편두통의 표적치료: 트립탄과 CGRP항체

김 병 건
을지의대 신경과

Triptans and CGRP monoclonal antibodies in Migraine

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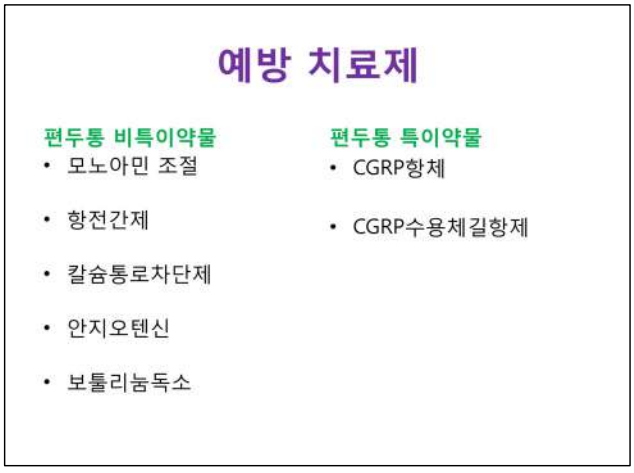
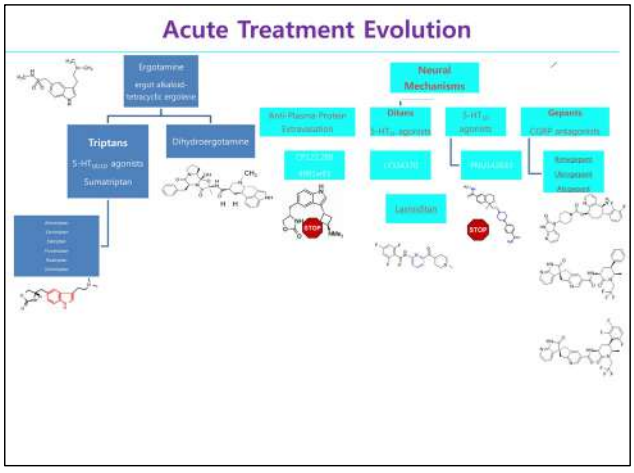
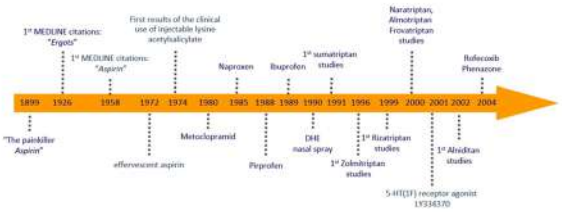




Milestones of acute medication in migraine



Milestones of acute medication in migraine

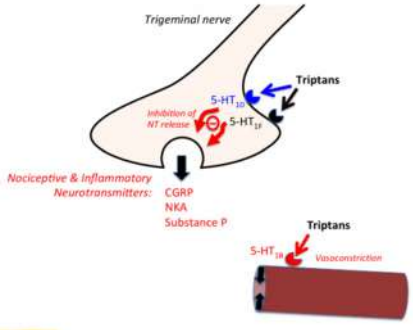
Triptans: approved indications

- Migraine without and with aura
  - not in FHM and migraine with brainstem aura
- Cluster headache (sumatriptan s.c; zolmitriptan i.n)
- Adolescents: almotriptan

Contraindications to triptans:

1) peripheral vascular disease,
2) coronary artery disease,
3) cerebrovascular disease,
4) uncontrolled hypertension.

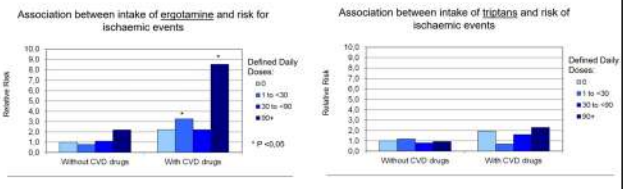
Proposed Mechanisms for Triptan Effect on Migraine



트립탄처방시 우려되는 점들

- I can't prescribe triptans because.....
  - The patient had chest tightness with a triptan
  - The patient is taking SSRIs or SNRIs
  - The patient is pregnant
  - The patient is breast-feeding

CVD risk : ergotamine vs triptans



Wammes-van der Heijden et al. Neurology 2006; 67: 1128-1134

A 2004 American Headache Society consensus statement noted that the cardiovascular risk for triptans is relatively small, with fewer than one adverse cardiovascular event per 1 million patients exposed.

Triptans and SSRIs: Serotonin syndrome?

