

Review Article

Erenumab aooe: a milestone for the preventive treatment of migraine

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ABSTRACT

Migraine is a complex neurological condition, which can affect the whole body and can result in many symptoms as nausea, vomiting, photophobia (Increased sensitivity to light), phonophobia (Increased sensitivity to sound) and osmophobia (Increased sensitivity to smell). Neurological symptoms that include visual disturbances such as blind spots, distorted vision, flashing lights or zigzag patterns. Other common symptoms includes- dizziness, vertigo, tingling sensations in the limbs, an inability to concentrate, confusion, difficulty in speaking, paralysis or loss of consciousness (in very rare cases). These symptoms, often called 'aura'. Migraine attacks may differ in their frequency, duration and severity, although, normally they last between 4 and 72 hours, and most people are symptom-free between attacks. There are many drugs for the treatment of acute attack of migraine which can be divided into mild, moderate and severe attacks. In mild case NSAIDs like Paracetamol, Ibuprofen are prescribed. In moderate cases Anti-emetics like metoclopramide, domperidone can be prescribe with combinations of NSAIDs or triptans as sumatriptan. In case of severe cases triptans can be prescribed with ergot alkaloids and antiemetics. Following drugs are prescribed for the prophylaxis of migraine as sodium valproate, amitriptyline (Tricyclic antidepressant), propranolol and metoprolol (beta blockers). Erenumab-aooe is a calcitonin gene-related peptide receptor antagonist. It is specifically indicated for the preventative treatment of migraine in adults. Erenumab-aooe is supplied as an injection for subcutaneous use. The recommended dosage is 70 mg injected subcutaneously once monthly. Some patients may benefit from a dosage of 140 mg injected subcutaneously once monthly, which is administered as two consecutive subcutaneous injections of 70 mg each. Erenumab-aooe is a human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor and antagonizes CGRP receptor function.

Keywords: CGRP receptor, NSAIDs, Osmophobia, Phonophobia, Photophobia

INTRODUCTION

A migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe. Typically, the headaches affect one half of the head, are pulsating in nature, and last from two to 72 hours. Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell.¹ Migraines are believed to be due to a mixture of environmental and genetic factors.²

About two-thirds of cases run in families.³ Changing hormone levels may also play a role, as migraines affect slightly more boys than girls before puberty and two to three times more women than men.⁴

The risk of migraines usually decreases during pregnancy. The underlying mechanisms are not fully known. They are, however, believed to involve the nerves and blood vessels of the brain.

Signs and symptoms

Migraines typically present with self-limited, recurrent severe headache associated with autonomic symptoms.⁵ About 15-30% of people with migraines experience migraines with an aura.⁶ It includes symptoms as nausea, vomiting, photophobia (Increased sensitivity to light), phonophobia (Increased sensitivity to sound) and osmophobia (Increased sensitivity to smell). Migraines are associated with major depression, bipolar disorder, anxiety disorders, and obsessive compulsive disorder. These psychiatric disorders are approximately 2-5 times more common in people without aura, and 3-10 times more common in people with aura.⁷ There are four possible phases to a migraine:

The prodrome phase

Which occurs hours or days before the headache including altered mood, irritability, depression or euphoria, fatigue, stiff muscles (especially in the neck), constipation or diarrhea, and sensitivity to smells or noise.⁸ This may occur in those with either migraine with aura or migraine without aura.

The aura phase

An aura is a transient focal neurological phenomenon that occurs generally last less than 60 minutes.⁹ Symptoms can be visual, sensory or motor in nature and many people experience more than one.

The pain phase

Also known as headache phase. Classically the headache is unilateral, throbbing, and moderate to severe in intensity.¹⁰ It usually comes on gradually and is aggravated by physical activity. In more than 40% of cases, however, the pain may be bilateral and neck pain is commonly associated with it. Bilateral pain is particularly common in those who have migraines without an aura. Less commonly pain may occur primarily in the back or top of the head. The pain usually lasts 4 to 72 hours in adults, however in young children frequently lasts less than 1 hour.¹¹ The frequency of attacks is variable, from a few in a lifetime to several a week, with the average being about one a month

The postdrome

The migraine postdrome could be defined as that constellation of symptoms occurring once the acute headache has settled.¹²

The person may feel tired or "hung over" and have head pain, cognitive difficulties, gastrointestinal symptoms, mood changes, and weakness.¹³ According to one summary, "Some people feel unusually refreshed or euphoric after an attack, whereas others note depression and malaise."¹³

Cause

The underlying causes of migraines are unknown. However, they are believed to be related to a mix of environmental and genetic factors. They run in families in about two-thirds of cases and rarely occur due to a single gene defect.¹⁴ While migraines were once believed to be more common in those of high intelligence, this does not appear to be true. A number of psychological conditions are associated, including depression, anxiety, and bipolar disorder.

