MAZIARCZYK, Alicja, MIAZGA, Dominika & SURDACKA, Laura. Monoclonal antibodies blocking CGRP for prevention of migraine. Journal of Education, Health and Sport. 2023;18(1):43-48. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.18.01.005
https://apcz.umk.pl/JEHS/article/view/43098
https://zenodo.org/record/7793415

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 14.03.2023. Revised: 14.03.2023. Accepted: 02.04.2023. Published: 02.04.2023.

Monoclonal antibodies blocking CGRP for prevention of migraine

Alicja Maziarczyk

Student, Wydział Lekarski, Uniwersytet Medyczny w Lublinie

alicja.maziarczyk00@gmail.com

ORCID: 0009-0001-6634-4215

Dominika Miazga

Student, Wydział Lekarski, Uniwersytet Medyczny w Lublinie

miazdominika@gmail.com

ORCID: 0000-0001-8715-9142

Laura Surdacka

Student, Wydział Lekarski, Uniwersytet Medyczny w Lublinie

laurasurdacka@gmail.com

ORCID: 0009-0006-3439-4003

ABSTRACT

Introduction and purpose

Monoclonal antibodies blocking calcitonin gene-related peptide (CGRP) are a novel treatment strategy developed specifically for prevention of migraine. Four drugs belong to this group: eptinezumab, fremanezumab and galcanezumab, which bind to the peptide; and erenumab, which blocks the CGRP receptor. CGRP is involved in nociception and plays a crucial role in the pathophysiology of migraine, as it is released in the trigeminal ganglion as a response to local cerebral vasoconstriction in order to cause dilation of the vessels and maintain cerebral blood flow. Moreover, administration of CGRP, especially among migraineurs, induces a migraine-type headache. The aim of the paper is to discuss the potential of monoclonal antibodies blocking CGRP for the prevention of migraine and to outline their safety and efficacy profile.

State of knowledge

Several randomised clinical trials have shown a significant efficacy of these drugs compared to placebo in reducing monthly migraine affected days, among patients suffering from both episodic and chronic migraine. Incidence rate of side effects is low; the most common were mild to moderate (e.g. pain at the injection site,

upper respiratory tract infections, nasopharyngitis, back pain and urinary tract infection). Anti-CGRP monoclonal antibodies exhibit a superior benefit-to-risk ratio than established preventive treatments.

Conclusions

Randomized controlled trials are still needed in order to compare different anti-CGRP monoclonal antibodies and asses their long-term safety profile. In conclusion, these drugs seem to provide promising prospects of improving the lives of migraineurs. As based on current knowledge, the benefits are superior to the likelihood of harm.

Keywords: CGRP monoclonal antibodies; Migraine prevention; Calcitonin gene-related peptide

Introduction and purpose

Migraine is a neurological disease characterized by attacks of severe headache, accompanied by associated symptoms of photophobia, phonophobia, nausea and vomiting. Aura is manifested as visual, sensory, speech, and/or motor disturbances and precedes the attack in 25% of patients [1,2]. Migraine remains the second largest cause of disability in the world, affecting over 1 billion people across all world regions, irrespective of race, culture or socioeconomic status [1,3,4]. The quality of life and the ability to participate in work, family, and social events are significantly reduced, resulting in addition of more stress, which is a migraine trigger [5]. Migraineurs are 2.5 times more likely to be depressed than those without migraine and 2–5 times more likely to suffer from anxiety disorders [6].

The mechanism of a migraine attack remains unclear. The aura was long thought to be caused by a sudden contraction of blood vessels in the brain, and the subsequent expansion of these vessels was thought to result in a headache. Currently, it is believed that a neuronal dysfunction, not ischemia, is responsible for the aura. Headache, on the other hand, is caused by stimulation of nociceptors in the meninges and blood vessels, as well as changes in central pain modulation. Sensory neurons of the trigeminal ganglion contain large amounts of CGRP (calcitonin gene-related peptide), as well as substance P and neurokinin A. It has been shown that during a migraine attack, the CGRP molecule is released from the trigeminal ganglion in response to contraction of cerebral arterioles to dilate these vessels and maintain normal blood flow. The release of substance P and neurokinin A also results in neurogenic inflammation and vasodilation, which consequently causes migraine headache. Because of the significant role of CGRP in the pathomechanism of the seizure, blockade of its release provides a mechanism of action for new antimigraine drugs [4,7].

