Calcitonin gene-related peptide (CGRP) is a key molecule released in acute migraine attacks—Successful translation of basic science to clinical practice

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Migraine is a highly prevalent neurovascular disorder afflicting more than 15% of the global population. Nearly three times more females are afflicted by migraine in the 18–50 years age group, compared to males. Migraine attacks are most often sporadic, but a subgroup of individuals experience a gradual increase in frequency over time; among these, up to 1%–2% of the global population develop chronic migraine. Although migraine symptoms have been known for centuries, the underlying mechanisms remain largely unknown. Two theories have dominated the current thinking—a neurovascular theory and a central neuronal theory with the origin of the attacks in the hypothalamus. During the last decades, the understanding of migraine has markedly advanced. This is supported by the early seminal demonstration of the trigeminovascular reflex 35 years ago and the insight that calcitonin gene-related peptide (CGRP) is a key molecule released in acute migraine attacks. The more recent findings that gepants, small molecule CGRP receptor blockers, and monoclonal antibodies generated against CGRP, or its canonical receptor are useful for the treatment of migraine, are other important issues. CGRP has been established as a key molecule in the neurobiology of migraine. Moreover, monoclonal antibodies to CGRP or the CGRP receptor represent a breakthrough in the understanding of migraine pathophysiology and have emerged as an efficacious prophylactic treatment for patients with severe migraine with excellent tolerability. This review describes the progression of research to reach the clinical usefulness of a large group of molecules that have in common the interaction with CGRP mechanisms in the trigeminal system to alleviate the burden for individuals afflicted by migraine.

Keywords: CGRP, CGRP receptor, gepants, migraine, monoclonal antibodies

Introduction

Migraine is established as the most prevalent and disabling neurovascular brain disorder with severe socioeconomic impact, affecting females to a higher degree than males (Fig. 1). It currently ranks as the sixth most prevalent disorder worldwide. It is a major cause of disability, thus posing a heavy burden on individuals and society [1]. Diagnostically, it is characterized by moderate to severe headache attacks, often unilateral, and accompanied by nausea, vomiting, photophobia, and phonophobia [2]. In many cases, it is initially associated with an aura phenomenon, lasting for 20–60 min, and often of visual nature. Experimental and clinical translational research has provided key observations adding to the understanding of the underlying neurobiology and as a stimulus for the development of novel therapies.
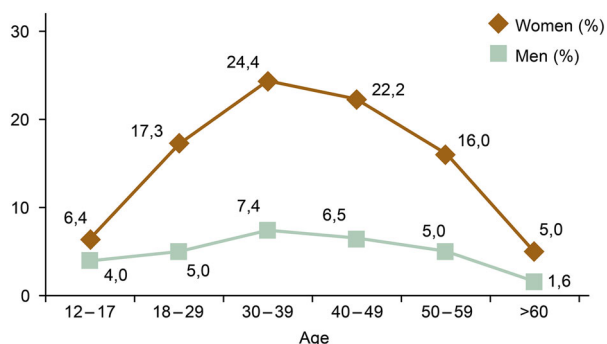
Fig. 1 *Global age-standardized prevalence of migraine in males and females [1].*

There is consensus on a genetic background of migraine clinically based on interviews with patients; however, genome-wide association screening (GWAS) studies have failed to produce data to pinpoint one specific locus [3]. Thus, migraine is likely a polygenic phenotype as GWAS studies initially reported 38 independent loci associated with the risk of migraine. More recent work reported that 123 loci are associated with the risk of migraine with links to all chromosomes [4]. It is therefore improbable that a single gene can be responsible for the origin of common forms of migraine.

