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CGRP antagonists and antibodies for the treatment of migraine

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Introduction: Migraine is a highly devastating neurovascular disorder that affects up to 16% of the population worldwide. In spite of intensive research, its origin remains enigmatic with no therapeutic option appropriate for all migraine patients. One of the leading hypotheses is related to the function of the calcitonin gene-related peptide (CGRP). Regardless, the pharmaceutical options currently applied for the acute and prophylactic treatment of migraine are not appropriate for all migraine patients.

Areas covered: This article is based on a literature review using the PubMed database and highlights the CGRP theory of the pathomechanism of migraine.

Expert opinion: Since migraine is a CGRP-related disorder, it appeared obvious to develop CGRP receptor antagonists that exert high efficacy, both intravenously and orally. Unfortunately, the frequent use of these antagonists results in an elevated liver transaminase level. In an attempt to bypass these harmful side effects, efforts should be made to modify these pharmacons. The use of fully humanized monoclonal antibodies (mAbs) that target CGRP and its receptors may also be possible. However, while Phase I and II clinical trials are promising, a long-term follow-up of these therapies is still needed.

1. Introduction

Migraine is a common neurovascular primary headache disorder with typical clinical features.

Its high prevalence and considerable socioeconomic and individual impacts have given rise to extensive scientific research activity. Migraine is divided into two major subtypes, with or without aura. The headache in migraine is characterized by unilateral pulsating moderate or severe pain with associated symptoms. The typical features in the phenomenon of migraine aura are the focal neurological symptoms, mainly involving visual disturbances. As concerns the frequency of migraine attacks, episodic and chronic forms are distinguished [1].

The pathomechanism of migraine is still unclear. One of the leading hypotheses is based on activation of the trigeminovascular system (TS). Several neuropeptides participate in this activation, calcitonin gene-related peptide (CGRP) playing a crucial role among them. CGRP exerts various biological effects through the peripheral and central nervous system (CNS). The functional CGRP-receptor (CGRP-R) complex has been well characterized, and novel therapeutic approaches target CGRP itself and its receptors [1].

The CGRP receptor antagonists (CGRP-RAs), called gepants, are small molecules that can be administered either intravenously or orally. The main aim behind the innovation of the gepants was avoidance of the adverse cardiovascular events

accompanying the 5-hydroxytryptamine (5-HT) 1B/1D receptor agonists (triptans), which currently comprise the standard acute treatment for migraine [2]. In randomized clinical trials, the efficacy of the gepants was superior to that of placebo [3]. One of their side effects, liver toxicity, was observed only following their extremely frequent use [3]. A more recent therapeutic option is the application of fully humanized monoclonal antibodies (mAbs) against CGRP and its receptors. Randomized clinical trials are ongoing [4].

2. Calcitonin gene-related peptide

The role of CGRP in the pathomechanism of migraine was proposed by Edvinsson nearly 30 years ago [5]. Together with calcitonin, amylin and adrenomedullin, CGRP belongs in the calcitonin gene peptide superfamily [6,7]. CGRP, a 37-amino acid neuropeptide derived from the gene encoding calcitonin [8-10], is formed from the alternative splicing of the calcitonin/CGRP gene located on chromosome 11. In humans, CGRP has two isoforms: α- and β-CGRP [11,12]. The β-isoform differs from the α-isoform in the amino acids located at positions 3, 22 and 25. The chemical structure of CGRP involves a disulfide bridge between residues 2 and 7 and an amidated C-terminus [13]. The cyclic cysteine^2–cysteine^7 motif has a basic role in receptor activation [14]. In the mammalian plasma, the half-life ($T_{1/2}$) of CGRP is ~ 10 min. In the human trigeminal ganglia (TRIG), CGRP-immunoreactive neurons account for up to 50% of all neurons [15,16]. It has been demonstrated through an *in situ* hybridization technique that 40% of all nerve cell bodies contain CGRP mRNA and CGRP [16,17]. Double immunostaining has shown that in the human TRIG CGRP is co-localized with nitric oxide synthase, substance P (SP), pituitary adenylate cyclase activating peptide (PACAP) and nociceptin, which may play a role in the pathomechanism of migraine [1,16,18,19].