State of knowledge

Current medications for migraine prophylaxis have been derived from various groups which were not originally created for the purpose of migraine treatment, such as blood pressure-lowering drugs or antiepileptic ones and are characterised by low efficacy and frequent side effects [8,9]. The aim of this paper is therefore to present and compare the results of research into the efficacy of new medications based on monoclonal antibodies that block CGRP or the CGRP receptor. These include erenumab, which works by blocking the receptor for CGRP and fremanezumab, galcanezumab and eptinezumab, which bind to the CGRP molecule and thus inhibit its action [10].

Erenumab (Aimovig) is a fully human IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary cells, with a recommended dose of 70 mg or 140 mg s.c. once a month. It was the first anti-CGRP monoclonal antibody approved by the FDA and the EMA. Fremanezumab (Ajovy) is a humanised IgG2Δa/kappa monoclonal antibody derived from a murine precursor, with a recommended dose of 225 mg s.c. once a month or 675 mg s.c. every three months. Galcanezumab (Emgality) is a recombinant humanised monoclonal antibody produced in Chinese hamster ovary cells. The recommended dosage is the first loading dose of 240 mg s.c., followed by 120 mg s.c. once a month. Eptinezumab (Vyepti) is a humanized IgG1 CGRP ligand antagonist, with a recommended dose of 100 mg in an i.v. infusion or a maximum of 300 mg every three months [5,11].

Two major placebo-controlled, randomized clinical trials studying the effectiveness of erenumab as migraine prevention in adults with episodic migraines have been conducted so far: ARISE [12], with 577 participants over

12 weeks, and STRIVE [13], with 955 participants, and results from months 4 to 6 compared to baseline. Another study on 667 patients has been conducted by Amgen [14] in order to assess the efficacy of erenumab as chronic migraine prophylaxis. Halo-EM [15] was a major placebo-controlled, randomized, 12 week clinical trial on 875 patients with episodic migraine, who were treated with fremanezumab; Halo-CM [16] was a similar one on 1130 participants with chronic migraine. Two trials on the effectiveness of galcanezumab have been conducted: Evolve-1 [17] on 858 adults with episodic migraine and Regain [18], designed for chronic migraine with 1117 participants. Finally, eptinezumab has been tested in two trials: PROMISE-1 [19] on 898 participants with episodic migraine and PROMISE-2 [20] with 1121 patients suffering from chronic migraine.

Based on clinical trials concerning episodic migraine listed in the previous paragraph, erenumab at a dose of 70 mg showed greater efficacy at 4-6 months of therapy than in the first 3 months, which indicates how much time is required to fully assess the efficacy of therapy. Also, administration of fremazenumab once a month at a dose of 225 mg proved more beneficial than 675 mg once every 3 months. In addition, galcanezumab at a dose of 120 mg appears to be the most effective in reducing monthly migraine days, with the number of these days decreasing by 4.7. Furthermore, increasing the dose of galcanezumab and eptinezumab does not result in an increase in their efficacy, which may indicate that there is a certain threshold dose of the drug above which the efficacy does not improve. The average reduction of migraine days per month among patients with episodic migraine is shown in diagram 1.

