In This Issue

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Erenumab-aooe (Aimovig™) for Prevention of Episodic Migraine

By: Mary Grace Fitzmaurice, Pharm.D.

Background: Migraines described as severe, throbbing headaches are often preceded by an aura of neurological symptoms (e.g., sensitivity to light and sound, dysphasia, and unilateral weakness).[1,2] These debilitating headaches, which can last hours to days, most commonly occur in women 30 to 39 years old.[1,3] Current preventative migraine treatments (e.g., beta blockers, calcium channel blockers, antidepressants, and anticonvulsants) have variable efficacy and in some cases unacceptable side effects.[4] Erenumab-aooe (Aimovig™;Amgen, Inc), a once-monthly injectable monoclonal antibody, could serve as a therapeutic option for patients unable to achieve migraine relief from other therapies. It was approved by the Food and Drug Administration (FDA) in May 2018 for the preventive treatment of migraine in adults.[5] The generic name of erenumab contains the suffix "aooe"; suffixes for new biological agents are now required by the FDA to help distinguish future biosimilar agents which possess the same generic name.[6]

Mechanism of Action: Calcitonin gene-related peptide (CGRP) is a potent vasodilator and pain sensitizer.[7] Release of CGRP from the activated trigeminal nerve results in consistent pain impulses sent to the brain and increased sensitivity to external stimuli such as light and sound.[8] Erenumab blocks the binding of CGRP to its receptor thus reducing the occurrence of migraines.[9]

Key Clinical Trial: A multi-center, randomized, phase III trial (STRIVE) evaluated erenumab for the prevention of migraines.[4] Patients (N=955) between the ages of 18 to 65 years old with a history of migraines with or without aura for at least 12 months before screening were randomly assigned

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Lofexidine (Lucemyra™) for Treatment of Opioid Withdrawal

By: Derek Montgomery, Pharm.D.

Background: Opioid use disorder (OUD), a chronic relapsing condition, has significant public health consequences.[1] Approximately 2 million Americans suffer from OUD with the majority abusing solely prescription opioids.[2] Opioid withdrawal in patients with OUD is often associated with symptoms of tachycardia, restlessness, and craving making it very difficult for patients to discontinue illicit drug use.[3] Until 2017, only two therapies were approved by the Food and Drug Administration (FDA) for the treatment of acute opioid withdrawal, methadone and buprenorphine, both of which have abuse potential.[4] Clonidine, a non-addictive agent, often used off-label to treat withdrawal, has a high rate of bradycardia and hypotension.[1,5] In May 2018, lofexidine (Lucemyra™; US WorldMeds), an agent similar to clonidine with less cardiovascular side effects, was FDA-approved for the mitigation of opioid withdrawal symptoms associated with abrupt opioid discontinuation in adults.[6]

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to receive erenumab 70 mg (n=317), erenumab 140 mg (n=319), or placebo (n=319) given subcutaneously once a month. The median age of the participants was 42 years old, 85% of whom were female. The primary endpoint was the difference in mean number of migraine days per month from baseline to the final 3 months (months 4 through 6) of the treatment phase. Key secondary endpoints were at least a 50% reduction from baseline in the mean number of migraine days per month and a change from baseline in the mean number of days of acute migraine-specific medication (e.g., triptans, ergotamine derivatives) use. With regards to the primary outcome, the reduction in mean migraine days per month was 3.2 days in the erenumab 70 mg group and 3.7 days in the erenumab 140 mg group, as compared with a reduction of only 1.8 days in the placebo group ($p<0.001$ for both treatment groups compared with placebo). A 50% reduction in the mean number of migraine days per month was seen at months 4 through 6 for 43.3% of patients in the 70 mg dose group and 50% of patients in the 140 mg dose group as compared to 26.6% of patients in the placebo group ($p<0.001$ for both treatment groups compared with placebo). There was also a statistically significant difference in mean number of days of acute migraine-specific medication use per month, with a reduction of 1.1 days in the 70 mg group and 1.6 days in the 140 mg group versus a reduction of only 0.2 days in the placebo group ($p<0.001$ for both treatment groups compared with placebo). The frequency and severity of adverse events were similar between both erenumab groups and placebo. Based on these results, the authors concluded that erenumab is a potential therapeutic option for migraine prophylaxis.

Safety and Immunogenicity: There are no contraindications to the use of erenumab.[5] The most common drug-related side effects that occurred in ≥3% of patients in clinical trials evaluating erenumab were injection site reactions and constipation. The incidence of anti-erenumab antibody development was 6.2% (48/778) in patients receiving the 70 mg dose and 2.6% (13/504) in patients receiving the 140 mg dose.

