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Research Article

Monthly Versus Quarterly Fremanezumab in Real Life: A Comparison of Effectiveness, Tolerability, and Adherence

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Background: While clinical trials have shown no differences between monthly and quarterly regimens of fremanezumab, limited real-life data exist for comparison. This study is aimed at comparing treatment regimens in real life.
Methods: This observational, multicentre study conducted a retrospective analysis of patients initiating monthly or quarterly fremanezumab. Primary endpoints were the comparison of monthly migraine days' reduction, adverse effects, and treatment discontinuation rates at 3 and 6 months. Secondary endpoints included changes in headache and medication intake frequencies, response rates, and patient-reported outcomes.
Results: One hundred and eleven patients were included, with a median age of 48.5 years, 91% women, and 54.1% with chronic migraine. Sixty-four patients received a monthly regimen and 47 a quarterly. Baseline characteristics were similar. Reductions in monthly migraine days did not differ between treatment regimens (−5 [IQR −9, −1] for monthly versus −6 [IQR −8, −3] for quarterly at 3 months, $p = 0.867$, and −5 [IQR −10, −2] versus −5.5 [IQR −8.5, −3] at 6 months, $p = 0.666$, respectively). Adverse effects and discontinuation rates were similar between groups. Secondary endpoints were comparable, except for a higher PGIC scale for the quarterly group at 6 months (6 [IQR 4–6] versus 4 [IQR 2–6], $p = 0.007$). No differences were observed in the subgroup analysis of episodic or chronic migraine.
Conclusions: Monthly and quarterly fremanezumab demonstrated comparable effectiveness, tolerability, and adherence in real life. Quarterly regimen may result in a more favorable global impression of change.

Keywords: fremanezumab; migraine; monthly; quarterly; real world

Summary

- Monthly and quarterly fremanezumab regimens showed comparable effectiveness, tolerability, and adherence in real life.
- Quarterly fremanezumab demonstrated a higher patient global impression of change after 6 months compared to the monthly regimen.

1. Introduction

Fremanezumab is the only subcutaneous monoclonal antibody (MAb) targeting the calcitonin gene-related peptide (CGRP) for the treatment of migraine with two different approved treatment regimens. While the other subcutaneous anti-CGRP MAbs, erenumab and galcanezumab, are both approved under fixed regimens of monthly administrations, fremanezumab has shown efficacy in both monthly and quarterly regimens [1–3].

Although head-to-head comparisons between monthly and quarterly fremanezumab regimens were absent in pivotal clinical trials, subsequent post hoc analyses have endeavored to elucidate potential discrepancies. Initially, an expositional-response modeling approach proposed comparable clinical benefits [4]. Conversely, a subsequent meta-analysis suggested superior efficacy for monthly administration ($p = 0.0008$), albeit with comparable rates of moderate or severe adverse effects ($p = 0.5$ and $p = 0.39$, respectively) [5]. However, these findings were later refuted upon identification of incorrect utilization of standard error instead of standard deviation, rendering the observed difference insignificant ($p = 0.17$) [6].

Despite these analyses, discrepancies between clinical trial data and real-world outcomes necessitate further investigation, and dedicated studies comparing monthly versus quarterly fremanezumab dosing in real life are scarce. However, in the FRIEND-1 real-world study, a secondary analysis of 53 patients suggested potential superiority of the monthly dose, albeit with limited statistical power due to disparate group sizes (44 monthly vs. 9 quarterly dosing) and a paucity of responders in the quarterly dosing cohort [7]. Subsequent expansion of this cohort in the FRIEND-2 study precluded direct comparison due to uneven distribution between groups (73.1% monthly vs. 26.9% quarterly) [8]. Furthermore, a US-based study hinted at higher adherence rates at 6 months with quarterly dosing (91.3% vs. 84.9% for monthly dosing, $p < 0.001$), albeit without concurrent assessment of effectiveness and safety variables [9]. Later, a subanalysis of a Japanese observational study reported comparable effectiveness between quarterly and monthly fremanezumab doses in migraine day's reduction across episodic and chronic migraine cohorts [10]. Lastly, a prospective real-world study comparing monthly and quarterly fremanezumab regimens reported overall comparable outcomes, although a slightly greater reduction in monthly migraine days (MMDs) was observed with the monthly regimen at 3 months [11].

