ejpmr, 2018,5(9), 242-246

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ERENUMAB-AOOE: PROMISING MONOCLONAL-ANTIBODY FOR PROPHYLAXIS OF MIGRAINE IN ADULTS

Ranjodh Jeet Singh[1] and Kanika Kohli[2]*

[1]Assistant Professor, Department of Pharmacology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.

[2]Assistant Professor, Department of Forensic Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.

***Corresponding Author: Kanika Kohli**
Assistant Professor, Department of Forensic Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.

Article Received on 12/07/2018 **Article Revised on 01/08/2018** **Article Accepted on 21/08/2018**

ABSTRACT

Introduction: Migraine is one form of disorder affecting the quality of life of patient and disabled brain disorder. The term chronic migraine refers to a clinical condition summarized by migranous headache on fifteen days usually per monthly episode. Most commonly patients on pharmacotherapy of migraine include Ergot derivatives, Triptans, Opioids, and Analgesics for a period range of ten days per month. Even though the pathology and physiology of migraine is not fully understood and established, but however several other risk factors which are associated as triggers of migraine are considered to deal with. The CGRP is involved in pathology and physiology of origin of neurovascular headaches viz migraine at both peripheral and central levels. The CGRP is highly expressed in trigeminal neurons (small myelinated Ad and unmyelinated C fibers) co-localized with other neuropeptides (e.g., substance P). The CGRP levels are increased into external jugular venous blood ipsilateral to pain during headache phase of migraine attack with or without aura. Also the saliva and serum CGRP levels are increased during migraine and interictally in patients with CM. Thus CGRP monoclonal antibodies are considered to target smooth muscle cells on blood vessels and glial cells and neurons located outside BBB, probably in brainstem paraventicular structures and trigeminal ganglion. Scope: Erenumab-aooe, CGRPr antagonist, being the latest approved drug administered via subcutaneous route as 70 mg per month for prophylactic regime of migraine in adult patients, the results documented as per clinical trials data are very promising and thus Erenumab-aooe is an emerging hope to improve the quality of life and make the patients able to perform their life activity with effectiveness. **Conclusion:** Chronic migraine is not fully treated as the pharmacotherapy response is at the poor level and also limited pharmacotherapy is available, however the emergence of Erenumab-aooe, CGRPr antagonist as the one of the latest drug approval for the prophylaxis of migraine in adults is by far the greatest scope for the better treatment module of migraine.

KEYWORDS: CM: chronic migraine, EM: episodic migraine, LSM: least square mean, MMD: monthly migraine days, ICHD: International classification of headache disorders, CGRPr: Calcitonin gene related peptide receptor, MHD: monthly headache days.

INTRODUCTION

The patients suffering from CM impose a substantial burden economically worldwide.[1] The headache disorders were collectively the third highest worldwide. The headache is not only painful, but patients of migraine are rendered as disabled. As according to the global burden of disease study lastly updated on 2013, migraine has been considered as the sixth highest cause worldwide, of years lost because of disability.[2] According to who, headache disorders comprise of migraine, medication overuse headache and tension type headache, as they are considered for high levels of ill health and disability.[2]

All over world, 20% of population suffers from migraine at some instance of their life; also the epidemiological studies have demonstrated that 4.5% of population of Western Europe has headache on ~ 15 days/month.[3]

According to ICHD-3 the patients of migraine are designated as with or without aura for a minimum period of eight days per month.[4]

The term 'Transformed Migraine' has been proposed to demonstrate the type of migraine which has evolved clinically, worse than before or have become more complicated over a period of time. [5] The management of 'Transformed Migraine' is often difficult as the

prominent headache will not present with typical clinical symptoms of the migraine, as it is now on a more severe form of headache.[5]

In approximately 200 AD, the term Migraine was derived from the Greek word 'Hemicrania' coined by Galen, proposing as migraine was well known in ancient world also.[6,7]

