

HEADACHE

Neurologist Ville Artto, MD, PhD Department of Neurology Helsinki University Central Hospital 16.4.2019

- Secondary or Primary Headache
- Migraine
- Tension Type Headache
- Cluster Headache

Headache patient

Common – 0.4-3.6% of all patients in ER

Emotional – Do I have a brain tumor?

 Benign (usually) – But it is important to recognize those who might have severe illness behind their headache symptoms

- Almost everybody suffers headaches at least sometimes (70-95%)
- Common cause to visit GP or other doctors
- Most common in young adults
- Major economic consequences:

Not only is headache painful, but it is also disabling. In the Global Burden of Disease Study, updated in 2013, migraine on its own was found to be the sixth highest cause worldwide of years lost due to disability (YLD). Headache disorders collectively were third highest.

World Health Organization

In the United Kingdom, for example, some 25 millior or school-days are lost every year because of migraine alone

Main Menu

Headache Classification and Diagnosis

Primary Headaches

- Migraine
- Tension-type
- Cluster headache

Secondary Headaches

- Tumor
- Meningitis
- Giant cell arteritis

Primary Headache 90%

Adapted from Headache Classification Committee of the IHS. Cephalalgia. 1988

Secundary causes of headache

- Subarachnoid Haemorrhage (SAH)
- Sinusthrombosis
- Expansion or thrombosis of aneurysm
- Pituitary apoplexy
- Dissection (cervical or cerebral)
- Hypertensive crisis
- PRES
- Sympatomimetic-induced vasospasm
- Vasculitis
- Vasoconstrictive angiopathies
- SIH
- Meningoencephalitis
- Sphenoid sinusitis
- etc.



History

- Are the features of the headache novel?
- Or has the headache features changed recently?
- Diagnostic evaluations before?

- What kind of medications for headache normally?
- What kind of medications for headache this time and how much?
- Other health problems and medications?

Clinical examination

- General condition
- Body temperature, blood pressure, heart rate
- Signs of a trauma
- ? Menignism
- Neuro-oftalmological examination
- General neurological examination









red flags



American Headache Society Headache Curriculum

Worrisome Headache Red Flags—"SNOOP"

- <u>SYSTEMIC SYMPTOMS</u> (fever, weight loss) or SECONDARY RISK FACTORS (HIV, systemic cancer)
- <u>NEUROLOGIC SYMPTOMS</u> or abnormal signs (confusion, impaired alertness or consciousness)
- **ONSET:** sudden, abrupt, or split-second
- <u>OLDER</u>: new onset and progressive headache, especially in middle age >50 yr (giant cell arteritis)
- **PREVIOUS HEADACHE HISTORY:** first headache or different (change in attack frequency, severity, or clinical features)

Secondary or primary headache

Migraine

- 1. Epidemiology
- 2. Migraine symptoms
- 3. Pathaphysiology
- 4. Migraine treatment
- 5. Chronic Migraine
- Tension type headacheCluster headache



Migraine epidemiology

- Prevalence of migraine
- 1. 18% in women
- $2. \qquad 6\% \text{ in men}$
- 3. $4^{\circ}/_{\circ}$ in children
- Migraine with aura (MA)
- Migraine without aura (MO)
- Familial (FHM) and sporadic hemiplegic migraine (SHM) 0.01%



Prevalence of Migraine



Common Disease





Important migraine comorbidities

- episodic neurological disorders epilepsy
- vascular disorders ischemic stroke, patent foramen ovale
- neuropsychiatric disorders depression, anxiety

Famous Migraneurs

Julius Caesar Saint Paul John Calvin Queen Mary Tudor Blaise Pascal Carolus Linnaeus Lewis Carroll Thomas Jefferson Friedrich Nietzsche Immanuel Kant Edgar Allan Poe

Frédéric Chopin Charles Darwin Karl Marx Ulysses S. Grant Peter Tchaikovsky Alfred Nobel Leo Tolstoy Sigmund Freud Virginia Woolf Princess Margaret Ben Zyskowicz

