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MINI-REVIEW ARTICLE

CGRP and CGRP-Receptor as Targets of Migraine Therapy: Brain Prize-2021

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Abstract: ***Background*:** Migraine is a highly prevalent primary headache with an unclear pathomechanism. During the last 40 years, numerous hypotheses have arisen; among them, the theory of the trigeminovascular system is the primary one. It serves as a skeleton in successful preclinical studies and in the development of effective therapeutic options for migraine headache.

***Objective*:** The brain prize (awarded annually by the Lundbeck Foundation) is the most prestigious tribute in neuroscience. The winners in 2021 were *Lars Edvinsson, Peter Goadsby, Michael Moskowitz* and *Jes Olesen*. They are the fathers of migraine pathomechanism, which led to revolutionary new treatments. This review summarizes their landmark findings.

***Methods*:** Data related to this topic were reviewed from PubMed records published between 1979 and May 2021. Searches were based on preclinical and clinical studies in the covered field. The findings were listed in chronological order. From a therapeutic perspective, only randomized controlled trials and meta-analysis were discussed.

***Results*:** The calcitonin gene-related peptide-related pathogenesis of migraine is based on the activation of the trigeminovascular system. The therapeutic triad for migraine is triptans, gepants, and calcitonin gene-related peptide-targeted monoclonal antibodies.

***Conclusion*:** In the past 40 years, the systematic work of leading headache scientists has resulted in robust theoretical and therapeutic knowledge in the preclinical and clinical study of migraine.

Keywords: Brain Prize, CGRP, migraine, monoclonal antibodies, trigeminovascular system, neuropeptides.

1. INTRODUCTION

Migraine, as a common and complex primary headache disorder, is a devastating neurovascular disease with high socio-economic and personal impact, although its pathomechanism is still enigmatic. The global age-standardized migraine prevalence is overall 14.4% (in women: 18.9% and in men: 9.8%) [1, 2], with disability continuously increasing with the progression of years. The Global Burden of Disease Study 2016 revealed that the global disability-adjusted life-years of migraine ranked in the 2nd position among all neurological disorders [3, 4].

The leading theory of the pathomechanism of migraine was developed in 1979 when ***Moskowitz*** proposed the trigeminovascular hypothesis, which was later renamed as the Trigeminovascular System (TS) [5, 6]. Hyperexcitability and sensitization of the TS are due to different neuropeptides (*e.g,* calcitonin gene-related peptide-CGRP and pituitary adenylate cyclase-activating peptide-PACAP) [7]. CGRP plays an essential role in the pathomechanism of migraine, both in the peripheral and central sensitization and hyperexcitability of the TS [8-10]. Peripheral sensitization produces the throbbing and pulsating features of the headache. Additionally, it plays a crucial role in the worsening of pain with routine physical activities. Central sensitization is behind the cephalic and extracephalic allodynia during a migraine attack [11-16]. The hyperexcitability and sensitization of the TS are strongly associated with CGRP, as remarkable clinical findings of the group of ***Goadsby*** and ***Edvinsson*** showed. CGRP plasma levels are elevated in cranial venous outflow during migraine attacks [17]. The development of the aura phase of a migraine attack and the stimulation of the peripheral branch of the TS, revealed by *Olesen* and his group, are due to the process of Cortical Spreading Depression (CSD) [18]. Chemically-induced animal migraine models and human clinical data revealed that Nitric Oxide (NO) can upregulate CGRP release in the TS [19, 20]. The gold standard acute migraine treatment, triptans, also work on the

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modification of CGRP release, both in the peripheral and central arms of the TS [21, 22]. The new view of the pathomechanism of migraine spots the connection between kynurenine metabolism, PACAP, and CGRP in the TS [23, 24].

CGRP, as a focus of migraine research, has led to novel therapeutic options, both for acute and preventative treatment of Episodic (EM) and Chronic Migraine (CM), like CGRP receptor antagonists (gepants and erenumab) and anti-CGRP monoclonal antibodies (mAbs) (eptinezumab, fremanezumab and galcanezumab) [25-28]. mAbs targeting the CGRP pathway are recently licensed, high-cost migraine drugs, which are real game-changers, have revolutionized the prophylactic treatment of migraine (Nagaraj *et al.* Neurol India 2021). All are approved by the FDA (Food and Drug Administration), while at present (during the manuscript preparation) eptinezumab is not approved by the EMA (European Medicine Agency).

Our strategy was to search PubMed's computer-based literature using the following search phrases: 'migraine' and 'CGRP' 'monoclonal antibody' 'gepants' 'NO' 'TS' 'TRIG' 'CSD' 'triptans' 'kynurenines' 'PACAP' 'meta-analysis'.

The present review intends to offer an updated summary of the results, focusing on the pathomechanism and latest therapeutic options associated with CGRP in migraines. Our aim was to order the remarkable statements and milestone findings of the related works of Brain Prize winners 2021: Lars Edvinsson, Peter Goadsby, Michael Moskowitz, and Jes Olesen.

2. CLINICAL FEATURES OF MIGRAINE

Based on the latest classification of the International Headache Society (International Classification of Headache Disorders 3rd edition- ICHD-3), migraine is one of the primary headache disorders [29]. The main types of migraine are migraine with and without aura. CM is a separate subtype of migraine, which is marked by 15 or more headache days per month for more than 3 months, and at least 8 days per month are migraine with or without aura attacks [29]. EM is divided into low-frequency (1-4 headache days per month) and high-frequency (5-14 days per month) subgroups.

Migraine consists of recurring paroxysmal headpain attacks with concomitant non-painful symptoms. Migraine, which can be considered as a cycling brain disorder, consists of different phases, like prodrome (premonitory phase), aura, headache and reconvalescence (postdrome) [30].

2.1. Prodrome (Premonitory phase)

It is defined by ICHD-3 as the period up to 48 hours before the onset of headache [29]. Its prevalence ranges between 71-87% [31]. Typical features of this preictal phase of migraine are the following: appetite changes, thirst, yawning, polyuria, fatigue, light and sound sensitivity, elated or depressed mood [29, 30, 32, 33].

2.2. Aura

Migraine with aura, which appears in approximately 20% of migraine patients, can be described as recurrent attacks which are preceded by unilateral fully reversible visual, sensory, speech, motor, brainstem or retinal neurological symptoms that last 5-60 minutes and are followed by migraine type head pain and associated symptoms [29].

2.3. Headache

Migraine without aura is characterized by a recurrent unilateral, pulsating, moderate-to-severe intensity headache lasting 4-72 hours. It is aggravated by modest physical activity: Nausea and/or vomiting, photophobia and phonophobia frequently occur [29].

Patients experiencing a migraine, with or without aura, also exhibit cranial autonomic symptoms, like lacrimation, conjunctival injection, eyelid edema, nasal congestion, during the headache phase. They can occur unilaterally (27-46% of the patients) or bilaterally (52-73%) [34-36]. It was an interesting finding that photophobia is more common in migraineurs with autonomic symptoms [36]. Cranial autonomic symptoms are frequent not only in Caucasians but also in Asian migraine patients [37]. Dizziness and vertigo also not rare concomitant signs during the prodromal and headache phases of migraine. Based on a recent systematic review and meta-analysis, dizziness (6.7-59.6%) and vertigo (6.4-44.7%) frequentlyoccurred during the course of the headache stage [38]. Allodynia, which is a painful response to an innoxious stimulus, can occur frequently (ranged 42-68%) during a migraine attack [39]. Allodynia is a sign of hyperexcitability and central sensitization of the TS. It can be localized as cephalic (on face and scalp) or generalized as extracephalic (mainly in the lower arm) [12, 13, 40].

2.4. Postdrome

The non-headache symptom phase, lasting up to 24-48 hours following migraine attacks (with or without aura), is common, affecting around 80% of patients [41]. Its characteristics are fatigue, tiredness, dizziness, hunger, mood changes, sensory sensitivities, inability to concentrate, and cognitive difficulties [29, 30]. The symptoms of this postdromal phase are similar to those of the premonitory phase of migraine [42].

