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REVIEW ARTICLE

CGRP and headache: a brief review

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Abstract
The advent of anti-CGRP medications is an example of translational research made real. Pioneering research by Drs. Lars Edvinsson and Peter Goadsby has yielded the monoclonal antibody therapeutics and will likely also result in the gepants. The availability of MABs represents a watershed moment in the treatment of migraine. These medications have specificity, as they were designed for primary migraine prevention. They work across a group of wide therapeutic targets, episodic migraine, chronic migraine, medication-overuse headache, and episodic cluster headache. They separate from placebo within 1 week, and often show clinical effects within a month or less. They have tolerability similar to placebo. There has been no significant or worrisome safety signal thus far in their use. They manifest unprecedented responder rates at ≥ 75% and even 100%. They lower all acute medication use and can convert patients from chronic migraine to episodic migraine and from acute medication overuse to non-overuse. They work in patients who have already had lack of success with at least 2–4 previous preventive medications. Pent-up demand for designer, well-tolerated, and effective migraine preventive medication in the USA has resulted in more than 100,000 individual patients prescribed erenumab from May to December of 2018, and the numbers continue to increase. The preventive treatment of migraine in the USA has shifted dramatically, and is likely to do so in the rest of the world as well.

Keywords CGRP · Migraine · Monoclonal antibodies · Gepants · Calcitonin gene-related peptide

Introduction

Calcitonin gene-related peptide (CGRP) was noted as a target in migraine pathogenesis by Drs. Lars Edvinsson and Peter Goadsby [1]. CGRP receptors localize almost everywhere migraine pathophysiology occurs, including the cortex, thalamus, limbic system, brainstem, dura mater, trigeminal and dorsal root ganglia, trigeminocervical complex, and spinal lamina 1.

Subsequently, CGRP and migraine were linked by clinical experiments. CGRP levels increase during migraine and fall interictally and after treatment with sumatriptan. Infusions of CGRP trigger migraine-like headache in migraineurs. CGRP receptor activation enables N-methyl-D-aspartate (NMDA) glutamate subreceptor activation in the cortex at initiation of cortical spreading depolarization/depression (CSD).

The gepants

Once CGRP was selected as a target for migraine translational research, the next step in development was characterization of the receptors and synthesis of receptor antagonists. The first antagonist was $CGRP_{8\text{-}37}$, a small molecule with a short half-life that consists of all but 7 amino acids of both the α-CGRP receptor (the canonical CGRP receptor) and the β-CGRP receptor. CGRP also binds to other receptors, including the non-canonical CGRP receptor (AMY1), adrenomedullin, and intermedin receptors.

Following characterization of $CGRP_{8\text{-}37}$, Doods and colleagues synthesized a series of small molecule CGRP receptor antagonists, now known as the gepants. The first gepant to be studied in humans was intravenous olcegepant, which in keeping with his seminal role in explicating CGRP, was described by Edvinsson [1]. Intravenous olcegepant terminated migraine at rates and with speed comparable to triptans [2].

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Given this proof of concept success, five more oral gepants have been studied in positive randomized controlled trials for acute treatment of migraine (BI 44370 TA, telcagepant, MK-3207, ubrogepant, and rimegepant), and one oral gepant given daily has been effective in episodic migraine (EM) prevention (atogepant). Gepants are metabolized in the liver, and the first three were associated with liver toxicity. So far, investigators studying ubrogepant, rimegepant, and atogepant have not reported liver abnormalities to such an extent as to prevent further development.

Phase 3, final regulatory randomized controlled trials (RCTs) on ubrogepant and rimegepant for acute migraine treatment have been completed and results announced but not fully published as of the time of this writing (February 2019). The US Food and Drug Administration (FDA), the American regulatory body, now requires two co-primary endpoints to be positive in acute migraine RCTs compared to placebo, 2-h pain freedom and 2-h freedom from the most bothersome symptom chosen by the patient at the onset of an attack from nausea, photophobia, or phonophobia.

