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EFFICACY OF ANTI-CGRP MONOCLONAL ANTIBODIES IN CHRONIC MIGRAINE

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ABSTRACT:
Background: Chronic migraine is an incapacitating neurological condition whose reaction toward standard prophylactic medicine is not very sufficient in a significant proportion of circumstances. Recently, monoclonal antibodies and CGRP have been identified as targeted therapy of migraine prophylaxis.
Objective: The current cross-sectional study aimed to evaluate efficacy of anti-CGRP monoclonal antibody in patients with chronic migraine.
Method: Cross-sectional study design was used to recruit 105 participants suffering from chronic migraine. Participants described 4 or more migraine attacks per month and exhibited previous failure of at least one prophylactic agent. Patients used either one of the four anti-CGRP anti-bodies that have been approved by FDA, for a period of 12 months. The main outcome consisted of alteration in monthly migraine days (MMDs). Secondary outcomes enclosed changes in MIDAS and HIT-6 results, acute medication use results, and patient satisfaction. Post- and pre-treatment comparisons were done by using paired t- tests.
Results: Mean age of participants was found to be 38.9 $\pm$ 8.8 years, with 71.4% females. Significant improvement in the mean migration-related disability scores (MMDs) after three months of treatment ($p < 0.001$) was recorded having reduced to 7.4 $\pm$ 2.9 as compared to 14.2 $\pm$ 3.1 at baseline. The MMDs decreased by 50% or more among 65.7% of the participants. MIDAS score was reduced from 32.5 + 8.4 to 17.6 $\pm$ 6.3 and the HIT-6 score decreased from 65.9 $\pm$ 5.2 to 58.3 $\pm$ 4.7 ($p < 0.001$). There was a reduction in acute exposure to medication (8.9 $\pm$ 3.0 to 4.3 $\pm$ 2.2 days/month) ($p < 0.001$). Lastly, 59 percent of sample demonstrated high satisfaction with the treatment plan.
Conclusion: Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies have proven to be effective in the reduction of migraine recurrence, functional impairment, and analgesic treatment in patients with chronic migraine.

Keywords: Chronic Migraine, CGRP, Effectiveness, Monoclonal Antibodies, Prophylaxis.

INTRODUCTION:

Migraine is a disabling and complex neurological condition with immediate personal and economic impacts on someone suffering it and with large population prevalence and years lived with disability costs globally in individuals under 50 years of age (1, 2). Chronic migraine (CM) is one of the more problematic subtypes of migraine, being described as persistent headaches that last 15 or more days

a month over a time span of at least three months, eight of which must meet typical criteria of migraine (3). Chronic migraine has severe symptomatic and functional impairment in patients with both physical, emotional, and occupational spheres, hence causing huge personal, societal, and economic costs (4).

The use of acute and preventive measures are currently the current management strategies of chronic migraine. Various standard prophylactic pharmaceuticals have been tested: beta-adrenergic blockers (e.g. propranolol), antiepileptic (e.g. topiramate, valproic acid), tricyclic antidepressants (e.g. amitriptyline), calcium channel blockers (e.g. flunarizine) with varied success (5, 6). It is important to note that these drugs were initially developed to treat a variety of different conditions and afterward modified to the use in migraine prophylaxis, which is why there is a rather low effectiveness and adherence, inability to tolerate and use them efficiently. Empirical evidence has demonstrated that about 80 % of patients abandon conventional prophylaxis before a year has ended, mainly due to adverse events or inadequate relief (7).

Recent developments in migraine pathogenesis have found the calcitonin gene-related peptide (CGRP) as the main neuropeptide pointing out a key mechanism in the process of migraine attacks (8). CGRP is said to be an active substance that gets released during migraine conditions and triggers vasodilation, neurogenic inflammation, and nociceptive transmission through trigeminovascular system (9). The discovery has also acted as a launching pad to the development of a new generation of monoclonal antibodies (mAbs), which prevent the activity of CGRP (ligand blockers) or bind to its receptor (receptor blockers), which offers a more precise line of defense (10).

Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies that are currently approved are as follows: erenumab (CGRP receptor antagonist) and fremanezumab, galcanezumab and eptinezumab (CGRP ligand blockers) (11). They are injected either subcutaneously or intravenously and the dosage is done monthly or quarterly (12). Anti-CGRP monoclonal antibodies do not use the hepatic or renal metabolic path; therefore, they do not penetrate the blood-brain-barrier, thus leading to fewer drug-to-drug interactions and a relatively more favorable safety profile compared to other traditional preventive therapies (13). It has been shown clinically that these agents are useful in reducing monthly migraine days (MMDs), as well as positively affecting health-related quality of life; they have also shown capabilities of reducing reliance on acute medications, but have mostly been used only in treatment-refractory patients, who are unable to respond to at least one or more classes of conventional prophylactic medication (14).

This overview presents a review of the extant evidence on anti-CGRP monoclonal antibodies efficacy, safety, and clinical use in chronic migraine, especially with a focus on patients with more than four MMDs who did not respond to conventional prophylactic treatment. A full picture of these new agents can guide clinicians in the best way to provide care to a population that has long fallen below the threshold on emerging treatment models.

