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editorial-office@sciformat.ca

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ERENUMAB, A NEW PREVENTIVE TREATMENT FOR MIGRAINE: MECHANISM OF ACTION, SAFETY AND EFFICACY

Mikołaj Jońca *(Corresponding Author, Email: joncamikolaj@gmail.com)*
Pomeranian Medical University, ul. Rybacka 1, 70-204 Szczecin, Poland
ORCID ID: 0009-0006-4435-1138

Natasza Kurys
Medical University of Lodz, Aleja T. Kościuszki 4, 90–419 Łódź, Poland
ORCID ID: 0009-0005-7090-259X

Mikhail Kazachok
Medical University of Warsaw, ul. Żwirki i Wigury 61, 02-091 Warszawa, Poland
ORCID ID: 0009-0006-2764-3710

Szymon Paruszewski
Medical University of Warsaw, ul. Żwirki i Wigury 61, 02-091 Warszawa, Poland
ORCID ID: 0009-0005-1822-244X

Julia Kupczak
Łazarski University, Świeradowska 43, 02-662 Warszawa, Poland
ORCID ID: 0009-0002-3423-8685

Aleksandra Dybcio
Medical University of Lublin, Al. Racławickie 1, 20-059 Lublin, Poland
ORCID ID: 0009-0006-7840-3290

Katarzyna Kupczyk
Southern Hospital in Warsaw, ul. Rotmistrza Witolda Pileckiego 99, 02-781 Warszawa, Poland
ORCID ID: 0009-0004-7532-7769

Dorota Szydłowska
Opole University, plac Kopernika 11A, 45-040 Opole, Poland
ORCID ID: 0000-0001-6763-6124

Adam Kubisa
Pomeranian Medical University, ul. Rybacka 1, 70-204 Szczecin, Poland
ORCID ID: 0009-0003-1320-9890

Mateusz Miluski
Pomeranian Medical University, ul. Rybacka 1, 70-204 Szczecin, Poland
ORCID ID: 0009-0003-5744-3291

ABSTRACT

Background: Migraine is a common, debilitating and one of the most disabling of the neurovascular disorders. The common treatment has been based on non-specific medications derived from other clinical disciplines such as beta-blockers, antiepileptics and antidepressants, which have variable efficacy and many unwanted side effects and are therefore frequently discontinued. The recent knowledge about the involvement of CGRP and its receptors in migraine pathophysiology has opened new avenues for anti-migraine treatment.
Objectives: The aim of this paper is to comprehensively review the mechanism of action, clinical efficacy, safety profile, and comparative effectiveness of erenumab - the first fully human monoclonal antibody designed specifically for migraine prevention.
Methods: A narrative review of the current medical literature was conducted using the PubMed database. The analysis included data from phase 2, 3 and 4 randomized controlled trials, long-term open-label extensions, and current international neurological guidelines.
Results: Erenumab is a monoclonal antibody that selectively targets the canonical CGRP receptor and functions as a competitive receptor antagonist. Binding of erenumab to the CGRP receptor does not result in vasoconstriction and does not interact with the CYP450 enzyme system. Studies including STRIVE, ARISE and LIBERTY trials have demonstrated the high efficacy of erenumab in the reduction of MMD in both EM and CM patients, including those who have failed multiple prior prophylactic treatments. The HER-MES trial has further confirmed the high tolerability of erenumab and a higher retention rate compared to topiramate. The safety profile is highly favorable, with injection site reactions and constipation being the most frequently reported adverse events. Furthermore, erenumab can safely be given alongside with novel acute treatments, such as gepants and ditans.
Conclusions: Erenumab holds great promise in migraine prophylaxis as it's offering a targeted, highly effective, and well-tolerated therapeutic option. Future research should focus on its long-term efficacy in a real-world setting. One important aspect will be to explore its safety during pregnancy and in children. An interesting and potentially clinically useful aspect for non-responders will be exploring the possibility of combining it with antibodies against other neuropeptide pathways, such as those involving PACAP.

KEYWORDS

Erenumab; Migraine Prophylaxis; CGRP; Monoclonal Antibodies

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Abbreviations

CGRP - calcitonin gene-related peptide
CYP450 - cytochromes P450
MMD - monthly migraine days
CM - chronic migraine
EM - episodic migraine
PACAP - pituitary adenylate cyclase-activating polypeptide
YLD - years lived with disability
CSD - cortical spreading depression
VIP - vasoactive intestinal peptide
ICHD-3 - 3rd edition of the International Classification of Headache Disorders
MIDAS - Migraine Disability Assessment
HIT-6 - Headache Impact Test
NSAID - non-steroidal anti-inflammatory drug
5-HT1B - 5-hydroxytryptamine receptor 1B

5-HT1D - 5-hydroxytryptamine receptor 1D
5-HT1F - 5-hydroxytryptamine receptor 1F
GABA - gamma-aminobutyric acid
TCA - tricyclic antidepressant
SNRI - serotonin norepinephrine reuptake inhibitor
CBT - cognitive-behavioral therapy
sTMS - single-pulse transcranial magnetic stimulation
IgG2 - immunoglobulin G2
DNA - deoxyribonucleic acid
CHO - Chinese hamster ovary
CALCRL - calcitonin receptor-like receptor
RAMP1 - receptor activity-modifying protein 1
cAMP - cyclic adenosine monophosphate
ADCC - antibody-dependent cellular cytotoxicity
CDC - complement-dependent cytotoxicity
EMA - European Medicines Agency
FDA - Food and Drug Administration
EHF - European Headache Federation
AHS - American Headache Society
SC - subcutaneous
TMDD - target-mediated drug disposition
FAERS - Food and Drug Administration Adverse Event Reporting System
MSMD - monthly specific medication days
OLE - Open Label Extension
FcRn - neonatal fragment crystallizable receptor
MRHD - Maximum Recommended Human Dose
IgG - immunoglobulin G
NMA - network meta-analysis
ODT - orally disintegrating tablet
RCT - randomised clinical trial
EBM - evidence based medicine
PAC1 - pituitary adenylate cyclase-activating polypeptide type 1 receptor

1. Epidemiology

Migraine is one of the most prevalent and debilitating neurological disorders worldwide, ranking as the second leading cause of disability, as measured by the YLD index [1, 2]. The estimated global prevalence of migraine is approximately 14–15%, making it a condition with a profound socioeconomic impact that generates billions in losses due to lost workdays and diminished productivity [2, 3]. There is clear gender bias as migraine occurs nearly threefold more frequently in women than in men primarily due to fluctuation in sex hormones particularly estrogen [3, 4]. The peak prevalence coincides with the most productive years of life, specifically the 35 to 39 age demographic, although migraine also significantly affects children and adolescents [1, 4].