Given the evidence presented, in routine clinical practice, there is no specific indication for one or another treatment regimen; the decision is based above all on the patient's preference. The present study is aimed at addressing this gap by comparing the real-world effectiveness, safety, and adherence of monthly versus quarterly fremanezumab dosing in a diverse cohort of migraine patients across various Spanish centers.

2. Methods

2.1. Patients. This observational retrospective study of prospectively collected data from three different Spanish headache centres included consecutive patients initiating monthly or quarterly fremanezumab treatment from December 2019 to August 2023, all diagnosed with migraine according to ICHD-3 criteria [12]. In accordance with Spanish national reimbursement criteria for treatment with MAb against CGRP, all enrolled patients must present more than eight MMDs and must have shown an inadequate response to at least three prior preventive treatments, with one of them being OnabotulinumtoxinA (BTX-A) for patients with chronic migraine [13].

Fremanezumab was administered subcutaneously either on a monthly basis (225 mg) or quarterly basis (675 mg). The choice of treatment frequency was tailored to individual patient characteristics, incorporating patient preferences, attending physician discretion, and concurrent use of oral preventive treatments or BTX-A.

2.2. Outcome Measures. All clinical data were prospectively collected at each center from the initiation of fremanezumab treatment, with quarterly scheduled visits and a minimum follow-up of 6 months. Baseline comorbidities were retrospectively extracted from clinical records. Collected variables included age, sex, time since migraine diagnosis, migraine subtype (episodic or chronic), time since chronification, presence of aura, prior migraine preventive treatments, concomitance of oral preventive treatments or BTX-A injections, and comorbidities. Quarterly collected clinical variables included MMDs, monthly headache days (MHD), frequency of MHDs by maximum intensity of pain (on a 4-point scale: none, mild, moderate, or severe), monthly acute medication intake (MAMI), Headache Impact Test (HIT-6), Migraine Disability Assessment test (MIDAS), Patients' Global Impression of Change (PGIC) scale (excluding baseline visit), presence of adverse effects, and reasons for treatment discontinuation, following the same data collection methodology as in previous works [14]. Patients recorded headache parameters (MMD, MHD, MAMI, and MHDs by maximum intensity) in standardized paper or electronic headache diaries presented at each clinical appointment. A headache day was defined as any calendar day with a documented headache episode. A migraine day was defined as a day with a headache that lasts at least 4 h and meets ICHD-3 criteria for migraine or probable migraine [12] or a day with a headache that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication.

The primary endpoints included comparison of reduction in MMD between the two dosing groups at 3 and 6 months, incidence of adverse effects, and treatment discontinuation rates. Secondary endpoints comprised: change in MHD and MAMI after 6 months, change in frequency of days by intensity, 50%, 75%, and 100% response rates, changes in HIT-6, MIDAS, and PGIC scale scores, and reasons for treatment discontinuation during the 6-month follow-up. Additionally, primary endpoints were compared between dosing groups in a subanalysis focusing solely on each migraine subtype (episodic or chronic). Lastly, a comparison between responders (≥ 50% reduction) and nonresponders (< 30%) was performed to assess potential baseline predictors of treatment response.

2.3. Statistical Analysis. Primary and secondary endpoints were assessed using a descriptive analysis. Categorical variables were presented as absolute frequencies. Demographic and clinical variables were presented as medians and ranges or means and standard deviations according to the distribution. The normality of the distribution of each variable was

TABLE 1: Demographic characteristics in each treatment regimen.

	Monthly	Quarterly	*p*
N	64	47	
Age (years)	50.1 (41.1–57.8)	46.6 (39.1–52.0)	0.310
Women	60 (93.8)	41 (87.2)	0.318
Time since diagnosis (years)	29.1 (15.7–38.1)	27.0 (18.5–35.1)	0.463
Chronic migraine	35 (54.7)	25 (53.2)	1
Time since chronification (years)	5.5 (2.8–9.7)	4.0 (1.9–9.6)	0.755
Aura	13 (20.3)	8 (17.0)	0.807
Comorbidities			
Anxiety	29 (45.3)	13 (27.7)	0.075
Depression	22 (34.4)	15 (31.9)	0.840
Obesity	13 (20.3)	5 (10.6)	0.201
Hypertension	6 (9.4)	4 (8.5)	1
Cardiovascular disease	0	1 (2.1)	0.423