METHODOLOGY:

Design:

This was a cross-sectional, observational research, which aimed at determining the effectiveness of the anti-CGRP monoclonal antibodies in the treatment of patients with chronic migraine. The study was carried out between [May 24 to March 2025] in outpatient department (OPD) belonging to tertiary care hospitals.

Sampling Technique:

A non-probability purposive sampling method was also adopted to recruit the participants. Eligible patients met requirements of the diagnostic criteria of chronic migraine through the ICHD-3 (15) and simultaneously were already taking one of the four Food and Drug Administration-approved anti-CGRP monoclonal antibodies: Erenumab, Fremanezumab, Galcanezumab, or Eptinezumab within 3 months.

Sample Size Calculation:
To determine the sample size a cross-sectional study sample-size formula was used (16) ; a total of 105 patients were included considering a 10 % non-response /exclusion rate.
$n = Z^2 * p * (1-p) / d^2$
The confidence interval was set at 95%.

Inclusion Criteria:
1. Adults aged 18 to 65 years, ability to meet the diagnostic criteria of chronic migraine (15).
2. Predicates of 4 or more migraine attacks per month,
3. History of poor tolerance toward at least one of the available conventional prophylaxis agents (e.g., beta-blockers, antiepileptic, tricyclic antidepressants) (17), and
4. 3 months or more of progressive use of anti-CGRP monoclonal antibody drugs.

Exclusion Criteria:
1. Participants with episodic migraine,
2. Simultaneous use of botulinum toxin, known contra-indication to anti-CGRP monoclonal antibodies,
3. Pregnancy/ breastfeeding and
4. Significant psychiatric disorders, cognitive impairment that would hinder the assessment were all exclusion criteria.

Outcome Measures:
- The main/primary outcome measure was the percent of patients who experienced a 50% or more decrease in monthly migraine days (MMDs) post 3 months anti-CGRP.
- Secondary outcome measures were modifications in Migraine Disability Assessment (MIDAS) score (18), Headache Impact Test-6 (HIT-6) score (19), decrease in acute medication, and treatment satisfaction as reported by the patients on a Likert scale ranking (1 = very dissatisfied; 5 = very satisfied) (20).

Data Collection Procedure:
Following written informed consent, the participants were administratively interviewed and also filled in a questionnaire in order to establish baseline demographic and clinical data. Review of medical charts was used to verify diagnosis, the history of prophylaxis failure. Patients were asked to write headache diaries during at least a 1-month period prior to and 3 months following the start of anti-CGRP therapy during which time they recorded MMDs. Disability and impact were assessed with standardization of MIDAS and HIT-6 tools, respectively. Treatment satisfaction was also measured by the Likert scale.

Data Analysis:
Microsoft Excel was used to enter data, and then results were analyzed in IBM SPSS Statistics version 25. Each variable was analyzed descriptively, following its demographics and clinical characteristics: categorical variables were reported as frequencies and percentages, whereas continuous variables were reported as mean values (standard deviation). The percentage of patients who experienced a 50 % or more reduction in MMDs was calculated at 95 % confidence intervals. Paired t-tests involving assessment of changes in MIDAS and HIT-6 scores before and after treatment were used based on normality distribution. A p-value of 0.05 and below was considered to be statistically significant.

RESULTS:
The study enrolled 105 patients that met the preset inclusion criteria. Average age was 38.9 $\pm$ 8.8 years, and 71.4 % of the sample were women. The participants met the following characteristics:
- All of them experienced at least four migraine attacks per month, and
- At least one conventional prophylactic agent had been unsuccessful previously.

Table 1: Characteristics of the participants.

Sr. No.:	Demographics	Mean (S.D.)	Frequency (Percentage)
1.	Age in years	38.9 (8.8)	
2.	**Sex**		
	Male		30 (28.6)
	Female		75 (71.4)
3.	Migraine Duration in years	8.1 (2.9)	
4.	Monthly Migraine Days (MMD)	15.1 (4.2).	
5.	**Prophylactic Failure**		
	One class		46 (43.8)
	Two or more classes		59 (56.2)
6.	**Received Anti-CGRP**		
	Eptinezumab		13 (12.4)
	Galcanezumab		23 (21.9)
	Fremanezumab		31 (29.5)
	Erenumab		38 (36.2)

Reduction in MMD Frequency:
After 3 months of anti-CGRP monoclonal antibody therapy, MMDs were reduced dramatically compared to the baseline of 14.2 ± 3.1 ($p < 0.001$) to 7.4 ± 2.9 ($p < 0.001$). The percentage of patients who were able to decrease MMDs by 50 % or more was 69 (65.7 %).

MIDAS and HIT-6 Scores:
The parallel betterment was registered on the migraine specific disability measures. The functional capacity was increased; the migraine-related disability index MIDAS score was decreased with 32.5 ± 8.4 to 17.6 ± 6.3 ($p < 0.001$) as well as the HIT-6 score that decreased to 65.9 ± 5.2 to 58.3 ± 4.7 ($p < 0.001$).