Studies of a rare condition, familial hemiplegic migraine, however, has been more successful in pointing towards a more specific single mechanism—increased sensitivity of central nervour system (CNS) glutaminergic signaling [5]. The debate is still ongoing regarding the importance of peripheral sites as the origin of migraine attacks, posing the question: does migraine start in the dura mater and/or in extracerebral arteries [6]? Do migraine attacks require a peripheral sensory input to be activated [7]? Recent imaging studies suggest that midbrain and brainstem structures are the drivers of migraine attacks [8]. Today, much evidence suggests that migraine attacks may start in the hypothalamus, sometimes already on the day before the headache (the prodromal phase), continue with the activation of the thalamus and the brainstem, and then the trigeminal system. The trigeminovascular system is likely necessary for the characteristic headache (the core of a migraine attack). Finally, after cessation of the headache phase there are imaging data showing that there are still alterations in the brain that correlate with CNS symptoms, such as tiredness (the postdrome) [9, 10]. Current debate favors the view that migraine is a CNS disorder, in which attacks starts in subcortical regions, exemplified by studies of premonitory symptoms [11] and supported by a series of elegant studies during continuous scanning of patients during the migraine cycle [12]. The imaging studies collectively point towards a hypothalamus–thalamus–brainstem pathway as a putative driver of the migraine biology [10]. Thus, the functional brain imaging studies have demonstrated brainstem areas to be specifically activated in migraine attacks, sometimes referred to as the "migraine generator" [13]. The link from the hypothalamus with the dorsal rostral pons, the spinal trigeminal nuclei, and sensory trigeminovascular system, are key parts in understanding the transmission of headache pain.

Historical background on the treatment of migraine

The American neurologist Harald Wolff [14] observed a widened temporal artery with pulsating quality in migraine patients that responded to administration of ergotamine with vessel constriction and reduced headache. Therefore, a vascular target seemed at this time a likely explanation of migraine and served as inspiration in the development of migraine therapies related to the role of 5-hydroxytryptamine (5-HT) and vasoconstriction [15]. The work ultimately resulted in the successful development of the triptan class of drugs, 5-HT$_{1B/1D}$ receptor agonists for acute treatment of migraine attacks introduced during the early 1980s [16]. The role of intracranial and extracranial vasculature was still in focus and postulated to be a key part of the migraine attack [17]. Studies of perivascular innervation of the intracranial circulation, first with a focus on the autonomic nerves and later with the immunohistochemistry of neuropeptides, revealed numerous colocalizations [18]. The first sensory neuropeptide in the intracranial arteries is substance P (SP), originating in the trigeminal ganglion [19–21]. It was soon proposed to be a key messenger molecule responsible for neurogenic inflammation and sensitization of nociceptors located in, for example, the dura mater [22]. This was soon followed by other neurokinins and calcitonin gene-related peptide (CGRP) that also originated in the trigeminal ganglion and colocalized with SP [23]. However, CGRP was, for nearly two decades, deemed not interesting, because it did not induce neurogenic inflammation [24] or did not activate the trigeminal neurons and only resulted in vasodilatation of meningeal arteries

[24]. Thus, much effort focused on SP, and specific neurokinin blockers were developed that were effective in the inhibition of neurogenic inflammation, the proposed decisive model [25]. However, when tested in randomized clinical trials they were all without effect on migraine [26–28], and hence abandoned as antimigraine treatment candidates. Recent detailed work has shed new light on SP and the related neurokinins, as well as on their receptors in different parts of the trigeminovascular system [29].

What inspired the continued work on CGRP mechanisms in migraine?

Soon after the discovery of CGRP [30], work was initiated to develop the immunohistochemistry and specific radioimmunoassay (for quantification) for the study of neuropeptides associated with the intracranial vasculature [18]. CGRP is a 37-amino acid peptide produced by neurons both in the CNS and in the peripheral nervous system [31]. The peptide exists in two forms, αCGRP and βCGRP, that differ by three amino acids in humans and are encoded by two different genes, CALCA and CALCB. CGRP was earlier shown to be a potent vasodilator in various parts of the vascular system [32–34]; it relaxed the cerebral arteries in association with increased levels of cyclic adenosine $3'5'$-monophosphate (cAMP), and the response was unrelated to the patency of the endothelium; later, CGRP was found to have effects throughout the body and in numerous organs [35]. The demonstration of CGRP in the trigeminal system verified its colocalization with SP, and surgical denervation removed these peptides from the intracranial perivascular innervation [23], while retrograde tracing verified its origin in neurons of the trigeminal ganglion [36].