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Prodromal symptoms

Yawning, graving for food, tiredness, irritability, etc



Vascular headache

Moderate or severe, unilateral, pulsating, made worse by physical activity, associated with nausea, vomiting, sensitivity to light and sound

Neurological aura symptoms

Visual, sensory, speech disturbance, hemiparetic, vertigo

Postdromal symptoms

"Hangover", tiredness, lethargy, burst of energy

VISUAL AURA



serves through the usual round of work and play, a degree ness and a cesire for rest are characteristic mighing. A vascular hold To exquisitely set head man itself enforce at tw. bu we only, or even the chief, memorism at work. M during an attack and exhibit diminished tone of skelet diuvsy. The relation of sle molex and fund of touch upon it in many one, and we will have stoye and stupor in the stutest contexts: the in migraine (migr ad classical migraine), the tend migraines o commutating sleep, and their tenare states. At the point we a relation to attention to i winti hship: the oc of intense dro a common 1 the occasional ad sleep of anusual and the typical profile hich many attacks f natural termination. Nowhere in the literature can we find more vivid and descriptions of migrainous stupor than in Liveing's monogr-

Zig-zag patterns generated during a migraine headache





http://www.tchain.com/otoneurology/disorders/central/migraine/mav.html



http://www.familydoctor.co.uk/htdocs/MIGRAINE/MIGRAINE_specimen.html

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The Primary Cause of the Migraine Headache Lies in the Brain



The hyperexcitable brain? CSD originating in the visual cortex

The dysmodulated brain? Activation in the dorsal pons



Brainstem activation specific to migraine headache

A Bahra, M S Matharu, C Buchel, R S J Frackowiak, P J Goadsby

The Lancet, Volume 357, Number 9261 31 March 2001

Brainstem activation during acute migraine

fMRI = functional Magnetic Resonance Imaging





Migraine and trigeminovascular system



Trigeminal-vascular activation Peripheral vasodilation and neurogenic inflammation Peripheral afferent signals to trigeminal ganglion

CNS pain signals relay to higher order structures (i.e. TNC and cortex)



The key pathway for pain in migraine

Trigeminovascular input from meningeal vessels is relayed to second-order neurons in the brainstem via the trigeminal ganglion. This input to the brainstem is then relayed to the sensory cortex

CGRP, calcitonin gene-related peptide; CNS, central nervous system; TNC, trigeminal nucleus caudalis. Russo AF. Annu Rev Pharmacol Toxicol. 2015;55:533-552; Bigal ME, et al. Arq Neuropsiquiatr. 2009;67(2-B):559-569.



Aura

"Cortical spreading depression"



Cortical Spreading Depression

- Wave of intense cortical neuron activity
 - ↑ rCBF
- Followed by neuronal suppression
 - ↓ rCBF
 - Often coincides with headache onset
- Velocity: 2-3 mm/min
- Possibly underlies visual aura
- Occurs in clinically silent areas of the cortex?
 - Migraine without aura



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Treatment of migraine

tricyclic

- avoidance of triggering factors (alcohol, lack of sleep, stress etc.)
- acute medications (NSAIDs, triptans, anti-emetics etc.)
- preventive medications (antihypertensives, antidepressants, antiepileptics etc.)
- non-pharmaceutical treatments (acupuncture etc.)
- CGRP antibodies

Figure 11: NNTs for two hour pain free



Bandolier: Evidence-based health care, January 2002 www.ebandolier.com

Combinations

- Antiemetics such as metoclopramide releave nausea but also help absorption of other acute medications
- Sumatriptan + Metoclopramide is more efficient than Sumatriptan alone

