Journal of Pain Research

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REVIEW

Calcitonin gene-related peptide receptor as a novel target for the management of people with episodic migraine: current evidence and safety profile of erenumab

This article was published in the following Dove Press journal:
Journal of Pain Research

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Abstract: Migraine is a highly disabling neurological condition, and preventative treatment still remains problematic, due to aspecificity of the majority of the currently available prophylactic drugs. Calcitonin-gene-related peptide (CGRP) plays a crucial role in migraine pathophysiology; agents aimed at blocking its activity have, therefore, been developed in recent years, among which are monoclonal antibodies (mAbs) against CGRP, to prevent migraine. Erenumab is the only mAb that targets the CGRP receptor instead of the ligand, with high specificity and affinity of binding. This review will report on the most recent data on erenumab characteristics and on the results of clinical trials on its employment in the prevention of episodic migraine (4–14 monthly migraine days): one Phase II and two Phase III trials (completed) and one Phase III trial (ongoing). Monthly subcutaneous administration (70 mg or 140 mg) of erenumab vs placebo for 3–6 months showed significantly higher efficacy in reducing the mean monthly number of migraine days and the use of migraine-specific medication, and in decreasing physical impairment and impact of migraine on everyday activities ($P<0.001$). A favorable safety profile was demonstrated by the lack of significant differences in the occurrence of adverse events in erenumab-treated vs placebo-treated patients. Global results so far obtained point to erenumab as a new promising candidate for the preventative treatment of episodic migraine. Licence applications for erenumab were recently submitted to the Food and Drug Administration in the USA and European Medicines Agency in Europe (May/June 2017).

Keywords: erenumab, episodic migraine, CGRP, CGRP receptor

Introduction

Migraine is a condition of recurrent pain episodes with highly disabling characterstics. Each episode has a duration of 4–72 hours; the pain, most often pulsating in quality and unilateral in location, is moderate to severe in intensity, aggravated by physical activity and typically accompanied by nausea and/or vomiting and phonophobia and photophobia. During the attack, the patient tends to isolate from any social context, most often lying in bed until resolution of the symptoms.[1] In the episodic form, the frequency of attacks is crucial in determining the burden of the disease and the therapeutic approach: low frequencies (1–3/month) can be handled with abortive medications only (eg, triptans, analgesics, non-steroidal-antiinflammatory drugs) and higher frequencies (4–14/month) necessarily need prophylactic medications in addition to symptomatics in order to prevent chronification (≥15 headache days/month).[2] Chronicity is then particularly problematic as very few preventative medications work in this phase and often

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submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JPR.S128143

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abuse of symptomatics occurs, leading to the complication of medication overuse headache and to an exponential increase of drug-related risks (eg, cardiocerebrovascular events and renal and gastrointestinal adverse events [AEs]).[3–7]

The current available options for prophylaxis include different drug classes, ie, calcium channel blockers (eg, flunarizine and cinnarizine), beta-blockers (eg, propanolol), and other antihypertensive compounds (eg, angiotensin-converting enzyme inhibitors and aldosterone receptor blockers), tricyclic antidepressants (eg, amitryptiline), or antiepileptic drugs (eg, topiramate and divalproex sodium).[2] The vast majority of these drugs are, however, non-specific, ie, primarily designed for other indications, and in prolonged administration – as required for migraine prevention – can have numerous side effects and possible interactions with other medications in comorbid patients.[8] Migraine, in fact, very often co-exists with a number of other medical conditions, ranging from psychiatric disorders, cardiovascular diseases, myofascial pain syndromes, fibromyalgia, to numerous forms of visceral pain, among which pelvic pain from endometriosis, primary dysmenorrhea, and irritable bowel syndrome, all often require concomitant medications.[7,9–14] In addition, the percentage of unsatisfactory response to these preventative treatments remains high especially in migraine at a high frequency of attacks.[2] An imperative need, therefore, exists for more specific prophylactic agents, which are mechanism-based.