The term migraine comprises as a neurological syndrome defined as headaches throbbing in nature, moderate to severe in intensity, altered perception, nausea. The patients may experience the sensory symptoms which comprises phonophobia, photophobia and thus approaching for dark and quiet room.[7]

The triggers for migraine[4,7]

- Drugs: Estrogen, Reserpine, Histamine, ranitidine, Hydralazine, Nitroglycerine etc.
- Preservatives in foods and sensitivity to chemicals: The food products such as alcoholic beverages, ice creams, caffeine, aged cheese, chocolates, and nature identical food preservatives as additives such as monosodium glutamate and nitrates may act as triggers of migraine.
- Environmental triggers: The gross changes in altitude, odour, bright light, walking in sunlight and strong winds may trigger or aggravate the attack of migraine.
- The emotional/psychological stress: This factor is most commonly involved as during stressful episodes, the brain releases certain chemical triggers which can aggravate vascular changes and lends patients to migraine.

Current prophylactic goals[7,8]

1) Prevention of progression of migraine.
2) To reduce the pharmacological management response of patient.
3) To reduce the use of obsolete/ineffective pharmacotherapy of acute headache medication to combat drug resistance.
4) To reduce the migraine duration, severity, frequency and disability.
5) To improve the patient's quality of life and ability to work/function properly.

The management of CM is a diverse complexed topic which primarily includes the modification of lifestyle to minimize the aggravating risk factors considered for trigger of migraine, the pharmacological management of associated co-morbid conditions, further the identification of overuse of medicine, pharmacological management of acute attacks and most importantly prevention/prophylaxis therapy. Thus judicious and properly necessitated pharmacotherapy for patients suffering from EM must be given when progression occurs, for prevention/prophylaxis of CM. This article will be focused for the Erenumab-aooe which is the latest drug approved for the prophylaxis of migraine in adults, intended to improve the quality of life of patients suffering from headache and also to prevent the migraine progression to CM.

These circumstance demands for the development of new Antimigraine drugs with a different mechanism of action as well as better expected results. Since long no drug formulation has come, although numbers of drugs are in pipeline and are undergoing clinical trials for new drug development for migraine. Other Antimigraine monoclonal antibodies belonging to CGRP-1 pathway are: eptinuzumab, fremanezumab, galcanezumab.

Etiology and pathogenesis of migraine

The CGRP is involved in pathology and physiology of origin of neurovascular headaches viz migraine at both peripheral and central levels. The CGRP is highly expressed in trigeminal neurons (small myelinated Ad and unmyelinated C fibers) co-localized with other neuropeptides (e.g., substance P). The CGRP-positive trigeminal nociceptive fibers form rich plexus on the intracranial blood vessels. When CGRP is released peripherally from activated trigeminal nociceptive endings, the CGRP produces edema, recruits inflammatory cells, increases blood flow, promotes neurogenic inflammation and thus produces migraine pain. During migraine, the CGRP may sensitize neuronal circuits reducing filtering of sensory inputs, leading to pain as well nausea, allodynia, phonophobia and photophobia.[9]

The CGRP levels are increased into external jugular venous blood ipsilateral to pain during headache phase of migraine attack with or without aura. Also the saliva and serum CGRP levels are increased during migraine and interictally in patients with CM. The intravenous injection of human aCGRP (2μg/ml for 20 min) produces migraine-like disorders, and produces experimentally induced migraine attack in 57% of the patients and aura symptoms in 28% in migranous with aura.[9]

Thus CGRP monoclonal antibodies are considered to target smooth muscle cells on blood vessels and glial cells and neurons located outside BBB, probably in brainstem paraventicular structures and trigeminal ganglion. Keeping in view the outburst role of CGRP, the research work has been started thereto to scientifically devise the drug as Erenumab-aooe as prophylactic management of migraine in adults.

