

Efficacy and Safety of Fremanezumab in the Preventive Treatment of Migraine: A Systematic Review of Randomized Clinical Trials

Eficácia e Segurança do Fremanezumabe para o Tratamento Preventivo da Migrânea: Uma Revisão Sistemática de Ensaios Clínicos Randomizados

Letícia Gomes Fonseca¹ , Norma Rafaella Uchôa Espíndola² , Nathália Carvalho Figuerêdo³ , Larissa Cahú da Silva Falcão³ , Wagner Gonçalves Horta⁴ 

¹Faculdade Pernambucana de Saúde, Recife, Pernambuco, Brazil, Medical Student;

²Centro Universitário Maurício de Nassau, Recife, Pernambuco, Brazil, Medical Student;

³Universidade Católica de Pernambuco, Recife, Pernambuco, Brazil, Medical Student;

⁴Hospital Universitário Oswaldo Cruz, Recife, Pernambuco, Brazil, PhD, Department of Neurology

ABSTRACT

Context: Migraine is a highly prevalent and disabling neurological condition, affecting approximately one billion people worldwide. It is the second most common type of primary headache. Among the existing therapeutic options, many demonstrate limited efficacy and significant side effects. Fremanezumab, a monoclonal antibody that selectively blocks CGRP, has been studied as a promising alternative for migraine prevention, as it acts directly on the pathophysiological mechanisms of the disease.

Objective: This systematic review aims to gather and analyze the results of randomized clinical trials evaluating the efficacy and safety of fremanezumab as a prophylactic strategy for migraine in adults.

Methods: Searches were conducted in the PubMed, Cochrane CENTRAL, and LILACS databases, covering publications from 2015 to 2025 in English, Portuguese, or Spanish. After independent and double-blinded screening of 511 records, 3 randomized clinical trials were included.

Results: In all analyzed studies, fremanezumab demonstrated superiority over placebo, with reductions ranging from 3.7 to 4.6 headache days per month and higher response rates ($\geq 50\%$ reduction), observed in up to 41% of treated patients. The most common adverse events were injection site reactions and nasopharyngitis, which were generally mild. The included studies showed good methodological quality and demonstrated benefits of fremanezumab in both treatment-responsive and treatment-refractory patients.

Conclusion: Fremanezumab appears to be an effective and safe option for the prophylaxis of episodic and chronic migraine. Nonetheless, longer-duration studies with more diverse populations and economic evaluations are needed to support its widespread, evidence-based adoption in clinical practice.

Keywords: Migraine, Fremanezumab, Monoclonal antibodies, Preventive treatment.

RESUMO

Contexto: A migrânea é uma condição neurológica altamente prevalente e incapacitante, afetando aproximadamente um bilhão de pessoas em todo o mundo. É o segundo tipo mais comum de cefaleia primária. Entre as opções terapêuticas existentes, muitas demonstram eficácia limitada e efeitos colaterais significativos. O fremanezumabe, um anticorpo monoclonal que bloqueia seletivamente o CGRP, tem sido estudado como uma alternativa promissora para a prevenção da migrânea, pois atua diretamente nos mecanismos fisiopatológicos da doença.

Objetivo: Esta revisão sistemática tem como objetivo reunir e analisar os resultados de ensaios clínicos randomizados que avaliaram a eficácia e a segurança do fremanezumabe como estratégia profilática para a migrânea em adultos. Métodos: As buscas foram realizadas nas bases PubMed, Cochrane CENTRAL e LILACS, abrangendo publicações de 2015 a 2025 em inglês, português ou espanhol. Após triagem independente e em duplo-cego de 511 registros, 3 ensaios clínicos randomizados foram incluídos.

Resultados: Em todos os estudos analisados, o fremanezumabe demonstrou superioridade em relação ao placebo, com reduções variando de 3,7 a 4,6 dias de cefaleia por mês e maiores taxas de resposta ($\geq 50\%$ de redução), observadas em até 41% dos pacientes tratados. Os eventos adversos mais comuns foram reações no local da injeção e nasofaringite, geralmente leves. Os estudos incluídos apresentaram boa qualidade metodológica e demonstraram benefícios do fremanezumabe tanto em pacientes responsivos ao tratamento quanto em refratários.

Conclusão: O fremanezumabe parece ser uma opção eficaz e segura para a profilaxia da migrânea episódica e crônica. No entanto, são necessários estudos de maior duração, com populações mais diversas e avaliações econômicas, para sustentar sua adoção ampla baseada em evidências na prática clínica.

Palavras-chave: Migrânea; Fremanezumabe; Anticorpos monoclonais; Tratamento preventivo.

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Corresponding author: Letícia Gomes Fonseca
letigfonsecaa@gmail.com

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Authors contribution:

Letícia Gomes Fonseca: conceptualization, data acquisition, interpretation, writing.