Migraine is neurovascular disorder and it occurs due to dilatation of cranial blood vessels.

Prevention and treatment

Preventive treatments of migraines include medications, nutritional supplements, lifestyle alterations, and surgery. Prevention is recommended in those who have headaches more than two days a week, cannot tolerate the medications used to treat acute attacks, or those with severe attacks that are not easily controlled. The goal is to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of abortive therapy.¹⁵ Another reason for prevention is to avoid medication overuse headache. This is a common problem and can result in chronic daily headache.¹⁶ Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50%.¹⁷ Guidelines are fairly consistent in rating topiramate, divalproex/sodium valproate, propranolol, and metoprolol as having the highest level of evidence for first-line use for prophylaxis.¹⁸ Recommendations regarding effectiveness varied however for gabapentin and pregabalin.¹⁸ Timolol is also effective for migraine prevention and in reducing migraine attack frequency and severity, while frovatriptan is effective for prevention of menstrual migraine.¹⁸ Tentative evidence also supports the use of magnesium supplementation.¹⁹ Increasing dietary intake may be better.²⁰ Amitriptyline and venlafaxine are probably also effective.²¹ Angiotensin inhibition by either an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist may reduce attacks.

REVIEW OF LITRETURE

Erenumab-aooe is a calcitonin gene-related peptide receptor antagonist. Erenumab-aooe is specifically indicated for the preventative treatment of migraine in adults. Erenumab-aooe is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells. It composed of 2 heavy chains, each containing 456 amino acids, and 2 light chains of the lambda subclass, each containing 216 amino acids, with an approximate molecular weight of 150 kDa. Aimovig is supplied as an injection for subcutaneous use. It is supplied as a sterile, preservative-free, clear to opalescent, colourless to light yellow solution for subcutaneous administration. The

recommended dosage of Aimovig is 70 mg injected subcutaneously once monthly. Some patients may benefit from a dosage of 140mg injected subcutaneously once monthly, which is administered as two consecutive subcutaneous injections of 70mg each. If a dose of Aimovig is missed, administer as soon as possible. Thereafter, Aimovig can be scheduled monthly from the date of the last dose. It was the first of the group of CGRPR antagonists to be approved in 2018.

Mechanism of action

Erenumab-aooe is a human monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) receptor and antagonizes CGRP receptor function. This is the receptor that is believed to transmit signals that can cause incapacitating pain.

Immunogenicity

The immunogenicity of Erenumab-aooe has been evaluated using an Immunoassay for the detection of binding anti- Erenumab-aooe antibodies. For patients whose sera tested positive in the screening immunoassay, and *in vitro* biological assay was performed to detect neutralizing antibodies. In controlled studies with Erenumab-aooe, the incidence of Erenumab-aooe antibody development was 6.2% (48/778) in patients receiving Erenumab-aooe 70 mg once monthly (2 of whom had *in vitro* neutralizing activity) and 2.6%(13/504) in patients receiving Erenumab-aooe 140 mg once monthly (none of whom had *in vitro* neutralizing activity).

Pharmacodynamics

In a randomized, double-blind, placebo-controlled study in healthy volunteers, concomitant administration of Erenumab-aooe (140mg intravenous, single) with sumatriptan (12mg subcutaneous, given as two 6mg doses separated by one hour) had no effect on resting blood pressure compared with sumatriptan alone. Erenumab-aooe is for subcutaneous use only.

Pharmacokinetics

Erenumab-aooe exhibits non-linear kinetics as a result of binding to the CGRP receptor. The C_{max} mean and AUC_{last} mean following subcutaneous administration of a 70mg once monthly and a 140mg once monthly dose in healthy volunteers or migraine patients are included in Table 1.

The effective half life of Erenumab-aooe is 28 days. The median peak serum concentrations were attained in approximately 6days, and estimated absolute bioavailability was 82%.Following a single 140mg intravenous dose, the mean(SD) volume of distribution during the terminal phase(V_z) was estimated to be 3.86 (0.77)L.

Table 1: Pharmacokinetic parameters of Erenumab-aooe.

	Erenumab-aooe70mg Subcutaneousl y Once Monthly	Erenumab-aooe70mg Subcutaneousl y Once Monthly
C_{max} mean(SD) ^{a,b}	6.1 (2.1) mcg/mL	15.8 (4.8) mcg/mL
AUC_{last} mean(SD) ^{a,b}	159 (58)day* mcg/mL	505 (139)day* mcg/mL
C_{min} (SD)		
Episodic migraine	5.7 (3.1) mcg/mL	12.8 (6.5) mcg/mL
Chronic migraine	6.2 (2.9) mcg/mL	14.9 (6.5) mcg/mL

^aSD=standard deviation

^bfrom a single-dose study

At low concentration, the elimination is predominantly through saturable binding to target (CGRP receptor), non-saturable proteolytic pathway.