- Based on 29 case, FDA released alert on serotonin syndrome taking both triptans and SSRIs (2006)
  - none met Hunter criteria of serotonin syndrome
- Serotonin syndrome is caused by activation of 5-HT1A and 2A receptors
  - Triptans work selectively at 5-HT 1B/1D
- Prospective study of 12,339 migraineurs using subcutaneous sumatriptan
  - 1784 concomitantly used an SSRI
  - No episodes of serotonin syndrome were reported
- In 2008, 1.4 million patients were co-prescribed both a triptan and a SSRI
  - 36% increase in co-prescription after FDA warning
- AHS "Currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs due to concerns for serotonin syndorm

Safety during pregnancy: pain killers

Research Submission

Final Results From the 16-Year Sumatriptan, Naratriptan, and Treximet Pregnancy Registry

Sara A. Ephross PhD ✉, Susan M. Sinclair PhD

First published: 7 May 2014 Full publication history

Lactation and triptans

- The AAP (미국소아과학회) considers sumatriptan as usually compatible with breastfeeding

Summary of AHS level of evidence

- **Level A:**
  - All triptans
  - NSAIDs: diclofenac, aspirin, naproxen, ibuprofen
  - Acetaminophen 1000 mg (for non-severe attacks)
  - Acetaminophen/aspirin/caffeine 500/500/130 mg
- **Level B:**
  - Metoclopramide IV
  - Tramadol/acetaminophen
  - Ergotamine/caffeine

A new era for migraine acute treatment

- CGRP antagonist (Gepants)
- 5-HT 1F agonist (Ditans)


The Journey of the Non-Vascular Relief for Migraine: From 'Triptans' To 'Ditans'

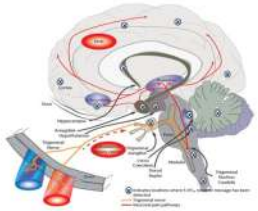
Author(s): Alpheres B. Xavier*, Mageshwaran Lakshmanan, Vikneswaran Gunaseelan.

Journal Name: Current Clinical Pharmacology

Volume 12 , Issue 1 , 2017 DOI : 10.2174/1574884712666170419155045

- Ditans
  - Lasmiditan, tablet, acute migraine, FDA approved Oct 2019 (Reyvow®)
- Gepants
  - Ubrogepant, tablet, acute migraine, FDA approved Dec 2019 (Ubrelvy®)
  - Rimegepant, tablet and fast dissolving tablet, acute migraine, FDA approved Feb 2020
  - Vazegepant, nasal spray, acute migraine

Lasmiditan (introduced in 2010, earned FDA approval in October 2019)

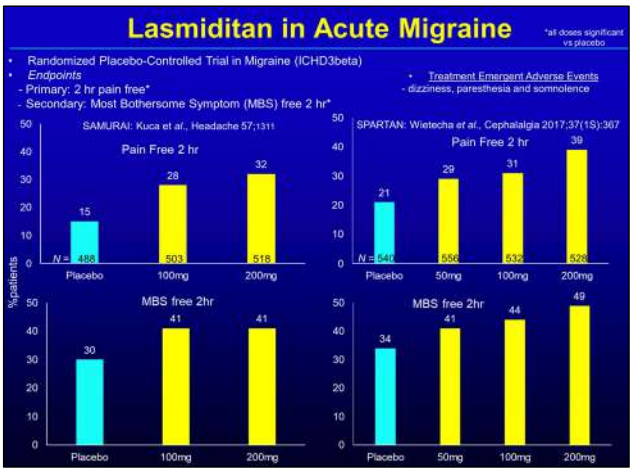


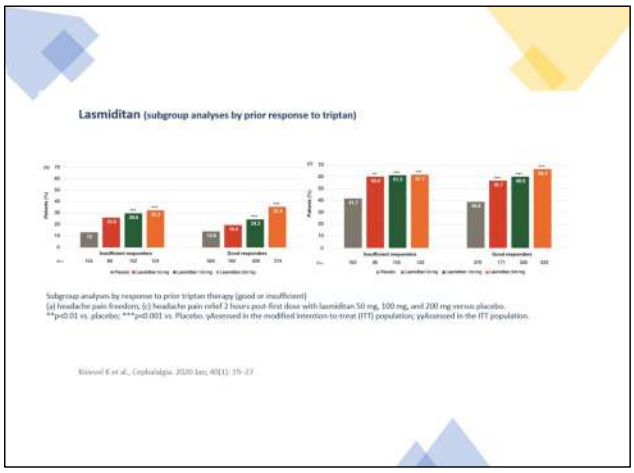
CNS Penetrant and Agonizes 5-HT_{1F} Receptors in Trigeminal Pathway