Norma Rafaella Uchôa Espíndola: conceptualization, data acquisition, interpretation, writing.

Larissa Cahú da Silva Falcão: data acquisition, writing.

Nathália Carvalho Figuerêdo: interpretation, writing.

Wagner Gonçalves Horta: manuscript revision.

INTRODUCTION

Migraine is a highly prevalent neurological condition and the third leading cause of disability worldwide. It is the second most common type of primary headache, with a higher prevalence among women aged 25 to 55 years, and is estimated to affect approximately one billion people globally¹⁻³. Classically, it is defined as a unilateral headache with a pulsating quality and moderate to severe intensity, often worsened by physical activity and lasting from 4 to 72 hours. It is typically associated with symptoms such as nausea, photophobia, and phonophobia, and may be accompanied or not by aura—fully reversible focal neurological symptoms that precede or accompany the headache. Visual symptoms are the most common, followed by sensory and language disturbances²⁻⁴. A prodromal phase may occur hours or days before the onset of pain, presenting symptoms such as fatigue, agitation, depression, nausea, and cravings for specific foods; these same symptoms may persist after the headache resolves²⁻⁵. Migraine can also be classified based on the frequency of attacks into episodic migraine, defined as fewer than 15 headache days per month, and chronic migraine, defined as 15 or more headache days per month, with at least 8 days presenting migraine features^{2,6}.

The pathophysiological basis of migraine involves alterations in the trigeminovascular system. This occurs through the release of vasoactive neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP), nitric oxide, and glutamate, which promote vasodilation and neurogenic inflammation^{3,7,8}. CGRP is a protein that plays a key role in the activation of meningeal and vascular nociceptors, as well as in the central and peripheral sensitization mechanisms implicated in the perpetuation of pain⁸⁻¹⁰. In a double-blind crossover study, intravenous infusion of CGRP was shown to trigger migraine attacks in patients, and other evidence has demonstrated elevated levels of this peptide in the peripheral blood of individuals with chronic migraine, underscoring its fundamental role in disease development^{10,11}. This pathophysiology is closely linked to environmental, hormonal, and genetic factors. Several elements may act as triggers for migraine attacks, including emotional stress, sleep disturbances, specific foods, and odors. These aspects must also be addressed during treatment to achieve adequate control of migraine episodes^{12,13}.

Preventive treatment is recommended for individuals with a well-established diagnosis of episodic or chronic migraine who experience four or more migraine attacks per month or debilitating symptoms. Commonly used conventional therapies include antidepressants, beta-blockers, anticonvulsants, and calcium channel blockers—medications not specifically developed for migraine treatment and which therefore do not target disease-specific mechanisms. As a result, these treatments often have a high side effect profile and limited efficacy, leading

to poor adherence¹⁴⁻¹⁷. In this context, new drug classes targeting the pathophysiology of migraine have gained prominence in recent years, particularly monoclonal antibodies directed against CGRP or its receptor^{18,19}. Fremanezumab is a humanized monoclonal antibody that selectively inhibits CGRP. It is administered subcutaneously and is available in two dosing regimens: 225 mg monthly or 675 mg quarterly. This medication has been evaluated in several clinical trials as a preventive agent for both episodic and chronic migraine. Its efficacy, safety, and tolerability have been the primary outcomes investigated in both short- and long-term studies^{14-16,20}.

Despite the growing relevance of the topic and the development of robust clinical trials showing promising results regarding the efficacy and safety of fremanezumab, there is still a lack of systematic reviews that critically and comprehensively synthesize the available evidence. Furthermore, many existing analyses assess fremanezumab in conjunction with other monoclonal antibodies, which hinders the interpretation of its isolated effects^{9,21,22}. In light of this scenario, the objective of this systematic review is to gather and analyze, based on the best available scientific evidence, the results of randomized clinical trials that evaluate the efficacy and safety of fremanezumab as a prophylactic strategy for migraine in adults.

METHODS

This systematic review followed the PRISMA 2020 guidelines. The research question was structured using the PICO model, considering adults with episodic or chronic migraine treated with fremanezumab, compared to placebo or other preventive therapies (figure 1). The outcomes evaluated were efficacy (reduction in the number of migraine days) and safety (adverse events).