Stimulation of the TRIG in humans and cats led to an increased level of CGRP in the plasma of the extracranial circulation [20]. Elevated serum levels of CGRP in the cranial outflow at the external jugular vein [21] and in the cubital vein have been detected during spontaneous migraine attacks. Support for the role of CGRP in migraine came from the discovery that the intravenous administration of CGRP could induce migraine-like attacks in migraine sufferers without crossing the blood–brain barrier [22].

In the TS, the release of CGRP is proposed in both the peripheral and the central branches of the neuronal elements of the TRIG [23]. In the intracranial meningeal vasculature, CGRP causes neurogenic inflammation (vasodilation, and plasma protein extravasation) and mast cell degranulation, this process leading to the peripheral sensitization of the TS. In the brainstem, CGRP causes central sensitization of the second-order neurons [1,23,24]. Even more data are emerging as concerns the existence of neuronal–glial interactions in the cranial ganglia. In the human TRIG, some of the satellite glial cells (SGCs) display calcitonin receptor-like receptor (CLR) and receptor activity modifying protein-1 (RAMP1) immunoreactivity [15]. CGRP immunoreactive fibers have been detected intraganglionically in the sphenopalatine ganglia in the vicinity of neurons. CLR and RAMP1 immunoreactivity has been observed in the SGCs [25]. The mechanism proposed in this respect involves the release of CGRP during the neuronal activation of the cranial ganglia, this CGRP then stimulating the SGCs, which release pro-inflammatory cytokines, thereby further modulating the neuronal response [3,25,26]. Human immunohistochemical studies have revealed CGRP-immunoreactive neurons in the locus coeruleus, which is one of the migraine generators in the brainstem [27]. One of the most recent preclinical studies demonstrated that the triptans and the glutamate receptor antagonist kynurenate inhibit CGRP release from the brainstem, indicating that the main site of action is the central terminals of the spinal trigeminal nucleus [28]. These experimental findings clearly reveal that CGRP plays a crucial role in the activation of the TS.

3. CGRP receptors

Following the recommendations of the International Union of Pharmacology Nomenclature Subcommittee for CGRP-Rs, CLR with RAMP1 forms the CGRP-1 receptor [29], that is, the CGRP-R. Calcitonin, CGRP, adrenomedullin and amylin belong in the family of G-protein-coupled receptors [7], while the CGRP-Rs belong in the secretin family (Class B) of the G-protein-coupled receptors [29]. The functional CGRP-R consists of three proteins: i) CLR is a seven-transmembrane-spanning protein, which forms the ligand binding site with; ii) RAMP1, determining the specificity of the receptor [30,31]; and iii) the CGRP-R component protein (RCP) couples the receptor to intracellular signal transduction pathways and to adenylyl cyclase (**Figure 1**) [32]. RAMP1, which belongs in the RAMP receptor superfamily, has single-transmembrane α-helix, extracellular N-terminal and intracellular C-terminal domains [33,34]. The RAMPs (RAMP1, RAMP2 and RAMP3)
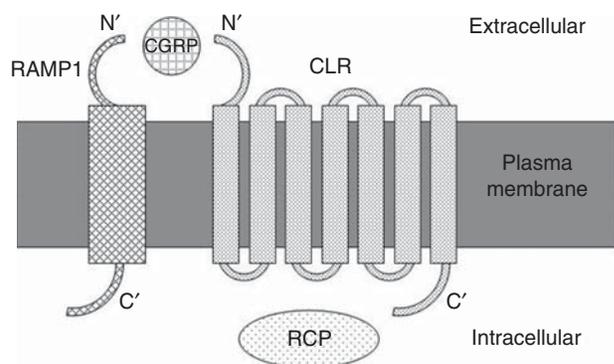
Figure 1. Scheme of the functional CGRP receptor. The functional CGRP-R consists of three proteins: CLR is a seven-transmembrane-spanning protein, which forms the ligand binding site, with a single-transmembrane-spanning protein RAMP1 determining the specificity of the receptor [30,31], while RCP couples the receptor to intracellular signal transduction pathways.