3. THE ROLE OF CALCITONIN-GENE RELATED PEPTIDES IN THE PATHOMECHANISM OF MIGRAINE

CGRP, a 37-amino acid neuropeptide, was identified in the early 1980s [43, 44]. In humans, it has two isoforms: α-CGRP and β-CGRP. α -CGRP appears widely in the peripheral and central nervous systems, while β-CGRP is expressed mainly in the enteric nervous system. CGRP acts on its functional receptor complex with seven transmembrane domains, which contain three elements: Calcitonin-Receptor-Like Receptor (CRLR), receptor-activity-modifying protein-1 (RAMP-1), and receptor-component protein (RCP) [45].

3.1. Preclinical and Clinical CGRP-related Studies in Migraine

3.1.1. Trigeminovascular System and CGRP

Historically, there was a long debate about intracranial pain-sensitive structures. Wolff and Ray, and later *Edvinsson*, then Keller & Marfurt revealed that the innervation of the cerebral and meningeal vasculature mainly originated from the trigeminal ganglion (TRIG) and it has peptidergic content [46-51].

Moskowitz and his research group proposed a pathophysiological link between migraine and the trigeminal innervation of the meninges - that was the first description of the trigeminovascular hypothesis [5]. Later on, they proposed a new functional connection named the Trigeminovascular System (TS), which mirrors the relationship between the peripheral (meningeal) afferents and the central (trigeminocervical complex) arm of the perikarya of TRIG [52]. The electrical stimulation model of the TS revealed that after the TRIG activation, structural alterations (swelling of club-like terminals) of CGRP immunoreactive perivascular sensory nerve terminals in rat cerebral dura mater were observed [53]. In the same model, the authors found that CGRP- immunoreactivity was depleted in the trigeminal nucleus caudalis (TNC), which suggested the role of CGRP in the central part of the TS [54]. It has been confirmed that CGRP does not just have a second messenger function but also potent vasoactive action - vasodilation in the TS [55, 56]. Modern, precise histochemical studies have characterized the distribution of different neuropeptides in the TS. CGRP-containing neurons, sensory fibers and CGRP-receptor elements occur in high numbers [57-63]. The first remarkable functional studies by *Goadsby* demonstrated that activation of the TRIG, in humans by thermocoagulation and in cats by electrical stimulation produced elevated plasma CGRP concentrations in the extracranial venous outflow [64]. The milestone observation was that plasma CGRP concentration was highly elevated in the external jugular vein during a spontaneous migraine attack in patients, while other neuropeptides (vasoactive intestinal peptide-VIP, substance P-SP, neuropeptide Y-NPY) remained unchanged [17]. It has been proved in a double-blind cross-over study that intravenous (IV) infusion of CGRP initiated delayed migraine-like headaches in migraineurs [65, 66]. Results of a preclinical human study suggest a possible sensory influence from the TRIG in the parasympathetic sphenopalatine ganglion guided by CGRP as a background for the occurrence of autonomic symptoms during a spontaneous migraine attack [67].

3.1.2. Cortical Spreading Depression and CGRP

One of the unique phenomena of the cerebral cortex is CSD, which is a slow propagation wave of neuronal and glial depolarization [68]. The first suggestion that CSD occurs in migraineurs during the aura phase of a migraine attack originated with ***Olesen*** and his colleagues [18]. Later on it was confirmed, using modern imaging techniques, that bilateral spreading of cerebral hypoperfusion existed during spontaneous migraine attacks [69]. Functional magnetic resonance imaging (MRI) studies demonstrated that in the human visual cortex spreading suppression of cortical activation was detected during migraine aura [70]. Some *in vitro* and *in vivo* animal experimental data support the hypothesis that CSD could induce CGRP activity in the TS. It has been proved that CSD could initiate cortical CGRP release, furthermore, CGRP antagonism could modulate CSD on cortical slices *in vitro*. *In vivo* experiments demonstrated that olcegepant, as a CGRP receptor blocker, could inhibit the repetitive CSD events in mice. Additionally, CSD could increase CGRP synthesis in the cerebral cortex and CGRP gene upregulation in rat brains [71]. Based on these observations, it can be proposed that through this process CGRP is released from both the peripheral and central branches of the TS [71-75].

3.1.3. Nitric Oxide and CGRP

Nitric oxide (NO) is formed from the terminal guanidino nitrogen of L-arginine in a catalyzed process of nitric oxide synthases (endothelial NOS-eNOS, neuronal NOS-nNOS, inducible NOS-iNOS) [20, 76, 77]. Clinical studies demonstrated that administration of glyceryl trinitrate (GTN) as a NO-donor can induce migraine pain of both types of migraine (migraine with and without aura) [20, 66, 78]. Preclinical studies showed that in GTN-treated rats nNOS and CGRP increased in cerebral dura mater, while in the TNC-only group, CGRP was elevated by immunohistochemical techniques [19]. In GTN-treated ovariectomized female rats, the area innervated by CGRP immunoreactive afferents decreased significantly, while estradiol-pretreatment inhibited the GTN effect [79].

An *in vitro* cell culture study demonstrated that a NO-donor triggered CGRP release from cultured primary TRIG neurons. Based on this finding, NO up-regulates migraine-related CGRP release in TRIG neurons. CGRP can stimulate NO release from satellite glial cells, while NO promotes CGRP release from them [80]. In experimental migraine animal models, it was revealed that a selective nNOS inhibitor could inhibit CGRP release from cerebral dura mater in rats [81]. Another experiment, in active, freely moving rats, showed that GTN pretreatment increased nNOS and CGRP in dura mater, but only CGRP in TNC [19]. A strong working hypothesis suggests that there is cross-talk signaling in TRIG cells (neurons and satellite glial cells). The CGRP, PACAP, and NO released from the neurons and glial cells can signal to neighbouring neurons and *vice versa* [82].

3.1.4. Triptans and CGRP

The discovery of triptans as 5-hydroxytryptamin $(HT)_{1B/1D}$ receptor agonists was a real breakthrough for the acute medication of migraine attacks [83, 84]. Interestingly, it has been proved that triptans act not only by influencing the serotonergic system, but also act on CGRP release in the animal model of trigeminal activation and during migraine attacks in humans [85-87]. Histochemical studies have shown that $5\text{-}HT_{1B/1D}$ receptors are co-localized with CGRP

in TRIG neurons and sensory fibers [88, 89]. It has been revealed that rizatriptan can block secretions of CGRP from cultured TRIG neurons [90]. Our research group revealed that sumatriptan pretreatment of electrical stimulation of TRIG prevented the disintegration of perivascular nerve terminals and elicited the accumulation of CGRP, which indicated that sumatriptan could prevent the release of CGRP from the perivascular sensory nerve terminals in the cerebral dura mater in rats [21]. We also demonstrated that eletriptan could block the perikarya and peripheral and central axon terminals of primary sensory neurons in TRIG after electrical stimulation in rats [22]. Naratriptan did not block capsaicin-induced CGRP release from peripheral terminals innervating the dura mater, but it stopped the release from brainstem slices in mice [91]. Sumatriptan, used for nitroglycerin-induced migraine attack in female migraine patients, caused a parallel reduction in plasma CGRP concentration and pain intensity [92].

3.1.5. Kynurenine Metabolism and CGRP

The essence of tryptophan metabolism is the kynurenine pathway, where the main factor is L-kynurenine (L-KYN), an endogenous antagonist of excitatory amino acid receptors [23, 93]. Kynurenic acid (KYNA) is synthesized by the enzyme kynurenine aminotransferase (KAT). The stimulation of TRIG decreased KAT-immunoreactivity in the Schwann cells in the cerebral dura mater. This was the first observation that indicated the importance of the kynurenine system in the pathomechanism of migraine [94].

A preclinical animal model of migraine revealed that L-KYN and a kynurenic acid derivative attenuated CGRP expression in nitroglycerin-induced activation of the TS in the upper cervical spinal cord of rats [95]. Capsaicin-stimulated CGRP release was not altered by KYNA in the peripheral part of the TS, while it was significantly reduced in the brainstem as a central part of the TS in mice [91]. Immunohistochemical data proved that CGRP receptor components (CLR and RAMP1) co-localized in rat and rhesus TRIG [96]. An experimental model of chemically-induced inflammation of TRIG revealed co-expression of nuclear

factor kappa B (NF-κB) and CGRP in TRIG neurons in rats, while KYNA has the capability to reduce this inflammation in TRIG [97]. In an animal model, GTN administration induced increased mRNA expression of CGRP in the TRIG and TNC, and also elicited hyperalgesia. Both processes were diminished by KYNA analogue 1 [98]. Novel results indicated that the topical application of inflammatory soup on rat cerebral dura mater increased CGRP in rat TNC, compared to the placebo, and it was attenuated by KYNA. This suggests N-methyl-D-aspartate (NMDA) receptor involvement in neurogenic inflammation in the TS [99]. Preclinical data suggest that elements of the kynurenine pathway may play a role in migraines and other neurological disorders.

