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RESEARCH SUBMISSIONS

A head-to-head observational cohort study on the efficacy and safety of monoclonal antibodies against calcitonin gene–related peptide for chronic and episodic migraine

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Abstract

Objective: To compare the effectiveness and safety of galcanezumab, fremanezumab, and erenumab for the treatment of chronic and episodic migraine, through real-world data.

Background: Monoclonal antibodies (mAbs) targeting the calcitonin gene–related peptide (CGRP) pathway have been tested extensively in several clinical trials for both episodic and chronic migraine, showing high effectiveness, safety, and tolerability; however, there are no prospective real-world studies intending to compare their efficacy and safety.

Methods: This is a prospective observational cohort study comparing the effectiveness and safety profiles of galcanezumab, fremanezumab, and erenumab for the treatment of chronic and episodic migraine. We enrolled 140 patients at the Headache Centre of University Federico II of Naples, with a history of multiple failed treatments with validated migraine preventatives. Framenezumab, erenumab, or galcanezumab were administered for 12 months. The mean monthly days with headache, Migraine Disability Assessment (MIDAS) score, and adverse events were evaluated during the run-in period and every 3 months by reviewing standardized paper patient headache diaries.

Results: We found a mean reduction of migraine monthly days from baseline of −12.0 (−9.8, −14.1) in the galcanezumab group, −12.3 (−10.2, −14.3) in the fremanezumab group, and −10.8 (−8.5, −13.1) in the erenumab group (for all, $p < 0.001$). We found a mean reduction of MIDAS score of −32.6 (−26.6, −38.5) in the galcanezumab group, −33.4 (−28.0, −38.9) in the fremanezumab group, and −29.2 (−23.0, −35.4) in the erenumab group (for all, $p < 0.001$). We found no significant differences between mAbs in the reduction of mean monthly days with headache and MIDAS score. We found a more rapid effect of galcanezumab and erenumab compared to fremanezumab in

Abbreviations: CGRP, calcitonin gene–related peptide; CM, chronic migraine; EHF, European Headache Federation; EM, episodic migraine; GLM-RM, general linear model for repeated measures; ICHD-3, International Classification of Headache Disorders, 3rd edition; mAbs, monoclonal antibodies; MIDAS, Migraine Disability Assessment; MOH, medication overuse headache; RCT, randomized clinical trial.

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medication overuse headache patients after 3 months of treatment (−10.8 and −11.1 vs. −4.0 days; $p = 0.029$).

Conclusion: Our results confirm the therapeutic benefits of anti-CGRP mAbs. There is no evidence that suggests that one antibody may be superior to the others in terms of effectiveness, both in chronic and episodic patients.

KEYWORDS
calcitonin gene–related peptide, erenumab, fremanezumab, galcanezumab, migraine, monoclonal antibodies

INTRODUCTION

Prophylactic treatment for chronic and episodic migraine has historically consisted of non–disease-specific drugs, such as anti-seizure medications, beta-blockers, anti-depressants, calcium channel blockers, and onabotulinumtoxinA.[1,2] Recently, disease-specific and mechanism-based treatments for the prophylaxis of migraine have become available. Four monoclonal antibodies (mAbs) targeting the calcitonin gene–related peptide (CGRP) pathway have been tested extensively in several randomized clinical trials (RCTs) for both episodic migraine (EM) and chronic migraine (CM). These trials also documented high effectiveness, safety, and tolerability.[3]

Erenumab, a monoclonal antibody targeting the CGRP receptor, was approved in 2018 by the European Medicines Agency and by the US Food and Drug Administration for the preventive treatment of migraine with more than four headache days per month.[4] Subsequently, other mAbs targeting the CGRP pathway, such as galcanezumab and fremanezumab, were approved with the same indications.[5,6]

