CGRP antagonists for the treatment of migraine: rationale and clinical data

CGRP is localized in primary spinal afferent C and Aδ fibers of the sensory ganglia and in the CNS, for example, in the colliculi and cerebellum. Trigeminal nerve activation results in antidromic release of CGRP that leads to vasodilatation via a CGRP-receptor complex (calcitonin-like receptor and RAMP1). At central synapses in the trigeminal nucleus caudalis, CGRP on second-order neurons transmits pain signals centrally. Calcitonin-like receptor and RAMP1 are widely expressed throughout the brain and in intracranial arteries and the trigeminal system. CGRP does not induce neurogenic inflammation or sensitization at peripheral meningeal sites, but relays nociceptive information to the second-order neurons in the brainstem. Recently developed CGRP-receptor antagonists have excellent antimigraine effects and a low side-effect profile. The CGRP-receptor antagonists reduce signaling in the trigeminovascular pathway at multiple sites and at central sites, however, the exact site of antimigraine effect is still under debate.

Keywords: CGRP • CGRP receptor antagonists • migraine • telcagepant • trigeminovascular reflex

Primary head-pain syndromes such as migraine and cluster headache are common types of chronic recurring head pain that are clinically well defined. The vaso-motor response of the sensory nerves in the peripheral circulation has a counterpart in the cerebral circulation with the trigeminal system. The pain-sensitive supratentorial structures are innervated by sensory nerve fibers arising from pseudounipolar neurons with their cell bodies in the first division (ophthalmic branch) of the trigeminal ganglion (TG), which connect to the CNS at second-order sensory neurons within the brain stem trigeminal nucleus caudalis (TNC) and at C1-3 [1]. Antidromic or local mechanical stimulation of sensory nerve endings causes dilatation of intracranial vessels via the release of CGRP from the trigeminovascular system in humans [2,3]. Moreover, release of CGRP from perivascular nerves in the meninges (dura mater) and in the cerebral circulation [2,4-6] is associated with migraine pain. Recent advances in our understanding of CGRP mechanisms, central pain processing and biology suggest that the pathophysiology of migraine is far more complex and that vascular activation may be just one of many factors involved in the migraine pathogenesis.

Basic facts on CGRP

Expression of CGRP

CGRP is a 37 amino acid neuropeptide, identified three decades ago [7]. The calcitonin gene was unexpectedly found to encode two different mRNAs and either calcitonin or αCGRP mRNA is expressed, depending on anatomical localization. αCGRP is the predominant expression product in the nervous system. A second CGRP gene has been discovered that forms βCGRP, and it is primarily
expressed in the enteric sensory system in the gut and inner organs [4]. Recent studies have shown that CGRP and its receptors are expressed in both the central and peripheral nervous systems. In the CNS, CGRP-containing cells have been found in a number of areas associated with migraine pathophysiology such as hypothalamus (trigger), superior colliculi (visual symptoms), inferior colliculi (phonophobia), brainstem and trigeminal complex (head pain, nausea) and cerebellum [5]. Specifically, these areas include the midbrain, the hypothalamus, the periventricular area, the anterior medullary velum, the dura mater, the hypothalamic nucleus, the periventricular gray, the area around the fasicculus retroflexus (parasagittal area), extending laterally over the lennus medialis [6,7]. In the mesencephalon, CGRP-positive cells are found in the periaqueductal area ventral to the medial geniculate body, extending dorsally along its major sensory afferents. CGRP-containing cell bodies are also seen in the paratrigeminal nucleus as well as in the superior colliculus. Peptidergic fibers containing CGRP have been found to innervate the anterior medullary velum as well [8]. The distribution of CGRP-containing fibers in the CNS in extensive receptor binding studies have shown large discrepancies and mismatches [9]. These anatomical studies suggested roles of CGRP in synaptic and metabolic regulation and as part of components in the central nociceptive system. In the hippocampus it may serve a role as a modulator of CNS injury/immune response [10]. Changes in CGRP binding may be altered in stress-related situations [11]. Interestingly, there is high expression of CGRP in the cerebellum and inferior olivary complex suggesting that it may play an important modulatory role in modulating pain transmission in the brainstem [12].

