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편두통 예방을 위한 erenumab의 유효성 및 안전성에 관한 체계적 고찰

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Systematic Review on the Efficacy and Safety of Erenumab for the Prevention of Migraine

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ABSTRACT

Objective: This study aimed to provide efficacy and safety information on the use of erenumab for prevention of episodic and chronic migraines. **Methods:** The keywords "Erenumab and migraine" were used to search the PubMed database to then compile efficacy and safety data for erenumab. Data from relevant Phase 2 and Phase 3 clinical trials were analyzed, using RevMan for statistical analysis. **Results:** Three clinical trials (one Phase 2 and two Phase 3 studies) were retrieved. All three trials used the same primary endpoint (change from baseline in monthly migraine days (CBMD)) to evaluate efficacy and safety of erenumab use for prevention of episodic and chronic migraines. Subcutaneous doses of erenumab (70 or 140 mg) were administered monthly in each trial, for 3 months (Studies 2, and 3) or 6 months (Study 1). The mean differences in CBMD in the 70 mg and 140 mg erenumab arms were −1.36 and −1.98, respectively, compared to that in the placebo arm. Some adverse events, such as nasopharyngitis and upper respiratory tract infection, were reported, but no differences in safety between erenumab and placebo were found to be significant. **Conclusions:** Erenumab showed superior efficacy in prevention of migraines compared to placebo. However, additional information regarding the long-term safety of erenumab should be collected. Therefore, post-marketing surveillance for adverse events is needed.

KEY WORDS: Erenumab, CGRP receptor antagonist, migraine, clinical trials, adverse events

Migraine affects about 11% of the population worldwide and can be classified as either episodic or chronic on the basis of the number of migraine and headache days per month.[1] Episodic cases account for more than 90% of migraine patients and are defined as either headache or migraine occurring fewer than 15 days per month with or without aura.[2,3] Chronic migraine accounts for 5-8% of patients and is defined as 15 or more headache days per month for more than three months, of which at least 8 days are migraine with or without aura.[3,4] Currently, several options are available for the management of migraine such as pain-relievers and preventive medications.[5] Serotonin agonists (triptans) are the mainstay of pain-relievers (for acute management of migraine attacks) along with NSAIDs and acetaminophen while preventive medications consist of onabotulinum toxin A, antiseizure agents, antidepressants, and beta-blockers.[5]

Recent progress regarding the pathogenesis of migraine, specifically via the calcitonin-gene-related peptide (CGRP)

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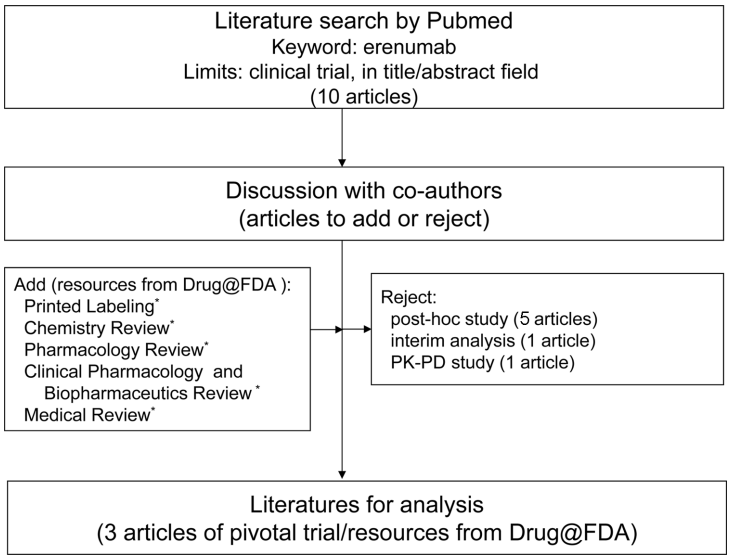


Figure 1. Flow chart of literature search process and analysis of the data for erenumab (*posted in Drug@FDA website).

pathway, has led to monoclonal antibody (mAb) development for migraine prevention.[6] CGRP is a peptide synthesized and released by neurons of the trigeminovascular system that plays a pivotal role in the etiology of migraine.[6] Migraine attack may be prevented by blockade of either CGRP itself or of its receptor.[7] On May 17, 2018, erenumab, a mAb against the CGRP receptor, got approval from the US Food and Drug Administration (US FDA) for the prevention of episodic and chronic migraine.[8,9] Recommended dosage by US FDA is 70 mg subcutaneous injection once monthly, and maximum dosage is 140 mg. Erenumab is not yet approved in Korea.