Note: Continuous data is represented in median (IQR) and categorical data in *n* (%).

evaluated with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Changes in median MMD, MHD, and MAMI were assessed using the Wilcoxon test and compared between groups by Mann–Whitney's *U* test. Differences in adverse effects and discontinuation at each visit were assessed using Fisher's exact test. A bivariate analysis was conducted to identify baseline variables associated with treatment response. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U* test. Variables with a p value < 0.05 in the bivariate analysis, along with those considered clinically relevant, were entered into a binary logistic regression model to identify independent predictors of response. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were interpreted with CIs of 95% and a significance level of 5%. Statistical analyses were performed in SPSS v.20 (SPSS Inc., Chicago, United States). No statistical power calculation was conducted prior to the study. The sample size was based on the available data from the participating centres.

2.4. Ethics Approval and Consent to Participate. The study was approved by the Ethical Committee of the coordinating center with Reference EOM015/24. The confidential information of the patients was handled in accordance with Spanish regulations.

3. Results

A total of 111 patients were included in the study. The median age was 48.5 years (IQR 40.0–56.6), all Caucasian, with 91% of the patients being women. Among them, 54.1% had chronic migraine, and 18.9% had aura. Monthly fremanezumab was prescribed in 64 cases, while the quarterly regimen was administered to the remaining 47 patients. Baseline demographic characteristics are summarized in Table 1, revealing no statistically significant differences between the two treatment groups.

Clinical characteristics at baseline are presented in Table 2. Both treatment arms demonstrated a statistically significant reduction in MMD at both 3 and 6 months compared to baseline (see Figure 1). The reduction in MMD at 3 months was −5 (IQR −9, −1) for the monthly regimen versus −6 (IQR −8, −3) for the quarterly regimen ($p = 0.867$), and −5 (IQR −10, −2) for monthly versus −5.5 (IQR −8.5, −3) for quarterly at 6 months ($p = 0.666$). The incidence of adverse effects did not significantly differ between the two treatment arms (see Figure 2), nor did the rates of treatment discontinuation after 3 and 6 months (see Figure 3). Adverse effects observed are listed in Table 3, with reasons for discontinuation detailed in Table 4.

The proportion of responders at ≥50%, ≥75%, and 100% did not significantly differ between the two treatment regimens (see Figure 4). Table 5 illustrates secondary endpoints, which were not statistically different between groups except for the PGIC at 6 months, significantly higher for the quarterly regimen (6 [IQR 4–6] versus 4 [IQR 2–6] for the monthly group, $p = 0.007$).

As a subgroup analysis, primary endpoints were assessed based on episodic or chronic migraine at baseline:

- For episodic migraine ($n = 51$), there were 29 patients in the monthly group and 22 patients in the quarterly group. Reduction in MMD was similar between monthly and quarterly regimens at 3 months (−4 [IQR −7, −1] vs. −4.5 [IQR −6, −1.8], respectively [$p = 0.992$]), and at 6 months (−3 [IQR −5.5, −1.5] for monthly dosing versus −5 [IQR −6.0, −2.8] for quarterly [$p = 0.140$]). The proportion of adverse events was comparable for monthly and quarterly regimens at both 3 months (20.7% vs. 18.2%, respectively, $p = 1.000$) and 6 months (10.3% vs. 13.6%, respectively, $p = 1.000$). No patients with episodic migraine

TABLE 2: Baseline clinical characteristics in each treatment regimen.

	Monthly	Quarterly	*p*
N	64	47	
MMD	14 (10–19.8)	12 (10–18)	0.626
MHD	15 (10.3–28.8)	16 (11–25)	0.546
Intensities			
Mild days/month	3 (0–8.5)	4 (1–8.8)	0.421
Moderate days/month	5 (2.5–8.5)	5.5 (3–8.8)	0.361
Severe days/month	7 (3–11.5)	5 (3–9)	0.097
MAMI	12 (10–16.8)	12 (10–18)	0.936
Medication overuse	35 (54.7)	28 (59.6)	0.699
HIT-6	66 (64–71.5)	66 (63–70)	0.615
MIDAS	55 (31.5–89)	53 (34.5–85)	0.634
Number of previous preventive treatments	4 (3–5)	4 (3–5)	0.529
Previous preventive treatments			
Topiramate	55 (85.9)	41 (87.2)	1
Beta-blocker	42 (65.6)	34 (72.3)	0.537
Amitriptyline	52 (81.2)	42 (89.4)	0.294
Flunarizine	38 (59.4)	30 (63.8)	0.696
Anti-hypertensive	7 (10.9)	9 (19.1)	0.278
OnabotulinumtoxinA	48 (75.0)	32 (68.1)	0.696
Others	26 (40.6)	17 (36.2)	0.521
Concomitant oral treatment	40 (62.5)	31 (66.0)	0.842
Concomitant OnabotulinumtoxinA	22 (34.4)	16 (34.0)	1