In 2019 the American Headache Society published a consensus position statement on migraine treatment for clinical practice. This statement suggests the use of mAbs in migraine patients with debilitating low-frequency EM, high-frequency EM, CM, and intolerance or inadequate response to a 6-week treatment of at least two preventive medications.[7] Since then, mAbs have been extensively proven to have a superior benefit–risk ratio compared to traditional prophylactic treatment, both in CM and EM.[8] Their effectiveness was further confirmed by real-world studies, reporting that mAbs are even more effective than what originally emerged from RCTs, without increasing evidence of adverse events incidence.[9–12] Based on RCTs and real-word data, the 2022 European Headache Federation (EHF) guidelines for migraine management suggest the use of eptinezumab, galcanezumab, fremanezumab, and erenumab as first-line preventive treatments of CM and EM[13]; however, EHF does not provide any advice on potential differences in effectiveness or clinical criteria for preferential choice among the three mAbs. This information may have clinical relevance because the available data on the effectiveness and safety of different anti-CGRP mAbs are derived from meta-analyses and network meta-analyses of RCTs each with a different design;[14,15] therefore, the potential difference among mAbs was not fully ascertained. The clinical dilemma of choosing the right pharmaceutical agent for the right patient, who may also have comorbidities, should be answered with evidence coming from direct head-to-head real-world data. To our knowledge, there are no prospective real-world studies comparing mAbs against CGRP in migraine.

We hypothesized that there could be a difference among mAbs for treatment of migraine in a real-world setting; therefore, our study intends to compare the effectiveness and safety of galcanezumab, fremanezumab, and erenumab for the treatment of CM and EM, through real-world data.

METHODS

This is a primary analysis of retrospective data from an observational cohort study comparing the effectiveness and safety profiles of galcanezumab, fremanezumab, and erenumab for the treatment of CM and EM meeting the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for migraine.[16] The study was approved by the University Federico II and Cardarelli hospital ethics committee and all patients gave written informed consent before any procedure linked to the study. The patient's identity was known only to the treating physician and privacy was guaranteed by assigning a pseudonym to each patient. We enrolled 140 patients with migraine at the Headache Centre of the University Federico II of Naples, who were offered for the first time a mAbs prescription between November 2020 and July 2021. A total of 29 patients were excluded from the study because of contraindications to the use of mAbs (severe arterial hypertension, history of cardiovascular or cerebrovascular disease) and 1 patient refused to start the treatment. The choice of mAb was in fixed order as each physician sequentially prescribed treatments in blocks of three (the order was erenumab, fremanezumab, galcanezumab, then another block of three would start). This was possible as treatments were prescribed through a common platform, mandatory for regulatory reasons, for all prescribing physicians. This made it possible to assign treatments in a fixed fashion without using centralized lists or interactive web response services. Inclusion criteria were: diagnosis of migraine fulfilling the ICHD-3 criteria, age greater than or equal to 18 years, and

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a history of ≥3 failed treatments with validated migraine preventatives at a standard dose for at least 2 months. Alternatively, preventive treatments had to be contraindicated. The duration of follow-up was 12 months. Demographics, detailed medical history, and the presence of comorbidities were recorded at baseline. During a 1-month run-in period and for the study duration, patients were asked to complete a paper and pencil headache diary. For this task they recorded daily presence of headache, headache duration, headache-related symptoms (photophobia, phonophobia, aura, nausea, vomiting, motion sensitivity), pain intensity using a 0–10 analogic scale (0 no pain, 1–3 mild, 4–7 moderate, 8–10 severe pain), and the use of acute medication to treat headache. Diaries were collected at each treatment prescription and in the absence of a filled-in diary, a prescription was not handed to the patient. For this reason, we did not have missing diaries at any time point, but it is still possible that patients did not fill them in while having a migraine attack.

Erenumab (monthly dose 140 mg), fremanezumab (monthly dose 225 mg), or galcanezumab (at initial dose of 240 mg and subsequent monthly doses of 120 mg) were administered according to manufacturers' recommendations. Patients were allowed to take their current preventive therapies if the dose had been stable for at least 3 months before starting anti-CGRP mAb treatment. Migraine-related clinical burden was assessed with the Migraine Disability Assessment (MIDAS) at baseline and every 3 months for 12 months. Mean monthly days with headache occurring during the run-in period, as well as during anti-CGRP mAb treatment, were evaluated by reviewing standardized paper patient headache diaries at baseline and every 3 months during follow-up visits. Migraine monthly days and MIDAS score have both proved to be reliable in clinical studies.[17]