As mentioned above, in addition to erenumab, several other anti-CGRP mAbs are being developed including eptinezumab, fremanezumab, and galcanezumab.[6,10] However, these three mAbs bind to CGRP, unlike erenumab which acts by blocking the CGRP receptor.[10] mAbs targeting the CGRP pathway have advantages over small molecules because the mAbs have excellent specificity against the target, longer half-life, reduced potential for hepatotoxicity, and less potential for drug-drug interactions.[7,11]

Erenumab, the only antibody targeting the CGRP receptor, is a fully human IgG2 mAb which binds to the receptor and blocks subsequent signaling.[6] CGRP is a key neurotransmitter in migraine pathogenesis.[12,13] CGRP released by trigeminal sensory neurons around the vascular space induces vasodilation and neurogenic inflammation which are direct causes of migraine.[8,12] The CGRP level increases when a migraine attack occurs, and it falls after treatment.[8] Therefore, the use of erenumab, a CGRP receptor blocker, may be a new strategy for the preventive management of migraine. The objective of this study is to provide clinicians with information on the efficacy and safety of the mAb medication, erenumab, for the prevention of episodic and chronic migraine.

Methods

A PubMed search was conducted with erenumab as a search term. Limits for Pubmed search were clinical trial and English in the title/abstract field. Identified studies were divided into Phase 2, Phase 3, interim analysis, post-hoc analysis, and pharmacokinetic/pharmacodynamic modeling studies. Resources such as printed labeling, chemistry review, pharmacology review, clinical pharmacology and biopharmaceutics review, and medical review posted in Drug@FDA website were included in this review, and post-hoc/interim analyses and pharmacokinetic/pharmacodynamic studies were excluded. Pivotal trials applied for new drug approval to US FDA were analyzed with regard to study design and outcomes of efficacy and safety. A flow chart of the article retrieval process is shown in Figure 1.

We have compiled the results of three pivotal trials from the published articles in the academic journals. Information from the clinicalTrials.gov website was also included. When data in one source conflicts with others, the data in the clinical Trials.gov website was primarily used and other data were used complementarily. Meta-analysis of the three trials was also performed using RevMan v5.3 (provided by Cochrane

Community) with focus on the efficacy (primary and secondary endpoints) and safety (discontinuation, adverse events) of erenumab.

Study design of the pivotal trials

All three pivotal trials were conducted in patients aged 18 to 65 years old with a history of episodic or chronic migraine (Table 1).[14-16] They were all multicenter, randomized, double-blind, placebo-controlled trials assessing the efficacy and safety of erenumab. STRIVE and Tepper *et al.*'s trials were conducted with three arms (70, 140 mg, and placebo) while the ARISE study was conducted with two arms (70 mg and placebo). The STRIVE and ARISE studies were Phase 3 trials in episodic migraine patients, and Tepper *et al.*'s study was a Phase 2 clinical trial in chronic migraine patients. Details of the study designs are given in Table 1.

The STRIVE and ARISE studies recruited patients with migraine or headache patients with identical inclusion criteria (Table 1).[17,18] The study by Tepper *et al.* also used similar but slightly different inclusion criteria.[19] The primary endpoint of all three studies was the change from baseline in mean monthly migraine days (CBMD). Since STRIVE was conducted for 24 weeks, the change was calculated using the average number of migraine days during the last three months. However, in the ARISE and Tepper *et al.*'s 12 week studies, the CBMD was calculated using the number of migraine days during the last four weeks of the studies. In Table 2, we compiled the results of the three clinical trials by treatment regimens: 140 mg, 70 mg, and placebo. The total values for each endpoint were calculated by the following equation: Σ(number of patients in each treatment regimen × result)/Σ(number of patients in each treatment regimen).