Note: Continuous data are represented in median (IQR) and categorical data in *n* (%).
Abbreviations: MAMI, monthly acute medication intake; MHD, monthly headache days; MMD, monthly migraine days.

discontinued treatment at 3 months, and only one patient per group discontinued at 6 months (3.4% monthly vs. 4.5% quarterly, $p = 1.000$). Baseline characteristics between monthly and quarterly regimens in this subgroup of episodic migraine patients were not statistically significantly different (see Table A1 in the Appendix section).

- For chronic migraine ($n = 60$), there were 35 patients in the monthly group and 25 patients in the quarterly group. Reduction in MMD was similar between monthly and quarterly regimen at both 3 months (−7 [IQR −11.5, −1] vs. −7 [IQR −10.5, −3], respectively [$p = 0.798$]) and 6 months (−9 [IQR −14.5, −2] for monthly dosing vs. −6.0 [IQR −14, −2.8] for quarterly [$p = 0.757$]). The proportion of adverse events was comparable for monthly and quarterly regimen at both 3 months (22.9% vs. 36.0%, respectively, $p = 0.384$) and 6 months (24.2% vs. 22.7%, respectively, $p = 1.000$). Treatment discontinuation rate was also similar between monthly and quarterly groups at both 3 months (5.7% monthly vs. 12.0% quarterly, $p = 0.640$) and 6 months (14.3% vs. 16.0%, respectively, $p = 1.000$). Baseline characteristics between monthly and quarterly regimen in this subgroup of chronic migraine patients were not statistically significantly different (see Table A2 in the Appendix section).

In the bivariate analysis comparing responders (≥ 50% reduction) and nonresponders (< 30%), female sex and absence of depression were significantly associated with higher odds of response (see the detailed analysis in Table A3 in the Appendix section). In the multivariate logistic regression model, only female sex remained independently associated with treatment response (OR: 0.1; 95% CI: 0.01–0.85; $p = 0.035$). No other variables showed a significant association.

There were five cases where the initial regimen was changed during treatment. At Month 3, two cases were switched from quarterly to monthly regimen, one due to general discomfort, one due to a sensation of wearing-off effect, and one case from monthly to quarterly due to inefficacy. At month 6, two cases were switched from quarterly to monthly due to a sensation of wearing-off effect. No formal analysis of the wearing-off effect was performed, as this retrospective study was based on quarterly averages of MHDs and did not include daily or weekly headache frequency data. Given the low number of regimen changes, all patients were analyzed according to their initially assigned regimen under the intention-to-treat principle.

There were no missing data on MMD, MHD, MAMI, medication overuse, and concomitant treatments. Patients who discontinued treatment at 3 months were considered

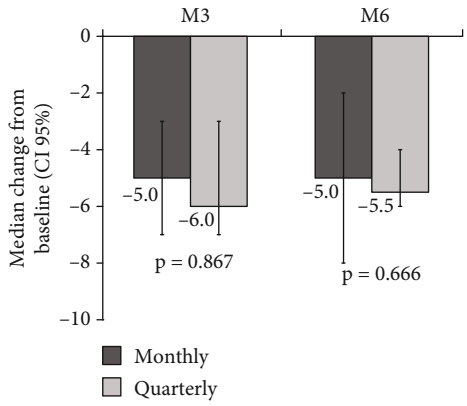

FIGURE 1: Median change in MMD after 3 (M3) and 6 months (M6) for each group of treatment. Confidence intervals of 95%. M3 = month 3; M6 = month 6.