Statistical analysis

A descriptive analysis is provided for baseline variables; this included frequency and percentage (for categorical variables), or mean and standard deviation (for continuous variables). We evaluated the difference between different antibody medication groups using a one-way analysis of variance or the chi-square test when appropriate. We analyzed the effect of antibodies on number of migraine days/month or MIDAS with a general linear model for repeated measures (GLM-RM). Because Mauchly's test of sphericity was significant, we used the Greenhouse–Geisser correction. Bonferroni correction was applied within the GLM-RM for a comparison between different antibody medication groups. We used the effect of time to estimate the overall reduction of migraine days/MIDAS after treatment, and the combined effect of time × group to estimate the impact of treatment groups on migraine days/MIDAS reduction. This was an intention-to-treat analysis and missing data were dealt with through the last observed carried forward method, which was applied to all patients not completing to final observation; that is, 6/45 for erenumab, 2/54 for fremanezumab, 3/41 for galcanezumab (Figure 1). Attrition rate was 13% for erenumab, 4% for fremanezumab, and 7% for galcanezumab. Partial eta square (η^2) was used as a measure of effect size. Significance was set at 0.05, two-tailed. Statistical analysis was performed using SPSS version 28.0.1.0 running on Mac OS 10.15.7. No statistical power calculation was conducted prior to the study, as this was meant as an exploratory analysis.

Ethics Statement

The study was approved at Federico II University and Cardarelli hospital ethics committee and all patients gave written informed consent before any procedure linked to the study.

RESULTS

We enrolled a total of 140 patients with migraine. A flow diagram is depicted in Figure 1. Demographic and baseline clinical characteristics of patients are fully reported in Table 1. Two or three or more previously failed treatments were reported in 42% of patients (59/140) or in 58% (81/140), respectively. We recorded comorbidities in 41% (57/140) of the patients, the most common being depression, anxiety, arterial hypertension, and autoimmune disorders.

Migraine monthly frequency showed an overall significant decrease in the whole cohort of patients during the 12-month follow-up period ($p<0.001$; $F=250.58$; $\eta^2=0.65$) without any significant differences between the three subgroups ($p=0.164$; $F=1.65$; $\eta^2=0.02$). Monthly migraine days showed a significant decrease after 3 months of follow-up ($p<0.001$; $F=345.34$), 6 months ($p<0.001$; $F=331.03$), and after 9 months of follow-up ($p<0.001$; $F=357.95$). The comparative analysis with monthly migraine days for each mAb is reported in Table 2A and shown in Figure 2A. We recorded a significant reduction of the MIDAS score in the whole cohort of patients during the 12-month follow-up period ($p<0.001$; $F=255.28$; $\eta^2=0.65$) without any significant differences between the three subgroups ($p=0.155$; $F=1.69$; $\eta^2=0.02$). The whole comparative analysis is reported in Table 2B. We found no significant difference in terms of effectiveness between treatments.

Headache type (i.e., CM vs. EM) did not impact the reduction of mean monthly days and MIDAS scores. The whole comparative analysis is reported in Table S1 in supporting information.

In patients with medication overuse headache (MOH), we found significant differences between mAbs in terms of reduction of migraine monthly days after 3 months of therapy ($p=0.029$; $F=3.63$, $\eta^2=0.06$). We found a mean reduction of −9.6 days (95% confidence interval [CI] −6.6, −12.6; $p<0.001$) in all treated patients, −10.8 (95% CI −4.9, −16.7; $p=0.003$) in galcanezumab-treated patients, −4.0 (95% CI +4.3, −12.3; $p=0.223$) in fremanezumab-treated patients, and −11.1 (95% CI −6.5, −15.7; $p<0.001$) in erenumab-treated patients. The same was true for MIDAS for patients with MOH. We found significant differences between mAbs in terms of reduction of MIDAS score after 3 months of therapy ($p=0.032$; $F=3.55$, $\eta^2=0.06$). We found a mean reduction of −26.1 (95% CI −18.0, −34.1; $p<0.001$) in all treated patients, −29.5 (95% CI −13.7, −45.3;

