Antimigraine Agents, Other
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
erenumab-aooe (Aimovig®)[1]	Amgen	Preventive treatment of migraine in adults
fremanezumab-vfrm (Ajovy®)[2]	Teva	Preventive treatment of migraine in adults
galcanezumab-gnlm (Emgality®)[3]	Eli Lilly	Preventive treatment of migraine in adults Treatment of episodic cluster headache in adults
rimegepant (Nurtec ODT™)[4]	Biohaven	Acute treatment of migraine with or without aura in adults*

* Rimegepant (Nurtec ODT) is not indicated for the preventive treatment of migraine.

OVERVIEW

Migraine Headache

Headache is one of the most common complaints by patients when presenting to a physician. Migraine accounts for 10% to 20% of all headaches in adults and affects over 39 million men, women, and children in the United States (US).[5,6] It is estimated that 18% of women, 6% of men, and 10% of children experience migraine; migraine is the sixth most disabling illness in the world.[7,8] The American Migraine Study 2 found that migraine causes decreased productivity and absenteeism from work for many patients, which creates a large economic impact for the US.[9] Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month.[10] The median frequency of migraine attacks among migraine sufferers is 1.5 per month.[11]

Migraine is a complex neurological condition that can involve debilitating headache and sensory changes.[12] During a migraine attack neurologic changes occur in the cortex, brainstem, hypothalamus, thalamus, as well as, peripheral and central portions of the trigeminovascular system. Migraine attacks are usually episodic, occurring < 15 days per month, but some migraine sufferers experience chronic daily headaches ≥ 15 days per month, often with migrainous features. Key features for the diagnosis of migraine headache includes an episodic headache lasting 4 to 72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity.[13] During the migraine at least 1 of the following are present: nausea and/or vomiting, or photophobia and/or phonophobia.

Several oral and non-oral treatments, including nonopioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs), ergotamine derivatives, triptans, and combinations, are available for acute migraine pain, depending on severity and associated systems such as nausea.[14] Due to well-established efficacy, the triptans have become the drugs of choice for treating migraine attacks. Response rate to triptans is about 60%. Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy.[15] Indications for preventive therapy include ≥ 4 migraine attacks per month or ≥ 8 migraine days per month; acute medication overuse; and debilitating migraine.[16,17] The 2012 (reaffirmed in 2015) practice guidelines by the American Academy of Neurology (AAN) and the American Headache Society (AHS) advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention (Level A).[18] Frovatriptan is established for short-term menstrually associated

migraine (MAM) prevention (Level A). Naratriptan, zolmitriptan (both for short-term MAM), antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention (Level B); however, no triptan is approved for the prevention of migraines. While there is a wide variety of agents to consider for episodic migraine prevention, side effects and failure to completely eliminate migraine attacks have resulted in an estimated adherence to therapy of only 20% after 1 year of treatment.[19] OnabotulinumtoxinA (Botox®) injection is indicated for prophylaxis of chronic migraine in adults.[20]

In 2018, the FDA approved the first calcitonin gene-related peptide (CGRP) inhibitors, erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality), for preventative treatment of migraines in adults. The American Headache Society (AHS) released a position statement on integrating new migraine treatments into clinical practice.[21] Unlike oral prophylaxis agents, the CGRP inhibitors do not require slow dose escalation, have a faster onset of therapeutic benefit, and have favorable tolerability profiles. The AHS recommends initiating CGRP inhibitors for migraine prophylaxis in patients ≥ 18 years of age with the following:

- Diagnosis of migraine (with or without aura) experiencing 4 to 7 monthly headache days with moderate disability and inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents
- Diagnosis of migraine (with or without aura) experiencing 8 to 14 monthly headache days and inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents
- Diagnosis of chronic migraine and either inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prophylactic agents or at least 6 months of onabotulinumtoxinA treatment

According to the AHS, response to CGRP inhibitor therapy should be assessed after 3 months (for monthly injections) or 6 months (for quarterly injections). Therapy should only be continued if clinically meaningful treatment benefit can be documented. The statement also addresses non-pharmacologic therapy, including neuromodulation and biobehavioral therapies.

