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THE ROLE OF CGRP MONOCLONAL ANTIBODIES IN MIGRAINE TREATMENT – EFFICACY, SAFETY, AND PERSPECTIVES FOR THE FUTURE: A SYSTEMATIC REVIEW

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Migraine is a widespread headache disorder occurring in every age group. It is divided into two types: chronic and episodic migraine. Many medications have been used in its treatment over the years with different degrees of effectiveness. In recent years, more attention has been given to the role of CGRP monoclonal antibodies for treatment, which are CGRP ligand antibodies (fremanezumab, galcanezumab, eptinezumab) and a CGRP receptor antibody (erenumab).

Aim of the study: This study aimed to analyze the efficacy and safety of using CGRP monoclonal antibodies in migraine treatment and discuss CGRP's role in migraine pathogenesis. Both chronic and episodic migraines were subjects of interest.

Material and methods: The search was conducted using the PubMed database. We analyzed articles published in the years 2017–2022. The used keywords were "Migraine", "Monoclonal antibodies", "CGRP", and "Calcitonin gene-related peptide".

Results: The number of articles found depended on the keyword used ("migraine" – 1875 results, "monoclonal antibodies" – 12173 results, "CGRP" – 352 results, and "calcitonin gene-related peptide" – 461 results). A total of 31 articles were quoted in this review. Positive results for treating migraines with CGRP ligand antibodies (fremanezumab, galcanezumab, eptinezumab) and CGRP receptor antibody (erenumab) were observed.

Conclusions: The use of CGRP ligand and receptor antibodies seems promising for migraine therapy due to their relatively mild side effects and high efficiency.

KEYWORDS: migraine, monoclonal antibodies, CGRP, calcitonin gene-related peptide

Background

Migraine is a widespread primary headache disorder affecting approximately 1 billion people worldwide [1]. In approximately one-fifth of cases, diseased people undergo their first attack within the first 5 years of life [2]. It can manifest itself as a persistent headache attack lasting 4 to 72 hours, characterized by unilateral, pulsating pain occurring with comorbidities such as nausea, photophobia, or phonophobia [3]. Whereas a migraine with aura consists of a headache and sensory, visual, or speech disturbances [4]. It is estimated that transition-focal neurological symptoms prelude a headache in one-third of patients [5]. The disease can be divided into chronic migraines, manifesting in rife headache at-

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tacks occurring at least 15 days per month for more than 3 months, and episodic migraines [6], which is its complement [7]. Although the pathological background of the migraine mechanism is not fully understood, it is considered to be multifactorial and related to both genetic and environmental factors [5]. Due to the lack of efficacy of commonly used drugs, such as triptans, propranolol, and epilepsy drugs, immunological treatment has expanded [8].

Calcitonin gene-related peptide (CGRP) is a neuropeptide produced in the central and peripheral nervous systems [9]. It consists of 37 amino acids, which exist in 2 isoforms encoded by alternative splicing of mRNA [10,11]. α-CGRP is predominant in the central nervous system, whereas β-CGRP occurs mainly in presynaptic endings of enteric sensory neuronal cells [10]. The CGRP receptor is a membrane heterodimer containing the calcitonin receptor-like receptor, which is a class B G-protein coupled receptor [12]. CGRP has been detected in the hypothalamus, thalamus, cerebellum, and trigeminal system, where it is synthesized [11]. In the peripheral nervous system, it is present in the fibers responsible for pain transmission – sensory Aδ fibers and unmyelinated C fibers [11,13]. CGRP released from C fiber endings can bind to the receptors on Aδ fiber endings for nociceptive transmission [13].

Aim of the study

The goal of this article was to gather information about the efficiency and safety of using CGRP monoclonal antibodies in migraine therapy and to discuss the role of CGRP in migraine pathogenesis.

Material and methods

The inclusion criteria used in the review were date of publication, compliance with the described topic, and reliability of the information.

Eligibility criteria

This was based on the publication date, which was the time slot between 2017 and 2022. The samples include patients suffering from chronic or episodic migraines regardless of sex. The phenomenon of interest was the response to CGRP monoclonal antibodies in patients with both types of migraine. Any patient reporting was evaluated. All kinds of observational studies were included. One can search for qualitative, quantitative, and mixed studies. Exclusion criteria included studies not reporting pre-specified efficacy or safety outcomes, patients with conditions other than chronic or episodic migraines, and the association of CGRP monoclonal antibodies with other interventions.

