Calcitonin gene-related peptide-targeted therapy in migraine: current role and future perspectives

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Almost 40 years ago, the discovery of the vasoactive neuropeptide calcitonin gene-related peptide (CGRP) and its role in migraine pathophysiology ushered in a new era in migraine treatment. Since 2018, monoclonal antibodies (mAbs) targeting the CGRP pathway are available for migraine prevention. The approval of these drugs marks a pioneering development, as they are the first pharmacological agents specifically tailored for migraine prevention. Introduction of these agents contrasts the historical reliance on traditional preventive medications initially formulated for other indications and later repurposed for migraine therapy. Although the emergence of evidence on the efficacy and safety of CGRP-targeted mAbs has raised the bar for treatment success in migraine, their efficacy in other headache entities, such as cluster headache, is low to moderate. Small-molecule CGRP receptor antagonists called gepants have also been proven to be effective both as acute and preventive migraine treatments. Furthermore, these agents have bridged the traditional categories of acute and preventive treatment strategies. Short-term prevention and treatment during the prodromal phase of migraine represent emerging strategies enabling clinicians to develop treatment approaches designed to meet changing patient needs; however, these strategies still require more formal evidence. Although solid data have been gathered, further research concerning the efficacy and long-term safety of drugs targeting the CGRP pathway and robust pharmacoeconomic evaluations are needed. Finally, randomised withdrawal and switching studies would facilitate the formulation of evidence-based guidance for the discontinuation of and switching between drugs targeting the CGRP pathway.

Introduction

Migraine is a complex neurovascular disorder affecting 14% of the world's population, which amounts to more than 1 billion people globally.[1,2] Moreover, this condition is the second leading cause of years lived with disability worldwide for all ages and the leading cause in women aged 16–49 years.[3] Patients with migraine also experience stigma, which can lead to increased disability, decreased quality of life, increased depression and anxiety, less care seeking, and poorer treatment outcomes.[4] The current armamentarium of treatments is based on the two pillars of acute and preventive treatments.[5,6] Of all treatments available, triptans were, until 2018, the only medications that were specifically designed for migraine.[7,8]

Most medications available for migraine prevention were not specifically targeted at migraine and were generally underused due to poor tolerability or insufficient efficacy. These medications have hence shown low rates of adherence and persistence.[9] In the realm of migraine treatment, the advent of therapies targeting the calcitonin gene-related peptide (CGRP) pathway marks a pioneering development as these agents are specifically designed for migraine and have shown robust efficacy, overall good tolerability, and a good safety profile in numerous pivotal clinical trials (figure 1). This paper will provide an update of the role of this drug class in migraine treatment and will elaborate on future perspectives and challenges (table 1).

Search strategy and selection criteria

We searched the PubMed database from its inception until Sept 1, 2024. Search terms used were: "calcitonin gene related peptide", "CGRP", "migraine", "erenumab", "eptinezumab", "fremanezumab", "galcanezumab", "atogepant", "rimegepant", "ubrogepant", and "zavegepant". Reference lists from publications identified with this search strategy were also reviewed. The US National Library of Medicine clinical trials database (ClinicalTrials.gov) was also searched with the use of the same terms. Relevant publications were selected with a preference for those reporting primary data, and for those published within the past 5 years. Only articles published in English were included.

Mechanism of action of drugs targeting the CGRP pathway

Migraine headache is thought to be caused by activation of the trigeminovascular system, which is associated with the release of neuropeptides from activated trigeminal nociceptors. One of these neuropeptides is CGRP—a potent vasodilator and modulator of cerebrovascular nociception.[10–12] Infusion of CGRP in patients with migraine might provoke migraine attacks.[13] Because of this evidence showing that CGRP might have an important role in the pathophysiology of migraine, researchers proposed that blockade of CGRP or its receptors might abort or even prevent migraine attacks.[10] CGRP is a neuropeptide that consists of 37 amino acids; this molecule exists in two homologue isoforms in humans. αCGRP is formed by alternate splicing of the calcitonin gene transcript and is thought to be expressed in the nervous system. The other form, βCGRP, is encoded by an alternative *CGRP* gene and is thought to be predominantly expressed in the enteric nervous system. However, this division between the sites of expression of αCGRP and βCGRP is not mutually exclusive and βCGRP can also be expressed in the nervous system. Human

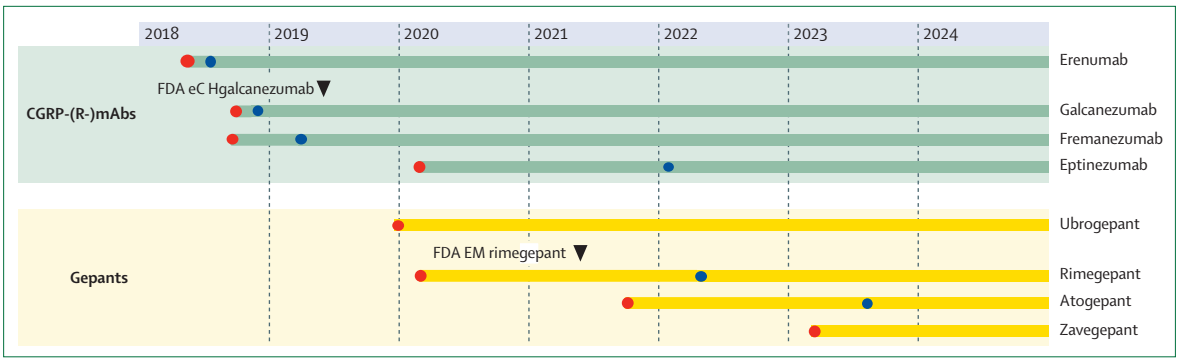

Figure 1: **Approval timeline of migraine drugs targeting the CGRP pathway**
Red dots indicate the FDA approval and blue dots indicate the EMA approval. CGRP=calcitonin gene-related peptide. CGRP-(R-)mAbs=monoclonal antibodies directed against CGRP or the CGRP receptor. eCH=episodic cluster headache. EM=episodic migraine (the FDA approved rimegepant as an acute treatment first; the EMA issued the approval for the acute and preventive treatment at the same time). EMA=European Medicines Aggency. FDA=US Food and Drug Administration.