A remarkable aspect of ubrogepant and rimegepant is that two pivotal RCTs have been completed for each, and the four studies are remarkably similar in outcomes. Two-hour pain freedom was 19.2% in three of the four trials and 19.6% in the other, with placebo response ranging from 11.8 to 14.3%, and all of the studies statistically significant. Two-hour freedom from MBS ranged from 36.6 to 38.9% and placebo from 25.2 to 27.8%. These results are unusually close for all endpoints and for active and placebo, suggesting that these gepants work quite comparably and that the four RCTs were completed without wide disparity in execution or results [3–6].

Tolerability was excellent for ubrogepant and rimegepant, and safety also seemed acceptable, in terms of liver signals. Further scrutiny of liver tests will be in order, but so far the results announced seem satisfactory.

The relatively low 2-h pain free numbers for both gepants, similar to naratriptan or dihydroergotamine (DHE), have been remarked upon [7]. The clinical utility of these acute medications will be predicated on several factors.

First, as they block the canonical CGRP receptor, they prevent vasodilation but do not cause vasoconstriction, so they should be useful in migraine patients with vascular disease or multiple vascular risk factors. Second, for patients who do not tolerate triptans, they will offer a potentially milder alternative. Third, for patients who do not respond to triptans, the gepants will offer an alternative mechanism of action for acute treatment.

An unanswered question is whether they will behave as naratriptan, a slow, gentle triptan best for patients with an indolent onset of migraine, or as DHE, which while slow in onset is associated with high sustained pain freedom and sustained pain relief, that is, low recurrence rates. Another question is whether the gepants will be effective acutely in patients on concomitant anti-CGRP receptor or anti-CGRP monoclonal antibodies (MABs) preventively.

Data on atogepant for migraine prevention were announced at the American Academy of Neurology (AAN) meeting in 2018. This phase 2 proof-of-concept dose-ranging RCT tested five daily atogepant dosing regimens and placebo in EM prevention. Average number of mean monthly migraine days per month at baseline was around 7, and atogepant in all doses dropped the mean monthly migraine days by about − 4 days per month, so by more than 50%. All dose schedules were significant versus placebo. The magnitude of effect appears comparable to the reduction from baseline for the anti-CGRP and anti-CGRP receptor MABs in EM prevention. Tolerability and safety again were reported as good; these data have not been fully published as of February 2019 [8].

Atogepant will be further studied for migraine prevention in pivotal RCTs. There are plans to evaluate daily rimegepant in migraine prevention as well. If successful, rimegepant would be the first medication with both acute and preventive indications [9].

Monoclonal antibodies

The idea of MABs targeting CGRP or its receptor was promulgated because of the liver toxicity of the early gepants and the fact that the MABs are eliminated through the reticuloendothelial system. They are large molecules that for the most part do not penetrate the blood–brain barrier. This makes peripheral mechanism of action most likely, although given that there is some central nervous system access and an unknown amount necessary for clinical effect, it remains possible that they have some central effects as well. Dr. Lars Edvinsson has characterized the difference in size between an anti-CGRP MAB and a gepant as the difference between a truck and a grain of rice.

Four MABs have been tested clinically in humans in migraine prevention, and all work to prevent EM and chronic migraine (CM), with and without aura, with and without medication overuse, and with and without numerous psychiatric and medical comorbidities. Three target the CGRP ligand itself, fremanezumab, galcanezumab, and eptinezumab, while one targets the canonical CGRP receptor, erenumab.

The MABs and migraine prevention

Regulatory trials for prevention of EM and CM have been completed on all four MABs. The pivotal RCTs for migraine prevention for erenumab, fremanezumab, and galcanezumab

have all been fully published. The open-label extension data have not all been published yet, and no pivotal trial for eptinezumab has yet been published, although some data have been presented.

Episodic migraine prevention

Separation of effect from placebo for all four MABs for migraine prevention occurs within the first week, and most patients in the RCTs had meaningful clinical benefit in the first month. The magnitude of effect for all four is similar.

Erenumab

Erenumab is an IgG2 fully human MAB targeting the canonical CGRP receptor and was studied in one 3-month RCT and one 6-month RCT for prevention of EM, both trials fully published. Average mean monthly migraine days at baseline for both studies was around 8, and the primary endpoint of drop in mean monthly migraine days was around − 3 days from baseline for both studies.