Other therapeutic classes that are indicated for migraine prevention or with compelling data to support their use in this setting including, NSAIDs, anti-epileptic agents, beta adrenergic blockers, select triptans, and onabotulinumtoxinA (Botox), are not addressed in this therapeutic class review. This review will focus on CGRP inhibitors.

Rimegepant (Nurtec ODT), the first CGRP inhibitor approved for the acute treatment of migraine, was approved in 2020. The AHS' position statement regarding integrating new migraine treatments into practice states that rimegepant may be considered in patients who have contraindications to or have failed to respond to or tolerate at least 2 oral triptans, as assessed by a validated questionnaire.[22]

Cluster Headache

Cluster headache (CH) is a severe, primary headache disorder characterized by extreme pain on one side of the head and autonomic symptoms (e.g., nasal congestion, lacrimation).[23,24] CH periods can persist for weeks to months with daily or more frequent attacks of 15 to 180 minutes in duration. The estimated lifetime prevalence of CH is more than one in 1,000. CH can be either episodic or chronic in nature with episodic CH being the predominant form. Individuals with episodic CH experience periods of attack followed by periods of remission, whereas individuals with chronic CH have minimal to no periods of remission between headache attacks.

In 2016, the AHS published an update to the American Academy of Neurology 2010 guidelines for the treatment of cluster headache.[25] The guidance recommends sumatriptan subcutaneous (SC) at a dose of 6 mg, zolmitriptan nasal spray at a dose of 5 mg or 10 mg, and 100% oxygen at 6 to 12 L/minute for the acute treatment of episodic or chronic CH (Level A recommendation [established as effective]). Pharmacological therapies considered to be probably effective (Level B) for episodic and chronic CH include sumatriptan nasal spray 20 mg as well as zolmitriptan oral at a 5 mg or 10 mg dose. Sphenopalatine ganglion stimulation is a potential nonpharmacological treatment option for patients with chronic CH who are not satisfied with current therapy (Level B); however, it is not routinely available in the US. Octreotide 100 mcg SC as well as lidocaine 10% nasal spray are considered to be possibly effective (Level C) for both episodic as well as chronic CH. As of the date of guideline publication, insufficient evidence (Level U) existed to support the use of dihydroergotamine nasal spray, somatostatin, or prednisone. In general, the strength of the recommendation for the treatment modality should be considered in conjunction with the potential safety profile, prescriber experience, patient-specific factors, and cost. Galcanezumab-gnlm (Emgality) is the first FDA-approved treatment for episodic CH that decreases the frequency of acute attacks.[26] It was not available at the time of the AHS guideline development.

PHARMACOLOGY[27,28,29,30]

Migraine onset is believed to involve stimulation of the trigeminovascular system leading to the release of inflammatory mediators during neurogenic inflammation and/or cortical spreading depression (CSD).[31] The neuropeptide, calcitonin gene-related peptide (CGRP) is expressed in the trigeminal ganglia and acts in both the periphery to enhance nociceptor sensitization and the central nervous system (CNS) to enhance sensory input, thereby intensifying pain perception. In the periphery, CGRP may cause endothelium- and nitric oxide-independent dilation of vascular beds, including intracranial arteries. Conflicting evidence suggests that elevated levels of CGRP may occur in external jugular blood flow during migraine attack. Moreover, administration of sumatriptan have been shown to normalize elevated CGRP levels in patients with migraine.

Erenumab-aooe (Aimovig) is a human immunoglobulin G2 (IgG2) monoclonal antibody that inhibits CGRP expression by binding directly to the CGRP receptor. Fremanezumab-vfrm (Ajovy) and galcanezumab-gnlm (Emgality) are humanized IgG2 and IgG4 monoclonal antibodies, respectively, that bind to the CGRP ligand and prevent its reaching the CGRP receptor.