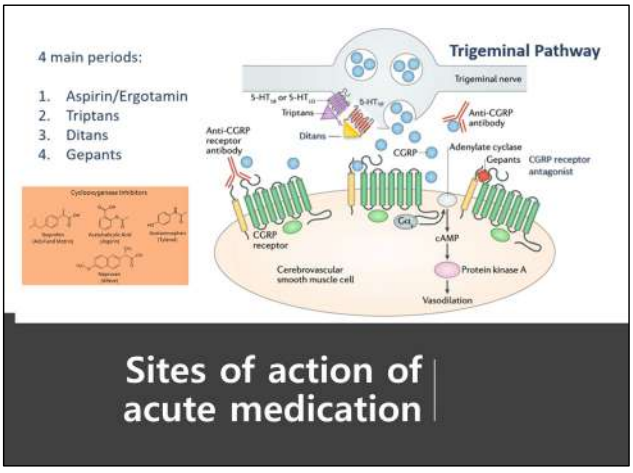
- >440-fold more selective for 5-HT_{1F} than 5-HT_{1B} and 5-HT_{1D} receptors
- Does not induce vasoconstriction
- Reduces activation of trigeminal nerve (peripheral and central)
- Inhibits release of CGRP

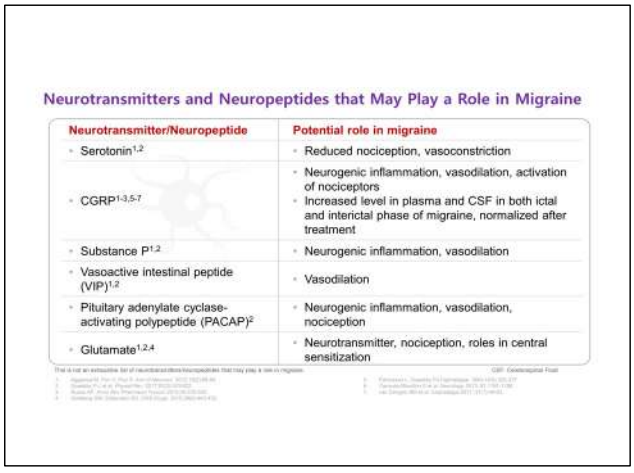
Agonism of 5-HT_{1F} receptors in the trigeminal pathway inhibits the activation of sensory nerves and pain transmission

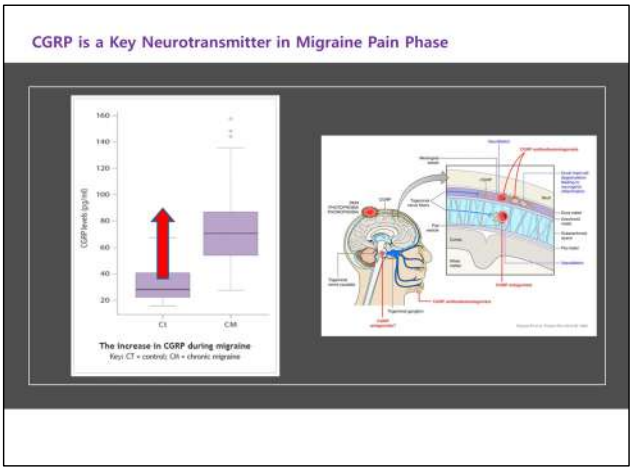
Nelson DL et al., *Cephalalgia* 2010;30:1159-69; Kuca B et al., Presented at AHS 2017. Abstract # IOR11B; Goadsby PJ et al., *New Engl J Med* 2002;346:257-70; Anderson CA et al., *In Behavioral Neurology & Neuropsychiatry*. 2013

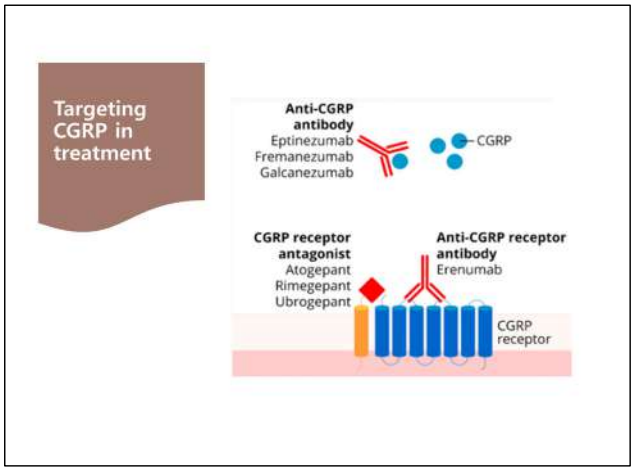

Lasmiditan in Acute Migraine
*all doses significant vs placebo
Randomized Placebo-Controlled Trial in Migraine (ICHD3beta)
Endpoints
- Primary: 2 hr pain free*
- Secondary: Most Bothersome Symptom (MBS) free 2 hr*
Treatment Emergent Adverse Events
- dizziness, paresthesia and somnolence
SAMURAI: Kuca et al., Headache 57;1311
SPARTAN: Wietecha et al., Cephalalgia 2017;37(1S):367
Pain Free 2 hr
MBS free 2hr
%patients
N = 488
503
518
N = 540
556
532
528
Placebo
100mg
200mg
50mg