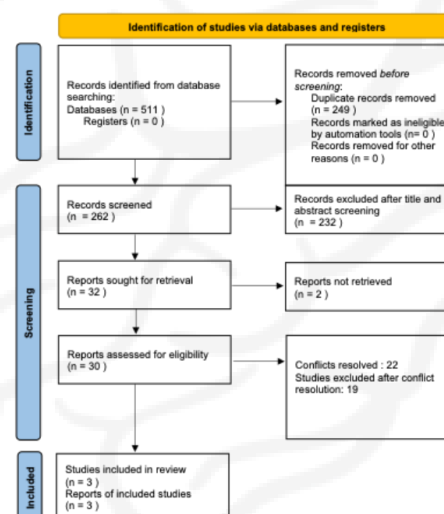


Figure 1 - PRISMA flow diagram of the study selection process for the systematic review.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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Searches were conducted in the PubMed, Cochrane CENTRAL, and LILACS databases, covering articles published between 2015 and 2025 in English, Portuguese, or Spanish. The search strategies combined descriptors related to migraine, fremanezumab, prevention, efficacy, and safety. The results were organized and analyzed using the Rayyan QCRI platform.

Randomized clinical trials providing quantitative data on efficacy and/or safety were included. Studies involving pediatric populations, other forms of headache, or lacking relevant data for the proposed outcomes were excluded.

Screening was performed independently and in a blinded fashion by two reviewers. Initially, 511 articles were identified, of which 344 were duplicates. After resolving the duplicate cases, 249 articles were definitively excluded and 262 records were screened, of these, 30 articles were assessed for eligibility. Among them, 22 presented conflicts during the selection process, which were resolved by the reviewers, resulting in the final inclusion of 3 studies. Extracted data included methodological characteristics, population, interventions, comparators, and relevant outcomes.

For the selected studies, the risk of bias was assessed by two independent reviewers using the Risk of Bias 2 (RoB 2) tool for randomized trials, developed by Cochrane.

RESULTS

This systematic review analyzed three randomized, double-blind, placebo-controlled clinical trials. All included studies had as their primary outcome the assessment of fremanezumab's efficacy in migraine prevention, defined as the reduction in the number of monthly migraine headache days (table 1).

Table 1 – Results of clinical trials included in the systematic review.

Study (Author, Year)	Population	Intervention	Comparator	Primary outcome	Results (mean reduction in headache days/month)	Response $\geq 50\%$	Adverse events	Risk of bias (Evaluated with the RoB 2 tool)
Ferrari et al., 2019 (FOCUS)	N = 838, chronic or episodic migraine, failure of 2 up to 4 preventives	Monthly (225 mg for EM or 675 + 225 mg for CM) or quarterly (675 mg) fremanezumab	Placebo	Reduction in migraine-type headache days	-4.1 (monthly), -3.7 (quarterly), -0.6 (placebo)	34% (monthly and quarterly), 9% (placebo)	55% (quarterly), 45% (monthly), 48% (placebo); severe: ~1% per group	Low risk
Silberstein et al., 2017 (HALO CM)	N = 1130, chronic migraine, 21-year history	Fremanezumab monthly or quarterly	Placebo	Reduction in migraine-type headache days	-4.6 (monthly), -4.3 (quarterly), -2.5 (placebo)	41% (monthly), 38% (quarterly), 18% (placebo)	71% (monthly), 70% (quarterly), 64% (placebo)	Low risk
Sakai et al., 2021	N = 571, chronic migraine (Japan/South Korea)	Fremanezumab monthly and quarterly	Placebo	Reduction in migraine-type headache days	-4.1 (monthly and quarterly), -2.4 (placebo)	29% (fremanezumab), 13% (placebo)	29.3–32.1% (fremanezumab), 28.3% (placebo)	Low risk

* Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898

The FOCUS study (Ferrari et al., 2019) was a phase 3B, multicenter trial conducted across 14 countries, aiming to evaluate fremanezumab's efficacy in patients with a documented failure to respond to other preventive migraine medications. The study included 838 participants aged 18 to 70 years with a diagnosis of episodic or chronic

migraine who met the inclusion criteria of having failed 2 to 4 preventive therapies in the past 10 years; 84% of them were women. The study compared quarterly subcutaneous fremanezumab (675 mg) and monthly dosing (225 mg monthly for episodic migraine and 675 mg loading dose + 225 mg monthly for chronic migraine) against placebo over a 12-week period. The primary outcome showed a mean reduction in migraine days of 4.1 days in the monthly group, 3.7 days in the quarterly group, and 0.6 days in the placebo group ($p < 0.0001$). A $\geq 50\%$ response rate was observed in 34% of fremanezumab-treated patients compared to 9% in the placebo group.

The HALO CM study (Silberstein et al., 2017) was a phase 3 multinational study focused on evaluating fremanezumab's efficacy in chronic migraine. It included 1,130 participants, 88% of whom were women, with a diagnosis of chronic migraine and at least a one-year history of the condition. Over 12 weeks, participants were randomized to receive monthly, quarterly, or placebo injections. Results showed a monthly reduction in headache days of 4.6 in the monthly group, 4.3 in the quarterly group, and 2.5 in the placebo group ($p < 0.001$). A $\geq 50\%$ reduction in headache days was achieved in 38% of the quarterly group and 41% of the monthly group, compared to 18% of the placebo group.