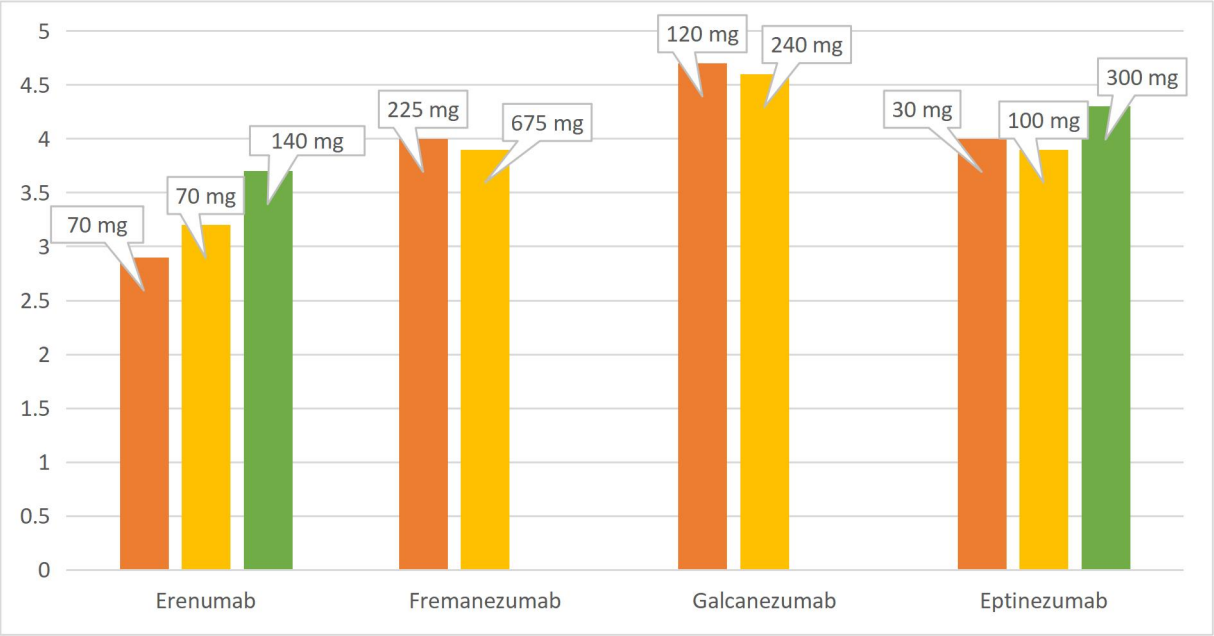

Diagram 1. Mean reduction of monthly migraine days – episodic migraine

The results regarding the percentage of patients with episodic migraine whose monthly number of attacks decreased by at least half are similar to the ones mentioned above, with galcanezumab being most effective at 120 mg and providing this result in as many as 62.3% of participants. The percentage of episodic migraine patients with at least a 50% reduction in monthly migraine days is shown in diagram 2.

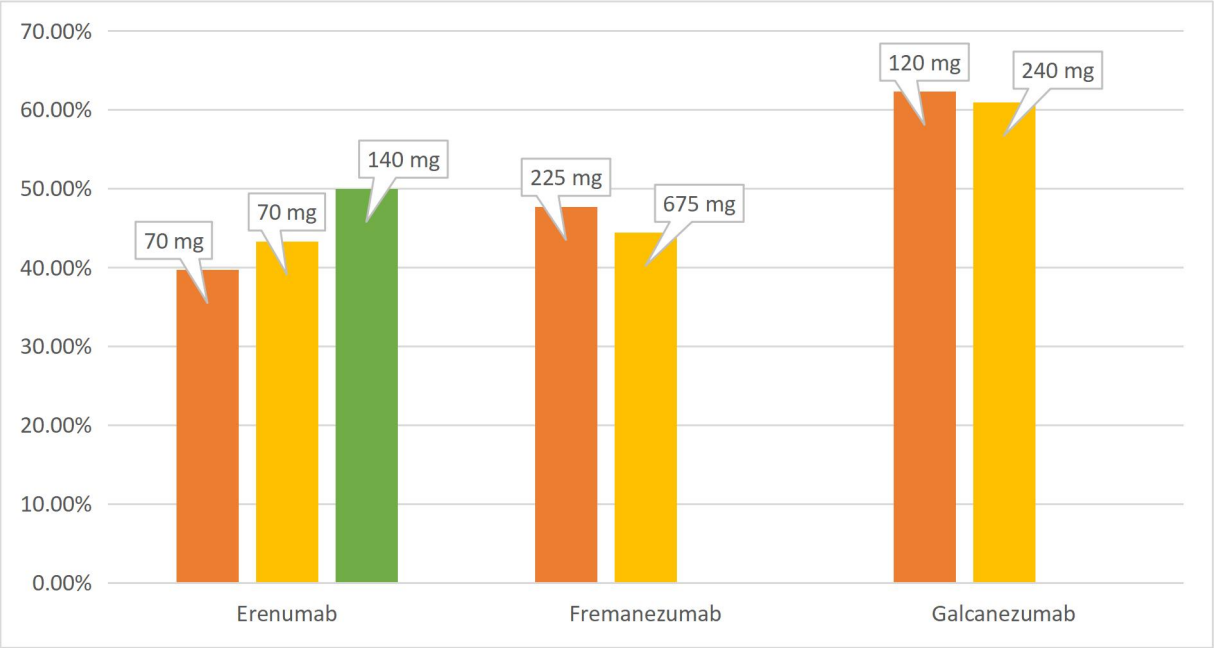

Diagram 2. The percentage of patients with at least a 50% reduction in monthly migraine days - episodic migraine

Similarly, in research concerning chronic migraine the administration of fremanezumab once a month demonstrated superior effects to a triple dose once every 3 months. Eptinezumab at a dose of 300 mg seems to be most effective regarding the decrease of monthly migraine days, with a result of up to 8.2 days. Again, increasing drug doses paradoxically does not result in an improvement in efficacy, and for fremanezumab and galcanezumab even reduces it. The average reduction of migraine days per month among patients with chronic migraine is shown in diagram 3.