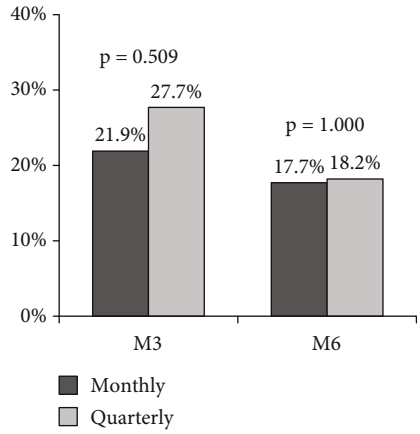

FIGURE 2: Proportion of adverse effects at month 3 (M3) and at month 6 (M6) for each group of treatment. M3 = month 3; M6 = month 6.

nonadherent and nonresponders for the global analysis at 6 months; however, they were excluded from the evaluation of quantitative outcomes at 6 months, including MMD, MHD, MAMI, and patient-reported scales. Data on monthly headache frequency, categorized by intensities, and HIT-6, MIDAS, and PGIC scales were not available for all patients; therefore, those patients were not included in the calculation of global medians for each of those variables at each visit. These missing data is shown in Table 5. No other missing data were reported.

4. Discussion

The present study represents one of the initial efforts aimed at comparing the effectiveness of monthly and quarterly fremanezumab regimens in real life. Overall, both regimens exhibited substantial benefits in reducing migraine frequency among our patients, alongside relatively good tolerability and adherence, aligning with previous reports on the real-world use of fremanezumab [7]. No statistically significant differences were observed between treatment regimens;

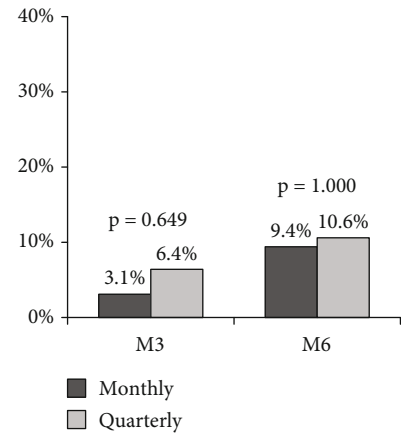

FIGURE 3: Treatment discontinuation rate after 3 (M3) and 6 months (M6) for each group of treatment. Patients who discontinued treatment at M3 are also accounted for in the proportion of discontinuation at M6. M3 = month 3; M6 = month 6.

a finding anticipated based on meta-analyses of pivotal trials affirming their comparable efficacy [6], further corroborated by the limited information available regarding early real-life studies [10].

Similar findings were reported in a recent prospective real-world study comparing monthly and quarterly fremanezumab [11], in which both regimens showed comparable effectiveness and tolerability; although a slightly greater reduction in MMD at 3 months was observed with the monthly regimen (−9 [IQR −6, −13] vs. −7 [−2, −10] for quarterly). In contrast, our study identified a higher PGIC score with quarterly administration—a factor not evaluated in the Italian study—potentially reflecting the impact of treatment convenience on patient-perceived benefit.

No statistically significant differences were observed when analyzing effectiveness, tolerability, and adherence between the different subgroups of episodic or chronic migraine. However, with only 51 episodic migraine patients and 60 chronic migraine patients, and considering each subgroup was divided into two arms depending on treatment regimen, subtle differences may have been obscured by the lack of statistical power due to the limited sample size.

In the exploratory analysis of potential predictors of response, female sex emerged as an independent predictor in the multivariate model. However, this finding should be interpreted with caution due to the marked sex imbalance in the sample (84 women vs. 9 men), with only one male classified as a nonresponder. This pronounced asymmetry may have resulted in an unstable OR estimate and an overestimation of the true association. Further studies with more balanced sex representation are needed to confirm this observation.

Overall, patients receiving a quarterly regimen reported a superior global impression of change measured with the PGIC scale (6 [IQR 4–6] compared to 4 [IQR 2–6] in the monthly group; $p = 0.007$). While objective clinical outcomes were

TABLE 3: Adverse effects during the follow-up.

Adverse effect [*n* (%)]	Monthly		Quarterly	
	M3 *n* = 64	M6 *n* = 62	M3 *n* = 47	M6 *n* = 44
Any	**14 (21.9)**	**11 (17.7)**	**13 (27.7)**	**8 (18.2)**
Constipation	8 (12.5)	8 (12.9)	11 (23.4)	6 (13.6)
Injection site reaction	4 (6.3)	2 (3.2)	0	2 (4.5)
Others	2 (3.2)	1 (1.6)	2 (4.2)	0

Note: Values in bold account for any adverse effect (including the ones accounted for in subsequent rows).