In addition, CGRP was earlier found in the CNS; however, recent in-depth mapping revealed an astonishing abundance of CGRP and its canonical receptor in the brain and in particular in migraine-related regions and the trigeminovascular system [37, 38]. The CGRP expressing regions are linked with many cerebral systems, some of which are related to those involved in migraine attacks.

From basic research to clinical proof

Initial reports describing the presence of CGRP in trigeminal neurons and its potent vasodilator effects mediated via adenylyl cyclase resulted in the demonstration of the trigeminovascular reflex (cerebral artery constriction activates the sensory perivascular nerve fibers to release CGRP to maintain the resting artery diameter and blood flow) [39]. This inspired me to suggest that CGRP is involved in the migraine pathophysiology [23, 32, 33, 39]. The first clinical observations by Goadsby and Edvinsson linked the release of CGRP to primary headaches. The initial study in patients with severe trigeminal neuralgia showed elevated levels of CGRP in the jugular vein (but CGRP elevation was not seen in the peripheral cubital fossa vein) and this was associated with facial flushing symptoms [40]. Subsequently, two studies were performed on migraine patients with acute severe attacks showing up in the emergency room because of the severity of the migraine pain. These studies revealed that only CGRP and not SP, neuropeptide Y, or vasoactive intestinal peptide were released during these acute attacks. Subcutaneous sumatriptan aborted the headache and normalized the CGRP levels [41, 42]. Subsequent mechanistic and immunohistochemical studies on patients and human tissues firmly established the importance of CGRP in migraine pathophysiology [31, 43]. Once the peptide has been released from the sensory nerve, it is only slowly removed from the extracellular space due to the lack of specific reuptake machinery. Another interesting aspect of neuropeptides in general is their volume transmission, diffusion-driven distribution into extracellular fluid over a relatively large distance [44]. Another feature of neuropeptides is the fact that they can be released at both synapses and nonsynaptic sites such as neurons and axons [45].

It was reported that the CGRP receptor is a G protein–coupled receptor that consists of a seven-transmembrane (7-TM) part, the calcitonin receptor-like receptor (CLR), and a 1-TM part, the receptor amplifying membrane protein 1 (RAMP1) (Fig. 2). When activated, it couples with a receptor component protein (RCP) and adenylyl cyclase [46, 47]. RCP has been suggested to be essential for CLR signaling [48]. Another important aspect of CGRP receptor signaling and regulation is the removal from the cell surface by internalization. Studies have examined this process, and evidence has revealed that tagged CLR/RAMP1 (the canonical CGRP receptor) is internalized into endosomes in response to CGRP [49].