In Poland, the lifetime prevalence of this condition is approximately 10%, which corresponds to the estimates of 3.5 - 4 million people that this problem affects [5]. Over 400 000 out of them, i.e. about 1% of the population, suffer from the most severe, chronic form of the disorder characterized by an extremely high health and socio-economic burden and severely reducing quality of life [4, 5]. However, there are many studies indicating that despite their high frequency, migraines are most frequently trivialized, therefore underdiagnosed and inadequately treated across all levels of the healthcare sector [5, 6].

2. Pathophysiology

The pathophysiology of migraine is highly complex and involves a multifactorial sensory processing dysfunction in the brain and the peripheral nervous system as a whole [7, 8]. The initiation of the migraine attack process, known as the prodromal phase, primarily occurs in the hypothalamus and the brainstem which can explain early mood, appetite and sleep disturbances that may occur hours prior to the actual headache [7, 9]. In turn, the phenomenon of migraine aura is driven by CSD. This is a slowly propagating wave of neuronal

and glial depolarization across the cerebral cortex, followed by a prolonged suppression of their activity in conjunction with altered blood flow consisting of hyperemia that transitions into oligemia [7, 10].

The fundamental mechanism generating pain is the activation of the trigeminovascular system [7, 8]. Of these neuropeptides the calcitonin gene related peptide (CGRP) has been historically and clinically the most studied and proven to cause the profound dilation of the meningeal blood vessels leading to a sterile neurogenic inflammation [8, 11, 12].

Studies reported over the last few years that the migraine aetiology may be multi peptidergic in nature [13, 14]. It is believed that PACAP and VIP play a fundamental role alongside CGRP [13, 15]. It has been demonstrated that PACAP and CGRP, despite eliciting similar symptoms in patients (such as allodynia and photophobia), operate via parallel, largely independent intracellular signaling pathways [14]. Furthermore, CGRP is released primarily from the trigeminal ganglion, whereas PACAP predominates in the parasympathetic sphenopalatine ganglion, thus being more relevant to autonomic symptoms in the migraine attack such as lacrimation and nasal congestion [13, 14, 15]. Ultimately, chronic activation of these pathways induces the development of peripheral and central sensitization that leads to cutaneous allodynia observed in migraine headaches [8, 9].

3. Symptoms and Diagnosis

Migraine is a phasic disorder. A full migraine attack can be divided into four phases: the prodromal phase, the aura (which occurs in about 25-30% of migraine attacks), the headache phase, and the postdromal phase [6, 9]. The aura most frequently takes the form of fully reversible visual disturbances (e.g., scintillating scotomas, zigzag lines) that gradually progress over a period of 5 to 20 minutes, and less commonly presents as sensory disturbances or transient aphasia [6]. The headache phase is defined by moderate to severe, unilateral, in most cases pulsating headache increasing in severity over time that significantly worsens with routine physical activity [6, 16]. The attack, usually lasting from 4 to 72 hours (without pharmacological intervention), is associated with a host of other symptoms, the most prominent being nausea, vomiting, and extreme sensitivity to light (photophobia) and sound (phonophobia) [16, 17].

The diagnosis of a migraine is based solely on a clinical history documented as precisely as possible in accordance with the international ICHD-3 criteria of 2018 [16, 18]. No specific blood biomarkers or findings in standard neuroimaging studies have been found relevant or characteristic, which means that the complete physical and neurological examination is essential in order to find out possible underlying conditions for secondary “migraine-like” headaches [15, 19]. These may mask serious and potentially life threatening disorders, such as ischemic stroke, intracranial arteriovenous malformations, meningiomas or traumatic brain injuries [17, 19]. This is achieved through the rigorous assessment of warning signs (the so-called "red flags") which must be diligently investigated [17].

From a clinical perspective, accurate classification of a patient’s headache disorder as being either episodic or chronic migraine is crucial due to the vastly increased burden of disease and the differing approach to the prophylaxis of chronic migraine [4]. There is likely a significant degree of inconsistency when it comes to classifying patients accurately due to the number of discrepancies identified in relation to the accuracy of pain phenotype classification and adherence to ICHD-3 criteria between primary care and specialist headache clinics [20].

Beyond assessing attack frequency, attack severity is also a very important criterion for the diagnosis and thus is an important criterion for the choice of acute therapy according to the individualized stratified care approach [21]. In routine clinical practice, migraine episodes are classified as mild, moderate, or severe, taking into account the subjective pain intensity and the extent to which it impairs the patient's ability to function normally [17, 21]. To objectify this assessment and precisely quantify the degree of disability caused by the disease over time (i.e., migraine burden), guidelines recommend the routine application of validated psychometric tools [3, 21]. The most widely used instruments include the MIDAS questionnaire and the short HIT-6 [21]. These tools not only facilitate an unambiguous definition of the patient's disease severity but also serve as a gold standard in monitoring the efficacy of the implemented therapeutic interventions [17, 21]. The ICHD-3 criteria precisely differentiate the main clinical states of migraine (Table 1) [16].