Calcitonin-gene-related peptide (CGRP) has been shown to play a crucial role in migraine pathophysiology; in recent years, agents directed at blocking CGRP activity, such as CGRP receptor antagonists or monoclonal antibodies (mAbs), have thus gained exponential importance as potential preventative treatments of the condition.[15–17] In this context, erenumab (AMG334, co-developed by Amgen and Novartis) holds a prominent place, being the only mAb against the CGRP receptor rather than against the ligand.[18,19] After a premise on the role of CGRP and its receptor in the generation of migraine pain, this review will focus on the pharmacology, mode of action, and pharmacokinetics of erenumab and then report the results of the clinical trials so far performed with this mAb in the prevention of episodic migraine.

CGRP, its receptor, and migraine pain

CGRP, a 37-amino acid peptide discovered 30 years ago,[20] is part of the calcitonin family of peptides, together with calcitonin, amylin, and adrenomedullin. In humans, it exists in two major forms: α-CGRP, implicated in migraine, is expressed in sensory neurons of the dorsal root ganglia, in the trigeminal system, and vagal ganglia, while β-CGRP is primarily expressed in the enteric nervous system.[17,21–25]

CGRP not only has a potent vasodilating action, mediated by the receptors in smooth muscles, but also has a pronociceptive action exerted through enhancement of substance P release from primary afferent terminals and modulation of the synaptic transmission of glutamate.[26–29]

Its role in migraine was originally entirely ascribed to its vasodilating action at the level of the intracranial arteries.[30] In migraineurs, CGRP intravenously administered can, in fact, trigger a migraine-like attack after 2–4 hours,[31–34] during which dilation is evidenced in both the middle meningeal artery and the middle cerebral artery; this migraine-like episode is resolved by administration of sumatriptan.[31] In non-migraine patients, intravenous CGRP only produces an initial mild headache without the characteristics of experimentally induced migraine.[32,35]

In recent times, however, it has become clear that the CGRP role in migraine goes far beyond its vascular action; the peptide, in fact, modulates neuronal excitability, particularly facilitating pain responses in the trigeminal system and trigeminal nucleus caudalis,[36–38] being thus implicated in mechanisms of both peripheral and central sensitizations underlying migraine pain.[39]

Neurogenic inflammation participates in peripheral sensitization and CGRP is involved in the entire process, thanks to its vasodilator property and its ability to increase the release of substance P, which induces plasma extravasation.[40] Another mechanism through which the peptide contributes to the phenomenon is through promotion of mast cell degranulation which results in the release of a number of inflammatory and proinflammatory substances.[41] By binding to its glial receptors, CGRP furthermore promotes release of cytokines in the trigeminal ganglia and nerve, which in turn produces sensitization of sensory neurons.[42,43]

The role of CGRP has also been suggested in cortical spreading drepression (CSD), underlying the aura phenomenon.[44] CSD can activate meningeal nociceptors, producing CGRP release from the peripheral terminals of the pia and consequent neurogenic inflammation and the initial response of transient hyperemia.[45] CGRP also seems to be implicated in other migraine-related phenomena, in addition to pain, eg, photophobia[46,47] and gastrointestinal symptoms, such as nausea.[48]

The involvement of CGRP in the pathophysiology of a migraine attack is also supported by numerous other data.

Stimulation of the trigeminal ganglion in humans and cats produces CGRP release;[49] in the course of a spontaneous migraine attack, CGRP levels are increased in the jugular outflow[50] and in saliva[51] with their reduction after administration of triptans.[52] CGRP serum levels are also elevated in between attacks in episodic[53] and chronic migraine;[54] this has led to the hypothesis that the peptide could represent a biomarker of the condition.

Based on all these elements, CGRP has produced increasing interest as a possible target for compounds devoted to migraine control.[19,55,56] Receptor antagonists were first developed, which compete with CGRP at the receptos sites. They showed promising results but the production of most of them had to be discontinued due to liver toxicity.[2,55,57]

mAbs against CGRP were then developed. Three of these macromolecules target the peptide. These are: ALD-403 (Alder BioPharmaceuticals, Bothell, WA, USA), LY2951742 (developed by Arteaus Therapeutics, Cambridge, MA, USA, with rights acquired by Eli Lilly and Co., Indianapolis, IN, USA), and LBR-101, now TEV-48125 (developed by Labrys Biologics-Pfizer, San Francisco, CA, USA, then acquired by Teva Pharmaceuticals, Petah Tikva, Israel). AMG334 (Amgen, Inc., Thousand Oaks, CA, USA; Novartis, Basel, Switzerland), ie, erenumab, is the only compound of the class that targets the receptor instead of the ligand.[19,58]

