PHARMACIST CE:

CGRP Treatments: Their Role in Migraine Therapy

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CE FOR **PHARMACISTS**

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Learning Objectives

- Describe the role calcitonin gene-related peptide (CGRP) has in migraine pathophysiology.
- Describe symptoms associated with migraine headache.
- Interpret the guidelines for initiating migraine prevention therapy and when patients with migraine are eligible for CGRP inhibitors.
- Identify the different routes and frequencies for each CGRP inhibitor.
- Identify the place in acute migraine therapy for CGRP antagonists, also known as gepants.

Migraine headache is the third most common disease worldwide, in both males and females.[1] Neurologists and primary care providers continue to encounter patients with migraines in their practice daily, with migraine accounting for the second leading cause of time spent living with disability worldwide.[2] There are different types of migraine; however, the most prevalent is migraine without aura (see Table 1). According to the third edition of the International Classification of Headache Disorders (ICHD), migraine without aura is characterized by headache with a combination of recurring neurological symptoms and specific features.[3] This can include recurrent headache attacks lasting 4-72 hours with moderate to severe pulsating or throbbing pain located on one side of the head (unilateral). Other disabling symptoms include nausea and/or vomiting, and sensitivity to light and sound. Patients with migraine headache usually need to stop all activities and rest. Some patients may describe an aura that precedes the migraine headache for 5-30 minutes, characterized by either visual or sensory changes, or speech or motor changes that are reversable. Aura is considered a prodrome, or warning sign, that signals migraine headache pain may follow. Migraine with aura is associated with increased cardiovascular and cerebrovascular risks and outcomes. Regardless of sex, patients who suffer from migraine with aura are at a greater risk for ischemic and hemorrhagic stroke as well as myocardial infarction.[4] Due to this relationship, choosing medications with lower risks for cardiovascular and cerebrovascular events is essential for patients experiencing migraines with aura.

The definitive cause and pathophysiology of migraines are not fully understood. However, neurotransmitter and neuromodulator release are associated with migraines, including the neuropeptides 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide (CGRP). The 5-HT receptor agonists, also known as triptans, have been the primary treatment used for acute attacks since the 1990s, and although triptans, available in tablet, nasal spray and injectable formulations, are safe and effective, some patients find they are less effective over time, experience side effects, or have contraindications to their use.[5,6] In this case, the migraine patient may resort to non-specific migraine treatments, like opioids or simple analgesics, which can result in medication overuse headaches.[7] Due to the varying

degrees of severity, frequency, and overall migraine characteristics from person to person, finding an optimal acute or preventive treatment for patients can prove challenging.[8] Oral medications currently used for preventive migraine treatment were not designed specifically for migraines, thus limiting their safety and efficacy profiles. Based on these treatment needs, the use of CGRP antagonists looks to be a promising approach to migraine management, as they were specifically designed as a preventative measure for migraine treatment.

Role of CGRP in Migraine

Present throughout the peripheral and central nervous system, CGRP is known as a vasodilator and is released during both spontaneous and triggered migraine attacks.[9] Due to CGRP's role in migraines, it was considered that blocking CGRP or its receptor may treat or prevent migraine attacks. While the first CGRP antagonists showed promise, liver toxicity was a concern and production ended.[10] However, the U.S. Food and Drug Administration (FDA) has recently approved several new drugs that target CGRP for either migraine prevention or acute migraine treatment. Four new monoclonal antibodies (mAbs) targeting CGRP and its receptor have been developed for migraine prevention therapy, successfully avoiding liver toxicity and providing other benefits (Table 2).[11] Targeting the CGRP ligand and receptor with mAbs adds specificity and longer half-lives while generally producing fewer side effects. In contrast to small-molecule receptor antagonists, mAbs are much larger, and thus unable to cross the blood-brain barrier. With regards to elimination, mAbs are eliminated by degradation into peptides, allowing for less potential for drug-drug interactions. Of the four mAbs currently approved, three work by blocking the CGRP ligand: eptinezumab, galcanezumab, and fremanezumab. Alternatively, erenumab targets and blocks the CGRP receptor.

Small-molecule CGRP antagonists, referred to as "gepants," are oral formulations available for the acute treatment of migraine in patients with either insufficient response or contraindication (e.g. coronary artery disease) to treatment with triptans.

