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EFFICACY OF ANTI-CGRP MONOCLONAL ANTIBODIES IN CHRONIC MIGRAINE

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Abstract

Chronic migraine (CM) poses significant challenges in management, particularly among patients unresponsive to conventional preventive therapies. This randomized, double-blind, placebo-controlled trial evaluated the efficacy of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) in adults with treatment-resistant CM. A total of 200 participants were included in this study to receive monthly subcutaneous injections of either anti-CGRP mAbs (erenumab, galcanezumab, or fremanezumab) or placebo over a 12-month period. The primary endpoint was the change in monthly migraine days (MMDs) from baseline to month 12. Secondary outcomes included ≥50% reduction in MMDs, changes in Migraine Disability Assessment (MIDAS) scores, and acute medication usage. The anti-CGRP mAb group demonstrated a significant reduction in MMDs (mean decrease: 11.9 days) compared to placebo (mean decrease: 7.6 days), with a mean difference of 4.3 days (95% CI: 2.1–6.5; $p<0.001$). Additionally, 65% of patients in the treatment group achieved a ≥50% reduction in MMDs versus 35% in the placebo group ($p<0.001$). MIDAS scores improved significantly in the treatment group, indicating reduced migraine-related disability. No severe adverse events were reported. These findings underscore the superior efficacy of anti-CGRP mAbs in reducing migraine frequency and disability among patients with refractory CM, highlighting their potential as a transformative therapeutic option in this population.

Keywords: Chronic migraine, anti-CGRP monoclonal antibodies, randomized controlled trial

Introduction

Chronic migraine (CM) is a debilitating neurological disorder characterized by headaches occurring on 15 or more days per month for more than three months, with at least eight days per month meeting criteria for migraine without aura. The condition significantly impairs quality of life and imposes substantial socioeconomic burdens. Traditional preventive treatments, including beta-blockers, anticonvulsants, and antidepressants, often yield suboptimal responses and are associated with adverse effects, leading to poor adherence and persistence.[1-3]

The pathophysiology of migraine involves the activation of the trigeminovascular system and the release of neuropeptides, notably calcitonin gene-related peptide (CGRP), which plays a pivotal role in migraine pathogenesis by promoting vasodilation and neurogenic inflammation. Elevated levels of CGRP have been observed during migraine attacks, and its infusion can induce migraine-like headaches in susceptible individuals.[4-6]

Advancements in understanding migraine biology have led to the development of targeted therapies, particularly monoclonal antibodies (mAbs) against CGRP or its receptor. These agents offer several advantages over traditional preventives, including specificity, favorable pharmacokinetics, and a reduced risk of systemic side effects due to their limited central nervous system penetration and minimal hepatic metabolism. Clinical trials have demonstrated the efficacy of anti-CGRP mAbs in reducing migraine frequency and improving patient-reported outcomes in both episodic and chronic migraine populations.[7-8]

Despite these promising results, there remains a need to evaluate the long-term efficacy and safety of anti-CGRP mAbs in real-world settings, particularly among patients with treatment-resistant CM. This study aims to address this gap by conducting a randomized, double-blind, placebo-controlled trial to assess the efficacy of anti-CGRP mAbs in reducing migraine frequency and disability in a population of adults with refractory CM.[9-10]

Methodology

This case control study was conducted over 12 months at King Edward Medical University in association multiple tertiary centres. The study protocol was approved by the institutional review boards of all participating centers, and verbal informed consent was obtained from all participants prior to enrollment.

Participants aged 18 to 65 years with a diagnosis of CM, as defined by the International Classification of Headache Disorders, 3rd edition (ICHD-3), and a history of inadequate response to at least two classes of preventive migraine medications were eligible for inclusion. Exclusion criteria included the presence of other significant neurological or psychiatric disorders, pregnancy or lactation, and use of other investigational drugs within 30 days prior to enrollment.

Sample size calculation was performed using Epi Info software, assuming a 30% difference in the proportion of patients achieving a ≥50% reduction in MMDs between the treatment and placebo groups, with a power of 80% and a two-sided alpha of 0.05. This yielded a required sample size of 90 participants per group, which was increased to 100 per group to account for potential dropouts.

Participants were randomized in a 1:1 ratio to receive monthly subcutaneous injections of either anti-CGRP mAbs (erenumab 70 mg, galcanezumab 120 mg, or fremanezumab 225 mg) or placebo. Randomization was stratified by center and baseline MMDs. Participants maintained headache diaries to record the frequency and severity of headaches, as well as acute medication usage.

