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Review

Calcitonin Gene-Related Peptide (CGRP)-Targeted Treatments—New Therapeutic Technologies for Migraine

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Abstract: Migraine is ranked as the third most common disorder worldwide and is considered one of the most disabling neurological conditions. Its treatment has mostly relied on medications that were non-specifically developed for migraine, thus accompanied by low adherence, inadequate effectiveness and intolerable side effects. These recent years have seen the development of new migraine-specific therapies targeting the calcitonin gene-related peptide (CGRP) and its receptor. These newly developed therapies, the small molecule gepants targeting the CGRP receptor and the anti-CGRP monoclonal antibodies (mAbs), are currently available in the market and FDA-approved for migraine treatment. As they are migraine-specific therapies, they largely expand their use to patients that could not tolerate previous treatments, either for systemic contraindications or drug-to-drug interactions, or where any other available option was not efficacious. Randomized controlled trials have demonstrated the efficacy of these new medications, with minor adverse effects reported (most commonly nausea and constipation). This article will review the mechanism of action, indications, contraindications, and tolerability profile of gepants and anti-CGRP mAbs, by summarizing the available literature. Finally, avenues for future research will be identified, so that upcoming controlled studies may be designed to fill such gaps.

Keywords: calcitonin gene-related peptide; migraine; gepants; monoclonal autoantibodies; preventive treatments

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1. Introduction

Migraine is a complex neurological disorder classified by the latest International Classification of Headache Disorders (ICHD-3) as a primary headache [1]. A diagnosis of migraine can be confirmed based on five or more attacks, in the presence of a headache lasting 4–72 h that is described as a pulsating, unilateral, moderate to severe pain [1]. Nausea and/or vomiting or photophobia and phonophobia should accompany the headache. In approximately one third of the cases, the migraine is preceded by a transient complex of unilateral, fully-reversible neurological symptoms (visual, sensory, speech, motor, brainstem or retinal) of the duration of 5–60 min [1]. This is called aura, and, according to its presence, the migraine is classified as migraine with aura or migraine without aura. Based on the number of monthly headache days (MHDs), it is defined as episodic when MHDs are fewer than 15 or chronic when MHDs are 15 or more for 3 months, with at least eight of them classifiable as monthly migraine days (MMDs) [1].

Migraine affects approximately 15% of the total population [2], and it manifests more often in females (18% in women vs. 6% in men in US adults) [3]. It is ranked as the third most prevalent disorder worldwide [4] and the third cause of disability in individuals under 50 years old [5–7]. However, despite being relatively common, it is still underdiagnosed and undertreated [8]. Indeed, only 29.4% of patients seek consultation for their chief complaint of migraine, and less than 20% receive a correct diagnosis [9]. Finally, only about 12% of those receive a treatment [9]. Traditionally, migraine treatments are divided into acute or

preventive, meant to abort headache attacks and migraine associated symptoms and to reduce severity and frequency of the attacks, respectively. Several are the reasons why the majority of patients do not seek consultation for their migraine, including uninsured or underinsured therapies [10,11], long-lasting and burdensome treatments, lack of specificity of older available drugs that are not devoid of systemic side effects, lack of access to specialty providers [11], and low patient adherence and tolerability [12], among others.

1.1. Acute Treatment

An acute treatment should be offered to all those patients with a physician-confirmed diagnosis of migraine. Acute treatments consist of pharmacological and/or non-pharmacological therapies. It should start from patient education (i.e., early identification of triggers and attacks) and lifestyle modification (such as proper diet, sufficient hydration, stress management, sleep hygiene, regular physical exercise) [13,14]. Guidelines stress on the importance of maintaining a migraine diary, for further personalization and assessment of the efficacy of the medication regimen [15]. Acute treatment has relied on non-migraine specific drugs (nonsteroidal anti-inflammatory drugs (NSAIDS), acetaminophen, nonopioid analgesic or caffeinated analgesic combinations) and on migraine-specific medications (triptans, ergotamine derivates, selective serotonin (5-HT_{1F}) receptor agonist such as ditans) [14]. Intravenous (IV) magnesium and antiemetic agents complete the list of probably effective acute treatments [14].