A remarkable clinical study in this field examined the serum level of kynurenine pathway metabolites in chronic migraine patients. It should be emphasized that the serum level of KYNA was reduced, while anthranilic acid was largely increased compared to healthy controls [100, 101]. Recently, our research lab detected alterations in triptophan catabolism during ictal and interictal periods in migraine patients. We found that, interictally, the plasma concentration of triptophan, L-KYN, KYNA, anthranilic acid, picolinic acid, 5-hydroxy-indoleacetic acid and melatonin were significantly decreased compared to healthy controls. In the ictal phase, antranilic acid, 5-hydroxy-indoleacetic acid and melatonin were significantly elevated. These results suggest a widespread metabolic imbalance of tryptophan catabolism in migraineurs [102] (Tuka *et al.* J Headache Pain 2021). A first-in-human phase 1 open-label study demonstrated that L-KYN administered intravenously was safe and well-tolerated in healthy volunteers [103]. These pivotal results open up a new field of research into kynurenine in migraine pathomechanisms and treatments.

3.1.6. PACAP and CGRP

PACAP is the second migraine-related vasodilator neuropeptide [104]. PACAP is strongly expressed in elements of the TS, like TRIG and TNC neurons and fibers [58, 59, 105]. The significant role of PACAP in the initiation of the migraine attack has been confirmed. One of the PACAP isoforms, namely PACAP1-38, can induce migraine-like attacks in patients with migraine without aura when infused intravenously [106]. During a spontaneous migraine attack, PACAP and CGRP plasma levels are altered [24]. During the interictal phase of migraine, plasma PACAP concentration was lower compared to the healthy controls; conversely elevated PACAP levels were detected during the ictal period [24]. Another preclinical study revealed that PACAP1-38 induced CGRP release from TNC, but not from TRIG in rats [107]. A chemically-induced model of the peripheral branch of the TS resulted in significant CGRP and prepro PACAP release in the TNC [108].

4. CGRP-TARGETED MIGRAINE TREATMENT

4.1. CGRP Receptor Antagonists - gepants

During the early 2000s, innovative pharmacology targeted the suppression of CGRP signaling in the TS, and developed CGRP-based small molecules, which, moreover, do not cause vasoconstriction as triptans do [14, 109] (Table **1**).

The first small molecule selective CGRP receptor antagonist (first-generation gepants), a dipeptide, BIBN4096BS, was developed [110]. The first proof-of-concept study revealed that intravenous (IV) olcegepant was effective in migraine attack treatment [111]. Unfortunately, its IV administration limited its widespread use in everyday clinical practice. The first oral gepant was telcagepant (MK-0974), and, later on, several other orally administered gepants were developed, but long-term and frequent use resulted in elevated gamma-glutamyl aminotransferase, thus discontinuing their administration [14, 109, 112, 113].

The second generation of orally administered gepants (ubrogepant, rimegepant, atogepant) were designed to avoid the liver enzyme elevation [114].

Table 1. CGRP-targeted therapies – gepants

CGRP Receptor Antagonist	Indications	Route of Administration	Dosing	Efficacy	Side Effects	Refs.
First Generation Gepants						
Olcegepant	EM Acute treament	IV	2.5 mg	a response rate of 66 percent, as compared with 27 percent for placebo	paraesthesia	[111, 114, 136]
Telcagepant	EM Acute treatment	Oral	150 mg	pain freedom at 2 hrs was 23.2% compared to placebo 10.7%	dry mouth, fatigue, somnolence, long-term and frequent use resulted in elevated GGT serum level	[112, 114, 136]
Second Generation Gepants						
Ubrogepant (UBRELVY™)	EM Acute treatment	Oral	50 mg 100 mg	pain freedom at 2 hrs was 20.8% compared to placebo 12.6%	nausea, somnolence, dry mouth	[114, 123, 136]
Rimegepant (NURTEC™)	EM Acute treatment _____ Preventive treatment	Oral (ODT) _____ Oral (standard tablet)	75 mg _____ 75 mg	pain freedom at 2 hrs 21% versus 11% (placebo) _____ LSM baseline change in mean MMDs was -4.3 days versus -3.5 days (placebo)	nausea, urinary tract infection _____ nasopharyngitis, nausea	[114, 129, 130, 136]
Atogepant	EM Preventive treatment	Oral	10 mg, 30 mg, 60 mg (once daily) _____ 30 mg and 60 mg (twice daily)	LSM baseline change in mean MMDs was at 10 mg once daily -4.0 days, at 30 mg once daily -3.8 days, at 60 mg once daily -3.6 days _____ at 30 mg twice daily -4.2 days at 60 mg twice daily -4.1 days versus placebo -2.9 days	nausea, fatigue	[114, 133, 136]
Third Generation Gepants						
Vazegepant	EM Acute treatment	Intranasal	10 mg, 20 mg	vazogepant was more effective than placebo: at 10 mg (22.5%), at 20 mg (23.1%) versus placebo (15.5%) (details are not applicable)	dysgeusia, nasal dyscomfort	[114, 135, 136]

Abbreviations: CGRP (Calcitonin Gene-Related Peptide), IV (Intravenously), EM (Episodic Migraine), GGT (Gamma-Glutamyltransferase) LSM (Least Square Mean), MMDs (Monthly Migraine Days) ODT (Orally Disintegrating Tablet).

A phase 2b randomized double-blind placebo-controlled dose-ranging (1 mg, 10 mg, 25 mg, 50 mg, 100 mg) study revealed that 100 mg ubrogepant (MK-1602) for acute treatment of migraine exhibited 2 hours post-dose pain freedom of 25.5% compared to the placebo (8.9%). The most common adverse events (AEs) were dry mouth (100 mg ubrogepant 4.9% *versus* placebo 3.9%), nausea (100 mg ubrogepant 6.9% *versus* placebo 3.5%) and fatigue (100 mg ubrogepant 2.9% *versus* placebo 2.7%) [115]. The ACHIEVE-I randomized controlled trial (RCT) for efficacy and safety of ubrogepant in acute migraine treatment showed that ubrogepant at doses of 50 mg and 100 mg achieved headache freedom at 2 hours after the initial dose (19.2% at 50 mg dose and 21.2% at 100 mg *versus* 11.8% placebo). The frequent AEs were nausea, somnolence and dry mouth (0.4% to 4.1%) [116]. ACHIEVE-II, a multicenter randomized double-blind placebo-controlled single migraine attack phase 3 trial, revealed that the pain freedom at 2 hours was 21.8% (ubrogepant 50 mg) and 20.7% (ubrogepant 25 mg) compared to 14.3% (placebo): The most common AEs were nau-

sea (2.0% at 50 mg dose; 2.5% at 25 mg dose *versus* 2.0% placebo) and dizziness (1.4% at 50 mg dose, 2.1% at 25 mg dose *versus* 1.6% placebo) [117]. A post hoc pooled analysis (ubrogepant 50 mg) of ACHIEVE-I and -II double-blind single attack phase 3 trials concerning time course of efficacy of ubrogepant for acute migraine treatment demonstrated that the pain-relief at 1 hour was 43% (ubrogepant) *versus* 37% (placebo), and pain-freedom at 2 hours was 20% (ubrogepant) *versus* 13% (placebo). Ubrogepant exerted a long-lasting effect [118]. A post hoc analysis of pooled data from the ACHIEVE-I and -II studies demonstrated that the efficacy and tolerability of ubrogepant did not change in migraine patients who were historically treated with triptans [119]. A long-term (52-week) phase 3, multicenter, randomized, open-label extension trial evaluating the safety of intermittent use of ubrogepant (50 mg or 100 mg) for the acute treatment of migraine (1 or 2 doses per attack) with or without aura demonstrated that treatment-related AEs were 10% for a 50 mg dose of ubrogepant and 11% for a 100 mg dose of ubrogepant [120].