		Participants, No. (%)				alue
	Sumatriptan- Naproxen Sodium	Sumatriptan	Naproxen Sodium	l	Sumatriptan- Naproxen Sodium vs Placebo	Sumatriptan Naproxen Sodium vs Sumatriptar
Efficacy population, No. Study 1	364	361	300	940		
Study 2	362	362	364	382		
Pain free at 2 h Study 1	125 (34)	90 (25)	53 (15)	33 (9)	<,001	629*
Study 2	107 (30)	82 (23)	57 (16)	37 (10)	<.001	02*
Healtache relief at S.b. Study 1	237 (65)	200 (55)	157 (44)	102 (28)	<.001	009
Study 2	207 (57)	152 (50)	158 (43)	103 (20)	<.001	.03
-leadache reliet at 2 h Study 1 Moderate	170 (75)	148 (64)	109 (48)	73 (32)	<,001*	.02*
Severe	67 (49)	52 (40)	48 (38)	29 (22)	<0014	.18*
Study 2 Moderate	139 (66)	127 (58)	110 (52)	74 (32)	<.001*	05*
Severa	58 (45)	65 (38)	48 (32)	35 (23)	<,001*	.20*
Absence of nausea at 2 h Study 1	260 (71)	238 (66)	248 (70)	233 (65)	,007	.07
Study 2	237 (65)	233 (64)	249 (68)	244 (64)	.71	.56
Absence of photophobia at 2 h Study 1	211 (58)	173 (48)	166 (47)	131 (36)	<.001	.007
Study 2	180 (50)	166 (46)	148.(41)	122 (32)	<,001	.22
Absence of phonophobia at 2 h Study 1	223 (61)	180 (50)	181 (51)	138 (38)	<.001	.002
Study 2	204 (56)	188 (52)	159 (44)	128 (34)	<.001	_14
-leadache relief at 4 h Study 1	285 (78)	240 (68)	195 (55)	133 (37)	<.001	<.001
Study 2	259 (72)	222 (61)	195 (54)	141 (37)	<.001	002
Absence of nausea at 4 h Study 1	295 (81)	257 (71)	240 (67)	199 (55)	<.001	002
Study 2	266 (73)	250 (69)	247 (68)	213 (56)	<.001	_14
Absence of photophobia at 4 h Study 1	271 (74)	221 (61)	202 (57)	137 (38)	<.001	<001
Study 2	248 (69)	213 (59)	185 (51)	144 (38)	<.001	004
Absence of phonophobia at 4 h Study 1	274 (75)	226 (63)	215 (60)	148 (41)	<.001	<.001
Study 2	259 (72)	224 (62)	193 (53)	146 (38)	<.001	.003

*Statistical comparison was not part of the original planned analyses. Analysis was performed post hoc without adjustments for multiple comparisons.

Candesartan for migraine prevention

Table 1. Intention-to-Treat Analysis of Efficacy Outcomes in 57 Migraine Patients During 12-Week Treatment Periods

	Outcome, Mean (SD)		Reduction With Candesartan		
	Candesartan	Placebo	Mean (SD)	Percentage	P Value*
Headache days (primary efficacy measure)	13.6 (10.7)	18.5 (12.5)	4.9 (10.6)	26	.001
Secondary efficacy measures Headache hours	95.0 (118)	139 (146)	43.9 (105)	31	<.001
Migraine days	9.0 (8.6)	12.6 (8.2)	3.5 (6.4)	28	<.001
Migraine hours	59.4 (66.6)	92.2 (76.8)	32.8 (61.7)	36	<.001
Headache severity Index†	191 (249)	293 (290)	102 (210)	35	<.001
Triptan doses	6.9 (10.3)	9.5 (14)	2.6 (10.0)	27	.03
Analgesic doses	12.7 (18.3)	18.9 (30.6)	6.2 (22.0)	33	.02
Disability level	14.1 (15.4)	20.6 (14.3)	6.5 (10.8)	32	<.001
Sick leave days	1.4 (5.2)	3.9 (12.0)	2.5 (8.9)	64	.01

Calculated by the Wilcoxon signed rank test. |See "Methods" section of text for explanation of headache severity index...