The common secondary endpoints of the three trials were the percentage of participants with at least 50% reduction from baseline in monthly migraine days, the change from baseline in monthly acute migraine-specific medication treatment days during the trials, the number of participants with adverse events, and the number of participants who developed antibodies to erenumab.[17-19] STRIVE and ARISE had additional secondary endpoints, which were the average impact on everyday activities and the average impact on physical impairment domain score measured using the Migraine Physical Function Impact Diary (MPFID).[17,18] Finally, an additional secondary endpoint in Tepper *et al.*'s study was the change in cumulative monthly headache hours from baseline.[19]

Change from baseline in mean monthly migraine days

In all the three trials, erenumab was compared with placebo. Erenumab at both 70 and 140 mg was more effective than placebo ($p < 0.01$) for the primary endpoint, CBMD (Figure 2). The STRIVE study measured change from baseline in mean monthly migraine days for the last three months of the double-blind treatment period, and erenumab revealed a superior response to placebo (−3.2, −3.7, and −1.8 days for 70 mg, 140 mg, and placebo, respectively) (Table 2). The mean difference in achievement of the primary endpoint in the 70 and 140 mg erenumab arm was −1.36 (95% CI: −1.38, −1.33) and −1.98 (95% CI: −2.00, −1.95), respectively, versus placebo arm ($p < 0.00001$, Figure 2). Heterogeneity indicator (I^2 value) between the studies was very high, 100% and 99% for CBMD in erenumab 70 mg versus placebo and erenumab 140 mg versus placebo, respectively, owing to different treatment regimens in the studies.

Migraine days and medication treatment days

Among the four common secondary endpoints in the three pivotal trials, two were efficacy indicators and the other two were safety indicators. In terms of the percentage of participants with at least a 50% reduction from baseline in monthly migraine days, erenumab arms were statistically significantly superior to the placebo arms. Odds ratio (non-event) for the ernumab arms compared to placebo arm was 0.48 (95% CI: 0.40, 0.58, $p < 0.00001$, Figure 3A). In terms of the change from baseline in monthly acute migraine-specific medication treatment days, erenumab arms were also statistically significantly superior to the placebo arms. Mean difference for the ernumab 70 and 140 mg arms compared to placebo arm was –0.82 (95% CI: –0.83, –0.80) and –1.41 (95% CI: –1.43, –1.39), respectively ($p < 0.00001$, Figure 3B and Figure 3C).

In terms of the 50% migraine days reduction, erenumab 140 mg arm did not reveal favorable result compared to erenumab 70 mg arm (non-event odds ratio: 0.82 (95% CI: 0.64, 1.05, $p = 0.11$). However, in terms of the migraine-specfic medication days, erenumab 140 mg arm did show very significantly favorable result compared to erenumab 70 mg arm (mean difference: −0.51 (95% CI: −0.52, −0.49, $p < 0.00001$).

Discontinuation and adverse events

In the three pivotal clinical trials involving 2,184 participants, discontinuation rates in erenumab 70 and 140 mg arms were 1.53 and 1.76% compared to 1.22% in the placebo arm (Table

Table 1. Summary of study designs for the three clinical trials of erenumab for the prevention of migraine