Table 1. Diagnostic criteria for migraine without aura, migraine with aura, and chronic migraine according to the ICHD-3 classification [16]. Abbreviations: ICHD-3: 3rd edition of the International Classification of Headache Disorders.

Diagnosis	Main Diagnostic Criteria
Migraine without aura	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C.Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis.
Migraine with aura	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis.
Chronic migraine	A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura C. On ≥8 days/month for >3 months, fulfilling any of the following: 1. criteria C and D for migraine without aura 2. criteria B and C for migraine with aura 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis

4. Current Therapeutic Strategies in Migraine Management

4.1 Acute (Abortive) Treatment

The primary goal of pharmacological acute treatment is the rapid, effective and safe achievement of headache relief and resolution of its associated symptoms, and to enable an immediate return to normal activity level [22, 23]. Medications utilized in this strategy are traditionally classified as non-specific drugs (with generalized analgesic effects) and migraine-specific agents [23, 24]. The selection of the optimal drug should be based on individual approach and the assessment of attack severity, the patient's comorbidities (i.e., risk profiling), and their experiences with previous treatments [22, 24].

NSAIDs - including ibuprofen, naproxen, diclofenac, or acetylsalicylic acid - constitute the cornerstone of first-line therapy for patients reporting mild to moderate attacks [22, 23]. Due to some clinical studies their bioavailability and efficacy in aborting attacks are significantly improved when used in combination with antiemetic and prokinetic agents, such as metoclopramide or domperidone [22, 24, 25]. This approach simultaneously alleviates the bothersome nausea, a common accompanying symptom of migraine, and stimulates normal peristalsis of the gastrointestinal tract, which is often impaired during an attack [24, 25].

In the setting of moderate to severe attacks, or in cases where non-specific drugs are ineffective, the standard of care is the introduction of specific medications. The first line of treatments relies primarily on triptans (e.g., sumatriptan, zolmitriptan, eletriptan) [23, 26, 27]. These are highly selective agonists of the 5-HT1B and 5-HT1D serotonin receptors [26, 28]. Their multidirectional mechanism of action involves inducing direct vasoconstriction of excessively dilated meningeal blood vessels, reducing the peripheral release of nociceptive inflammatory neuropeptides (mainly CGRP) from trigeminal nerve endings, as well as inhibiting pain transmission within the brainstem nuclei [27, 28, 29]. The use of ergot alkaloid derivatives, such as ergotamine and dihydroergotamine, is of mainly historical value, due to their non-linear pharmacokinetics and the substantial risk of systemic adverse effects, including sustained coronary vasospasm [29, 30]. In recent years, for patients with significant cardiovascular contraindications to triptans, newer generations of specific drugs with distinct mechanisms of action have been introduced into the guidelines - ditans (highly selective 5-HT1F receptor agonists) and gepants (small-molecule, oral CGRP receptor antagonists) [31, 32].

4.2 Prophylactic Treatment

Pharmacological prophylaxis is recommended in the following situations: excessive frequency (typically four or more headache days per month), extremely prolonged attacks, and when acute treatment is completely ineffective, poorly tolerated, or overused [33, 34, 35]. The principal objective of this long-term therapeutic intervention is to significantly reduce the number, duration, and severity of pain episodes, thus allowing for an improvement in the quality of life of the patients and preventing the progression of episodic migraine into a treatment-refractory chronic form [34, 35].

The majority of non-specific preventive drugs were introduced for other primary uses in cardiology, neurology or psychiatry [33, 36]. First-line therapy relies on classic β-adrenergic blocking agents without intrinsic sympathomimetic activity (e.g., propranolol, metoprolol, or timolol) [34, 37]. A second key therapeutic class with documented strong preventive efficacy is antiepileptic drugs, specifically topiramate and valproic acid [34, 36]. By modulating ion channels (sodium and calcium) and enhancing GABAergic neurotransmission, they reduce cortical excitability, thereby preventing the initiation of CSD [35, 37]. Antidepressants, including TCAs (e.g., amitriptyline) and SNRIs (e.g., venlafaxine), are also widely used in headache prevention [34, 38].

The main clinical challenge in the use of traditional prophylactic drugs is their relatively unfavorable adverse effect profile [36, 39]. Not uncommon side effects, including drastic weight gain, chronic fatigue, dizziness, hypotension, cognitive impairment, or significant hair loss, frequently result in decreased therapeutic compliance and, consequently, self-discontinuation of treatment by patients within the first few months [39, 40]. With precise injection technique onabotulinumtoxinA has been approved as a highly efficient prophylactic treatment for the most severe form of migraine, chronic migraine [40, 41]. This therapy exhibits a very favorable tolerability profile and effectively prevents the peripheral sensitization of meningeal nociceptors by inhibiting the vesicular release of neurotransmitters [41].

4.3 Non-Pharmacological Strategies and Lifestyle Modifications

Non-pharmacological management plays a fundamental role in the comprehensive management of the disease and must always be considered as part of the drug-based therapy, or as the sole therapy in cases of mild symptoms of the disease [42, 43]. In this sense, it should be recommended to every newly diagnosed patient [42]. Maintaining a detailed "headache diary" in which patients can record all possible stimuli is an invaluable clinical tool, enabling the accurate identification and avoidance of patient-specific triggers [42, 43]. These primarily include severe emotional stress, circadian rhythm disruptions, sleep deprivation, fasting, specific dietary components (e.g., monosodium glutamate, tyramine in aged cheeses, aspartame, alcohol), although fluctuations in estrogen levels during the menstrual cycle may also play a relevant role [43, 44].

According to American and European neurological guidelines, the application of behavioral methods should be part of a comprehensive treatment plan [42, 45]. The highest level of evidence is attributed to biofeedback, relaxation training, and professional CBT, which effectively modulate the central nervous system's response to painful stimuli and assist in coping with psychological tension [44, 45]. Modern, minimally invasive devices for transcutaneous supraorbital nerve stimulation (Cefaly) or sTMS are also gaining recognition in challenging clinical cases [46].