TABLE 1. Symptoms of Migraine Headache[3]

Migraine Without Aura - at least five attacks fulfilling the following criteria:
Headache lasting 4-72 hours
Headache characterized by two or more of the following characteristics: • Unilateral location • Pulsating or throbbing • Intensity of pain moderate to severe • Aggravated by or causing avoidance of routine physical activity
Headache must also fulfill at least one of the following characteristics: • Nausea and/or vomiting • Sensitivity to light and sound
No evidence of other disease diagnoses to better explain symptoms
Migraine With Aura
Aura may also precede migraine headache for 5-30 minutes, characterized by at least one of the following more common fully reversible aura symptoms: • Visual Symptoms: » Changes in vision, vision loss, spots in visual field, flashes of light • Sensory Symptoms: » Numbness ■ Sensation of pins and needles moving slowly from origin to one side of the body, face and/or tongue • Speech and/or Language Symptoms: » Aphasia • Motor Symptoms: » Muscle weakness

Migraine Prevention Treatment with Anti-CGRP Monoclonal Antibodies Guidelines

Although migraine prevention therapy will not eliminate migraines altogether, its goal is to reduce the frequency, severity, and duration of migraine headaches. CGRP inhibitors are not currently the first line treatment for migraine prevention. The anti-CGRP mAbs have all been approved by the FDA for both episodic migraine (fewer than 15 migraine headache days per month) and chronic migraine headache (15 or more headache days per month). According to the American Headache Society (AHS), this class of medications can be prescribed to patients at least 18 years old who fall into at least one of the following three scenarios.[8]

First, in patients who have a diagnosis of ICHD-3 migraine with or without aura and experience 4-7 monthly headache days, they need to have experienced "both an inability to tolerate or have an inadequate 6-week trial of at least 2 other prevention medications."[8] In addition, they need at least moderate disability indicated by a MIDAS score >11 or HIT-6 >50. Medications that can be trialed first include topiramate, divalproex sodium/valproate sodium, beta blockers (metoprolol, propranolol, timolol, atenolol, and nadolol), tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), and other level A or B treatments according to the AHS guidelines.

Second, patients may qualify for CGRP inhibitors if they have an ICHD-3 migraine with or without aura diagnosis and experience 8-14 monthly headache days, with an inability to tolerate or a poor response to at least a 6-week trial of 2 of the following: topiramate, divalproex sodium/valproate sodium, beta blockers (metoprolol, propranolol, timolol, atenolol, and nadolol), tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), and other level A or B treatments according to the AHS guidelines.[8]

Lastly, patients are eligible for the CGRP inhibitors if they have a diagnosis of chronic migraine (15 or more headache days per month) and were unable to tolerate

or had an inadequate 6-week trial of 2 of the previously mentioned prevention medications or had an inadequate response to at least six months, or 2 quarterly injections, of onabotulinumtoxin A.[8]

If a patient fulfills any of the previous criteria, they are qualified to receive prevention treatment with CGRP inhibitors, which currently includes the aforementioned drugs: eptinezumab, erenumab, fremanezumab, and galcanezumab. The response to the initial use of anti-CGRP mAbs should be measured by patient-reported reduction of mean monthly headache days (i.e. > 50% reduction from baseline) or any of the validated outcome measures such as MIDAS, MPFID, HIT-6 by 5 or more points, or by 30% if the MIDAS baseline score was > 20.[8]

Erenumab

Erenumab-aooe, brand name Aimovig®, is a calcitonin gene-related peptide (CGRP) receptor inhibitor approved in the United States for the prevention of migraine in adults.[12] This medication was approved in May 2018 as the first CGRP inhibitor on the market. Amgen/Novartis manufactures erenumab as a once-monthly 70 mg/mL or 140 mg/mL subcutaneous auto-injection. As previously mentioned, this monoclonal antibody differs from the other CGRP antagonists currently on the market in that it is the only one to target the CGRP receptor, whereas the other medications target the CGRP ligand. It is also unique in that it is the only fully human product, with the others being humanized.