Rimegepant (Nurtec ODT) is a small molecule inhibitor of the calcitonin gene-related peptide receptor.

PHARMACOKINETICS[32,33,34,35]

Drug	T_{max} (day)	Half-life (days)	Metabolism	Excretion
erenumab-aooe (Aimovig)	6	28	at low concentrations, predominantly through saturable binding to target (CGRP receptor); at higher concentrations, through a proteolytic pathway	--
fremanezumab-vfrm (Ajovy)	5-7	31	enzymatic proteolysis into small peptides and amino acids	--
galcanezumab-gnlm (Emgality)	5	27	enzymatic proteolysis into small peptides and amino acids	--
rimegepant (Nurtec ODT)	1.5 hours	11 hours	primarily by cytochrome P450 3A4 (CYP3A4); no major metabolites	Feces: 78% Urine: 24%

T_{max} = time to maximum serum concentration; nr = not reported

Administration of rimegepant after a high-fat meal has led to a delay in the T_{max} by 1 hour, a reduction of the maximum concentration reached by 42% to 53%, and a reduction in overall exposure (area under the curve [AUC]) by 32% to 38%.

CONTRAINDICATIONS/WARNINGS[36,37,38,39]

Erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), galcanezumab-gnlm (Emgality), and rimegepant (Nurtec ODT) are contraindicated in patients with hypersensitivity to any component of the product. Hypersensitivity reactions including rash, pruritus, and urticaria have been reported in clinical trials with fremanezumab-vfrm; most events were mild to moderate in severity, but some led to therapy discontinuation or required corticosteroids therapy. Most occurred within hours of administration; however, some occurred days or weeks after administration. Anaphylaxis and angioedema have been reported in the postmarketing experience for erenumab-aooe and galcanezumab-gnlm.

Constipation with complications has been observed with erenumab-aooe use.

DRUG INTERACTIONS[40,41,42,43]

No drug-drug interactions are reported for erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), or galcanezumab-gnlm (Emgality).

Avoid concomitant administration of rimegepant (Nurtec ODT) with strong CYP3A4 inhibitors due to a significant increase in rimegepant exposure. Increased exposure can also occur with concurrent administration with a moderate CYP3A4 inhibitor; another dose of rimegepant should not be taken within 48 hours when used concomitantly with a moderate CYP3A4 inhibitor.

Coadministration of rimegepant and a strong or moderate CYP3A4 inducer may result in loss of effectiveness of rimegepant and should be avoided.

Rimegepant is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters. Concurrent use may lead to a significant increase in rimegepant exposure and should be avoided with an inhibitor of any of these transporters.

ADVERSE EFFECTS[44,45,46,47]

Injection site reaction, including pain, erythema, and pruritus, have been reported with the injectable CGRP agents: erenumab-aooe (Aimovig) 5% to 6% (3% placebo); fremanezumab-vfrm (Ajovy) 43% to 45% (38% placebo); and galcanezumab-gnlm (Emgality) 18% (13% placebo). Muscle spasms/cramps and constipation were reported in ≤ 3% in patients treated with erenumab-aooe. Adverse effects were found to be comparable with galcanezumab-gnlm (Emgality) when utilized for the treatment episodic cluster headache.

While anti-drug antibodies were detected for erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality), the available data were limited to determine their impact on safety and efficacy.

In clinical trials with oral rimegepant, the most common adverse reaction was nausea (2% versus 0.4% with placebo).

SPECIAL POPULATIONS[48,49,50,51]

Pregnancy

There are no adequate data regarding to inform of developmental risks associated with the use of erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), galcanezumab-gnlm (Emgality), or rimegepant (Nurtec ODT) in pregnant women.

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Fremanezumab-vfrm has a long half-life that should be considered for women who are pregnant or plan to become pregnant.

Pediatrics

Safety and effectiveness of the products in this review have not been established in pediatric patients.