One study (ARISE, the 3-month study) evaluated placebo and 70 mg erenumab, while the other (STRIVE, the 6-month study) evaluated placebo, 70 mg, and 140 mg erenumab doses [10, 11]. The secondary endpoint was the percentage of patients who had ≥ 50% reduction in mean monthly migraine days and was about 40% for the 70-mg dose and 50% for the 140-mg dose.

A third fully published study evaluated erenumab 140 mg for EM patients who had had a lack of success with ≥ 2–4 previous migraine preventive medications for 3 months (LIBERTY), with the primary endpoint that percentage of patients with at least ≥ 50% reduction in mean monthly migraine days at 3 months compared with placebo. About 30% achieved this with 140 mg erenumab and about 14% with placebo, which was statistically significant. This suggests that erenumab works in patients in whom it is likely that the MAB will first be used, that is, those with previous preventive medication failures [12].

The most common adverse events were injection site reactions or respiratory symptoms. Safety data on an EM open-label extension for 1 year was published, and that study is planned to continue for 5 years. One death occurred, and "autopsy showed evidence of severe coronary atherosclerosis and presence of cardiac stimulants (phenylpropanolamine and norpseudoephedrine) in the liver; this event was considered not related to treatment per the investigator." [13]

US FDA approved doses for erenumab are 70 and 140 mg subcutaneous, administered by the patient at home monthly using an autoinjector.

Fremanezumab

Fremanezumab is an IgG2 fully humanized (≈ 5% murine) MAB targeting the CGRP ligand. It was studied in one 3-month regulatory trial (HALO) for EM prevention, comparing a monthly 225-mg dose and a quarterly 675-mg dosing regimen with placebo and fully published. Both dosing protocols worked better than placebo. The baseline migraine days was around 9, and the medication dropped mean monthly migraine days by about − 3.5 days. The percentage of patients with ≥ 50% reduction in migraine days was about 45%. The percentage of patients with ≥ 75% reduction in migraine days at 12 weeks was about 33% [14].

Other endpoints showing improvement included reduction of headache days, and longer and longer headache-free day periods. Fremanezumab was studied in an RCT of patients with a lack of success with ≥ 2–4 previous migraine preventive medication classes, and this was reported as positive, but has not been presented or published at the time of this writing (February 2019).

Again, injection site reactions and respiratory symptoms were the adverse events most frequently reported for fremanezumab. One death occurred more than 3 months after the last dose by diphenhydramine overdose suicide, felt not to be treatment related [14].

US FDA approved doses for fremanezumab are 225 mg subcutaneous monthly or 675 mg subcutaneous quarterly administered by the patient at home monthly using a pre-filled syringe.

Galcanezumab

Galcanezumab is an IgG4 humanized (≈ 10% murine) MAB targeting the CGRP ligand. It was studied in two 6-month RCTs for EM prevention (EVOLVE 1 and 2), both full published [15, 16]. Both trials evaluated 120-mg and 240-mg doses of galcanezumab and placebo, but the 240-mg dose was not more effective than the 120-mg dose, and only the latter was approved by the US FDA for use. Baseline mean monthly migraine days was 9 days, and drop from baseline was around − 4.5 days.

The percentage of patients with ≥ 50% reduction in migraine days was around 60%. The ≥ 75% responder rates for 120 mg was around 33% at 6 months [15, 16].

Subsequently, 100% responder rates, defined as having a 100% reduction in mean monthly migraine days for a month in a row was published, and "on an average month in the 6-month double-blind phase" was 13.5% for galcanezumab 120 mg and 5.9% for placebo. Interestingly, "few galcanezumab patients had ≥ 4 months of 100% response… [but] more than a third of the patients with episodic migraine treated with galcanezumab 120 mg…achieved 100% response for at least 1 month. More patients had 100% monthly

response in the last 3 months of the 6-month double-blind period. For those with 100% response for at least 1 month, the average time between nonconsecutive monthly headache days for the entire treatment period was nearly 1 month and approached 2 months for patients with 3 or more months of 100% response." [17]

The most common adverse events were injection site reactions, but neither constipation nor respiratory symptoms exceeded placebo. No deaths occurred in the galcanezumab clinical program [15, 16].