**General functions of CGRP**

Centrally, evidence is emerging that CGRP may play an important autocrine and paracrine function in many areas. Activation of CGRP receptors on cultured TG neurons increased endogenous CGRP mRNA levels and promoter activity [12]. CGRP has also been shown to differentially regulate cytokine secretion from cultured TG glia [13]. Although CGRP has a number of effects, its most pronounced action is that of intracranial vasodilatation and in transmission of nociception [14]. The mechanism of function of CGRP is its effect on peripheral vasculature. It acts on smooth muscle cells and causes vasodilation via a nonendothelial mechanism through activation of adenylyl cyclase [15]. The release of perivascular peptides relax cerebrovascular smooth muscle due to their vasodilator properties and CGRP nerve fibers mediate dilatation of cerebral arteries. CGRP is also expressed in the heart, gastrointestinal tract and the peripheral nervous system [16]. While some studies have suggested that the CGRP receptors are situated presynaptically on primary afferent endings to regulate nociceptive transmission and thereby modify signals to the CNS [17], other studies have suggested that a set of novel developed antibodies towards calcitonin-gene related peptide (CLR) and RAMPI suggest that CGRP plays an important role in the trigeminovascular reflex [14,16].

There is a dense supply of thin CGRP-containing nerve fibers in lamina I/II of the trigeminal complex suggesting that it may play an important role in the trigeminovascular reflex [14,16]. The CGRP-positive perivascular nerve fibers in intracranial vessels (dural as well as cerebral) originate in the first division of the TG while the other branches of the fifth cranial nerve supply other parts of the head with sensory innervation. There is significantly more CGRP immunoreactivity than that of substance P; however, these peptides colocalize in the perivascular nerves. Electrical field stimulation or capsicain treatment [14,15] causes local vasodilation and release of CGRP from the perivascular nerve fiber endings. These effects are attenuated by administration of a CGRP receptor blocker acting postsynaptically or a triptan acting at presynaptic sites to suppress release [14,15] and as a vasoconstrictor of human intracranial arteries [32].

The CGRP-containing nerve cell bodies constitute more than 40% of the neurons in the TG; they have functional connections with neurons in the TNC and in related extensions down to the C1–2 level on the other side. Early horseradish peroxidase tracing studies showed a dense network of connections between the TG neurons and the TNC. These studies strongly suggest that there is release of CGRP from the trigeminovascular system during activation of the TG [15].

**Role of CGRP in migraine pathophysiology**

The potential role of CGRP in migraine pathophysiology was first suggested in 1984 [17] and a growing body of evidence suggests a pivotal role for CGRP in the pathogenesis of primary headaches [18,19]. In spontaneous migraine attacks there is significant release of CGRP but not of any other neuropeptides [20–22]. The role of the sensory nerves located around the intracranial vessels has been analyzed in humans in conjunction with stimulation of the TG; this resulted in unilateral blood flow increases, release of CGRP and a set of novel developed antibodies towards calcitonin-gene related peptide (CLR) and RAMPI suggest that CGRP plays an important role in the trigeminovascular reflex [14,16]. The trigeminal nerve fibers mediate dilatation of cranial arteries [32] and have an important role in the trigeminovascular system during activation of the TG [14,16].

Current theory proposes that migraine is a disease with a genetic predisposition. Anttila et al. [17] reported an association in a genome-wide association study of migraine, which suggests a site that regulates the expression of the primary glutamate transporter in the brain, EAAT2/Glut-1. For hemiplegic migraine there are data to suggest that alterations in ion channel genes render CNS neurons unstable and capable of initiating a migraine attack [43,46]. The current view of migraine pathophysiology further suggests that the trigeminal system is an essential part of the disease expression. Hypothetically, the mechanisms involve activation of the trigeminovascular reflex as a defense mechanism towards cerebrovascular constriction elicited either due to spreading depression [44–46] or other localized cerebrovascular vasospasm [47]. The cerebral circulation requires high and constant flow and metabolism. Hypothetically, cerebral vascular constriction is sensed by the trigeminal sensory nerve fibers with a subsequent antidromic release of CGRP to maintain local brain blood flow within normal limits. This view is supported by studies of patients who have suffered with subarachnoid hemorrhage. The cerebral levels of CGRP were depleted and the administration of CGRP could reverse the vasospasm [48–50]. The trigeminal activation results in orthodromic activation of neurons in the trigeminal nerve, activating second-order neuron involvement and mediation of the central aspects of pain within the two regions of termination; sensory C-fibers in lamina I/II and Aδ-fibers in lamina V/VI. This is supported by the fact that patients who have suffered a subarachnoid hemorrhage have a higher rate of developing migraines [51,52].