Tronvik 2003 JAMA

CGRP Calcitonin Gene Related Peptide





12	Discourse of CCDD	1982		
	Discovery of CGRP	and the second second	CGRP antibodies made to measure and localize CGRP in the	
CGRP as the target of new migraine therapies — successful translation from bench to clinic	Locano - Inc.	1984	trigeminal-cerebrovascular system, where it was found to be a potent vasodilator	
Tari Landonen ¹⁻¹ (soual Algored Research Algore Hearing) ^{1,1} med Daniel M. Committie Algore ("Manimum dell'angone a serie cogod transmonte de Algoret Net Jahogene Langole (E. Lymond Angone a series cogod algoret net series and political Laboret in	CGRP first proposed to play a role in migraine	1985		
Dispersive Patients and Dispersive Large equipped associated on Patients and Patien	Presence of CGRP confirmed	1986	Discovery of the trigeminovascular reflex: a physiological role for CGRP	
In the set of the distribution of the distribution of the set of t	high levels in children. decreased levels with age	1987	First measurement of CGRP	
	First demonstration in patients	1988	released by trigeminal stimulation in humans	
excert of the sequence which applies (1997) ACORD applies for the set of at the sequence of	that CGRP is released during an acute migraine attack	1990	Sumatriptan shown to normalize	
		1993	CGRP levels during acute migraine attack in parallel with	
	Demonstration that CGRP release by trigeminal activation	1994	relief of headache symptoms	
	is inhibited by triptans	1998	Characterization of the multicomponent CGRP receptor that consists of CALCRL, RAMP1	
	First characterization of compounds that block the CGRP receptor: the gepants	2000	and RCP	
		2002	Infusion of CGRP shown to trigger migraine attack in patients prone to migraine	
	CGRP receptor blocker intravenous olcegepant shown to alleviate headache during a migraine attack	2004		
	Clinical trials begin to test	2005	Merck files patent for use of CGRP antibodies for migraine treatment	
	telcagepant and other gepants in acute migraine	2006	Antibodies against CGRP	
	Overview of all clinical trials of gepants to date indicates efficacy in acute migraine with no	2007	shown to block CGRP responses in vitro and in vivo	
	cardiovascular or other serious adverse effects	2010	Merck halts development of telcagepant owing to liver toxicity: elevated liver enzymes	
	Clinical trials begin to evaluate use of anti-CGRP	2011	after 3-month treatment for migraine prophylaxis	
	antibodies for prophylaxis of frequent and chronic migraine	2013	Anti-CGRP antibody (galcanezumab; LY2951742) shown to be effective in episodic	
	Anti-CGRP antibody (eptinezumab; ALD403), given intravenously, shown to be effective for	2014	migraine without serious adverse effects (phase II trial)	
	prevention of episodic migraine phase II trial)	2015	Anti-CGRP antibody (fremanezumab TEV-48125) shown to be effective in chronic migraine (phase IIb trial)	
	Phase III trials of the antibodies eptinezumab, erenumab, fremanezumab and galcanezumab	2016	Antibody Largeted to the orally active	
	produce positive results for migraine prevention	2017	CGRP receptor gepant, shown (crenumab; to be effective AMG 334) in acute	
	Expected review of antibody migraine therapies by FDA and European Medicines Agency	2018	Amo 334) In acute shown to be migraine effective in without serious episodic adverse effects migraine (phase (phase lib trial)	