Dosing and Administration: The usual dose of erenumab is 70 mg given subcutaneously once a month, however some patients may benefit from a 140 mg monthly dose given as two consecutive 70 mg injections.[5] Erenumab is stored in the refrigerator. Prior to injecting, it should be warmed to room temperature for at least 30 minutes. It can be injected in the abdomen, thigh, or upper arm by both patients and caregivers.[5,10]

Cost and Availability: Erenumab is available as the brand-name product Aimovig™, supplied as 70 mg/mL single-dose prefilled SureClick® autoinjector NDC 55513-841-01 or as a pack of two 70 mg/mL single-dose prefilled autoinjectors NDC 55513-841-02 which may be used for the 140 mg dose.[5] The average wholesale price of Aimovig™ is $690 for a one-month supply of either 70 mg individual or two-pack of 70 mg autoinjectors.[9] The needle shield within the white cap of the autoinjector contains latex and may cause an allergic reaction in patients who are sensitive to latex.[5]

Formulary Status: Erenumab is not currently on the CCHS Formulary.

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Mechanism of Action: Like clonidine, lofexidine is a centrally-acting alpha-2 adrenergic agonist.[7] Alpha-2 adrenergic agonists reduce the release of norepinephrine preventing the adrenergic side effects associated with opioid withdrawal. A key difference between lofexidine and clonidine is their affinities to the alpha-2 adrenergic receptor subtypes, which is theorized to be responsible for lofexidine's lower incidence of bradycardia and hypotension.

Key Clinical Trial: One of the phase III studies involved in the FDA-approval of lofexidine was a randomized, multicenter, double-blind, placebo-controlled trial.[4] Patients (N=264) were randomized 1:1 to receive either 0.8 mg of lofexidine hydrochloride (HCL) four times daily (n=134) or matching placebo (n=130) for 5 days. The active treatment intervention was followed by 2 days of both intervention groups receiving placebo and a final day of no study medication to assess a post-treatment washout period. The study had two co-primary endpoints which were the Gossop Short Opioid Withdrawal Scale (SOWS-Gossop) score at day three of the study and time-to-dropout. The SOWS-Gossop scale is a subjective patient performed survey to assess withdrawal symptoms which ranks ten symptoms on a scale from zero to three, with zero being no symptoms and three being severe symptoms. A difference of two to four points is considered a clinically significant difference in withdrawal symptoms. The lofexidine group had a mean SOWS-Gossop score at day three of 6.32 (standard deviation (SD) ±4.71) versus the placebo group score of 8.67 (SD ±5.54) for a decrease of 2.4 points (p=0.0212). Since the study period was so short, the time to discontinuation of therapy was measured in 6 hour time quadrants. The mean time to early termination of therapy was longer for the lofexidine group than the placebo group (6.9 time quadrants versus 6.4 time quadrants respectively, p=0.0034). However overall retention in the study was low with only 37% of the lofexidine group (n=50) and 27% of the placebo group (n=35) completing the entire 8 day study period (p=0.0867). Based on the results of this study, the authors concluded that lofexidine could be considered as a non-opioid alternative for treatment of opioid withdrawal symptoms

Safety: The most common side effects of lofexidine are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.[6] Lofexidine could prolong the QT interval, so ECG monitoring is recommended in patients with conditions or medications which could lengthen the QT interval. It is recommended to avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, severe bradycardia, chronic renal failure, and congenital long QT syndrome.

Dosing and Administration: The recommended initial dose of lofexidine is three 0.18 mg tablets given four times daily by mouth at 5 or 6 hour intervals.[6] During the period of peak withdrawal symptoms (usually the first 5 to 7 days after the last use of opioids) dosing should be guided by symptoms and side effects with the maximum single dosage to not exceed 0.72 mg (four tablets) or total daily dose of 2.88 mg (16 tablets). There should be at least 5 to 6 hours between each dosage. Specific dosage adjustments based on renal or hepatic impairment are included in the package insert. Therapy can be continued for up to 14 days and should be titrated in response to patient's symptoms. A withdrawal effect leading to reflex hypertension can be seen with abrupt discontinuation of lofexidine, therefore, a gradual dose reduction over 2 to 4 days is recommended. Lofexidine will not completely prevent the symptoms of opioid withdrawal and should be used as part of a complete treatment plan.

Cost and Availability: Lofexidine is available as a 0.18 mg tablet containing 0.2 mg of lofexidine HCL.[6] Two sizes are available; a bottle of 36 tablets, NDC 27505-050-36, and a bottle of 96 tablets, NDC 27505-50-96. The average wholesale price is $24.83 per tablet leading to a cost of approximately $2085 for a 7 day course of therapy at the recommended initial dosing.[8]

Formulary Status: Lofexidine is not currently on the CCHS Formulary.

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