Erenumab-aooe

Erenumab-aooe is a Calcitonin gene related peptide receptor antagonist. It is administered as 70 mg injection subcutaneously once a month. In some clinical cases, the benefit is from a dosage of 140 mg injection subcutaneously per month, which is usually administered as two consecutive subcutaneous injections of 70 mg each. If the patient has missed the dose, the sooner administration is recommended. Thus Erenumab-aooe

can be scheduled for the pharmacotherapy from the date of last dose of acute administration.[10]

Management of migraine

The management constitutes NSAIDs or migraine-specific drugs viz. Triptans, ergotamine. The prophylaxis including non-pharmacological measures such as exercise, nutrition, psychological rehabilitation is found to be beneficial in patients suffering from migraine. But many patients require prophylaxis due to severity of disease comprised by severe functional impact and/or frequent attacks. The aim of prophylaxis is to decrease the frequency of migraine days.[11,12]

Erenumab-aooe preparation comes as a prefilled autoinjector with needle cap with prefilled syringe containing dry natural rubber, a derivative of latex, which may cause allergic reactions, thus case sensitivity is predicted. Although Erenumab-aooe is entitled for patient self administration to improve compliance, thus patient must be properly explained, counseled and trained for this desired intended purpose and all important instructions viz. to allow Erenumab-aooe to sit at room temperature for atleast 30 minutes, protected from sunlight.[9]

Protein binding: Erenumab-aooe is capable of 50% to 99% total inhibition of CGRPr with dosages of 255 ng/ml and 1134 ng/ml.[13]

Metabolism: Erenumab-aooe CGRP antibodies concludes the low risk for hepatotoxicity and drug-drug interactions, since they are predominantly metabolized into single amino acids and peptides.[14]

Route of elimination: The two elimination phases are observed for Erenumab-aooe. At low concentrations, elimination is mainly through saturable binding to CGRP receptor, while at higher concentrations elimination of Erenumab-aooe is primarily through a non-specific, non-saturable proteolytic pathway. These phases correspond to studies that demonstrated the two parallel elimination pathways: (a) slow non-specific elimination pathway through hepatic reticuloendothelial system, and (b) rapid saturable elimination pathway mediated by internalization or degradation of Erenumab-aooe-receptor complex.[13,15]

Efficacy and Safety in Clinical Trials: The clinical efficacy and safety of Erenumab-aooe has been evaluated by the clinical trials in patients with established diagnosis of migraine in adults.

Main clinical studies

In Phase 2/3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety and efficacy of two doses of subcutaneous Erenumab-aooe every 4 weeks for 12 weeks duration in subjects with CM (≥8 MMD, ≥15 MHD at baseline). 667 patients were randomized (3:2:2) to receive placebo, Erenumab-aooe 70 mg and Erenumab-aooe 140 mg.

In Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety and efficacy of two doses of subcutaneous Erenumab-aooe every 4 weeks for 24 weeks duration in subjects with EM (≥ 4 and <15 MMD with <15 MHD at baseline). 955 patients were randomized (1:1:1) to receive placebo, Erenumab-aooe 70 mg and Erenumab-aooe 140 mg.

Favorable effects

In Phase 2/3, Erenumab-aooe at 70 and 140 mg decreased the number of MMD (primary endpoint) from baseline mean of ~18 days by 6.64 (7.47, 5.81) and 6.63 (7.45, 5.80) days, compared to decrease in placebo group of 4.18 (3.50, 4.86) days, resulting in a Difference in LSM of -2.46 and -2.45, respectively, and p-values of <0.001.

The secondary endpoint MMD responder rates (≥50% reduction in MMD from baseline to last 4 weeks of 12-week treatment) were 23.5%, 39.9%, 41.2% for placebo, Erenumab-aooe 70 mg and 140 mg, projecting adjusted odds ratios of 2.18 (1.46, 3.27) and 2.34 (1.56, 3.51) and p-values of <0.001.

Again in phase 2/3, Monthly acute migraine-specific medication treatment days were decreased by 1.58, 3.45, and 4.13, for placebo, Erenumab-aooe 70 mg and 140 mg, resulting in difference in LSM of -1.86 (-2.60, -1.13) and -2.55 (-3.28, -1.82) vs placebo and p-values of <0.001.