Geriatrics

Clinical studies of any of the CGRP inhibitors did not include an adequate number of patients aged ≥ 65 years to determine whether elderly patients respond differently from younger patients.

Hepatic Impairment

Hepatic impairment is not expected to affect pharmacokinetics of erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), or galcanezumab-gnlm (Emgality). No dedicated clinical studies to evaluate the impact of hepatic impairment have been conducted for these agents.

No dosage adjustment of rimegepant is needed in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Its use should be avoided in patients with severe impairment (Child-Pugh C) due to increased drug plasma concentrations.

Renal Impairment

Renal impairment is not expected to affect pharmacokinetics of CGRP inhibitors. No formal clinical studies to evaluate the impact of renal impairment have been conducted for erenumab-aooe, fremanezumab-vfrm, or galcanezumab-gnlm.

No dosage adjustment of rimegepant is needed in patients with mild, moderate, or severe renal impairment. Its use has not been evaluated in those with end-stage renal disease (ESRD) or on dialysis; it should be avoided in patients with ESRD.

DOSAGES[52,53,54,55]

Drug	Indication	Dosage	Availability
erenumab-aooe (Aimovig)	Preventive treatment of migraine	70 mg SC once monthly; some patients may benefit 140 mg SC once monthly	70 mg/1 mL and 140 mg/1 mL single-dose prefilled syringe or SureClick® autoinjector (carton contains 1 syringe or autoinjector)
fremanezumab-vfrm (Ajovy)	Preventive treatment of migraine	225 mg once SC monthly or 675 mg every 3 months (administer as 3 consecutive 225 mg injections) When switching dosage options, administer the first dose of the new regimen on the next scheduled date of administration	225 mg/1.5 mL single-dose prefilled syringe (carton contains 1 syringe) 225 mg/1.5 mL single-dose prefilled autoinjector (cartons containing 1 or 3 autoinjectors)
galcanezumab-gnlm (Emgality)	Preventive treatment of migraine	240 mg SC (administered as 2 consecutive 120 mg injections) once as a loading dose, followed by 120 mg SC once monthly	120 mg/1 mL single-dose prefilled syringe and single-dose prefilled pen (carton contains 1 prefilled syringe or pen)
	Treatment of episodic cluster headache	300 mg SC (administered as 3 consecutive 100 mg SC injections) at the onset of symptoms, followed by 300 mg SC monthly through the end of the cluster period	100 mg/1 mL single-dose prefilled syringe (carton contains 3 prefilled syringes)
rimegepant (Nurtec ODT)	Acute treatment of migraine	75 mg orally; place tablet on or under the tongue Do not exceed 75 mg in a 24-hour period; safety of treating > 15 migraines in a 30-day period has not been established	Orally disintegrating tablet (ODT): 75 mg blister pack

SC = subcutaneously

Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm should be administered by SC injection only and may be self-administered with proper training. Inject in the abdomen, thigh, or upper arm. Do not inject into skin that is tender, bruised, red, or hard.

Erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm should be stored under refrigeration and placed at room temperature for at least 30 minutes prior to administration.

Components of the erenumab-aooe (Aimovig) prefilled syringe and autoinjector contain dry natural rubber (a derivative of latex), which may cause allergic reactions in latex-sensitive individuals.

Rimegepant ODT should be taken immediately after opening the blister pack.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the US comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in US, single-blind or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

erenumab-aooe (Aimovig)

In the double-blind STRIVE study, 955 patients ages 18 to 65 years with episodic migraine (defined as 4 to 14 migraine days per month), with or without aura, were randomized 1:1:1 to erenumab-aooe 70 mg, erenumab-aooe 140 mg, or placebo administered SC monthly for 6 months.[56] At baseline, mean migraine days per month (MDM) was 8.3 in the overall study population. By months 4 to 6, the mean MDM (primary endpoint) was reduced by 3.2 days in the 70 mg group (difference from placebo, -1.4 [95% confidence interval {CI}, -1.9 to -0.9]; p<0.001) and 3.7 days in the 140 mg group (difference from placebo, -1.9 [95% CI, -2.3 to -1.4]; p<0.001) compared to 1.8 days in the placebo group. A reduction in mean MDM ≥ 50% was achieved in 43.3% of patients in the 70 mg group (odds ratio [OR], 2.13 [95% CI, 1.52 to 2.98]; p<0.001) and 50% of patients in the 140 mg group (OR, 2.81 [95% CI, 2.01 to 3.94]; p<0.001) versus 26.6% in the placebo group. Serious adverse events were similar between all groups.