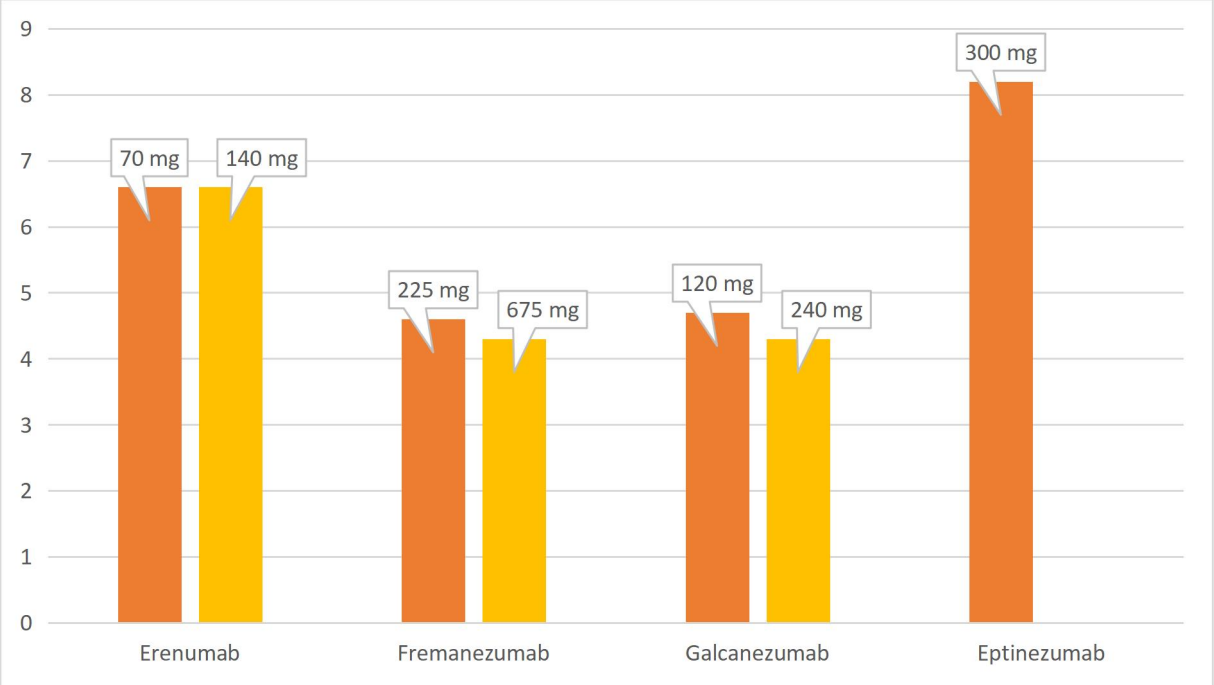

Diagram 3. Mean reduction of monthly migraine days – chronic migraine

Taking into consideration the percentage of patients with chronic migraine whose monthly number of attacks decreased by at least half, erenumab at 140 mg and fremazenumab at 225 mg appeared to be the most effective, where this response occurred in 41% of participants. However, there are no data for eptenizumab. The

percentage of chronic migraine patients with at least a 50% reduction in monthly migraine days is shown in diagram 4.

