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CGRP Antagonists in Migraine Prophylaxis

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Introduction

Migraine headache is a common disabling neurological disorder. A headache condition can be classified as chronic migraine (CM) if headaches occur on 15 or more days per month for more than 3 months.[1] Episodic migraine (EM) is a similar condition, but headaches occur less frequently, typically between 4 to 14 days per month.[1] Additionally, headaches must have migraine features (e.g. aura, gastrointestinal symptoms, sensitivity to light) on at least 8 of the 15 migraine days to be considered chronic.[1] Calcitonin Gene-Related Peptide (CGRP) antagonists are the most recent class of preventative migraine therapies. The purpose of this newsletter is to review existing medications used to prevent migraine and the role of CGRP antagonists in patients with migraine.

Several therapies are used for abortive therapy of acute migraine including triptans, ergotamines, non-steroidal anti-inflammatory drugs (NSAIDs), and combination analgesics containing aspirin, caffeine and acetaminophen. These medications are effective for the acute treatment of migraines and are taken at onset of migraine symptoms.

Individuals who experience at least two headaches per month, experience migraines uncontrolled by acute treatment, or have extreme disability from migraines may be eligible for migraine prevention therapies.[2] For patients experiencing greater than 8 migraines per month it is important that a physician assesses for medication overuse, or rebound migraine headaches as this is a common occurrence in patients experiencing an extensive number of headache days per month. Patients can experience medication overuse headaches with the repeated use of analgesics, such as NSAIDs or acetaminophen, if taking ≥ 15 days per month for greater than 3 months.[3] Additionally, other analgesics or combinations of medications may lead to rebound headache if used ≥ 10 days per month for greater than 3 months.[4]

The goal of preventive therapy is to reduce duration, frequency and severity of migraine attacks, thus improving patient's overall quality of life.[2] Evidence suggests that traditional migraine preventative therapies, such as topiramate, reduce headache frequency as patients were twice as likely to reduce their number of monthly migraine days by 1.2 days when compared with placebo (-1.20; 95% confidence interval (CI) -1.59 to -0.80).[5] The American Academy of Neurology (AAN) and the American Headache Society (AHS) recommendations for the prevention of migraines include agents listed in **Table 1**.

Table 1. Evidence Level of Existing Migraine Preventative Therapies[6,7]

Level A - Established Efficacy (≥2 Class I studies)			
Topiramate	Metoprolol	Divalproex sodium	
Propranolol	Timolol	Sodium Valproate	
		OnabotulinumtoxinA*	
Level B - Probably Effective (1 Class I or 2 Class II studies			
Amitriptyline	Venlafaxine	Atenolol	Nadolol
Level C - Possibly Effective (1 Class II study)			
Lisinopril	Candesartan	Clonidine	Guanfacine
Carbamazepine	Nebivolol	Pindolol	Cyproheptadine
Level D - Ineffective or Insufficient Data			
Verapamil	Gabapentin	Bisoprolol	Lamotrigine

* Recommended for prophylaxis of chronic migraine only.[7]

Calcitonin Gene-Related Peptide Antagonists

Calcitonin Gene-Related Peptide, a potent pro-inflammatory, pain signaling vasodilator found within the central and peripheral nervous systems, is the main target for new agents aimed at preventing migraines.[8] During migraine attacks, CGRP levels decrease after the administration of triptan agents.[8] Additionally, elevated serum CGRP levels have been found in EM and in even greater levels in CM.[8] New migraine prophylactic agents are targeted monoclonal antibodies with long half-lives, that alter the CGRP pathway by either antagonizing the CGRP receptor complex, or by targeting CGRP itself.[8] The 3 Food and Drug Administration (FDA) approved CGRP antagonists are erenumab (Aimovig•), fremanezumab (Ajovy•), and galcanezumab (Emgality•). All 3 medications are indicated for migraine prophylaxis. Galcanezumab has an additional indication for treatment of cluster headache. Studies that evaluated the CGRP antagonists for prophylaxis of both EMs and CMs are presented in **Table 2**. The definition of CM and EM used in the studies is as previously described in the first paragraph. The primary efficacy outcome in all of the trials was change in monthly (4-week span) migraine days. All studies reported an average reduction between 1.0 to 2.1 migraine days compared to placebo. Trial design for individual drugs are summarized below. A fourth CGRP antagonist, eptinezumab, is currently being studied in Phase 3 trials and additional drugs are in the pipeline. Eptinezumab is administered via intravenous infusion every 3 months, which is a unique route of administration for this class of drugs, as all drugs within this class are administered subcutaneously (SC).