The pharmacokinetics of Erenumab-aooe was not affected by age, gender, race or subtypes of migraine spectrum (episodic or chronic migraine) based on population pharmacokinetics analysis. Population pharmacokinetic analysis of integrated data from the Erenumab-aooe clinical studies did not reveal a difference in the pharmacokinetics Erenumab-aooe in patients with mild or moderate renal impairment relative to those with normal renal function. Patient with severe renal impairment (eGFR<30mL/min/1.73m²) have not been studied. No dedicated clinical studies were conducted to evaluate the effect of hepatic and renal impairment on the pharmacokinetics of Erenumab-aooe.

Adverse effects

Table 2: Adverse effects occurring with an incidence of at least 2% for either dose of Erenumab-aooe and at least 2% greater than placebo during the first 3 months in studies 1, 2 and 3.

Adverse Effects	Erenumab-aooe 70mg subcutaneously once monthly N=787%	Erenumab-aooe 140mg subcutaneously once monthly N=507%	Placebo N=890%
Injection site reactions ^a	6	5	3
Constipation	1	3	1
Muscle cramps and spasm	< 1	2	< 1

^aInjection site reactions include multiple adverse reactions related terms, such as injection site pain and injection site erythema.

Drug interaction

Erenumab-aooe is not metabolized by cytochrome P450 enzymes. Therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. Erenumab-aooe did not affect the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and norgestimate. In a study in healthy volunteers, concomitant administration of Erenumab-aooe with sumatriptan had no effect on the pharmacokinetics of sumatriptan.

DISCUSSION

FDA approval

The FDA approval of Erenumab-aooe as a preventive treatment of episodic or chronic migraine was based on three randomized, double-blind, placebo-controlled studies: two studies in patients with episodic migraine (4 to 14 migraine days per month)(Study 1 and Study 2) and one study in patients with chronic migraine (≥ 15 headache days per month with ≥ 8 migraine days per month) (Study 3). The studies enrolled patients with a history of migraine, with or without aura, according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria.

Study 1

A randomized, multi-center, 6-month, placebo-controlled, double-blind study evaluating Erenumab-aooe for the preventive treatment of episodic migraine. A total of 955 patients with a history of episodic migraine were randomized to receive either Erenumab-aooe 70 mg (N = 317), Erenumab-aooe 140 mg (N = 319), or placebo (N = 319) by subcutaneous injection once monthly (QM) for 6 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives) and NSAIDs during the study. The primary efficacy endpoint was the change from baseline in mean monthly migraine days over months 4 to 6. Subjects in the Erenumab 70 mg and 140 mg treatment arms experienced reductions of 3.2 and 3.7 days from baseline in monthly migraine days, respectively, as compared to a 1.8-day reduction in the placebo arm.

Study 2

A randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating Erenumab-aooe for the preventive treatment of episodic migraine. A total of 577 patients with a history of episodic migraine were randomized to receive either Erenumab-aooe 70 mg (N = 286) or placebo (N = 291) by subcutaneous injection once monthly for 3 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives) and

NSAIDs during the study. The primary efficacy endpoint was the change from baseline in monthly migraine days at month 3. The subjects receiving Erenumab experienced a statistically significant 2.9-day reduction from baseline in monthly migraine days, as compared to a 1.8-day reduction in the placebo arm.

Study 3

A randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating Erenumab-aooe as a preventive treatment of chronic migraine. A total of 667 patients with a history of chronic migraine with or without aura were randomized to receive Erenumab-aooe 70 mg (N = 191), Erenumab-aooe 140 mg (N = 190), or placebo (N = 286) by subcutaneous injections once monthly for 3 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives) and NSAIDs during the study. The primary efficacy endpoint was the change from baseline in monthly migraine days at month 3. The reduction in migraine days was statistically significant for both the 70 mg and 140 mg doses. Patients experienced a 6.6-day reduction from baseline in monthly migraine days in each of the Erenumab treatment arms as compared to a 4.2-day reduction in the placebo arm.

Use in specific populations

Pregnancy

There is no adequate data on the developmental risk associated with the use of Erenumab-aooe in pregnant women. No adverse effects on offspring were observed when pregnant monkeys were administered Erenumab-aooe throughout gestation.

Lactation

There are no data on the presence of Erenumab-aooe in human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric

Safety and effectiveness in pediatric patients have not been established.

Geriatric

Clinical studies of Erenumab-aooe did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Generic name

Erenumab-aooe is the generic name of the drug.

Dosage form

Injection.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not Required

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