, *MMD* Monthly Migraine Days, *MHD* Monthly Headache Days, *MAI* monthly analgesic intake, *NRS* Numerical Rating Scale, *HIT-6* Headache Impact Test-6

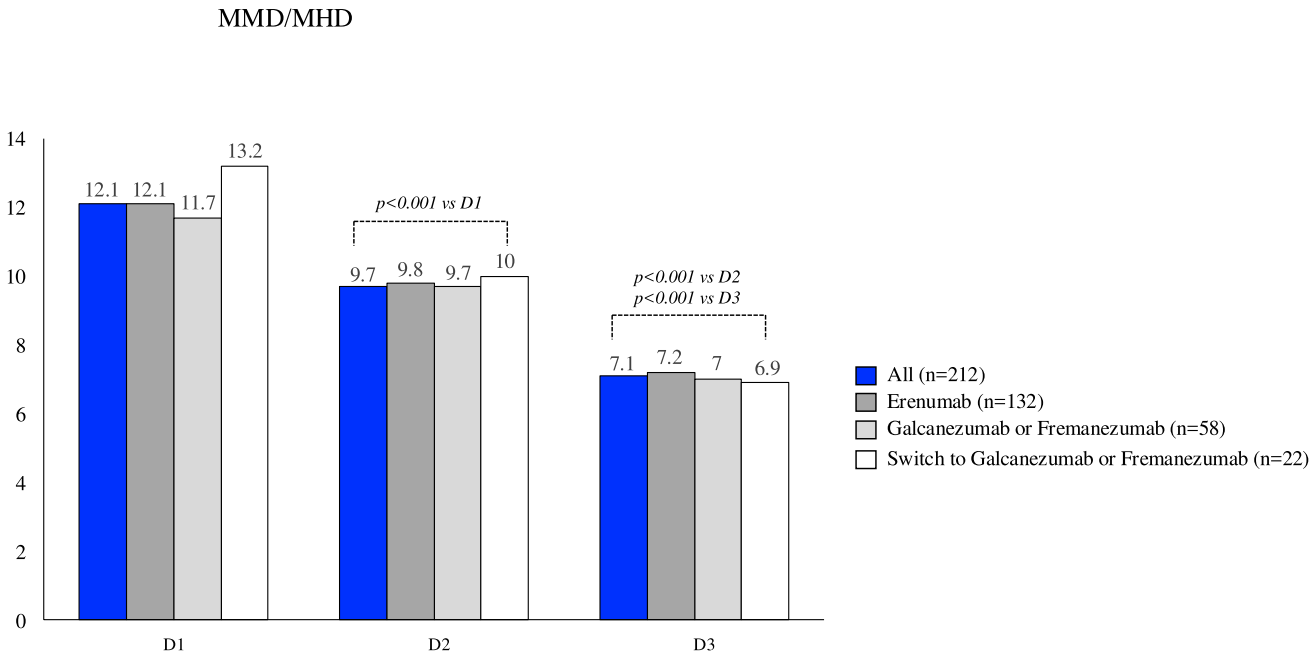

Fig. 4 Change in monthly migraine days (MMD) or monthly headache days (MHD) following treatment with anti-CGRP mAbs across the entire migraine population. *D1*: first month of treatment discontinuation after the first anti-CGRP treatment cycle; *D2*: first month of treatment discontinuation after the second anti-CGRP treatment cycle; *D3*: first month of treatment discontinuation after the second anti-CGRP treatment cycle; *All*: all patients treated with anti-CGRP mAbs; *Erenumab*: patients treated with erenumab across the three treatment cycles; *Galcanezumab or Fremane*zumab: patients treated with Galcanezumab or Fremanezumab across the three treatment cycles; *Switch to Galcanezumab or Fremanezumab*: patients who switched from Erenumab to Galcanezumab or Fremanezumab at any time across the three treatment cycles

baseline, D1 vs. T1 (weeks 45–48), T2 (weeks 45–48) vs. T1 (weeks 45–48), T2 (weeks 45–48) vs D1, D2 vs. T2 (weeks 45–48), D2 vs. D1, T3 (weeks 45–48) vs. D2, T3 (weeks 45–48) vs. T2 (weeks 45–48), T3 (weeks 45–48) vs. T1 (weeks 45–48), and D3 vs. T3 (weeks 45–48), are detailed in Table 3. Statistically significant improvements were observed across all clinical outcomes in most comparisons between T and D time points. The exceptions, which did not reach statistical significance, include changes in NRS during weeks 45–48 between T2 and T1, T3 and T2, and T2 and T1, as well as variations in MHD between T2 and T1.