The results from TG stimulation in trigeminal neuralgia patients led us to investigate neuropeptides associated with the autonomic and sensory nervous system in patients with migraine attacks [53]. The concentrations of neuropeptide Y (NPY; marker for sympathetic nerves), vasoactive intestinal peptide (VIP, parasympathetic activity), and CGRP and substance P (markers for sensory nerves) were analyzed in the cranial venous outflow. There were no changes in the levels of NPY, VIP or substance P during migraine attacks. However, a marked increase in CGRP levels were observed in patients during attacks of migraine with aura or without aura [26]. The release of CGRP rather than substance P is possibly due to the fact that the intracranial circulation is preferentially innervated by CGRP-containing neurons [21]. In addition, glycerol injection into the TG induced a slight increase in human cerebral blood flow (CBF) [54]. While cutaneous stimulation in trigeminal neuralgia resulted in facial flushing and associated CGRP release [44]. These studies strongly suggest that there is a set of novel developed antibodies towards calcitonin-gene related peptide (CLR) and RAMPI suggest that CGRP plays an important role in the trigeminovascular system during activation of the TG [14].

In the setting of nitroglycerin is used to elicit migraine-like attacks [55]. Further experiments using this model have provided supportive data demonstrating a linear correlation between the increased levels of CGRP and the intensity of the headache [56]. It is worth noting that low pain results in no significant increase in venous CGRP, an observation supported by Juhasz et al. [57] and Kruse et al. [58]. In addition, Fanciullacci et al. [59] observed that nitroglycerin did not elicit cluster headache attacks if the patient was not in a ‘prone status’. Hence the disease was active and a small stimulation could then elicit the full cluster headache attack. Studies of the perfused middle cerebral artery (MCA) [58,60] showed that CGRP does not readily pass the blood–brain barrier (BBB), which agrees well with this supposition. The nerve fibers are situated in the adventitia and act on the receptors located in the smooth muscle cells. Thus, a low concentration of CGRP would likely occur in mid-moderate attacks but it is necessary to have a large release to measure the peptide in the cranial venous effluent. Any negative data would fall into this category [58]. We have discussed a number of data. Our view is that it is due to a methodological error that the Copenhagen group could not confirm what other
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CGRP antagonists for the treatment of migraine

Clinical studies on CGRP receptor antagonists for migraine

Olcegepant

The ability of CGRP receptor antagonists to treat acute migraine attacks was initially established with olcegepant (BIBN 4096 BS). In a proof-of-concept study, intravenously administered olcegepant was effective in relieving acute migraine pain and associated symptoms and was well tolerated with no cardiovascular

The most potent of these, olcegepant demonstrates extremely high affinity for the human CGRP receptors with an IC₅₀ of 1.6 nM [73,84]. Interestingly, the antagonist is three log units more potent in human tissues as compared with that seen in experimental animals. The reason for this was revealed by Malle et al. [84], who showed that olcegepant was dictated strictly by hRAMP1. The region between amino acids 66–112 is critical for determining the pharmacology of these small molecule antagonists. The exact molecular mechanism by which RAMP1 modulates antagonist binding sites resides in an exchange of one nucleotide in RAMP1 [84].