	Target	Indication	Route	Dose	T_{max}	Half-life	Frequency
Monoclonal antibodies							
Erenumab	Receptor	EM and CM prevention	Subcutaneous	70 or 140 mg	4–11 days	27 days	Monthly
Fremanezumab	Ligand	EM and CM prevention	Subcutaneous	225 or 775 mg	5–11 days	31 days	Monthly or once every 3 months
Galcanezumab	Ligand	EM and CM prevention	Subcutaneous	120 mg*	7–14 days	27 days	Monthly
Eptinezumab	Ligand	EM and CM prevention	Intravenous	100 or 300 mg	End of infusion (30 min)	27 days	Once every 3 months
Small molecules (gepants)							
Atogepant	Receptor	EM and CM prevention	Oral	10, 30, or 60 mg	1–2 h	~11 h	Once daily
Rimegepant	Receptor	EM prevention and acute treatment	Oral	75 mg	1·5 h	~11 h	Alternate day or prn, up to 75 mg
Ubrogepant	Receptor	Acute treatment	Oral	50 or 100 mg	1·5 h	5–7 h	prn, up to 200 mg
Zavegepant	Receptor	Acute treatment	Nasal spray	10 mg	30 min	5–8 h	prn, up to 10 mg

CM=chronic migraine. CGRP=calcitonin gene-related peptide. EM=episodic migraine. prn=pro re nata. T_{max}=time to peak drug concentration. *A loading dose of 240 mg at the first month is administered.

Table 1: **Armamentarium of the available drugs targeting CGRP**

αCGRP and βCGRP differ by three amino acids only, and share similar biological effects.[14,15]

Gepants are small-molecule competitive CGRP receptor antagonists at the canonical CGRP receptor. Antagonism of the amylin-1 receptor (a second potent CGRP receptor) might also contribute to gepants' effect.[16] Intravenous olcegepant was the first gepant that proved effective in the acute treatment of migraine more than two decades ago,[17] but further clinical development of gepants was halted because of hepatotoxicity and formulation issues.[18,19] These hindrances led to the development of a novel class of drugs—monoclonal antibodies (mAbs) directed against CGRP acting as CGRP scavengers or directed against the CGRP receptor acting as a CGRP receptor antagonist. Currently, there are three mAbs that bind to CGRP (eptinezumab, fremanezumab, and galcanezumab) and one mAb that binds to the CGRP receptor (erenumab). These agents are administered subcutaneously, except for eptinezumab which is administered intravenously. As the plasma half-life of the mAbs is about 1 month and because of the long time to peak drug concentration (T_{max}) after subcutaneous administration, these drugs are intended for the prophylactic treatment of migraine. Eptinezumab, given its rapid availability after intravenous injection, does have an acute effect as substantiated by one randomised controlled trial (RCT).[20]

Liver toxicity associated with first-generation gepants was thought to not be related to CGRP receptor antagonism but rather to the chemical drug structure itself after which multiple lines of candidate drugs with molecular modifications were explored.[21] Gepants are taken orally, except for the first representative of the third-generation gepants, zavegepant, which is administered intranasally. However, whether intranasal delivery of zavegepant offers any pharmacokinetic advantages compared with the oral administration has not been comfirmed. Indeed, intranasal delivery might have a local effect on the trigeminovascular system as the nasal cavity is lined with trigeminal nerve endings.[22]