A distinct and increasingly popular subcategory of prophylaxis comprises dietary modifications and targeted nutraceuticals [47, 48]. The compounds with preventive effects most thoroughly investigated in controlled clinical trials include high doses of riboflavin (vitamin B2-typically 400 mg/day), coenzyme Q10

(150-300 mg/day), and organic magnesium salts [47, 48]. These substances stabilize mitochondrial energy metabolism and the electron transport chain that is usually depressed in neurons in individuals with migraine [47]. The toxicological profile of the use of nutraceuticals as therapeutic agents is close to zero and the side effects are generally not clinically important. This type of prophylaxis can therefore be of particular value when it is desirable to keep to a minimum as possible the use of other prophylactic drugs such as when planning pregnancy, during pregnancy or lactation [48, 49].

Table 2. Overview and categorization of traditional, non-modern pharmacological strategies in migraine management [22, 26, 35].

Clinical strategy	Therapeutic category	Principal mechanism of action and desired clinical effect	Representative active substances
Acute treatment	NSAIDs	Non-specific alleviation of nociceptive pain intensity and inhibition of the inflammatory cascade	Ibuprofen, naproxen, diclofenac, acetylsalicylic acid
Acute treatment	Serotonin receptor agonists (Triptans)	Targeted, potent vasoconstriction of meningeal blood vessels, specific attack abortion via presynaptic 5-HT1B and 5-HT11D receptors	Sumatriptan, zolmitriptan, eletriptan
Acute treatment	Antiemetic and prokinetic drugs	Improvement of analgesic absorption from the gastrointestinal tract and control of severe nausea accompanying the attack	Metoclopramide, domperidone
Prophylaxis	β-adrenergic blocking agents (Beta-blockers)	Generalized reduction of autonomic cardiovascular hyperreactivity, decrease in attack frequency	Propranolol, metoprolol, timolol
Prophylaxis	Antiepileptic drugs	Modulation of cation channels and inhibition of pathological hyperexcitability, prevention of CSD	Topiramate, valproic acid
Prophylaxis	Antidepressant drugs (TCAs/SNRIs)	Elevation of the pain threshold, migraine prevention (with particular emphasis on the form coexisting with tension-type headache)	Amitriptyline, venlafaxine
Prophylaxis	Selected neurotoxins	Inhibition of peripheral neurotransmitter release, treatment reserved exclusively for chronic migraine	OnabotulinumtoxinA

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; 5-HT1B: 5-hydroxytryptamine receptor 1B; 5-HT1D: 5-hydroxytryptamine receptor 1D; CSD: cortical spreading depression; TCAs: tricyclic antidepressants; SNRIs: serotonin norepinephrine reuptake inhibitors.

5. Erenumab

5.1 Mechanism of Action

Erenumab is a novel, fully human monoclonal antibody (IgG2 isotype), designed and synthesized using recombinant DNA technology in CHO cells [50, 51]. This drug represents a breakthrough in migraine prophylaxis because, unlike previously utilized therapies, it exhibits a highly specific, targeted mechanism of action directed at the CGRP pathway [11, 52].

In contrast to other monoclonal antibodies used in migraine that bind the CGRP ligand itself, erenumab binds directly and with extremely high affinity (at the picomolar level) to the canonical CGRP receptor [51, 53]. This receptor is a complex heterodimer consisting of the CALCRL and RAMP1 [54]. Erenumab acts as a potent, competitive antagonist, blocking the binding site at the interface of the CALCRL and RAMP1 domains [55]. Through this selective binding, erenumab completely prevents endogenous CGRP from attaching to the receptor, thereby inhibiting the pathological intracellular signaling cascade, including the activation of adenylate cyclase and the secondary production of cAMP [54, 56].

Blocking the CGRP receptor within the trigeminal ganglion (which is located outside the blood-brain barrier) and on meningeal blood vessels effectively prevents CGRP-induced vasodilation and inhibits the development of sterile neurogenic inflammation and the transmission of pain signals [56, 57]. Crucially from a pharmacological perspective, because erenumab belongs to the IgG2 isotype, it lacks innate effector activity [58]. This means that the drug does not induce ADCC or CDC, and therefore does not cause the lysis or damage of cells and neurons physiologically expressing the CGRP receptor [52, 58].

5.2 Indications for use

According to the approvals by the EMA and the FDA, erenumab is indicated for the prophylaxis of migraine in adult patients who have at least 4 MMD at the time of making the treatment decision [59, 60].

In accordance with the recommendations of international headache societies (including the EHF and the AHS), erenumab therapy should be considered in both episodic migraine (4-14 headache days per month) and chronic migraine (≥15 headache days per month, including at least 8 days with migraine-type features) [21, 61]. This indication also encompasses patients classified as treatment-refractory, who have demonstrated a lack of efficacy, poor tolerability, or the presence of contraindications to at least two standard classes of oral prophylactic medications [61, 62].

5.3 Contraindications for use

The primary and absolute contraindication to the use of erenumab is clinically confirmed hypersensitivity to the active substance or to any of the excipients present in the formulation (e.g., sucrose, polysorbate 80, glacial acetic acid) [59, 63]. Given that the needle cover of the pre-filled syringe and the pre-filled pen may contain dry natural rubber (a derivative of latex), there is a potential risk of acute allergic reactions in patients with severe latex allergies; this requires special caution and individualized risk assessment [59].

Due to the lack of adequate clinical data, the use of the drug is currently not recommended in children and adolescents under 18 years of age [59]. Furthermore, although clinical trials have not demonstrated a direct negative impact of erenumab on the cardiovascular system, patients with severe, recent cardiovascular events (such as myocardial infarction, stroke, or unstable angina pectoris within the preceding 12 months) were excluded from the research programs; hence, extreme caution is warranted in individuals with advanced ischemic disease [60, 64].

