

Early Therapeutic Response as a Predictor of Long-Term Outcomes in Patients with Episodic and Chronic Migraine Treated with Fremanezumab

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Migraine is a common and disabling neurological disorder. Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP), such as fremanezumab, represent an advancement in prophylactic therapy.

Aim was to evaluate the effectiveness of fremanezumab in real-world clinical practice and to investigate whether early therapeutic response can predict long-term treatment outcomes

A retrospective observational study included 52 patients with episodic migraine (EM) and chronic migraine (CM) treated with fremanezumab at the University Clinical Center Niš between 1 August 2024 and 1 December 2025. Monthly headache days (MHD) and pain intensity assessed by the Visual Analog Scale (VAS) were recorded at baseline, after the third dose, and after the sixth dose. The primary outcome was $\geq 50\%$ reduction in MHD at 6 months. Early response was defined

as $\geq 50\%$ reduction in MHD after 3 months. Multivariate logistic regression was used to identify independent predictors.

Mean MHD decreased from 13.79 ± 7.50 to 4.31 ± 6.17 after 6 months ($p < 0.001$), while VAS decreased from 9.06 ± 1.06 to 4.65 ± 2.74 ($p < 0.001$). A $\geq 50\%$ response was achieved in 84.6% of patients, without significant differences between EM and CM groups ($p = 0.248$). Early therapeutic response was a strong independent predictor of long-term outcome (OR = 28.55; 95% CI 2.98–273.70; $p = 0.004$).

Fremanezumab is effective and well tolerated in real-world settings. Early response after three months may have important prognostic value and can guide treatment decisions.

Keywords: migraine fremanezumab calcitonin gene-related peptide

**RANI TERAPIJSKI ODGOVOR KAO PREDIKTOR DUGOROČNOG ISHODA KOD
PACIJENATA SA EPIZODIČNOM I HRONIČNOM MIGRENOM LEČENIH
FREMANEZUMABOM**

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Migrena je čest i onesposobljavajući neurološki poremećaj. Monoklonska antitela usmerena na kalcitonin-gen-povezani peptid (CGRP), poput fremanezumaba, predstavljaju napredak u profilaktičkoj terapiji.

Cilj rada bila je procena efikasnosti fremanezumaba u realnoj kliničkoj praksi i ispitavanje da li rani terapijski odgovor može predvideti dugoročne ishode lečenja.

Retrospektivna opservaciona studija obuhvatila je 52 pacijenta sa epizodičnom (EM) i hroničnom migrenom (CM) lečenih fremanezumabom u Univerzitetskom kliničkom centru Niš u periodu od 1 Avgusta 2024. do 1 Decembra 2025. godine. Mesečni broj dana sa glavoboljom (MHD) i intenzitet bola procenjen vizuelnom analognom skalom (VAS) praćeni su na početku, nakon treće i nakon šeste doze terapije. Primarni ishod bio je $\geq 50\%$ redukcija MHD nakon 6 meseci. Rani terapijski

odgovor definisan je kao $\geq 50\%$ redukcija MHD nakon 3 meseca. Multivarijantna logistička regresija korišćena je za identifikaciju nezavisnih prediktora.

Prosečan broj dana sa glavoboljom mesečno smanjen je sa $13,79 \pm 7,50$ na $4,31 \pm 6,17$ nakon 6 meseci ($p < 0,001$), dok je VAS smanjen sa $9,06 \pm 1,06$ na $4,65 \pm 2,74$ ($p < 0,001$). Terapijski odgovor ($\geq 50\%$ redukcija MHD) postignut je kod 84,6% pacijenata, bez statistički značajne razlike između EM i CM grupa ($p = 0,248$). Rani terapijski odgovor bio je snažan

Fremanezumab je efikasan i dobro podnošljiv u realnim kliničkim uslovima. Rani terapijski odgovor nakon tri meseca može imati značajnu prognostičku vrednost i pomoći u donošenju terapijskih odluka.