Clinical

Therapy

Experimental

Laboratory

SEVIEWS

EVIEWS					
	Discovery of CGRP	1982	CCRP antihodies	made to measur	-
CGRP as the target of new migraine		1984	CGRP antibodies made to measure and localize CGRP in the trigeminal-cerebrovascular system		n
therapies — successful translation from bench to clinic	CGRP first proposed to	1985	where it was found vasodilator	d to be a potent	
intel 242-262. We cannot see the provide provide a second or the indications of the probe- cility on the probest of the proper second or the proper second or the indications of the probe- tion of the probest of the proper second or the proper second or the proper second or the proper memory bound of the proper second or the proper second or the proper second or the proper time of the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or the annual properties of the proper second or the proper second or the proper second or the annual properties of the proper second or the proper second or the proper second or the advergence of the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or the advergence of the proper second or the proper second or the proper second or the proper second or the proper second or the proper second or	play a role in migraine	Contraction of the local division of the loc	Discovery of the		
En un effis het Lindersberger auf alle die die Lindersberger auf die die Berger auf die die Berger auf die die Berger auf die	Presence of CGRP confirmed	1986	trigeminovascular physiological role		
	in human cerebral vasculature; high levels in children. decreased levels with age	1987			
From the straight or approximate provide backing of the process of the large processing processing the straight of the processing processing processing the straight of the processing processing processing the straight of the processing proces	decreased levels with age	1988	First measuremen released by trigen stimulation in hum	ninal	
and the strength of the state o	First demonstration in patients that CGRP is released during an	1990	stantation in num		
The second secon	acute migraine attack	1993	Sumatriptan show CGRP levels durin	ig acute	
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		2015	Anti-CGRP antibody (fremanezumati: TEV-48125) shown to be effective in		
	Phase III trials of the antibodies eptinezumab, erenumab, fremanezumab and galcanezumab produce positive results for migraine prevention	2016	Antibody	(phase llb trial) Ubrogepant, a	10
		2017	CGRP (eceptor (crenumab: AMG 334)	orally active gepant, shown to be effective in acute	
	Expected review of antibody migraine therapies by FDA and European Medicines Agency	2018	shown to be effective in episodic migraine (phase lib trial)	migraine without seriou adverse effect (phase llb trial	5
	Experimental Clinical	-			
	Laboratory Therapy				


• The role of CGRP

The complex role of CGRP in migraine pathophysiology may involve multiple processes in both the CNS and in the periphery, including:





a) Binding to the CGRP receptor



b) Binding to the CGRP



Potential effects of Erenumab



CGRP, calcitonin-gene related peptide; CGRP-R, CGRP receptor; TN, trigeminal nerves. Tepper S, et al. Lance Neurol. 2017;16:425-434.; Sun H, et al. Lancet Neurol. 2016;15:382-390.; Russo AF. Annu Rev Pharmacol Toxicol 2015;55:533–552.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Erenumab for Episodic Migraine

Peter J. Goadsby, M.D., Ph.D., Uwe Reuter, M.D., Yngve Hallström, M.D., Gregor Broessner, M.D., Jo H. Bonner, M.D., Feng Zhang, M.S., Sandhya Sapra, Ph.D., Hernan Picard, M.D., Ph.D., Daniel D. Mikol, M.D., Ph.D., and Robert A. Lenz, M.D., Ph.D.

ABSTRACT

BACKGROUND

We tested erenumab, a fully human monoclonal antibody that inhibits the calcitonin gene-related peptide receptor, for the prevention of episodic migraine.

METHODS

We randomly assigned patients to receive a subcutaneous injection of either erenumab, at a dose of 70 mg or 140 mg, or placebo monthly for 6 months. The primary end point was the change from baseline to months 4 through 6 in the mean number of migraine days per month. Secondary end points were a 50% or greater reduction in mean migraine days per month, change in the number of days of use of acute

From the National Institute for Health Research-Wellcome Trust King's Clinical Research Facility, King's College Hospital, London (P.J.G.); the Department of Neurology, Charité Universitätsmedizin Berlin, Berlin (U.R.); the Neuro Center, St. Göran Hospital, Stockholm (Y.H.); the Department of Neurology, Headache Outpatient Clinic, Medical University of Innsbruck, Innsbruck, Austria (G.B.); Mercy Research St. Louis (I.H.B.): and

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Results – Monthly migraine days

Data presented are least squares mean and 95% CI; *p<0.001 for each group vs placebo, not adjusted for multiplicity; Endpoint averaged over months 4, 5, and 6. MMD, monthly migraine days; PBO, placebo.