All mAbs have a preferential peripheral site of action (at sites involved in migraine generation); therefore, given their large size, only 0.1–0.5% of them pass the blood–brain barrier.[55,56] They have several advantages, such as target specificity and prolonged half-life, which make them suitable for monthly administration in preventing migraine. They have also been shown to be deprived of significant hepatotoxicity. Initially, there was concern about employment of these compounds because of their blocking action of the vasodilating activity of CGRP, potentially involving cardiovascular repercussions (eg, inhibition of cardioprotective mechanisms during ischemia, or the triggering of medication-induced hypertension).[19] However, various preclinical studies (monkeys and rats) so far performed have shown that even long-term inhibition of CGRP with mAbs does not produce relevant electrocardiogram or hemodynamic changes.[18,58–60] Also human studies have shown no significant cardiovascular side effects or changes in the results of laboratory tests.[61]

Several clinical studies have been conducted with all the molecules, showing promising results in migraine prevention.[18,62,63] Here we will concentrate on erenumab, which, as already stated, is the only mAb acting specifically on the receptor, instead on the free ligand. The theoretic advantage of an mAb targeting the receptor instead of the ligand is based on its higher specificity. This should involve a reduction of the side-effects, particularly long-term ones, linked to a complete blockade of CGRP action. So far, however, specific data comparing the effects vs side effects of mAbs targeting the ligand vs the receptor are still lacking; therefore, this assumption needs to be verified in future studies.

The CGRP receptor

The CGRP receptor complex is located at sites that are crucial to the triggering of migraine, including the cerebrovasculature, trigeminocervical complex in the brainstem, and the trigeminal ganglion. The receptor family on which CGRP and other peptides of the group act includes calcitonin receptor-like receptor (CLR) linked to a small transmembrane spanning protein, called RAMP1 (receptor activity modifying protein 1), which is indispensable to gurantee functionality.[28] RAMP1 facilitates the cell-surface expression of CLR and is essential for the binding of CGRP to its receptors. Among other residues, Y66, F93, H97, and F101 form a binding site for CLR by clustering together on the same aspect of the extracellular portion of RAMP1, probably in close proximity to its entrance into the plasma membrane.[64]

It is considered that the true receptor for CGRP is constituted by CLR/RAMP1 complex. However, the family of RAMP proteins includes three members: RAMP1, RAMP2, and RAMP3. RAMP1 also associates with the receptor for calcitonin, forming a receptor for amylin, the related peptide, but this also possesses high affinity for CGRP. Dimerization of the CLR and RAMP2 creates a receptor that is highly responsive to the related peptide adrenomedullin (AM1 receptor). The RAMP3 receptor confers a second adrenomedullin receptor (AM2 receptor) that also has some selectivity for CGRP.[28] There are slso other combinations of CLR or the calcitonin receptor with RAMPs; as a result, receptors can be generated which are responsive to CGRP. The action of CGRP is potentially also exerted downstream of activation of the described receptors, in a cell type-dependent manner, though the physiological meaning of these actions is still unclear. In synthesis, receptor site and action of CGRP are both complex; more than one receptor which is responsive to CGRP can be expressed in crucial sites of the described system.[65] Receptor selectivity is, therefore, particularly important for any agent aimed at antagonizing a specific CGRP action, without affecting the actions mediated by the other receptors (see the following section).

Erenumab

Pharmacology, mode of action, and pharmacokinetics

Ideal characteristics of an mAb targeting the receptor for CGRP are based on several considerations. Firstly, the binding site of CGRP on the calcitonin receptor-like receptor (CRLR)-receptor activity-modifying protein-1 (RAMP1) CGRP-receptor complex is broad;[65] as a consequence, the most effective blockade can be achieved by an antibody able to span the distance between these subunits of the receptor. Secondly, since the CGRP receptor complex shares similarities with other receptors of the family, it is essential for its blockade to be highly selective to avoid side effects linked to blocking of the other receptors. Furthermore, a long serum half-life of the antibody is key to allow administration to patients for preventative treatment at relatively long time intervals, which enhances patients' compliance.[62] All pharmacokinetic studies confirmed that erenumab has ideal requisites to this aim.