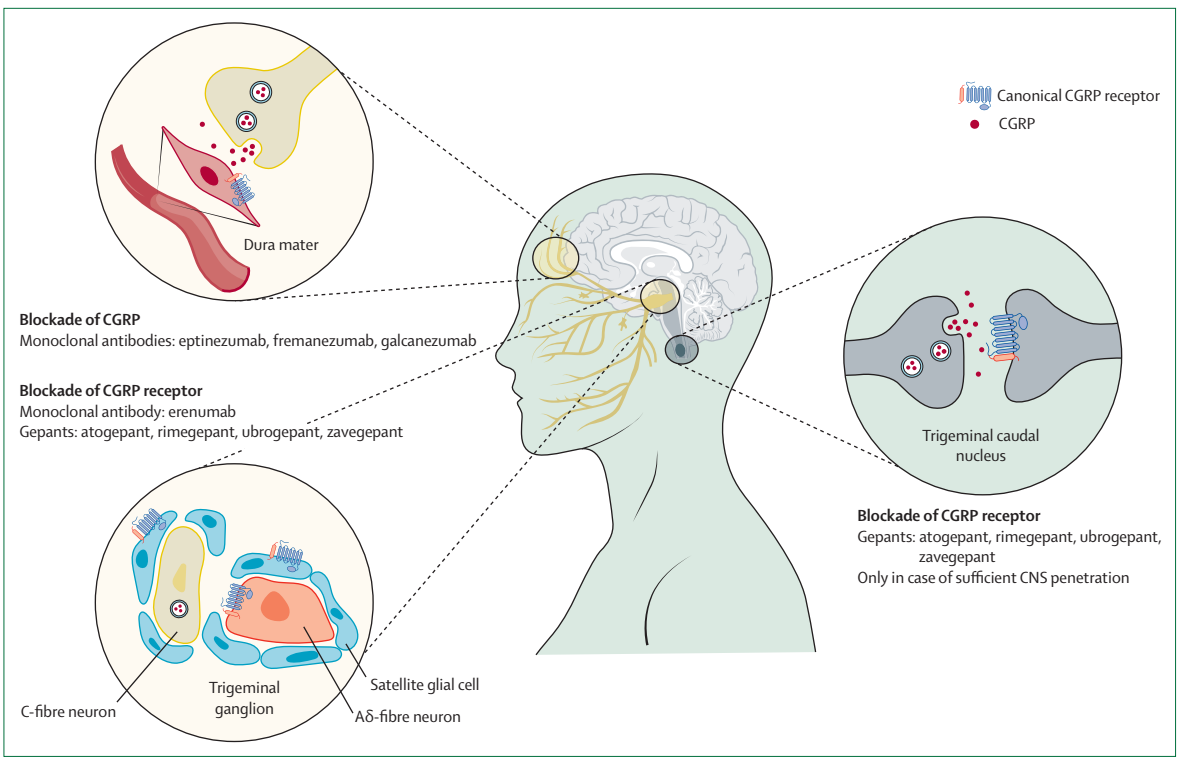

Figure 2: **Overview of drugs acting through blockade of CGRP or its receptor with their three possible sites of action**
In the trigeminal ganglion, CGRP or its receptor is expressed in unmyelinated C-fibre neurons and myelinated Aδ-neurons, both involved in nociception. CGRP released locally might also activate satellite glial cells contributing to peripheral sensitisation. In the dura mater, CGRP released from peripheral C-fibre terminals acts on vascular smooth muscle cells of meningeal arteries. Both CGRP-(R-)mAbs and gepants act at both sites (depicted in yellow). CGRP released from central terminals of C-fibres acts on second order neurons in the trigeminal caudal nucleus. Here only gepants possibly have an effect because of the restricted brain access of the CGRP-(R-)mAbs. This site is depicted in grey as even for gepants it needs to be elucidated whether they exert an effect at therapeutic doses. CGRP=calcitonin gene-related peptide. CGRP-(R-)mAbs=monoclonal antibodies directed against CGRP or the CGRP receptor.

Gepants are relatively small molecules (<1 kDa) compared with the CGRP pathway mAbs (~150 kDa), which are largely excluded from the brain by the blood–brain barrier. The CGRP receptors outside the blood–brain barrier are, however, also believed to be the main target of gepants, with only low central CGRP receptor occupancy in patients with migraine with clinically used doses. Whether enhanced central CGRP receptor antagonism with higher doses would provide an additional therapeutic benefit is not known.[23,24]

The mAbs directed against CGRP or the CGRP receptor (CGRP-(R-)mAbs) and gepants all inhibit the same pathway (figure 2). It is nevertheless tempting to speculate what the clinical implications of these agents' different mechanisms of action could be. A mAb acting at the CGRP receptor is likely to reach a binding equilibrium earlier than ligand-directed mAbs, because CGRP receptors are constitutively present and CGRP is released instantaneously. For the ligand-binding mAbs, it has not been confirmed whether subtle differences in their binding potencies to αCGRP and βCGRP exist, but it seems likely that they all have affinity for both isoforms.[25,26] However, such information is based on data collected in the state of equilibrium, which is unlikely to be reached in the clinical context as CGRP is instantaneously released. For the CGRP receptor-binding drugs (erenumab and gepants), it is important to consider whether there are receptors other than the canonical CGRP receptor, to which CGRP might also bind. The amylin type 1 receptor,[27] but recently also the adrenomedullin 1 receptor,[28] have been suggested as alternative modulators for the effects of CGRP. On the other hand, for the ligand-binding mAbs, peptides other than CGRP might also bind to the CGRP receptor. These additional receptors or peptides might represent a disadvantage in the context of non-response to the CGRP-inhibiting drugs. However, parallel mechanisms that can mediate a CGRP-like effect might also offer an advantage in view of cardiovascular safety, as CGRP is a rescue molecule in the cardiovascular system.

CGRP-(R-)mAbs

Response rates: from late responders to super-responders

All four CGRP-(R-)mAbs are approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for migraine prophylaxis based on pivotal study programmes in both episodic migraine (<15 headache days per month) and chronic migraine (headache occurring

on ≥15 days per month for more than 3 months, which, on at least 8 days per month has the features of migraine). Overall, approximately half of the patients achieved a 50% or greater reduction in monthly migraine days (MMDs).[29,30] Onset of action occurs within the first week of treatment, for eptinezumab even after 2 h when administered during a migraine crisis.[20] Differences in eligibility criteria, used endpoints, assessment periods, and different placebo responses due to the route of administration render a direct comparison of CGRP-(R-)mAbs almost impossible.[31] Along with the reduction in migraine days, a multitude of primary and secondary endpoints were reached, including an improvement in quality of life and a reduced migraine burden. Subgroup analyses in patients with medication overuse have been done for all CGRP-(R-)mAbs and showed clear benefit. A dedicated randomised placebo-controlled trial[32] with erenumab in patients with non-opioid chronic migraine with medication overuse achieved remission within 6 months. For the timing of treatment efficacy assessment after initiation, a 3-month period is usually maintained and recommended by the European Headache Federation (EHF), although a swifter response can be seen in a large subset of patients.[33] However, late responders exist as shown by the only 6-month placebo-controlled trial[34] in patients with episodic migraine and chronic migraine, in which more than one-third of initial non-responders became responders after their second eptinezumab infusion. At the other end of the spectrum, a smaller but non-negligible number of participants in phase 3 clinical trials had an at least 75% or even up to 100% MMD reduction (so called super-responders). A 100% response of 3 up to 6 consecutive months was rare across all trials.