	STUDY 1 (STRIVE) (NCT02456740; Goadsby 2017)	STUDY 2 (ARISE) (NCT02483585; Dodick 2018)	STUDY 3 (Tepper *et al.*) (NCT02066415; Tepper 2017)
Subjects (n)	955	577	667
Sites	121 in US, Canada, Belgium, Czech Republic, Finland, Germany, Netherlands, Poland, Slovakia, Sweden, UK, Turkey	69 in Denmark, France, Greece, Portugal, Russian Federation, Spain, Switzerland, US	69 in Canada, US, Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, UK
Design	mc, r, db, pc, pg, phase 3 trial		mc, r, db, pc, pg, phase 2 trial
Inclusion criteria	• history of migraine (with or without aura) for ≥12 mo prior to screening according to the ICHD-3/HIS • migraine frequency: ≥4 and <15 migraine days per month on average across the 3 mo prior to screening and during baseline phase • headache frequency: <15 headache days per month on average across the 3 mo prior to screening and during baseline phase • patients who demonstrated at least 80% compliance with the eDiary		• history of at least 5 attacks of migraine with or without aura • ≥4 distinct headache episodes, each lasting ≥4 h OR if shorter, associated with use of a triptan or ergot-derivative • patients who demonstrated at least 80% compliance with the eDiary
Exclusion criteria	• older than 50 yo at migraine onset • history of cluster headache or hemiplegic migraine headache • unable to differentiate migraine from other headaches • no therapeutic response with >2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial • used a prohibited medication, device, or procedure within 2 mo prior to the start of the baseline phase or during the baseline phase • concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 mo prior to the start of the baseline phase or during the baseline phase. If only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study		• older than 50 yo at migraine onset • history of cluster headache or hemiplegic migraine headache • unable to differentiate migraine from other headaches • failed >3 medication categories due to lack of efficacy for prophylactic treatment of migraine • used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase • received botulinum toxin in head or neck region within 4 mo prior to screening
Duration	6 months	12 weeks	12 weeks
Treatment regimen	pbo (n = 319) / Erenumab 70 mg qM SC × 6 mo (n = 317) / Erenumab 140 mg qM SC × 6 mo (n = 319)	pbo (n = 291) / Erenumab 70 mg qM SC × 3 mo (n = 286)	pbo (n = 286) / Erenumab 70 mg qM SC × 3 mo (n = 191) / Erenumab 140 mg qM SC × 3 mo (n = 190)
Primary endpoints	change from baseline in mean monthly migraine days for the last 3 months	change from baseline in monthly migraine days	
Secondary endpoints	• percentage of participants with at least a 50% reduction from baseline in monthly migraine days in the last 3 months of the double-blind treatment phase • change from baseline in monthly acute migraine-specific medication treatment days to the last 3 months of the double-blind treatment period • change from baseline in mean monthly average physical impairment domain score measured by mpfid in the last 3 months of the double-blind treatment phase • change from baseline in mean monthly average impact on everyday activities score measured by mpfid in the last 3 months of the double-blind treatment phase	• percentage of participants with at least a 50% reduction from baseline in monthly migraine days at week 12 • change from baseline in monthly acute migraine-specific medication treatment days at week 12 • percentage of participants with at least a 5-point reduction from baseline in average impact on everyday activities domain score measured by mpfid at week 12 • percentage of participants with at least a 5-point reduction from baseline in average impact on physical impairment domain score measured by mpfid at week 12	• percentage of participants with at least a 50% reduction in monthly migraine days from baseline • change from baseline in monthly acute migraine-specific medication treatment days • change from baseline in cumulative monthly headache hours

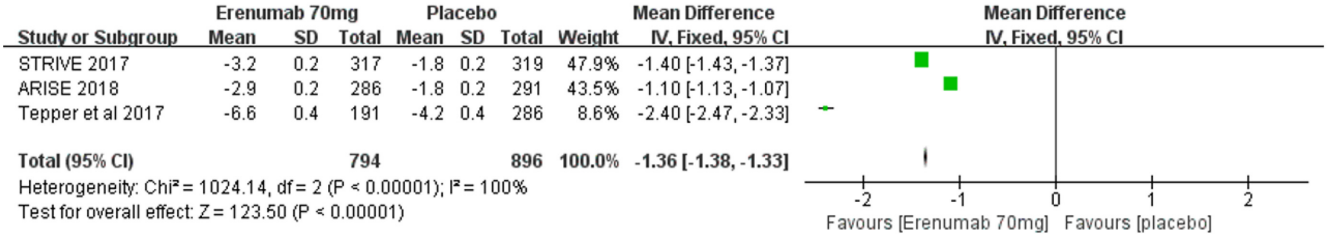
db: double-blind, ICHD-3/IHS: International Classification of Headache Disorders classification by International Headache Society, mc: multi-center, mpfid: migraine physical function impact diary; pbo: placebo, pc: placebo-controlled, qM; monthly, r: randomized, SC: subcutaneous injection