The 1-year open-label data for both EM and CM patients have been fully published. The investigators noted that treatment-attributed adverse events had a frequency ≥ 10% of patients and were injection site pain, nasopharyngitis, upper respiratory tract infection, injection site reaction, back pain, and sinusitis. Laboratory values, vital signs, or electrocardiograms did not show any clinically meaningful differences between galcanezumab doses. Overall mean reduction in monthly migraine headache days over 12 months for the galcanezumab dose groups was − 5.6 (120 mg) [18].

In the US FDA approved prescribing information, galcanezumab is given in the first month as a 240-mg loading dose and then 120 mg subcutaneous monthly thereafter administered by the patient at home monthly using either an autoinjector or a pre-filled syringe.

Eptinezumab

Eptinezumab is an IgG1 humanized (≈ 10% murine) MAB targeting the CGRP ligand. It is the only MAB in development which will be administered intravenously. It was studied in a year-long RCT with quarterly infusions (PROMISE-1), and the likely doses will be 100 mg and 300 mg.

The mean monthly migraine days at baseline was around 8. The drop from baseline over weeks 1–12 was around − 4, similar to the other MABs. Because the study is placebo controlled, it is useful to evaluate the responder rate at 1 year. Here, the magnitude of efficacy is unparalleled, and 54% of patients had a ≥ 75% reduction in mean monthly migraine days [19].

Since eptinezumab is administered intravenously, there were no injection site reactions, and the most common adverse events were respiratory. Eptinezumab has not yet been submitted to regulatory authorities for approval as of February 2019.

Chronic migraine prevention

Erenumab

The three commercially available MABs were all tested in positive 3-month RCTs for CM prevention, and all three studies have been fully published. In the erenumab pivotal trial, patients had about 18 mean monthly migraine days at baseline, and these dropped by − 6.6 days for both the 70-mg and the 140-mg dose by 12 weeks [20]. In the open-label extension trial at 1 year, the drop was − 8.5 days for the 70 mg and − 10.5 days for the 140-mg dose [21, 22].

The secondary endpoint of the percentage of patients who had ≥ 50% reduction in mean monthly migraine days was about 40% for the 70-mg dose and 50% for the 140-mg dose at 12 weeks. Open-label extension data reported that these responder rates improved in those who continued to use erenumab across 1 year, with both doses showing 67% of patients with ≥ 50% responder rates and 41% of patients using the 140 mg having a ≥ 75% responder rate [20–22].

As in all of the MAB trials, acute migraine medication days of use dropped for the active group compared with placebo. In addition, over half of patients treated with erenumab in the CM trial converted from CM to EM by 12 weeks, and there was substantial conversion from acute medication overuse to non-overuse [20, 22–24].

Fremanezumab

The fremanezumab 3-month registration RCT for CM prevention (HALO) used 225 mg monthly or 675 mg quarterly dosing regimen versus placebo. The definition for days in the primary endpoint was a bit different, but essentially the mean monthly migraine days were about 16 days at baseline and dropped by − 4.6 days for the 225 mg monthly group and by − 4.3 days for the 675 mg quarterly group [25].

The secondary endpoint of the percentage of patients who had ≥ 50% reduction in mean monthly migraine days was about 41% for the monthly group and 38% for the quarterly group at 12 weeks. These numbers did not increase at 6 months [22, 25, 26]. Again, fremanezumab showed benefit in a variety of other endpoints, including reduction in use of all acute migraine medication days, and improvement in patient-reported outcomes.

Galcanezumab

As with the other two commercially available MABs in the US, galcanezumab was studied for CM prevention in a 3-month RCT (REGAIN) comparing placebo, 120 mg, and 240 mg of galcanezumab. The mean monthly migraine days at baseline was a little over 19 days. The reduction at 12 weeks was − 4.83 days for the later US FDA approved 120-mg galcanezumab dose.