5.4 Pharmacokinetics and Pharmacodynamics

Erenumab is intended for SC administration, most commonly injected into the abdomen, thigh, or the outer area of the upper arm [59]. The recommended standard dose is 70 mg administered once every 4 weeks. In a subset of patients (particularly those with treatment-refractory forms), the administration of a 140 mg dose (either as a single 140 mg injection or two consecutive 70 mg injections), also administered every 4 weeks, is permissible and recommended [59, 65].

From a pharmacokinetic standpoint, erenumab exhibits non-linear kinetics at low doses and linear (dose-proportional) kinetics at higher, therapeutic doses (70 mg and 140 mg) [66]. This is a consequence of TMDD, in which the drug's clearance proceeds in parallel via two pathways: a saturable pathway based on direct binding to the CGRP receptor, and a non-saturable reticuloendothelial clearance pathway typical for immunoglobulins [53, 66]. The total absolute bioavailability of the drug following subcutaneous administration is estimated at approximately 82% [53].

The maximum serum concentration (Cmax) is typically reached at a time (tmax) of 4 to 6 days post-injection, and steady-state is achieved after approximately 12 weeks of regular administration, which fully coincides with the onset of optimal preventive efficacy in patients [53, 67]. The estimated volume of distribution (Vd) in the central compartment is approximately 3.6 L, suggesting that the distribution of erenumab is primarily confined to the vascular space and interstitial fluid [66, 67]. Because erenumab is an antibody, it undergoes enzymatic degradation into short peptides and individual amino acids, primarily involving lysosomes - similarly to endogenous bodily proteins [67]. The effective half-life (t1/2) of erenumab is highly favorable, averaging 28 days (ranging from 21 to 35 days), which fully justifies and enables a convenient once-monthly dosing regimen [53].

5.5 Adverse Effects

The safety profile of erenumab was demonstrated convincingly in a number of rigorous clinical trials [68]. Due to its large molecular weight and high target specificity, the drug does not cross the blood-brain barrier to a significant extent, which completely eliminates the occurrence of central nervous system adverse effects (such as depression, somnolence, or brain fog) This provides a major advantage over conventional prophylactic drugs as aforementioned adverse effects frequently constitute a major obstacle to their successful usage [68, 69].

The most frequently reported adverse event, occurring with a frequency of 5% to 6%, was local injection site reactions. These occurred in between 5% to 6% of the study population and were generally mild, temporary and manifested as pain, erythema, pruritus, and slight edema [70]. A clinically significant, specific side effect is constipation, reported by 1-3% of patients in clinical trials [69, 70]. This stems from the physiological role of CGRP in stimulating motility and maintaining proper transit within the gastrointestinal tract [71]. Thus, blockade of CGRP receptors with these therapies may cause constipation. Following reports of severe constipation that in some cases required hospitalization and surgical intervention due to obstruction, which were found in the FAERS, the EMA has required that a note be included to the summary of product characteristics and a warning to be included regarding the risk of constipation and the importance of early recognition of symptoms and dietary management to prevent problems [71, 72].

Moreover, based on post-marketing surveillance signals, regulatory agencies have asked for the continued monitoring of the de novo onset of arterial hypertension or the exacerbation of previously controlled hypertension [73]. Other adverse effects with an incidence of ≥1% included mild muscle spasms and skin itching (pruritus) [59, 70].

5.6 Clinical Efficacy in Migraine Treatment

The efficacy, safety and long term tolerability of erenumab has been demonstrated in a large, multinational clinical trial program involving thousands of patients with either EM or CM [74].

5.6.1 Erenumab in EM

The STRIVE study (NCT02456740) is the largest Phase III trial evaluating erenumab in EM. This multicenter, double-blind, placebo-controlled study included 955 participants with 4–14 MMD [51]. Patients were randomized to receive placebo, 70 mg of erenumab, or 140 mg of erenumab once a month for 24 weeks [51]. The results at 6 months demonstrated a clear superiority of the drug: the mean reduction in monthly migraine days was -3.2 days for the 70 mg dose and -3.7 days for the 140 mg dose, compared to a reduction of only -1.8 days in the placebo group ($p<0.001$ for both groups vs. placebo) [51, 75]. Furthermore, the proportion of patients who achieved a clinically significant reduction of at least 50% in migraine days was an impressive 43.3% and 50.0% in the 70 mg and 140 mg dose groups, respectively (vs. 26.6% in the control group) [51].

In parallel, the ARISE study (NCT02483585) was conducted, a 12-week Phase III trial involving 577 patients. It evaluated the 70 mg dose and confirmed its efficacy as it achieved a statistically significant reduction in MMD compared with placebo (-2.9 vs. -1.8) as well as in the MSMD [76].

5.6.2 Erenumab in CM

There is a multicenter, 12-week, double-blind Phase II/III trial published in the New England Journal of Medicine that assessed the efficacy of erenumab in reducing the number of migraine attacks in 667 patients with CM and a mean of 18 MMD [77].

Participants received either 70 mg of erenumab, 140 mg of erenumab, or a placebo [77]. At 12 weeks, a reduction of 6.6 migraine days was observed in both erenumab-treated groups (compared to a decrease of 4.2 days in patients receiving placebo) [77, 78]. A substantial proportion of patients were also reclassified from

the chronic form to a significantly milder episodic form, confirming the potent neuromodulatory properties of the antibody [78].

A distinct and critically important group of patients was evaluated in a 12-week Phase IIIb trial named LIBERTY (NCT03096834). It focused on a challenging population of 246 patients with episodic migraine who had previously documented failure or intolerance to 2 to 4 different classes of preventive anti-migraine medications [79]. In the LIBERTY trial, only the highest erenumab dose of 140 mg was utilized. The applied therapy resulted in a more than threefold higher rate of achieving a ≥50% reduction in migraine days compared to placebo (30.3% vs. 13.7%, p=0.002) [79, 80]. Also of clinical importance to this group of patients is the reduction in migraine-related disability as measured by the MIDAS scale as patients whose migraine is poorly controlled are also ones of the most neglected [80].