In parallel, the industry worked to develop small CGRP blocking drugs—the first of these was olcegepant, which soon paved the way for several
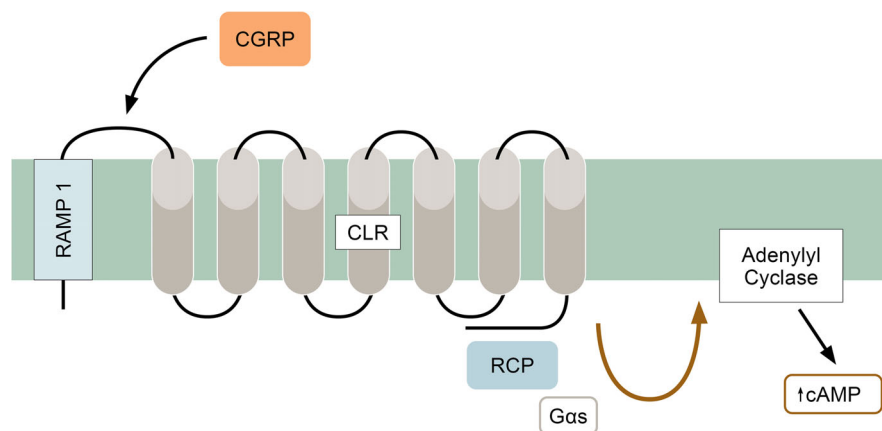
Fig. 2 *The components of the calcitonin gene-related peptide (CGRP) receptor (CLR and RAMP1) and the signal pathway from RCP (receptor component protein) to the adenylyl cyclase system. Upon release of CGRP, it docks into the space between CLR and RAMP1, causing its activation [31]. This complex is then internalized into the cell.*
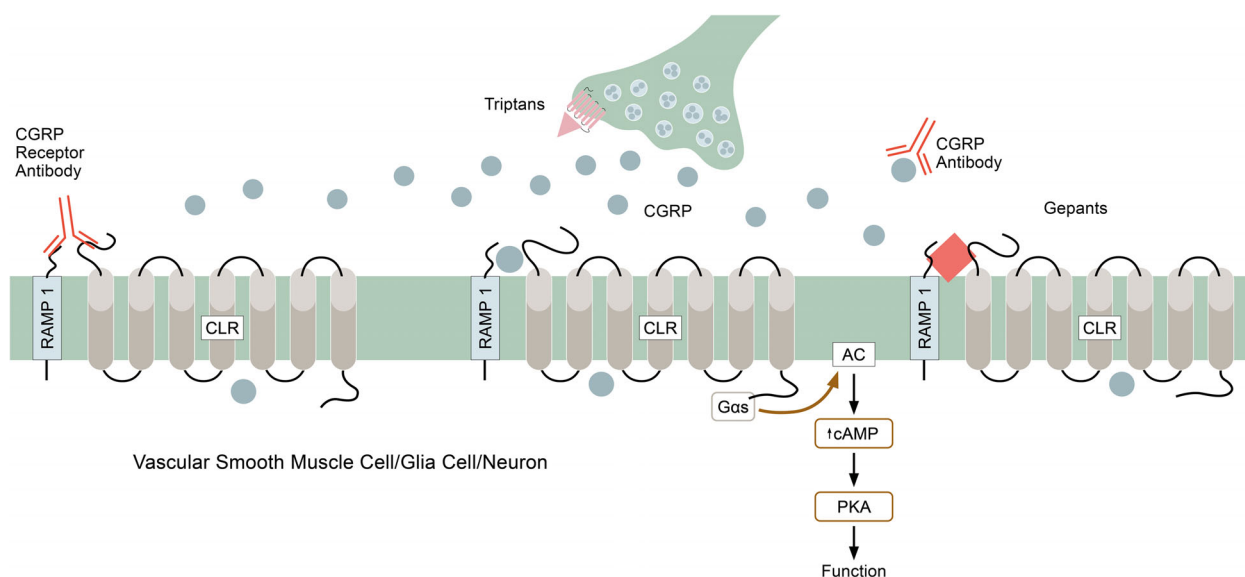
Fig. 3 *Released calcitonin gene-related peptide (CGRP) is prevented from activating the CGRP receptor in several ways. (i) Presynaptic triptans may reduce the release of CGRP. (ii) Small molecule gepants may compete with CGRP at the receptor site. (iii). Monoclonal antibodies may adhere to CGRP, forming a large complex that does not fit at the receptor site. (iv) Specific monoclonal antibodies directed towards the N-terminals of CLR and of RAMP1, which effectively blocks CGRP from reaching the active receptor site [31].*

others in the new drug class "gepants" (Fig. 3). The developed small molecule receptor antagonists were shown to be competitive antagonists at the human CLR/RAMP1 receptor [50, 51]. After additional basic studies [51, 52], olcegepant was given intravenously to patients with acute migraine attacks [53]. Olcegepant not only aborted the attack rapidly, but pain freedom persisted in some patients for up to 24 h. Further proof of the importance of CGRP came, when intravenous (iv) CGRP resulted in migraine-like attacks more frequently in migraine patients than in healthy subjects [54].