A recent study by Shi et al[66] showed powerful actions of erenumab in inhibiting the binding of [125I]-CGRP to the human CGRP receptor (Ki of 0.02 nM, a 20-fold greater potency than that of telcagepant, Merck's CGRP receptor antagonist) and in antagonizing CGRP in a functional assay (completely inhibiting the production of cAMP stimulated by CGRP with an IC50 value of 2.3 nM, comparable to that of telcagepant). It also showed species (human and cynomolgus monkey receptors) and receptor-family specificity and pharmacodynamic activity, being 5,000-fold more selective for the CGRP receptor than for other receptors of the human calcitonin family. In cynos, erenumab also dose-dependently prevented the increases in dermal blood flow induced by capsaicin on days 2 and 4 post-dosing, indicating a powerful, selective, and full antagonistic action on the CGRP receptor.[66]

The pharmacokinetics of erenumab was also characterized in the study by Vu et al,[67] together with its inhibitory effects on capsaicin-induced dermal blood flow (CIDBF), which is a validated tool to assess the target engagement of compounds potentially inhibiting CGRP in the context of migraine therapy. The study pooled data from a single- and multiple-dose study in healthy subjects and migraine patients. Capsaicin stimulations were performed repeatedly, and dermal blood flow and concentrations of serum erenumab were measured. The authors conducted a population analysis using a nonlinear mixed-effects modeling, also evaluating the outcome on model parameters of gender, age, and body weight. Subcutaneous absorption half-life and bioavailability were 1.6 days and 74%, respectively. Maximum inhibition determined by erenumab was 89% (95% confidence interval [CI]: 87–91%). The required concentrations of the compound, to obtain 50% and 99% of maximum inhibition, were 255 ng/mL and 1134 ng/mL, respectively. Increased body weight was linked to clearance of erenumab, though producing no effect on the inhibitory effect on CIDBF. The authors concluded that the pharmacokinetics of erenumab resulted in potent inhibition of CIDBF.

In reporting the results of two Phase I studies, evaluating safety, pharmacokinetics, and pharmacodynamics of single and repeated administrations of erenumab in healthy subjects and migraine patients, de Hoon et al[68] concluded that erenumab has a nonlinear pharmacokinetic profile ranging from 1 mg to 70 mg, with the linear portion of the clearance from 70 mg to 210 mg being consistent with other human immunoglobulin G2 antibodies. A >75% inhibition of capsaicin-induced dermal blood flow was produced by single doses of erenumab, apparently without dose dependency for a dose ≥21 mg. The compound proved to have a satisfactory safety profile, being well tolerated.

As all other mAbs, and unlike small molecules, erenumab does not raise hepatotoxicity concerns (it is not eliminated through hepatic, biliary, or renal routes) and involves a significantly reduced risk of drug-to-drug interactions.[68]

Efficacy, quality of life, daily functioning, and adherence

Efficacy of erenumab in episodic migraine has been evaluated and is still currently being assessed in several Phase II and III studies (Table1).

Study NCT01952574 (Phase II; https://clinicaltrials.gov/ct2/show/NCT01952574)[69] in episodic migraineurs (4–14 monthly migraine days) was a randomized, double-blind, placebo-controlled, multicenter study (59 headache and clinical research centers in Europe and North America) of 12 weeks. It evaluated the effects of erenumab vs placebo on the change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase (primary endopoint). A total of 483 patients were assigned to the different groups from August 6, 2013, to June 30, 2014 (160 placebo; 108 erenumab 7 mg; 108 erenumab 21 mg, 107 erenumab 70 mg). At week 12, there was a difference of −1.1 days in the main change in monthly migraine days between the dose of 70 mg erenumab and placebo (−3.4±0.4 standard error vs −2.3±0.3 days, respectively [95% CI: −2.1 to −0.2]; P=0.021). In contrast, the 7 mg and 21 mg dose produced mean changes of −2.2±0.4 and −2.4±0.4 in monthly migraine days, which did not differ significantly from placebo. On the

