CGRP MABs: A New Day in Migraine Therapy

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CONFLICT OF INTEREST:

My spouse, significant other, or I have not had any relevant financial relationships during the past 12 months.
OBJ ECTives

- Epidemiology – disease burden
- Migraine Definition
- Anatomy and Pathophysiology
- CGRP
- CGRP MABs
When I was somebody,…
USS Carl Vinson, CVN-70
NAS Whidbey Island, WA
Global burden of disease
15% suffer from migraine
Typically onset soon after menarche
Wax and wane until post menopause

Migraine #2 (persistent)
Overlapping conditions:
Back and neck pain #1, 6;
Depressive Disorders #3
Anxiety Disorders #9
Opioid Use disorders #19
(MOH, Epidemic)
Migraine or severe headache Prevalence in US adult population

Prevalence estimate from several US government surveys from 1997-2015

Females – 20.7%
Males – 9.7%
Overall prevalence – 15.3%

>65 years old - 5.1%

Reasons for ER visits:
GI pain
Chest pain
Cough
Fever
Headache (#5)
Primary Headaches

**Primary Headaches:**
1. Migraine
2. Tension type Headache
3. Trigeminal autonomic cephalgia (TAC)
4. Exertional and other Has (a grab bag of other headaches)

**Secondary Headaches:** (what our patients worry about)
5. Post traumatic
6. Vascular disease
7. Abnormal ICP, neoplasms, hydrocephalus
8. Substances
9. CNS infection
10. Metabolic
11. Cervicogenic, eyes, sinuses, jaw
12. Psychiatric HA
13. Neuralgias
Migraine Criteria

**Migraine without aura**
A. At least 5 attacks fulfilling B-D
B. Headache attack lasting 4-72 hours untreated or unsuccessfully treated
C. HA with at least 2:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe intensity
   4. Aggravated by or avoid routine physical activity (walking, climb stairs)

D. During HA have at least 1:
   1. Nausea and/or vomit
   2. Photo AND phonophobia

E. Not attributed to another disorder

**Chronic Migraine:**
Headache > 15 days per month for more than 3 months
Most of headaches fulfill criteria for migraine (>= 8 days per month).

International Classification of Headache Disorders (ICHD)
Head Pain Anatomy

5th Nerve - Ophthalmic division (mostly)
- large cerebral arteries
- large venous sinuses
- dura mater
- pial vessels

Neurotransmitters - TriG ganglion:
- CGRP
- Substance P
Head Pain Anatomy

Pain sensitive structures
large cerebral arteries
large venous sinuses
dura mater
pial vessels

Sagittal Sinus
Dura
Parenchymal Arteries
Pial Arteries
Scalp Arteries
Extracranial Arteries
Migraine Pathophysiology

Pathophysiology:
Exact mechanisms - Unknown
A complex neurovascular disorder

Central Theory:
Central neurons activated within the brain, spread to central blood vessels.
Or, brain blood vessels play a key role.
Or, both are important.

Peripheral Theory:
Initial event occurs in Periphery;
Activates peripheral pain nociceptors (CGRP)
Information - brainstem trigeminal nucleus,
Then - deeper brain centers,
Migraine established.
Migraine Pathophysiology

Central or peripheral – overlapping anatomic structures
Central – Trigeminal CC, Hypothalamic pontine axis, or Cortical spreading depolarization
Peripheral – dura mater/meninges (neuropeptides involved in vasodilation, inflammation, and pain)

Targets implicated through research?

How can migraine be terminated or prevented (Treatments)?
Location has effect on therapeutic options:
Alter central processing (NSAIDs, neuromodulation, CNS meds)
Target CSD or aura (AEDs, CCBs, anti-glu meds, neuromodulation – transcranial magnetic stim)
Prevent CGRP release (triptans, ergots, onabotulinumtoxin A)
Take out CGRP or its receptor to prevent its effects (Monoclonal ABs)
Prevent return of signal from periphery to CNS (triptans, ergots)
Peripheral Activation of Migraine