Table 2. Efficacy indicators of erenumab reported by the three clinical trials

Treatment regimen		CBMD (least-squares mean ± SE)	≥50% reduction (No. of patients(%))	CBTD (least-squares mean ± SE)	CBEAS (least-squares mean ± SE)	CBPIS (least-squares mean ± SE)
STUDY 1 (STRIVE)	E 140 mg (n = 319)	-3.7 ± 0.2	159(50.0)	-1.6 ± 0.1	-5.9 ± 0.4	-4.8 ± 0.4
	E 70 mg (n = 317)	-3.2 ± 0.2	135(43.3)	-1.1 ± 0.1	-5.5 ± 0.4	-4.2 ± 0.4
	pbo (n = 319)	-1.8 ± 0.2	84(26.6)	-0.2 ± 0.1	-3.3 ± 0.4	-2.4 ± 0.4
STUDY 2 (ARISE)	E 70 mg (n = 286)	-2.9 ± 0.2	112(39.7)[$]	-1.2 ± 0.1	-4.33 ± 0.4	-3.18 ± 0.4
	pbo (n = 291)	-1.8 ± 0.2	85(29.5)	-0.6 ± 0.1	-3.2 ± 0.4	-1.9 ± 0.4
STUDY 3 (Tepper *et al.*)	E 140 mg (n = 190)	-6.6 ± 0.4	77(41)	-4.1 ± 0.3		
	E 70 mg (n = 191)	-6.6 ± 0.4	75(40)	-3.5 ± 0.3		
	pbo (n = 286)	-4.2 ± 0.4	66(23)	-1.6 ± 0.2		
Total	E 140 mg (n = 509)	-4.8	128.4	-2.5	-3.7	-3.0
	E 70 mg (n = 794)	-3.9	112.3	-1.7	-3.8	-2.8
	pbo (n = 896)	-2.6	78.6	-0.8	-2.2	-1.5

CBEAS: change from baseline in mean monthly average impact on everyday activities score measured using MPFID (migraine physical function impact diary); CBMD: change from baseline in mean monthly migraine days; CBPIS: change from baseline in mean monthly average physical impairment domain score measured using MPFID; CBTD: change from baseline in monthly acute migraine-specific medication treatment days; E: erenumab; pbo: placebo; SE: standard error

A.



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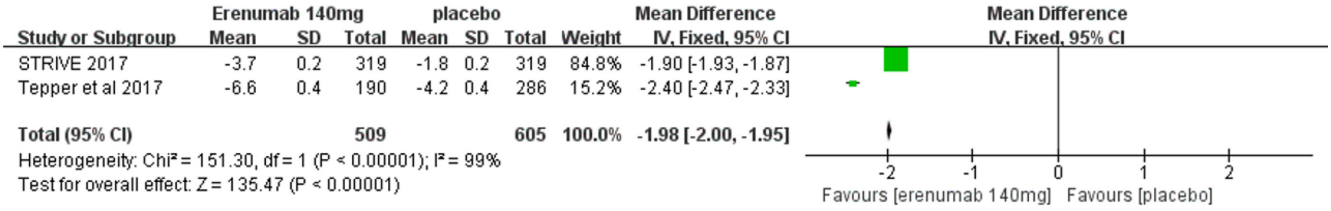

Figure 2. Meta-analysis of CBMD in the three clinical trials. A. Erenumab 70 mg versus placebo; B. Erenumab 140 mg versus placebo. CBMD = change from baseline in monthly migraine days

3). Numbers in Table 3 indicate percentages of the events reported during each study. The discontinuation rate was highest in the STRIVE study and lowest in Tepper *et al.*'s study, but in all trials the discontinuation rates were less than 5%. The odds ratio of the discontinuation rates in the erenumab arm was 0.86 ($p = 0.69$) versus the placebo arm, demonstrating that there was no significant difference between the erenumab arm and the placebo arm (Figure 4).