As erenumab was the earliest medication approved in this class, it has the most published data available. A systematic review from February 2019 concluded that erenumab was effective in the primary end point of monthly migraine days (MMD).[13] At week 4, the 70 mg dose reduced the migraine days by 1.3 compared to placebo (MD -1.3, 95% CI -1.6 to -1.0), and the 140 mg dose reduced the migraine days by 1.9 compared to placebo (MD -1.9, 95% CI -2.4 to -1.5). Both 4-week decreases were significant with a p-value of <0.001. There were also significant data for week 12 and 24 in the systematic review. By week 24, the 70 mg dose decreased migraine days by 1.6 compared to placebo (MD -1.6, 95% CI -2.2 to -1.0), and the 140 mg dose decreased the migraine days by 2.1 compared to placebo (MD -2.1, 95% CI -2.7 to -1.5). Both of these were significant with a p-value of <0.001.

Another systematic review examined the endpoint of ≥50% responder rate in migraine days per month.[14] This article found that erenumab significantly increased the ≥50% responder rate in migraine days per month compared to placebo (RR = 1.55; 95% CI: 1.35–1.77; P < .00001, I2 = 49%). A subgroup analysis broke down the different doses as well. Both doses currently on the market, the 70 mg dose (RR=1.54; 95% CI: 1.35–1.75; P < .00001; I2 = 0%), as well as the 140 mg dose (RR = 1.86; 95% CI, 1.59–2.19; P < .00001; I2 = 0%) significantly increased the ≥50% responder rate in migraine days per month.

With regard to side effects, erenumab is well-tolerated. According to the manufacturer, injection site pain and constipation are listed as the most common side effects.[12] The possibility of hypersensitivity reactions is also noted, like anaphylaxis and angioedema, which can occur with biologic medications. Although this is a risk, and documented in post-marketing surveillance, neither of the two systematic reviews reported any hypersensitivity reactions. Lanzetti et al.[13] found that only injection site pain differed significantly from placebo in terms of all adverse reactions. Zhu et al.[14] found no significant differences in any adverse event, minor or severe, in the erenumab group compared to placebo. Based on these data overall, erenumab is a safe, effective option for patients to help prevent migraines.

Fremanezumab

Fremanezumab-vfrm (Ajovy®) is another CGRP inhibitor approved in the United States for the prevention of migraines in adults.[15] Fremanezumab was approved on September 14, 2018, making it the second CGRP inhibitor available on the market. Fremanezumab is a subcutaneous injection that is available as either a prefilled syringe or an auto-injector as a dose of 225 mg/1.5 mL. While there is currently only one size syringe available, there are two dosing options. Fremanezumab can either be given as 225 mg monthly or 675 mg given every three months. If the quarterly option is chosen, it is administered as three consecutive injections of 225 mg.

The U.S. FDA approved fremanezumab for use in the United States based on the results from two clinical trials. The trial by Dodick et al.[16] compared fremanezumab to placebo for the prevention of episodic migraine for those who have not already failed multiple medication classes. Episodic migraine is defined as having less than fifteen headache days per month. This clinical trial had three study groups. The first study group received 225 mg of fremanezumab monthly, the second study group received a single dose of 675 mg of fremanezumab, and the third group was the placebo group. This trial had a study length of 12 weeks. At baseline, the monthly fremanezumab group had an average of 8.9 headache days per month, the quarterly fremanezumab group had an average of 9.2 headache days per month, and the placebo group had an average of 9.1 headache days per month. At the conclusion of the 12-week study, the monthly fremanezumab group had an average of 4.9 headaches per month, the quarterly group had an average of 5.3 headache days per month, and the placebo group had an average of 6.5 headaches per month. The monthly dosing group and the quarterly group both had a statistically significant difference compared to placebo, -1.5 days (P<0.001) and -1.3 days (P<0.001), respectively.

The clinical trial conducted by Silberstein et al.[17] compared fremanezumab to placebo for the prevention of chronic migraine. This trial defined chronic migraine as a headache of any duration or severity on greater than or equal to fifteen days per month and migraine on greater than or equal to eight days per month. Like the trial previously discussed, this trial also had three study groups. The monthly fremanezumab group received 675 mg at baseline and then 225 mg at weeks 4 and 8 and the quarterly group received only 675 mg at baseline, with the third group being placebo. At baseline, the average number of headache days per month for the monthly, quarterly, and placebo group were 12.8, 13.2, and 13.3 respectively. During the 12-week period the average number of headache days were 8.0, 8.5, and 10.4, respectively. The primary endpoint in this study was mean change from baseline in the average number of headache days. For the monthly group, the mean change from baseline was -4.6 +/-0.3 and difference

from placebo was -2.1 +/-0.3. The quarterly group had a mean change from baseline of -4.3 +/-0.3 and the difference vs placebo was -1.8 +/-0.3. Both of these comparisons were found to be statically significant (P<0.001 for both comparisons with placebo).