Ključne reči: migrena, fremanezumab, kalcitonin-gen-povezani peptid

INTRODUCTION

Migraine is a complex neurological disease whose main characteristic is recurrent headache of moderate to severe intensity, typically of unilateral localization, accompanied by nausea and/or urge to vomit, as well as photo- and phonophobia; it is divided into episodic (EM) and chronic (CM) depending on the number of headache days per month, whereby ≥ 15 days is taken for chronic (1). In the period from 1990 to 2021, a significant increase in the global burden of migraine was recorded; the prevalence of the disease increased by more than 58%, which corresponds to an increase in the number of cases from approximately 732 million to more than 1.16 billion, while the incidence increased by about 42%. Women have higher absolute rates of prevalence and incidence, but in men a multiple faster growth trend is recorded. The most pronounced increase in burden was observed among adolescents younger than 20 years (2). In the pathophysiology of migraine, a key role is played by activation of the trigeminovascular system and the release of calcitonin gene-related peptide (CGRP), which represents one of the main mediators of neurogenic inflammation and pain transmission (3). In the prophylactic treatment of migraine, a large number of drugs are used, among which is fremanezumab. Fremanezumab is a fully humanized monoclonal antibody that selectively blocks calcitonin gene-related peptide (CGRP), a molecule involved in the development of migraine. It has shown a favorable safety profile, including cardiovascular and cerebrovascular safety, in patients with episodic and chronic migraine (4).

AIM

To evaluate the effectiveness of fremanezumab in real-world clinical practice and to investigate whether an early therapeutic response can predict long-term treatment outcomes.

MATERIALS AND METHODS

Study design and participants

At the University Clinical Center Niš (UKC Niš), a retrospective, observational study with longitudinal follow-up was conducted, which included patients with a diagnosis of episodic (EM) or chronic migraine (CM), treated with fremanezumab in the period from August 1, 2024 to December 01, 2025. The diagnosis of migraine in the included patients was established in accordance with the valid international diagnostic criteria (ICHD-3). In these patients,

fremanezumab was administered once monthly, subcutaneously. The assessment of efficacy was performed one month after the third dose ($\approx$ 3rd month) and after the sixth dose ($\approx$ 6th month of therapy). The analysis included patients in whom complete data were available on the monthly number of headache days (MHD) and pain intensity assessed by the visual analog scale (VAS, 0–10) before the initiation of therapy, as well as after the third and sixth dose. Patients with incomplete documentation were not included in the final analysis. Data were collected from medical records and analyzed anonymously, without identification information. For the purpose of comparability with clinically relevant assessment time points, the analysis focused on baseline values, as well as values after the third and sixth dose of therapy. The study was conducted in accordance with the principles of the Declaration of Helsinki. The data were analyzed anonymously, without patient identification data. The study was conducted with the approval of the Ethics Committee of UKC Niš (number 35809) and ICMJE recommendations.

Variables and outcomes assessed

The demographic characteristics of the patients included sex, age, and type of migraine, that is, whether it was episodic or chronic migraine. The primary outcome of the study was therapeutic response, defined as a $\geq 50\%$ reduction in monthly headache days (MHD) after the sixth dose compared to baseline values. Secondary outcomes included a $\geq 75\%$ reduction in MHD after the sixth dose, the absolute change in the number of headache days, change in pain intensity assessed by the VAS scale, as well as comparison of therapeutic response between the EM and CM groups. Early therapeutic response was defined as a $\geq 50\%$ reduction in MHD after the third dose of therapy.

Statistical analysis

Descriptive statistics were presented as mean value $\pm$ standard deviation (SD) for continuous variables, and as absolute and relative frequencies for categorical variables. The normality of distribution of continuous variables was assessed using appropriate tests. For comparison of continuous variables between two independent groups (EM vs. CM), the Mann–Whitney U test was used. Changes within the same group (baseline values vs. sixth dose) were assessed using the paired t-test. Although MHD and VAS score values were lower already after the third dose, and the additional reduction was maintained after the sixth dose, for the statistical assessment

of change within the same group in this analysis, the paired t-test between baseline values and values after the sixth dose was used. For comparison of categorical variables, Fisher's exact test was applied. In order to identify independent predictors of therapeutic response ($\geq 50\%$ reduction in MHD at the sixth month), multivariate logistic regression analysis was performed. The regression model included type of migraine, age, baseline number of headache days, and early therapeutic response. The results were presented as odds ratio (OR) with a 95% confidence interval. Statistical significance was defined at the level of $p < 0.05$. Statistical data processing was performed using SPSS 20 software.