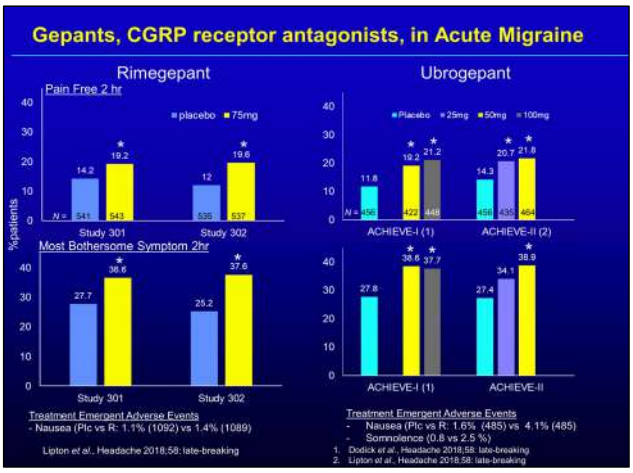

Lasmiditan (subgroup analyses by prior response to triptan)

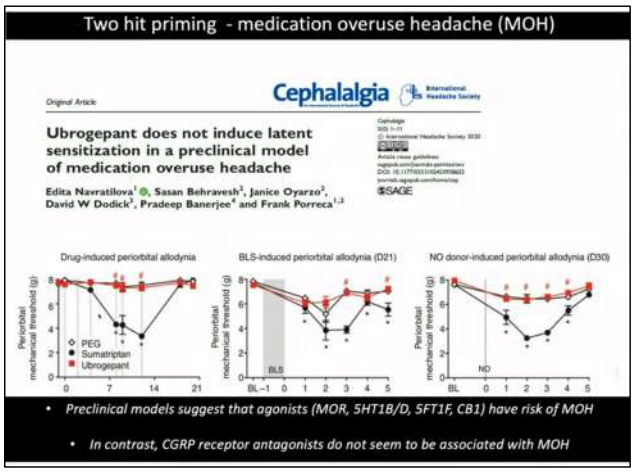

4 main periods:
1. Aspirin/Ergotamin
2. Triptans
3. Ditans
4. Gepants
Trigeminal Pathway
Trigeminal nerve
Triptans
Ditans
Anti-CGRP antibody
Anti-CGRP receptor antibody
CGRP
Adenylate cyclase
Gepants
CGRP receptor antagonist
CGRP receptor
cAMP
Protein kinase A
Cerebrovascular smooth muscle cell
Vasodilation
Cyclooxygenase Inhibitors
Sites of action of acute medication

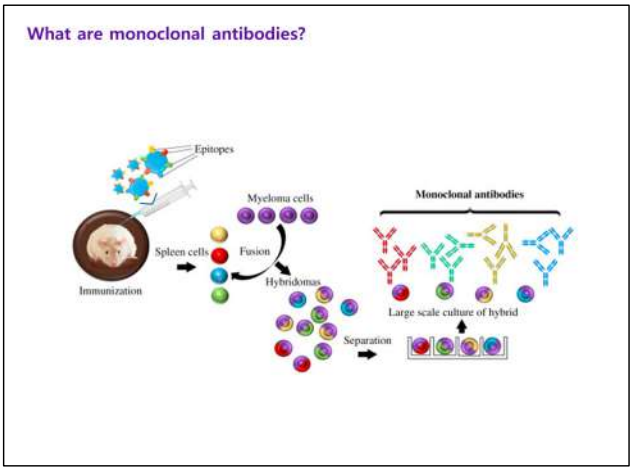

Neurotransmitters and Neuropeptides that May Play a Role in Migraine
Neurotransmitter/Neuropeptide
Potential role in migraine
Serotonin[1,2]
Reduced nociception, vasoconstriction
CGRP[1-3,5-7]
Neurogenic inflammation, vasodilation, activation of nociceptors
Increased level in plasma and CSF in both ictal and interictal phase of migraine, normalized after treatment
Substance P[1,2]
Neurogenic inflammation, vasodilation
Vasoactive intestinal peptide (VIP)[1,2]
Vasodilation
Pituitary adenylate cyclase-activating polypeptide (PACAP)[2]
Neurogenic inflammation, vasodilation, nociception
Glutamate[1,2,4]
Neurotransmitter, nociception, roles in central sensitization