The accessibility to over-the-counter analgesics and a frequent use of acute medications for other indications other than headaches have been linked to the increased risk of developing medication overuse headaches (MOH). Patients with migraine are prone to overuse medication to prevent or manage headaches. The repeated use of acute medications on more than 10 or 15 days per month for more than 3 months, according to the class of drug ([16] for review), has been associated with increased frequency and intensity of headache attacks. In order to prevent MOH, awareness among patients, the public, physicians and health-workers (*e.g.*, pharmacists) should be promoted [17].

1.2. Preventive Treatment

The lack of specificity of current medications is particularly noticeable in those prescribed as prophylaxis (i.e., preventive treatment). A preventive treatment should be offered not only to individuals suffering from chronic migraine but should also be proposed to those patients with moderate or severe disability in the presence of few MMDs (from 3 to 6 days per month or more) [14,18]. Other criteria to select preventive therapies include elevated risk of MOH, ineffective or contraindicated acute medications, patient preference and uncommon subtypes of migraine (i.e., hemiplegic migraine, brainstem migraine, prolonged aura and/or migrainous infarction) [14].

So far, the available preventive treatments were not designed specifically for migraine (e.g., β-blockers, antidepressants and antiepileptics) [19], thus limiting their use due to contraindications and side effects [14]. Together with an intrinsic low effectiveness and tolerability of these therapies, this may partly explain why only 3–13% of individuals with migraine are adherent to preventive therapies [18,20], a percentage that tends to decrease over time [21]. Nevertheless, efforts should be made to educate and direct our patients towards a preventive strategy that may help limit the incidence of MOH.

Recently, the biomedical research has assisted with the spreading of new therapies specifically developed to address a unique target, i.e., the calcitonin gene-related peptide (CGRP) and its receptor [14,22].

2. CGRP and CGRP Receptor

CGRP is a 37-amino acid peptide existing in two isoforms similar for structures and role in terms of vasodilation activity, α and β. CGRP is mainly found in unmyelinated Aδ and C sensory nerve fibers, and it is widely distributed in bodily non-neuronal tissues and in the central nervous system [23]. As such, it produces a variety of biological effects on

the myocardium, skin, endocrine and gastrointestinal systems, and skeletal and smooth muscle [24]. CGRP acts as potent vasodilator, mediator of neurogenic inflammation, sensory neurotransmitter and regulator of gene expression [25]. Hence, it plays an important role in the development of central and peripheral sensitization, common to many chronic pain conditions [26,27]. Specifically, CGRP acts as a proinflammatory neuropeptide released by the trigeminovascular nociceptive system, crucial in the pathophysiology of migraine [28]. The receptor is a G-protein coupled receptor [28]. As CGRP receptors are located on smooth muscle cells of cerebral and meningeal blood vessels, the release of CGRP by meningeal C-fibers causes blood vessel vasodilation. Thus, blocking CGRP release is thought to prevent or abort pain signal [29]. However, the exact mechanism of CGRP in pain is still unclear, and the meningeal blood vessels as a target appear to be only one of the proposed modes of action.

CGRP antagonist pathways have been investigated either as acute or preventive therapies [22].

3. Small Molecule CGRP Receptor Antagonists: Gepants

The recent enthusiasm towards CGRP blockage as target of migraine medications originated from the observation that telcagepant (a CGRP receptor antagonist) could help prevent migraine [30]. Nevertheless, soon after the first years of research, clinical development of these initial first-generation gepants (such as telcagepant and olcegepant) was interrupted, due to the risk of liver toxicity with long-lasting use [31,32]. Since then, second-generation gepants have been developed and approved for migraine prophylaxis, as listed in Table 1. The second generation of gepants have shown no significant serious side effects, including cardiovascular problems or liver toxicity [33]. Recently, third-generation zavegepant via oral and nasal administration is currently being studied for the acute treatment of migraine [34,35].

To date, three gepants are FDA approved for treatment of migraine: rimegepant and ubrogepant for acute migraine, and atogepant for preventive use in episodic migraine. Of note, rimegepant has also been approved as a migraine preventive treatment, with an every-other-day intake [36–39]. Defined criteria have been recommended by the American Headache Society Consensus Statement to initiate an acute treatment with gepants [14], which can be mainly summarized in contraindications or inability to tolerate triptans or in an inadequate response to two or more oral triptans. Detailed criteria are displayed in Figure 1. To establish the efficacy of gepants, the treatment of at least three migraine attacks should be attempted before evaluating the response, which should be measured using validated questionnaires (Table S1 for response to acute treatment; Table S2 for response to preventive treatment).