In phase 3, Erenumab-aooe at 70 and 140 mg decreased the number of MMD (primary endpoint) from baseline mean of around 8 days by 3.23 (3.58, 2.88) and 3.67 (4.02, 3.33) days, respectively, compared to decrease in placebo group of 1.83 (2.18, 1.48) days, resulting in difference in LSM of -1.40 and -1.85, respectively, and p-values of <0.001.

The secondary endpoint, MMD responder rates (≥50% reduction in MMD from baseline to last 3 months of the 24-week treatment) were 26.6%, 43.3%, 50.0% for placebo, Erenumab-aooe 70 mg and 140 mg, projecting adjusted odds ratios of 2.13 (1.52, 2.98) and 2.81 (2.01, 3.94) and p-values of <0.001.

Again in phase 3, Monthly acute migraine-specific medication treatment days were decreased by 0.20, 1.13, and 1.61, for placebo, Erenumab-aooe 70 mg and 140 mg, resulting in a difference in LSM of -0.94 (-1.23, 0.64) and -1.42 (-1.71, -1-12) versus placebo and p-values of <0.001.

The results were found to be consistent with respect to different main endpoints and also between the main studies of developmental programme. The results for the

primary endpoint MMD were supported by consistent positive effects on 50% responder rate, decrease of acute migraine-specific treatment and positive effects on patients' quality-of-life, as reported par patient-reported outcome scales.

Also the subgroup analyses from two pivotal studies demonstrated that subgroups of patients with CM or EM who had failed >1 or >2 previous pharmacotherapy achieved similar or better results on MMD decrease compared to patients who were pharmacologically naïve or hadn't failed any previous pharmacotherapy.[16]

Unfavorable effects as documented in main clinical studies of Erenumab-aooe

The total 2,500 patients have been treated with clinical trial studies. Out of these, >1,300 patients were exposed for ∼12 months duration.

The results based upon 12 weeks placebo controlled studies, common AEs that occurred with ≥ 1% in Erenumab-aooe 70 mg or 140 mg group and ≥ 2 times rate of placebo group are summarized as follows:

- Muscle spasm was reported for 0.4%, 0.1%, and 2.0% of subjects in the placebo, 70 mg, and 140 mg groups.
- Generalized pruritus was reported for 0.1%, 0.0%, and 1.2% of subjects in the placebo, 70 mg, and 140 mg groups.
- Injection site pain was reported for 1.7%, 3.7%, and 1.6% of subjects in the placebo, 70 mg, and 140 mg groups.
- Constipation was reported in 1.1%, 1.3%, and 3.2% of subjects in placebo, 70 mg, and 140 mg groups.
- Injection site erythema was reported for 0.2%, 1.0%, and 2.0% of subjects in the placebo, 70 mg, and 140 mg groups.

As per documented data no death or serious Hypersensitivity Reactions anaphylaxis or signal identified in data submitted. However, in some cases, chronology or recurrence of event after re-challenge supports causality with Erenumab-aooe. There were cases of swelling/oedema but non-serious and not requiring discontinuation of Erenumab-aooe.[16]

Balance of benefits and risks

Even though a mean absolute reduction of monthly migraine days (MMD) of approx. 7 days in CM (compared to approx. 4 days for placebo) and approx. 3-4 days in EM (compared to approx. 2 days for placebo) may not seem impressive, 40% of patients in CM and of up to 50% in EM (compared to 24% in CM and 27% in EM for the placebo groups, respectively) experienced a 50% reduction of MMD which indicates that the results are of clinical relevance.[16] This benefit is considered to outweigh the risks considering the rather low incidence of non-severe adverse events.

Although according to clinical trial data, the mean absolute decrease of MMD of ∼ 7 days in CM (as compared to approximately 4 days for placebo) and approximately 3-4 days in EM (compared to approximately 2 days for placebo), but 40% of patients of CM and upto 50% in EM (compared to 24% in CM and 27% in EM for placebo have experienced a 50% decrease of MMD which demonstrates the clinical results as of clinically relevance. Thus benefit has over powered the risks for the consideration of the rather low incidence of non severe adverse events cascades of Erenumab-aooe.