A phase 1 single center open-label randomized 3-way cross-over single-dose pharmacokinetic interaction study of ubrogepant in healthy participants did not show treatment-emergent AEs (TEAEs) after co-administration of ubrogepant (100 mg) and sumatriptan (100 mg) (Jakate *et al.* Headache 2020). The pooled safety data from ACHIEVE-I and -II trials using ubrogepant alone or ubrogepant and sumatriptan treatment together revealed that treatment-related TEAEs were 14.9% in the ubrogepant 100 mg group, while only 12.8% in ubrogepant plus triptan group [121]. A randomized phase 1b drug-drug interaction two-arm, multicenter, open-label, study revealed that the pharmacokinetics and safety profile of ubrogepant, when it was co-administered with erenumab and galcanezumab did not change [122].

A meta-analysis of three RCTs evaluating the efficacy and safety of ubrogepant for the acute treatment of EM revealed that the effect of ubrogepant with pain-freedom at 2 hours post-dose was significantly higher compared to the placebo (ubogepant 20.8% *versus* placebo 12.6%). The evaluation of treatment-related AEs within 48 hours or 30 days for ubrogepant *versus* the placebo revealed that the risk ratio (RR) was 1.07 at 48 hours and 1.03 at 30 days [123]. A recent meta-analysis of five RCTs of ubrogepant as a treatment for acute migraine demonstrated that the 2 hours post-dose pain-relief was significantly higher in the verum group, than in the placebo group (odds ratio: 1.71). The safety profiles of ubrogepant and the placebo were similar. The common AEs between the ubrogepant-treated group and the placebo group showed that the incidence of headache was 7.89% (ubrogepant group) *versus* 8.68% (placebo group), of oropharyngeal pain was 9.18% (ubrogepant group) *versus* 3.47% (placebo group), while of nasopharyngitis it was 4.58% (ubrogepant group) *versus* 6.25% (placebo group) [124].

A real-world cohort study evaluating the efficacy, tolerability and safety of ubrogepant both in EM and CM revealed that headache freedom at 2 hours after taking the drug was achieved in 19% of the patients, while headache relief (>75% of all treated attacks) at 2 hours after taking ubrogepant was observed in 47.6% of the migraineurs. The most common AEs were fatigue (27.4%), dry mouth (7.5%) and nausea/vomiting (6.6%) [125, 126].

A dose-ranging (10, 25, 75, 150, 300 or 600 mg), randomized, double-blind, placebo-controlled study of BMS-927711 (later called rimegepant) for the acute treatment of migraine revealed that the pain-freedom at 2 hours post-dose was 31.4% (75 mg verum), 32.9% (150 mg verum), 29.7% (300 mg verum) and 24.4% (600 mg verum) *versus* 15.3% (placebo). The commonly occuring AEs were nausea (3%-75 mg, 3%-150 mg, 4%-300 mg and 8%-600 mg), dizziness (1%-75 mg, 2%-150 mg, 0%-300 mg and 4%-600 mg) and vomiting (2%-75 mg, 0%-150 mg, 0%-300 mg and 2%-600 mg) [127]. A multicenter, double-blind, randomized, placebo-controlled phase 3 trial investigating the efficacy and safety of rimegepant (BMS-927711) (75 mg oral standard tablet) in the acute treatment of low-frequency EM revealed that in a modified intention-to-treat analysis of patients at 2 hours post-dose pain-freedom was 19.6% (rimegepant) *versus* 12.0% (placebo). The most common AEs were nausea (1.8%-rimegepant *versus* 1.1%-placebo) and urinary tract infection (1.5%-rimegepant *versus* 1.1%-placebo) [128]. A multicenter, double-blind, randomized, placebo-controlled phase 3 trial was conducted to compare the efficacy and safety of an Orally Disintegrating Tablet (ODT) formulation of rimegepant (75 mg single dose) in the acute treatment of migraine. The results demonstrated that rimegepant ODT was superior to the placebo at 2 hours post-dose pain-freedom (21% *versus* 11%). The most common AEs were nausea (2% in rimegepant group versus. <1% in the placebo group) and urinary tract infection (1% in verum group *versus* 1% in placebo group), and no serious AEs were reported [129]. A multicenter, randomized, double-blind, placebo-controlled phase 2/3 trial investigating the standard oral rimegepant 75 mg tablet every other day for preventive treatment of migraine with and without aura or CM patients (at least 4 and not more than 18 migraine attacks per month) revealed that rimegepant had superior efficacy to the placebo. The least-square mean (LSM) change was -4.3 days for rimegepant and -3.5 days for the placebo in mean number of monthly migraine days (MMDs) during weeks 9-12. The most common AEs were nasopharyngitis (4%-rimegepant *versus* 2%-placebo) and nausea (3%-rimegepant *versus* 1%-placebo) [130].

A meta-analysis of 65 clinical trials of gepants (telcagepant, rimegepant, ubrogepant) for the acute treatment of nausea-freedom after 2 hours in EM revealed that the overall combined effect size with an odds ratio was 1.29, which supported the efficacy of gepants for the treatment of the most bothersome symptom (eg, nausea) of migraine attacks [131]. A subgroup meta-analysis of the comparative efficacy of FDA-approved oral CGRP receptor antagonists (ubrogepant and rimegepant) *versus* the placebo in the treatment of acute migraine demonstrated that the analysed gepants were significantly more effective than the placebo (odds ratio of pain-freedom at 2 hours post-dose was 1.83) [132].

For prevention of EM, atogepant, as an orally administered pharmacon, was investigated in a double-blind randomized phase 2b/3 trial examining a range of oral doses (10 mg to 60 mg once or twice daily). It showed a significant decrease in MMDs in all five atogepant dose groups, and it was safe and well-tolerated. Across the 12-week treatment period, the LSM baseline change in mean MMDs compared to the placebo was the following: atogepant 10 mg once daily -4.0 days, 30 mg once daily -3.8 days, 60 mg once daily -3.6 days, 30 mg twice daily -4.2 days and 60 mg twice daily -4.1 days *versus* placebo -2.9 days. The most common TEAEs were nausea (at 10 mg once a day atogepant - 5% to 60 mg once a day atogepant - 12% *versus* placebo - 5%) and fatigue (at 10 mg once day atogepant - 1% to 60 mg twice a day atogepant - 10% *versus* placebo - 3%) [133]. A recent open-label randomized five-way cross-over single-center phase 1 drug-drug interaction trial investigating the safety of single dose (60 mg) atogepant co-administered with acetaminophen (100 mg) or naproxen (500 mg) in healthy persons revealed that this combination was safe and well-tolerated, and no drug-drug interactions were reported [134].

The third generation, intranasally administered gepant, vazegepant, is now referred to as zavegepant [135]. Vazegepant is a high affinity and structurally unique (distinct from rimegepant) small molecule CGRP receptors antagonist. At the time of writing, the results of the clinical study of vezagepant had been announced but were not yet published. A randomized, dose-ranging (5-20 mg), placebo-controlled pivotal phase 2/3 clinical trial (BHV3500-201) investigating the efficacy and safety of vazegepant in the acute treatment of migraine showed promising results. Doses of 10 mg and 20 mg vazegepant were more effective than the placebo (10 mg vazegepant - 22.5%, 20 mg vezagepant - 23.1% *versus* placebo - 15.5%). The reported AEs, dysgeusia, and nasal discomfort were mild [136].

Overall, the clinical importance of gepants in the acute treatment of migraine is that these drugs can be used as second-line therapy in the triptan non-responder group of the patients (30-40% of migraineurs) [137]. Moreover, the gepants have a place in the therapeutic palette among migraine patients who are intolerant to triptans or fear their cardiovascular side effects [138]. Until now, ubrogepant (Dec 23, 2019) and rimegepant (Feb 27, 2020) have been approved by the FDA for the acute treatment of migraine, while the application of atogepant for migraine prevention has been accepted (March 30, 2021) by the FDA [109].

4.2. CGRP-targeted Monoclonal Antibodies (mAbs)

In the last couple of decades, migraine-specific prophylactic treatment was not available. The widely used and recommended preventive drugs for migraines are beta-adrenergic receptor blockers, calcium ion channel blockers, antiepileptics and antidepressants [139, 140]. The novel pharmacological technique which can produce humanized or fully human mAbs against CGRP and CGRP receptors opened up a new option for patients. Consistent preclinical and clinical research targeting the crucial role of CGRP in the pathomechanism of migraine has led to the first phase 1 clinical study of mAbs in migraine prophylaxis.