In the double-blind ARISE study, 577 patients with episodic migraine were randomized 1:1 to placebo or 70 mg erenumab-aooe administered SC monthly for 3 months, and 570 patients were included in the efficacy analysis.[57,58,59] By 3 months, the mean MDM was reduced by 2.9 days in the treatment group compared to 1.8 days in the placebo group (treatment difference, -1 [95% CI, -1.6 to -0.5]; p<0.001). A mean MDM ≥ 50% reduction was achieved in 39.7% of patients in the treatment group versus 29.5% of patients in the placebo group (OR, 1.59 [95% CI, 1.12 to 2.27]; p=0.01). Safety and adverse events were similar between both groups.

The double-blind LIBERTY trial assessed erenumab-aooe in 246 adults with episodic migraine, with or without aura, who had failed 2 to 4 prophylactic migraine treatments in terms of efficacy and/or tolerability.[60,61] Patients were randomized 2:1 to SC erenumab-aooe 140 mg (two 70 mg injections) or placebo every 4 weeks for 12 weeks. At week 12, 30% of patients in the erenumab-aooe group achieved mean MD ≥ 50% reduction compared with 14% of patients in the placebo group (OR, 2.7 [95% CI, 1.4 to 5.2]; p=0·002). Safety and adverse events were similar between both groups.

A double-blind study (NCT02066415) was conducted in 667 adults with a history of chronic migraine (defined as ≥ 15 headache days per month with ≥ 8 migraine days per month), with or without aura. Patients were randomized 3:2:2 to placebo, erenumab-aooe 70 mg, or erenumab-aooe 140 mg given SC monthly for 3 months.[62] At the end of the study, the mean MDM in both the 70 mg and 140 mg groups was reduced by 6.6 days compared to 4.2 days in the placebo group (treatment difference, -2.5 [95% CI, -3.5 to -1.4]; p<0.001). A reduction in mean MDM ≥ 50% was achieved in 39.9% of patients in the 70 mg group and 41.2% of patients in the 140 mg group versus 23.5% of patients in the placebo group (p<0.001). Safety and adverse event profiles were similar between all groups.

fremanezumab-vfrm (Ajovy) versus placebo

The double-blind HALO EM study (NCT02629861) assessed the safety and efficacy of fremanezumab-vfrm in 1,875 patients with episodic migraine (defined as < 15 headache days per month).[63] Patients were randomized 1:1:1 to fremanezumab-vfrm 225 mg monthly, fremanezumab-vfrm 675 mg every 3 months, or placebo monthly for 3 months. At baseline, mean MDM was 8.9, 9.3, and 9.1 in the fremanezumab-vfrm 225 mg and 675 mg groups and placebo group, respectively. By month 3, the mean MDM was reduced by 3.7 days in the 225 mg group and 3.4 days in the 675 mg group compared to 2.2 days in the placebo group (p<0.001 for each dose versus placebo). A reduction in mean MDM ≥ 50% was achieved in 47.7% of patients in the 225 mg group (difference from placebo, 19.8%; p<0.001) and 44.4% of patients in the 675 mg group (difference from placebo, 16.5%; p<0.001) versus 27.9% in the placebo group. Serious adverse events were similar between all groups.