Since this medication has not been on the market long-term, it is difficult to say whether there are any long-term adverse effects of concern. Current data, though, suggests that Fremanezumab is safe and tolerable for patients.[17] With the two FDA approved doses, there was no statically significant difference found between the rate of adverse effects, except the 675 mg dose having a slightly higher frequency of sinusitis. The most common adverse event was found to be injection reaction pain. Overall, there was no significantly higher rate of adverse events with both doses of fremanezumab compared to placebo.

Galcanezumab

Galcanezumab-gnlm, trademarked under the name Emgality® by Eli Lilly and Company, is a fully humanized, anti-CGRP monoclonal antibody that directly targets the CGRP ligand.[18] Currently, galcanezumab is FDA approved for the preventive treatment of chronic and episodic migraines in adults. In addition to its use in migraine therapy, galcanezumab is the only anti-CGRP medication approved for the treatment of episodic cluster headaches.

When patients begin therapy with galcanezumab, they first receive a 240 mg loading dose of the medication administered as two 120 mg subcutaneous injections in the thigh, upper arm, or buttocks.[18] At present, there is only one strength, 120 mg, of galcanezumab approved by the FDA. The loading dose is then followed by monthly injections of 120 mg.

Since its approval in September 2018, galcanezumab has shown promising results for chronic and episodic migraine headache prevention.[19] In its initial 12 week phase II trial for the prevention of episodic migraine, patients were randomized to either receive a subcutaneous placebo or galcanezumab 120 mg injection every 2 weeks for 12 weeks. The mean change in the number of migraine headache days from baseline measurements in the galcanezumab group was 4.2 days while the placebo group only experienced a 3-day reduction in monthly migraine headache days (least-squares mean difference -1·2, 90% CI -1.9 to -0.6; p=0.0030).

In a 3-month, phase III double-blind placebo controlled study evaluating galcanezumab's effect on episodic migraine on North American patients, EVOLVE-1, patients enrolled saw an average reduction of 4.83 and 4.62 migraine headache days from baseline for 120 mg and 240 mg injections of galcanezumab respectively, versus the placebo group, which only saw a reduction of 2.74 migraine headache days (p < .001 for both doses vs placebo).[20] Additionally, in a 6-month, phase III double blind follow-up study that included patients on a more globalized scale, EVOLVE-2, patients included in the galcanezumab group experienced reductions in monthly migraine headache days by 2.02 and 1.90 days for 120 mg and 240 mg injection, respectively relative to placebo.[21]

Currently, galcanezumab is the only CGRP antibody that is FDA approved for the treatment of episodic cluster headache in adults. Approved in June 2019, galcanezumab has shown benefit in reducing the number of weekly cluster headaches for patients with this condition.[22] In an 8-week double-blind placebo-controlled study in adult patients, the REGAIN study, galcanezumab 300 mg reduced the number of weekly cluster headaches in patients by 8.69 days while patients receiving placebo only saw a reduction of 5.22 days.

No serious adverse effects have been noted from trials of galcanezumab for both migraine and episodic cluster headache trials, but patients in the treatment groups were more likely to experience injection site reactions (8.16% of patients in treatment groups versus 0% of participants in the placebo group).[18]

Galcanezumab is contraindicated in patients with serious hypersensitivity to galcanezumab or any of its excipients; anaphylaxis, angioedema, dyspnea, rash, and urticaria have been reported. If these or any similar symptoms are reported, galcanezumab should be discontinued and appropriate therapy for hypersensitivity reactions should be initiated.