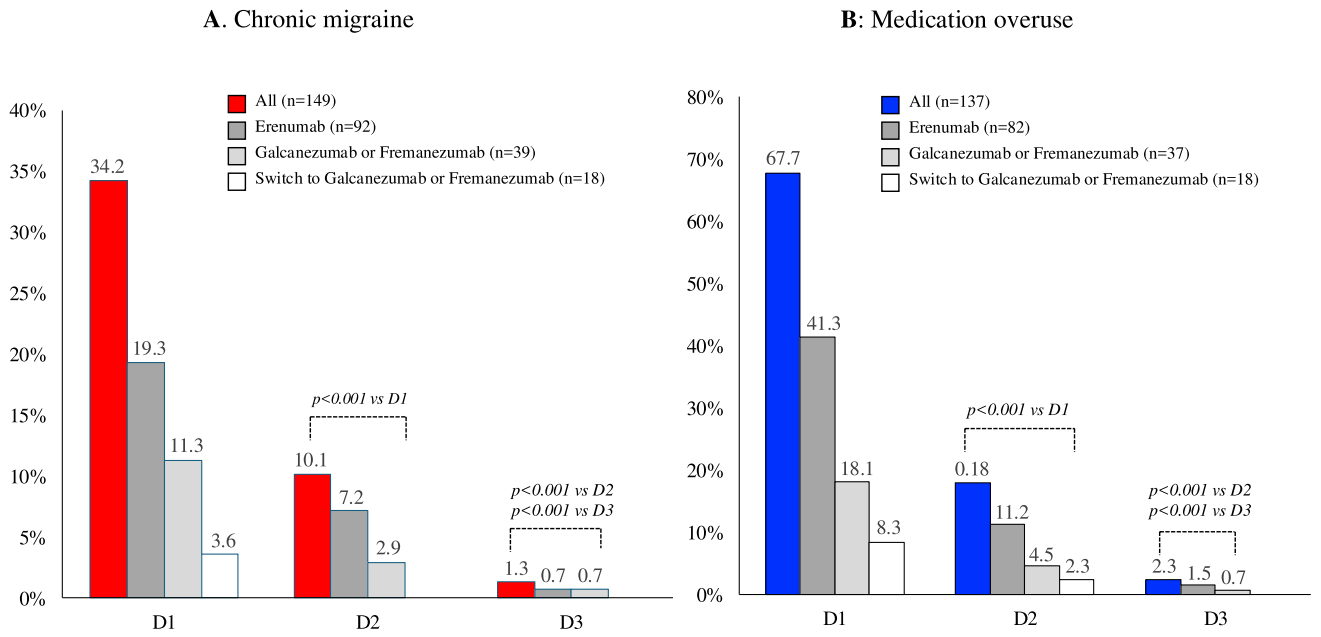

Fig. 5 Proportion of patients relapsed from episodic migraine to chronic migraine (box A) and from non-medication overuse to medication overuse (box B) at D1, D2, and D3. *D1*: first month of treatment discontinuation after the first anti-CGRP treatment cycle; *D2*: first month of treatment discontinuation after the second anti-CGRP treatment cycle; *D3*: first month of treatment discontinuation after the second anti-CGRP treatment cycle; *All*: all patients treated with anti-CGRP mAbs; *Erenumab*: patients treated with erenumab across the three treatment cycles; *Galcanezumab or Fremane*zumab: patients treated with Galcanezumab or Fremanezumab across the three treatment cycles; *Switch to Galcanezumab or Fremanezumab*: patients who switched from Erenumab to Galcanezumab or Fremanezumab at any time across the three treatment cycles

We also examined potential correlations between sociodemographic or clinical characteristics and the ≥ 50% response rate across all time points (Supplementary Table 2). Notably, only MHD demonstrated a consistent and significant association at D1 (25.8 ± 4.9, p0.001), D2 (23.2 ± 4.5, $p < 0.001$), and D3 (22.2 ± 5.0, $p < 0.001$). Additional significant associations were observed, including shorter disease duration at D2 ($p = 0.032$) and higher medication overuse at D2 ($p < 0.001$) and D3 ($p = 0.020$) among ≥ 50% responders. Moreover, the minimal reduction in HIT-6 score in responders at D2 was only marginally significant ($p = 0.047$). While BMI at D1 ($p = 0.022$) was significantly associated with a ≥ 50% response rate, the small sample size in the lower BMI class limits the consistency of this finding.

Mild and transient adverse events, primarily constipation and injection site reactions, were reported by 25.9% of patients. No serious adverse events were observed, and no patient discontinued therapy due to adverse events (Supplementary Table 3).

Discussion

This multicenter, prospective, real-world study demonstrates a significant and progressive increase in the proportion of patients with HFEM or CM who maintain a ≥ 50% response rate to subcutaneous anti-CGRP mAbs during the first month after treatment discontinuation following each 12-month treatment cycle.

Specifically, 25% of patients remained responders at D1, 53.8% at D2, and 77.8% at D3. At the same time points, a progressive and significant reduction in migraine frequency, analgesic intake, pain severity, and associated disability was observed. Although a numerically higher proportion of responders was noted among patients treated with anti-CGRP mAbs targeting the ligand (galcanezumab, fremanezumab) compared to those targeting the receptor (erenumab), this difference did not reach statistical significance. These findings build upon our previous research [17], highlighting that at D3, the percentage of responders increases by approximately 25% compared to D2. This supports the potential benefits of extending preventive treatment with anti-CGRP mAbs for a duration of least three years, particularly in patients with HFEM or CM who have experienced multiple prior therapeutic failures. Although our study exclusively evaluates migraine outcomes during the first month after treatment discontinuation, as required by AIFA regulations, the results suggest that repeated or long-term use of anti-CGRP mAbs may positively influence the pathophysiological mechanisms underlying migraine, potentially modifying its clinical course over time.