Severe adverse events (SAE) were defined as any event that resulted in a fatal or life-threatening situation, persistent or significant disability or incapacity, congenital anomaly or birth defect in the offspring of the participants, or hospitalization or prolongation of existing hospitalization. The incidences of SAE in erenumab 70, 140 mg, and placebo arms were 2.12, 1.57, and 1.97% of patients, respectively (Table 3). The odds ratio of SAE and adverse events (AE) in the erenumab arms

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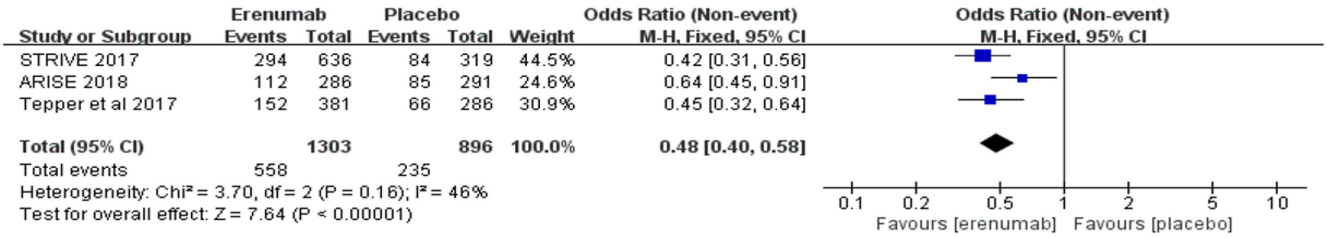

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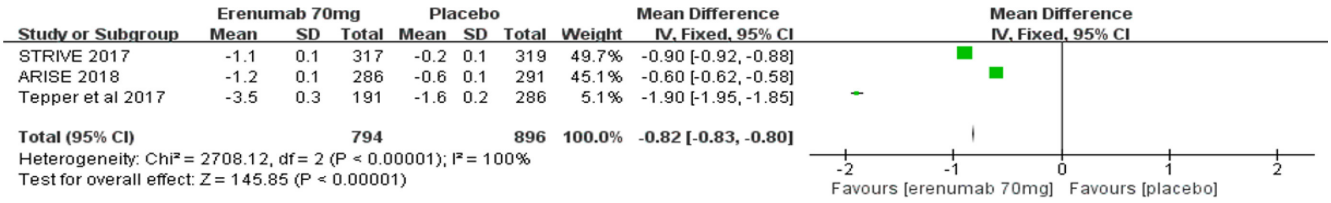

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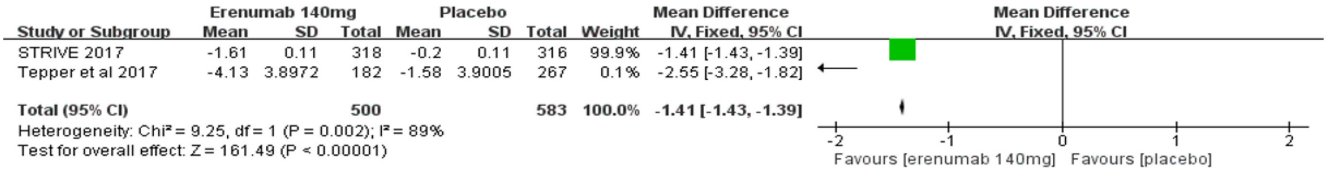


Figure 3. Meta-analysis of the efficacy-indicator secondary endpoint in the three clinical trials. (A): percentage of participants with at least a 50% reduction from baseline in monthly migraine days. (B): the change from baseline in monthly acute migraine-specific medication treatment days (70 mg versus placebo). (C): the change from baseline in monthly acute migraine-specific medication treatment days (140 mg versus placebo)

Table 3. Discontinuation rates, severe adverse events (SAE), and adverse events (AE) in the three clinical trials