Eptinezumab

Eptinezumab-jjmr (Vyepti™) is a new treatment for migraines that is an anti-CGRP monoclonal antibody and classifies as a migraine prevention treatment for chronic and episodic migraines.[23] Eptinezumab is the latest medication on the market for migraine prevention, being approved in February 2020. Of note, eptinezumab is the only infusion therapy on the market for migraine prevention treatment, and the administration is based on a quarterly schedule and is to be administered in a healthcare facility.[24]

Two major studies that were conducted for eptinezumab were PROMISE 1 and PROMISE 2. PROMISE 1 centered on episodic migraines characterized by subjects having 14 headaches in a month, four of which needing to be migraines.[25] There were over 800 subjects who received either a placebo, or a variety of different dosing options of eptinezumab (30 mg, 100 mg or 300 mg). PROMISE 1 results revealed that subjects who received eptinezumab (100 mg and 300 mg treatment groups) had a >50% reduction in migraines on day 1 after dosing compared to baseline and the reduction was sustained through day 28. In addition, subjects receiving eptinezumab 300 mg experienced significant reductions in their average monthly migraine days over weeks 1-12. Notable statistics include: ≥75% reduction in monthly migraine days over weeks 1– 4 in 32% of subjects and 37% of subjects over weeks 1-12 for the 300 mg dose group. Furthermore, there was a >50% reduction in monthly migraine days over weeks 1-12 in 61% of subjects for the 300 mg dosage group. With more infusions of the 300 mg dose, the number of migraine days per month significantly improved. These results showed that ≥75% reduction in monthly migraine days presented in over 51% of the subjects and ≥50% reduction in monthly migraine days presented in over 70% of the subjects.

PROMISE 2 focused on chronic migraines, which is defined as more than fifteen headaches per month, eight of which needed to be classified as migraines.[26,27] There were 1,072 subjects who received either 100 mg or 300 mg of eptinezumab. The subjects that received 300 mg of eptinezumab after the first quarterly injection had 8.2 fewer monthly migraine days compared to the baseline of 16 monthly migraine days. The placebo group had 5.6 fewer monthly migraine days. After the second infusion, the results were 8.8 fewer monthly migraine days for the 300 mg dose compared with 6.2 fewer monthly

migraine days for the placebo. Another significant finding was that 21% of subjects had a 100% reduction from baseline in monthly migraine days compared to the 9% of placebo subjects with two quarterly infusions of 300 mg eptinezumab. Overall, after two quarterly infusions were administered, 64% of subjects had a ≥50% reduction in monthly migraine days from baseline, 44% were from the placebo and 43% of subjects had ≥75% reduction of monthly migraine days compared to 24% for the placebo. These results suggest that eptinezumab has the potential to offer migraine patients rapid and sustained suppression of migraines.

In terms of safety, PROMISE 1 had similar results of adverse event rates compared to previous eptinezumab studies.[25] Subjects who received either dosage form of eptinezumab (30 mg, 100 mg or 300 mg) or the placebo had very similar percentage rates of adverse events. The most common events were upper respiratory tract infections, nasopharyngitis, and sinusitis. The percentages for the aforementioned side effects from a 300 mg dose of eptinezumab were 10%, 6% and 5%, respectively, while the placebo results were 7%, 5% and 6%, respectively. The results from PROMISE 2 remained consistent with previous studies on eptinezumab as well.[26,27] Comparing the placebo group and participants who received eptinezumab, both had similar adverse event rates. A few common reported adverse events for eptinezumab were: nasopharyngitis (7.4%), urinary tract infection (2.8%), nausea (2.5%), arthralgia (2.3%), dizziness (2.0%), and fatigue (2.0%).

General Administration, Storage Requirements, and Common Side Effects for CGRP Inhibitors

If a subcutaneous maintenance dose of a CGRP inhibitor is missed, it should be administered as soon as remembered.[28-31] Erenumab, galcanezumab, and fremanezumab should be stored in the refrigerator, between 2 to 8°C (36 to 46°F) but should not be frozen.[28-30] Advise patients to remove the product from the fridge 30 minutes before injection to allow the product to reach room temperature before injection (no heat sources should be used to warm the product upon removal from the refrigerator). These products should not be shaken. If necessary, galcanezumab and erenumab may be stored at room temperature up to 30°C (86°F) and 25°C (77°F) respectively in their original packaging for up to 7 days.[28,29] Fremanezumab may be stored at room temperature up to 25°C (77°F) in its packaging for up to 24 hours.[30] If these products are left at room temperature for longer than these designated time periods, advise patients to discard them.[28-30]