RESULTS

A total of 52 patients were included in the analysis. The mean age of the subjects was 42.29 ± 10.13 years, with a predominance of female patients (47; 90.4%), while there were 5 male patients (9.6%). Episodic migraine (EM) was present in 26 patients (50%), while 26 patients (50%) had chronic migraine (CM). The baseline number of monthly headache days was significantly higher in patients with chronic migraine compared to episodic migraine (20.46 ± 4.00 vs. 7.12 ± 2.45 days; $p < 0.001$). The baseline VAS score was also higher in the CM group (9.38 ± 0.90) compared to the EM group (8.73 ± 1.12 ; $p = 0.028$). The basic demographic and clinical characteristics of the subjects are presented in Table 1.

Table 1. Baseline characteristics of the subjects

Variable	Value
Number of patients	52
Age, years	42.29 ± 10.13
Female sex	47 (90.4%)
Male sex	5 (9.6%)
Episodic migraine	26 (50.0%)
Chronic migraine	26 (50.0%)

Number of monthly headache days at baseline (MHD)	13.79 ± 7.50
Pain intensity at baseline (VAS)	9.06 ± 1.06
Patients with adverse events	9 (17.3%)

Therapy effectiveness

After the third dose of fremanezumab, a marked reduction in monthly headache days was recorded. The mean MHD decreased from 13.79 ± 7.50 to 4.65 ± 5.73 days. The therapeutic effect remained stable during further follow-up, with a mean MHD of 4.31 ± 6.17 days after the sixth dose (paired t-test, $p < 0.001$), as shown in Figure 1. The mean VAS score decreased from 9.06 ± 1.06 to 4.54 ± 2.62 after the third dose, while after the sixth dose it was 4.65 ± 2.74 (paired t-test, $p < 0.001$), as shown in Figure 2. In both groups (EM and CM), a statistically significant improvement was recorded. The absolute reduction in MHD was more pronounced in the CM group (-13.27 ± 7.07 days) compared to the EM group (-5.69 ± 2.54 days; $p < 0.001$), which reflects the higher baseline disease burden in patients with chronic migraine.