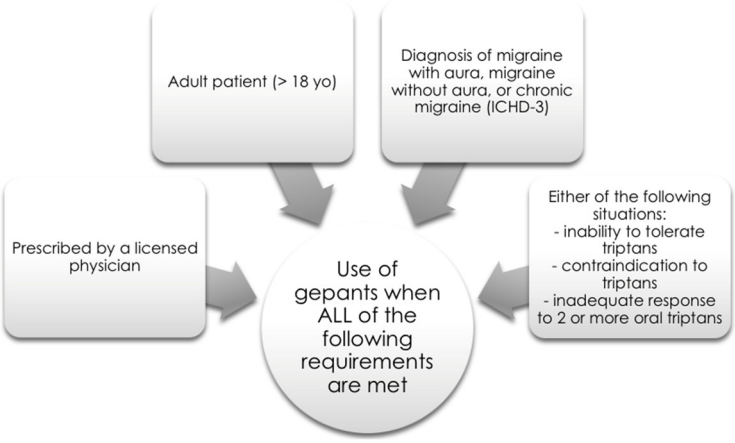

Figure 1. Criteria for starting an acute treatment with gepants. ICHD-3: International Classification of Headache Disorders, 3rd edition.

3.1. Mechanism of Action

Gepants are CGRP receptor antagonists, thanks to a species-specific residue located at the interface between RAMP1 and CALCRL, the site of antagonist binding [22,40]. By binding to the CGRP receptor, gepants prevent the interaction between CGRP and its receptor [41]. Atogepant was shown to have a higher affinity at the CGRP receptor binding site than that of ubrogepant [37]. Gepants are metabolized via hepatic CYP3A4 enzyme system [37].

3.2. Indications

The lack of vasoconstrictor activity makes the use of gepants suitable for patients with cardiovascular risk factors that should avoid triptans, for those with triptan-induced MOH, and for those who failed to respond to triptans [42]. Moreover, gepants can poorly penetrate the blood–brain barrier (BBB), thus leading to minor central effects [43].

3.3. Contraindications

As gepants are strong CYP3A4 inducers, their use in concomitance with other CYP3A4 inducers, CYP3A4 inhibitors and OATP inhibitors should be carefully evaluated [44]. Moreover, gepants should be avoided during pregnancy [45].

3.4. Side Effects

Common side effects of gepants include fatigue and nausea. Studies have shown that compared to certain triptans (i.e., rizatriptan, sumatriptan and zolmitriptan), rimegepant and ubrogepant were associated with fewer risks of adverse effects [46]. A meta-analysis on rimegepant did not observe any significant liver damage nor any significant adverse side effect compared to placebo [47]. Furthermore, studies on ubrogepant and rimegepant did not reveal any occurrence of MOH in animal models [48] and in humans after 52 weeks of administration [49].

Table 1. FDA-approved gepants for the treatment of acute and preventive migraine in adults. ALT: alanine aminotransferase; AST: serum aspartate aminotransferase; BID: twice per day; FDA: Food and Drug Administration; QD: once per day; MMD: monthly migraine days; T_{max}: time to maximum concentration. [a] Results according to available meta-analysis.

Gepants	Ubrogepant (MK-1602)	Rimegepant (BMS-927711)		Atogepant (MK-8031)
FDA indication	Acute treatment of migraine	Acute treatment of migraine	Preventive treatment of episodic migraine	Preventive treatment of episodic migraine
Route	Oral	Oral	Oral	Oral
T_{max}	1.5 h	1.5 h	1.5 h	1–2 h
Half-life	5–7 h	11 h	11 h	11 h
Recommended dose	50 or 100 mg	75 mg	75 mg every other day	10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID, 60 mg BID
Max dose	200 mg/24 h	75 mg/24 h	75 mg/24 h	All to be taken QD
Contraindications	Concomitant administration with potent CYP3A4 inhibitors; end-stage renal disease	History of hypersensitivity; severe hepatic impairment (Child–Pugh C); end-stage renal disease; concomitant administration with potent CYP3A4 inhibitors, P-glycoprotein		History of hypersensitivity; severe hepatic impairment (Child–Pugh C); severe renal impairment and end-stage renal disease
Adverse effects	Nausea, somnolence, dry mouth, nasopharyngitis, head	Nausea, urinary tract infection, dizziness, increased AST and ALT, nasopharyngitis		Nausea, fatigue, constipation, upper respiratory infection, urinary tract infection, sleepiness
Efficacy compared to placebo [a]	20.8% of participants were pain-free at 2 h (vs. 12.6% with placebo). Reduction of migraine-associated symptoms in 37.3% (vs. 27.6% with placebo) [50–53]	15.1–19.6% were pain-free at 2 h (vs. 6.4–12.0% with placebo) Reduction by 1.16 to 4.3 MMDs [36,38,39,49,54–59]		Reduction by 3.6–4.2 MMDs [60–64]