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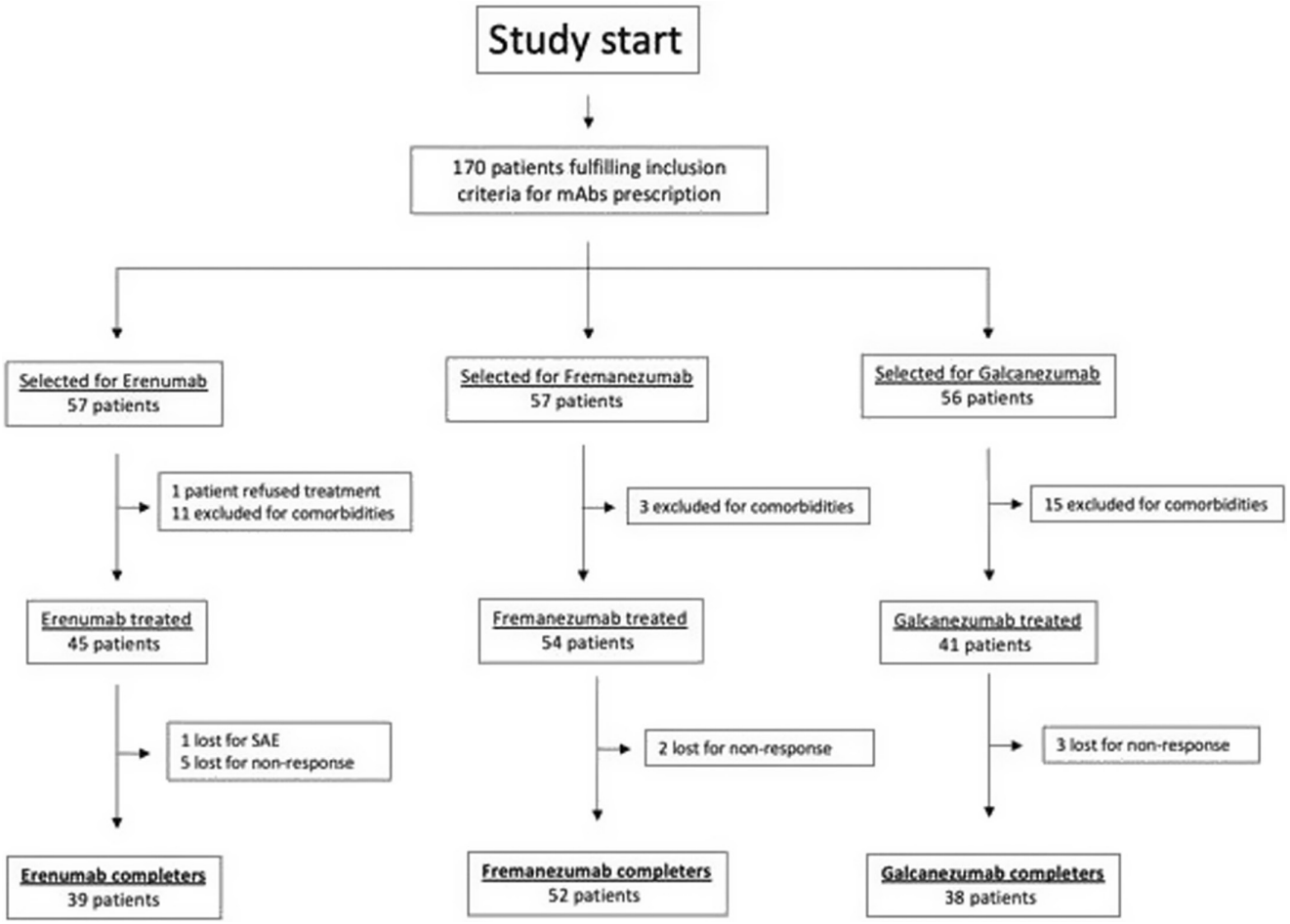

FIGURE 1 Participant disposition flow diagram. mAbs, monoclonal antibodies; SAE, serious adverse event.

$p = 0.002$) in galcanezumab-treated patients, −11.0 (95% CI +11.7, −33.7; $p = 0.111$) in fremanezumab-treated patients, and −30.0 (95% CI −17.5, −42.5; $p < 0.001$) in erenumab-treated patients (Figure 2B).

During the 12-month treatment period, mild adverse events were reported by 48/140 (34%) patients enrolled. We observed 13/140 (9%) mild adverse events in the galcanezumab group, 11/140 (8%) in the fremanezumab group, and 24/140 (17%) in the erenumab group. The most common adverse events were new or worsened constipation, injection site non-specific reaction, and fatigue. No patient suspended treatment due to mild adverse events. Ten patients discontinued treatment because of lack of efficacy (three patients in the galcanezumab subgroup, two patients in the fremanezumab subgroup, five patients in the erenumab subgroup). There was no switch from one mAb to another. One serious adverse event was reported by one patient in the erenumab subgroup (myocardial infarction) who discontinued treatment. This patient had comorbidities in the form of arterial hypertension, dyslipidemia, and obesity.