The currently available antibody-based antimigraine drugs are eptinezumab (humanized IgG1), erenumab (fully human IgG2), fremanezumab (humanized IgG2) and galcanezumab (humanized IgG4) [109, 141] (Table **2**).

4.2.1. Eptinezumab

Eptinezumab (humanized IgG1kappa mAb) selectively binds to the CGRP ligand. It is administered intravenously. It was approved by the FDA on Feb 21. 2020.

A phase 2b parallel group double-blind, randomized, placebo-controlled, dose-ranging clinical trial of eptinezumab for the prevention of CM revealed that 300 mg (33.3%), 100 mg (31.4%, 30 mg (28.2%) and 10 mg (26.8%) of eptinezumab resulted in a decrease of more than 75% in migraine responder rates over weeks 1-12 *versus* the placebo (20.7%). TEAEs were similar to the placebo, including upper respiratory tract infection (300 mg - 10.7%, 100 mg - 6.6%, 30 mg - 5.7%, 10 mg - 6.9% *versus* placebo 5.0%), dizziness (300 mg - 1.7%, 100 mg - 9.8%, 30 mg - 2.5%, 10 mg - 8.5% *versus* placebo 7.4%) and nausea (300 mg - 6.6%, 100 mg - 7.4%, 30 mg - 3.3%, 10 mg - 4.6% *versus* placebo 7.4%) [142]. The PROMISE-1 (Prevention of Migraine *via* Intravenous Eptinezumab Safety and Efficacy) trial, a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 study of eptinezumab in prevention of EM, revealed that 300-mg (-4.3 days) and 100-mg doses (-3.9 days) of eptinezumab significantly reduced MMDs over weeks 1-12 compared to the placebo (-3.2 days). The most common TEAEs were upper respiratory tract infection (300 mg - 10.3%; 100 mg - 9.9% *versus* placebo - 7.2%) and nasopharyngitis (300 mg - 6.3%; 100 mg - 7.6% and placebo - 5.4%) [143].

The PROMISE-2 trial, a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 study of eptinezumab in the prevention of CM, demonstrated that the reduced MMDs over weeks 1-12 at 100 mg dose of eptinezumab was -7.7 days (vs. placebo -5.6 days) and at 300 mg dose of it was -8.2 *versus* placebo (-5.6 days). The most common TEAEs were nasopharyngitis (300 mg - 9.4%; 100 mg - 5.3% *versus* placebo - 6.0%) and upper respiratory tract infection (300 mg - 5.4%; 100 mg - 4.2% and placebo - 5.5%) [144].

The PROMISE-2 through 24 weeks of eptinezumab treatment for the prevention of CM was performed as follows: the first dose was given at day 0 and the second dose at week 12. The reduction of mean MMDs after the first dose: 300 mg: -8.2 days, 100 mg: -7.7 days *versus* the placebo: 5.6 days. The decrease of mean MMDs after an additional dose of eptinezumab was at 300 mg dose -8.8 days and at 100 mg dose, -8.2 days compared to the placebo (-6.2%). The most frequent TEAEs were nasopharyngitis (eptinezumab 300 mg after both doses: 9.4%; 100 mg: 5.3% *versus* placebo: 6.0%) and upper respiratory tract infection (eptinezumab 300 mg

Table 2. CGRP-targeted therapies - monoclonal antibodies.

Antibody Against CGRP Receptor	Type	Indications	Route of Admin	Dosing	Efficacy	Side Effects	Refs.
Erenumab (AIMOVIG®)	Fully human IgG2	EM and CM Preventive	SC	70 mg or 140 mg monthly	EM: LHH (AE/50%): 3 (STRIVE study); LHH (AE/50%): 1.6 (ARISE study) CM: decrease of MMDs -6.6 days compared to -4.2 days of placebo	EM: STRIVE study: nasopharyngitis, upper respiratory tract infection ARISE study: upper respiratory tract infection, injection site pain, nasopharyngitis CM: constipation, injection site pain, upper respiratory tract infection, nausea	[114, 141, 170, 180, 186]
Eptinezumab (VYEPTI™)	Humanized IgG1 kappa	EM and CM Preventive	IV	100 mg or 300 mg quarterly	EM: LHH (AE/50%): 3.4 (PROMISE-1 study) CM: LHH (AE/50%): 5.1 (PROMISE-2 study)	EM: PROMISE-1 study: upper respiratory tract infection, nasopharyngitis CM: PROMISE-2: upper respiratory tract infection, nasopharyngitis	[114, 141, 148, 186]
Fremanezumab (AJOVY®)	Humanized IgG2A	EM and CM Preventive	SC	225 mg monthly or 675 mg quarterly	EM: LHH (AE/50%): 2.6 (HALO-EM study); CM: LHH (AE/50%): 2.8 (HALO-CM study)	HALO-EM study: injection site reaction (pain, erythema, induration) HALO-CM study: injection site reaction (pain, erythema, induration)	[114, 141, 157, 186]
Galcanezumab (EMGALITY®)	Humanized IgG4	EM and CM Preventive	SC	120 mg monthly with 240 mg loading dose	EM: LHH (AE/50%): 4.0 (EVOLVE-1 study); 7.2 (EVOLVE-2 study) CM: LHH (AE/50%): 1.4 (REGAIN study)	EM: EVOLVE-1 study: injection site pain EVOLVE-2 study: injection site pain CM: REGAIN study: injection site pain	[114, 141, 166, 186]

Abbreviations: AE (Adverse Event), CGRP (Calcitonin Gene-Related Peptide), CM (Chronic Migraine), EM (Episodic Migraine), LHH (Likelihood to Help *versus* Harm: ratio of NNTH/NNTB), NNTH/NNTB (the number of patients needed to be treated to harm / the number needed to be treated for a specific beneficial outcome), Ig (Immunoglobulin), IV (Intravenously), MMDs (Monthly Migraine Days), SC (Subcutaneously).

after both doses: 5.4%; 100 mg: 4.2% *versus* placebo: 5.5%) [145]. The subgroup analysis of the PROMISE-2 trial with a dual diagnosis of CM and medication overuse headache patients revealed that eptinezumab decreased the MMDs at 300 mg dose -8.6 days and at 100 mg dose -8.4 days compared to placebo -5.4 days. The most frequent drug-related TEAEs were nasopharyngitis (10.2% - 300 mg dose of eptinezumab and 5.0% - 100 mg dose *versus* 6.9% - placebo) and upper respiratory tract infection (5.4% - 300 mg dose of eptinezumab and 3.6% - 100 mg dose *versus* 5.5% - placebo) [146]. The PREVAIL study, a long-term (2-year), open-label phase 3 trial for evaluating safety and tolerability of IV eptinezumab given in repeated 300 mg doses (every 12 weeks for up to 8 doses) in CM patients, revealed that the most common TEAEs were nasopharyngitis (14.1%), upper respiratory tract infection (7.8%), sinusitis (7.8%) and bronchitis (5.5%) [147]. The pooled analysis of the above clinical trials concerning the comprehensive safety and tolerability of IV eptinezumab in migraineurs demonstrated that the most common drug-related TEAEs were mild-to-moderate in intensity, such as upper respiratory tract infection (at all doses 7.6% *versus* placebo 6.1%), nasopharyngitis (at all doses 6.7% *versus* placebo 5.2%) and dizziness (at all doses 3.3% *versus* placebo 2.7%) [148].

4.2.2. Fremanezumab

Fremanezumab (humanized IgG isotype 2A) selectively targets CGRP as a ligand. Its route of administration is subcutaneously (SC). It was approved by the FDA on September 14. 2018.