Table 1 Erenumab in episodic migraine: Phase II and Phase III studies

Protocol and date of completion	Population active vs placebo	Modality of administration	Primary efficacy outcome	Adverse events (AEs)
NCT01952574 Phase II, randomized double-blind placebo-controlled, June 2014	483 (108, 108, 107 vs 160)	7, 21, 70 mg sc once/month for 12 weeks	Week 9–12 vs basis decrease in migraine days; 70 mg vs placebo (P<0.03)	Fatigue, nasopharyngitis, headache, vertigo
NCT02483585 – ARISE Phase III, randomized double-blind placebo-controlled, March 2017	577	70 mg sc for 12 weeks	Weeks 9–12 vs basis decrease in migraine days and migraine medications; 70 mg vs placebo (0.001<P<0.003)	Upper respiratory tract infection, injection site pain, nausea, nasopharyngitis
NCT02456740 – STRIVE Phase III, randomized double-blind placebo-controlled, June 2017	955	70, 140 mg sc once/month for 24 weeks	24 weeks vs basis: decrease in number of monthly migraine days, migraine medications, MPFID-EA, and MPFID-PI; 70 mg and 140mg vs placebo (P<0.001)	Upper respiratory tract infection, injection site pain, nausea, nasopharyngitis
NCT03096834 CAMG334A2301, Phase IIIb, randomized double-blind, March 2019, followed by a 1 year open label phase	382	Single dose sc once/month for 12 weeks	Reduction in migraine days and improvement in patients' quality of life	N/A

Abbreviations: MPFID-EA, impact of migraine on everyday activities as evaluated via the Migraine Physical Function Impact Diary; MPFID-PI, mean physical impairment domain score as measured by the Migraine Physical Function Impact Diary; N/A, not applicable sc, subcutaneous.

whole, the results of the study supported the notion that erenumab at the dose of 70 mg could be effective in preventing episodic migraine.

Study NCT02483585 (ARISE, Phase III) was recently completed (March 2017; https://clinicaltrials.gov/ct2/show/NCT02483585). It was a multicenter, randomized, 12-week, double-blind, placebo-controlled study in the prevention of episodic migraine at a high frequency of attacks. A total of 577 patients aged 18–65 years were randomized to receive once-monthly subcutaneous erenumab (70 mg) or placebo in a 1:1 ratio (respectively: 286 patients, 85.7% women, mean age 42.3 years, 90.6% white, or 291 patients, 84.9% women, mean age 42.2 years, 89% white). Patients enrolled in ARISE were experiencing between 4 and 14 migraine days each month with an average of ~8.3 migraine days per month at baseline. The primary endpoint was the change in monthly migraine days from baseline to the last 4 weeks of the 12-week treatment phase (the number of migraine days between weeks 9 and 12).

In the time frame of completion of the double-blind treatment phase at month 3, secondary outcome measures were the proportion of subjects presenting at least a 50% reduction from baseline in monthly migraine days, the change from baseline in monthly acute migraine-specific medication treatment days, the change from baseline in physical impairment (to evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least a 5-point reduction from baseline in mean physical impairment domain score as measured by the Migraine Physical Function Impact Diary [MPFID]), and the change from baseline in impact on everyday activities (to evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least a 5-point reduction from baseline in mean impact on everyday activities domain score as measured by the MPFID).

This study showed that erenumab vs placebo significantly reduced the mean monthly number of migraine days (2.9 vs 1.8 days, respectively), from baseline to weeks 9–12 of treatment (P<0.001), increased odds of achieving a 50% or higher reduction in this same parameter (group rate of 39.7% vs 29.5% for a 50% or greater reduction in monthly number of migraine days; odds ratio [OR] 1.6; P<0.02), and reduced the number of monthly days of use of migraine-specific medication (1.2 vs 0.6 reduction; P<0.003).