Efficacy in patients with non-successful previous treatment attempts

For all four available CGRP-(R-)mAbs, dedicated clinical trials[35–38] have been done in patients with two to four non-successful previous treatment attempts. Although the LIBERTY study with erenumab 140 mg focused on episodic migraine, the three other studies included patients with episodic migraine and chronic migraine.[35–38] The primary endpoint was met in all four studies and so were numerous secondary endpoints showing that CGRP-(R-)mAbs are valuable therapeutic options for patients who did not respond to multiple previous attempted treatments. How the number of previous preventive treatment non-responses to non-specific oral preventives predicts the conditional probability for a response to the next non-specific oral preventive or the first CGRP-(R-)mAb is unknown.

Evidence from real-world studies

The effectiveness of CGRP-(R-)mAbs was shown in several large real-world studies with erenumab, galcanezumab, and fremanezumab with 50% responder rates ranging from 56% to 77%.[39-44] For eptinezumab, which was approved later and is administered intravenously which requires access to day clinic facilities, the small REVIEW study[45] has shown results in line with the other CGRP-(R-)mAbs. In general, real-world data for all CGRP-(R-)mAbs reveal higher MMD reductions and higher 50% responder rates compared with RCTs. As for the super-responders, a review[46] encompassing 61 real-world studies involving more than 18 000 patients revealed that between 20·2% and 73·8% of patients on a CGRP-(R-)mAb obtained a 75% response at week 12 after treatment initiation, which is a substantially higher rate than the results obtained in RCTs.

Short-term and long-term disease-modifying or wearing-off effects

In clinical practice, some patients mention the subjective decline of efficacy towards the end of the treatment interval. No formal evidence for a wearing-off effect has however been shown as demonstrated in a single centre real-world study[47] with erenumab and fremanezumab. Placebo-controlled trials longer than 6 months have not been done mostly because of logistical and ethical reasons. Therefore, it is difficult to make definitive statements on either a disease-modifying or wearing-off effect (tachyphylaxis) of CGRP-(R-)mAbs. Although long-term open-label studies have been published up to 5 years, little information is provided for up to half of the patients who are lost to follow-up.[48] Moreover, dropout rates up to 60% have been described as seen in a 1-year real-world chronic migraine study in which a sustained at least 30% MMD reduction at all timepoints was only achieved by 34% of patients, suggesting the absence of a true disease-modifying effect.[49]

Anti-drug antibodies

A treatment with any therapeutic protein can possibly lead to the induction of an immune response, resulting in the formation of anti-drug antibodies with or without neutralising antibodies, the latter possibly reducing the therapeutic protein's efficacy. Depending on the type and magnitude, this immunogenic response might affect treatment efficacy and lead to adverse effects including hypersensitivity or anaphylactic reactions. Although erenumab is a fully human mAb and the mAbs targeting the CGRP ligand have been humanised to varying degrees, they all have the capacity to provoke immune reactions. Low but variable titres of treatment-emergent anti-drug antibodies have been observed in a low number of patients for all CGRP-(R-)mAbs; however, these antibodies do not affect efficacy, safety, or tolerability of the treatment.[50] In some patients, these antibodies seemed to be transient.[51] Testing for neutralising antibodies in clinical practice is currently not recommended.[33]

Discontinuation of and switching between CGRP-(R-)mAbs

Conventional oral preventive drugs are usually administered for 6–12 months to minimise side-effects and to

reconsider the underlying disease burden given the natural fluctuating disease course of migraine.[52] Moreover, a possible carryover effect of the prophylactic agent after discontinuation cannot be excluded based on scarce evidence.[52,53] CGRP-(R-)mAbs have partly challenged this classic treatment strategy, mostly due to their excellent tolerability. Patients are more inclined to continue a well tolerated treatment. Real-world studies consistently showed a deterioration in more than half of the patients about 3 months after discontinuation of CGRP-(R-)mAbs.[54,55] However, no blinded withdrawal studies similar to a discontinuation study with topiramate have been done to determine when to stop treatment in patients who have a good long-term response to a CGRP-(R-)mAb.[55] In the absence of these trials, it still seems good practice to at least discuss a treatment pause with patients. The European Headache Federation recommends a pause after 12–18 months and a subsequent re-initiation of treatment in patients who deteriorate.[33]

Several open-label studies have shown that switching from one CGRP-(R-)mAb to another might be useful; however, no formal guidelines can be made in the absence of randomised trials. Intuitively, it would make sense to switch towards a mAb targeting the ligand when erenumab did not work or vice versa. However, this approach has not been properly tested. Although, as outlined by the EHF, switching might represent the best therapeutic option for an individual patient, the chance of success does seem to decline with the number of trials. This result was shown by one report where the effectiveness of eptinezumab was maintained but clearly reduced in patients with resistant migraine who have not responded to at least four approved non-specific prophylactic migraine drugs next to other CGRP-(R-)mAbs up to all three other mAbs.[56]