The recognition of the important role of CGRP in migraine triggered further efforts to target CGRP and its receptor as a therapeutic approach for

migraine treatment. Since the dipeptide olcegepant was not suited for oral use, other pharmaceutical companies explored this target in more detail and developed their own gepants. The second gepant to appear clinically was telcagepant. The subsequent trials met the primary as well as the secondary endpoints and were well tolerated [55, 56]. However, in prophylaxis studies, reversible liver toxicity was observed, resulting in halting of its further development. The liver issue has now been solved with a new group of gepants. Their chemical structures and the developmental process of novel gepants have now been revealed in some detail [57]. At present, we are seeing the appearance of a further series of gepants for both acute and prophylactic use (ubrogepant, aterogepant, and rimegepant). These gepants have successfully passed the required randomized clinical trials for the treatment of migraine and are available in the United States [58, 59].

After 2 decades of basic research on the CGRP family of peptides, the focus now aimed at finding other means or molecules that can be used to block the CGRP responses [31]. A different approach was to examine whether specific antibodies could be designed toward CGRP. Two lines of research appeared; one was the further development of monoclonal antibodies (mAbs) binding CGRP, where we now have three different molecules on the market (eptinezumab, fremanezumab, and galcanezumab). The understanding of the uniqueness of the CGRP receptor led AMGEN to construct an mAb recognizing the N-terminal of the two components of the canonical CGRP receptor: CLR and RAMP1. Erenumab is a highly specific antagonist against the CGRP receptor. The research behind it provided tools that could assist in further understanding of migraine pathophysiology. CGRP-related therapies offer considerable improvements over existing drugs; as they are designed selectively to act on the trigeminal pain system, they are more specific and have few or mild adverse effects [60]. The development of the small molecules, gepants, resurfaced with CGRP receptor antagonists such as atogepant, rimegepant, and ubrogepant; they are effective for acute relief from migraine headache attacks and can also be useful as prophylactics.

Monoclonal antibodies

Basic research in the field of neuropeptides relied on methods to produce reagents for immuno-histochemistry and radioimmunoassay for their quantification of the production of specific and selective antibodies directed towards various parts of the molecule under study [61]. Usually, these antibodies were polyclonal and therefore not suited for therapy. By using humanized or human antibodies, side effects were reduced and target specificity improved. Thus, the mAbs have high specificity towards the target and long half-lives; they are metabolized by the reticuloendothelial system and not by the liver enzymes and have, therefore, a low potential for liver or renal toxicity. Due to their large molecular size, the mAbs cross the blood–brain barrier (BBB) only in very low concentrations [62], which limits possible CNS side effects that would be expected due to the rich expression of CGRP and CGRP receptors in numerous regions within the brain [38].

Patients with multiple attacks per month, as commonly seen in frequent episodic migraine (EM) or chronic migraine (CM), need prophylactic drugs. Those that are available were found by serendipity and include β-adrenoceptor blockers, antidepressants, antiepileptics, and botulinum toxin [63]. The first three of these drugs have widespread effects in the CNS, are not specific for the migraine targets, and are often accompanied by side effects that limit their usage [63]. More than 90% of patients treated with these drugs have, after 1 year, stopped taking them due to either low efficacy or unwanted side effects.

The first published results with mAbs aimed at the trigeminovascular system showed a somewhat different pharmacological profile compared to the gepants [64, 65]. Although the CGRP-directed antibody reduced the vasodilatory effect of CGRP, the inhibition was not competitive. Today, four mAbs are available: erenumab is a human mAb designed to bind the N-terminals of CLR and RAMP1 of the CGRP receptor, thereby stopping CGRP from activating the receptor [66]. The other three mAbs (fremanezumab, galcanezumab, and eptinezumab) are directed towards the 37-amino acid molecule, acting equally well at α- and β-CGRP [67]. Collectively, these molecules have all emerged as effective and well tolerated for the preventive treatment of migraine. They are much larger than other preventive medications, which, as said, limits their ability to pass the BBB [68, 69]. The tolerability profile is excellent and does not differ to any major extent from their control groups.