A major advantage of a CGRP receptor blocker is the lack of oral bioavailability. The blocker of the receptor is a second vasodilator involves the involvement of the CGRP receptor component. The direct action of the antagonist is still not clear. With a closed cranial window model [72] olcegepant was found to inhibit dilation of dural (meningeal) arteries after systemic CGRP (intravenously) and neuronal CGRP from perivascular nerves following transcranial electrical stimulation. These findings are in accordance with previous studies, since olcegepant inhibits Ca²⁺- and RCP stimulation increase in facial blood flow in experimental studies [72]. By contrast, the antagonist did not significantly inhibit changes in the tone of cerebral arteries or of local cortical cerebral blood flow [73]. This indicates that the effect of the compound is mainly extracerebral and that the antagonist does not readily pass the BBB, which correlates with the results from a clinical study [84].

Perfusion of the isolated MCA showed that neither CGRP nor olcegepant passed the BBB to a major degree [72]. In healthy volunteers the CGRP antagonist prevented CGRP-induced headache and associated CGRP symptoms (flushing and sensation of heat). The increase in MCA diameter was small and not blocked by olcegepant; it is suggested that this is probably due to the reduction in blood pressure with a compensatory compensatory vasomotor dilation of the MCA. By contrast, the CGRP-induced effect was more pronounced in the superficial temporal and radial arteries and blocked by the CGRP antagonist [73].

CGRP antagonists are also capable of blocking CGRP-induced vasodilatation in the human cranial vessels [73]. This effect was demonstrated both in vitro and in vivo, suggesting that the antagonist has a short half-life and cannot be absorbed orally. A breakthrough in the CGRP field came with the development of a monoclonal antibody, potent CGRP receptor antagonists [72] and some molecular modifications of this compound [72].
Telcagepant 300 to 600 mg were shown to be effective in treating both acute migraine pain and migraine associated symptoms (Table 3). The efficacy and safety profiles of telcagepant were confirmed subsequently in three additional large pivotal Phase III acute efficacy migraine trials involving a total of 3293 telcagepant-treated patients (n = 2015). All three trials demonstrated that both telcagepant 300-mg capsule/280-mg tablet and 150-mg capsule/140-mg tablet (300- and 150-mg capsules are bioequivalent to 280- and 140-mg tablets, respectively) are effective in treating migraine head- ache (2 h headache relief, 2 h headache freedom and 2–24 h sustained pain freedom; Table 2) and migraine associated symptoms (photophobia, phonophobia and nausea; Table 2). The multiple attack study showed that telcagepant 140 and 280 mg have consistent responses (Table 3). One-year data were presented for telcagepant 150 mg (280- and 140-mg tablets), showing that these patients experienced headache frequencies similar to those of the placebo group. These data support the hypothesis that the efficacy of telcagepant given at a fixed dose in combination with sumatriptan is equivalent to the same dose of sumatriptan alone. A multiple attack study showed that telcagepant 140 and 280 mg have consistent responses (Table 3).

### Tolerability of telcagepant
Telcagepant was well tolerated with an adverse event (AE) rate similar to that of placebo (Table 3). In a long-term safety study, telcagepant was used by 641 patients for acute migraine attacks for up to 18 months and was generally well tolerated in long-term intermittent treatment [53]. The most worrying part of the CGRP receptor antagonist projection has been the increase in transaminiases. This was not a problem when administrating telcagepant intermittently for single acute attacks of migraine, however, moving into prophylaxis showed a slightly disturbing picture. According to the NIH clinical trials registry, a Phase IIa randomized, double-blind, placebo-controlled, parallel assignment clinical trial (NCT0797667, MK0974–049) assessing telcagepant (140 and 280 mg oral, twice-daily for 12 weeks) for the prevention of migraine in otherwise healthy migraineurs was initiated (n = 600 planned). This trial was terminated in April 2009 because some subjects experienced elevated liver enzymes during the last part of the trial. None of these patients fulfilled the criteria of Hey’s law (a prognostic indicator that a pure drug induced liver injury leading to jaundice, with no hepatic transplant, has a case fatality rate of 10–50% [55]). The exposure achieved in this study was much higher than the acute migraine dose due to an accumulation of drug with daily treatment. Similar hepatic signal were not seen with acute intermittent therapy suggesting that the potential for hepatic toxicity may be time and dose dependent.