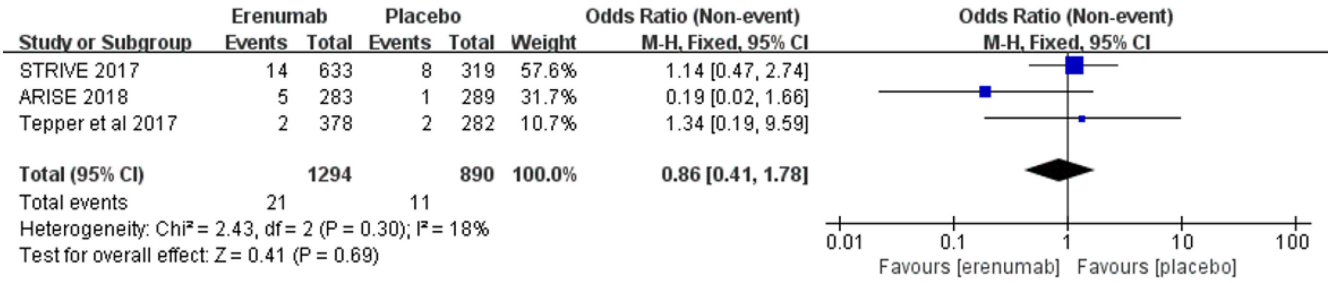
	Discontinuation rate (%)			SAE incidence (%)			AE incidence (%)		
	E 140 mg (n = 507)	E 70 mg (n = 787)	pbo (n = 890)	E 140 mg (n = 507)	E 70 mg (n = 787)	pbo (n = 890)	E 140 mg (n = 507)	E 70 mg (n = 787)	pbo (n = 890)
Total	1.76	1.53	1.22	1.57	2.12	1.97	52.35	50.78	52.70
STUDY 1 (STRIVE)	2.2	2.2	2.5	1.9	2.5	2.2	55.5	57.3	63.0
STUDY 2 (ARISE)	-	1.8	0.3	-	1.1	1.7	-	48.1	54.7
STUDY 3 (Tepper *et al.*)	1	0.0	<1 (approx 0.7)	1	3	2	47	44	39

AE: adverse events; E: erenumab; pbo: placebo; SAE: severe adverse events

were 1.16 (95% CI: 0.63, 2.14, $p = 0.63$) and 0.90 (95% CI: 0.76, 1.07, $p = 0.23$), respectively, compared to placebo arm (Figure 4). And there was no significant difference between the erenumab 140 and 70 mg arms in terms of discontinuation rate, incidences of SAE and AE. During the clinical trials, 25 participants experienced SAE as a result of erenumab injection, and incidence of the events was in the order of nasopharyngitis, upper respiratory tract infection, sinusitis, and injection site pain.

AE were defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing the informed consent forms even if the event was not considered to be related to study treatment. The percentage of patients reporting AE during the three clinical trials were 50.78, 52.35, and 52.70% in the erenumab 70, 140 mg and placebo arms, respectively (Table 3). The AE that occurred during the three clinical trials were nasopharyngitis, upper respiratory tract infection, injection-site pain, nausea, influenza, migraine, constipation, fatigue, sinusitis, arthralgia, urinary tract infection, back pain and muscle spasms.

A.



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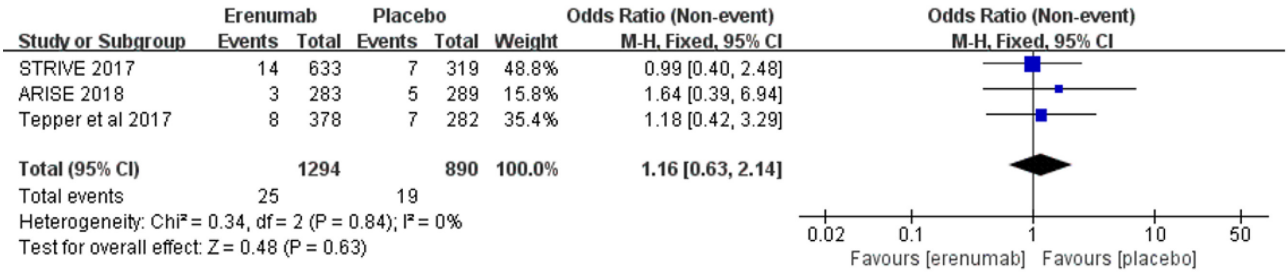