Modified from [31].

C': C-terminus; CGRP: Calcitonin gene-related peptide; CGRP-R: CGRP receptor; CLR: Calcitonin receptor-like receptor; N': N-terminus; RAMP1: Receptor activity modifying protein-1; RCP: CGRP receptor component protein.

contain 148 – 175 amino acids [35]. RAMP1 is distributed in different human organs, including the heart, pancreas and brain [34,36]. As concerns the functional CGRP-Rs, the main role of RAMP-1 is the transport of CLR to the cell membrane surface [31,37]. The sequence of agonist potency of the CGRP-R complex is: α-CGRP > adrenomedullin ≥ amylin ≥ calcitonin [33,34]. The stable extracellular domain complex involves extracellular N-terminal regions of CLR and RAMP-1 [38]. This complex determines the species-selectivity and specificity for CGRP-R antagonists with high-affinity binding [34,39]. Immunoreactivity for CLR and RAMP1 has been demonstrated in the human TRIG: 37% of the neurons express CLR and 36% RAMP1 [15]. CGRP-Rs component and receptor binding sites were recently identified in the human and rhesus monkey cerebellar cortex [40].

4. CGRP-R antagonists

In view of the unclear pathomechanism of migraine and the lack of efficacious treatment of migraine attacks, novel agents acting on the CGRP-Rs have been proposed as a new therapeutical approach. Evidence-based medicine has indicated that the triptans are of Level A for the acute treatment of migraine headache [41]. The mode of action of triptans involves 5-HT 1B/1D receptor agonism, leading to vasoconstriction and neuropeptide release inhibition [42]. Serious adverse cardiovascular events related to triptans are extremely rare. However, triptan-associated chest symptoms may be observed. In patients with overt cardiovascular disease or at high cardiovascular risk, the use of triptans is contraindicated [2]. In order to avoid these side effects, and to treat

migraineurs who are poor responders to triptans, or for whom triptans are contraindicated, the pharmacological challenge arose of identifying a new target and synthesizing a new molecule for this purpose.

The first such nonpeptide CGRP-RA tested was SB-273779, with a potency value of K_i = 310 nM for the human CGRP-R [43]. Its modest receptor affinity revealed that further pharmacological research was needed.

A number of small molecule CGRP-RAs have been developed to date for clinical use, including olcegepant (BIBN4096BS), telcagepant (MK-0974), MK-3207, MK-1602, BMS-694153, BMS-927711 and BI44370TA [44]. There are some others in the preclinical phase, such as MK-8825, BMS-742413, thiazolidinones, tyrosine surrogates and polyethylene glycolated (PEGylated) peptides.

The most studied compounds are the 'gepants,' for example, olcegepant and telcagepant.

Olcegepant (BIBN4096BS: [R-(R*,S*)])-N-[2-[[5-amino-1-[[4-(4-pyridinyl)-1-piperazinyl]carbonyl]pentyl]amino]-1-[(3,5-dibromo-4-hydroxyphenyl)methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3(2H)-quinazolinyl)-   1-piperidinecarboxamide) was the first discovered potent (K_i = 0.010 nM) and selective CGRP-RA [45]. Determination of its affinity through use of a neuroblastoma cell line of human origin (SK-N-MC), which is very close to the human CGRP-R [46], revealed that olcegepant has a higher affinity than that of the endogenous CGRP ligand itself, and a 150-fold higher affinity relative to its antagonist CGRP(8-37) [45]. It exhibits strong selectivity, not binding to the other receptor family members such as the calcitonin, amylin or adrenomedullin receptors [45]. The relatively high molecular weight (Mw = 870) and the low oral bioavailability (%F < 1) of olcegepant meant that only its intravenous application was feasible [34,45]. In a single-center, double-blind, placebo-controlled, randomized trial, intravenously administered single rising doses (0.1 to 10 mg) of olcegepant showed its favorable safety profile, and no serious adverse events were detected in healthy volunteers (55 males and females). Pharmacokinetically the mean maximum concentration (C_{max}) was dose proportional (C_{max} = 0.87 mg/ml), resulting in a terminal $T_{1/2}$ of ~ 2.5 h, and the mean renal clearance was ~ 2 L/h [47,48]. A multicenter, double-blind, randomized (126 patients with migraine), clinical proof-of-concept study revealed the effectiveness of olcegepant for the treatment of acute migraine attacks [49]. In a small, double-blind, cross-over study where chemically (glyceryl trinitrate) induced attacks of migraine without aura were treated with olcegepant, no efficacy was observed [50]. Despite the favorable effects of olcegepant in spontaneous migraine attacks and the low rate of its side-effects, its intravenously administration limited its wide clinical use (**Table 1**).