#### Comparison of telcagepant with triptans
In one randomized clinical trial, telcagepant 300-mg capsules were compared to placebo and zolmitriptan (5 mg oral) in a trial involving 738 patients (Table 2). Telcagepant was associated with greater headache relief and a smaller number of patients that were headache free at 2 h as compared to placebo and zolmitriptan [56]. Telcagepant tablets are bioequivalent to 280- and 140-mg tablets, respectively. *Number of treated patients.

††Number of patients in the end point full analysis-set.

§Number of patients in the end point full analysis-set.

¶p < 0.0001 for the telcagepant 150 mg versus zolmitriptan 5 mg pairwise comparison.

**Number of treated patients.
was equivalent to zolmitriptan 5 mg (Table 2). Based on results from a meta-analysis, rizatriptan 10 mg (41%) and almotriptan (33%) seem superior to telcagepant (26%) for pain freedom at 2 h, whereas rizatriptan 10 mg (25%) showed no difference from telcagepant 300 mg (19%) for sustained pain freedom (2–24 h) (Table 4).

In a post hoc analysis, data from the randomized, controlled trial of telcagepant (150, 300 mg) zolmitriptan 5 mg, or placebo for a moderate/severe migraine, responder rates were analyzed according to patients’ self-reported history of triptan response (Table 3). This suggests that different patients may respond to triptans or telcagepant 300 mg.

Compared to triptans, telcagepant appears to have less of the AEs that are commonly associated with triptans (Table 3). In a long-term tolerability study, fewer triptan-related AEs, such as asthenia, chest discomfort, fatigue, myalgia, dizziness, paresthesia and throat tightness, were reported by 10.4% within 48 h of patients treated with zolmitriptan 5 mg (n = 345).† Data are proportion (%) of patients with number of patients with the AE (n) within parenthesis.

MSD on 29 July 2011, the telcagepant program was, however, discontinued.

Other CGRP receptor antagonists investigated in clinical trials

Merck also advanced a second oral CGRP receptor antagonist, MK-3207, to clinical trials because it showed a better oral bioavailability and was a more potent drug (Table 4). However, in clinical testing it was found to induce liver enzyme elevations after a 4-week dose-finding development of MK-3207 was, therefore, discontinued. It is believed by some researchers that hepatotoxicity may be a class effect demonstrated by the discontinuation of development of both MK-3207 and telcagepant. Future developments on CGRP receptor antagonists will prove this right or wrong.

The initial absorption of BI 44370 TA, another oral CGRP receptor antagonist, is delayed and reduced during migraine attacks, but overall absorption is not meaningfully affected (Table 5). In a recently published Phase II trial, efficacy of the drug in acute migraine attacks was shown in a dose-dependent manner (Table 5). The primary end point, pain-free after 2 h, was reached by significantly more subjects in the BI 44370 TA 400 mg (207/3 = 27.4%) and eletriptan 40 mg (24/69 = 34.8%) groups compared with placebo (67/70 = 9.6%, p = 0.016), but not by subjects in the BI 44370 TA 200-mg group (14/65 = 21.5%; Table 5). The effect of BI 44370 TA 50 mg (5/64 = 7.8%) was similar to that of placebo. Analysis of secondary end points supported the conclusion from the primary analysis. The frequency of AEs was low in all groups. Increased liver function tests were found in one subject. Detailed review of the subject’s medical status showed concomitant drugs and diseases as well as alcohol consumption. It is, therefore, difficult to draw a conclusion. The beneficial effect of BI 44370 TA has to be replicated in a large Phase III trial.

Where do the gepants act in migraine?

Although it has been demonstrated that CGRP receptor antagonism is an effective way to abort acute migraine attacks and treat migraine-associated symptoms, questions remain as to how CGRP receptor antagonists work. Provided the gepants have access to the receptor sites in the CNS or in the periphery, including vasculature, they are potent and selective inhibitors of CGRP receptors in man.

