Asian Journal of Research and Reports in Neurology

2(1): 46-53, 2019; Article no.AJORRIN.52626

Using Calcitonin Gene-related Peptide Monoclonal Antibodies for Migraine Headache Treatment and Prevention

Nour Al-Kharrat[1] and Gunay Arsoy[1*]

[1]Faculty of Pharmacy, Near East University, Northern Cyprus, Turkey.

Authors' contributions

This work was carried out in collaboration between both authors. Author NAK designed the study and wrote the first draft of the manuscript. Author GA managed the literature searches. Both authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Takashi Ikeno, Department of Social Psychiatry, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan.
Reviewers:
(1) Mai Sabry Saleh, National Research Centre, Egypt.
(2) Maria Rosa Avila-Costa, National University of Mexico, Mexico.
Complete Peer review History: http://www.sdiarticle4.com/review-history/52626

Review Article

Received 02 September 2019
Accepted 07 November 2019
Published 14 November 2019

ABSTRACT

Novel drugs are available now for treating and preventing migraine attacks. Those new drugs have a special strategy to treat migraine by modifying the signaling of calcitonin gene- related peptide (CGRP) which is a strong neuropeptide released from the nerves. Monoclonal antibodies (mAbs) have been developed for targeting the CGRP pathway by binding the CGRP ligand (eptinezumab, galcanezumab fremanezumab,) or the CGRP receptor (erenumab). Recent studies show that mAbs have several advantages over small molecule antagonists, including high selectivity and reduced potential for drug–drug interactions. In this article we reviewed literature to assess whether mABs can be used for treatment of acute and chronic migraine safely compared to classical antimigraine agents.

Keywords: Migraine; CGRP; monoclonal antibodies; treatment; prevention.

**Corresponding author: E-mail: gunay118@hotmail.com;*

ABBREVIATIONS

BBB : Blood–brain barrier;
CGRP : Calcitonin gene-related peptide;
CLR : Calcitonin like receptor;
CM : Chronic migraine;
CNS : Central nervous system;
CTR : Calcitonin receptor;
EM : Episodic migraine;
mAb : Monoclonal antibody;
RAMP : Receptor activity-modifying protein;
RCP : Receptor component protein;
TGVS : Trigeminovascular system;

1. INTRODUCTION

Migraine is a common chronic brain disorder, characterized by recurrent headache attacks and associated disabling symptoms that display significant personal, familial and societal impact [1]. More than one out of 10 civilians is affected by migraine, much more often the women [2]. Depending on the frequency of attacks, migraine is divided into episodic (less than 15 days with headache per month) and chronic migraine (more than 15 days with headache per month) [3].

Migraine is a neurobiological disorder [4]. At least three messenger molecules are involved in pain signaling during migraine attacks: nitric oxide, 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide (CGRP) [5].

The main symptom of migraine is throbbing or pulsatile headache, with moderate to severe pain that intensifies with movement or physical activity. Unilateral and localized pain is felt in the frontotemporal and ocular area, but the pain may be anywhere around the head or neck and lasts 4-72 hours. Associated symptoms may include nausea (80%) and vomiting (50%) and light-headedness [4].

Physical findings during a migraine headache may include cranial/cervical muscle tenderness, conjunctival injection, tachycardia or bradycardia, hypertension or hypotension, hemisensory or hemiparetic neurologic deficits (ie, complicated migraine) and adie-type pupil (ie, poor light reactivity, with near dissociation from light) [4].

Generally, one out of five patients treated with any migraine-preventive pharmaceutical agent will discontinue treatment because of tolerability and safety reasons indicating the need for novel and better antimigraine therapies [6-8].

2. THE ROLE OF CGRP IN MIGRAINE

Migraine headache is associated with release of calcitonin-gene-related peptide (CGRP). Indeed, CGRP release has been demonstrated in both triggered and spontaneous migraine attacks, and CGRP levels are reduced by effective treatment with a triptan [9-11]. The subsequent development of selective non-peptide CGRP receptor antagonists through clinical trials provided additional proof of the importance of CGRP in migraine [12].

CGRP is a 37-amino acid neuropeptide that exists in two isoforms that differ by three amino acids in the human and have different tissue distributions [13].

CGRP is the most potent microvascular dilator currently known, and its vasodilator activity is observed in the cerebral, coronary and kidney vascular beds [14-15].