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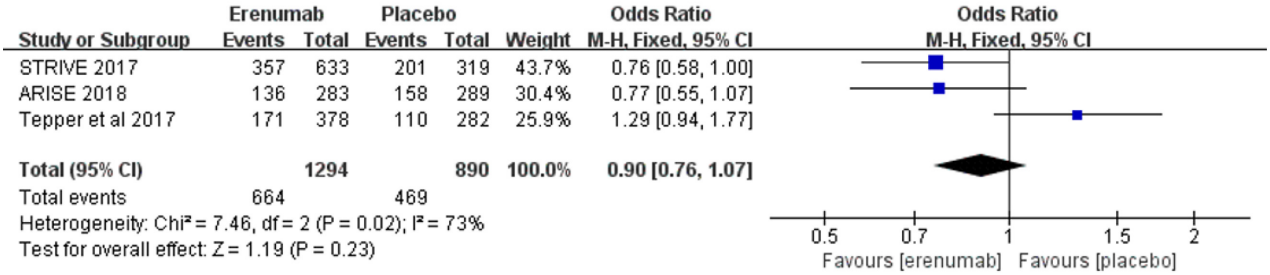

Figure 4. Safety of erenumab in the three clinical trials. A. Discontinuation; B. Incidence of severe adverse events; C. Incidence of adverse events.

In the STRIVE study, erenumab revealed significant efficacy for the primary endpoint (change from baseline in mean monthly migraine days to the last three months of the double-blind treatment period) and for most secondary endpoints compared with placebo at both 70 and 140 mg. We performed meta-analysis of the three clinical trials and the results showed that the efficacy of erenumab was superior to that of the placebo.

In contrast, erenumab did not show a significant difference in SAE or AE incidences and discontinuation rate compared to placebo. For example, in the STRIVE study, the incidence of nasopharyngitis in the erenumab arm was 10.4% compared to 10.0% in the placebo arm

Generally, an increase in the values of the safety markers including discontinuation rate and incidences of SAE and AE may be expected as the dosage increases. However, there was little difference between the 70 and 140 mg dose groups in terms of the major three safety markers. Furthermore, SAE incidences were lower in the 140 mg group than in the 70 mg group. In conclusion, erenumab does not appear to cause more AE when its dosage is increased, indicating that a higher dose does not affect the safety of erenumab up to 140 mg subcutaneous injection monthly.

A possible limitation of these trials was that their maximum duration was six months (six months for the STRIVE study, and three months for the ARISE and Tepper *et al.* studies).

The safety and efficacy profiles of erenumab may change in a long-term result study. Another limitation of these trials was that they only considered two doses of erenumab when they studied dose dependency. The efficacy and safety outcomes might have been different if the clinical trials had been performed with several doses.

Erenumab was generally well tolerated during the three clinical trials. Most common AE reported during the trials were nasopharyngitis and upper respiratory tract infections, both associated with an immune reaction. Although erenumab is not considered a mAb with immunosuppressive activity, possibility of the alteration in the immune reaction does exist as evidenced by the incidences of nasopharyngitis and upper respiratory tract infections. Therefore, clinicians should be aware of any potential adverse immune responses when administrating erenumab to patients.

Conclusions

We compiled the results of the three pivotal clinical trials of erenumab for the prevention of episodic and chronic migraine, and also performed meta-analysis of the therapeutic outcome mostly based on the data reported in the clinicaltrials.gov website. Erenumab resulted in superior efficacy profile compared to placebo in terms of the change from baseline in mean monthly migraine days. Erenumab also showed significant progress in terms of reducing migraine headache days and frequency of taking migraine-specific medications. However, considering that major adverse events for the new drug were infectious disease in the nasopharynx and upper respiratory tract, clinicians should use caution in the use of erenumab. Also, lack of evidence for long term safety beyond six months should be borne in mind.

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Conflicts of interests

The authors have no conflicts of interest to disclose.

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