Erenumab (Aimovig®)

Two phase 3 randomized control trials (RCTs), ARISE and STRIVE, evaluated the efficacy of 70 mg and 140 mg monthly erenumab compared to placebo in reducing EM frequency over the span of 3 and 6 months respectively. Both trials included patients with EM who had experienced migraine for at least 12 months prior to study enrollment.[9,10] Those who had failed more than two classes of migraine prevention treatments, had used onabotulinumtoxin-A within 4 months, or used a device for migraine within 2 months of screening were excluded.[9,10] Both trials resulted in a statistically significant reduction in monthly migraine days with erenumab 70 mg (-2.9 to -3.2 days) and 140 mg (-3.7 days) compared to placebo (-1.8 days, $p<0.001$ for all comparisons).[9,10] The recommended dose of erenumab is 70 mg injected SC once monthly, with some patients benefiting from 140 mg monthly.[11]

Fremanezumab (Ajovy®)

Fremanezumab was evaluated in two phase 3 RCTs for both chronic and episodic migraine prophylaxis.[12,13] Disqualifying criteria included using opioids or barbiturates on more than 4 days during the pretreatment baseline or failing 2 or more preventative migraine medication classes after 3 months of treatment.[12,13] Additionally, use of onabotulinumtoxinA 4 months prior to screening or use of devices for migraine 2 months prior to screening was not permitted.[12,13] Both studies compared fremanezumab 225 mg monthly or 675 mg every three months to placebo. However, in HALO the participants in the monthly arm received a 675 mg injection at baseline followed by a 225 mg injection at weeks 4 and 8. This dosing protocol was not assessed in the EM study.[12,13] In the HALO study, fremanezumab significantly reduced the number of migraine days (675 mg, -4.3 days and 225 mg, -4.6 days) compared to placebo (-2.5 days, p <0.001 for both doses).[13] The recommended dose of fremanezumab is 225 mg SC once a month or 675 mg (given as 3 consecutive injections of 225mg each) every 3 months.[14]

Galcanezumab (Emgality®)

Two phase 3 RCTs, EVOLVE-1 and EVOLVE-2, compared galcanezumab 120 or 240 mg monthly to placebo in patients with EM.[15,16] The majority of subjects (60.0% to 65.5%) had previously used migraine preventative agents; however, only 4.9% and 14.3% had failed 2 or more medications respectively.[15,16] Patients were excluded if they failed treatment with three or more migraine prophylactic agents from Level A or Level B in **Table 1**.[15,16] Other exclusion criteria included using opioids or barbiturates more than twice per month or exposure to any therapeutic antibody within the past 12 months.[15,16] These studies differed from previous trials as concomitant use of a migraine prophylactic agent was not permitted.[15,16] The EVOLVE-1 study differed from EVOLVE-2 as it only assessed patients in North America, whereas the latter was a global study.[15] In the EVOLVE-1 study, galcanezumab significantly reduced the number of migraine days (120 mg, -4.7 days and 240 mg, -4.6 days) compared to placebo (-2.8 days p<0.001 with both doses; **Table 2**)[15]. In the EVOLVE-2 study, galcanezumab significantly reduced the number of migraine days (120 mg, -2.02 days and 240 mg, -1.90 days) compared to placebo (-2.3 days p<0.001 with both doses; **Table 2**).[16] The recommended dose of galcanezumab is to begin with a 240mg loading dose followed by monthly doses of 120mg administered via the SC route.[17]

Safety Data

In general, CGRP antagonists are well tolerated and discontinuations due to adverse events were similar compared to placebo. The most common adverse events (AEs) reported during clinical trials included injection site pain, induration, and erythema.[9,10,12,13,15,16] Considering CGRP possesses vasodilatory properties that can be released during ischemia, there is a theoretical risk that patients with existing cardiovascular conditions may be at a higher risk for a cardiac event when CGRP is inhibited.[9] In the ARISE trial, it was noted that cardiac related AEs were low and did not differ between comparators.[9] However, ARISE excluded patients with history of myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or revascularization 12 months prior to study screening.[9] Therefore, more data is needed to delineate cardiovascular risk.

