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Does erenumab reduce monthly migraine frequency from baseline in adults with episodic migraines?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSRACT

OBJECTIVE: The objective of this selective EBM review is to determine "Does erenumab reduce monthly migraine frequency from baseline in adults with episodic migraines?"

STUDY DESIGN: An EBM review of three double blind, RCTs (randomized control trials) that were published in peer reviewed journals.

DATA SOURCE: The three studies were found on PubMed, published after 2011, and chosen based upon the ability to answer the patient-oriented outcome and objective.

OUTCOMES: All studies used the same criteria from the self- reported diaries: "Migraine days were defined as the onset, continuation, or recurrence of a qualified migraine headache for at least 30 minutes with either ≥2 pain features or ≥1 non-pain symptom or the use of an acute migraine medication". The pain features included unilateral, throbbing, moderate to severe, or exacerbated with physical activity. The non-pain symptoms included nausea/vomiting, or photophobia/ phonophobia. The primary outcome was a reduction from baseline in monthly migraine days, with secondary outcomes of ≥50% reduction from baseline for patients.

RESULTS: Three studies concluded that erenumab is effective at reducing monthly migraine days, with a significant number of patients having ≥50% reduction from baseline per month. Dodick et al. had an odds ratio of 1.59 (95% CI, 1.12 to 2.27), a p-value of 0.010 when compared to the placebo, with a NNT of 10. Sakia et al. had an odds ratio of 5.60 (95% CI, 2.60 to 12.6) with a p-value for erenumab compared to the placebo of <.001. The NNT was 5. Wang et al. had a calculated NNT of 10, an odds ratio of 1.5 (95% CI, 1.1 to 2.1) and a p-value=0.007 for erenumab compared to the placebo.

CONCLUSIONS: All studies concluded that erenumab is effective at reducing monthly migraine days, with a statically significant number of subjects achieving a ≥50% reduction from baseline. Recently, erenumab was found to be superior to topiramate at reducing migraines. Additionally, the 3-year safety data and efficacy of erenumab did not demonstrate additional concerns. Further research is needed to compare erenumab with monthly injectables like Emgality® instead of daily pills.

KEYWORDS: Erenumab, episodic migraine, trial, prevention

INTRODUCTION

Migraine is a benign episodic primary headache disorder with symptoms lasting 4-72 hours, which may include visual/sensory/motor disturbances. The diagnosis of migraine includes a normal physical exam, presenting with two of these symptoms: unilateral, throbbing pain, worsening with movement, and moderate to severe intensity. Additionally, the patient must present with one of these: nausea/vomiting or light/sound sensitivity. Episodic migraines occur less than 15 times per month.

Approximately 10% of the worldwide population suffers from migraines, which equates to about 800,000,000 people worldwide, and approximately 40 million people in the United States, particularly adults aged 20-50.[1] Women are 3 times more likely to be impacted by migraines.[1] There is also a large genetic component for this disorder.[2] Migraines impair quality of life, resulting in missed days, significant disruption to daily life, and feeling incapacitated.[2] Additionally, $78 billion in the United States is spent each year with respect to migraines.[3] Patients with episodic migraines spend about $2,000 per year and are estimated to lose up to $4,000 a year due to being incapacitated during their migraines.[3] There are roughly 4 million emergency department visits and 4 million office visits each year for these patients.[4]

The pathophysiology of migraines is believed to be due to trigeminal neuronal dysfunction, leaving the brain always at risk of a migraine. The pain is a result from neurogenic inflammation, along with cortical spreading depression, and neuropeptide release, resulting in pain and vasodilation of vessels in the brain. There are also triggers such as stress, lack of sleep, red wine, etc. It is unclear if serotonin and dopamine play a role.

The usual treatments for this condition include: NSAIDs, Excedrin (acetaminophen, ASA, caffeine), ergotamine preps, such as cafergot, serotonin agonists, such sumatriptan, CGRP

agonists, such as rimegepant, transcranial magnetic stimulation, or daily doses of beta blockers, TCAs, anticonvulsants, and botox for prevention.[5] However, most of these medications were not designed specifically to prevent migraine disorder and have cardiac and GI side effects, resulting in poor tolerability and compliance.[6]

Erenumab is a monoclonal anti-body that is designed to block the canonical calcitonin gene-related peptide receptor, which is a key migraine pathway that causes vasodilation and release of inflammatory mediators.[5] This medication is designed to prevent migraines for those who have failed initial prevention therapies due to lack of effectiveness or side effects.[5] Erenumab is a subcutaneous injection once a month, instead of a daily pill. Therefore, increased patient compliance, specific neuropeptide receptor blockade designed for migraines, and proposed improvement in efficacy is why erenumab is being proposed as a preventative agent.