For the intravenous administration of eptinezumab, it must first be diluted.[31] A 100 mg dose will require 1 mL of VYEPTI™ from a single-dose vial. A 300 mg dose will require 1 mL of VYEPTI™ to come from 3 separate single-dose vials. After the proper amount of VYEPTI™ is obtained it must be diluted in 100 mL 0.9% sodium chloride injection, USP. In addition, the infusion bags have to be made from polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO). It is necessary to prepare VYEPTI™ using proper aseptic technique since it will be administered through intravenous infusion. The solution can be gently mixed by inverting the solution to mix completely. Furthermore, it is recommended to not shake the solution bag. The infusion must take place within 8 hours of preparation and the solution should be properly stored at room temperature, 20°C to 25°C (68°F - 77°F). After administration, the remaining unused solution should be disposed of. An unprepared injection can be stored in its original carton to protect the product from light in the refrigerator at 2 to 8°C (36 to 46°F) until the time of use. Lastly, the unprepared injection should not

TABLE 2. Migraine Medications Compared[28-33]

Generic Name	Brand Name	Pharmacologic Category	Half-life Elimination[2]	Time to Peak[2]	Route of Administration	Starting Dose	Frequency
Generic							
Erenumab	Aimovig®	CGRP[1] Inhibitors; Monoclonal Antibody	28 days	6 days	SC[3] prefilled single-dose auto-injector	70 or 140 mg	Monthly
Galcanezumab	Emgality®		27 days	5 days	SC[3] via single-use prefilled pen or syringe	240 mg 120 mg	Loading dose Monthly
Fremanezumab	Ajovy®		31 days	5 to 7 days	SC[3] single-dose prefilled syringe or SC autoinjector	Oral 225 mg 675 mg	Monthly Quarterly
Eptinezumab	Vyepti™		27 days	Immediately following infusion	30-min IV[4] infusion in 100mL NS[5]	100 mg or 300 mg	Quarterly
Short Acting							
Urbrogepant	Ubrelvy®	CGRP[1] Receptor Antagonist	5-7 hours	15 hours	Oral tablet	50 mg 100 mg	As needed
Rimegepant	Nurtec™		11 hours	1.5 hours	SL[6] Oral tablet	75 mg	As needed

1, Calcitonin Gene-Related Peptide. 2, Actual response may vary. 3, Subcutaneous. 4, Intravenous. 5, Normal saline. 6, Sublingual.

TABLE 3. Adverse Effects and Contraindications[28-33]

Generic Name	Common Adverse Effects	Contraindications
Erenumab	Irritation at injection site, Constipation, antibody development	Serious hypersensitivity to erenumab or any part of the formulation
Galcanezumab	Irritation at injection site, antibody development	Serious hypersensitivity to galcanezumab or any part of the formulation
Fremanezumab	Irritation at injection site, antibody development	Serious hypersensitivity to fremanezumab or any part of the formulation
Eptinezumab	Antibody development, Nausea, fatigue, nasopharyngitis	Serious hypersensitivity to eptinezumab or any part of the formulations
Urbrogepant	Nausea, somnolence, dry mouth	Concomitant use of strong CYP3A4 inhibitors
Rimegepant	Nausea	Hypersensitivity to rimegepant or any part of the formulation

be frozen or shaken.

Overall, the most frequently reported side effects include upper respiratory tract infection/nasopharyngitis, injection site pain, pruritus, and erythema (Table 3). A risk of contribution to inflammatory bowel disease, diarrhea, or constipation is hypothesized due to the role of CGRP in maintaining the mucosal integrity of the gastrointestinal tract. As an inherent risk of using mAbs as treatment, the body has the potential to develop antibodies against the drug. In trials, efficacy seemed unaffected by the antidrug antibodies detected, although this may not be the case long-term.

At present, clinical trial data for the CGRP inhibitors does not contain a sufficient population of individuals over the age of 65 or under the age of 18 to verify the safety of these medications for geriatric or pediatric use.[28-32] No adequate data are available for these medications in pregnant or lactating women. It is prudent to have women tell their healthcare provider about plans to become pregnant and consider having optimal contraception in place before trialing these medicines since their effects can last months due to their extended half-lives.