In order to achieve oral administration, a new CGRP-RA, **telcagepant** (MK-0974: N-[(3R,6S)-6-(2,3-difluorophenyl)hexahydro-2-oxo-1-(2,2,2-trifluoroethyl)-1H-azepin-3-yl]-4-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxamide), was developed [51,52]. The bioavailability

Table 1. CGRP receptor antagonists for treatment of migraine.

	Potency K_i (nM)	Route of administration	Study
BIBN4096BS (Olcegepant)	0.010	Intravenous	Phase III
MK-0974 (Telcagepant)	0.770	Oral	Phase III
MK-3207	0.021	Oral	Phase II
MK-1602	0.013	Oral	Phase II
BMS-694153	0.013	Oral	Phase II
BMS-927711	0.027	Oral	Phase II
BI 44370 TA	Not available	Oral	Phase II

CGRP: Calcitonin gene-related peptide.

of telcagepant in dogs was 35%, and the renal clearance was 17 ml/min/kg [37,52], while in rats the bioavailability was 20% and the renal clearance was 9.4 L/min/kg [37,52]. In humans, telcagepant displayed strong oral bioavailability (%F = 45) and its renal clearance was 27 ml/min/kg [48]. *In vitro* experiments revealed that telcagepant is a strong antagonist of the human CGRP-Rs (K_i = 0.77 nM) [53]. It exhibited high species selectivity: ~ 1500-fold higher affinity for human as compared with rat and dog CGRP-Rs [53]. Its tritiated analog displayed reversible and saturable binding properties on human neuroblastoma (SK-N-MC) membranes [54], and behaved in a monophasic concentration-dependent manner in competition binding experiments, with fast association and dissociation kinetics [54]. Telcagepant did not induce the contraction or relaxation of human isolated coronary arteries, a finding suggestive of its cardiovascular safety profile [55]. Similarly, it did not exert any contractile or relaxant effects on human-isolated cerebral and middle meningeal arteries [56]. Human pharmacokinetic clinical studies indicated that telcagepant is rapidly absorbed with a T_{max} of 1.5 h, a terminal $T_{1/2}$ of ~ 6 h and a C_{max} of 0.55 mg/ml [48,57]. In one randomized clinical trial, telcagepant monotherapy did not elevate the mean arterial pressure in migraine patients during the headache-free period [58]. As concerns migraine attack therapy, an early Phase II proof-of-concept study showed that telcagepant doses of 300 – 600 mg were more effective than placebo, and was well tolerated [59]. In a randomized (1380 migraine patients), parallel-treatment, placebo-controlled, double-blind trial, telcagepant (300 mg) exhibited the same effectiveness as that of zolmitriptan (5 mg), as concerns the pain relief and pain freedom end points, and toward the migraine accompanying symptoms such as photophobia, phonophobia or nausea, but with fewer side effects for acute migraine treatment [60]. Telcagepant at a dose of 150 mg proved better than placebo [60-62]. Another randomized (1263 migraineurs) controlled trial led to the conclusion that oral telcagepant (140 or 280 mg) was consistently effective for the treatment of up to four migraine attacks [63].