A multicenter randomized placebo-controlled phase 2b study for TEV-48125 for preventive treatment in high-frequency EM demonstrated that the LSM difference in the reduction of MMDs focusing on placebo *versus* fremanezumab was -281 days (225 mg fremanezumab) and -2.64 days (675 mg fremanezumab). AEs occurred in 46% of patients (at 225 mg dose of fremanezumab) and 59% of migraineurs (at 675 mg dose of fremanezumab) compared to 56% (in placebo group) [149]. In a randomized, double-blind, placebo-controlled, parallel-group trial (HALO-EM study) fremanezumab was administered quarterly or monthly for prophylaxis of EM. It revealed a significant decrease of mean MMDs (8.9-4.9 days for fremanezumab monthly, 9.2-5.3 days for the single, higher dose of fremanezumab *versus* 9.1-6.5 days for the placebo group). The most common AEs in the fremanezumab groups were injection site reactions, such as pain (29.6-30%), erythema (17.9-18.9%) and induration (09.6-24.5%) [150]. Fremanezumab administered quarterly or monthly for prophylaxis of CM in a phase 3 trial (HALO-CM study) demonstrated that it was effective and well-tolerated. The LSM ($\pm$SE-standard error) decrease of the average number of headache days per month was 4.3$\pm$0.3 (quarterly fremanezumab) and 4.6$\pm$0.3 (monthly fremanezumab) compared to 2.5+0.3 (placebo). The main AEs in fremanezumab groups were injection site reactions (pain: 26-30%, induration: 20-24%, erythema: 20-21%) [151]. A subanalysis of long-term (12-month) phase 3 RCT from HALO-EM and HALO-CM studies revealed that the mean weekly number of migraine days decreased substantially, 30-42%, during the first 2 weeks and it remained stable for at least 2 weeks of the first and second quarter. The migraine patients receiving monthly or quaterly fremanezumab did not experience a wearing-off effect toward the end of the dosing interval [152]. A randomized, double-blind, placebo-controlled, parallel-group phase 3b (FOCUS) study was performed in EM and CM patients who previously failed to react with up to four migraine preventive medication classes. This FOCUS study revealed a reduction in average MMDs *versus* the placebo. The LSM ($\pm$SE) difference *versus* placebo was -3.1 with quarterly fremanezumab and -3.5 with monthly fremanezumab. The AEs were similar to the placebo (pain: 3-4% in fremanezumab groups *vs.* 3% in the placebo group, induration: 4-4% in fremanezumab groups *vs.* 5% in placebo group, erythema 5-7% in fremanezeumab groups *vs.* 6% in placebo group) [153].

A recent subgroup analysis by country (Czech Republic, USA and Finland) of the FOCUS study investigated the efficacy and safety of monthly and quarterly administration of fremanezumab. It revealed that the average number of MMDs was reduced compared to the placebo regardless of country and continent. The LSM difference of efficacy of fremanezumab was -1.9 days (quarterly fremanezumab) and -3.0 days (monthly fremanezumab) in the Czech Republic, -3.7 days (quarterly fremanezumab) and -4.2 days (monthly fremazenumab) in the USA and -3.0 days (quarterly fremanezumab) and -3.9 days (monthly fremanezumab) in Finland. The AEs were comparable across countries [154].

A long-term 52-week, multicenter randomized, double-blind, parallel-group study revealed the long-term safety, tolerability and efficacy of fremanezumab administered monthly or quarterly in EM or CM patients. MMDs were reduced by -7.2 days (quarterly) and -8.0 days (monthly) in CM patients, while -5.2 days (quarterly) and -5.1 (monthly) in EM patients from the baseline to 52 weeks. Regarding AEs in CM patients, injection site induration was 30% (quarterly) and 35% (monthly), injection site pain was 29% (quarterly) and 33% (monthly) and injection site erythema was 25% (quarterly) and 31% (monthly). In EM patients, injection site induration was 29% (quarterly) and 38% (monthly), injection site pain was 30% (quarterly) and 32% (monthly) and injection site erythema was 25% (quarterly) and 27% (monthly) [155]. The meta-analyses of RCTs concerning efficacy, safety and optimal treatment strategy of fremanezumab in migraine prevention revealed that the pharmacon showed good efficacy with mild AEs, and the single high dose of 675 mg and 225 mg fremanezumab administered monthly demonstrated the optimal balance between efficacy and safety at 12 weeks [156, 157]. There are some new data from fremanezumab dose selection phase 1 trial in children planning to design a phase 3 clinical study in pediatric migraineurs, which has suggested a dose of 120 mg of fremanezumab in patients weighing <45 kg [158].

4.2.3. Galcanezumab

Galcanezumab (humanized IgG isotype 4) binds CGRP as a ligand. Its route of administration is SC. It was approved by the FDA on September 27, 2018.

The EVOLVE-1 (Evaluation of LY2951742 in the Prevention of Episodic Migraine) randomized, double-blind, placebo-controlled phase 3 trial in EM demonstrated that reduced MMDs were 4.7 days (120 mg galcanezumab) and 4.6 days (240 mg galcanezumab) *versus* 2.8 days (placebo). The common (TEAE) was injection site pain, which was 16.0% at 120 mg dose of galcanezumab, 20.5% at 240 mg dose of galcanezumab and 17.4% in the placebo group [159].

EVOLVE-2, a global double-blind 6-month phase 3 RCT evaluating efficacy and safety of galcanezumab in EM, revealed that the mean MMDs were reduced by 4.3 days (120 mg galcanezumab group), 4.2 days (240 mg galcanezumab group) *versus* 2.3 days (placebo group). Migraine Disability Assessment (MIDAS), Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive and Patient Global Impression of Severity as key secondary endpoints were superior to placebo in both doses (120 mg and 240 mg) of galcanezumab. TEAEs as injection site pain was 9.3% (galcanezumab 120 mg), 8.8% (galcanezumab 240 mg) and 8.5% (placebo). Injection site erythema occurred in 2.7% (galcanezumab 120 mg), 3.1% (galcanezumab 240 mg) and 0.9% (placebo). Injection site pruritus existed in 2.7% (galcanezumab 120 mg), 3.1% (galcanezumab 240 mg) and 0.0% (placebo) [160].

The REGAIN randomized, double-blind, placebo-controlled phase 3 study, which involved a 3-month long double-blind placebo-controlled treatment phase and 9-month long open-label extension, revealed that the mean number of MMDs were decreased by -4.8 days (galcanezumab 120 mg)

and -4.6 days (galcanezumab 240 mg) *versus* -2.7 days (placebo). The most common TEAE was injection site pain (6% at 120 mg galcanezumab, 7% at 240 mg galcanezumab *versus* 4% at placebo group) [161]. A long-term (12 months) multicenter, randomized, open-label phase 3 two galcanezumab dosing (120 mg and 240 mg) regimen study revealed that, from an efficacy point of view, the mean reduction in MMDs was -5.6 days (120 mg galcanezumab) and -6.5 days (240 mg galcanezumab). The most frequent TEAE was injection site pain (17.1% in 120 mg dose galcanezumab and 19.9% in 240 mg dose galcanezumab group) [162].

The CONQUER study, a multicenter, randomized, double-blind, placebo-controlled, phase 3b trial focused on the efficacy and safety of galcanezumab (120 mg SC) in migraine patients in whom prophylactic medication from two to four categories had failed. The reduction of the number of MMDs was significantly greater in the verum group (4.1 days compared with baseline 13.4 days) *versus* placebo (1.0 day compared with baseline 13.0 days). The rate of TEAEs was similar to the placebo (galcanezumab 51% *versus* placebo 53%). The most common AEs were injection site pain (25% in galcanezumab 120 mg group *versus* 6% in placebo group) and erythema (3% in galcanezumab 120 mg group *versus* 3% in placebo group) [163].The post-hoc analysis of the CONQUER study showed early onset of effect of galcanezumab beginning the first day after treatment initiation and maintained all subsequent weeks and months in migraine patients who had failed previous preventive drug treatments [164]. A recently published, phase 2 RCT from Japan focused on treatment satisfaction with galcanezumab (120 mg and 240 mg) for 6 months in EM patients, revealed that the Patient Global Impression of Improvement response rates and Patient Satisfaction with Medication Questionnaire-modified scale response rates were significantly higher compared with the placebo [165]. The meta-analysis of EVOLVE-1, EVOLVE-2 and REGAIN phase 3 RCTs demonstrated that galcanezumab was effective and well-tolerated in prophylactic treatment for migraine patients [166]. A systematic review and meta-analysis of six clinical studies revealed that the overall effect size of galcanezumab (120 mg and 240 mg) over the placebo in mean difference in the number of MMDs was 2.22 days. The safety outcome demonstrated that RR of injection site pain between both dose groups of galcanezumab (120 mg and 240 mg) compared to the placebo was 1.35, while RR of nasopharyngitis was 0.93 and of upper respiratory tract infection was 1.61 [167].