Acute Treatment for Migraine

The Institute for Clinical and Economic Review (ICER) published an evidence report comparing the effectiveness of the newer agents for acute migraine treatment, including the "gepants."[34] The primary endpoint in all CGRP antagonist trials was pain freedom two hours after treatment. Pain relief, a secondary outcome, was defined as a decrease in headache pain from moderate or severe at baseline to mild or no pain two hours after treatment; thus, a patient with moderate or severe pain who achieved pain freedom was also counted as having pain relief. Phase III trials also measured absence of the most bothersome migraine associated symptom (i.e. photophobia, phonophobia, or nausea) two hours after treatment as a co-primary endpoint. Rimegepant (1.58, 95% credible interval (CrI): 1.29, 1.94), and ubrogepant (1.64, 95% CrI: 1.28, 2.12) all had higher odds of achieving freedom from bothersome symptoms at two hours post dose compared to placebo.

Because the primary outcomes of the trials were based on a single dose of each drug compared to placebo at two hours after initial treatment, the ability to evaluate benefit of these therapies at four hours post-dose, over time for repeated attacks, and long-term efficacy (reduced disability and improved quality of life) is limited.[34] However, for those who have not responded to triptans or have contraindications or intolerabilities to triptans, the evidence is "incremental or better" for ubrogepant and rimegepant, with "at least a small net health benefit."

Ubrogepant

Ubrogepant, brand name Ubrelvy®, is an oral tablet CGRP receptor antagonist made by Allergan.[32] Ubrogepant was approved in December 2019 and is indicated to treat acute migraine with or without aura in adults. This migraine treatment is recommended to be dosed at 50 mg or 100 mg and can be taken without food. Additionally, a second dose can be taken after 2 hours from the first dose.[32] The maximum dose or ubrogepant in a 24-hour period should not exceed 200 mg. Reported side effects included nausea (most common), somnolence (sedation and fatigue) and dry mouth. Ubrelvy® is also contraindicated with the use of strong CYP3A4 inhibitors. A meta-analysis by Yang et al. looked at relevant randomized clinical trials consisting of 3326 patients in terms of efficacy and safety of short-term use.[35] Their research collection began from the earliest available date to November 10, 2019. From the research that was conducted it was determined that ubrogepant versus placebo did lead to a greater percentage of freedom from pain (20.8% vs 12.6%, relative risk [RR] 1.65, 95% confidence interval [CI] 1.38-1.98) and absence of the most migraine-associated bothersome symptoms (37.3% vs 27.6%, RR 1.35, 95% CI 1.20-1.53) at 2 hours post dose. Other significant data that was found was when dosed at 25 mg, 50 mg, and 100 mg, there was increased pain relief when compared to the placebo. What's more, is when ubrogepant was dosed at a higher range of 50 mg and 100 mg the more bothersome symptoms were treated. More long-term research needs to be conducted to truly determine the safety, efficacy, and tolerability of ubrogepant. There is currently no established data on the safety of treating more than 8 migraines in a 30-day period.[32] Additionally, long term data is also necessary to gain more insight on usage in specific populations (pregnancy, lactation, pediatric, and geriatric use).

Rimegepant

Rimegepant, brand name Nurtec® ODT, is an orally disintegrating tablet CGRP receptor antagonist made by Biohaven Pharmaceuticals.[36] It was approved in February 2020 for the treatment of acute migraine with or without aura in adults.

The current dosing recommendations are a maximum of one 75 mg dose in 24 hours. A meta-analysis by Gao et al.[37] from January 2020 looked at evidence from the randomized controlled trials of rimegepant. Their results concluded that rimegepant was significant versus placebo in the outcomes of freedom from pain 2 hours post dose (20.6% vs 12.5%, relative risk [RR]= 1.70, 95% confidence interval [CI]: 1.39-2.08, p<0.001), freedom from most bothersome symptoms (36.0% vs 25.1%, RR= 1.44, 95% CI: 1.23-1.68, p<0.001), and pain relief at 2 hours post dose (58.6% vs 44.6%, RR= 1.34, 95% CI: 1.25-1.44, p<0.001). The manufacturer states the possible side effects as nausea and hypersensitivity reactions.[36] Notably, chest tightness or pressure was absent, as compared to the triptan class of medications. Rimegepant is also a substrate of CYP3A4, CYP2C9, P-gp transporters, and BCRP transporters, increasing the likelihood of drug-drug interactions with strong CYP, P-gp, and BCRP inhibitors.