The primary outcome was the change in MMDs from baseline to month 12. Secondary outcomes included the proportion of patients achieving a ≥50% reduction in MMDs, changes in MIDAS scores, and the frequency of acute medication use. Safety assessments included monitoring for adverse events, vital signs, and laboratory parameters.

Data were analyzed using intention-to-treat principles. Continuous variables were compared using independent t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were compared using chi-square or Fisher's exact tests. A p-value of <0.05 was considered statistically significant.

Results

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Anti-CGRP mAb Group (n=100)	Placebo Group (n=100)	p-value
Age (years), mean ± SD	45.2 ± 10.3	44.8 ± 9.7	0.72
Female, n (%)	84 (84%)	82 (82%)	0.68
Duration of CM (years)	7.5 ± 3.2	7.8 ± 3.5	0.56
Baseline MMDs, mean ± SD	20.1 ± 3.5	19.8 ± 3.7	0.48
Baseline MIDAS score	65.4 ± 12.7	64.9 ± 13.1	0.74

Table 2: Primary and Secondary Outcomes at Month 12

Outcome	Anti-CGRP mAb Group	Placebo Group	Mean Difference (95% CI)	p-value
Change in MMDs, mean ± SD	-11.9 ± 4.2	-7.6 ± 3.9	-4.3 (-6.5 to -2.1)	<0.001
≥50% reduction in MMDs, n (%)	65 (65%)	35 (35%)		<0.001
Change in MIDAS score, mean ± SD	-30.2 ± 10.5	-18.7 ± 9.8	-11.5 (-14.2 to -8.8)	<0.001
Reduction in acute medication use (%)	58%	32%		<0.001

Table 3: Adverse Events

Adverse Event	Anti-CGRP mAb Group (n=100)	Placebo Group (n=100)	p-value
Injection site reactions	12 (12%)	10 (10%)	0.65
Constipation	8 (8%)	6 (6%)	0.58
Fatigue	5 (5%)	4 (4%)	0.73
Serious adverse events	0 (0%)	0 (0%)	-

Explanation: The anti-CGRP mAb group exhibited a significantly greater reduction in MMDs and MIDAS scores compared to placebo. A higher proportion of patients achieved a ≥50% reduction in MMDs, and there was a notable decrease in acute medication usage. Adverse events were mild and comparable between groups.

Discussion

The findings of this randomized controlled trial demonstrate the superior efficacy of anti-CGRP monoclonal antibodies in reducing migraine frequency and associated disability among patients with treatment-resistant chronic migraine. The significant reduction in monthly migraine days and improvement in MIDAS scores highlight the therapeutic potential of these agents in a population that has historically been challenging to treat.[11-12]

Previous studies have established the role of CGRP in migraine pathophysiology and the efficacy of anti-CGRP mAbs in episodic migraine. However, data on their effectiveness in chronic migraine, particularly among patients unresponsive to traditional preventives, have been limited. This study addresses this gap by providing robust evidence supporting the use of anti-CGRP mAbs in this subset of patients.[13-14]

The observed ≥50% response rate in 65% of patients aligns with findings from other clinical trials and real-world studies, suggesting consistent benefits across diverse populations. The significant reduction in acute medication usage further underscores the impact of these agents in decreasing

reliance on symptomatic treatments, which is particularly relevant given the risk of medication overuse headache in chronic migraine patients.[15-17]

Safety profiles were favorable, with no serious adverse events reported and a low incidence of mild side effects. This aligns with existing literature indicating the tolerability of anti-CGRP mAbs, making them a viable option for long-term management.[18]

One of the strengths of this study is the rigorous methodology, including randomized allocation, double-blinding, and the use of validated outcome measures. The inclusion of a well-defined, treatment-resistant population enhances the generalizability of the findings to clinical practice.

However, certain limitations should be acknowledged. The study's duration, while sufficient to assess efficacy, may not capture long-term safety and sustained effectiveness. Additionally, the exclusion of patients with significant comorbidities may limit the applicability of results to broader patient populations.[19]

Future research should focus on long-term outcomes, cost-effectiveness analyses, and comparative studies with other preventive treatments to further delineate the role of anti-CGRP mAbs in chronic migraine management. [20]

Conclusion

Anti-CGRP monoclonal antibodies significantly reduce migraine frequency and disability in patients with treatment-resistant chronic migraine, offering a promising therapeutic option for this challenging population. This study fills a critical gap in the literature by providing high-quality evidence of efficacy and safety in a real-world setting. Future studies should explore long-term outcomes

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