A real-life multicenter prospective observational cohort study (the GARLIT study: GAlcanezumab in Real Life migraine patients in ITaly) for galcanezumab SC (120 mg monthly with the first loading dose of 240 mg) for the prevention of high-frequency EM and CM revealed that MMDs were reduced by 8 days in high-frequency EM and monthly headache days were decreased by 13 days in CM patients after 6 months of therapy. After 6 months of galcanezumab treatment, 77.2% of CM patients converted to EM. AEs were observed in up to 10.3% of migraineurs. The most common AEs at 6 months were gastro-intestinal signs (*e.g.,* nausea, constipation) (2.5%) and arthralgia, skin reaction, and dizziness (0.6%, respectively). Galcanezumab showed higher effectiveness in real-life settings than in RCTs [168].

4.2.4. Erenumab

Erenumab (fully human IgG2) competitively and reversibly binds to CGRP receptor components (CLRL and RAMP1), and it is administered SC. It was approved by the FDA on May 17, 2018.

A multicenter randomized double-blind placebo-controlled phase 2 dose-ranging trial of efficacy and safety of AMG334 (7 mg, 21 mg and 70 mg) for the prevention of EM demonstrated that a dose of 70 mg significantly reduced the MMDs at week 12 (-2.3 days of 70 mg *versus* -1.1 days of placebo). The most common AEs were nasopharyngitis (7 mg - 9%, 21 mg - 5%, 70 mg - 6%, placebo - 8%), fatigue (7 mg - 5%, 21 mg - 2%, 70 mg - 4%, placebo - 2%) and headache (7 mg - 4%, 21 mg - 1%, 70 mg - 3%, placebo - 1%) [169]. A multicenter randomized double-blind placebo-controlled phase 2 study investigating the efficacy and safety of erenumab (70 mg and 140 mg) for the prevention of CM revealed that both doses of erenumab reduced the MMDs (-6.6 days compared to -4.2 days of placebo). The reported AEs were 39% in the placebo group, 44% in the 70 mg-dose group and 47% in 140 mg-dose erenumab treated group. The most frequent AEs were injection site pain (70 mg - 4%, 140 mg - 4%, placebo - 1%), upper respiratory tract infection (70 mg - 3%, 140 mg - 3%, placebo - 1%) and nausea (70 mg - 2%, 140 mg - 3%, placebo - 2%) [170]. The STRIVE trial (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention), a phase 3 RCT of erenumab at doses of 70 mg and 140 mg for a 6 month-period in patients with EM, revealed that the mean number of MMDs was reduced by -3.2 days in 70 mg-dose group and -3.7 days in 140 mg-dose group compared to -1.8 days in the placebo group. The physical impairment scores and every day-activities scores were improved in borh verum groups compared to the placebo. AEs were similar between the erenumab and placebo groups. The most common ones were nasopharyngitis (70 mg - 9.9%, 140 mg - 11%, placebo - 10%) and upper respiratory tract infection (70 mg - 6.7%, 140 mg - 47%, placebo - 5.6%) [171]. A post-doc analysis of the data from the STRIVE study noticed that the reduction of the frequency of monthly migraine attacks (LSM change from baseline to -1.99 at 70 mg and -2.22 at 140 mg erenumab compared to -1.32 for the placebo) led to a decrease of MMDs (LSM change from baseline to -3.23 at 70 mg and -3.67 at 140 mg erenumab *versus* -1.83 for the placebo), and the duration of migraine attacks was decreased by a lesser amount [172]. The ARISE study (A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention), a large multinational, placebo-controlled phase 3 trial of erenumab 70 mg in EM resulted in a LSM treatment difference of -1.0. The safety profile of erenumab was similar to the placebo. The most common AEs were upper respiratory tract infection (7 mg erenumab - 6.4%, placebo - 4.8%), injection site pain (70 mg erenumab - 6.0%, placebo - 4.2%)

and nasopharyngitis (70 mg erenumab - 5.3%, placebo - 5.9%) [173]. The LIBERTY trial was conducted as a 12-week long randomised, double-blind, placebo-controlled, phase 3b study investigated erenumab (140 mg SC) in patients with EM in whom two to four previous preventive drug treatments had failed. Regarding efficacy as a 50% or greater reduction from baseline in the mean number of MMDs, 30% of patients in the verum group *versus* 14% in the placebo group found the treatment effective. Injection site pain was the most common and equivalent TEAE in the two study groups (6% in erenumb group and 6% in placebo group) [174]. Analysis of the effect of erenumab on patient-reported functional outcomes from the LIBERTY study showed that erenumab was efficacious on functional outcomes [175]. The long-term (64-week long) open-label extension phase of the LIBERTY study, evaluating the efficacy and safety of erenumab (140 mg SC) in EM resulted in a 50% responder rate (≥50% reduction in MMDs from baseline), increased from 29.9% to 43.3% at week 61-64, which pointed to the sustained efficacy of erenumab monotherapy. The most common AEs were nasopharyngitis (30.8%) and injection site pain (5.4%) [176]. A real-life observational study evaluating the efficacy and safety of erenumab treatment over 6 months, mainly (94.4%) in CM patients and in medication overuse headache patients (71.9%), revealed that after the complete 6 dose treatment of erenumab the median MMDs decreased from 19 days to 4 days. The main AE was constipation (13.5%) [177]. The subgroup analysis of the study mentioned above demonstrated that 68.1% of CM patients on an at least 6-month, erenumab treatment converted to EM (from 26.5 to 7.5 median MMDs) [178]. Another real-world observational study examining erenumab and galcazenumab in refractory migraine patients who had not had success with at least three preventative medications reported that after 12 weeks the headache frequency decreased -9.1 headache days per month (erenumab) and -8.5 migraine days per month (galcanezumab) from the baseline. The most frequently reported drug-related AEs were constipation (20%) and fatigue (7.1%) [179]. A meta-analysis of erenumab RCTs revealed significantly greater reductions in baseline MMDs (70 mg: mean difference -1.3; 140 mg: mean difference -1.9). It can be concluded that erenumab is an efficacious and well-tolerated prophylactic, therapeutic option both in EM and CM [180]. A newly published systematic review and meta-analysis, which includes data of 8 clinical trials evaluating the AEs of erenumab revealed that a significant heterogeneity of estimated incidence of AEs was observed. This heterogeneity can be connected to treatment duration for back pain, while influenza, upper respiratory tract infection and Body Mass Index for nasopharyngitis [181].

The latest published long-term 5-year, open-label treatment phase following a 12-week RCT evaluating efficacy and safety of erenumab (70 mg, which increased to 140 mg) in EM prevention study revealed that the mean change in MMDs from a baseline of 8.7 days was -5.3 days and the average reduction of MMDs were 62.3% at year 5, and the change in monthly acute migraine-specific medication days were -4,4 days at the end of 5 years. Incidence rates of AEs were 123/100 patient-year [182].

A real-life cohort study evaluating MMDs after the discontinuation of erenumab (98.1% of the patients) and galcanezumab (1.9% of the patients) one-year long treatments revealed that the migraine frequency quickly returned. After treatment interruption, the MMDs were 6 days in the first month and these numbers rose to 11 days in the third month [183].