4. CGRP Monoclonal Autoantibodies

As alternatives to small molecules targeting CGRP transmission pathway, recent advances have permitted the development of selective monoclonal antibodies (mAbs) that bind either to CGRP molecule or to its receptor, thus inhibiting its release. A treatment with anti-CGRP mAbs can be initiated after certain requirements are met (Figure 2).

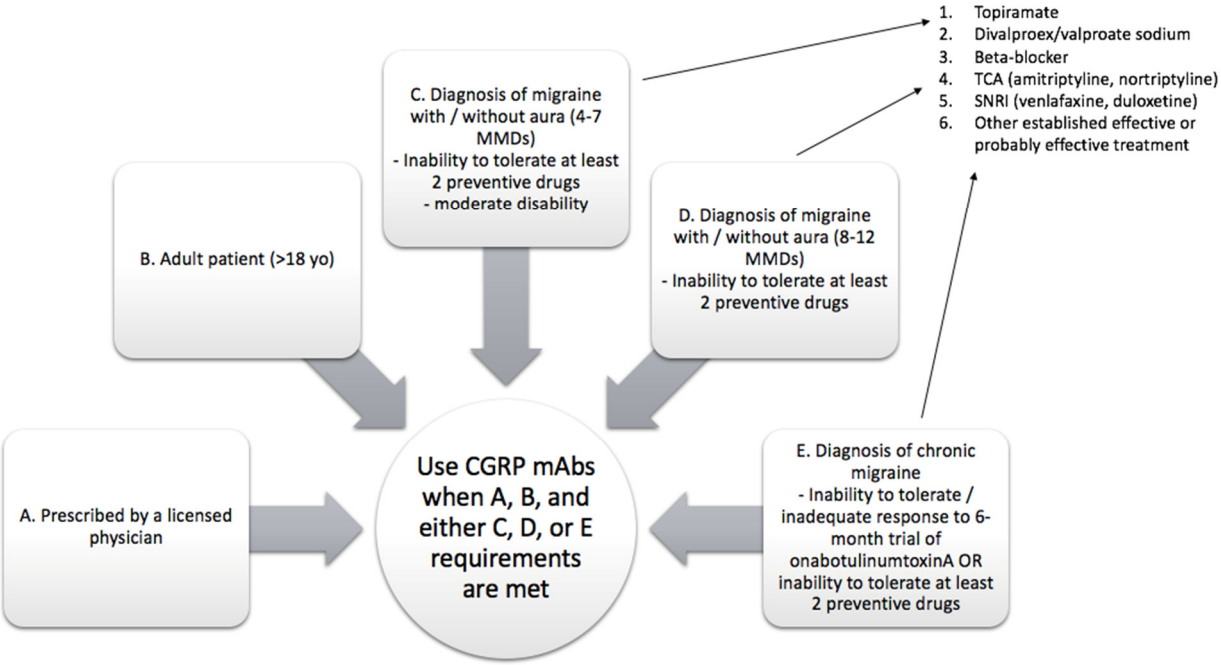

Figure 2. Criteria for starting a preventive treatment with anti-CGRP mAbs, according to the classification of migraine as defined by the International Classification of Headache Disorders, 3rd edition. CGRP: calcitonin-gene related peptide; MMDs: monthly migraine days; SNRI: serotonin norepinephrine reuptake inhibitors; TCA: tricyclic antidepressants.