TABLE 4: Reasons for discontinuation during the follow-up.

Discontinuation reason [*n* (%)]	Monthly		Quarterly	
	M3 *n* = 64	M6 *n* = 62	M3 *n* = 47	M6 *n* = 44
Any	**2 (3.1)**	**4 (6.5)**	**3 (6.4)**	**2 (4.5)**
Lack of efficacy	1 (1.6)	3 (4.8)	3 (6.4)	2 (4.5)
Intolerance	1 (1.6)	1 (1.6)	0	0

Note: Values in bold account for any adverse effect (including the ones accounted for in subsequent rows).

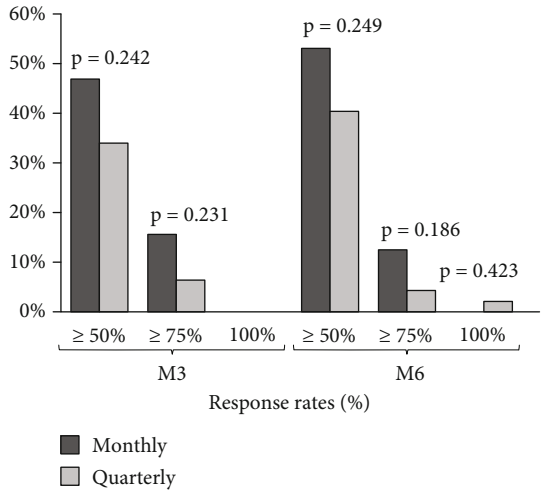

FIGURE 4: Proportion of ≥ 50%, ≥ 75%, and 100% responders after 3 (M3) and 6 months (M6) for each group of treatment. Patients who discontinued treatment at M3 are also accounted for as nonresponders at M6. M3 = month 3; M6 = month 6.

comparable between groups, this difference in subjective assessment may reflect greater convenience and treatment satisfaction associated with less frequent injections. Quarterly administration may reduce treatment burden and minimize illness salience by decreasing the frequency of reminders of their condition, potentially enhancing the patient's perception of overall improvement [15].

The proportion of adverse effects in our cohort was lower compared to fremanezumab clinical trials [1, 3]; but higher than previously reported adverse effects in real-life [7, 8]. This could be partially explained by the higher prevalence of psychiatric conditions in our cohort compared to those in the FRIEND studies. Nonetheless, all reported adverse events, primarily constipation, were mild and only necessitated treatment interruption in two cases, both in the monthly regimen group. Local injection site reactions were less frequent, occurring in only six cases in the monthly group and two cases in the quarterly group.

Changes in treatment regimen during follow-up were infrequent; however, notably, three cases were switched from quarterly to monthly dosing due to a sensation of wearing-off effect, indicating an increase in headache days in the last weeks of the quarterly dosing interval. Although no significant wearing-off effect has been demonstrated for either treatment regimen in clinical trials [16] or most real-life studies [17], a Japanese real-world study reported patient-reported wearing-off in 6.7%–11.7% of those on monthly dosing and 9.8% on quarterly, despite no increase in mean weekly migraine days over time [18]. This highlights the need for further studies using daily or weekly headache data to better assess this phenomenon.

Fremanezumab's pharmacokinetic profile supports both monthly and quarterly administration, with a half-life of approximately 30 days ensuring sustained therapeutic exposure. While the 675 mg quarterly dose produces a higher peak serum concentration (~105 μg/mL) than the 225 mg monthly dose (~30 μg/mL), monthly administration yields more stable plasma levels due to greater accumulation and higher trough concentrations [19]. These differences may influence tolerability in peak-sensitive patients or those prone to injection-site reactions. Additionally, the gradual decline in drug concentrations toward the end of the quarterly interval may contribute to perceived wearing-off effects in a subset of patients, despite overall average exposure and efficacy being comparable across regimens. Given that both regimens reach steady state around 6 months and show similar reductions in MMDs, treatment choice should probably be guided primarily by patient preference, tolerability, and adherence.

This study has several notable strengths. It represents the largest real-world cohort to date specifically designed to

TABLE 5: Secondary endpoints of effectiveness and patient-reported outcomes at M6.