Because CGRP is widely expressed in the body, discussion is ongoing regarding possible cardiovascular or intestinal side effects [70]. A common question is why are there so few peripheral effects, and would there not be interactions with pain systems generally [71]? The mAbs have now been approved by regulatory authorities FDA and EMA, and greater than 500,000 patients are on these treatments. Numerous patients have reported that "the CGRP directed medications have transformed their lives" [60]. Amazingly, the mAbs have effects both in EM and CM patients who have not responded well to other available preventive treatments [72, 73]. The American Headache Society has provided a statement paper for which patients should have the mAbs for migraine prophylaxis [74].

A site of antimigraine effect

The debate regarding the site of action of gepants and mAbs is ongoing. Currently, there is consensus that the mAbs cannot pass the BBB, hence the place for relieving the migraine pain is peripheral [62, 69, 75], suggesting action on the trigeminovascular system [31]. Interestingly, studies of the trigeminal system using quantitative and semiquantitative methods have revealed that the trigeminal ganglion (TG) is freely accessed by molecules in the blood, molecules that can have effects on its cellular structures [75, 76]. There is no alteration in the integrity of the BBB during migraine attacks [77]. Thus, reportedly, there was no alteration in the BBB (interictal and ictal) in acute glyceryl trinitrate–induced migraine attacks [78]. Furthermore, magnetic resonance imaging performed during the aura phase reported no evidence of increased BBB permeability [79]. In addition, the BBB was intact in spontaneous attacks of migraine without aura [80]. Furthermore, induced dural inflammation in a preclinical model did not show effects on BBB integrity calculated as the permeability surface area [75].

Where could the CGRP directed medications act to produce their effects? The studies have shown that the brain is protected from passage of the gepants and triptans (less than 2–3% passes the BBB), and for the mAbs less than 0,01% passes the BBB. Then the trigeminal system offers the most logical site of action of these acute and prophylacitc drugs [68, 75]. From available data, it is obvious that mAbs act on sites outside the BBB, putatively within the trigeminovascular system, the central or peripheral aspects of the sensory C- and Aδ-fibers [81, 82]. Given this suggestion, there are at least four tentative places for the action of the anti-CGRP drugs: (i) the most peripheral ends of the C- and Aδ-fibers, in part located in the adventitia of intracranial vasculatures and on the dura mater with mast cells [83], (ii) the trigeminal ganglion with neurons and satellite glial cells [84, 85], (iii) the trigeminal nucleus caudalis, though it is limited by the BBB [11, 86], and recently (iv) the nodes of Ranvier, which offers a novel target site [87]. The debate is ongoing and possibly several of these sites may be involved.

The details of the molecular interaction of mAbs have been studied. Manoukian et al. showed in a cell model that CGRP induces a concentration-dependent increase in cAMP and CGRP receptor internalization at different concentrations (EC$_{50}$ 8.4 pM vs. 7.9 nM, respectively). The lack of effect of the antibodies and gepants at the resting stage agrees with human data, where the small molecule CGRP antagonist telcagepant [88, 89] and the CGRP antibody fremanezumab or the CGRP receptor antibody erenumab did not have vasomotor effects by themselves [90, 91]. An experimental anti-CGRP molecule (8E11) and an anti-CGRP receptor antibody (AA58) blocked both effects, but the cAMP effect occurred at lower concentrations [92]. Using a combination of flow cytometry and confocal microscopy, the study showed that CGRP and the CGRP receptor were internalized and localized to the endosomes. It has been suggested that the endosomes and not the plasma membrane is the site of pain transmission [93]. Hypothetically, the increase in CGRP may contribute to migraine pain via CGRP receptor internalization and endosomal signaling [92].