In the HALO CM study (NCT02621931), 1,130 adults with a history of chronic migraine (defined as ≥ 15 headache days per month) were randomized 1:1:1 to fremanezumab-vfrm 675 mg initially followed by 225 mg monthly, fremanezumab-vfrm 675 mg given every 3 months, or placebo once monthly for 3 months total.[64] The results showed that the mean number of MDM in the 225 mg group and the 675 mg group were reduced by 4.6 days and 4.3 days, respectively, compared to 2.5 days in the placebo group (p<0.001 for both doses versus placebo). A reduction in mean MDM ≥ 50% was achieved in 40.8% of patients in the 225 mg group and 37.6% of patients in the 675 mg group versus 18.1% of patients with placebo (p<0.001 for both doses).

galcanezumab-gnlm (Emgality) versus placebo

The 6-month, double-blind EVOLVE-1 (n=858) and EVOLVE-2 (n=915) studies evaluated efficacy and safety of galcanezumab-gnlm in adults with episodic migraine.[65,66] Patients were randomized 2:1:1 to monthly SC placebo, galcanezumab-gnlm 120 mg, or galcanezumab-gnlm 240 mg. Patients in the 120 mg galcanezumab-gnlm arm received a 240 mg loading dose. The mean baseline migraine frequency in the studies was 9 MDM. In both trials, the primary endpoint of mean change from baseline in the number of MDM over 6 months was met for both galcanezumab-gnlm doses. In EVOLVE-1, treatment with galcanezumab-gnlm significantly reduced the mean MDM by 4.7 days (120 mg dose) and 4.6 days (240 mg dose), compared with placebo (2.8 days) (p<0.001 for both doses versus placebo); in EVOLVE-2, mean MDM were reduced by 4.3 days (120 mg) and 4.2 days (240 mg dose), and 2.3 days with placebo (p<0.001 for both doses versus placebo). Galcanezumab-gnlm was well tolerated.

The 3-month, double-blind REGAIN trial evaluated treatment with galcanezumab-gnlm in 1,113 adults with chronic migraine (defined as ≥ 15 headache days per month, of which ≥ 8 were migraines).[67] Patients were randomized 2:1:1 to monthly placebo, galcanezumab-gnlm 120 mg, or galcanezumab-gnlm 240 mg. All patients in the 120 mg galcanezumab-gnlm arm received a 240 mg loading dose. At

baseline, mean number of monthly migraine headache days at baseline was 19.4. The primary endpoint of mean change from baseline in the number of monthly migraine headache days over 3 months was met for both galcanezumab-gnlm doses: reduction of 4.8 days (120 mg dose), 4.6 days (240 mg dose), compared to 2.7 days for placebo ($p<0.001$ for both doses versus placebo). Galcanezumab-gnlm was well tolerated.

An 8-week, double-blind study (NCT02397473) evaluated the efficacy and safety of galcanezumab-gnlm in adults with episodic cluster headache.[68] Patients (n=106) were required to have with an attack frequency of a minimum of 1 attack every other day and at least 4 total attacks with no greater than 8 attacks each day for 7 consecutive days and a CH period of at least 6 weeks duration. Patients were randomized 1:1 to placebo or galcanezumab-gnlm 300 mg given SC at month 0 and month 1. At baseline, the mean number of CH attacks per week was similar between the 2 study groups (17.8 with galcanezumab versus 17.3 with placebo). The primary endpoint of overall mean change from baseline in the number of weekly CH attacks from week 1 through 3 was met for galcanezumab-gnlm: reduction of 8.7 attacks per week, compared to 5.2 attacks for placebo ($p=0.04$). Galcanezumab-gnlm was well tolerated.