Gepants

Ubrogepant

Ubrogepant was the first gepant to receive FDA approval in 2019, for the acute treatment of migraine in adults. This drug is primarily eliminated (87%) via the hepatic route with a minor contribution by renal elimination;[57] therefore this agent should be avoided in end-stage renal disease. Two pivotal RCTs in moderate to severe migraine showed the effect of ubrogepant 50 mg or 100 mg compared with placebo on the coprimary endpoints of freedom from pain and the absence of most bothersome symptom at 2 h after dosing.[58,59] The therapeutic gain compared with placebo on 2 h pain-free rates was, however, modest (less than 10%). A post hoc analysis of pooled trial data showed that the efficacy was not different between triptan responders and triptan-insufficient responders.[60,61] Ubrogepant administered during the prodromal phase of migraine was also shown to be effective.[62] Pooled data showed that the most common side-effects were nausea (up to 4%) and somnolence (up to 3%).[57] As for the combination with analgesics, the co-administration of ubrogepant on one hand and sumatriptan, paracetamol or naproxen on the other hand was found to be well tolerated without a clinically meaningful alteration in pharmacokinetics for either drug.[63,64]

Atogepant

Atogepant was tested for migraine prevention at different doses (10, 30, or 60 mg, two times 30 mg, and two times 60 mg per day). The drug is approved by the FDA and EMA for the prevention of episodic migraine and chronic migraine. Elimination of atogepant is primarily hepatic and renal clearance is a minor additional route; therefore a dose reduction to 10 mg is recommended in case of end-stage renal disease.[65] No clinically relevant pharmacokinetic interactions were observed between atogepant and sumatriptan in a small study in healthy volunteers.[66] A meta-analysis[67] of four RCTs concluded that atogepant is effective for the prevention of both episodic migraine and chronic migraine and is well tolerated. Atogepant was also shown to be efficacious in patients with chronic migraine and medication overuse.[68] Episodic migraine prevention with atogepant 60 mg was tested in a population that had previously not responded to two to four classes of conventional oral preventive treatments where clinically relevant MMD reductions compared with placebo were observed.[69]

Rimegepant

Rimegepant is a dual agent as it is approved by the FDA and EMA for both acute treatment and episodic migraine prevention. Rimegepant is available as an orally disintegrating tablet, created to improve patient convenience (allowing administration without liquids) and response by optimising the absorption rate with a lower and less variable T_{max}.[70] Rimegepant's elimination is 96% hepatic. In four pivotal phase 3 trials, rimegepant was more effective than placebo at relieving pain and the most bothersome symptom for the acute treatment of migraine.[70,71] The most common adverse event was nausea (up to 2%). Based on a post hoc analysis of pooled results from three phase 3 RCTs, rimegepant was shown to be effective for acute treatment of migraine in adults with a history of insufficient response to triptans.[72] Rimegepant was later also shown to be safe and effective for preventing migraine in a phase 2/3 trial including 747 patients with both episodic migraine and a small sample of patients with chronic migraine.[73]

Zavegepant

Zavegepant is the only nasal spray among the currently available gepants. The drug is FDA approved for the acute treatment of migraine. Zavegepant is primarily metabolised through the liver; the renal route is a minor route of elimination. Therefore, this medication should not be used in case of severe renal impairment. Co-administration of intranasal decongestants should be avoided as it theoretically might decrease absorption.

Zavegepant offers an alternative treatment option for people who cannot take oral medications due to nausea or vomiting.[74] As previously mentioned, the added value of the intranasal administration compared with the oral formulation remains a matter of debate.[22] The nasal formulation of sumatriptan might offer some pharmacokinetic advances but the gut remains, however, the primary site of absorption.[75] In a phase 2/3 trial, zavegepant nasal spray was shown to be effective for acute treatment of migraine.[76] Similar results were obtained in a phase 3 RCT with zavegepant 10 mg nasal spray. A therapeutic gain of close to 10% was observed on the co-primary endpoints of pain freedom and freedom of most bothersome symptom 2 h after treatment.[77] No data are available on the efficacy in triptan non-responders. The most common adverse events were dysgeusia (up to 18%), nasal discomfort, nausea, and vomiting.

Positioning of gepants in the acute treatment landscape

No trial comparing any gepant to any other acute treatment is currently available. One rimegepant phase 2b trial showed a numerically higher therapeutic gain for sumatriptan 100 mg (tested in one of the trial arms), although the trial was not powered for this specific comparison.[78] Indirect comparisons, however, assessing respective 2 h pain-free rates suggest that gepants have only moderate efficacy, most probably substantially lower than triptans and in line with the efficacy of paracetamol (figure 3).[86,87] Notwithstanding, in acute treatment there is no one-size-fits-all treatment strategy, and multiple attempts are often necessary to determine the optimal treatment regimen for every individual. Switching within and between drug classes, use of a higher dose or combination therapy and advising patients to treat the headache early can all improve patient outcomes. Due to cost issues, gepants will most probably stay reserved for patients with a historical insufficient response to triptans, for whom both rimegepant and ubrogepant have proven to be effective.[88] Another targeted group might be patients with contraindications to other acute treatments. However, clinical practice has shown that for triptans this subset of patients might be smaller than expected due to the fact that these drugs seem safer from a cardiovascular point of view than traditionally thought.[89] Finally, since all clinical trials with gepants were single attack trials, data concerning the consistency of effect across multiple migraine crises are currently unavailable.