A very recent systematic review on the use of CGRP-RAs (telcagepant, olcegepant and MK-3207) in the treatment of migraine with aura concluded that there were no treatment effects on either aura frequency or migraine headache after aura [64].

Another investigated CGRP-RA was **MK-3207**, with a more (40 – 65-fold) potent binding affinity (K_i = 0.021 nM) than that of telcagepant, and with fast absorption (median T_{max} ~ 1 – 2 h) [65]. A randomized clinical dose-finding trial was conducted for the acute treatment of migraine, but its asymptomatic liver toxicity let to further clinical development being abandoned [66].

A large Phase II dose-finding study was recently performed with **MK-1602** for the treatment of acute migraine attacks, but the final conclusion has not yet been reported [67].

Another human CGRP-RA, **BMS-694153**, has high affinity (K_i = 0.013 nM) and significant CYP3A4 inhibition [68].

BMS-927711 is a newly synthesized, highly potent (K_i = 0.027 nM), selective and competitive CGRP-RA [69]. A randomized double-blind, multicenter, placebo-controlled, dose-ranging study to identify its optimum dose for the acute treatment of migraine demonstrated its efficacy versus placebo at several different doses (75, 150 and 300 mg) [70].

In a proof-of-concept and dose-finding Phase II trial to assess the efficacy and tolerability of three doses (50, 200 and 400 mg) of **BI 44370 TA** in acute migraine attacks, it was concluded that the compound acted in a dose-dependent manner [71].

A preclinical study on the CGRP-RA **MK-8825** in nitroglycerin-induced hyperalgesia in animal models of pain demonstrated analgesic activity [72]. In another nitroglycerin-induced animal headache model, MK-8825 did not increase the activity of the second-order neurons in the trigeminal nucleus caudalis in the early phase of chemical stimulation [73].

BMS-742413, a new synthetic CGRP-RA, demonstrated outstanding aqueous solubility, and good bioavailability when administered intranasally in the rabbit [74].

Thiazolidinones (Mw = 693 and 707) have good oral bioavailability and potency (K_i = 0.030 nM, IC_{50} = 1 nM), with good physicochemical properties and potent CNS penetration [48]. In another preclinical study, the synthesis and synthetic aperture radar of novel CGRP-RAs derived from heterocyclic **tyrosine surrogates** led to the possibility of the intranasal route of administration. One of them, Compound 3, exhibited good intranasal bioavailability (%F = 42) and potency (K_i = 0.0073 nM) [75]. A potent and selective **PEGylated peptide** antagonist to the CGRP-R with improved pharmacokinetic profile and plasma stability was recently synthesized [9].

The CGRP-R positron emission tomography (PET) tracer [^{11}C]MK-4232 [76] has been developed for use in clinical PET studies [77]. Human PET studies revealed that telcagepant (in the low dose of 140 mg orally) achieved low CGRP-R occupancy in the brain, while a high dose (1120 mg) resulted in moderate CGRP-R occupancy. These data may suggest that the CGRP-R antagonism does not occur purely centrally [77].

In clinical trials for acute migraine therapy, the CGRP-RAs displayed favorable effects, but their frequent administration was associated with liver toxicity (the elevation of liver transaminases), which limited their clinical use. The results of the latest preclinical studies are promising for development for the treatment of migraine.

5. Anti-CGRP mAbs

The recombinant DNA technique opened up the possibility for the development of humanized antibodies (5 – 10% murine sequence, 90 – 95% human). mAbs have been approved as drugs for different indications for > 20 years. For therapeutic administration, at least 25 mAbs are currently used [78]. The main pharmacological features of mAbs are: i) a large molecular size; ii) a prolonged $T_{1/2}$ value (around 45 days); iii) slow distribution and target specificity; iv) inability to cross the blood–brain barrier; v) regarding to not related to cytochrome P450 isoenzymes resulted a decreased potential for drug–drug interactions; and vi) liver toxicity via binding to specific oligosaccharides [9]. The large size and the relatively poor membrane permeability of the mAbs mean that they can be administered only parenterally [4,78-80].