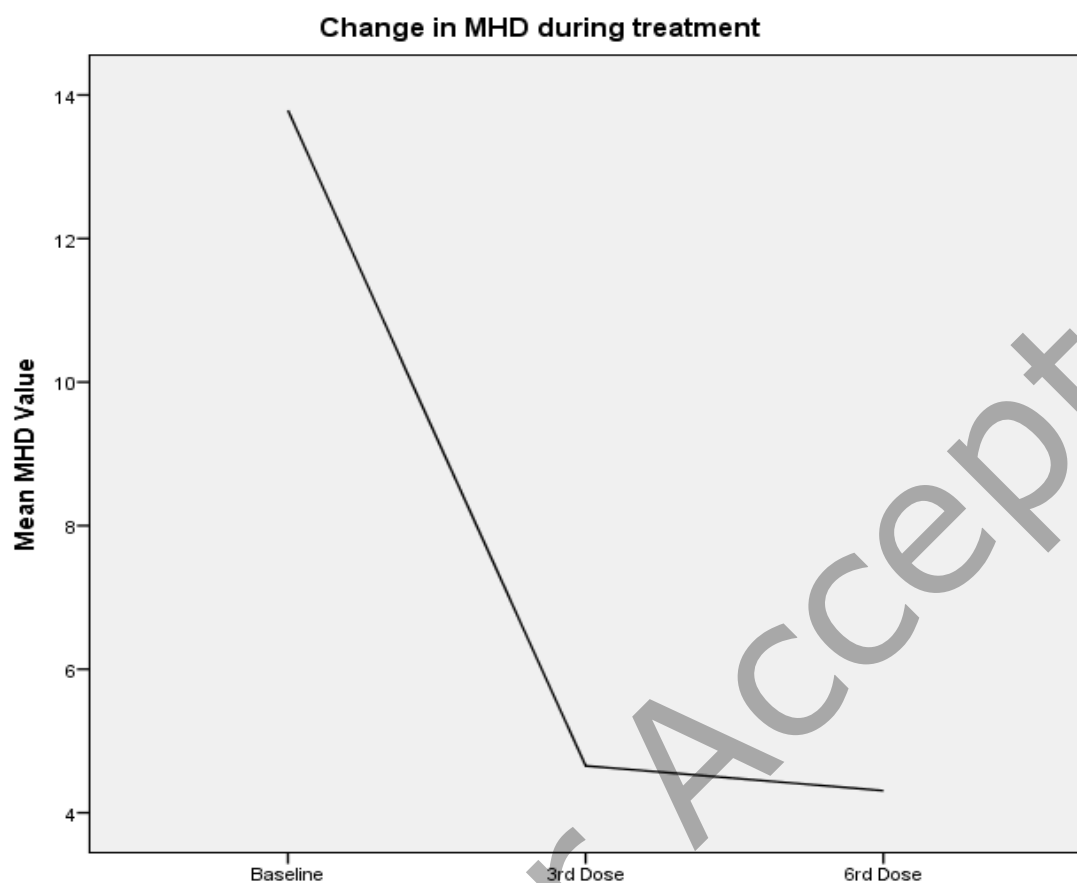


Figure 1. Change in the mean number of monthly headache days (MHD) at baseline, after the third and after the sixth dose of fremanezumab