OBJECTIVE

The objective of this selective EBM review is to determine "Does erenumab reduce monthly migraine frequency from baseline in adults with episodic migraines?"

METHODS

There were strict criteria for selecting studies to answer the clinical question based upon research quality, populations, interventions, comparisons, outcome measurements, study design, and patient-oriented outcomes. The criteria were adults 18-65 years old with ≥4 or <15 migraine days per month, excluding adults >50 years old with new onset of migraines, the intervention of erenumab 70mg compared to a placebo, and the outcome of reduction in frequency from baseline in monthly migraine days. All studies were RCTs. All articles were written in English and published in peer review journals, which were found on PubMed by key word searches of "erenumab", "episodic migraine", "trial", and "prevention". Inclusion criteria entailed published

clinical trials regarding episodic migraines after 2011. Exclusion criteria comprised of research published before 2011 and the topic of chronic migraines.

The population studied in this review were adults 18-65 with episodic migraines, their demographics and characteristics are found in Table 1. Each study used the intervention of erenumab 70mg. The measured outcome in this EBM review is a reduction in frequency from baseline in monthly migraine days. Statical significance was reported using p-values and CI (confidence intervals), EER (experimental event rate), CER (control event rate), RBI (relative benefit increase), ABI (absolute benefit increase), and NNT (number needed to treat).

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Dodick[5] (2018)	RCT	546	18-65	Adults 18-65 with ≥4 and >15 migraine days per month for at least 12 months prior to the study, women of childbearing years had to be using contraception	>50 yo migraine onset, hx of cluster HA or hemiplegic migraine, no response to >2 migraine prevention classes, medical conditions that could prevent completion/ interfere with results interpretation	6	Erenumab 70mg Vs. Placebo
Sakai [6] (2019)	RCT	475	20-65	Adults 20-65 with a diagnosis of migraine for ≥12 months via ICHD, ≥4 and <15 migraine days per month, averaging across 3 months	>50 yo migraine onset, hx of cluster HA or hemiplegic migraine, no response to >2 migraine prevention classes, botox w/in 4 months, procedures for migraines 2 months prior, >1 prevention med	12	Erenumab 70mg Vs. Placebo
Wang [7] (2021)	RCT	900	18-65	Adults 18-65yo, diagnosed with migraine via ICHD, ≥4 and <15 migraine days per month and <15 HA days per month across 3 months	>50 yo at onset of migraines, no response to >2 migraine prevention meds, botox w/in 4 months, ergotamines or triptans on ≥10 days per month, analgesics on ≥ 15 days per month, opioid or butalbital analgesics >4 days per month	29	Erenumab 70mg Vs. Placebo

OUTCOMES MEASURED

All three studies used self-reporting electronic headache diaries to track symptoms, then were computed as migraine days based upon the following criteria: "Migraine days were defined as the onset, continuation, or recurrence of a qualified migraine headache for at least 30 minutes with either ≥2 pain features or ≥1 non-pain symptom or the use of an acute migraine medication".[5,6,7] The pain features included unilateral, throbbing, moderate to severe, or exacerbated with physical activity.[5,6,7] The non-pain symptom including nausea/vomiting, or photophobia/ phonophobia.[5,6,7] The primary outcome measured for each study was a mean reduction in monthly migraine days, with secondary outcomes of ≥50% reduction from baseline.