Migraine is a disorder with a highly heterogeneous course, which can remain stable, fluctuate, worsen, or spontaneously improve over time. The distinction between episodic migraine and CM, defined by a frequency of < 15 or ≥ 15 days per month, often fails to capture the progressive nature of this condition in many patients [19]. To address this limitation, the concept of "migraine progression" has been introduced in recent years, describing clinical scenarios marked by a gradual increase in migraine frequency and associated disability in some individuals [20]. Migraine progression is a slow, evolving process driven by progressive central sensitization and long-term synaptic and neuronal changes [21]. This process is influenced by various factors, including clinical characteristics of migraine (e.g., attack frequency, cutaneous allodynia, and nausea), treatment-related aspects (e.g., ineffective therapies, medication overuse, or underuse), as well as demographic characteristics, lifestyle factors, and comorbidities [1].

Similar to other paroxysmal disorders of the central nervous system, such as epilepsy, effective treatment should be administered for an adequate duration to promote the progressive desensitization of specific neural transmission pathways and the reversal of the pathophysiological mechanisms driving disease progression [2]. This goal has remained unattainable in migraine management with traditional preventive treatments, primarily due to the frequent premature discontinuation of therapies caused by limited efficacy, poor tolerability, or both [5]. The introduction of anti-CGRP mAbs has brought new hope for modifying the disease course and has reshaped the landscape of migraine prophylaxis. However, while randomized-controlled trials have typically evaluated treatment responses over 3–6 months, real-world studies have yet to examine treatment durations beyond 1 year [22, 23].

While the findings of our study suggest a potential progressive disease-modifying effect of anti-CGRP monoclonal antibodies with extended treatment, it is important to acknowledge that the observed increase in the percentage of responders during the first month after treatment discontinuation cannot be solely attributed to the pharmacological effects of the therapy. This improvement also reflects concurrent reductions in analgesic use, reduced disability, enhanced psychological well-being, and an overall improvement in quality of life—all well-established factors in mitigating the potential progression of migraine. The reduction in migraine days helps break the vicious cycle of migraine perpetuation, progressively reducing avoidant behaviors, cephalalgiophobia, and stigma—key factors that sustain the migraine condition. Moreover, prospective real-world studies have reported improvements in depressive symptoms among migraine patients treated with anti-CGRP mAbs targeting either the receptor or the ligand, independent of reductions in migraine frequency [24–26].

This study is not without limitations. First, we assessed only the first month following the discontinuation of each anti-CGRP monoclonal antibody treatment cycle. Second, eptinezumab was not included in our analysis, as it was only recently introduced in our country. Third, the majority of patients (62.3%) received erenumab, with smaller proportions treated with galcanezumab or fremanezumab. Fourth, our findings pertain exclusively to patients with HFEM or CM may not be generalizable to individuals with lower frequency migraine. Finally, the validity of our results applies specifically to patients with at least three prior preventive treatment failures and an average long interval (approximately 30 years) between migraine onset and the initiation of anti-CGRP treatment. The strengths of this study include its prospective multicenter design, the participation of ten headache centers representing seven regions across Northern, Central, and Southern Italy, and the comprehensive assessment of sociodemographic factors, comorbidities, concomitant medications, and migraine phenotypes using a shared semi-structured questionnaire.

In conclusion, we report that extended (3-year) treatment with anti-CGRP mAbs leads to a progressive improvement in migraine frequency, pain severity, analgesic use, and disability, as observed during the first month of discontinuation after each T. These findings support the hypothesis of a progressive modification of the migraine course. However, these promising results require further validation through extended, randomized-controlled studies incorporating treatment discontinuation periods of at least 5 months, accounting for the drug's half-life, to more comprehensively assess the long-term impact of this therapeutic approach.

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Data availability The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Conflict of interest Piero Barbanti reports personal compensation for consulting, serving on a scientific advisory board, speaking, research support, collaborated for clinical trials, or other activities with Abbvie, Alder, Allergan, Amgen, Angelini, Assosalute, Bayer, Biohaven, DOC Pharma, Eli-Lilly, Fondazione Ricerca e Salute, GSK, Lundbeck, Noema Pharma, Organon, Pfizer, Teva, Viatris, Visufarma, and Zambon, and serves as President with Italian Association of Headache Sufferers. Cinzia Aurilia received travel grants from Eli-Lilly, FB-Health, Lusofarmaco, and Teva, and honoraria from Novartis, Eli-Lilly, and Teva; Paola Torelli received travel grant, honoraria as a speaker, or for participating in advisory boards from Novartis, Teva, Eli Lilly, and

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