DISCUSSION

To date, several meta-analyses have been conducted to investigate the possible differences among mAbs in terms of effectiveness and safety. In the network meta-analysis of Wang et al. involving 8926 patients and collecting data derived from 18 RCTs, pooled results showed that eptinezumab, galcanezumab, fremanezumab, and erenumab were similarly effective in reducing monthly migraine days.[14] Soni et al. analyzed seven RCTs involving 5164 people with CM and found that all treatments were comparable to each other.[15] Recently, in the network meta-analysis of Yang et al. involving 5634 patients and collecting data from 13 RCTs, pooled results showed that monthly 140 mg erenumab was the best choice to reduce the number of acute migraine-specific medication use days[18]; however, a subsequent network meta-analysis of Wang et al., involving 3052 patients and collecting data from seven RCTs, pointed out that, conversely, anti-CGRP mAbs are superior to anti-CGRP receptor mAbs in reducing monthly migraine days.[19] Indeed, although certainly useful, meta-analyses investigating anti-CGRP mAbs often combine trials with different inclusion criteria: some focusing only on CM, some on EM, and some combining both, and thus their conclusions may be biased. For this reason, real-world evidence may provide useful evidence for the choice of the specific mAbs in certain patient subtypes. Currently, there is only one real-life study on a smaller series of patients, which compared galcanezumab, fremanezumab, and erenumab for the preventive treatment of CM and EM.[20] They retrospectively examined 57 patients with CM and 20 patients with

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TABLE 1 Baseline demographic and clinical characteristics.

	Total patients	Galcanezumab	Fremanezumab	Erenumab	*p* value	F/χ^2
Number of patients	140	41 (29%)	54 (39%)	45 (32%)		
Age, years	42.2 ± 12.2	42.2 ± 14.0	40.9 ± 12.0	43.7 ± 10.7	0.528	0.64[b]
Sex						
Female	111 (79%)	32 (78%)	45 (83%)	34 (76%)	0.619	0.96[a]
Male	29 (21%)	9 (22%)	9 (17%)	11 (24%)		
Disease duration, years	17.0 ± 10.8	16.4 ± 9.8	17.3 ± 11.9	17.2 ± 10.3	0.877	0.13[b]
Concomitant preventive treatments	63 (45%)	17 (41%)	26 (48%)	20 (44%)	0.832	0.37[a]
Monotherapy	47 (75%)	13 (77%)	20 (77%)	14 (70%)	0.950	0.71[a]
Polytherapy	16 (25%)	4 (24%)	6 (23%)	6 (30%)		
Headache diagnosis						
Chronic migraine	89 (64%)	27 (66%)	34 (63%)	28 (62%)	0.934	0.14[a]
Episodic migraine	51 (36%)	14 (34%)	20 (37%)	17 (38%)		
MOH	20 (14%)	6 (15%)	4 (7%)	10 (22%)	0.062	5.55[a]
Comorbidities	100 (71%)	26 (41%)	41 (41%)	33 (40%)	0.386	1.91[a]
Headache days per month	20.7 ± 7.5	20.8 ± 6.9	20.6 ± 8.0	20.7 ± 7.7	0.986	0.01[b]
MIDAS score	56.0 ± 20.4	56.3 ± 18.9	55.6 ± 21.6	56.1 ± 20.6	0.987	0.01[b]

Note: Values are mean ± standard deviation (SD) or number (%).

Abbreviations: MIDAS, Migraine Disability Assessment scale; MOH, medication overuse headache.

[a]χ^2 test.

[b]*F* at analysis of variance test.

TABLE 2 Monthly migraine days and MIDAS score reduction compared to baseline.