4.2.5. Meta-analyses of CGRP-targeted mAbs Treatment in Migraine

A meta-analysis was aimed at the placebo and nocebo phenomena in clinical trials which involve CGRP-targeted mAbs in migraine prevention. The data demonstrated that the 50% responder rates in EM were 32.7% in the placebo-arm *versus* 50.8% in the verum-arm (anti-CGRP mAbs), while in CM the placebo-arm showed 23.6% and the verum-arm had 43.8% responder rate. Regarding the nocebo phenomenon, in placebo-treated EM patients, the proportion of drop-outs due to AEs (nocebo) was 1.9%, while in CM patients, it was 1.4%. In the verum-arm (anti-CGRP mAbs) of EM the ratio of drop-outs due to AEs was 2.7%, while with CM it was 1.4%. These results suggest that the stronger placebo and weaker nocebo phenomena in these RCTs may determine anti-CGRP mAbs treatment success [184]. A systematic review and meta-analysis were conducted focusing on proportional contextual effects (PCE) of CGRP mAbs in EM and CM. The PCE means the ratio between the reduction of MMDs in the placebo group and in the verum group after 3 months of treatment. The pooled PCE was 0.66 in EM and 0.68 in CM. Two-thirds of the therapeutic benefit of anti-CGRP mAbs in migraine is originated from the PCE effect [185]. A systematic review and likelihood to help *versus* harm (LHH) analysis of CGRP-based mAbs for migraine prevention were recently published. The LHH values mean the ratio of NNTH/NNTB (the number of patients needed to be treated to harm / the number needed to be treated for a specific beneficial outcome). Efficacy, safety and benefit/risk outcomes of erenumab (STRIVE and ARISE), fremanezumab (HALO-EM), galcanezumab (EVOLVE-1 and EVOLVE-2) and eptinezumab (PROMISE-I) in the prophylaxis of EM were analysed. The LHH (AE/50%) of erenumab 70 mg in the STRIVE trial was 3, and in the ARISE trial was 1.6. The LHH (AE/50%) of fremanezumab 225 mg in the halo-EM study was 2.6 and of galcanezumab 120 mg in the EVOLVE-1 study was 4.0, and in EVOLVE-2 was 7.2, while of eptinezumab 100 mg in the PROMISE-1 study was 3.4. In the prophylaxis of CM, LHH (AE/50%) of fremanezumab 225 mg monthly in the HALO-CM trial was 2.8, of galcanezumab 120 mg in the REGAIN study was 1.4, and of eptinezumab 100 mg in PROMISE-2 was 5.1 [186]. Another systematic review and network meta-analysis concerning the efficacy (changes in MMDs) and safety of CGRP-targeting mAbs revealed that fremanezumab 225 mg (-2.19 days), galcanezumab 120 mg (-2.10 days), erenumab 70 mg (-1.61 days) and eptinezumab 100 mg (-1.43 days) significantly reduced MMDs compared to the placebos. Regarding the safety profile of the four mAbs, the incidences of TEAEs were the following: gal-

canezumab *vs.* placebo (relative risk-RR: 1.11), fremanezumab *vs.* placebo (RR: 1.05), eptinezumab *vs.* placebo (RR: 1.03) and erenumab *vs.* placebo (RR: 0.98). The pooled RR of serious AEs due to erenumab (RR: 1.15), fremanezumab (RR: 1.16), eptinezumab (RR: 1.25) and galcanezumab (RR: 2.95) compared to the placebo [187].

5. SUMMARY

One of the biggest challenges in the clinical management of migraine is that up to one-third of migraineurs need prophylactic drug treatment. Prophylactic migraine treatment is considered effective if the drug decreases the attack frequency by at least 50% within 3 months and diminishes the duration of the headache phase and the intensity of head pain [139, 140]. Based on the results of clinical trials, the currently available CGRP-targeted mAbs fulfill these strict criteria. Even more, the application of these medications gives a chance to avoid the development of medication overuse headaches due to the reduced need of acute migraine drugs. The management of CM is difficult; therefore, CGRP-related mAbs give a bright perspective in this therapeutic field [188].

In daily clinical practice, the rate of adherence is a decisive aspect for clinicians, which ranges considerably (from 25% to 94%) among migraineurs regarding their prophylactic medications [189, 190]. There is hope that CGRP-targeted mAbs with a remarkably better safety profile will result in an increase in adherence rates in this population [191].

The unique effect of these pharmacons is that those migraine patients for whom multiple previous standard-of-care preventative drug treatments failed (so they were considered difficult-to-treat patient groups) showed clear-cut improvements. Another beneficial feature of these drugs is their early onset and sustained efficacy, which occurs after one week of their administration.

Overall, all the currently available CGRP-targeting mAbs (eptinezumab, fremanezumab, galcanezumab and erenumab) are highly effective in the prophylaxis of both EM and CM. They are safe and well-tolerated with the most frequent AEs as injection site reactions and, for erenumab, constipation. Their administration is simple with long-lasting action. Evenmore their long-term immunogenicity is limited. Nonetheless, their use still requires cautious attention to their contraindications like cerebrovascular and cardiovascular events [109, 192].

CONCLUSION

The Brain Prize winners in 2021 were *Lars Edvinsson (Sweden), Peter Goadsby (UK), Michael Moskowitz (USA)* and *Jes Olesen (Denmark)*. These outstanding scientists are pioneers in migraine research. They discovered and proved the key mechanisms of the role of CGRP in migraines. Additionally, they have built a robust pathway between the role of CGRP in the TS associated with CSD, NO, PACAP and the kynurenine system. Moreover, their activities have opened the door and marked new directions for preclinical and clinical work in the migraine bedside-to-bench-to-bedside research field. The results of their ground-breaking work led to CGRP-based treatment of migraine, like CGRP receptor antagonists (ubrogepant, rimegepant, atogepant) and an antibody against CGRP receptor (erenumab) and antibodies against CGRP as a ligand (fremanezumab, galcanezumab, eptinezumab). This CGRP-targeted mechanism-based therapy has had a huge impact on millions of migraineurs (Table **3**).

Table 3. Migraine-related milestone discoveries of Brain Prize winners 2021.

Discoveries and Main Hypotheses	Year	Researcher	Refs.
Trigeminovascular hypothesis	1979	Moskowitz MA	[5]
Trigeminovascular system	1983	Moskowitz MA	[52]
The first description of CGRP localization and function in the cerebral circulation	1984	Edvinsson L	[50]
CGRP release after trigeminal stimulation in humans	1988	Edvinson L Goadsby PJ	[64]
CGRP release during an acute migraine attack	1990	Edvinsson L Goadsby PJ	[17]
The first suggestion of CSD occurring during the aura phase of migraine	1990	Olesen J	[18]
Triptans block trigeminal activation and CGRP release in animals and humans	1993-1994	Edvinsson L Goadsby PJ	[86, 87]
Nitric oxide triggers migraine attacks	1994	Olesen J	[78]
CGRP co-localized with 5-HT $_{1/B}$ and $_{1/D}$ receptors in human TRIG neurons and sensory fibers	2001-2002	Edvinsson L	[88, 89]
CGRP IV infusion triggers the migraine attack	2002	Olesen J	[65]
PACAP IV administration triggers the migraine attack	2009	Olesen J	[106]
Sumatriptan reduced elevated PACAP plasma level during the migraine attack	2014	Edvinsson L Goadsby PJ	[193]
Kynurenic acid modulates experimentally induced inflammation in the trigeminal ganglion	2015	Edvinsson L	[97]

Abbreviations: CGRP: Calcitonin Gene-Related Peptide, CSD: Cortical Spreading Depression, 5-HT: 5-hydroxy-tryptamine, IV: Intravenous PACAP: Pituitary Adenylate Cyclase-Activating Peptide, TRIG: Trigeminal Ganglion.

LIST OF ABBREVIATIONS

AE	=	Adverse Event
CGRP	=	Calcitonin Gene-Related Peptide
CM	=	Chronic Migraine
CRLR	=	Calcitonin-Receptor-Like Receptor
CSD	=	Cortical Spreading Depression
EM	=	Episodic Migraine
EMA	=	European Medicine Agency
FDA	=	Food and Drug Administration
GTN	=	Glyceryl Trinitrate
5-HT	=	5-Hydroxy-Tryptamine
ICHD-3	=	International Classification of Headache Disorders 3rd edition
IV	=	Intravenous(ly)
KYNA	=	Kynurenic Acid
KAT	=	Kynurenine Aminotransferase
LHH	=	Likelihood to Help *versus* Harm
L-KYN	=	L-Kynurenine
LSM	=	Least Square Mean
MIDAS	=	Migraine Disability Assessment
MMD	=	Monthly Migraine Day
MRI	=	Magnetic Resonance Imaging
mAb	=	monoclonal Antibody
NMDA	=	N-Methyl-D-Aspartate
NNTB	=	Number of patients Needed to be Treated for Benefit
NNTH	=	Number of patients Needed to be Treated to Harm
NO	=	Nitric Oxide
NOS	=	Nitric Oxide Synthase
NF-kappa B	=	Nuclear Factor kappa-light-chain-enhancer of activated B cells
PACAP	=	Pituitary Adenylate Cyclase-Activating Peptide
PCE	=	Proportion of Contextual Effects
RAMP-1	=	Receptor-Activity-Modifying Protein-1
RCP	=	Receptor-Component Protein
RCT	=	Randomized Controlled Trial
RR	=	Relative Risk
SC	=	Subcutaneous (ly)
TNC	=	Trigeminal Nucleus Caudalis
TRIG	=	Trigeminal Ganglion
TS	=	Trigeminovascular System

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

Dr. László Vécsei is the Editorial Board Member of the journal CNS & Neurological Disorders - Drug Targets.

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