Open questions concerning CGRP-based therapies for headache prevention

Predictors of response

Biomarkers that predict efficacy or side-effects with an acceptable accuracy and are useful in clinical practice have yet to be identified. The standard trial-and-error approach for preventive treatments is mostly maintained even in the CGRP era, in which the choice for any preventive treatment is based mostly on patient comorbidities, preferences, and insurance coverage. Several attempts at identifying prognostic markers have been undertaken. Whereas some negative prognostic markers, such as daily headaches, psychiatric comorbidities, allodynia, or a high number of unsuccessful previous preventive treatment trials, refer to the refractory character of migraine, other phenotypic indicators including obesity might be related to pharmacokinetic properties.[90-92] Whereas genetic variation could possibly explain part of the response, there is only little evidence of specific allelic variants to be involved in the clinical response to erenumab.[93] Overall, the need to tailor migraine preventive treatments with a precise and individualised approach remains unmet.

Indirect and direct comparative trials versus other preventive agents

Whereas multiple indirect comparisons have shown a slight benefit of drugs targeting the CGRP pathway compared with conventional migraine prophylactics including onabotulinumtoxinA, only one double-blind RCT comparing a CGRP-(R-)mAb with a non-CGRP oral prophylactic has been done.[30,94–96] The HER-MES trial[97] was a multicentre randomised, controlled, double-blind, double-dummy 6 months study in 777 patients with migraine. Erenumab was shown to be vastly superior compared with topiramate concerning the primary endpoint of treatment discontinuation due to adverse events. The 50% responder rate and the quality of life assessments also showed a superiority of erenumab. The APPRAISE open-label study showed that in the episodic

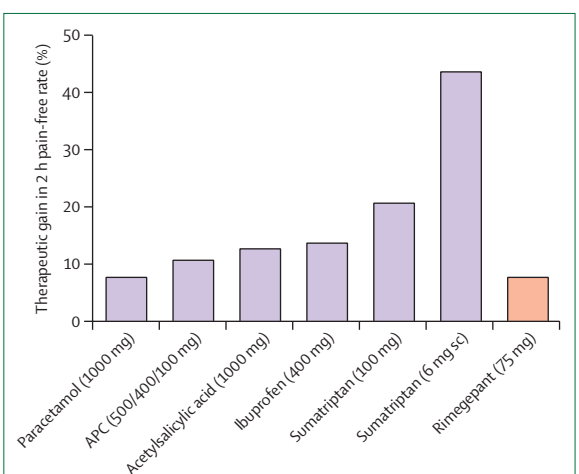

Figure 3: **Indirect comparison of selected analgesics concerning the 2 h pain-free rate**

Results for verum minus placebo (therapeutic gain). The number of randomised trials of which results were pooled is: two for paracetamol,[79] six for APC,[80] five for acetylsalicylic acid,[81] six for ibuprofen,[82] 16 for oral sumatriptan,[83] 13 for sumatriptan,[84] and four for rimegepant.[85] Although the same endpoint is used, trials differ both from eligibility criteria and treatment protocol hampering a direct comparison. A list of individual trials can be found in the appendix. APC=acetylsalicylic acid, paracetamol, and caffeine. sc=subcutaneous.

See **Online** for appendix

	Agent	Condition
Adults		
Acute		
NCT05509400	Rimegepant	Triptan unsuitable EM
NCT06221111	Rimegepant	Irritable bowel syndrome
NCT06473597	Rimegepant *vs* rizatriptan	Adult migraine patients
NCT06241313	Atogepant	EM
NCT06103734	Zavegepant (consistency)	Migraine
Preventive		
NCT04804033	Zavegepant	CM
NCT03941834	Rimegepant	Refractory trigeminal neuralgia
NCT05518123	Rimegepant	Treatment-resistant EM
NCT06417775	Ubrogepant (for 7 days starting 3 days before menstruation)	Menstrual migraine
NCT05748483	Atogepant *vs* topiramate	EM and CM
NCT04098250	Erenumab	Post-traumatic headache
NCT05684692	Erenumab	Schwannomatosis
NCT04417361	Galcanezumab	Vestibular migraine
NCT05452239	Eptinezumab	Medication overuse headache
NCT05937152	Eptinezumab	Diabetic polyneuropathy
Children and adolescents		
Acute		
NCT05125302	Ubrogepant	EM
NCT04649242	Rimegepant	EM
Preventive		
NCT05156398	Rimegepant	EM
NCT05711394	Atogepant	EM
NCT03832998	Erenumab	EM
NCT03836040	Erenumab	CM
NCT04464707	Fremanezumab	CM
NCT04616326	Galcanezumab	Adolescents with CM
NCT03432286	Galcanezumab	EM
NCT05897320	Eptinezumab	EM
NCT04965675	Eptinezumab	Adolescents with CM

Unless otherwise specified the trial is placebo-controlled. EM=episodic migraine. CM=chronic migraine.

Table 2: **Currently recruiting and planned blinded clinical trials with drugs targeting the calcitonin gene-related peptide pathway**

migraine cohort significantly more patients on erenumab had at least 50% MMD reduction than patients on non-specific oral prophylactics.[98] The CHALLENGE-MIG trial[99] compared galcanezumab with rimegepant in mostly preventive treatment-naive patients with episodic migraine in an RCT with a double-blind, double-dummy design. The trial did not show any differences between both study groups for the primary endpoint (50% responder rate). As for comparisons within the class of CGRP-(R-)mAbs, no blinded comparative studies have been done. One retrospective real-world study showed a significantly higher proportion of super-responders with CGRP-mAbs compared with erenumab.[100] A meta-analysis of observational cohort studies showed a higher 50% responder rate with galcanezumab and fremanezumab compared with erenumab.[101] Although these differences might reflect a true neurobiological difference in efficacy, further evidence is needed to draw formal conclusions on this matter.