Results from a 5-year OLE study for patients from the episodic trial, published by Ashina et al., represent exceptional scientific value [81]. It demonstrated an unprecedented sustained high efficacy of the drug - after 5 years of therapy, over 71% of patients maintained a reduction in MMD of greater than 50%, and more than one-third of the patients (approximately 35%) achieved complete freedom from migraine (the so-called 100% response) [81]. This confirms not only the absence of tachyphylaxis, but also that this particular drug is safe from the long term perspective as no significant or unforeseen cumulative toxicities were reported after many years of administration [81, 82].

Table 3. Overview of key randomized clinical trials evaluating the efficacy of erenumab [51, 76, 77, 79].

Trial Name (Phase)	Study Population	Sample Size (N)	Double-Blind Phase Duration	Dosage Administered (Erenumab vs. Placebo)	Key Findings and Clinical Achievements (Primary/Secondary endpoints)
STRIVE (Phase 3)	EM (4–14 MMD)	955	24 weeks	70 mg once monthly 140 mg once monthly Placebo	Statistically significant reduction in MMD (-3.2 days for 70 mg; -3.7 days for 140 mg vs. -1.8 for placebo). Over 50% of patients on the 140 mg dose halved their headache days.
ARISE (Phase 3)	EM (4–14 MMD)	577	12 weeks	70 mg once monthly Placebo	Rapid onset of action, significant advantage in reducing the number of days requiring acute migraine-specific medication (triptans)..
Tepper et al. trial (Phase 2/3)	CM (≥15 headache days)	667	12 weeks	70 mg once monthly 140 mg once monthly Placebo	Reduction of 6.6 MMD in both erenumab arms (vs. 4.2 in the placebo group). More than twice the likelihood of converting a patient from a CM to an EM phenotype.
LIBERTY (Phase 3b)	Treatment-refractory EM (2 to 4 prior pharmacotherapy failures)	246	12 weeks	140 mg once monthly Placebo	Exceptionally high efficacy in "hard-to-treat" patients- 30% treatment response (≥50% reduction in MMD) compared to 13% on placebo. Radical decrease in functional disability on the MIDAS scale.

Abbreviations: EM: episodic migraine; CM: chronic migraine; MMD: monthly migraine days; MIDAS: Migraine Disability Assessment.

5.7 Drug Interactions

In the case of erenumab, classic pharmacokinetic drug-drug interactions are not anticipated. As previously mentioned, the drug is not metabolized by hepatic enzymes belonging to the CYP450 family, does not undergo renal excretion, and is not a substrate for transmembrane efflux transporters (so-called efflux pumps) [66, 83]. Thus, all common drug interaction factors known from traditional polypharmacy are excluded [83].

In dedicated clinical trials involving healthy volunteers, potential interactions between erenumab and sumatriptan - commonly used as acute treatment for migraine attacks - were precisely evaluated [84]. It was unequivocally demonstrated that the concomitant administration of both preparations does not affect the resting pharmacokinetics of sumatriptan in the slightest, nor does it alter its ability to rapidly abort migraine attacks in humans [84]. The impact of erenumab on combined oral contraceptives (preparations containing ethinylestradiol and norgestimate) was also investigated; no clinically significant changes in their absorption, metabolism, or overall pharmacokinetics were observed, which guarantees the complete safety of maintaining contraceptive efficacy during erenumab immunotherapy [85].

5.8 Impact on Pregnancy and Lactation

The approach to the use of erenumab during pregnancy and lactation is currently based on rigorous data from animal models and the lack of controlled studies in pregnant women [59, 86]. Due to its macromolecular structure and being a large-molecule immunoglobulin G, there is a physiologically justified assumption that erenumab, like other natural IgG proteins, has the ability to cross the placental barrier via active transport dependent on the FcRn, particularly during the advanced second and the entire third trimesters of pregnancy [86].

Preclinical studies on reproductive and developmental toxicity were conducted using a cynomolgus monkey model, in which the drug was administered throughout the entire duration of pregnancy [86]. These studies demonstrated no direct or indirect adverse effects on fetal development, viability, or postnatal toxicity at any dose level up to 50-fold the MRHD [59, 86].

Despite the encouraging results of toxicological studies, in accordance with strict registration guidelines and the recommendations of the EMA, to maintain the highest level of safety, it is recommended to strictly avoid the use of the preparation in pregnant women [59]. There is not enough data to confirm whether or not erenumab is excreted into human breast milk. Although it is assumed antibodies undergo degradation in the newborn's gastrointestinal tract, due to insufficient knowledge, it is strongly advised to weigh the benefits of treating the mother against the possible to the breastfed infant [59, 86].

6. Comparison of Erenumab Efficacy with Other Therapeutic Options

The introduction of erenumab into daily clinical practice signifies a turning point in migraine prevention, offering patients a treatment based on the direct pathophysiology of the disease [87]. The real impact of erenumab on this very disabling condition can only be assessed by evaluating the effectiveness and safety of this new option relative to first-line oral preventive therapy drugs and in relation to the new, modern therapeutic approaches that have also been validated, such as the other anti-CGRP monoclonal antibodies, gepants and ditans [65, 87].

6.1. Erenumab vs. Classical Oral Prophylactic Drugs

Before the monoclonal antibodies came on the scene, preventive therapy for migraine was based on non-specific drugs borrowed from other fields of medicine and various therapeutic classes, such as antiepileptic drugs, beta-blockers or antidepressants [65, 88]. Although they demonstrate moderate efficacy in many patients, their use is severely limited by a set of very unpleasant side effects which are the main reason for the discontinuation of therapy [87, 88]. This best evidence of erenumab's superiority in this regard is provided by the results of the first-ever Phase IV head-to-head trial, HER-MES (study of erenumab against topiramate) [87].