Clinical effects of the CGRP antibodies

The mAbs either bind to the CGRP receptor, or the α and β isoforms of CGRP. They are not broken down by liver enzymes, which adds to their long half-life in plasma, varying between 3 and 5 weeks. The mAbs are effective in EM and CM and have few side effects. The mAbs have, during the last few years, passed phase III, some even phase IV, and are now on the market in numerous countries [60, 94]. Since there are no direct comparative trials, we have to rely on meta-analysis papers; the overall conclusion is that their efficacy is good with few and mild side effects [95, 96]. The mAbs have

been proposed as disease-modifying drugs since they can help to slow down the natural progression of migraine [97]. All mAbs studies showed a significant reduction in their primary endpoints, either meaning change from baseline in monthly migraine days (MMD) or a change in headache hours from baseline [98].

Erenumab is a humanized IgG_{2A} mAb that targets the CGRP receptor [66]. Early onset of its efficacy has been documented in many trials. In the first week, 43% of EM and 26% of CM patients receiving erenumab 140 mg had a $\geq$50% decrease in weekly migraine days [99]. Furthermore, CM patients treated with erenumab for a month disclosed a reduction by 12.2 MMD, along with a reduction in the use of medication, the intensity of pain, and disability. Subcutaneous erenumab, 70 mg and 140 mg monthly, has been evaluated in phase III randomized controlled trials (RCTs) (STRIVE and ARISE) for the prevention of EM [99, 100]. Besides significant reduction in the use of antimigraine drugs, erenumab led to substantial improvements. The most common side effects noted were upper respiratory tract infection and pain at the injection site. In the STRIVE trial, besides a drop in the number of MMD, statistically significant reductions in the number of days requiring the use of antimigraine drugs and improvement in physical functioning scores and daily activities were observed [100]. Phase IIIb LIBERTY trial examining EM patients with a history of 2–4 preventive drug failures verified the supremacy of erenumab 140 mg and established that erenumab worked well for patients with refractory migraine [73]. Recently, a 5-year open-label study validated that erenumab is a safe drug with effects that remain over this period [101, 102]. Lipton et al. reported that CM can reverse to EM within a year of erenumab treatment [103].

Eptinezumab is the only CGRP mAb designed for iv use quarterly. It is a fully humanized $IgG_{1\lambda}$ mAb targeting both α and β isoforms of CGRP [104]. Phase III RCTs have assessed eptinezumab for prophylaxis of EM (PROMISE-1) and CM (PROMISE-2) [105]. There was $\geq$75% reduction in MMD observed in 24.7%, 22.2%, and 29.7% of patients medicated with eptinezumab 30, 100, and 300 mg, respectively, over 12 weeks. Interestingly, the occurrence of migraine on the first day after the infusion was significantly reduced by approximately half. In the PROMISE-2 trial, the doses of 100 and 300 mg showed significant reductions in

MMDs over the 6-month trial period. The $\geq$75% migraine responder rates (RRs) were up to 38.5% (100 mg) and 42.3% (300 mg dose) and 22.7% (placebo) (months 4–6). The $\geq$50% migraine RRs were 60.7% (100 mg), 63.4% (300 mg dose), and 44.5% (placebo) (months 4–6). A 1-year open-label safety study of 300 mg eptinezumab in CM (PREVAIL) reported a reduction in migraine-associated disability and improvement in patient functioning [106]. In addition, besides effective prevention, eptinezumab was found to achieve headache pain freedom after 4 h and absence of most bothersome symptoms after 2 h as compared to placebo [107].