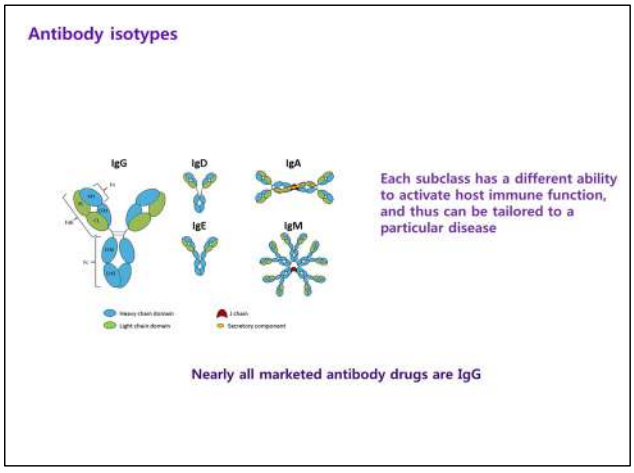

CGRP is a Key Neurotransmitter in Migraine Pain Phase
The increase in CGRP during migraine

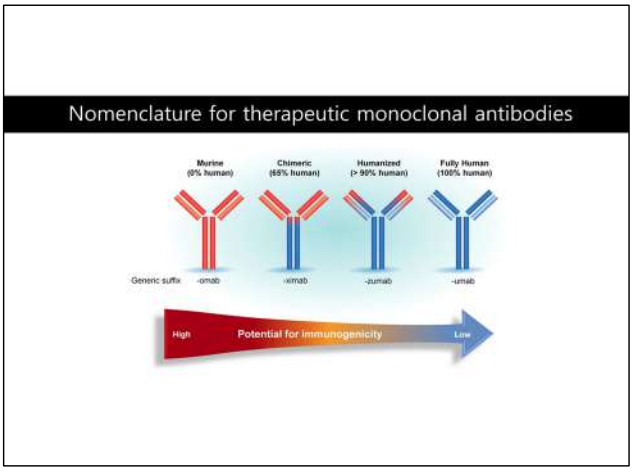

Targeting CGRP in treatment
Anti-CGRP antibody
Eptinezumab
Fremanezumab
Galcanezumab
CGRP
CGRP receptor antagonist
Atogepant
Rimegepant
Ubrogepant
Anti-CGRP receptor antibody
Erenumab
CGRP receptor

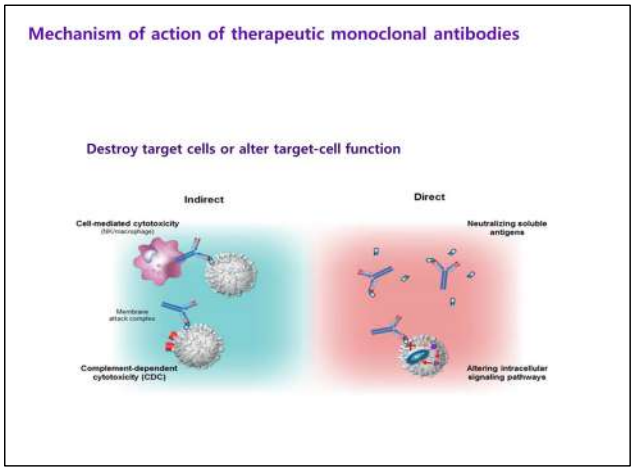

Gepants, CGRP receptor antagonists, in Acute Migraine
Rimegepant
Ubrogepant
Pain Free 2 hr
placebo
75mg
Study 301
Study 302
Most Bothersome Symptom 2hr
Treatment Emergent Adverse Events
- Nausea (Plc vs R: 1.1% (1092) vs 1.4% (1089)
Lipton et al., Headache 2018;58: late-breaking
Placebo
25mg
50mg
100mg
ACHIEVE-I (1)
ACHIEVE-II (2)
Treatment Emergent Adverse Events
- Nausea (Plc vs R: 1.6% (485) vs 4.1% (485)
- Somnolence (0.8 vs 2.5 %)
1. Dodick et al., Headache 2018;58: late-breaking
2. Lipton et al., Headache 2018;58: late-breaking