Search strategy

The search was conducted using the PubMed database. The used keywords were "Migraine", "Monoclonal antibodies", "CGRP", and "Calcitonin gene-related peptide".

Data collection process

Each of the three authors reviewed the scientific articles independently. First, we read abstracts and then the entire selected publications. The extracted data items included the following information: safety and efficiency of the CGRP monoclonal antibodies in migraine therapy. The risk of bias for each study was assessed independently by the same authors. The collected data was presented in text form to allow for a thorough understanding of the topic under discussion.

Results

The number of articles found depended on the keyword used ("migraine" – 1875 results, "monoclonal antibodies" – 12173 results, "CGRP" – 352 results, and "calcitonin gene-related peptide" – 461 results). A total of 31 qualified articles were quoted in this review.

CGRP plays a crucial role in migraine pathogenesis as an endogenous vasodilator [11] as it participates in a final common pathway in smooth muscle cells by decreasing intracellular free calcium concentrations, resulting in muscle relaxation [10]. Activated trigeminal nerve fibers deliver CGRP, other vasodilators, neurotransmitters, and proinflammatory mediators, which increase CGRP synthesis, causing a migraine attack [14]. Moreover, it is involved in peripheral sensitization [15], perception [14], and nociceptive transmission together with substance P and bradykinin [10]. However, a CGRP infusion in migraine patients provokes migraine-like attacks, which were not developed in control subjects [16].

In a randomized, double-blind clinical trial with 1890 patients aged 18–70 years suffering from chronic or episodic migraines, they received quarterly or monthly dosing of fremanezumab via subcutaneous injections over 12 months. The quarterly dosage was 675 mg once every 3 months with a placebo taken every month. The monthly dose for patients with chronic migraines was 675 mg, and 225 mg for pa-

tients with episodic migraines, followed by a dose of 225 mg monthly. Drug supply reduced the monthly number of migraine days and migraine-related ailments during the one-year trial [17].

Goadsby et al. pointed out that the most common adverse events related to fremanezumab are injection-site induration, pain, erythema [17,18,19], hemorrhage, rash, swelling, and pruritus [17]. Serious adverse events occurring in patients in the clinical trial were status migrainosus, basal cell carcinoma, cerebrovascular accident, migraine, malignant melanoma, osteoarthritis, and retinal tear [17]. Other publications report the occurrence of diarrhea, anxiety, and depression as grounds for discontinuing participation in the trial [18,19]. The other mentioned side effects comprise infectious diseases, such as upper respiratory tract infections, nasopharyngitis [17,19], sinusitis, urinary tract infections, bronchitis, and influenza. The most common cardiovascular adverse event is hypertension [17], although the risk of cardiovascular events has not been thoroughly investigated [19]. The risk of using CGRP monoclonal antibodies during pregnancy and lactation is unknown, the concern is whether it is safe. One of the hypotheses is that due to increased CGRP levels during pregnancy, plasma volume is expanded as a consequence of vasodilation. Therefore, it is believed that blocking CGRP elevation would presumably affect hypertension development in pregnant women. The fremanezumab molecule is large, eventuality of secretion into the breast milk is doubtful, however, safety during breastfeeding requires more research. The greatest risk of breastfeeding occurs in the first 3 days postpartum when spaces between breast alveolar cells are larger, enabling huge immunoglobulins like fremanezumab molecules to pass into the milk, constituting a threat to the infant [19]. Table 1 presents the characteristics of the analyzed articles included in this review.