Medication Usage Reduction:
At the same time, the average number of days per month of acute and active medication use was reduced from 8.9 ± 3.0 to 4.3 ± 2.2 days per month days ($p < 0.001$) which highlights a clinically significant improvement in disease management.

Satisfaction among Patients:
According to the response of patients to the anti-CGRP therapy, 62 (59.0%) responded to the question, noting that they were either satisfied or very satisfied with it, and 15 (14.3%) responded who reported to being dissatisfied with it according to the Likert scale. All the above findings are encouraging evidence that anti-CGRP therapy is safe and efficacious in the treatment of chronic migraine.

DISCUSSION:
The current cross-sectional study tested the short-term effectiveness of anti-CGRP monoclonal antibodies (mAbs) in chronic migraine (CM) resistance to the conventional prophylaxis. There was a great improvement in the number of migraine days per month (MMDs), migraine-related disability (MIDAS) scores and headache impact (HIT-6) scores at the end of three months of treatment. These findings provide clinical data in favor of the effectiveness of CGRP-focused therapies in bearers of refractory migraine.
The major finding, which was a mean decrease of 6.8 MMDs monthly, matched the efficacy across randomized controlled trials that were conducted, including the HALO CM and the STRIVE trial, which showed reductions of Fremanezumab and Erenumab, respectively, in individuals with CM, again indicating similar levels (21, 22). Sixty-four per cent of subjects had a 50 per cent reduction or more in MMD, possibly higher than the 40-57 per cent response rates described in pivotal trials (23,

24). This above average result can be the indication of real-life advantages under the conditions where CGRP-targeted medicines will be prescribed to properly chosen individuals.

There was also a clinically significant change in the disability related to migraine as signified by reduced MIDAS and HIT-6 scores. The significance of these outcomes is that the functional limitations and the impairments of quality of life are huge contributors of disease burden in CM. The investigation supports the existing body of research that anti-CGRP mAbs decreases the frequency of headaches but at the same time leads to improvement in patient-reported outcomes in many domains of functioning (11).

Another finding was related to the decrease in the use of acute medication, which is a secondary but a clinically significant indicator of better migraine control. Medication-overuse headache (MOH) is a frequent co-morbidity in CM, with frequent use of analgesics both a precipitant factor in MOH and a complication of an extensive MOH (25). The reported reduction in the number of medications points to a twofold therapeutic advantage of CGRP-based treatment in both decreasing the number of headache attacks and the reliance on crisis acute drugs.

Additional context was patient satisfaction and almost 60 percent of the research participants answered in the affirmative on the Likert scale. Even though, satisfaction is a subjective measure, it indicates acceptability and tolerability in the real world application. The observation confirms the safety profiles of anti-CGRP monoclonal antibodies, which are usually well-tolerated and would have fewer systemic adverse effects than conventional prophylactic agents (26).

The current study supports the recommendations developed by the German Neurological Society and the German Migraine and Headache Society, with the latter recommending the use of anti-CGRP monoclonal antibodies in patients with chronic migraine who were found to be unresponsive to a usual pharmacotherapy (12). Especially important is that there is a statistically significant clinical effect found in patients who previously failed to respond to one or more prophylactic classes, indicating a specific therapeutic advantage of these biologic agents when used in especially refractory groups.

Clinical Implications:

The findings from the current research supports the therapeutic potential of anti-CGRP monoclonal antibodies in treating chronic migraine and use in resistant patients to traditional prophylaxis (27). These agents are now set to play the key role in personalized management of migraine with greater access and the accumulation of additional real-world evidence. Longer-term efficacy, cost-effectiveness, and comparative studies of anti-CGRP agents to existing prophylactics, should therefore be prioritized in future.

Conclusion:

In this study, empirical evidence was given to substantiate the fact that anti-CGRP monoclonal antibodies are an effective and tolerable treatment used in the preventive treatment of chronic migraine in patients with high attack frequency who have not shown responses to standard dose prophylaxis. The clinically relevant improvement appeared in terms of the attenuation of monthly migraine days, disability scores (MIDAS, HIT-6), and usage of acute medicine after 3 months of treatment. In addition, the strong level of patient satisfaction points out towards the fact that these targeted biologics are acceptable clinically.

Study Strengths:

One of the main strengths of the current research is the inclusion of rigorous eligibility based on the criteria: all the participants had solid criteria of chronic migraine and were also reported to have failed more than one prophylactic regime. Moreover, the use of standardized measures of outcomes, and, specifically, the Migraine-Specific Disability Assessment Scale (MIDAS) and the Headache Impact Test-6 (HIT-6) has further increased the reliability of the findings.

Limitations:
There are a number of limitations that should also be considered. To start, the design as a cross-sectional study will not allow a firm causal inference to be made; despite the within each subject comparisons being done, there was no control cohort to give the actual cause of outcomes to be solely attributed to the anti-CGRP therapies. Second, efficacy or adverse events that can even emerge after follow-up (with a limit of 3 months) might not be reflected. Lastly, selection in tertiary centers brings in a potential selection bias and thus there is no guarantee that the same will be generalizable to primary care or resource-limited environments.

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