	Baseline	3 months	6 months	9 months	12 months
A					
Galcanezumab	20.8 ± 6.9	−11.0 (−9.3, −12.8)*	−11.6 (−9.6, −13.5)*	−11.8 (−9.8, −13.8)*	−12.0 (−9.8, −14.1)*
Fremanezumab	20.6 ± 8.0	−9.6 (−7.8, −11.4)*	−11.5 (−9.5, −13.6)*	−12.0 (−9.9, −14.0)*	−12.3 (−10.2, −14.3)*
Erenumab	20.7 ± 7.7	−7.9 (−6.2, −9.7)*	−8.9 (−6.9, −10.9)*	−10.1 (−8.0, −12.2)*	−10.8 (−8.5, −13.1)*
Total patients	20.7 ± 7.6	−9.5 (−8.5, −10.5)*	−10.7 (−9.5, −11.8)*	−11.3 (−10.1, −12.5)*	−11.7 (−10.5, −12.9)*
B					
Galcanezumab	57.3 ± 18.8	−29.8 (−25.1, −34.5)*	−31.5 (−26.3, −36.7)*	−31.9 (−26.6, −37.2)*	−32.6 (−26.6, −38.5)*
Fremanezumab	55.6 ± 21.6	−25.9 (−21.2, −30.7)*	−31.1 (−25.5, −36.6)*	−32.5 (−27.7, −38.0)*	−33.4 (−28.0, −38.9)*
Erenumab	56.1 ± 20.6	−21.5 (−16.7, −26.3)*	−24.0 (−18.5, −29.6)*	−27.1 (−21.6, −32.8)*	−29.2 (−23.0, −35.4)*
Total patients	56.0 ± 20.4	−25.6 (−22.9, −28.4)*	−28.9 (−25.8, −32.1)*	−30.6 (−27.5, −33.7)*	−31.8 (−28.5, −35.1)*

Note: Values are mean (95% confidence interval).

Abbreviation: MIDAS, Migraine Disability Assessment scale.

*$p < 0.001$.

EM (in the EM subgroup it was performed only an ad-interim analysis) with a 6-month follow-up. Their results did not show a statistically significant difference in the average number of migraine days per month, mean monthly symptomatic medications intake, MIDAS score, and Headache Impact Test-6 questionnaires. The limited number of patients, the heterogeneous baseline clinical characteristics of each subgroup, and the high prevalence of medication overuse make conclusions difficult.

The present study is a prospective real-world study aiming at comparing the safety and effectiveness of mAbs against CGRP in a large population of patients with CM and EM. Our cohort is composed of 140 patients, equally distributed for each of the three treatments in terms of demographics, comorbidities, and severity of disease. That allowed us to compare the three monoclonal antibodies against CGRP taken into consideration without major bias of selection.

Our findings confirmed that galcanezumab, fremanezumab, and erenumab are suitable and safe in the preventive therapy for CM and EM. Interestingly, the reduction of mean monthly days with headache was considerably higher than what was reported in

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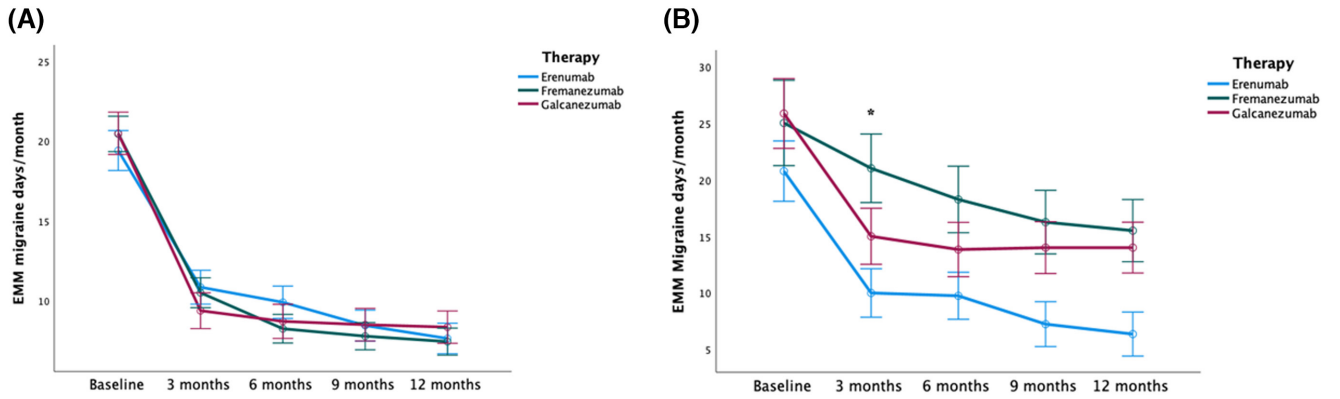