RESULTS

Dodick et al. conducted a double blind RCT to examine the efficacy of erenumab at reducing monthly migraine days in adults ages 18-65 with episodic migraines. There were 546 participants selected based upon the inclusion and exclusion criteria listed in Table 1, who were randomized to either 70mg of erenumub or a placebo for 3 months.[5] Subjects were randomized based upon a computer-generated system, and the intervention and placebo were packaged, colored, and sized identically. Patients were administered a subcutaneous injection once a month and recorded their symptoms/timing of migraines in a daily headache eDiary. There were adverse events reported in the erenumab and placebo group, most commonly an upper respiratory tract infection, then pain at injection site, nasopharyngitis, gastrointestinal side effects and pruritic rash.[5] There was a total of 6 discontinuations due to adverse events, with 5 of those being from the erenumab group due to fatigue, urticaria, irritable bowel syndrome, affect lability, and allergy to arthropod sting.[5]

Monthly migraine days were quantified from the daily electronic headache diaries based upon the migraine criteria, which was defined in the outcomes measured section of this EBM review with reference to timing of the migraine, pain features, and non-pain symptoms.[5] After 3 months, the comparison in efficacy was made between erenumab and the placebo in reducing monthly migraine headaches. The researchers examined the number of participants who had ≥50% reduction in monthly migraines. Amongst the 282 people in the erenumab group, 112 (39.7%) had ≥50% reduction, while the placebo group of 288, only had 85 (29.5%), who experienced ≥50% reduction.[5] This comparison had an odds ratio (95% CI) of 1.59 (1.12 to 2.27) and a p-value of 0.010.[5] The results are summarized below in Table 2. Therefore, erenumab was statistically superior at reducing migraine days by ≥50% from the baseline versus the placebo. The NNT was calculated from the dichotomous data, which was 10 as indicated by Table 3. This means that for every 10 people treated with erenumab for their episodic migraines, one more will have reduced monthly migraine days when compared to the placebo.

Table 2. ≥50% Reduction from Baseline in Monthly Migraine Days After 12 Weeks

	Erenumab 70mg (n=282)	**Placebo (n=288)**
≥50% Reduction from Baseline (n, %)	112 (39.7%)*	85 (29.5%)

**p=0.010 for erenumab compared to the placebo*

Table 3. Calculations for NNT for Dodick et al.

	EER	**CER**	**RBI**	**ABI**	**NNT**
Dodick	0.40	0.30	0.33	0.10	10

Sakia et al. performed a double blind RCT to examine the effectiveness of erenumab at reducing monthly migraine days in patients with episodic migraines. The study selected 475 adults (20-65 years old), who met the inclusion and exclusion criteria as recorded in Table 1. Subjects were randomized to 3 different doses of erenumab or placebo for 6 months, but for the sake of consistency in this EBM review, the focus will be 70mg of erenumab.[6] The randomization of subjects occurred via a schedule generated by the study sponsor. The subjects were administered

monthly injections of either erenumab or placebo and asked to report symptoms daily in their eDiary. There were adverse events reported in the erenumab group of gastrointestinal side effects, pruritic rash, pain at injection site.[6] There were 12 discontinuations due to patient request, sponsor decision, pruritic rash, and protocol specified criteria.[6]

Monthly migraine days were measured from the daily electronic headache diaries from the migraine criteria, which was characterized in the outcomes measured section of this review with reference to timing, pain features, and non-pain symptoms of a migraine.[6] The researchers examined the effectiveness of erenumab with respect to the placebo, for a ≥50% reduction from baseline in monthly migraine days after 4-6 months with the data shown in Table 4. There were 135 subjects randomized to 70mg of erenumab, and after 4-6 months 39 (28.9%) subjects had ≥50% reduction from baseline in monthly migraine days.[6] There were 136 subjects randomized to the placebo group and after 4-6 months 10 (7.4%) subjects had ≥50% reduction from baseline in monthly migraine days.[6] This comparison had an odds ratio (95% CI) of 5.60 (2.60 to 12.6) with a p-value for erenumab compared to the placebo of <.001, which was statistically significant for efficacy of erenumab efficacy.[6] The calculated NNT was 5 as indicated by Table 5. Consequently, for every 5 people treated with erenumab for their episodic migraines, one more will have reduced monthly migraine days when compared to the placebo.

Table 4. ≥50% Reduction from Baseline in Monthly Migraine Days After 4-6 Months

	Erenumab 70mg (n=135)	**Placebo (n=136)**
≥50% Reduction from Baseline (n, %)	39 (28.9%)*	10 (7.4%)

**p= <.001 for erenumab compared to the placebo*

Table 5. Calculations for NNT for Sakia et al.