The significant decrease of MMD, more responder rates and decrease of acute migraine medication days as compared to placebo effect and improvement of quality of life related scales and positive outcomes for the adult patient suffering from CM or EM have suggested the benefits of Erenumab-aooe as a choice drug with good compliance for prophylaxis of migraine in adults.

CONCLUSION

Based on review of available data, Erenumab-aooe is the active drug approved by FDA (food and drug administration, United States) for prophylaxis of migraine in adults. As per Indian pharmaceutical companies have also been decided to go with Erenumab-aooe availability for acute prevention of migraine in adults, because of superior efficacy and safety as documented by clinical trials data and fewer adverse drug reactions. Although the trending concern of drug resistance, the drug must be used with rational drug therapy and evidence based medicine and only on restricted prescription.

ACKNOWLEDGEMENT

The author wants to acknowledge the support and critical suggestions from Dr Kanika Kohli, Assistant Professor, Department of forensic medicine, Maharishi Markandeshwar institute of medical sciences and research, Mullana, Ambala, Haryana, India.

Footnotes

Source of support: Nil.

Conflict of interest: None declared.

REFERENCES

1. Buse D., Manack A., Serrano D., Reed M., Varon S., Turkel C., et al. (2012). Headache impact of episodic and chronic migraine: results from the American Migraine Prevalence and Prevention study. Headache, 2012; 52: 3–17.
2. http://www.who.int/news-room/fact-sheets/detail/headache-disorders (assessed on 07/07/18)
3. Welch K., Goadsby P. (2002) Chronic daily headache: nosology and pathophysiology. Curr Opin Neurol, 2002; 15: 287–295.

4. International Headache Society, International classification of headache disorders. Cephalalgia, 2004; 24(Sup.1): 1–160.
5. Mathew NT, Stubits E, Nigam MP. Transformation of episodic migraine into daily headache: analysis of factors. Headache, 1982; 22(2): 66–68.
6. Critchley M. Migraine: From Cappadocia to Queen Square. Background to Migraine In: Smith R, ed. London: Heinemann. Volume 1; 1967.
7. Goyal M, Bansal M. Understanding migraine: an overview. IJCP., 2010; 21(3): 137-141.
8. Silberstein SD, Winner PK, Chmiel JJ. Migraine preventive medication reduces resource utilization. *Headache*, 2003; 43: 171-8.
9. Barbanti P, Aurilia C, Fofi L, et al. The role of anti-CGRP antibodies in the pathophysiology of primary headaches. Neurol Sci., 2017; 38: 31–35.
10. http://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761077s000lbl.(assessed on 07/07/18)
11. Silberstein Stephen D, hans-chrisoph Diener, David W. Dodick, Peter J. Goadsby, Richard B. Lipton, Jes Olesen. Chronic migraine-classification, characteristics and treatment. Nature reviews Neurology, 2012; 8: 162-171.
12. Evers et al. acute therapy and prophylaxis of migraine. Neurology, 2008; 27(10): 933-949.
13. Vu T, Ma P, Chen JS, de Hoon J, Van Hecken A, Yan L, Wu LS, Hamilton L, Vargas G: pharmacokinetic-Pharmacodynamic Relationship of Erenumab (AMG 334) and Capsaicin-Induced Dermal Blood Flow in Healthy and Migraine Subjects. Pharm Res., 2017 Sep; 34(9): 1784-1795.
14. Deen M, Correnti E, Kamm K, Kelderman T, Papetti L, Rubio-Beltran E, Vigneri S, Edvinsson L, Maassen Van Den brink A: Blocking CGRP in migraine patients- a review of pros and cons. J headache pain., 2017 Sep 25; 18(1): 96.
15. https://www.drugbank.ca/drugs/DB14039#fda-reference (assessed on 05/07/18)
16. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp(assessed on 12/05/18)