Monoclonal antibodies: An alternative to small molecules for blocking CGRP transmission in patients with migraine is the use of selective monoclonal antibodies that bind to either CGRP or the CGRP receptor. Currently, four antibodies (one for CGRP receptor and three for CGRP itself) have been studied in clinical trials for episodic and chronic migraine [16-21]. Erenumab is an anti-CGRP receptor antibody and administered once per month by subcutaneous injection [22-23]. Eptinezumab, fremanezumab, galcanezumab are the antibodies that targeted to sites on CGRP itself. Eptinezumab is formulated for intravenous administration and intended for dosing once every 3 months [24]; fremanezumab administered once per month via subcutaneous injection [25]; and galcanezumab, also administered subcutaneously on a monthly basis. The therapeutic goal of this approach is migraine prophylaxis, meaning a reduction in the number of migraine days experienced by patients who have frequent attacks. Studies shows that using of these antibodies has successfully decreased the number of migraine days in episodic migraine [21-27].

Advantages and disadvantages: Anti- CGRP and anti- CGRP receptor antibodies have several advantages over other treatment options. Patient adherence and tolerability are both better with the antibodies. The antibodies have a prolonged serum half- life (20–50 days), which means that patients can take the medication infrequently. In addition, antibodies bind to their target site with

Table 1.Studies comparing the efficacy and safety of anti- migraine antibodies (AMG)

Referance number	Study name	Study aim	Study design	Results
23	Safety and efficacy of AMG 334 (Erenumab) for prevention of episodic migraine	assessed the safety and efficacy of AMG 334, a fully human monoclonal antibody against the CGRP receptor, for migraine prevention.	Randomized, double-blind, placebo-controlled	These results suggest that AMG 334 70 mg might be a potential therapy for migraine prevention in patients with episodic migraine and support further investigation of AMG 334 in larger phase 3 trials
41	CGRP, a target for preventive therapy in migraine and cluster headache	Assess the safety, tolerability, and efficacy of monoclonal anti-CGRP antibody, in the preventive treatment of high-frequency episodic migraine	Systematic review of clinical data	Efficacy of anti-CGRP monoclonal antibodies spells a promising future for the many patients suffering from migraine, and possibly also for the smaller but severely affected population with cluster headache.
22	Safety and efficacy of Erenumab for preventive treatment of chronic migraine	Assess the efficacy and safety of (Erenumab), a fully human monoclonal antibody against the CGRP receptor, in Patients with chronic migraine.	Randomized, double-blind, placebo-controlled phase 2 trial	In patients with chronic migraine, erenumab 70 mg and 140 mg reduced the number of monthly migraine days with a safety profile similar to placebo, providing evidence that erenumab could be a potential therapy for migraine prevention. Further research is needed to understand long-term efficacy and safety of erenumab, and the applicability of this study to real-world settings.
39	Effect of Different Doses of Galcanezumab vs Placebo for Episodic Migraine Prevention	Tested Galcanezumab, a fully human monoclonal antibody that inhibits the calcitonin gene–related peptide receptor, for the prevention of episodic migraine.	Randomized double blind, placebo-controlled	Monthly subcutaneous injections of galcanezumab, both 120mg and 300mg, demonstrated efficacy (repeated-measures analysis) for the preventive treatment of migraine and

Referance number	Study name	Study aim	Study design	Results
				support further development in larger phase 3 studies. All dosages were safe and well tolerated for the preventive treatment of episodic migraine.
42	Calcitonin gene-related peptide monoclonal antibodies for migraine prevention	The objective of this study is to systematically assess the Clinical efficacy and safety of CGRP-mAbs for migraine therapy.	Review article/ Comparisons across randomized controlled studies	This meta-analysis suggests that CGRP-mAbs are effective in anti-migraine therapy with few adverse reactions, but more and larger sample-size RCTs are required to verify the current findings
43	Calcitonin-gene-related peptide pathway mAbs and migraine prevention	provide an update on published Phase 2 and Phase3 trials, safety/tolerability data, pharmacokinetics and mechanism of action of these biologicals.	Review article	Although efficacy of all four drugs is modest over placebo in episodic and chronic migraine prevention and overall comparable with available oral preventive treatments, current tolerability and (short-term) safety data of this new treatment approach certainly promise a major step forward for migraine patients.

high affinity and selectivity, thus reducing the potential for unwanted, off- target effects. Furthermore, in contrast to small exogenous molecules such as the gepants, antibodies are not processed by the liver, thus avoiding the potential for liver toxicity and hepatic drug interactions. No adverse cardiovascular or cerebrovascular effects of the antibodies under development have been reported to date [28-33].