We tested erenumab, a fully human monoclonal antibody that inhibits the calcito- From the National Institute for Health

Erenumab (AMG 334) in episodic migraine

Interim analysis of an ongoing open-label study

4

ABSTRACT

Messoud Ashina, MD, PhD David Dodick, MD Peter J. Goadsby, MD, PhD Uwe Reuter, MD Stephen Silberstein, MD Feng Zhang, MS Julia R. Gage, PhD Sunfa Cheng, MD Daniel D. Mikol, MD, PhD Robert A. Lenz, MD, PhD

Correspondence to Dr. Ashina: ashina@dadInet.dk **Objective:** To assess long-term safety and efficacy of anti-calcitonin gene-related peptide receptor erenumab in patients with episodic migraine (EM).

Methods: Patients enrolled in a 12-week, double-blind, placebo-controlled clinical trial (NCT01952574) who continued in an open-label extension (OLE) study will receive erenumab 70 mg every 4 weeks for up to 5 years. This preplanned interim analysis, conducted after all participants had completed the 1-year open-label follow-up, evaluated changes in monthly migraine days (MMD), achievement of \geq 50%, \geq 75%, and 100% reductions, Headache Impact Test (HIT-6) score, Migraine-Specific Quality of Life (MSQ), Migraine Disability Assessment (MIDAS), and safety. Data reported as observed without imputation for missing data.

Results: Of 472 patients enrolled in the parent study, 383 continued in the OLE with a median exposure to erenumab of 575 days (range 28-822 days). Mean (SD) MMD were 8.8 (2.6) at parent study baseline, 6.3 (4.2) at week 12 (beginning of OLE), and 3.7 (4.0) at week 64 (mean change from baseline [reduction] of 5.0 days). At week 64, 65%, 42%, and 26% achieved \geq 50%, \geq 75%, and 100% reduction in MMD, respectively. Mean HIT-6 scores were 60.2 (6.3) at baseline and 51.7 (9.2) at week 64. MSQ and MIDAS improvements from baseline were maintained through week 64. Safety profiles during the OLE were similar to those in the double-blind phase, which overall were similar to placebo.

Conclusions: One-year efficacy, supported by functional improvements and favorable safety and tolerability profiles, supports further investigation of erenumab as a preventive treatment in patients with EM.

Clinicaltrials.gov identifier: NCT01952574.

Classification of evidence: This study provides Class IV evidence that for patients with episodic migraine, erenumab reduces long-term MMD and improves headache-related disability and migraine-specific quality of life. Neurology® 2017;89:1237-1243

Results – Monthly migraine days



Data are mean (95% CI). n = total number of patients with observed MMDs at each visit.. CI = confidence interval; EM = episodic migraine; MMD = monthly migraine day; OLE = open-label extension.

Ashina et al. Neurology, 2017;89:1237-1243

Erenumab (AMG 334) in episodic

migraine

Interim analysis of an ongoing open-label study

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- A total of 307 patients (80%) completed 1 year of open-label treatment.
- For patients enrolled in the OLE, mean monthly migraine days were 8.8 days at baseline, 6.3 at week 12, and 3.7 at week 64.
- At week 64
- a) 184 (65%) patients had achieved $\geq 50\%$ reduction
- b) 119 (42%) had achieved $\geq 75\%$ reduction
- c) 73 (26%) had achieved 100% reduction in monthly migraine days.