	Monthly $n = 62$	Quarterly $n = 44$	p
Δ MHD	−6 (−15, −2)	−4.5 (−7.7, −2)	0.104
	$n = 62/62$	$n = 44/44$	
Intensities			
Δ Mild days/month	−1.5 (−4.3, 1.3)	−1 (−3, 0.8)	0.522
Δ Moderate days/month	−1 (−5, 1)	−1 (−4, 0)	0.605
Δ Severe days/month	−3 (−7.3, 0)	−2.5 (−3.8, 0)	0.106
	$n = 58/62$	$n = 40/44$	
Δ AMDM	−5.5 (−10, −2)	−5 (−7, −2.3)	0.316
	$n = 62/62$	$n = 44/44$	
Δ HIT6	−6 (−11.5, 0)	−8 (−13, −3)	0.485
	$n = 62/62$	$n = 43/44$	
Δ MIDAS	−27 (−48.5, −3)	−28 (−57.8, −1.8)	0.952
	$n = 53/62$	$n = 38/44$	
PGIC	4 (2–6)	6 (4–6)	0.007
	$n = 60/62$	$n = 43/44$	

Note:Continuous data are presented in median (IQR). Missing data are shown below each variable. Δ = change between baseline and M6.
Abbreviations: MAMI, monthly acute medication intake; MHD, monthly headache days.

compare monthly and quarterly fremanezumab regimens and, to our knowledge, is only the second study with this objective. Compared to the recent Italian prospective study [11], our cohort includes a larger sample size, incorporates patient-reported global impression of change, and explores potential predictors of response. The multicenter design enhances the generalizability of findings, and the inclusion of both episodic and chronic migraine subgroups broadens clinical applicability.

Some limitations must be acknowledged in this study. Firstly, the follow-up was restricted to 6 months postinitiation of fremanezumab treatment, potentially overlooking patients with delayed responses or presenting delayed adverse events. Secondly, while all clinical follow-up variables were prospectively collected, the assessment of baseline comorbidities was retrospective, potentially introducing information biases if certain conditions were overlooked or not documented in clinical records, and the utilization and dosing of concomitant treatments were poorly controlled. Finally, the overall sample size was relatively small, especially when stratifying into different arms to compare episodic and chronic migraine, resulting in low statistical power. Further investigations are warranted to validate these findings and elucidate potential disparities between monthly and quarterly fremanezumab dosing.

5. Conclusion

Monthly and quarterly regimens of fremanezumab demonstrate comparable effectiveness, tolerability, and adherence in real life. Patients receiving the quarterly dose may perceive a more favorable global impression of change.

Appendix A

TABLE A1: Demographic and clinical characteristics in each treatment regimen group for patients with episodic migraine ($n = 51$).

	Monthly	Quarterly	p
N	29	22	
Age (years)	49.2 (43.4–56.1)	43.8 (36.2–49.9)	0.123
Women	27 (93.1)	18 (81.8)	0.383
Aura	6 (20.7)	1 (4.5)	0.124
Comorbidities			
Anxiety	10 (34.5)	4 (18.2)	0.225
Depression	7 (24.1)	5 (22.7)	1
Obesity	7 (24.1)	1 (4.5)	0.117
Hypertension	3 (10.3)	3 (13.6)	1
Cardiovascular disease	0	0	
MMD	10 (9–12)	10 (9–11)	0.779
MHD	10 (9–12)	10 (9–11.5)	0.637
MAMI	10 (9–12)	10 (9–11.5)	0.692
Medication overuse	8 (27.6)	7 (31.8)	0.766
HIT-6	64 (62.2–67.8)	66 (61.5–68.0)	0.534
MIDAS	51 (29.3–73.8)	50 (31.0–69.5)	0.777
Concomitant oral treatment	17 (58.6)	13 (59.1)	1
Concomitant OnabotulinumtoxinA	7 (24.1)	5 (22.7)	1

Note: Continuous data is represented in median (IQR) and categorical data in *n* (%).
Abbreviations: MAMI, monthly acute medication intake; MHD, monthly headache days; MMD, monthly migraine days.

TABLE A2: Demographic and clinical characteristics in each treatment regimen group for patients with chronic migraine ($n = 60$).