Table 2. Study Results for CGRP Antagonists[7-11]

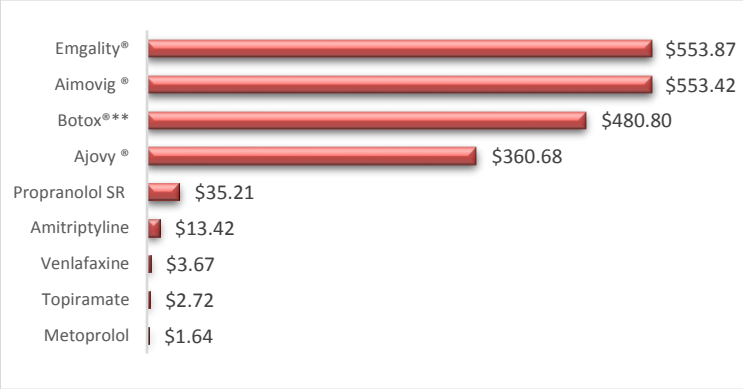
	Diagnosis	Study Comparator Arms	Primary Endpoint: Change in Monthly Migraine Days
Erenumab			
ARISE (N=577)[9]	Episodic Migraine	70 mg monthly vs. Placebo	LSMD -1.0 95% CI -1.6 to -0.5 p<0.001
STRIVE (N=955)[10]	Episodic Migraine	70 mg monthly or 140 mg monthly vs. Placebo	**70 mg vs. placebo** LSMD -1.4 95% CI -1.9 to -0.9 p<0.001 **140 mg vs. placebo** LSMD -1.9 95% CI -2.3 to -1.4 p<0.001
Fremanezumab			
HALO[13] (N=1130)	Chronic Migraine	675 mg every 3 months or 675 mg LD, 225 mg monthly vs. Placebo	**675 mg vs. placebo** LSMD -1.8 p<0.001 CI NR **225 mg vs. placebo** LSMD -2.1 p<0.001 CI NR
Dodick DW, et al.[12] (N=875)	Episodic Migraine	675 mg every 3 month or 225 mg monthly vs. Placebo	**675 mg vs. placebo** LSMD -1.3 95% CI -1.79 to -0.72 p<0.001 **225 mg vs. placebo** LSMD -1.5 95% CI -2.01 to -0.93 p<0.001
Galcanezumab			
EVOLVE-1[15] (N=858)	Episodic Migraine	120 mg monthly or 240 mg monthly vs. Placebo	**120 mg vs. placebo** LSMD -1.9 95% CI -2.5 to -1.4 p<0.001 **240 mg vs. placebo** LSMD -1.8 95% CI -2.3 to -1.2 p<0.001
EVOLVE-2[16] (N=915)	Episodic Migraine	120 mg monthly or 240 mg monthly vs. Placebo	**120 mg vs. placebo** LSMD -2.0 95% CI -2.6 to -1.5 p<0.001 **240 mg vs. placebo** LSMD -1.9 95% CI -2.4 to -1.4 p<0.001

Abbreviations: CI=confidence interval; LD=loading dose; LSMD=least squares mean difference; mg=milligrams; N=number; NR=not reported

Study Limitations

Several limitations were identified in an analysis of the CGRP antagonist studies. All studies excluded participants who had previously failed a certain number of migraine prophylactic agents. Also, the number of prophylaxis naïve patients was surprisingly high, thus making it difficult to apply efficacy and safety data from these studies to individuals in which CGRP antagonists are most likely indicated**.** Additionally, several studies enrolled a majority of Caucasian female subjects, therefore evidence is greatly limited in males and other ethnic groups. All of the studies analyzed compared their treatment to placebo only, despite the fact that there are a number of well-established prophylactic agents that are used in practice. Lastly, trials analyzed patient responses over a short period of three to six months and the absolute change in monthly migraine days was modest at best. Due to evidence limitations and high cost of CGRP inhibitor therapies **(Figure 1),** traditional migraine preventative agents are still recommended by the AAN/AHA and are outlined in **Table 1.**

Figure 1. Monthly Migraine Prevention Agents*



* Costs based on a 30-day supply of approved max daily dosages for migraine prevention. Costs obtained from the Oregon Health Authority's Average Actual Acquisition Cost (AAAC) Rate Listing Effective as of September 17, 2019.
** 30-day cost estimate is based on average wholesale price (AWP).

Conclusion

The CGRP antagonist class has demonstrated efficacy in reducing the average monthly migraine days compared to placebo. Short-term studies, exclusion of patients with comorbidities and lack of direct comparative efficacy and safety evidence between the CGRP antagonists are limitations to current evidence. For these reasons, all CGRP antagonists require prior authorization prior to dispensing in the Medicaid Fee-For-Service population.

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