Table 1. Summary of articles included in the review

1st Author	Number of patients	Inclusion criteria	Exclusion criteria	Outcomes and results	Limitations
Ashina M [1]	888	Adults aged 18–75 with a diagnosis of migraine per the International Classification of Headache Disorders (ICHD) criteria	Patients with uncontrolled or untreated psychiatric conditions, pain syndromes, diabetes, cardiovascular diseases, and neurological diseases	The ≥75% migraine responder rates occurred in 24.7% of patients treated with eptinezumab 30 mg, 22.2% for 100 mg, and 29.7% for 300 mg, compared with 16.2% for placebo, with ≥50% responder rates of 50.2%, 49.8%, 56.3%, and 37.4%, respectively	Limited geographic diversity, low number of male patients
Lipton RB [7]	656	Patients with chronic migraines	Patients with fibromyalgia or poorly controlled hypertension	In 53.1% of the 358 erenumab-treated completers had a reversion to episodic migraines; monthly reversion rates to episodic migraines were typically higher among patients receiving 140 mg versus 70 mg	Dose-specific chronic to episodic migraine reversion rates and efficacy data were based on 4-week headache day data and may not be representative of outcomes based on 12-week headache day data
Wang X [8]	8 926	Adults diagnosed with migraines according to the International Classification of Headache Disorders second edition (ICHD-II), or the third edition (ICHD-III)	Trials that only compared different doses of a single CGRP monoclonal antibody; trials that only compared a CGRP monoclonal antibody with other pharmacologically active drugs; trials that assessed CGRP binding monoclonal antibodies in pediatric migraine patients	Most treatments, including erenumab, fremanezumab, and galcanezumab, were significantly more effective than placebo. Fremanezumab was superior to eptinezumab in reducing the frequency of headache attacks by at least 50%	Several trials did not provide treatment-emerging adverse events; the inclusion criteria varied in the different trials; some trials only included patients with episodic migraines, some included patients with chronic migraines, and some mixed these two subtypes of disease
Chen YY [15]	1 049	Randomized controlled trials (RCTs) comparing CGRPmAbs or BoNT-A to placebo in the treatment of chronic migraines	RCTs with N-of-one designs or cross-over designs were excluded	Fremanezumab had an effect similar to BoNT-A in the reduction of headache days at week 12. Galcanezumab reduced more migraine days than BoNT-A at week 12; fremanezumab showed similar findings	CGRPmAbs and BoNT-A were compared indirectly by using a placebo as a common comparator; the variations in the placebo effect sizes and heterogeneity between BoNT-A trials might influence results; the number of trials included was insufficient

Table 1 contd.

1st Author	Number of patients	Inclusion criteria	Exclusion criteria	Outcomes and results	Limitations
Goadsby PJ [17]	1 890	Adults aged 18–70 with a history of migraines according to the ICHD-III	Use of onabotulinumtoxinA during the 4 months before screening; use of opioids or barbiturates on >4 days/month for migraine or any other reason, previous failure of ≥2 preventive medications after an adequate therapeutic trial; use of an intervention or device for migraines during the 2 months before screening	Fremanezumab reduced monthly migraine days (CM quarterly – 7.2 days, CM monthly – 8.0 days, EM quarterly – 5.2 days, EM monthly – 5.1 days) and headache days of at least moderate severity (CM quarterly – 6.4 days, CM monthly – 6.8 days, EM quarterly – 4.4, EM monthly – 4.2 days) from baseline to 12 months	No placebo control; small numbers of patients with treatment-emergent positive electronic C-SSRS responses or suicidal ideation AEs
Dodick DW [18]	875	Women and men aged 18–70 with a history of migraines based on the International Classification of Headache Disorders 3 beta version (ICHD-3 beta) diagnostic criteria for at least 12 months prior to screening and with onset prior to age 50 years	Patients who had previous treatment failure with 2 classes of migraine-preventive medications were excluded	The proportion of patients with response rates of at least a 50% reduction in mean number of monthly migraine days during the 12-week treatment period were 47.7% for the fremanezumab monthly dosing group and 44.4% for the fremanezumab single-higher-dose group compared with 27.9% for the placebo group	The study did not include treatment-refractory patients with more than 2 failed preventive drug clusters or those who had continuous headaches; the trial was limited to the evaluation of endpoints at a short-term follow-up of 3 months after randomization
Zhao X [21]	3 565	The study was a randomized-controlled trial (RCT) on CGRP monoclonal antibodies for migraine prophylaxis; the patients were diagnosed with migraine according to the ICHD-3, beta version or ICHD-II; no limitations on the time of publication, and blind or publication types	Patients older than 65 years old, gravidas, patients with a history of major cardiovascular or cerebrovascular diseases	Galcanezumab at 120, 150, 240, and 300 mg significantly reduced MMDs (120 mg: MD – 1.79, 95% CI – 2.06 to – 1.53, P<0.00001; 150 mg: MD – 1.20, 95% CI – 1.28 to – 1.12, P<0.00001; 240 mg: MD – 1.85, 95% CI – 1.94 to – 1.76, P<0.0001; 300 mg: MD – 0.62, 95% CI – 0.73 to – 0.51, P<0.00001)	The study was restricted to eligibility criteria, in which merely five studies were included in the analysis; some of the studies were completed by the same researchers, which may lead to publication bias;
Han L [22]	3 166	Patients diagnosed with chronic migraines according to the ICHD-3; intervention was CGRP monoclonal antibodies	No data	CGRP monoclonal antibodies improved 50% responder rates (OR = 2.42, 95% CI = [2.04, 2.87]) and 75% responder rate (OR = 1.95, 95% CI = [1.30, 2.91], as compared with placebo	Lack of the best dose or regimen of CGRP monoclonal antibodies for preventive treatment of chronic migraines