rimegepant (Nurtec ODT) versus placebo

A randomized, double-blind, placebo-controlled trial (NCT03461757) evaluated the efficacy of rimegepant for the acute treatment of migraine with and without aura in adults.[69,70] Patients were randomized to 75 mg (n=732) or placebo (n=734) and instructed to treat a migraine of moderate to severe headache pain intensity with a one dose. Rescue medication, such as NSAIDs, acetaminophen, and/or an antiemetic, was allowed 2 hours after the initial treatment; triptans were not allowed within 48 hours of initial treatment. At baseline, approximately 14% of patients were taking preventive medications, and no patients were taking agents that act on the CGRP pathway. The percentage of patients who were free of headache pain at 2 hours post dose was significantly higher with rimegepant than placebo (21.2% versus 10.9%, respectively; $p<0.001$). The proportion of patients free of the most bothersome migraine symptom (MBS) (e.g., photophobia, phonophobia, nausea) was significantly higher with rimegepant than placebo (35.1% versus 26.8%, respectively; $p=0.001$). In addition, rimegepant treatment compared to placebo, respectively, resulted in significantly more patients who demonstrated pain relief at 2 hours (59.3% versus 43.3%; $p<0.001$) and sustained pain freedom at 2 to 48 hours (13.5% versus 5.4%; $p<0.001$), significantly fewer patients using rescue medication within 24 hours (14.2% versus 29.2%; $p<0.001$), and significantly more patients reporting normal function at 2 hours (38.1% versus 25.8%; $p<0.001$).

SUMMARY

Migraine is a complex neurological condition that can involve debilitating headache and sensory changes. Migraine attacks are usually episodic (< 15 headache days per month), but some migraine sufferers experience chronic daily headaches at least 15 days per month, often with migrainous features.

Triptans have become the drugs of choice for treating acute migraine attacks with a response rate of about 60%. Studies suggest that 38% to 50% of migraineurs are candidates for preventive therapy. Indications for preventive therapy include ≥ 4 migraine attacks per month or ≥ 8 migraine days per month; acute medication overuse; and debilitating migraine. General first-line recommendations for either episodic or chronic migraine prophylaxis include oral medications such as select beta-blockers,

anti-epileptics, and antidepressants; however, side effects and failure to completely eliminate headache pain result in low adherence to preventive therapy, estimated at 20% after 1 year of treatment. OnabotulinumtoxinA (Botox) injections are FDA-approved for chronic migraine prophylaxis only.

Calcitonin gene-related peptide (CGRP) may play a significant role in enhanced pain perception during a migraine attack. In 2018, the FDA approved 3 injectable anti-CGRP monoclonal antibodies, erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy), and galcanezumab-gnlm (Emgality). All 3 injectable agents are shown to be effective and well tolerated for the preventive treatment of episodic and chronic migraines. With proper training, each agent may be self-administered SC once monthly; galcanezumab-gnlm's dosing regimen includes an initial loading dose. Fremanezumab-vfrm may also be dosed once every 3 months by administering 3 consecutive injections.

The FDA also approved the oral small molecule CGRP inhibitor rimegepant (Nurtec ODT), available as the only orally disintegrating table for use on an as-needed basis, for the treatment of acute migraine attacks. Rimegepant is not indicated to prevent migraine attack.

The American Headache Society (AHS) recommends incorporating CGRP inhibitors in preventive migraine therapy in patients experiencing episodic or chronic migraine who cannot tolerate or have had and inadequate response to a 6-week trial of at least 2 oral prophylactic agents; alternatively, intolerance or inadequate response to at least 6 months of onabotulinumtoxinA is appropriate in patients with chronic migraine. Similarly, rimegepant, the only CGRP inhibitor approved for the acute treatment of migraine, is recommended in patients who have failed at least 2 oral triptan agents or are not candidates for triptan use.

One of the 3 FDA approved anti-CGRP monoclonal antibodies, galcanezumab-gnlm (Emgality), also has received approval for the treatment of cluster headache (CH) based on data demonstrating a significant reduction in the number of CH attacks per week compared to placebo. CH are extremely painful headaches on 1 side of the head accompanied by autonomic symptoms. The AHS guidelines for treating CH do not currently address the use of galcanezumab-gnlm due to the recent approval; however, galcanezumab-gnlm is the first FDA-approved therapy to decrease the frequency of episodic CH attacks.

REFERENCES

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