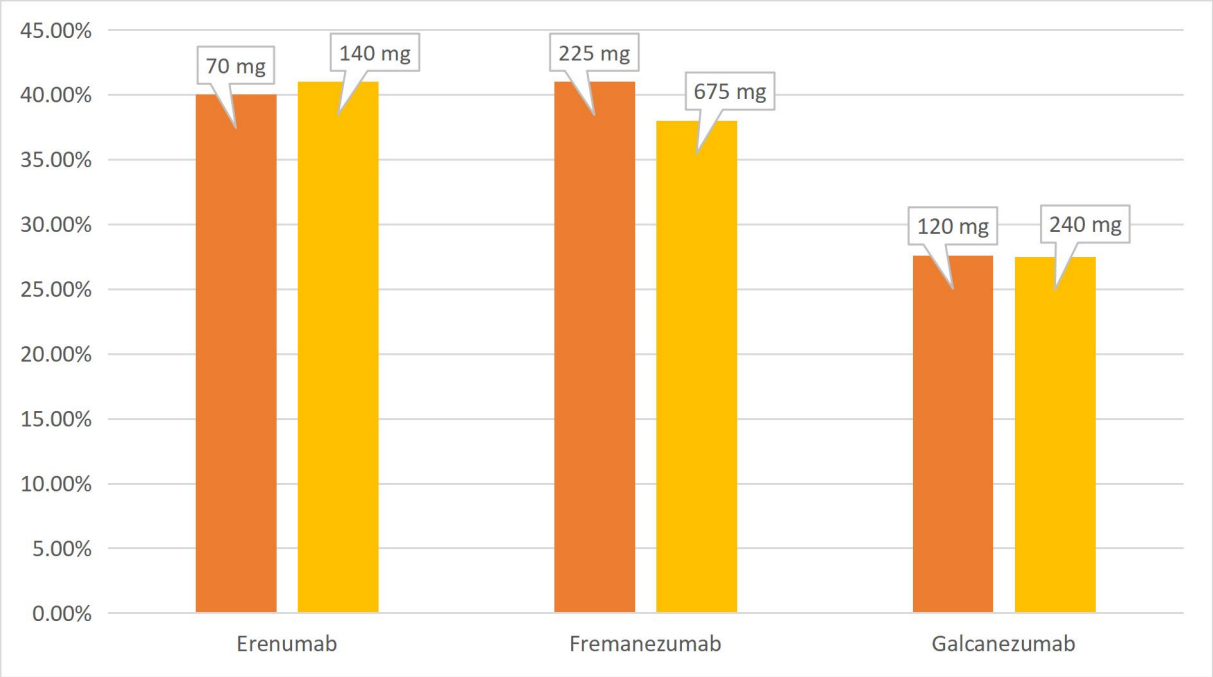

Diagram 4. The percentage of patients with at least a 50% reduction in monthly migraine days - chronic migraine

The analysis of results obtained so far in separate studies on efficacy of particular monoclonal antibodies blocking CGRP or the CGRP receptor suggests that galcanezumab at 120 mg is most effective in the treatment of episodic migraine, whereas eptinezumab is more appropriate for the treatment of chronic migraine. Naturally, randomized controlled trials are still needed in order to compare different anti-CGRP monoclonal antibodies and asses their long-term safety.

As far as side effects of anti-CGRP monoclonal antibodies are concerned, they are usually mild and occur relatively infrequently, with nasopharyngitis, sinusitis, upper respiratory tract infections and injection site reactions being most common [10,21]. They do not exhibit harmful effects on the liver as no toxic metabolites are formed during their metabolism, nor do they cross the blood-brain barrier. Potential side effects include hypertension and myocardial ischemia, as CGRP is found in nerves leading to the heart and blood vessels; impaired wound healing; inflammatory bowel disease, diarrhoea and constipation; pituitary dysfunction. Long-term side effects and efficacy after discontinuation remain unknown [10,21]. There is a risk of developing antibodies directed against the drug [21].

Conclusions

In conclusion, anti-CGRP monoclonal antibodies show greater efficacy, especially in patients for whom "classical" prophylactic treatment has proven ineffective, and a much more favorable safety profile compared to current medications [10]. These drugs seem to provide promising prospects of improving the lives of migraineurs. As based on current knowledge, the benefits are superior to the likelihood of harm.

References

1. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the Trigeminal System in Migraine. Headache. 2019 May;59(5):659-681. doi: 10.1111/head.13529. Epub 2019 Apr 14. PMID: 30982963; PMCID: PMC6593989.
2. Lucas C. Migraine with aura. Rev Neurol (Paris). 2021 Sep;177(7):779-784. doi: 10.1016/j.neurol.2021.07.010. Epub 2021 Aug 9. PMID: 34384631.
3. R P, S C N, S H, K R. Migraine Disability, Quality of Life, and Its Predictors. Ann Neurosci. 2020 Jan;27(1):18-23. doi: 10.1177/0972753120929563. Epub 2020 Jul 3. PMID: 32982095; PMCID: PMC7499825.
4. Edvinsson L. CGRP and migraine: from bench to bedside. Rev Neurol (Paris). 2021 Sep;177(7):785-790. doi: 10.1016/j.neurol.2021.06.003. Epub 2021 Jul 15. PMID: 34275653.