Two hit priming - medication overuse headache
Cephalalgia
Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache
Drug-induced periorbital allodynia
BLS-induced periorbital allodynia (D21)
NO donor-induced periorbital allodynia (D30)
PEG
Sumatriptan
Ubrogepant
• Preclinical models suggest that agonists (MOR, 5HT1B/D, 5FT1F, CB1) have risk of MOH
• In contrast, CGRP receptor antagonists do not seem to be associated with MOH


What are monoclonal antibodies?
Epitopes
Myeloma cells
Monoclonal antibodies
Spleen cells
Fusion
Immunization
Hybridomas
Large scale culture of hybrid
Separation


Antibody isotypes
IgG
IgD
IgA
IgE
IgM
Each subclass has a different ability to activate host immune function, and thus can be tailored to a particular disease
Nearly all marketed antibody drugs are IgG


Nomenclature for therapeutic monoclonal antibodies
Murine (0% human)
Chimeric (65% human)
Humanized (> 90% human)
Fully Human (100% human)
Generic suffix
-omab
-ximab
-zumab
-umab
High
Potential for immunogenicity
Low


Mechanism of action of therapeutic monoclonal antibodies
Destroy target cells or alter target-cell function
Indirect
Direct
Cell-mediated cytotoxicity
Neutralizing soluble antigens
Complement-dependent cytotoxicity (CDC)
Altering intracellular signaling pathways

CGRP mAbs vs gepants (small molecule drugs)

mAbs	Gepants
Larger (~150kD); mainly extracellular	Smaller (<1 kD); able to enter cells and cross blood-brain barrier
Parenteral administration	Oral administration possible
Longer dosing interval (half-life: days to weeks)	Shorter dosing interval (half-life: hours)
Not eliminated via hepatic, renal or biliary routes	Elimination via hepatic, renal and/or biliary routes
Lower risk of drug-drug interactions	Drug-drug interactions possible

CGRP Monoclonal Antibodies in Clinical Trials

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
Market name	AIMOVIG	EMGALITY	AJOVY	VYEPTI
FDA approval	May 2018	Sep 2018/ 국내승인	Sep 2018	Feb. 2020
Target	**CGRP receptor**	CGRP peptide	CGRP peptide	CGRP peptide
Sponsor	Amgen/ Novartis	Lilly	Teva	Alder
Dosing	**70/140mg** SC monthly	**Loading 240mg** then 120mg SC monthly	225mg SC monthly **675 mg SC Quarterly**	**Quarterly IV**
Characteristics	Human	Humanized	Humanized	Humanized
Being Studied for	EM (STRIVE, ARISE, LIBERTY) CM Tx resistant migraine	EM (EVELOVE1,2) CM (REGAIN) Tx resistant migraine Episodic cluster Chronic cluster (no effect)	EM (HALO) CM (HALO) Refractory migraine Episodic cluster Chronic cluster (no effect) Posttraumatic headache	EM (PROMISE 1) CM (PROMISE 2)

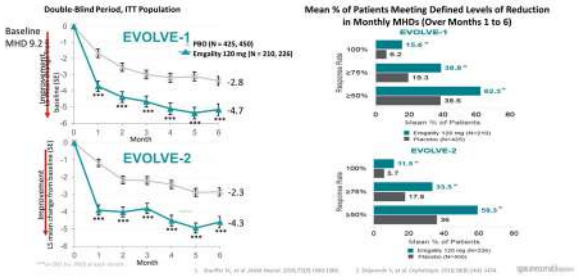
Bigal S. *Br J Clin Pharmacol.* 2015;79:886-895.; Walter S, Bigal ME. *Curr Pain Headache Rep.* 2015;19(3):6.; Vu T, et al. *Pharm Res.* 2017;34:1784-1795.; de Hoon J, et al. *Clin Pharmacol Ther.* 2017 Jul 24; epub ahead of print (doi: 10.1002/cpt.799).

CGRP항체의 장점 vs 단점

- 효과
  - 빠른효과
  - 75% 이상 반응
  - 기존치료에 실패한 환자에서도 효과적
  - 기존치료와 병용가능
- 긴반감기
- 단기안전성
- 군발두통에도 효과
- 비싼 가격
- 임신 5개월전 약제중단
- 장기안전성
- Wearing off

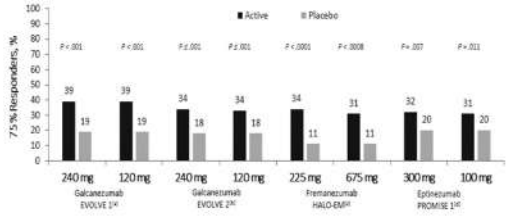
EM

- Sustained Response Through Month 6, Starting from Month 1[1,2]
- ≥ 50 reduction : **1/2** , ≥ 75 % reduction: **1/3**, 100% reduction: **10%**