	EER	**CER**	**RBI**	**ABI**	**NNT**
Sakia	0.29	0.074	2.9	0.22	5

Wang et al. organized a double blind RCT to evaluate erenumab's effectiveness at reducing monthly migraine days in adults (18-65) by assessing 900 subjects, who were randomized via

Interactive Response Technology to 2 doses of erenumab and a placebo, however for uniformity's sake only the 70mg dose of erenumab will be evaluated. The subjects met the inclusion and exclusion criteria outlined in Table 1. Subjects received a monthly injection for 3 months and monitored their symptoms and migraine timing in a daily electronic diary. There were 29 patients who discontinued the study due to lost follow up or subject choice.[7] The most frequent adverse events were nasopharyngitis, constipation, pyrexia, and dizziness, however those did not lead to discontinuation.[7]

Monthly migraine days were measured from the headache diaries based upon the migraine criteria, previously defined in this EBM review with reference to timing and features of a migraine.[7] The efficacy of erenumab was assessed for a ≥50% reduction from baseline in monthly migraine days after 3 months as displayed in Table 6. There were 182 (55.3%) out of the 329 subjects in the erenumab group and 148 (44.8%) out of 330 from the placebo group that had ≥50% reduction from baseline in monthly migraine days after 3 months.[7] This comparison had an odds ratio (95% CI) of 1.5 (1.1 to 2.1) with a p-value for erenumab compared to the placebo of 0.007, which was statistically significant for erenumab at reducing migraine days than the placebo.[7] The NNT from this study was 10, found in Table 7. Therefore, with every 10 people treated by erenumab for their episodic migraines, one more will have reduced monthly migraine days when compared to the placebo.

Table 6. ≥50% Reduction from Baseline in Monthly Migraine Days After 3 Months

	Erenumab 70mg (n=329)	**Placebo (n=330)**
≥50% Reduction from Baseline (n, %)	182 (55.3%)*	148 (44.8%)

**p=0.007 for erenumab compared to the placebo*

Table 7. Calculations for NNT for Wang et al.

	EER	**CER**	**RBI**	**ABI**	**NNT**
Wang	0.55	0.45	0.22	0.10	10

DISCUSSION

All studies were double blind RCTs with reported dichotomous data, which were able to be calculated for a NNT for treatment effect of erenumab. All studies had losses of less than 20%, with all losses accounted for, and no severe side effects for subjects. However, a limitation of the 3 studies is that they examined the efficacy of erenumab over 3-6 months, which was not a significant time to adequately assess the long-term safety and effectiveness of the drug. These studies did not rule out whether erenumab's effectiveness will remain steady over time, nor what additional side effects could be experienced with a longer duration of receiving injections. The studies also only examined patients with episodic migraines, but excluded patients that began migraine onset after age 50.

Erenumab was FDA approved in 2018 and is only indicated for migraine prevention as a subcutaneous monthly injection.[8] It does not need dosing alterations for renal or hepatic impairments, although there hasn't been enough testing on adults >65 years old for safety data.[8] The only contraindication for this medication was a severe hypersensitivity reaction, however patients with known cardiovascular disease should be cautious with this medication regarding the risk of hypertension.[8] The precautions were listed as: constipation, hypersensitivity, and new-onset hypertension that may result in hospitalization.[8] There are no black box warnings.[8]

CONCLUSIONS

Based upon the three studies analyzed in this EBM review, erenumab does reduce monthly migraine frequency from baseline in adults with episodic migraines. Erenumab was statistically significant for reducing episodic migraine days per month by ≥50% from patient's baseline with a large treatment effect in each study. Recently, a study is compared the effectiveness of erenumab versus topiramate, which found more patients on erenumab that

achieved a ≥50% reduction in migraines than those taking topiramate.[9] Additionally, a study evaluated the 3-year efficacy of erenumab, which found the drug to be safe and efficacious over 3-years with no additional concerns or side effects when compared to the shorter studies already examined in this review .[10] Future studies could follow patients overtime to assess long term safety data. Additionally in the future, studies could compare the effectiveness at reducing migraine days between erenumab and other monthly injectables such a Emgality® in addition to evaluating its effectiveness with patients who suffer from chronic migraines.

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