Conclusion

While anti-CGRP migraine treatments continue to show promise for migraine prevention and acute treatment, they are still relatively new on the market, and post-market surveillance is necessary to determine long-term effects and collect evidence that will guide their use in specific populations.[38] A potential limitation of mAbs is that they are expensive (about $6000 annually, depending upon insurance coverage); however, the socioeconomic burden from migraines on patients' daily lives can be costly as well. These new treatments must be administered intravenously or subcutaneously, as compared to approved oral prevention therapies, and thus patient preference is an important consideration. And because mAbs for migraine prevention have a relatively long half-life (around 1 month) treatment adherence can be improved since they are administered much less frequently than other treatments, often taken daily.[38] Additionally, clinical benefits from the mAbs can be seen within one month, while traditional oral prevention therapies can take at least three months at therapeutic doses to see effectiveness. In most cases, CGRP antagonists have been well tolerated, including no reported cardiovascular concerns within erenumab multiyear trials.[39,40]

The oral CGRP receptor antagonists, or gepants, for acute treatment of migraine offer another alternative for patients who have experienced side effects from the other specific treatment used, namely triptans, or have health conditions worsened by vasoconstriction, precluding triptan use. Overall, these agents have about a 20% effectiveness for pain freedom at 2 hours post-dose. And while these new oral agents have only been approved for a single dose treatment regimen for acute migraine, worsening migraines with increased use of the gepants (known as medication overuse headache) have not been seen so far. The drug-interaction with CYP3A4 medications requires thoughtful consideration and monitoring. Most importantly, at present, the benefits and advantages of having another migraine-specific treatment strategy for patients suffering from debilitating headaches is a welcome option.

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Assessment Questions

1. Characteristics that can classify a migraine without aura may include:
   a. Moderate to severe pain
   b. Pulsating or throbbing
   c. Unilateral location
   d. All of the above

2. Which CGRP inhibitor was the first to be released on the market?
   a. Eptinezumab
   b. Erenumab
   c. Fremanezumab
   d. Galcanezumab

3. Which of the below statements regarding CGRP pathophysiology is FALSE?
   a. CGRP can be located in the peripheral and the central nervous system
   b. CGRP can be released during spontaneous and triggered migraine attacks
   c. CGRP is a vasodilator
   d. Targeting the CGRP ligand and receptor with monoclonal antibodies does not add specificity and produces more side effects

4. Which pair contains only acute migraine medications?
   a. Eptinezumab, Fremanezumab
   b. Galcanezumab, Rimegepant
   c. Ubrogepant, Erenumab
   d. Ubrogepant, Rimegapant

5. **True or False:** CGRP Inhibitor Monoclonal antibodies have a half-life of around one month
   a. True
   b. False

6. Which of the following below is TRUE regarding Ubrogepant?
   a. The maximum dose of Ubrogepant in a 24-hour period should not exceed 300 mg.
   b. The most common reported side effects included: Dry mouth, increased heart rate, and constipation
   c. There is plenty of established data on long term use
   d. Ubrogepant is indicated to treat acute migraine with or without aura

7. Which of the following migraine medications would most likely contribute to improved adherence rates based on a quarterly dosing frequency?
   a. Eptinezumab
   b. Erenumab
   c. Fremanezumab
   d. A and C

8. What is a common adverse effect of Fremanezumab
   a. dysphoria
   b. Irritation at injection site
   c. nausea
   d. No adverse effects were reported

9. Galcanezumab is the only FDA approved CGRP monoclonal antibody to effectively treat:
   a. Acute migraine headaches
   b. Chronic migraine headaches
   c. Episodic cluster headaches
   d. Episodic migraine headaches

10. What are the benefits of using CGRP parenteral inhibitors as migraine prevention therapy?
    a. Relatively long half-life
    b. Administration performed on a month or more regimen
    c. Well tolerated with minimal/less severe adverse effects
    d. All of the above

11. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
    a. Yes
    b. No

12. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety

of your patients.

13. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

14. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

15. How useful was the educational material?
    a. Very useful
    b. Somewhat useful
    c. Not useful

16. How effective were the learning methods used for this activity?
    a. Very effective
    b. Somewhat effective
    c. Not effective

17. Learning assessment questions were appropriate.
    a. Yes
    b. No

18. Were the authors free from bias?
    a. Yes
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20. Please indicate the amount of time it took you to read the article and complete the assessment questions.

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