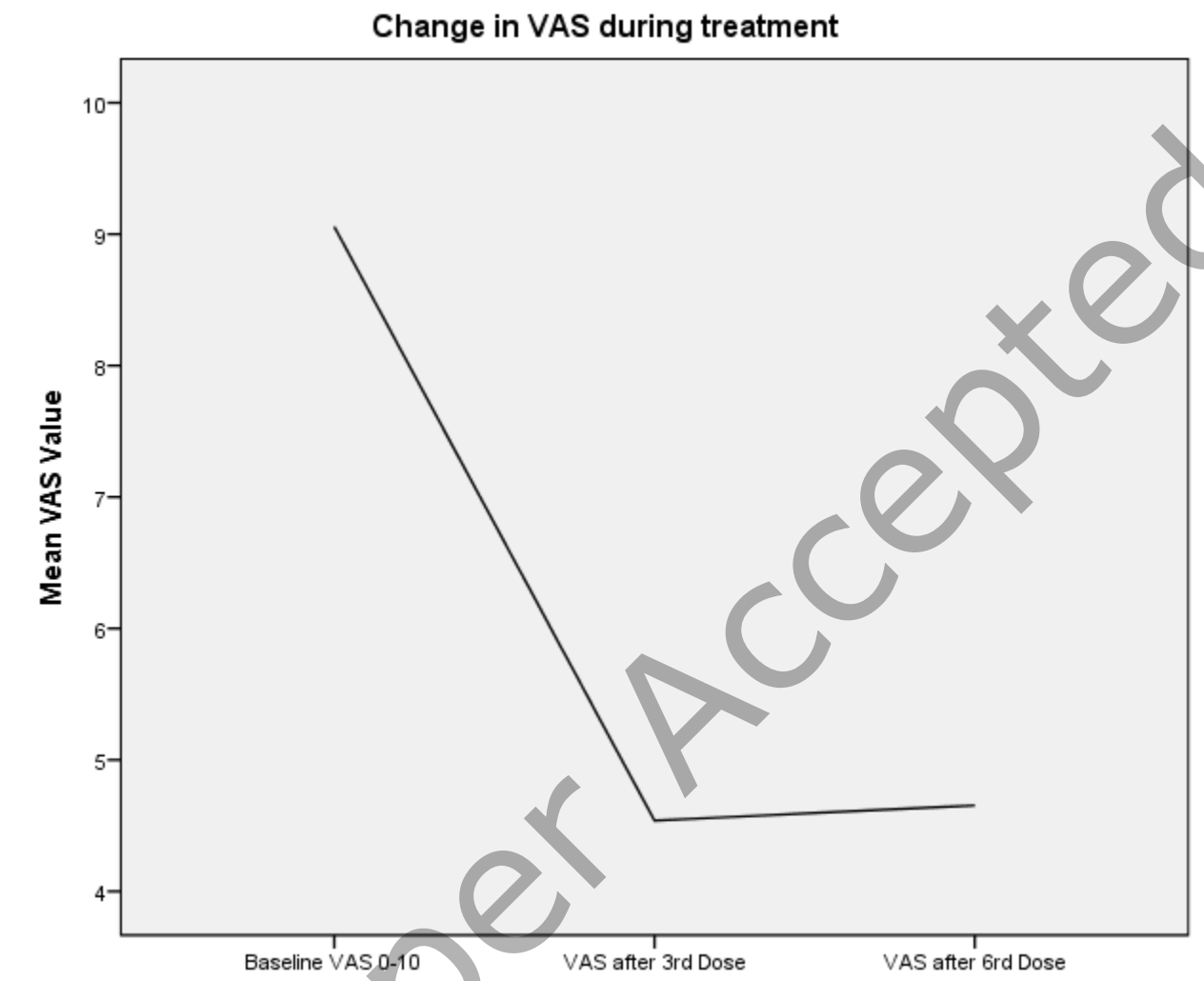


Figure 2. Change in the mean VAS value at baseline, after the third and after the sixth dose of fremanezumab

Analysis of therapeutic response

After the sixth dose, $\geq 50\%$ reduction in monthly headache days was achieved by 44 patients (84.6%). In the EM group, 24 out of 26 patients (92.3%) achieved $\geq 50\%$ reduction, while in the CM group the response was achieved in 20 out of 26 patients (76.9%). The difference between the groups was not statistically significant (Fisher's exact test, $p = 0.248$). A $\geq 75\%$ reduction in MHD was achieved by 33 patients (63.5%), without a statistically significant difference between

the EM and CM groups. These data are presented in Figure 3. To further assess the stability of the early therapeutic response, responder status at the third and sixth months was compared. Of the 44 patients who achieved a $\geq 50\%$ reduction in monthly headache days after the third dose, 41 (93.2%) remained responders at month 6, while 3 (6.8%) no longer met the response criterion. Among the 8 patients who did not achieve an early response, 3 (37.5%) subsequently achieved a $\geq 50\%$ reduction in monthly headache days by month 6, while 5 (62.5%) remained non-responders.