CGRP-based therapy for non-migraine conditions

Among the CGRP-(R-)mAbs only galcanezumab (300 mg) has received FDA approval for the prophylaxis of episodic cluster headache; however, the drug is not approved by the EMA for this indication.[102] In a controlled, randomised, blinded study[103] in patients with episodic cluster headache, galcanezumab induced a significant reduction of 3·5 weekly attacks compared with placebo across weeks 1–3. A real-world observation study showed that 83% of patients with episodic cluster headache achieved at least 50% reduction of weekly attacks after a single dose of 240 mg galcanezumab.[104] Two other RCTs on episodic cluster headache, however, did not meet the primary endpoint (eptinezumab) or were stopped prematurely after futility analysis (fremanezumab). In chronic cluster headache, two randomised double-blind studies have been performed with galcanezumab and fremanezumab, both showing no benefit (the latter also stopped prematurely).[105] In contrast to these negative trials, some real-world observations illustrated a benefit of CGRP-(R-)mAbs in small cohorts of patients with chronic cluster headache.[106,107] These less promising results might reflect the lower ictal increase in CGRP blood concentrations in cluster headache compared with migraine.[108] As for other disorders one negative placebo-controlled, double-blind, randomised trial[109] with erenumab was published on trigeminal neuralgia, whereas another trial with fremanezumab in post-traumatic headache was negative as well.[110] Further trials in headache next to other entities are awaited (table 2).

Tolerability and safety profile

Before CGRP-(R-)mAbs and gepants were widely used and real-world evidence was collected, some side-effects, such as constipation and increased blood pressure, had been predicted based on knowledge on the mechanisms of action of CGRP provided by preclinical experimental models.[90,111–114] Whereas some of these side-effects indeed seem to occur in real life (figure 4), the adverse event profiles for this drug class seem very favourable. Both clinical trials and real-world studies have a discontinuation rate due to adverse events approaching that of placebo in RCTs.[30] The rate of adverse events seems much lower for CGRP-targeted drugs than for classic migraine preventive drugs such as valproate, amitriptyline, and topiramate.[94]

The biggest concern during the development of the second-generation and third-generation gepants was

most probably liver toxicity, as that was the issue with the first-generation gepants. Although some reassuring data have been gathered, patients with even slightly elevated liver function tests were excluded from most if not all RCTs with gepants. A quantitative toxicology model of drug-induced liver injury predicted that each of the four currently approved gepants would be significantly less likely to cause liver injury than telcagepant.[120] However, further long-term real-world data, also in more challenging patient profiles, are highly needed. As for now, manufacturers recommend avoiding use in patients with severe hepatic impairment.[115]

In contrast to triptans, gepants do not induce vasoconstriction, neither on cranial or on coronary arteries.[121] Whereas reassuring data are emerging regarding the safety of gepants in patients with migraine and high cardiovascular risk, more long-term studies are needed to firmly evaluate this issue.[121-124] Indeed, since CGRP has a physiological role as an ischaemia safeguard, worsening of coincidental ischaemic events is possible.[112] In mice cerebral ischaemia models, olcegepant, and rimegepant increased the infarct risk and size and worsened the outcome.[125] Clinical trials with gepants were not enriched with patients with cardiovascular disease; patients with a clinically significant vascular event within the last 6 months were even largely excluded from all RCTs.

Medication-overuse headache, defined as a headache occurring on 15 or more days per month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute headache medication, has not been observed with gepants in real-world studies lasting up to 1 year.[126] This finding is in line with evidence from preclinical rat models.[127] However, caution is warranted as this is a long-term therapy for a substantial subset of patients.

Due to scarcity of data and as a precautionary principle, gepants and CGRP-(R-)mAbs are contraindicated during pregnancy. Given the substantially shorter half-life of gepants versus mAbs, gepants might be preferred for migraine prevention by women who are planning a pregnancy.[128] In clinical practice, women might be counselled to stop the use of gepants a week before attempting pregnancy. For CGRP-(R-)mAbs the advice is to stop their use 6 months before attempting pregnancy.[33] For breastfeeding, concentrations of gepants in breastmilk are low to very low.[119] As all CGRP-(R-)mAbs are large proteins, their amount in milk is likely to be very low and is possibly digested in the infant's gastrointestinal tract with minimal absorption, however, caution is warranted.

One of the potential side-effects that has been observed only in real-world studies, and a topic of ongoing debate, is the occurrence of increased blood pressure after the use of CGRP-(R-)mAbs. CGRP might have a protective role in the development of hypertension.[129] Although some studies did report an increased blood pressure,[116] other studies reported no increase after the initiation of CGRP-(R-)mAbs.[130–132] Possible reasons for these discrepancies, such as patient population, mode of blood pressure measurements, and time of follow-up, should be elucidated in future studies.