Recent pharmacological research led to a novel target for the treatment of migraine headache with humanized mAbs against CGRP [3,4]. Whereas the small-molecule CGRP-RAs were developed only for the acute treatment of episodic migraine, the anti-CGRP mAbs were designed for the prophylaxis of frequent episodic and chronic migraine in severe cases [3]. In view of the large size of the mAbs, they cannot be administered orally, but only parenterally (subcutaneously or intravenously) [4]. The dosage varies as a function of the interval between the administration of the mAbs [4]. Poor compliance may be one of the determining factors behind failed migraine prophylaxis [81]. The possibility of rare dosing as an advantageous feature of the mAbs could improve the compliance of the patients in the prophylaxis of migraine.

The latest International Headache Society classification-3 β version describes chronic migraine as headache on 15 or more days per month for > 3 months, with the features of migraine headache on at least 8 days per month [82].

The humanized mAbs **LY2951742** (developed by Arteus Therapeutics) and **ALD403** (developed by Alder Biopharmaceuticals) have been investigated against episodic migraine.

In a Phase I, first-in-human clinical trial, the safety and tolerability profile of **LY2951742** (single or multiple subcutaneous injection) were evaluated in healthy male subjects. The compound proved to be well tolerated with linear pharmacokinetics, and T_{max} was 7 – 14 days [4,67,83-85]. In one randomized, placebo-controlled, double-blind, Phase II trial, LY2951742 (150 mg of dose; subcutaneously once every other week for 12 weeks) was assessed for efficacy and safety in the prevention of episodic migraine headache with or without aura. The final results have not yet been published [4,67,83,86].

ALD403 has been investigated in a randomized, double-blind, single-dose, ascending-dose, clinical Phase I trial to determine the safety, tolerability and pharmacokinetics of this anti-CGRP mAb, administered by intravenous infusion and subcutaneous injection. In the first part of this study healthy volunteers were tested, and in the second part ALD403 was compared with placebo or sumatriptan. The final findings have not yet been revealed [4,67,83,87].

In another double-blind, randomized, placebo-controlled, proof-of-concept Phase Ib study, ALD403 was tested to evaluate the safety, pharmacokinetics and efficacy of a single dose of the compound administered intravenously in patients with frequent episodic migraines [4,67,83,88].

LBR-101 (developed by Labrys Biologics – TEVA), a fully humanized potent, selective and specific anti-α- and β-CGRP mAb, was investigated in Phase I trials in frequent episodic and chronic migraine [4,9,67,83]. One of these early trials related to the safety and tolerability of the compound as compared with placebo administered intravenously in single and multiple doses to healthy volunteers; it proved to be well tolerated [9]. Further studies dealt with the safety and bioavailability of intravenous and subcutaneous LBR-101 in healthy volunteers [83,89]. In a Phase IIb placebo-controlled trial, subcutaneously administered low and high doses of the compound were examined in chronic migraine [83,90]. Another Phase IIb randomized study analyzed the efficacy of LBR-101 in high-frequency episodic migraine patients [83,91]. The cardiovascular and hemodynamic parameters (blood pressure, heart rate and electrocardiographic findings) of healthy, > 40-year-old women remained in the normal ranges following the administration of LBR-101 [92]. This was also discussed at the Annual Meeting of the American Academy of Neurology 2014. New data have emerged from preclinical studies concerning the long-term inhibition of CGRP. Chronic intravenous administration of LBR-101 did not affect the cardiovascular and hemodynamic parameters in cynomolgus monkeys (**Table 2**) [93,94].