So far, four mAbs have been FDA-approved as preventive treatment for episodic and chronic migraine (Table 2). They have all demonstrated to be successful in decreasing the number of MMDs compared to placebo (with an overall mean difference of −2.07 MMDs) [65], with no significant difference between the four mAbs [66]. A significant reduction in the intake of acute migraine medications was also observed according to a recent meta-analysis [65], with potential reduction and cessation of MOH [67]. Although benefits have been shown within 24 h after the first administration [68], the efficacy of anti-CGRP mAbs in preventing migraine attacks should be assessed after at least 3 months for those mAbs with monthly administration [14,69–71] and after at least 6 months for those with quarterly administration (i.e., fremanezumab). Validated outcome questionnaires can be used to evaluate the effectiveness of the preventive therapy (Table S2). Continuation or discontinuation of a treatment with mAbs should be leveraged depending on whether meaningful outcomes are seen, such as reduction in MHDs or in migraine-related interference (migraine disability, interference in physical function or daily activities; see [14] for a detailed review). Approximately 15–25% of those that receive an anti-CGRP therapy tend to interrupt the treatment due to insufficient efficacy (as defined as less than 30% of reduction in MHDs) [72,73]. Especially in these cases, switching to another class of mAbs was reported to be effective in approximately one-third of the individuals at three months of the new therapy [74]. This has been demonstrated on patients not responding to erenumab, provided that they did not suffer from daily headache [74], with galcanezumab being most often the second class of mAbs tried [75]. In another trial, patients were not responding to galcanezumab as the first attempt of mAb; after switching to erenumab, the therapy was effective in almost 65% of the cases [76]. Overall, the possibility of switching

among different class of mAbs is supported by the fact that erenumab and galcanezumab have been shown to activate distinct brain networks [77], thereby having different mode of action [78].

4.1. Mechanism of Action

Three mAbs target the CGRP molecule (fremanezumab, galcanezumab, eptinezumab), whereas one mAb acts at the CGRP receptor (erenumab). Three of them are administered subcutaneously (erenumab, fremanezumab and galcanezumab), whereas eptinezumab is administered as IV infusion. A meta-analysis suggested that fremanezumab and galcanezumab have high affinity for the CGRP ligand released by the trigeminovascular system, which may likely explain their high efficacy in migraine prevention compared to traditional therapies [65].

4.2. Indications

As mAbs are not metabolized by the liver CYP enzymes, but rather via the reticuloendothelial system [65], these pharmacological alternatives are the drug of choice in presence of hepatic drug-to-drug interactions and in patients with liver dysfunctions. Studies on mAbs have not observed any cardiovascular nor cerebrovascular effects. Moreover, thanks to their large size, mAbs are less likely to cross the BBB, although growing evidence has suggested the presence of facilitated transport of immunoglobulin-G (IgG) to the central nervous system [79].

4.3. Contraindications

Hypersensitivity to drugs is the major contraindication for the use of mAbs. Patients with a known allergy to latex should also avoid administration of erenumab [80]. An analysis of the World Health Organization (WHO) pharmacovigilance database on 94 safety reports of mAbs used during pregnancy and lactation did not reveal any significant toxicity, birth defects or increased spontaneous abortion, when compared to the full database [81]. However, due to the lack of long-term safety data, the safety of mAbs administration during pregnancy has yet to be assessed [81].

4.4. Side Effects

Thanks to the selectivity and high affinity of mAbs to their target, mAbs are overall safe and well tolerated [22]. The undesired side effects are limited to transient injection-site reactions (pain, erythema, bruising), although no difference was found with placebo [82]. Other side effects, as reported by a meta-analysis, include nausea, urinary tract infections, migraine, nasopharyngitis, sinusitis, constipation, diarrhea and muscle spasms [65]. Recent studies have demonstrated the potential development of anti-drug antibodies (ADAs) against anti-CGRP mAbs, ranging between 1–18% depending on different drug and patient vulnerability [83]. However, adverse events related to ADAs are rare [83]. At the current state of the art, the risk of long-term CGRP blockage is currently not known due to the novelty of these therapies in the market [65], the presence of CGRP throughout the body and the potent vasodilator properties of CGRP in the vascular system [23].

Table 2. Comparison of four anti-CGRP mAbs for migraine prevention. CGRP: calcitonin gene-related peptide; CM: chronic migraine; eCH: episodic cluster headache; EM: episodic migraine; FDA: Food and Drug Administration; IV: intravenous; mAbs: monoclonal antibodies; SC: subcutaneous. [a] Results according to available meta-analysis. * For episodic CH the recommended dose is 300 mg.