The secondary endpoint of the percentage of patient who had ≥ 50% reduction in mean monthly migraine days was about 27.6% for the 120-mg dose at 12 weeks. As with all of the MABs, mean acute migraine medication days decreased and patient-reported outcomes improved [27].

Eptinezumab

The 3-month CM preventive RCT for eptinezumab (PROMISE-2) has not been published as of this writing (February 2019), but was presented in abstract form. Baseline mean monthly migraine days was around 16. The drop from weeks 1–12 with eptinezumab was − 7.7 days for 100 mg and − 8.2 days for 300 mg [28].

For secondary endpoints, the ≥ 50% reduction in mean monthly migraine days weeks 1–12 was 57.6% for 100 mg and 61.4% for 300 mg. The ≥ 75% responder rates were 26.7% for 100 mg and 33.1% for 300 mg.

Days of migraine-specific acute medication use dropped, and patient-reported outcomes improved [29]. In the preventive eptinezumab trials, the likelihood of a migraine decreased by > 50% in the first 24 h after infusion [30].

The issue of vascular safety

Because CGRP is a potent endogenous vasodilator, there has been concern on removing it or its receptor in the setting of ischemia, and the potential loss of compensatory mechanisms [31]. Two prospective RCTs were run on medications targeting the CGRP receptor, telcagepant and erenumab. In both, patients with documented coronary artery disease and ongoing angina had baseline exercise tolerance tests and then were given either active medication or placebo and the stress test repeated. Neither reported any significant changes in angina, EKG changes, or stress test duration in group mean data [32, 33].

Rimegepant, BHV-3500 (another gepant), and erenumab have each been tested for vascular effects on explanted arteries, including human coronary, cerebral, or internal mammary arteries. The medications did not provoke vasoconstriction [34, 35].

There have been numerous sub-analyses of MAB use in patients with one or more vascular risk factors, including erenumab [36] and fremanezumab [37, 38]. None has demonstrated overall increased reports of vascular adverse events in studies so far, and no clear treatment-related vascular adverse events have been established [22, 39].

Cluster headache

Both fremanezumab and galcanezumab have been studied in RCTs for episodic cluster headache (ECH) and chronic cluster headache (CCH). Neither had successful studies in prevention of CCH. The results of the fremanezumab ECH prevention study have not been announced as of February 2019.

Galcanezumab 300 mg successfully prevented ECH in an 8-week RCT, presented in abstract form. Baseline cluster headache attacks per week was 17.3 for placebo and 17.8 for the galcanezumab group and dropped in the active group by − 8.7 attacks to 12.1 attacks per week.

Secondary endpoints included the ≥ 50% responder rate, which was 76% for galcanezumab [40]. Galcanezumab has been submitted to the US FDA for the indication of ECH prevention and received an expedited status, making approval for use in episodic cluster headache prevention likely in 2019.

Conclusions

The advent of anti-CGRP medications is an example of translational research made real. Pioneering research by Drs. Lars Edvinsson and Peter Goadsby has yielded the monoclonal antibody therapeutics and will likely also result in the gepants.

The availability of MABs represents a watershed moment in the treatment of migraine. These medications have specificity, as they were designed for primary migraine prevention. They work across a group of wide therapeutic targets, episodic migraine, chronic migraine, medication overuse headache, and episodic cluster headache. They separate from placebo within 1 week and often show clinical effects within a month or less. They have tolerability similar to placebo. There has been no significant or worrisome safety signal thus far in their use. They manifest unprecedented responder rates at ≥ 75% or even 100%. They lower all acute medication use and can convert patients from CM to EM and from acute medication overuse to non-overuse. They work in patients who have already had lack of success with ≥ 2–4 previous preventive medications.

Pent-up demand for designer, well-tolerated, and effective migraine preventive medication in the USA has resulted in more than 100,000 individual patients prescribed erenumab from May to December of 2018, and the numbers continue to increase. The preventive treatment of migraine in the USA has shifted dramatically, and is likely to do so in the rest of the world as well.

Compliance with ethical standards

Conflict of interest Grants for research (no personal compensation): Alder, Allergan, Amgen, ATI, Dr. Reddy's, ElectroCore, eNeura, Neurolief, Scion Neurostim, Teva, Zosano.

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