Another argument is the apparently very high dose of CGRP antagonists and triptans needed to treat a migraine attack. The limited passage over the BBB of not only triptans, but also CGRP antagonists may be due to high protein binding, low inherent passage through the BBB and being substrate for the efflux pump of P-glycoprotein. The CGRP antagonists, olcegepant and telcagepant, are very potent drugs (74) with an IC50 of 0.1 and 10 nM, respectively.

### Table 3. Adverse events of telcagepant within 48 h after intake in the studies MK-0974-011 and MK-0974-016.

<table>
<thead>
<tr>
<th>AE</th>
<th>Telcagepant 150 mg (n = 334; % [n])</th>
<th>Telcagepant 150 mg MK-0974-011 (n = 352; % [n])</th>
<th>Telcagepant 300 mg MK-0974-011 (n = 381; % [n])</th>
<th>Placebo MK-0974-011 (n = 349; % [n])</th>
<th>Placebo MK-0974-016 (n = 366; % [n])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>28.4 (95)</td>
<td>30.7 (117)</td>
<td>34.1 (120)</td>
<td>34.6 (128)</td>
<td>30.7 (107)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5.4 (18)</td>
<td>4.5 (17)</td>
<td>6.0 (21)</td>
<td>5.1 (19)</td>
<td>5.2 (19)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.5 (15)</td>
<td>3.7 (14)</td>
<td>5.1 (18)</td>
<td>2.7 (10)</td>
<td>4.0 (14)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.2 (14)</td>
<td>2.4 (9)</td>
<td>5.1 (18)</td>
<td>5.4 (20)</td>
<td>5.7 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.9 (13)</td>
<td>3.4 (13)</td>
<td>4.5 (16)</td>
<td>4.6 (17)</td>
<td>3.7 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.2 (14)</td>
<td>3.7 (14)</td>
<td>4.3 (15)</td>
<td>6.5 (24)</td>
<td>2.3 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.6 (2)</td>
<td>0.8 (3)</td>
<td>2.3 (8)</td>
<td>1.6 (6)</td>
<td>0.6 (2)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1.2 (4)</td>
<td>1.3 (5)</td>
<td>1.7 (6)</td>
<td>2.2 (8)</td>
<td>1.4 (5)</td>
</tr>
<tr>
<td>Epigastic pain</td>
<td>ND (0)</td>
<td>1.0 (4)</td>
<td>3.2 (12)</td>
<td>ND (0)</td>
<td>1.6 (6)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>0.3 (1)</td>
<td>ND (0)</td>
<td>ND (0)</td>
<td>0.3 (1)</td>
<td>ND (0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0.0 (0)</td>
<td>ND (0)</td>
<td>ND (0)</td>
<td>0.9 (3)</td>
<td>ND (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>ND (0)</td>
<td>0.8 (3)</td>
<td>0.5 (2)</td>
<td>ND (0)</td>
<td>2.2 (8)</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>1.8 (6)</td>
<td>ND (0)</td>
<td>0.6 (2)</td>
<td>ND (0)</td>
<td>0.3 (1)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>ND (0)</td>
<td>0.5 (2)</td>
<td>ND (0)</td>
<td>1.4 (5)</td>
<td>ND (0)</td>
</tr>
<tr>
<td>Throat tightness</td>
<td>0.0 (ND)</td>
<td>ND (0)</td>
<td>ND (0)</td>
<td>0.3 (1)</td>
<td>ND (0)</td>
</tr>
<tr>
<td>Triptan</td>
<td>2.1 (7)</td>
<td>ND (0)</td>
<td>4.0 (14)</td>
<td>ND (0)</td>
<td>3.4 (12)</td>
</tr>
</tbody>
</table>

| Data are proportion (%) of patients with number of patients treated with telcagepant 5 mg (n = 345).