5. Peters GL. Migraine overview and summary of current and emerging treatment options. Am J Manag Care. 2019 Jan;25(2 Suppl):S23-S34. PMID: 30681821.
6. Rammohan K, Mundayadan SM, Das S, Shaji CV. Migraine and Mood Disorders: Prevalence, Clinical Correlations and Disability. J Neurosci Rural Pract. 2019 Jan-Mar;10(1):28-33. doi: 10.4103/jnrp.jnrp_146_18. PMID: 30765967; PMCID: PMC6337984.
7. Edvinsson L. Role of CGRP in Migraine. Handb Exp Pharmacol. 2019;255:121-130. doi: 10.1007/164_2018_201. PMID: 30725283.
8. Silberstein SD. Topiramate in Migraine Prevention: A 2016 Perspective. Headache. 2017 Jan;57(1):165-178. doi: 10.1111/head.12997. Epub 2016 Nov 30. PMID: 27902848.
9. Ha H, Gonzalez A. Migraine Headache Prophylaxis. Am Fam Physician. 2019 Jan 1;99(1):17-24. PMID: 30600979.
10. Rivera-Mancilla E, Villalón CM, MaassenVanDenBrink A. CGRP inhibitors for migraine prophylaxis: a safety review. Expert Opin Drug Saf. 2020 Oct;19(10):1237-1250. doi: 10.1080/14740338.2020.1811229. Epub 2020 Sep 21. PMID: 32811190.
11. Szkutnik-Fiedler D. Pharmacokinetics, Pharmacodynamics and Drug-Drug Interactions of New Anti-Migraine Drugs-Lasmiditan, Gepants, and Calcitonin-Gene-Related Peptide (CGRP) Receptor Monoclonal Antibodies. Pharmaceutics. 2020 Dec 3;12(12):1180. doi: 10.3390/pharmaceutics12121180. PMID: 33287305; PMCID: PMC7761673.
12. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, Palmer K, Picard H, Mikol DD, Lenz RA. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018 May;38(6):1026-1037. doi: 10.1177/0333102418759786. Epub 2018 Feb 22. PMID: 29471679.
13. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Wright IK, Chou DE, Klatt J, Picard H, Lenz RA, Mikol DD. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. Neurology. 2020 Aug 4;95(5):e469-e479. doi: 10.1212/WNL.0000000000010019. Epub 2020 Jul 7. PMID: 32636324; PMCID: PMC7455346.
14. 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 Jun;16(6):425-434. doi: 10.1016/S1474-4422(17)30083-2. Epub 2017 Apr 28. PMID: 28460892.
15. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018 May 15;319(19):1999-2008. doi: 10.1001/jama.2018.4853. PMID: 29800211; PMCID: PMC6583237.
16. 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 Nov 30;377(22):2113-2122. doi: 10.1056/NEJMoa1709038. PMID: 29171818.
17. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018 Sep 1;75(9):1080-1088. doi: 10.1001/jamaneurol.2018.1212. Erratum in: JAMA Neurol. 2019 Jul 1;76(7):872. PMID: 29813147; PMCID: PMC6143119.
18. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology. 2018 Dec 11;91(24):e2211-e2221. doi: 10.1212/WNL.0000000000006640. Epub 2018 Nov 16. PMID: 30446596; PMCID: PMC6329331.
19. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, Pederson S, Allan B, Smith J. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia. 2020 Mar;40(3):241-254. doi: 10.1177/0333102420905132. Epub 2020 Feb 19. PMID: 32075406; PMCID: PMC7066477.
20. Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, Pederson S, Allan B, Cady R. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology. 2020 Mar 31;94(13):e1365-e1377. doi: 10.1212/WNL.0000000000009169. Epub 2020 Mar 24. PMID: 32209650; PMCID: PMC7274916.
21. Deen M, Correnti E, Kamm K, Kelderman T, Papetti L, Rubio-Beltrán E, Vigneri S, Edvinsson L, Maassen Van Den Brink A; European Headache Federation School of Advanced Studies (EHF-SAS). Blocking CGRP in migraine patients - a review of pros and cons. J Headache Pain. 2017 Sep 25;18(1):96. doi: 10.1186/s10194-017-0807-1. PMID: 28948500; PMCID: PMC5612904.