The ARISE study, of 12-weeks duration, is followed by an open-label treatment phase (28 weeks) which should be completed in October 2017.

Study NCT02456740 (STRIVE, Phase III) is a multicenter, randomized 24-week, double-blind, placebo-controlled study in episodic migraine prevention which was completed in June 2017. The results were illustrated by Goadsby et al during the 69th Annual Meeting of the American Academy of Neurology in Boston.[70]

After screening, patients underwent a 4-week baseline period during which they kept electronic migraine diaries. A total of 955 patients were then randomized to receive once-monthly subcutaneous placebo (n=319, 86% women, 87%

white, mean age, 41.3 years), or erenumab 70 mg (n=317, 85% women, 89% white, mean age, 41.1 years), or erenumab 140 mg (n=319, 85% women, 92% white, mean age, 40.4 years) in a 1:1:1 ratio, for 6 months.

Patients experienced between 4 and 14 migraine days each month, with an average of 8.3 migraine days per month at baseline. Patients who previously had failed two preventative medications were excluded. Slightly more than half the participants had no previous exposure to a preventative therapy. The primary endpoint was the change in mean monthly migraine days from baseline over the last 3 months of the double-blind treatment phase of the study (months 4, 5, and 6). In the time frame of completion of the double-blind treatment phase at 24 weeks, secondary outcome measures were the: 1) proportion of subjects with at least 50% reduction from baseline in monthly migraine days; 2) change from baseline in mean monthly acute migraine-specific medication treatment days; 3) change from baseline in physical impairment (mean physical impairment domain score as measured by MPFID); 4) change from baseline on impact on everyday activities (mean impact on everyday activities domain score as measured by the MPFID).

In the last 3 months of treatment, a reduction of 3.2 days of monthly migraine days was observed for erenumab 70 mg and 3.7 for erenumab 140 mg vs 1.8 for placebo, with a statistically significant difference between both doses of active treatment vs placebo ($P<0.001$). The percentage of patients presenting a 50% or greater reduction of mean monthly number of migraine days was 43.3% for erenumab 70 mg and 50% for erenumab 140 mg vs 27% for placebo (ORs 2.13 and 2.81). There was also a greater reduction of migraine-specific medication days for the acute attack in the active arms vs the placebo arm: 1.1 and 1.6 days for erenumab 70 mg and 140 mg vs 0.2 days for placebo ($P<0.001$).

Patients treated with erenumab 70 mg reported a 5.5 point decrease on the impact of migraine on everyday activities (MPFID-EA) as evaluated by the MPFID. Patients treated with erenumab 140 mg showed a 5.59-point reduction for this same parameter, while placebo-treated patients showed a 3.3-point reduction. The difference among the active groups and placebo group was highly significant ($P<0.001$).

Physical impairment (MPFID-PI) decreased by 4.2 and 4.8 points in the erenumab 70 mg and 140 mg arms, respectively, vs only 2.4 points for the placebo arm ($P<0.001$).

Study NCT03096834 (CAMG334A2301, Phase IIIb) is ongoing, currently recruiting participants. This is a 12-week double-blind, randomized, multicenter study comparing the efficacy and safety of a once-monthly subcutaneous single dose of erenumab against placebo in adult episodic migraine patients (4–14 monthly migraine/days) who have failed two to four prophylactic migraine treatments. Patients providing consent and meeting inclusion criteria will undergo examinations to determine eligibility. Those entering the study have a 50% chance of receiving either erenumab or placebo. After the first 12-week double-blind phase, patients have the choice to remain in the study for the open-label phase, lasting 1 year, during which they will continue to receive erenumab once a month. The enrollment estimate is 220 patients, aged 18–65 years, for a completion date in March 2018.

Effectiveness is measured by reviewing reduction in migraine days and improvement in patient quality of life. In particular, in the time frame of the last month (Month 3) of the Double-Blind Treatment Epoch (DBTE), the primary outcome measure is the percentage of patients with a 50% response in the reduction of Monthly Migraine Days (MMD) (as assessed via patient report in the headache e-diary). In the time frame from baseline to the last month (Month 3) of the DBTE, secondary outcome measures are changes in 1) number of monthly migraine days, 2) MPFID "impact on everyday activities" domain score, 3) MPFID "physical impairment" domain score, 4) number of monthly acute migraine-specific medication treatment days, 5) percentage of patients with a 75% response (patient report in the headache e-diary), 6) percentage of patients with a 100% response (patient report in the headache e-diary).