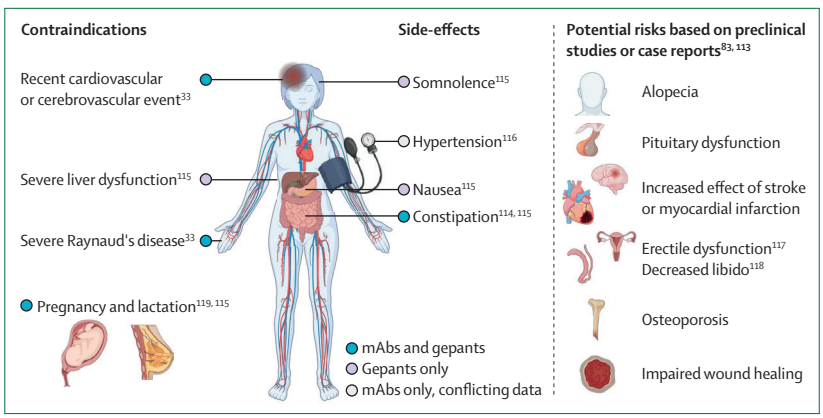

Figure 4: **Safety profile of drugs targeting the CGRP pathway**
CGRP=calcitonin gene-related peptide. mAbs=monoclonal antibodies.

For more on **Drugs and lactation database** see https://www.ncbi.nlm.nih.gov/books/NBK501922/#IX-E

Global access to treatment

Socioeconomic and insurance status next to geographical disparities and cultural misconceptions contribute to the inequities that exist within the health-care system when treating headache disorders.[133,134] Although both the EHF and the American Headache Society recommend CGRP-targeted therapies as a first-line treatment option, very few countries have incorporated this strategy, mostly due to cost issues and ensuing reimbursement policies, insurance coverage limitations, and substantial out-of-pocket costs. On a global level, most of the world does even not have access to this drug class at this stage.[135] Major barriers to accessing a modernised treatment regimen remain for a substantial group, if not most patients.[136]

From a scientific perspective, there is a known absence of representativity and diversity of the patient population participating in clinical research.[91] The majority of trials do not even mention the participant's race, and when mentioned, in most cases no distinction is made beyond white people versus people of other races with the vast majority of patient samples being designated as white.[137] As such, there is a large unmet need for safety and efficacy data broken down by race, considering the intersectionality between various factors besides race including sex, gender, socioeconomic status, and age.[138] The neurological community has a responsibility to deliver equitable care to all and address the disparities both from a clinical and research aspect.[134,136]

Future directions and challenges

One of the major achievements of the group of CGRP-targeted drugs is to have blurred the traditional dividing line marking acute and preventive treatment strategies. The gepants have a possible dual capacity to both treat

and prevent; however, this property has only been formally proven for rimegepant. Furthermore, they seem to have no association with medication overuse headache, their tolerability profile seems favourable, and they have a swift preventive effect. Next to preliminary data on the efficacy of gepants in the prodromal phase, treatment regimens that transcend traditional categories of acute and preventive treatment could become more popular. One treatment regimen already used anecdotally is the so-called situational or short-term prevention or mini prophylaxis where patients treat before symptoms develop in situations of increased headache probability (eg, the menstrual period).[139,140] Although this approach might be tempting, its evidence is at this stage purely anecdotal but at least one RCT with ubrogepant in menstrual migraine is currently ongoing (table 2). Furthermore, it offers the potential disadvantage of unnecessary use of drugs for anticipated migraine attacks that would not have developed even in the absence of treatment, leading to potential adverse events and adding to direct medical costs.[141] Another open and very hard to tackle question is whether the as needed use of gepants could have a preventive effect in migraine as suggested by one 52-week open-label study with rimegepant.[142]

Given their possible role both as an acute and a preventive treatment the logic next step would be to combine CGRP-targeted therapies, either one acute and one preventive treatment or even more than one preventive treatment. Very few trials have looked at these combination treatments. Three small studies and one bigger study evaluated the combined use of CGRP-(R-)mAbs as a preventive agent with ubrogepant or rimegepant as acute migraine treatment, and the combination was found to be safe and well tolerated.[143–146] Two studies[147,148] assessed the combined use of atogepant and ubrogepant yielding similar findings without meaningful pharmacokinetic changes. From a mechanistic perspective, it is conceivable that drugs directed at either CGRP or its receptor might have additive effects,[112] but also drugs that are both directed at the CGRP receptor might have mechanistically additive pharmacological actions.[149] Further large-scale research is surely needed to assess the safety and long-term consequences of dual CGRP suppression.

Finally, promising phase 2 results were recently published with a mAb targeting pituitary adenylate cyclase-activating polypeptide, a new avenue for migraine prophylaxis.[150] Although further phase 3 trials are needed before this new class of drugs can enter the migraine market, it is fascinating to speculate on how this new treatment could eventually add to already existing treatments such as drugs targeting the CGRP pathway.

Conclusions

Although non-specific acute and preventive drugs remain the mainstay of migraine treatment on a global scale, drugs targeting the CGRP pathway represent a mechanism-specific approach to both acute and preventive migraine treatment with a proven efficacy and an excellent safety and tolerability profile. Not only has this class of drugs, because of translational neurobiology spanning several decades, increased the quality of life of many migraine patients, they have also highlighted migraine as a neurovascular disorder and as such helped to reduce the stigma associated with migraine. The dual role of gepants both as an acute and preventive treatment might allow for a more customised treatment approach. Nevertheless, the exact place of drugs targeting the CGRP pathway in the treatment armamentarium remains a matter of debate, mostly due to cost issues. However, efficacy questions also remain, mostly concerning gepants as an acute treatment. Given the ubiquity of CGRP receptors in humans, well designed safety studies remain an important research target.

Contributors

JV, KP, UR, and AMVDB contributed to the literature search, writing of the review, creation of tables and figures, and revision in response to internal review. All authors approved the final manuscript.

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