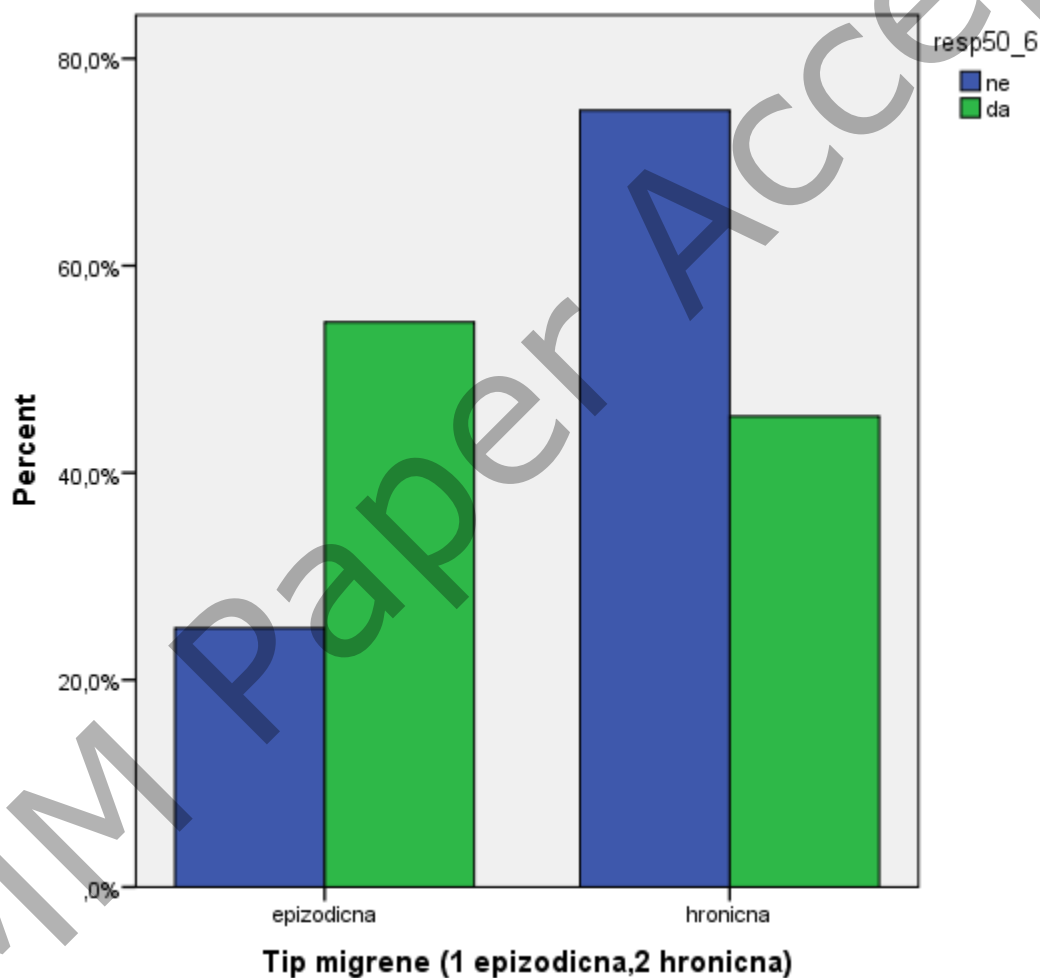


Figure 3. Proportion of patients with $\geq 50\%$ reduction in the number of monthly headache days after the sixth dose of fremanezumab in the groups with episodic and chronic migraine.

Predictors of therapeutic response

In order to identify independent predictors of $\geq 50\%$ therapeutic response at the sixth month, a multivariate logistic regression analysis was performed, as shown in Table 2.

Table 2. Multivariate logistic regression for predictors of $\geq 50\%$ therapeutic response after the 6th dose of fremanezumab.

Predictor	OR	95% CI	p
Migraine type	0.12	0.01–2.57	0.176
Age	1.05	0.93–1.19	0.447
Baseline MHD	0.93	0.78–1.11	0.425
Early therapeutic response.	28.55	2.98–273.70	0.004

The model was statistically significant ($\chi^2 = 15.23$; $df = 4$; $p = 0.004$), with Nagelkerke $R^2 = 0.44$. Early therapeutic response was the only independent predictor of long-term therapeutic success (OR = 28.55; 95% CI 2.98–273.71; $p = 0.004$). Patients who achieved $\geq 50\%$ reduction after the third dose had approximately 28 times higher likelihood of achieving therapeutic response after the sixth dose as well. Type of migraine, age, and baseline number of headache days were not statistically significant independent predictors ($p > 0.05$).

DISCUSSION

The main finding of this study is that the use of fremanezumab in real clinical practice led to a significant reduction in headache frequency and pain intensity during a six-month follow-up in patients with episodic and chronic migraine. In addition, early therapeutic response after the third dose proved to be a strong predictor of long-term therapeutic outcome. The observed effect can be explained by the mechanism of action of fremanezumab. Fremanezumab selectively binds CGRP, a key neuropeptide in migraine pathophysiology. By blocking circulating CGRP, it prevents receptor activation and inhibits pain signaling pathways (5–7). Blockade of CGRP signaling leads to a reduction in trigeminovascular activation and modulation of central sensitization, which in a

certain number of patients may result in a relatively rapid therapeutic effect. Patients who show an early response likely represent a subgroup with a more pronounced CGRP-dependent pathophysiology of migraine, which is why the therapeutic effect is more stable over time.

Preventive therapy represents a key approach in the modern treatment of migraine, whereby the development of monoclonal antibodies targeting CGRP or its receptor represents a significant therapeutic advance in the preventive treatment of migraine, enabling targeted modulation of key pathophysiological mechanisms with a favorable safety profile (8,9). In our cohort of 52 patients, fremanezumab significantly reduced headache frequency and pain intensity over six months. The mean number of monthly headache days (MHD) was reduced from 13.79 ± 7.50 to 4.31 ± 6.17 days/month ($p < 0.001$), and VAS from 9.06 ± 1.06 to 4.65 ± 2.74 ($p < 0.001$).

These results confirm the effectiveness of anti-CGRP therapy in routine practice and are consistent with the pivotal HALO studies, in which fremanezumab showed a significant reduction in monthly migraine days compared to placebo in episodic and chronic migraine; in the HALO studies, the reduction in migraine days was lower (8,9). However, it is important to emphasize that real-world analyses have reported response rates of up to 70%, although these results usually come from selected populations that completed treatment per protocol. (10).