6. Anti-CGRP-R mAbs

Currently, the only anti-CGRP-R mAb is **AMG 334** (a compound developed by Amgen), which has undergone Phase I and Phase II studies of episodic and chronic migraine. An ascending single-dose, randomized, double-blind, placebo-controlled Phase Ib trial was performed on healthy volunteers and migraine patients. The compound was administered intravenously or subcutaneously. The detailed data are not yet available [4,83,95]. Another Phase I ascending, multiple-dose study evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of the compound administered subcutaneously to healthy subjects and migraineurs [4,83,96]. In a Phase IIb randomized, double-blind, placebo-controlled trial, the efficacy and safety of three subcutaneous doses of AMG 334 were evaluated from the aspect of the prevention of episodic migraine [4,67,83,97]. The effects of AMG 334 in two subcutaneous doses were investigated on chronic migraine in

Table 2. mAbs targeting the CGRP for treatment of migraine.

	Migraine state	Route of administration	Dosing	Study
LY2951742	Episodic	Subcutaneous	Twice per month	Phase IIa
ALD403	Episodic	Intravenous	Only once	Phase Ib/IIa
LBR-101	Episodic and chronic	Subcutaneous	Once per month	Phase IIb

CGRP: Calcitonin gene-related peptide; mAbs: Monoclonal antibodies.

Table 3. mAb targeting the CGRP receptor for treatment of migraine.

	Migraine state	Route of administration	Dosing	Study
AMG 334	Episodic and chronic	Subcutaneous	Once per month	Phase IIb

CGRP: Calcitonin gene-related peptide; mAb: Monoclonal antibody.

another Phase IIb study [4,83,98]. The available data from the Amgen clinical trials indicate that new results are expected in the near future (**Table 3**).

7. Conclusion

The acute and prophylactic treatment of migraine is still not fully solved. The current standard of care for migraine is not entirely effective for all migraine sufferers. Moreover, poor tolerability and unfavorable side effects impede the widespread use of a number of compounds developed for treatment. Both nonspecific and specific drugs are used for the acute treatment of migraine headache, among them are non-steroidal anti-inflammatory drugs (NSAIDs), ergotamine and its derivatives and triptans. The well-known disadvantageous features of NSAIDs are their gastrointestinal and renal disturbances. Ergotamine can cause systemic vasoconstriction, and the triptans coronary vasospasm. Specific prophylactic drugs for migraine headache are not yet available. The drugs used for this purpose are anti-epileptics, antidepressants, β-adrenergic receptor blockers or calcium ion channel antagonists.

In consequence of the leading hypothesis of migraine, CGRP became one of the candidate molecules that may play a crucial role in the pathomechanism of migraine. CGRP has functions of peripheral and central sensitization, pain transmission and vasomotor activation. It also acts on its functional receptor complex. Preclinical and clinical investigations have proceeded in two directions: the GGRP-RAs have been tested for the acute and CGRP-targeted mAbs for the preventive treatment of migraine headache. The CGRP-

RAs demonstrate high efficacy against migraine attacks, but the liver toxicity observed following their frequent use could limit their clinical spread.

Further pharmacological development is needed to overcome this unfavorable side effect of the CGRP-RAs. Fully humanized mAbs targeting CGRP or its receptor directly appear more promising for the prophylactic treatment of frequent episodic and chronic migraine.

The future tasks include the discovery of the exact mechanism of migraine headache and the development of personalized medicinal products.

8. Expert opinion

Migraine is one of the most disabling primary headache disorders, afflicting 16% of the population worldwide, with a female:male ratio in adults of 3:1. The precise pathomechanism of migraine has not yet been elucidated. Controversies persist concerning the origin of migraine headache. The attacks could arise either in the cortical structures of the brain or in distinct brainstem nuclei. The phenomenon of cortical spreading depression observed in the aura phase of migraine may support the cortical theory, while the activation of distinct brainstem nuclei, called 'migraine generators,' for example, the periaqueductal gray matter, the locus coeruleus and the raphe nuclei, is in the background of the brainstem hypothesis of migraine. Another aspect of controversy is that of vascular versus neuronal routes. The vasodilatation in intracranial or extracranial blood vessels could play a role in migraine pain. Activation of the TS may be crucial in its pathogenesis. Migraine can be explained as an altered function of the neuronal elements of the TS. Appropriate animal migraine models do not exist. The present animal models allow only partial testing of the current leading working hypotheses, for example, electrical stimulation of the cranial ganglia and superior sagittal sinus (neurogenic inflammation and expression of the immediate early proto-oncogenes), chemical stimulation through the systemic administration of glyceryl trinitrate (vascular alterations and expression of the immediate early proto-oncogenes) and the closed cranial window model (vascular alterations). In the coming years, development of an experimentally useful migraine model that will shed light on the complex pathomechanism of migraine and will serve innovative pharmaceutical research will be a great challenge. We consider that future scientific research should deal with both the cortical and brainstem and the vascular and neuronal theories.