A primary disadvantage of antibodies is that they are not orally active and must be administered by injection. Injection- site reactions, including pain, are common but these reactions are usually mild and transient and are less likely with intravenous administration than with subcutaneous administration [28-34]. The risks of long- term blockade of CGRP signaling are not known. One concern relates to the role that CGRP plays as a potent vasodilator throughout the vascular system [14]. Consequently, chronic reduction of CGRP has the potential to cause cardiovascular pathophysiology, such as hypertension, cardiac dysfunction and episodes of coronary or cerebral ischemia [35,36]. To date, no cardiovascular adverse effects of anti- CGRP and anti- CGRP receptor antibodies have been reported [37-40].

3. CLINICAL TRIALS

Studies compare between antibodies and placebo show that antibodies are more effective in reducing the frequency of migraine with similar safety profiles. All these studies carried out by giving different doses of antibodies versus placebo to the patients.

4. LIMITATIONS AND RECOMMENDATIONS

Based on the studies, we may consider mABs as an effective new treatment of acute and chronic migraine. The high selectivity, less adverse effects and no drug-drug interaction increase the adherence of patients because of less frequency and long duration of action. Sometimes, they can prevent the episodes of migraine for about 3 months. However, it is still hard to give these medications to all migraine patients because they are expensive and cannot be given orally.

The antibody trials have so far mainly included people of middle age who are not at high risk of stroke or acute myocardial infarction. Elderly patients, in whom ischemic events are of greater concern, are less likely to experience migraine and are therefore unlikely to need the antibody medications. However, further studies are needed to focus on geriatric and cardiovascular problems of these drugs.

5. CONCLUSION

Overall, clinical trials have shown that the anti-migraine antibodies are effective, well tolerated and safe.

The anti- CGRP antibodies also seem to have similar efficacy and safety profiles.

The safety profile with mAbs is favorable, with no serious side effects recorded and no circulatory effects. Data emerging from trials with mAbs suggest that this specific blockade of the CGRP pathway may provide a safe and specific novel therapeutic approach in migraine and so are attracting great interest.

More research is needed to understand long-term efficacy and safety of antibodies, and the applicability of real-world settings.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1545–1602.
2. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinica features, and pathophysiology of migraine. Lancet Neurol. 2017;16:76–87.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808.

4. Burstein B, Noseda R, Borsook D. Migraine: Multiple processes, complex pathophysiology. J Neurosci. 2015;35: 6619–6629.
5. Akerman S, Romero-Reyes M, Holland PR. Current and novel insights into theneurophysiology of migraine and its implications for therapeutics. Pharmacol Thr; 2016.
6. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78:1337–1345.
7. Gracia-Naya M, Santos-Lasaosa S, Rı´os-Go´mez C, Sánchez-Valiente S, García-Gomara MJ, Latorre-Jiménez AM, Artal-Roy J, Mauri-Llerda JA. Predisposing factors affecting drop-out rates in preventive treatment in a series of patients with migraine. Rev Neurol. 2011;53:201–208.
8. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35:478–488.
9. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. Cephalalgia. 2019;39(3):366-373.
10. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. Cephalalgia. 2002;22(1):54-61.
11. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine like attacks in patients with migraine with aura. Cephalalgia. 2010;30(10):1179-1186.
12. Cernuda-Morollon E, Larrosa D, Ramon C, Vega J, Martinez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology. 2013;81(14):1191-1196.
13. Warfvinge K, Edvinsson L. Distribution of CGRP and CGRP receptor components in the rat brain. Cephalalgia. 2019;39(3):342-353.
14. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev. 2014;94(4):1099–1142.
15. MaassenVanDenBrink A, Meijer J, Villalon CM, Ferrari MD. Wiping out CGRP: potential cardiovascular risks. Trends Pharmacol Sci. 2016;37(9):779–788.
16. Goadsby PJ, Edvinsson L. Joint 1994 Wolff award presentation. Peripheral and central trigeminovascular activation in cat is blocked by the serotonin (5HT)-1D receptor agonist 311C90. Headache. 1994;34(7):394-399.
17. Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. Cephalalgia. 1994;14(5):320-7.
18. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann. Neurol. 1993;33(1):48-56.
19. Goadsby, PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. Brain. 1994;117(3):427-34.
20. Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. Br. J. Clin. Pharmacol. 2015;80(2):193-9.
21. Bell IM. Calcitonin gene- related peptide receptor antagonists: new therapeutic agents for migraine. J. Med. Chem. 2014;57(19):7838-58.
22. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, Winner P, Leonardi D, Mikol D, Lenz R. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double- blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425-434.
23. Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, Saper J, Cady R, Chon Y, Dietrich J, Lenz R. Safety and efficacy of AMG 334 for prevention of episodic migraine: A randomised, double-blind, placebo- controlled, phase 2 trial. Lancet Neurol. 2016;15(4):382-90.
24. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J, ALD403 study investigators.Safety and efficacy of ALD403, an antibody to calcitonin gene-

related peptide, for the prevention of frequent episodic migraine: a randomised, double- blind, placebo controlled, exploratory phase 2 trial. Lancet Neurol. 2014;13(11):1100-1107.

25. Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, Loupe PS, Ma Y, Goadsby PJ. TEV-48125 for the preventive treatment of chronic migraine: efficacy at early time points. Neurology. 2016;5;87(1):41-8.
26. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo- controlled study. Lancet Neurol. 2014;13(9):885-92.
27. Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: A double-blind, randomized, placebo controlled, dose- ranging trial. Cephalalgia. 2014; 34(2):114-25.
28. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E. Fremanezumab for the preventive treatment of chronic migraine. N. Engl. J. Med. 2017;377(22):2113-2122.
29. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. A controlled trial of erenumab for episodic migraine. N. Engl. J. Med. 2017;377(22): 2123-2132.
30. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, Burstein R, Loupe PS, Ma Y, Yang R, Silberstein SD. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: A multicentre, randomised, double- blind, placebo- controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091-100.
31. Schuster NM, Rapoport AM. Calcitonin gene- related peptide- targeted therapies for migraine and cluster headache: A review. Clin. Neuropharmacol. 2017;40(4):169-174.
32. Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. Headache. 2017;57(2):47-55.
33. Hou M, Xing H, Cai Y, Li B, Wang X, Li P, Hu X, Chen J. The effect and safety of monoclonal antibodies to calcitonin gene- related peptide and its receptor on migraine: a systematic review and meta-analysis. J. Headache. 2017;18(1): 42.
34. Gonzalez- Hernandez A, Marichal-Cancino BA, MaassenVanDenBrink A, Villalon CM. Side effects associated with current and prospective antimigraine pharmacotherapies. Expert Opin. Drug Metab. Toxicol. 2018;14(1):25-41.
35. Juul R, Aakhus S, Björnstad K, Gisvold SE, Brubakk AO, Edvinsson L. Calcitonin gene- related peptide (human alpha-CGRP) counteracts vasoconstriction in human subarachnoid haemorrhage. Neurosci. Lett. 1994;170(1):67-70.
36. Aubdool AA, Thakore P, Argunhan F, Smillie SJ, Schnelle M, Srivastava S, Alawi KM, Wilde E, Mitchell J, Farrell-Dillon K, Richards DA, Maltese G, Siow RC, Nandi M, Clark JE, Shah AM, Sams A, Brain SD.A novel alpha- calcitonin gene- related peptide analogue protects against end- organ damage in experimental hypertension, cardiac hypertrophy, and heart failure. Circulation. 2017;136(4):367-383.
37. Gonzalez- Hernandez A, Marichal-Cancino BA, MaassenVanDenBrink A, Villalón CM. Side effects associated with current and prospective antimigraine pharmaco therapies. Expert Opin. Drug Metab. Toxicol. 2018;14(1):25-41.
38. Alder BioPharmaceuticals Inc. Alder Reports Phase 2b Trial of ALD403 Meets Primary and Secondary Endpoints Demonstrating Migraine Prevention in Patients with Chronic Migraine; 2016.
39. Skljarevski V, Oakes TM, Zhang Q, Ferguson MB, Martinez J, Camporeale A, Johnson KW, Shan Q, Carter J, Schacht A, Goadsby PJ, Dodick DW. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: A randomized clinical trial. JAMA Neurol. 2018;75(2):187-193.
40. Matchar DB, Young WB, Rosenberg JH, Pietrzak MP, Silberstein SD, Lipton RB, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks; 2000.
Available:http://www.aan.com/professionals/practice/guidelines.cfm
41. Khan S, Olesen A, Ashina M. CGRP, a target for preventive therapy in migraine

and cluster headache: Systematic review of clinical data. Cephalalgia. 2019;39(3): 374-389.

42. Mitsikostas DD, Reuter U. Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: Comparisons across randomized controlled studies. Curr Opin Neurol. 2017;30(3):272-280.

43. Paemeleire K, MaassenVanDenBrink A. Calcitonin-gene-related peptide pathway mAbs and migraine prevention. Curr Opin Neurol. 2018;31(3):274-280.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/52626