	Monthly	Quarterly	*p*
N	35	25	
Age (years)	51.9 (34.3–58.4)	45.8 (38.9–51.0)	0.988
Women	33 (94.3)	23 (92.0)	1
Aura	7 (20)	7 (28)	0.543
Comorbidities			
Anxiety	19 (54.3)	9 (36)	0.196
Depression	15 (42.9)	10 (40)	1
Obesity	6 (17.1)	4 (16)	1
Hypertension	3 (8.6)	1 (4)	0.634
Cardiovascular disease	0	1 (4)	0.417
MMD	18 (15–27.5)	18 (15.3–25.8)	0.946
MHD	28 (20–30)	25.5 (18.3–30)	0.407
MAMI	16 (14.5–24.5)	18.5 (13.3–25.8)	0.804
Medication overuse	27 (77.1)	21 (84.0)	0.745
HIT-6	70 (64.5–74.0)	68 (64.3–73.5)	0.164
MIDAS	62 (31.5–108.0)	54.5 (40.0–107.8)	0.714
Concomitant oral treatment	23 (65.7)	18 (72.0)	0.779
Concomitant OnabotulinumtoxinA	15 (42.9)	11 (44.0)	1

Note: Continuous data is represented in median (IQR) and categorical data in *n* (%).
Abbreviations: MAMI, monthly acute medication intake; MHD, monthly headache days; MMD, monthly migraine days.

TABLE A3: Demographic and clinical characteristics in responders ≥ 50% versus nonresponders (< 30%).

	Responders ≥ 50%	Nonresponders < 30%	*p*
N	46	47	
Age, years	48.3 (41.4–54.3)	50.3 (43.3–58.9)	0.282
Women	45 (97.8)	39 (83.0)	**0.030**
CM	24 (52.2)	27 (57.4)	0.679
Aura	6 (13.0)	9 (19.1)	0.574
Comorbidities			
Anxiety	17 (37.0)	21 (44.7)	0.529
Depression	12 (26.1)	23 (48.9)	**0.032**
Obesity	6 (13.0)	7 (14.9)	1
Hypertension	4 (8.7)	5 (10.6)	1
Cardiovascular disease	1 (2.2)	0	0.495
Previous oral treatments (number)	4 (3–5)	4 (3–5)	0.912
Previous OnabotulinumtoxinA	31 (67.4)	35 (74.5)	0.499
MMD	14 (10–17.3)	15 (10–23)	0.416
MHD	15.5 (10–28)	15 (11–30)	0.540
MAMI	11 (9–15.3)	13 (10–26)	0.077
Medication overuse	23 (50.0)	31 (66.0)	0.144
HIT-6	65 (63–70.5)	68 (64–72)	0.157
MIDAS	52 (30–78.8)	55 (38.5–93.3)	0.209
Concomitant oral treatment	26 (56.5)	35 (74.5)	0.083
Concomitant OnabotulinumtoxinA	15 (42.9)	11 (44.0)	1

Note: Continuous data is represented in median (IQR) and categorical data in *n* (%). Statistically significant results are marked in bold (p values < 0.05).
Abbreviations: MAMI, monthly acute medication intake; MHD, monthly headache days; MMD, monthly migraine days.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

A.M.V., S.C., J.C., and J.P. have received honoraria from Teva, Lilly, Lundbeck, Organon, Roche, UCB, Bial, Chiesi, Allergan, Esai, Zambon, Kern Pharma, Pfizer, Biogen Idec, Novartis, TEVA, Merck, Janssen, Neuraxpharm, Genzyme, Sanofi, Bayer, Almirall, and/or Celgene. L.M.C.S. and S.M.G.-S. have received honoraria from Lilly and Teva. M.H.-V. has received honoraria for participating on advisory boards and for collaborations as consultant, scientific communications, speaker, and research support as well as funding for travel and congress-attending expenses for Abbie-Allergan, Novartis, Lilly, Almirall, Chiesi, Esai, Exeltis, Kern Pharma, Menarini, TEVA, Lundbeck, Pfizer, Organon, and Zambon. His research group has received research grants from Abbie-Allergan and has received funding for clinical trials from Lilly, Novartis, and TEVA.

Author Contributions

A.M.-V. and S.C. contributed to the collection, analysis, and interpretation of the data and to the writing of the manuscript. L.M.C.S., J.C., J.P., and S.M.G.-S. contributed to the collection of the data. M.H.-V. contributed to the collection and interpretation of the data and to the revision of the manuscript. All authors read and approved the final manuscript.

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