Efficacy of erenumab was also demonstrated in studies on chronic migraine prevention: NCT02066415 (Phase II, completed in April 2016),[71,72] and NCT02174861 (Phase II), which assessed the long-term (13 months) safety and efficacy of this mAb (completed in May 2017; an Open-Label Extension-OLE-Study). In a study by Tepper et al, 667 patients with chronic migraine received placebo, or 70 mg or 140 mg doses of erenumab (randomized 3:2:2 to subcutaneous injections, every 4 weeks for 12 weeks); 637 completed treatment. Erenumab 70 mg and 140 mg significantly reduced monthly migraine days vs placebo ($P<0.0001$). There was a difference of −1.1 days in the main change in monthly migraine days between 70 mg erenumab group and placebo.

In summary, all completed studies on episodic migraine showed clinically significant effectiveness of erenumab at a minimum dose of 70 mg on the main migraine variables. Both studies NCT01952574 and ARISE showed the same

difference of −1.1 days in the main change in monthly migraine days with the 70 mg dose vs placebo for a 3-month duration of treatment. ARISE also showed a 0.6 day reduction of the acute migraine-specific medication days and a 10.2% increase in the percentage of patients presenting a 50% or higher reduction of monthly migraine days with the same dose vs placebo. A 6-month duration treatment, as carried out in the STRIVE study, enhanced efficacy for the same dose of 70 mg vs placebo, reducing by 1.4 the mean monthly number of migraine days and by 0.9 the migraine-specifc medication days and enhancing by 16.3% the percentage of patients presenting a 50% or greater reduction of mean monthly number of migraine days.

STRIVE also showed higher effects with the 140 mg dose vs placebo: a reduction of 1.9 migraine days and 1.4 migraine-specific medication days and an increase of 23% in the percentage of patients presenting a 50% or greater reduction of mean monthly number of migraine days.

In conclusion, the average response rate and reduction of mean monthly number of migraine days are similar across studies for the same duration of treatment and same dose of erenumab, 70 mg. The higher dose of 140 mg provides slightly better outcomes, but the cost/benefit ratio of dose increasing will need to be explored further in future studies, especially for longer-term treatments.

Safety and tolerability

Safety and tolerability of erenumab were assessed in the same efficacy studies reported in the previous sections.

In study NCT01952574 (Phase II),[69] the most common reported AEs were headache, nasopharyngitis, and fatigue.

One patient in the 7 mg erenumab group had a ruptured ovarian cyst and one patient in the 70 mg erenumab group presented migraine and vertigo; none of these events, however, proved related to the treatment. Globally, the percentage of recorded events was very similar and not significantly different among groups: 50% (54 patients) in the 7 mg erenumab group, 51% (54 patients) in the 21 mg erenumab group, and 54% (57 patients) in the 70 mg erenumab group vs 54% (82 patients) in the placebo group. Neutralizing antibodies were found in 3% of treated patients (317), but no specific link could be demonstrated between their appearance and the occurrence of AEs. Other safety indicators (eg, electrocardiogram, laboratory tests, and vital signs) were all unaltered by treatment. This study will be followed by an open-label extension phase of up to 256 weeks, which should be completed in March 2020, to assess the long-term safety of the compound.

In the ARISE study, AEs of any type were reported by 48.1% of erenumab-treated patients and 54.7% of placebo-treated patients, with 1.1% vs 1.7% reporting serious AEs. Respiratory tract infection occurred in 6.4% vs 4.8% of erenumab- and placebo-treated patients, respectively. Injection site pain was reported by 6.0% vs 4.2% of the patients and nasopharyngitis by 5.3% vs 5.9%. No significant differences in AEs were present between the erenumab and placebo groups.