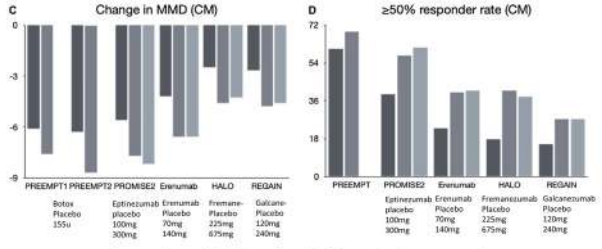


Clinical Benefit of Anti CGRP mAbs : 75% Super-responder rate in EM

- At least 1/3 of patients had a 75% reduction in MMD



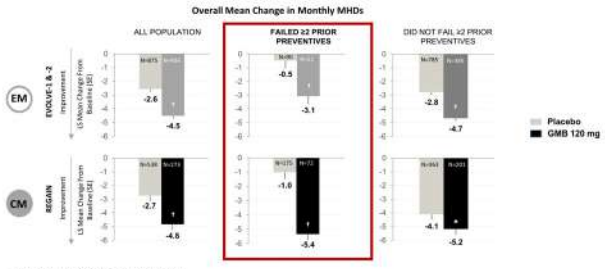
Efficacies in Preventing Chronic Migraine



Comparison of CGRP mAbs trials for migraine prevention

Hsiangkuo Yuan et al. Headache 2019;59:20-32

CGRP mAbs: Effective in Treatment resistant migraine



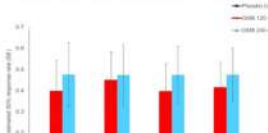
*p<.05 (vs. PBO); †p<.001 (vs. PBO).
GMB: Galcanezumab; ITT: Intent-to-treat; LS: Least squares; MHD: Migraine headache day

Dalf Agnello G, et al. Efficacy of Galcanezumab in Patients Who Failed Prior Preventive Treatments for Migraine: Results from EVOLVE-1, EVOLVE-2, and REGAIN Studies. Presented at: 12th European Headache Federation Congress (EHF);Sep 28-30, 2018; Florence, Italy.

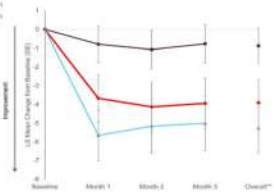
Galcanezumab after treatment failure to Onabotulinum toxin A in patient with CM

- Galcanezumab shows preliminary efficacy in preventing migraines in patients who had previously received onabotulinumtoxinA, including nonresponders

Estimated Proportion of 50% Responders for MHDs: OnabotulinumtoxinA Failures*

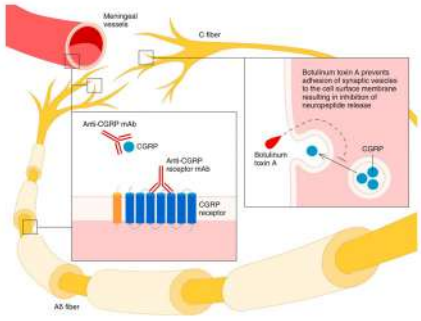


Change From Baseline in Number of MHDs: OnabotulinumtoxinA Failures*



*Failure defined as lack of efficacy or safety/tolerability issues.
**Overall refers to the mean of the 3 mo.
Aliani J, et al. AHS 2018. Poster PS106LB.

Dual Therapy with Botox

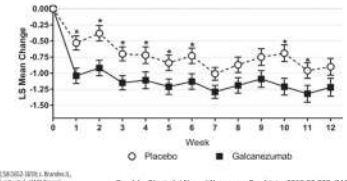


Good Safety Profiles in Clinical Trials

Oral	Propranolol	Valproate	Topiramate	Amitriptyline
Dropout rate due to AEs	20%	8%	22%	12%

mAb	Erenumab 70mg, 140mg	Galcanezumab 120mg, 240mg	Fremanezumab 225mg, 625mg	Eptinezumab 100mg, 300mg
Dropout rate due to AEs	2.2% in each group	4.2%, 2.3%	1.7% in each group	2% in each group

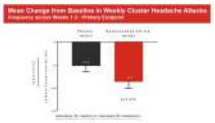
ONSET of EFFICACY
24 hour -1week
Demonstrated clinical benefit often within 1 month