As a key factor, CGRP may unify these different aspects of the hypotheses of the pathomechanism of migraine. CGRP is a neuropeptide with various neurobiological effects, including vasodilation and the capability of neuronal sensitization. Its chemical structure is well-defined and its functional receptor is also well-established. In view of its strong role in TS activation, scientific efforts are currently being made to target CGRP itself and its receptors. However, the weakness of the

CGRP theory in migraine is that, besides CGRP, several other factors, such as 5-HT, PACAP, SP, neuropeptide Y, vasoactive intestinal peptide, nitric oxide, glutamate, gamma-amino-butyric acid (GABA), orexin, neurokinin-A, endothelins, dopamine, adipokines, leptin, endocannabinoids and neuro-trophins, could all play a role in the pathomechanism of migraine. One question that arises is whether the alterations (increases or decreases) detected in the above-listed substances in migraineurs are causal or observational findings. One major goal could be to find a specific and stable biomarker for the diagnosis and prognosis of migraine.

In recent decades, the triptans have become the gold standard for the acute treatment of migraine. However, numerous patients do not respond well to the triptans, which are selective 5-HT 1B/1D agonists. One of the possible explanations could be that migraine is not related only to the serotonergic system, but is a multifactorial neurological disorder, which involves ion-channel disturbances, an imbalance of the excitatory and inhibitory neurotransmission, neurodegenerative processes and the genetic background. Future drug development should involve a multi-targeted drug approach or network pharmacology. As concerns the vasoconstrictor effects of the triptans, it should be emphasized that their cardiovascular safety profile favors their use in the absence of contraindications. In an attempt to bypass the vasoconstrictor activity of triptans, the CGRP-RAs have been developed, among them the gepants. In view of the high efficacy of gepants, their appropriate dosing should become a feature of the clinical practice of acute migraine treatment in the near future. The goals of the development of novel types of CGRP-RAs are to improve their pharmacokinetic and pharmacodynamic profiles, and to establish a simple mode of their administration that is acceptable for the patients.

From the aspect of the prophylaxis of severe migraine, a new possibility to reach the CGRP itself or the CGRP-R is the use of fully humanized mAbs. Thanks to the long half-lives of mAbs, infrequent dosing is a possibility. As compared with the current everyday pill-taking, this would be favorable from the aspect of the compliance and the quality of life of the patients. The CGRP-directed mAbs do not cross the blood–brain barrier, which can be both an advantage and a disadvantage. Their blood–brain barrier penetration promotes the avoidance of the common CNS side effects such as dizziness, nausea, vomiting, vertigo, visual disturbances and somnolence. The disadvantage is the fact that the mAbs cannot reach the neuronal elements of the brain, for example, the 'migraine generators,' thalamus and cortical structures. In consequence of the wide distribution of CGRP and its receptors throughout the body, questions emerge concerning the selectivity of mAbs. One pitfall in the treatment of chronic migraine is the development of medication overuse headache, a condition that is highly difficult to manage. The CGRP-targeted mAbs could provide a possibility for successful therapy in this field. If the mAbs display high efficacy in Phase III and IV clinical trials, the background of the initiation of migraine headache, should be completely reconsidered, attention being paid to the peripheral part of the TS. Further, it would suggest the development and screening of new potentially effective pharmacons.

The ultimate goal of the development of novel acute and prophylactic anti-migraine drugs is to attain effective, well-tolerated, easily-administered, economic medication with a low side-effect profile.

Declaration of interest

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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