In the STRIVE study, erenumab proved to be well tolerated. Erenumab- and placebo-treated groups did not differ significantly regarding the occurrence of AEs, both serious and nonserious. Serious AEs were reported in 2.5% and 1.9% of the cases in the erenumab 70 mg and 140 mg groups vs 2.2% of the cases in the placebo group; none of the events appeared treatment related. The most frequent AEs were nasopharyngitis and upper respiratory tract infection. The most common nonserious AE was a reaction at the injection site.

Antibodies against erenumab developed in about 6% of the patients in the active groups (8% for the 70 mg arm and 3.2% for the 140 mg arm). Neutralizing antibodies were only found in one patient of the 70 mg group, and none in the 140 mg group.

The favourable profile of safety and tolerability of erenumab was also confirmed by studies in chronic migraine. In a study by Tepper et al,[72] AEs occurred in 39%, 44%, and 47% of the patients in the placebo, 70 mg, and 140 mg groups, respectively. The most common AEs were upper respiratory tract infection, nausea, and pain at the injection site; serious AEs occurred in 3%, 3%, and 1% of the patients respectively; none of these occurred in >1 patient in any of the groups or produced discontinuation. No neutralizing antibodies were recorded in the active groups. There were no significant changes in vital signs and laboratory or electrocardiogram findings. The satisfactory safety profile of erenumab in this study is also indicated by the low withdrawal rate from the study.

Conclusion, approval status, and potential place in therapy

Erenumab, the only available mAb against the CGRP receptor, has proven effective in the prevention of episodic migraine in Phase II and III trials conducted so far, with a satisfactory safety profile, also confirmed by Phase II and III studies in chronic migraine. Erenumab thus seems particularly suitable for migraine preventative treatment, representing an important step forward in the field, especially as the modality of administration, typically every month, has a high potential of enhancing patents' compliance, which represents

a problem with the classic prophylactic agents that need to be assumed daily.[62,73] The studies conducted so far did not differentiate among different migraine subtypes (eg, with and without aura) or age and sex of the treated patients, so it is not known if erenumab has similar or different effects in various subpopulations of migraineurs, which would be of interest to know in future trials on the compound to identify the best responder target population. Another important aspect regards the numerous comorbidities in migraine, especially painful, particularly frequent in female patients, such as visceral pain from single and multiple organs, often giving rise to phenomena of viscero-visceral hyperalgesia, myofascial pain syndromes, or fibromyalgia.[9–14,74,75] Future studies should also address the crucial issue of possible differential effects of the preventative treatment via blockade of the CGRP receptor in subgroups of migraine patients with and without comorbidities. Erenumab is to be co-commercialized by Amgen and Novartis in the USA. While Amgen retains exclusive commercialization rights in Japan, Novartis has exclusive commercialization rights in Europe, Canada, and rest of the world. A Biologics License Application was submitted by Amgen to the US Food and Drug Administration for erenumab in May 2017, based on the global data of the erenumab program so far obtained (four Phase II and III clinical studies), which enrolled more than 2,600 migraine patients reporting four or more migraine days per month, with some of them receiving erenumab for up to 3 years. The most recent data on trials with erenumab were presented at the 59th Annual Scientific Meeting of the American Headache Society in Boston in June 2017.

In Europe, the Marketing Application for AMG334 by Novartis was accepted by the European Medical Agency in June 2017. The company declared that they will work with the European Health Authorities on their goal to make their fully human mAb erenumab, the first new therapy available to migraineurs in over a decade.

Disclosure

In the past 3 years, MAG received funding from Epitech Group, Helsinn Healthcare, and IBSA Institute Biochimique for research unrelated to the topic of the present paper, and honoraria from Helsinn Healthcare, IBSA Institute Biochimique, and royalties from IASP Press. GA received honoraria from Epitech Group and Helsinn Healthcare. PM was in the Advisory Board of Teva, Allergan, Amgen, Novartis, Electrocore. He received Educational Grants from Allergan, ACRAF, and Pfizer; royalties from Springer; research grants from Elytra Pharma and Sanofi; travel reimbursements from EFIC, EHF, and SpringerNature, and an editorial grant from SpringerNature. RC and FC report no conflicts of interest in this work.

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