Fremanezumab binds equally well with α and β isoforms of CGRP. It is a humanized $IgG_{2\kappa}$ mAb evaluated at doses of 225 mg administered monthly and 675 mg quarterly for the prevention of EM (HALO-EM) [108]. The phase III study, HALO-CM trial assessed the doses of 675 mg quarterly and 225 mg monthly for the prevention of CM [109]. Patients treated with fremanezumab with concurrent medication overuse headache (overuse of antimigraine drugs) had reported a statistically significant reduction of monthly medication use days compared to placebo [110]. A long-term study (52 weeks) from the HALO trials showed that fremanezumab reduced MMD in patients with EM and CM by −5.1 and −8.0 days, respectively [111]. Side effects observed were redness at the site of injection, induration at the site of injection, diarrhea, anxiety, and depression [108]. The FOCUS trial was a phase III trial in EM and CM patients who had failed 2–4 preventive medications [72]. Fremanezumab was effective with MMD reduction in both patient populations. Interestingly, a post hoc analysis stratified the results by age and sex and reported that fremanezumab was effective in all age groups and equally between men and women [112].

Galcanezumab is a humanized IgG_4 mAb acting well at both α and β forms of CGRP. Subcutaneous monthly doses of 120 mg or 240 mg have been investigated for the prophylaxis of EM (EVOLVE-1 and EVOLVE-2) and CM (REGAIN) [113–116]. Analysis of the three trials revealed a greater number of EM or CM patients treated with galcanezumab achieved $\geq$50% reduction in MMD compared to placebo, establishing the efficacy of this antibody [114]. The EVOLVE-1 trial on the prevention of EM compared galcanezumab (120 mg and 240 mg) with a placebo. Galcanezumab displayed fast onset starting at month 1 that lasted

through month 6. Patients had lesser MMDs needing acute treatment. Galcanezumab improved both Migraine Disability Assessment (MIDAS) and daily functioning scores compared to placebo [116]. In the EVOLVE-2 trial, the side effects seen were pain at the local injection site, local reactions, and itching [115]. REGAIN (evaluation of galcanezumab in the prevention of CM) comprised a 3-month double-blind, placebo-controlled treatment phase and a 9-month open-label extension phase [113]. Common side effects of galcanezumab were pain at the site of injection, upper respiratory tract infection, reactions at the local site of administration, backache, and sinusitis [113]. In a 1-year open-label study of self-administered subcutaneous monthly injections as prophylactic therapy, both 120 mg and 240 mg doses were found to be safe and associated with a reduction in MMD [117]. Long-term galcanezumab lead to improvement in functional impairment and disability [118].

The overall results from the clinical trials of mAbs against CGRP and the CGRP receptor have collectively demonstrated stable effects in EM and CM. The response remained for more than 5 years of therapy, with remaining efficacy and with few side effects. These novel treatments designed to target the specific pathophysiology of migraine, where CGRP plays a key role, already have an important place in the therapy of severe migraine. Long-term risks, especially in comorbid conditions, have so far not disclosed severe side effects. The role and interaction of these mAbs are now monitored in special subsets of the population, such as pregnant and lactating women and in children, and in other conditions where the CGRP family of peptides may have a role.

Conclusion

The current view suggests that migraine has an elusive genetic background. Various triggers may elicit attacks, whether due to stress or fluctuations in hormones, which trigger cells in the hypothalamus to initiate the attack. The connectivity in the brain implies the involvement of the thalamus and brainstem regions, ultimately resulting in enhanced activity in the trigeminal system and sensitization at both central and peripheral sites. The new specific CGRP-directed medications aim to play down this activity.

CGRP was earlier proposed to be involved in migraine pathophysiology [32] and later basic and clinical research formed the foundation for a new group of specific remedies, mAbs directed towards CGRP or the CGRP receptor, and small molecule drugs (gepants) acting on the CGRP receptor [31]. The mAbs are now approved for prophylaxis of migraine, and the first of the gepants are in clinical use. The experience has been reviewed by several groups and is very encouraging [60]. It took basic research more than 3 decades to be translated to clinical practice, but the result for the patients has been extraordinary [31]. Ongoing work aims to unravel the biology of CGRP signaling, expand the clinical evidence for the role of CGRP in migraine headache, and potentially find other ways to treat the different patient groups of primary headache disorders, like cluster headache, inter alia. All in all, the latest findings have provided new insights into the central role of the trigeminal system in the pathophysiology of migraine pain.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest in this work.

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