In the HER-MES trial, 777 patients with migraine (both episodic and chronic) were randomized to receive subcutaneous erenumab (70 mg or 140 mg) with oral placebo, or oral topiramate at an optimal, tolerated dose of 50 to 100 mg daily combined with a subcutaneous placebo [87]. The primary endpoint was the verification of drug tolerability, measured by the percentage of patients discontinuing therapy due to adverse events. The results proved unprecedented: in the erenumab group, only 10.6% of patients discontinued treatment due to side effects, in dramatic contrast to a staggering 38.9% of patients in the topiramate group (OR=0.19; $p<0.001$) [87]. Furthermore, erenumab demonstrated a significant advantage in primary efficacy: as many as 55.4% of patients treated with erenumab achieved at least a 50% reduction in MMD, whereas only 31.2% achieved this goal in the topiramate group (OR=2.76, $p<0.001$) [87]. Topiramate was often discontinued because of paresthesias, changes in cognitive functions, and negative affective effects. None of these were related to the pathophysiological mechanism that is targeted by erenumab [65, 87].

6.2. Comparison with Other Monoclonal Antibodies Targeting the CGRP Pathway

In addition to erenumab, three other monoclonal antibodies with anti-migraine activity have been approved in recent years: galcanezumab, fremanezumab, and eptinezumab [88, 89]. The fundamental pharmacological difference is the fact that erenumab is the only drug in this class that binds directly to the canonical CGRP receptor, whereas the other three antibodies are targeted at binding the ligand itself (free CGRP peptide) circulating in the plasma and extracellular fluid [89, 90].

Due to the lack of extensive head-to-head trials between the individual antibodies, the primary source of knowledge regarding their relative efficacy is advanced Bayesian NMAs [88, 89]. The results of analyses, such as those conducted by Han et al. and Frank et al., indicate that all four antibodies are highly effective compared to placebo and are characterized by a very similar, safe clinical profile [89, 90]. Certain mathematical models within NMAs suggest a minimal statistical superiority of fremanezumab (at a dose of 225 mg monthly) and galcanezumab (120 mg) over lower doses of erenumab in the context of the absolute number of reduced migraine days [89]. Nevertheless, it is considered that the absolute differences are extremely subtle (often less than a one-day difference in MMD), and the unique mechanism of erenumab gains immense significance in treatment-refractory patients [90]. Observational studies on the phenomenon of drug switching (the so-called class switch) have demonstrated that in patients who did not respond to ligand-binding antibodies (e.g., galcanezumab), the implementation of a receptor-binding antibody (erenumab) can unlock therapeutic benefits, which strongly confirms the complementarity of these methods in headache clinical practice [89, 90].

6.3. Comparison with a New Generation of Targeted Oral Medications: Gepants

The new developments in the field of migraine therapy constitute a major breakthrough with the availability of gepants (including ubrogepant, rimegepant, atogepant, and zavegepant) [11, 31]. Gepants are small-molecule, non-peptide, fully reversible CGRP receptor antagonists [11]. In contrast to erenumab (which is a potent, macromolecular immunoglobulin requiring subcutaneous injections with a monthly release profile), gepants can be administered orally (in the form of standard tablets or ODTs) or intranasally, and due to their low molecular weight, they are characterized by a relatively short half-life [31, 91].

Blocking CGRP transmission via gepants leads to a potent inhibition of pathological intracranial vasodilation and the suppression of neurogenic inflammation without concurrently inducing a vasoconstrictive effect, which distinguishes them from traditional triptans [11, 31]. The unique kinetics of gepants have blurred the historical boundary between acute and preventive treatment, to which prophylactic erenumab is still strictly bound [91]. Medications with rapid absorption, such as ubrogepant or intranasal zavegepant, were designed strictly for the acute abortion of an ongoing migraine attack [32]. For example, the ACHIEVE I trial proved that ubrogepant achieves rapid freedom from pain at 2 hours, serving as an excellent, cardiovascularly safe alternative for patients in whom triptans are contraindicated [32].

On the contrary, atogepant, with a slightly different binding profile and an optimized distribution, is approved for chronic therapy. According to the ADVANCE trial, patients taking it orally on a daily basis achieved reductions in MMD very similar to those recorded for erenumab [91, 92]. Rimegepant, on the other hand, occupies a unique position, possessing a dual registration: both for the acute abortion of an attack and for prophylaxis (taken every other day) [31, 92]. In relation to erenumab, gepants represent an excellent form of chronic treatment for patients preferring oral therapy over injections, as well as an indispensable tool for extinguishing isolated, refractory attacks in patients who are already under the protective umbrella of erenumab (rescue therapy), although combining drugs targeting the same receptor requires further, long-term safety observations [11, 92].

6.4. Comparison with a New Generation of Centrally Acting Drugs: Ditans (Lasmiditan)

The newest and probably the most interesting class of anti-migraine drugs are ditans, although so far the only one authorized for clinical use is lasmiditan [93, 94]. Erenumab blocks the CGRP receptor peripherally (without significantly penetrating the blood-brain barrier), while lasmiditan acts based on an entirely different, prominently central mechanism [93].

Lasmiditan is a highly selective, strongly lipophilic agonist of the 5-HT1F serotonin receptor [93]. Its mechanism of action is revolutionary because it bypasses the 5-HT1B receptors, which are responsible for the burdensome coronary vasoconstriction characteristic of commonly used triptans [93, 94]. Due to its structure, lasmiditan freely crosses the blood-brain barrier, stimulating 5-HT1F receptors scattered deep within the central nervous system (including the trigeminal ganglion, the trigeminal nucleus caudalis, and within the thalamus) [93, 94]. This activation results in an intracellular cascading inhibition of the peripheral and central

release of not only CGRP but also glutamate, which literally suppresses the development and reduces the process of central sensitization, clinically manifesting as cutaneous allodynia (scalp pain upon touch) during a migraine attack [93, 94].