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Migraine

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1.5.1 Chronic migraine *New entrant to classification*

A. Headache fulfilling criteria C and D for 1.1 *Migraine without aura* on ≥15 d/mo for >3 mo

B. Not attributed to another disorder



ICHD-II. Cephalalgia 2004; 24 (Suppl 1) ©International Headache Society 2003/4

Chronic migraine

- Difficult version of migraine
- Headache more than 15 days per month and 8 migraine headache days (for at least three months)
- Prevalence 1,4-2,2%
- 3 years follow up 26% in remission (less than 10 headache days per month)

- Quality of life and working order lower than other migraine patients. Higher usage of health care system.
- Etiology unknown. Most likely complex
- Sensititation of sentral pain pathways?
- Treatment: Topiramate, Botulinumtoxin, detoxification if medication overuse, CGRP antibodies

Riskfactors for chronification of migraine

- Obesity
- Low education
- Female
- Diabetes
- Arthritis
- Allodynia
- High frequency of migraine attacks (> 10 headache days per month)
- Too much pain medications, especially opioids

Migraine and BMI

Proportion of migraine subjects with 10 or more headache days per month



Bigal, M. E. et al. Neurology 2006;66:545-550

Erenumab in the treatment of chronic migraine

Baseline 18 monthly migraine days

Safety and efficacy of erenumab for preventive treatment of @ (@) () chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial

Stewart Tepper, Messaed Ashina, Lee Einster, Jan J. Bandas, Devel Eadell, Stephen Sillerstein, Taul Winner, Devel Levend, David Mike Robert Lenz

Summar

Background The rakitenin gene-related peptide (CGRP) pathway is important in migraine pathophysiology. We user searches the issues and the difficult pathon and the cGRP receptor. In relative/relation with chronic migraine (CGRP) and the cGRP receptor (CGRP) and the cGRP receptor (CGRP) and the component of the

Methods This was a phase 2, randomised, double-blind, placebos-controlled, multicentre study of erremunab for adults aged 13-65 years with thronic migraine, enrolled from 60 headache and clinical research centres in North America and Europe. Charnic migraine was defined as 15 cm more headache days per month, of which eight on more were migraine days. Patients were randomly assigned [3:22] to subcutaneous placebo, eremunah 70 mg, or ereminan 140 mg, given ever 4 weeks for 12 weeks. Randomisation was centrally rescuted using an interactive voice or web response system. Patients, study investigators, and study sponsor personnel were manded to trottmene assignment. Thom the system of the system of



PBO n=281, erenumab 70 mg n=188, and erenumab 140 mg n=187. Baseline monthly migraine days, mean (SD): PBO 18.2 (4.7), erenumab 70 mg 17.9 (4.4), erenumab 140 mg 17.8 (4.7). Data are LSM (SE) change from baseline. Efficacy analysis set.; ^a Using a prespecified method for controlling for multiple comparisons, the p-values are considered statistically significant for the primary endpoint. LSM, least squares mean; PBO, placebo; SD, standard deviation; SE, standard error;

Tepper et al. Lancet Neurology, 2017;16:425-43-

Articles







PBO n=281, erenumab 70 mg n=188, and erer mg 17.9 (4.4), erenumab 140 mg 17.8 (4.7). Da controlling for multiple comparisons, the p-value placebo; SD, standard deviation; SE, standard e

Tepper et al. Lancet Neurology, 2017;16:425-434



Meta-analysis

Monthly migraine days fr	om baseline	% Weight
Erenumab		
Goadsby et al (2017) (9)	-1.40 (-1.43, -1.37)	33.43
Tepper et al (2017) (10)	-2.40 (-2.47, -2.33)	33.32
Sun et al(2016) (11)	-1.10 (-1.19, -1.01)	33.25
Subtotal (I-squared = 99.7%, p = 0.000)	-1.63 (-2.31, -0.96)	100.00
Eptinezumab		
Dodick et al(2014) (12)	-1.00 (-2.20, 0.20)	100.00
Subtotal (I-squared = .%, p = .)	-1.00 (-2.20, 0.20)	100.00
Galcanezumab		
Skljarevski et al(2017) (13)	-1.10 (-1.18, -1.02)	99.08
Dodick et al(2014) (14)	-1.20 (-2.01, -0.39)	0.92
Subtotal (I-squared = 0.0%, p = 0.810)	-1.10 (-1.18, -1.02)	100.00
Fremanezumab		
Cohen et al(2017) (15)	-1.65 (-1.89, -1.41)	81.56
Bigal et al(2015) (16)	-2.60 (-4.10, -1.10)	18.44
Subtotal (I-squared = 33.7%, p = 0.220)	-1,83 (-2.55, -1.10)	100.00
Overall (I-squared = 99.1%, p = 0.000)	-1.52 (-1.92, -1.11)	
NOTE: Weights are from random effects analysis		