CGRP mAbs	Erenumab (AMG334)	Fremanezumab (TEV-48125)	Galcanezumab (LY2951742)	Eptinezumab (ALD403)
FDA indication	Prevention of EM and CM	Prevention of EM and CM	Prevention of EM, CM and eCH	Prevention of EM and CM
Target	CLR/RAMP1 (receptor)	CGRP	CGRP	CGRP
Route of administration	SC	SC (IV load for cluster headache)	SC	IV
Frequency	Monthly	Monthly/quarterly	Monthly	Quarterly
Half-life	28 days	31 days	28 days	31 days
Recommended dose	70 or 140 mg	225 mg (monthly); 675 mg (quarterly)	120 mg *	100 to 300 mg
Starting dose	70 or 140 mg	225 mg or 675 mg	240 mg as loading dose	
Contraindications	Hypersensitivity to drug, latex allergy, cardiovascular risk	Hypersensitivity to drug	Hypersensitivity to drug	Hypersensitivity to drug
Adverse reactions	Reaction at injection site, constipation, cramps, muscle spasms, elevated blood pressure, nervous system disorders, musculoskeletal disorders, vascular events, drug-induced liver injury, palpitation, arthralgia	Reaction at injection site (rash, pruritus, urticaria) up to one month after administration in 21.2% compared to 17.7% in placebo; headache, nasopharyngitis, gastroenteritis, back pain	Reaction at injection site	Infusion reaction
Efficacy compared to placebo [a]	−1.61 to −1.73 MMDs [69,73,84–95]	−2.19 to −2.38 MMDs [71,96–102]	−2.10 to −2.42 MMDs [70,89,103–108]	−1.43 MMDs [68,109–111]

4.5. mAbs for Cluster Headache

Cluster headache (CH) has been described by the ICHD-3 as a severe, unilateral pain, located in the orbital, supraorbital and/or temporal region, with a duration of 15–180 min and a frequency of once every other day up to eight times daily [112]. In addition, ipsilateral autonomic signs or symptoms and/or a sensation of restlessness or agitation accompany the pain [112]. The reason why certain mAbs have been tested for the treatment of CH is that an activation of the trigeminal–autonomic reflex (trigeminal sensory system and parasympathetic system) has been reported with release of CGRP during a CH attack. Moreover, other evidence suggesting a role of CGRP in CH is that the administration of CGRP to CH patients is able to trigger an attack, especially in episodic CH [113–115]. Also, CGRP levels were increased after a CH attack was induced by systemic administration of nitroglycerin [116]. On the contrary, when a CH attack was provoked by vasoactive intestinal polypeptide or PACAP38, levels of GCRP did not seem to increase [117]. Based on this rational, anti-CGRP mAbs have been investigated in few studies for the treatment of CH. So far, galcanezumab has been approved for the treatment of episodic CH [118], whereas it was not reported to be effective on patients with chronic CH according to a phase 3 randomized clinical trial [119]. Nevertheless, a retrospective study conducted on 22 patients with chronic CH revealed that galcanezumab or erenumab was effective in reducing attack frequency by 50% in more than half of them (55%) [120]. Finally, trials with fremanezumab for CH have been discontinued [121].

5. Comparison between mAbs and Gepants, and Their Combination

To the best of our knowledge, only one meta-analysis has investigated the difference between gepants and mAbs, and no comparative study has been performed so far. According to this paper, no significant differences were observed between rimegepant and two mAbs (erenumab and galcanezumab) in the change of MMDs and Migraine Disability Assessment Test (MIDAS) scores at the 12-week timepoint [36]. However, rimegepant was found to be superior to erenumab in Migraine-Specific Quality of Life Questionnaire version 2 (MSQv2) but to be inferior to galcanezumab in the role-function restrictive MSQv2 domain [36]. As for the effectiveness and safety of introducing gepants in patients already

in treatment with mAbs, a few anecdotal reports suggest that a combination thereof may further reduce attack frequency, decreasing the intake of multiple acute drugs with minimal side effects [122–124]. Among the reported adverse events, the most severe consisted of viral gastroenteritis, dizziness and first-degree atrioventricular block, which spontaneously resolved with discontinuation of the therapy [58].