In the study by Sakai et al. (2021), conducted in Japan and South Korea, 571 patients with chronic migraine were evaluated over 12 weeks, comparing monthly and quarterly fremanezumab regimens with placebo in an Asian population. Results showed a reduction of 1.7 migraine days per month in both treatment groups compared to placebo ($p < 0.001$). A $\geq 50\%$ response rate was observed in 29% of patients in the fremanezumab group versus 13% in the placebo group. Secondary outcomes such as reduced use of acute medications and improvements in headache-related disability (Headache Impact Test scores) were also observed.

All three studies assessed the safety of fremanezumab through adverse event monitoring. The most common side effects were injection site reactions (e.g., erythema, induration) and nasopharyngitis, while serious adverse events or treatment discontinuations were rare. In the FOCUS study, adverse events occurred in 55% of the quarterly group, 45% of the monthly group, and 48% of the placebo group. Serious adverse events were reported in about 1% of participants in each group and were not treatment-related. In the HALO study, adverse events occurred in 70% of the quarterly group, 71% of the monthly group, and 64% of the placebo group. In the Asian study, adverse events occurred in 29.3% and 32.1% of the fremanezumab groups, compared to 28.3% in the placebo group.

All studies were assessed for risk of bias using the Cochrane RoB 2 tool, which evaluates randomization, deviations from intended interventions, missing data, outcome measurement, and selective reporting. All three

included trials demonstrated a low risk of bias across all domains, resulting in an overall low risk of bias.

DISCUSSION

This systematic review gathered evidence from randomized clinical trials evaluating the efficacy and safety of fremanezumab in the prevention of episodic and chronic migraine. The included studies had strong methodological designs, with proper randomization, double-blind procedures, and placebo control, as well as a low overall risk of bias, enhancing the reliability of the findings. A consistent and significant reduction in the number of migraine days was observed, along with a clinically meaningful proportion of patients achieving a $\geq 50\%$ response rate.

However, most trials only assessed a relatively short treatment duration (12 weeks), limiting insights into long-term efficacy and safety. Moreover, there was limited reporting on subgroups with multiple comorbidities, such as psychiatric or cardiovascular conditions, which restricts the generalizability of findings to more complex clinical scenarios.

Comparison among the studies revealed generally consistent results, with some noteworthy differences. The HALO CM study (Silberstein et al., 2017) reported the most substantial reductions in monthly migraine frequency, especially in the monthly dosing group, which achieved a $\geq 50\%$ response rate in 41% of participants. The FOCUS study (Ferrari et al., 2019), which included patients with prior therapeutic failures to multiple prophylactic drug classes, demonstrated significant benefits even in treatment-refractory individuals, highlighting fremanezumab's potential in more challenging clinical contexts. Conversely, the study by Sakai et al. (2021) in an Asian population showed more modest reductions in migraine days, although still statistically significant. These differences may reflect pharmacogenomic factors, cultural variations in symptom perception and reporting, or divergent clinical profiles of the participants.

Nonetheless, all studies agreed on the good tolerability of fremanezumab, with mild adverse events and very low discontinuation rates.

Despite the promising findings, several critical gaps remain. The lack of follow-up beyond three months hinders assessment of the durability of therapeutic effects and long-term safety—both vital aspects given the chronic and disabling nature of migraine. Additionally, the cost-effectiveness of fremanezumab in various healthcare systems, especially in resource-limited settings, remains uncertain. Future research should include direct comparisons with other anti-CGRP monoclonal antibodies and conventional preventive treatments to better define patient profiles most likely to benefit. Studies with more diverse populations, patient-centered outcomes (e.g., quality of life, productivity, and functionality), and robust

pharmacoeconomic evaluations will be essential to guide clinical and policy decisions based on evidence.

CONCLUSION

The findings of this systematic review reinforce that fremanezumab is an effective and safe alternative for the prophylaxis of both episodic and chronic migraine. The analyzed studies demonstrated clinically significant reductions in migraine frequency and a considerable proportion of patients achieving satisfactory response rates—even among those with a history of therapeutic failure. Its targeted mechanism of action on CGRP, subcutaneous administration route, and low incidence of serious adverse events contribute to a promising therapeutic profile compared to conventional treatments.

Nevertheless, caution is warranted when generalizing the results. Most trials had limited follow-up durations and predominantly female, homogeneous populations, limiting extrapolation to more diverse clinical contexts. Therefore, there is a clear need for future studies assessing long-term use of fremanezumab, its effectiveness in specific subgroups, and its cost-effectiveness in different healthcare settings.

In summary, fremanezumab stands out as a valuable therapeutic innovation for preventive migraine management, particularly in patients who do not respond to or tolerate first-line treatments. However, its full integration into clinical practice should be guided by future evidence that expands its applicability, safety, and real-world feasibility.

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