Study	Adverse events		%
ID		RR (95% CI)	Weight
Erenumab			
Goadsby et al(2017) (9)		0.91 (0.80, 1.03)	51.42
Tepper et al(2017) (10)		1.12 (0.90, 1.39)	25.33
Sun et al(2016) (11)	C	1.00 (0.80, 1.26)	23.24
Subtotal (I-squared = 28.5%, p = 0.247		0.98 (0.87, 1.11)	100.00
Eptinezumab			
Dodick et al(2014) (12)		1.08 (0.82, 1.43)	100.00
Subtotal (I-squared = .%, p = .)		1.08 (0.82, 1.43)	100.00
Galcanezumab			
Skljarevski et al(2017) (13)		1.01 (0.76, 1.33)	28.25
Dodick et al(2014) (14)		1.07 (0.90, 1.28)	71.75
Subtotal (I-squared = 0.0%, p = 0.712)		1.05 (0.91, 1.22)	100.00
Fremanezumab			
Cohen et al(2017) (15)		1.26 (0.89, 1.78)	46.82
Bigal et al(2015) (16)		0.82 (0.62, 1.08)	53.18
Subtotal (I-squared = 71.5%, p = 0.061)		1.00 (0.66, 1.52)	100.00
Overall (I-squared = 8.2%, p = 0.367)	\Diamond	1.00 (0.92, 1.08)	101
NOTE: Weights are from random effects	analysis		

 \bullet

Secondary or primary headache

- Migraine
- Tension type headacheCluster headache



Tension Type Headache



- Probably the most common cause of headache
- Continous headache instead of attacks
- Gets worse typically during the day
- Mild or moderate intensity
- Bilateral pain
- "A band around a head"
- Tenderness of the pericranial (head and neck) muscles

Tension Type Headache

- Diagnosis is based on a patient history and normal examination
- Treatment
 - Exercise
 - Physiotherapy

 - Occupational ergonomics
 NSAID (+BZD in evenings)
 - Amitriptyline
 - Nortriptyline



- Secondary or primary headache
- Migraine
- Tension type headache
- Cluster headache



http://www.clusterkopf.de/ http://medlineplus.gov/

"The Cluster-triad"

- **1.** pain attacks in clusters
 - Attack: 15-180 min
 - 1-8 attacks per days
 - Duration of a cluster: from 7 days to 1 year
- 2. pain around the eye (trigeminal distribution)
- **3.** symptoms of the autonomic neurvous system



Cluster headaches may involve pain around one eye, along with drooping of the lid, tearing and congestion on the same side as the pain







Hypothalamic activation in cluster headache attacks Arne May, Anish Bahra, Christian Büchel, Richard S J Frackowiak, Peter J Goadsby

fMRI = functional Magnetic Resonance Imaging

Treatment of Cluster Headache

- Preventive medications: Calcium channel blocker Verapamil, Topiramate, Valproic acid, Melatonin, Lithium, Corticosteroids
- Acute treatments: Oxygen, triptans
- Deep brain stimulation, Occipital nerve stimulation and Sphenopalatine ganglion stimulation





Summary

- Mostly headache is caused by migraine, tensiontype headache or some other primary headache
- Migraine might have major impact on quality of life
- Migraine might even act as a risk factor for ischemic stroke
- Migraine causes major economical burden
- Headache is mostly benign, but however it might be extremely devastating