Similar to acute gepants, lasmiditan is not used for purely prophylactic purposes (like erenumab) but serves for the immediate abortion of ongoing attacks. In two massive Phase III clinical trials (the SAMURAI and SPARTAN studies), lasmiditan demonstrated an exceptionally high capacity to induce pain freedom at 2 hours post-oral dose consumption (ranging from 28.2% to 38.8%, depending on the dose) [94]. The primary adverse symptoms of this class, resulting directly from the central penetration of lasmiditan, are severe dizziness, somnolence, and paresthesias (which necessitates a driving ban for patients for at least 8 hours after taking the medication) [93, 94]. Another advantage of this class of drugs is the absence of vasoconstrictive effects, as opposed to triptans; thus they are also an alternative for patients presenting with high cardiovascular risk (e.g., post-myocardial infarction) [93]. From a cross-sectional perspective, ditans could be administered together with erenumab to form the excellent clinical duo. While erenumab is thought to provide the benefits of the "disease-lifting" that occurs with meningeal vessel stabilization by reducing migraine frequency, lasmiditan could provide a safe and intended endpoint to the cycle of migraine attack in the form of termination of the prolonged glutamate-mediated neurotransmission that occurs in the brainstem between the trigeminal nucleus and the cerebral vasculature during migraine attacks [87, 93, 94]

7. Discussion and Conclusions

7.1. Clinical Implications and the Paradigm Shift in Treatment

The introduction of erenumab in clinics was indeed a game changer in the field of neurology and pain medicine [56]. Migraine prophylaxis over the decades has been largely based on trial-and-error approach with a whole range of non-specific medications which were found to be effective in the management of migraines by accident [11]. Hence the first CGRP receptor monoclonal antibody in clinical use, erenumab, marked the beginning of precision (targeted) medicine in the management of headaches [11, 56].

From a clinical perspective, the greatest value of erenumab is not solely its ability to reduce MMD, but primarily the drastic improvement in therapeutic compliance and adherence [39]. The classical molecules such as topiramate or amitriptyline are often poorly tolerated by patients because of the side effects on the central nervous system such as cognitive alterations and sedation, which can be prejudicial to the quality of life of active patients and more harmful than the migraine itself. [39]. Erenumab, due to its macromolecular structure and lack of significant blood-brain barrier penetration, bypasses these issues, as proven by direct comparative studies [56, 90]. The high efficacy of the drug in patients with treatment-refractory migraine offers a chance to restore normal social and occupational functioning for individuals previously considered therapeutically hopeless [90]. Erenumab was pronounced safe to be combined with novel acute medications (gepants and ditans), thus allowing for the design of highly individualized treatment based on a layered strategy of complementary pharmacology without the risk of polypharmacy or liver drug-drug interaction [21].

7.2. Limitations of This Study and Previous Research

When interpreting the data presented in this paper, some important factors must be kept in mind. Firstly, this work is a narrative literature review rather than a systematic meta-analysis, and so the potential for selection bias cannot be excluded. Secondly, it relies heavily on the results of rigorous RCTs. Although these represent the gold standard of EBM, their highly selected patient populations often do not fully reflect the clinical picture of a patient in daily ambulatory practice (who is frequently burdened with numerous comorbidities, such as advanced depression, fibromyalgia, or obesity) [95].

However, an additional problem arises as a significant amount of the available literature concerning erenumab was sponsored by the entities responsible for its production, which always requires a critical approach and must be taken into consideration during interpretation of the presented data [95]. There is also a noticeable gap in direct head-to-head trials between individual anti-CGRP antibodies (e.g., erenumab vs. galcanezumab), forcing researchers to rely on indirect network meta-analyses that do not always precisely reflect actual differences in efficacy [89].

7.3. Future Research Directions and Perspectives

Despite the established position of erenumab, a number of uncertainties remain to be clarified. According to the authors, further studies are necessary to assess the efficacy and safety of erenumab and the other anti-CGRP monoclonal antibodies in a time frame significantly longer than the 5 years already explored. In fact, the authors observe that the migraine is a chronic condition that can last for decades and points out the need for post-marketing surveillance of rare adverse effects, such as severe constipation and the changes in blood pressure and microvascular reaction to ischemia (for example during a myocardial infarction) due to prolonged CGRP blockage [64,95].

Researchers are working to address several other issues. One of these is looking at the safety of erenumab in populations that were excluded from the original clinical trials. Any data they get from the ongoing pediatric trials will be especially important to look at, as they may pave the way for the drug's approval for children and adolescents under 18 years of age suffering from severe forms of migraine [96]. Moreover, it is also essential to establish international pregnancy registries to objectively assess the potential risks of using the drug in women for whom, due to the drastic course of the disease, discontinuing prophylaxis during pregnancy is not feasible [86].

Finally, great hopes are tied to research on the pathomechanisms of treatment resistance. It is estimated that approximately 30-40% of migraine patients do not exhibit an optimal response to CGRP pathway blockade [90]. With the aim of hopefully improving treatments in the future the exploration of other vasoactive neuropeptides has been intensified. Monoclonal antibodies targeting PACAP and its receptor PAC1 are already being evaluated in advanced clinical trials [13, 14]. It is expected that in the near future, patient profiling (perhaps based on specific phenotypic biomarkers) will allow for precise determination of whether a given patient will derive greater benefit from CGRP pathway blockade (erenumab) or the PACAP pathway, which will be another milestone in the personalization of headache medicine [14].

Author Contribution:
Conceptualization: MJ, KK, MK
Methodology: NK, DS
Validation: MM, AK
Formal analysis: MK, SP
Investigation: JK, MM
Resources: AD, MK
Data curation: AD, KK
Writing-original draft preparation: AK, KK, JK, DS, NK
Writing-review and editing: SP, MM, AD
Visualization: MJ, JK
Supervision: DS, SP
Project administration: NK, MJ

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