Our results are comparable to those reported for erenumab and other anti-CGRP therapies in terms of MHD reduction, the results of our trial are in the range between the highest and lowest reductions, for example some studies report an absolute reduction of 14 days after 3 months of therapy (11), while others reported a smaller change in episodic migraine patients of 3.3 days (12). After 6 months, some showed an absolute reduction of 13 days (11,13), while others showed a reduction of only 4.3 days (14). These findings fall within a range similar to our results with fremanezumab, indicating that anti-CGRP therapy consistently reduces migraine frequency, regardless of the specific antibody, while patient heterogeneity and individual response contribute to variability of effect.

Differences from randomized trials are expected due to study design and real-world data collection (absence of placebo control), as well as heterogeneity in data collection in everyday practice. Nevertheless, the high response rate in our cohort ($\geq 50\%$ response 84.6% after the 6th dose) may reflect a combination of patient selection, good adherence, and the fact that there was

no loss to follow-up. Additionally, a small sample size may lead to greater fluctuations in percentages compared to larger multicenter real-world registries. In accordance with clinical expectations, patients with chronic migraine had a higher baseline burden (20.46 ± 4.00 vs 7.12 ± 2.45 MHD), as well as a greater absolute reduction in MHD after 6 months (13.27 ± 7.07 vs 5.69 ± 2.54 ; $p < 0.001$). This pattern is often seen in other studies, as a higher baseline headache frequency leaves more room for absolute reduction (8,9).

The key finding of this study lies in the fact that it analyzes the predictive value of early therapeutic response in real-world conditions, which is still insufficiently explored in the literature. Early therapeutic response ($\geq 50\%$ reduction in the number of headache days after the 3rd dose) was strongly associated with long-term therapeutic outcome. Patients who achieved an early therapeutic response had a significantly higher likelihood of achieving a $\geq 50\%$ response after the 6th dose (OR = 28.55; 95% CI 2.98–273.71). However, the high odds ratio value in our study requires caution in interpretation. A relatively small sample size and a small number of non-responders may lead to statistical amplification of the effect, which is reflected in the wide confidence interval. Nevertheless, from a clinical perspective, these results suggest that the assessment of therapeutic response after three months is clinically useful in everyday work. In patients without an early response, a change in therapeutic strategy may be considered. The comparison of responder status between the third and sixth months showed that the absence of an early response did not necessarily mean that treatment would be unsuccessful. Of the patients who responded early, 93.2% remained responders at month 6, while 37.5% of patients without an early response achieved a $\geq 50\%$ reduction in monthly headache days by month 6. Thus, although early response was strongly associated with response at six months, some patients may require a longer period of treatment before a clinically relevant response becomes evident.

The safety profile in our cohort was favorable; adverse events were recorded in 17.3% of patients, most commonly mild local reactions at the injection site. This is in line with published data on the tolerability of fremanezumab in clinical trials and long-term studies (8,9,15). A reduction in pain intensity on the VAS score by 4.40 points confirms that the therapeutic effect is not limited only to attack frequency, but also includes a significant alleviation of pain intensity, which has a direct impact on functionality and quality of life of patients, with similar findings also reported in other

studies (16). Improvement in quality of life is significant, considering that the global burden of migraine has shown a marked increase from 1990 to 2021, whereby although women still represent the population with a higher overall disease burden, the growth trend indicates a more rapid increase in migraine burden among men (2). Limitations of this analysis include the retrospective design, a single-center population, and potential heterogeneity in the documentation of MHD and VAS parameters in real-world conditions. Additionally, the high response rate may partly reflect the selection of patients included in therapy. In real-world studies, patients with greater motivation for treatment and better adherence to therapeutic recommendations are often included, which may influence the estimated effectiveness of therapy. Despite this, real-world data complement the results of randomized clinical studies and provide additional insight into effectiveness and predictors of response in everyday clinical practice.

CONCLUSION

In conclusion, our results indicate that fremanezumab represents an effective and well-tolerated therapeutic option in real clinical practice, whereby early therapeutic response may have significant prognostic value and practical application in treatment decision-making, which should be confirmed in larger prospective studies.

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