6. Future Avenues of Research

As migraine can also present in children and adolescents, despite presenting with other phenotypical features, it is important for future studies to address the lack of migraine preventive treatment under the age of 12 years old [124]. This is especially true if we consider the disabling impact of migraine during such a crucial period of life that will likely influence a lifespan [125]. So far, previous studies have found that cognitive behavioral therapy (CBT) plus amitriptyline was superior to amitriptyline and education alone in reducing migraine-related disability and headache days [126]. Recently, a clinical trial did not observe any significant difference in the efficacy of amitriptyline vs. topiramate vs. placebo at this young age [127]. As for CGRP selective therapies, early recommendations published in 2018 suggested that anti-CGRP mAbs should be proposed to those post-pubertal adolescents suffering from frequent migraine (i.e., $\geq$8 days per month), refractory to old preventive treatments [128]. Besides this review, to the best of our knowledge the only evidence derives from a retrospective multisite cohort study performed on 112 adolescents with refractory headache [129]. In this study, the administration of mAb was found to be effective in reducing the headache frequency by 2 days per month at the first follow-up (average of 2.7 $\pm$ 2.3 months), with a significant functional improvement reported by 30% of the participants. However, some shortcomings limit the generalizability of these results. First, the selected participants were heterogeneous in that they included adolescents diagnosed with either chronic migraine, daily persistent headache or post-traumatic headache. Moreover, the study was conducted on different mAbs (erenumab, galcanezumab and fremanezumab). Lastly, the second and last follow-up was performed at 4.6 $\pm$ 1.9 months, which already showed a certain degree of reduction in efficacy ($-$2 vs. $-$1.4 days/months) and functional improvement (31% vs. 22.4%) compared to the first timepoint. Besides the efficacy, it will also be important to address the recommended dose, as, so far, the dosage has been translated from adult research. At this regard, a study has tested a dose selection of subcutaneous 75 mg for fremanezumab in patients aged 6–11 years weighing < 45 kg (130), concluding that a monthly dose of 120 mg in pediatric patients weighing < 45 kg is recommended according to pharmacokinetic data [130,131]. There are currently ongoing studies specifically looking at the CGRP targeting pathway in children and adolescents (as reviewed in [132]), and few years will pass before seeing the results.

As for gepants, no data are available on children and adolescents at the current state of the art [133], and, to the best of our knowledge, there are only a few ongoing studies looking at gepants for acute [134–137] or preventive migraine treatment [137,138]. Due to the paucity of trials in this selected age group [132], future studies targeting CGRP and specifically enrolling adolescents with episodic or chronic migraine for longer observation period are needed. Moreover, in light of the lack of comparative trials between mAbs and gepants, studies that test the effectiveness of the two alone or in combination are advocated. Finally, an important point to consider is that the market is already in possession of useful drugs for migraine treatment. However, sometimes these drugs are not used in the correct patient (whether it is for drug contraindication, side effects, low adherence or subject's variability in sex, body mass index, age or ethnicity) [139]. As a consequence, there is a continued search for new effective targets and agents (e.g., targeting PACAP39, PAC1 receptor, G-protein coupled receptors, glutamate, ion channels, among others) [140] instead of improving our clinical intuition and skills in linking the best effective drug to the most appropriate patient. Finally, as to date available studies combining mAbs and gepants are very few, new trials with high quality methodology and larger sample size are advocated.

7. Limitations

This review is not exempt from some limitations. First, all clinical indications reflect FDA directions; as such, it may not be generalizable to a broader system. Second, although this review responds to an attempt to be as comprehensive as possible, it is limited to published research articles. As unpublished data, dissertations and other non-peer reviewed formats have been excluded, these results may be influenced by publication bias.

8. Conclusions

These recent years have seen the development of new migraine-specific pharmaceutical targets and therapies, such as small molecules CGRP receptor antagonist (gepants) and monoclonal autoantibodies directed against CGRP or its receptor. Due to the high affinity to their target and to the specificity of such medications, these new treatments largely extend their use to patients who could not tolerate previous therapies, either for systemic contraindications or drug-to-drug interactions, or that did not benefit from any available options. Efforts should continue researching new effective strategies to improve migraine care and lead to more individualized treatments.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/futurepharmacol3010008/s1. Table S1: Validated acute treatment outcome questionnaire. Table S2: Validated preventive treatment outcome questionnaire.

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