Discussion

Migraines are a widely spread neurological disease divided into two types: chronic and episodic. As many drug groups used in its treatment are not efficient enough, new therapy techniques have been considered. Since the CGRP role in migraine pathogenesis has been proved, scientists have developed its molecule and receptor as a target for monoclonal antibodies.

As it has been proved that the CGRP participates in the migraine attack origination, it has become a potential pharmacological target for its treatment. Thus, the monoclonal antibodies, which are CGRP receptor complex antagonists (erenumab) [20] and the monoclonal antibodies against the CGRP molecule (galcanezumab, eptinezumab, fremanezumab) have been developed [21]. When used for prophylaxis, they reduced the monthly number of days with migraine attacks [8]. Treating chronic migraines is infrequent, although as a preventive treatment method for episodic migraines seems promising [22]. However, the safety and efficacy of CGRP monoclonal antibodies require further investigation [8]. Used in the prevention of both chronic and episodic migraines [23,24,25] and episodic cluster headaches [26], monoclonal antibodies targeted the CGRP molecule or its receptor [23,24,25,26,27,28]. They are administered via subcutaneous or intravascular injections. Due to their large size and instability in the gastrointestinal

environment, oral administration is objectionable [29]. Whereas erenumab is a fully human antibody, CGRP molecule antagonists, consisting of galcanezumab, eptinezumab, and fremanezumab, are humanized [26]. It needs to be underlined that CGRP levels vary between age, sex, and hormones, affecting its activity, with a noticeably superior role in women [30]. According to the latest reports, CGRP gained importance as a potential target for oncological treatment. As CGRP gene expression affects stem cell regulation, tumor stem cell differentiation and migration can be modulated by switching off or switching on CGRP gene expression [31]. Evidence for the involvement of the immune system is varied, but not specific enough to indicate a distinct role for these cells. But this system seems to be involved, at least partly, in the pathogenesis of migraines [30]. The tolerability and immunogenicity of monoclonal antibodies depend on antibody type and the quantity of non-human or extraneous sequences in the molecule [26].

Limitations

Due to the limited amount of data, the efficacy and safety of using CGRP monoclonal antibodies in migraine treatment is not fully known. Therefore, there is a lack of data including this therapy in pregnant and nursing women. As the treatment is not widely used it still requires further investigation.

Conclusion

A described use of CGRP monoclonal antibodies includes the treatment of both chronic and episodic migraines, as well as attack prevention. The tolerability of CGRP antibody therapy depends on the antibody type. The most common side effects include injection-site induration, pain, infections, hypertension, rash, and swelling. Serious adverse events include status migrainosus, basal cell carcinoma, cerebrovascular accident, migraine, malignant melanoma, osteoarthritis, and retinal tear. However, they occur relatively rarely, and their relationship with CGRP injection is uncertain. The risk of using CGRP monoclonal antibodies during pregnancy and lactation is unknown. Thus, the therapy seems promising for the future but requires further investigation and more data.

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