FIGURE 2 Monthly migraine days in erenumab, fremanezumab, and galcanezumab patients (A) and in patients with medication overuse headache (B). Error bars represent standard error means. EMM, estimated marginal means. [Color figure can be viewed at wileyonlinelibrary.com]

RCTs, in line with other real-world studies. Significant differences among mAbs in the reduction of mean monthly days with headache, MIDAS score, and mean monthly acute medications intake were not found. Similarly, no differences were found between CM and EM patients. This indicates that there is no clear difference among the mAbs in terms of effectiveness, and thus the choice of which mAb treatment to administer should be assessed by other outcomes.

The reduction in terms of monthly headache days occurred mainly within the first 3 months of treatment, followed by a slightly further decrease in the following months. This is particularly evident in the galcanezumab group, although not significantly different from other mAbs. This may be due to the manufacturers' recommendation of a first initial loading dose of galcanezumab and may lead the neurologist to the choice of galcanezumab when looking for a faster clinical response.

The reduction in terms of monthly headache days and MIDAS scores in patients with MOH showed a significant superiority of erenumab and galcanezumab compared to fremanezumab after 3 months of treatment. This suggests that the first two mAbs could be used to achieve a faster clinical outcome in patients with MOH. Due to the risk of medication overuse, a faster-acting preventive treatment is strongly suggested.

We observed a low rate of mild adverse events, erenumab being the most responsible for these events and, especially, for new or worsening constipation. This confirms similar results coming from clinical trials as well as other real-world studies and may be physiologically explained by its target being the CGRP receptor instead of the CGRP itself.[21,22] Further studies should be designed to determine whether erenumab should be administered in patients with a history of constipation. This study carries some limitations within it. This was a prospective observational study, and it may be biased due to its non-randomized and controlled design. Patients were followed for 12 months, and long-term differences among mAbs may not have been evident. Also, the study enrolled a limited number of patients, suggesting that future trials should specifically address some of our findings to draw definite conclusions.

CONCLUSIONS

Among adult patients with CM or EM and prevention medication failure, galcanezumab, fremanezumab, and erenumab were found to be effective and well-tolerated treatments. The results of this real-world study reinforce the therapeutic benefits of mAbs against CGRP. There is no evidence that suggests that one antibody may be superior to the others in terms of effectiveness.

AUTHOR CONTRIBUTIONS

Study concept and design: Cinzia Valeria Russo, Simone Braca. *Acquisition of data*: Cinzia Valeria Russo, Simone Braca, Francesco Saccà, Angelo Miele, Mattia Sansone, Roberto De Simone, Antonio Stornaiuolo. *Analysis and interpretation of data*: Cinzia Valeria Russo, Simone Braca, Francesco Saccà. *Drafting of the manuscript*: Cinzia Valeria Russo, Simone Braca, Francesco Saccà. *Revising it for intellectual content*: Cinzia Valeria Russo, Simone Braca, Francesco Saccà, Angelo Miele, Mattia Sansone, Roberto De Simone, Antonio Stornaiuolo. *Final approval of the completed manuscript*: Cinzia Valeria Russo, Simone Braca, Francesco Saccà, Angelo Miele, Mattia Sansone, Roberto De Simone, Antonio Stornaiuolo.

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CONFLICT OF INTEREST STATEMENT

Cinzia Valeria Russo received personal compensation from Sanofi Genzyme and Merck Serono. **Mattia Sansone, Simone Braca, Angelo Miele**, and **Antonio Stornaiuolo** declare no conflicts of interest. **Francesco Saccà** received public speaking honoraria from Alexion, Argenx, Biogen, Mylan, Novartis, Roche, Sanofi, and Teva; he also received compensation from advisory boards and consultation fees from Alexion, Almirall, Argenx, Avexis, Biogen, Forward Pharma, Lexeo Therapeutics, Merk, Novartis, Novatek, Roche, Sanofi, and

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Takeda. **Roberto De Simone** received personal compensation from Lilly for oral presentations (2020–2021).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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