**AE**: Adverse event; ND: No data reported.

**Data taken from [14,164].**
Table 5. Efficacy of BI 44370, eletriptan and placebo.

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>Headache free at 2 h (% [n])</th>
<th>Headache relief at 2 h (% [n])</th>
<th>Absence of photophobia at 2 h (% [n])</th>
<th>Absence of phonophobia at 2 h (% [n])</th>
<th>Absence of nausea at 2 h (% [n])</th>
<th>2-24 h sustained pain freedom (% [n])</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI 44370 50 mg (oral; n=64)</td>
<td>8 (5)</td>
<td>31 (20)</td>
<td>39 (25)</td>
<td>42 (27)</td>
<td>61 (39)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>BI 44370 200 mg (oral; n=65)</td>
<td>22 (14)</td>
<td>51 (33)*</td>
<td>46 (30)</td>
<td>54 (35)</td>
<td>58 (38)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>BI 44370 400 mg (oral; n=65)</td>
<td>27 (20)**</td>
<td>56 (41)*</td>
<td>56 (41)**</td>
<td>63 (46)***</td>
<td>70 (51)**</td>
<td>20 (15)*</td>
</tr>
<tr>
<td>Placebo (n=70)</td>
<td>9 (6)</td>
<td>19 (13)</td>
<td>33 (23)</td>
<td>41 (29)</td>
<td>46 (32)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Eletriptan 40 mg (oral; n=69)</td>
<td>35 (24)*</td>
<td>56 (39)*</td>
<td>64 (44)*</td>
<td>64 (44)***</td>
<td>65 (45)***</td>
<td>22 (15)**</td>
</tr>
</tbody>
</table>

Data are proportion (% [n]) of patients with number of patients fulfilling and point (p) or either parenthesis.

* p < 0.005, ** p < 0.01, *** p < 0.025 for the active versus placebo comparison.

Data taken from [154].

on human brain and MMA. The plasma concentration after oclegepant 2 mg is approximately 200 nM and for 300 mg telcagepant it is approximately 4 µM. There is, therefore, a huge difference between the low concentration of oclegepant and telcagepant needed for CGRP blockade of human cranial arteries and the concentration needed for an effect in migraine.

Another argument for a central site of action of CGRP antagonists was found in cats where the CGRP antagonist BIBN4096BS (oclegepant) inhibited the stimulation-induced neuronal firing in the brainstem [116]. The data suggested that there are central CGRP receptors in the trigeminocephalic complex that can be inhibited by CGRP receptor blockade. Here the ED50 of oclegepant used was 31 µg/kg (45), which is roughly equivalent to 2 mg iv in man.

Given the high potency of oclegepant and telcagepant, it was initially anticipated that a relatively low dose of telcagepant would likely be efficacious by blocking peripheral CGRP receptors. Indeed, in capsaicin-induced vasodilatation study, it was shown that the EC50 to block peripheral CGRP receptor-mediated vasodilatation was determined to be at 300 or 900 nM [111]. The relatively flat concentration-response curve above 900 nM indicates that at or above this plasma concentration, telcagepant is maximally blocking the peripheral CGRP receptor in humans. Thus, it was surprising that relatively high doses of telcagepant (150 and 300 mg) were necessary to achieve antinociceptive blockade of CGRP receptor antagonists for the treatment of migraine


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The gepants have been shown to block CGRP responses in cranial arteries. They are hypothesized to also have effects on migraine.

Where do the gepants act in migraine?

■ The ability of CGRP receptor antagonists to treat acute migraine attacks has been established in clinical trials. Adverse events related to patients have been similar to placebo. The most worrying aspect of the CGRP receptor antagonist project has been an elevation of liver transaminases. Where do the gepants act in migraine?

■ The gepants have been shown to block CGRP responses in cranial arteries. They are hypothesized to also have effects on different parts of the trigeminal system and in migraine-related regions in the CNS. Conclusion

The gepants are an established and well-defined group of CGRP blockers. They are proven to have good antimigraine effects in clinical trials with low degrees of side-effects.

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Executive summary

Background

• Migraine is a frequent disorder worldwide (13% of adults) that is receiving much attention. The pain is related to the trigeminal-sensory system.

Basic facts on CGRP

• CGRP is widely expressed in the CNS and PNS, and is particularly related to the sensory nerves. CGRP is a potent vasodilator and its receptors in humans. As pointed out in this review there are now at least three major drug companies with strong interest in migraine and the entry of a clinical program from BMS offers future hope that this form of migraine therapy will soon reach the patients.

References

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