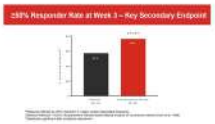


Goadsby PJ, et al. J Neurol Neurosurg Psychiatry 2019;90:939–944

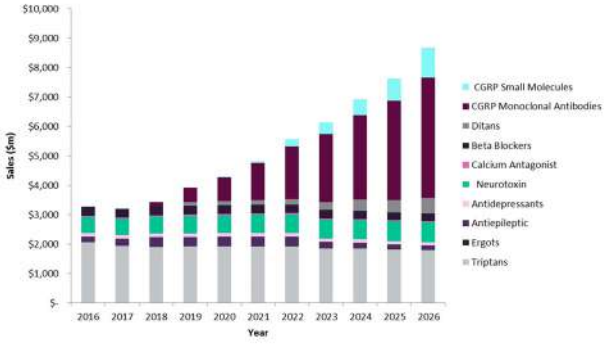
CGRP mAbs in Cluster headache

- galcanezumab 300 mg
  - reduced the weekly cluster headache attack frequency across Weeks 1 to 3
  - a ≥50% reduction in the weekly cluster headache attack frequency at Week 3.

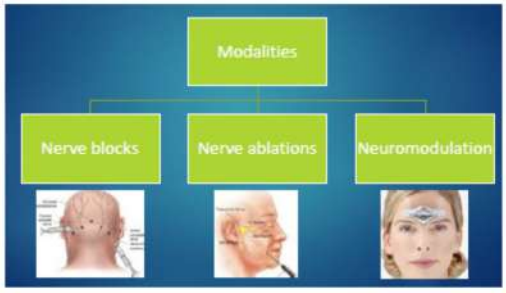




Global Sales in the Migraine Market



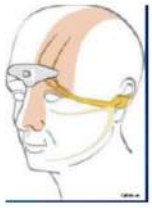
How do we target the PNS?



Neuromodulation

- Implantable nerve stimulation (Occipital, SPG, Vagus)
- Transcutaneous nerve stimulation
  - Cefaly: external trigeminal nerve stimulation (eTNS)
- Vagus Nerve Stimulation
  - gammaCore: Noninvasive vagus nerve stimulation (nVNS)
- Remote Nonpainful Electrical Upper Arm Skin Stimulation
  - Nerivio: Remote Electrical Neuromodulation (REN)

Transcutaneous supraorbital nerve stimulation (tSNS)



- Anatomical connection between solitary nucleus & TNS
- May involve modulation of central pain processing centers
- Increase in metabolism of orbitofrontal cortex and rostral angeriorcingulate cortex in migraineurs after 3 months of Cefaly use
- Approved for acute migraine treatment in 2017

Cefaly

- Safe, well-tolerated
- Considerations: cost

Non-invasive VNS in Acute Migraine

- Mechanism of action may involve :
  - Inhibition of nociceptive pathways that converge on TNC
  - Decreasing CSDs
  - Inhibition of dural evoked trigeminocervical nociceptive firing
- Approved for acute migraine treatment in 2018

GammaCore

- Safe, relatively well tolerated
- Considerations: cost
- Use in special populations

Transcranial magnetic stimulation for Migraine

- Randomised double-blind placebo controlled study
- *Include*: 30% aura episodes, aura leads to headache 90%
- *Exclude*: Prolonged aura, MOH
- TMS- 0.9T for 180 μs; Sham- click and vibrate
- *Primary endpoint:* 2 hr pain free plus non-inferiority for nausea/photo/phono
- *Blinding:* Thought they got active, 67% Sham and 72% active

50

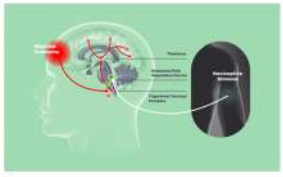
Sham Active

eNeura Bankruptcy: What Does this Mean for Patients?

Neurol 2010;9:973)

Remote Electrical Neuromodulation (REN)

Mechanism of action: Conditioned Pain Modulation (CPM)



- Stimulates C and Aδ nociceptive sensory fibers of the upper arm
- Between depolarization thresholds & pain threshold.
- The noxious information reaches the brainstem.
- Activates descending pain inhibitory pathway, involving the brainstem pain regulation center.
- Release serotonin and NE.
- Inhibit pain signal from the TCC

Nerivio

- 86 EM (MOA/MWA)
- 2-8/month
- 20 minutes of stimulation ASAP after migraine attack onset
- 50% pain reduction at 2 hour : 64% vs. 26% for sham stimuli

편두통 치료제

편두통 비특이치료제
- AAP, NSAIDs
- 모노아민 조절
- 항전간제
- 칼슘통로차단제
- 안지오텐신
- 보툴리눔독소

편두통 특이치료제
- 5HT 1B/1D 작용제
- 5HT 1F 작용제
- CGRP수용체길항제
- CGRP항체
- 신경조절
  - tSNS
  - nVNS
  - REN