Central pain sensitization and sustained headache

CGRP

Headache 2018;58:4-16
BACKGROUND - Calcitonin Gene Related Peptide

Calcitonin Gene-Related Peptide (CGRP)
1982 – Discovered, bioassays, α- and β-CGRP isoforms
1985 - one of most potent cerebral vasodilators known.
   Localized - sensory nerve terminals peripheral and central nervous system

Trigeminal system:
The primary neurotransmitter in the Trigeminal system.
Found in C fibers along cerebral/meningeal arteries

BACKGROUND - Calcitonin Gene Related Peptide

**Roles in migraine** (Trigeminal functional anatomy):
Pain transmission from periphery to the CNS via trigeminal system
Peripheral potent vasodilator
Central sensitization in brainstem

*Cephalalgia. 22 (1): 54–61*
Calcitonin receptor-like receptor (CLR)
G-coupled protein receptor (GPCR)
7-transmembrane-domain protein
Couples with a receptor activity modifying protein (RAMP-1),
to form a functional unit.
CLR cytoplasmic tail then stimulates Receptor Component Protein (RCP),
and second messenger systems activate like
nitric oxide synthase (ie, cAMP, NOS)

CGRP BIND CLR
COUPLE with RAMP
ACTIVATE 2nd Messenger

Increase NOS, cAMP

J. Headache Pain. 2018 Nov 8;19(1):105
BACKGROUND - Calcitonin Gene Related Peptide

CGRP is broadly distributed in body, multiple systems and functions:

(α-CGRP = nervous system isoform)

Sensory
Digestive

Vascular
Vestibular
Hemopoietic
Immunomodulatory
Nociceptive

J Headache Pain. 2018;19:22
BACKGROUND - Calcitonin Gene Related Peptide

CGRP **released** from large dense vesicles, acts at specific receptors

**No reuptake** system

Metabolized by **proteinase**

**Can diffuse** far from point of release - measureable in serum
Elevated CGRP levels frequently reported during spontaneous migraine or Cluster H attacks.

Treatment with triptans aborts headache, and decreases serum rise in CGRP level.


CGRP levels are elevated interictally in CM,
OnabotulinumtoxinA treatment decreases the interictal CGRP levels.

Pain. 2015;156:820-824

CGRP infusion triggers delayed migraine-like attacks in roughly 68% migraine subjects but not in healthy controls and individuals with tension-type headaches.


CGRP infusion provokes Cluster H-like attacks in active-phase episodic Cluster H and chronic Cluster H

JAMA Neurol. 2018;75:1187-1197
Small Molecule (Gepants) CLR antagonists

BIBN 4096 BS:
Prevented Headache triggered by CGRP infusion.

2004 - First clinical trial for Acute Migraine Treatment - BIBN 4096 BS (Olcegepant, Boehringer Pharm)
Patients treated within 6 hours of HA onset, moderate to severe pain
Significant superiority to placebo
Response rate 66% (21/32) over placebo 27% (11/41)
HA relief = reduce pain to mild or zero within 2 hours

Endpoints:
Response rates at 2 hours, 24 hours, HA recurrence, improvement in nausea, photophobia, phonophobia and functional capacity, time to meaningful relief.
Most frequent side effect was paresthesia
No serious adverse events

Supported the crucial role of CGRP in acute migraine.

Small Molecules (Gepants)

Several similar CLR antagonists small molecules tested very successfully in Phase 2 (Efficacy) vs Placebo in Acute Migraine

Liver Toxicity – repeated use.
Class effect?

None passed Phase 3 (Safety and Efficacy) – so far.
Small Molecules (Gepants)

Gepants do not cross the BBB!!!

2006 - Monoclonal antibodies vs CGRP?
Monoclonal antibodies
Clonal (identical) human antibodies grown in cell cultures.
Bind to very specific parts of another protein.
Precisely target specific processes in the body.
Remain active weeks or months,
(migraine process inhibited during that time)
Large glycoproteins.
Do not cross the Blood Brain Barrier (BBB)

Antibody structure:
2 identical heavy and light chains
Composed of constant and variable regions
Variable region confers binding specificity
CGRP MAB Site of Action

CGRP MABs
Block CGRP by:
- binding the CLR receptor sites
- binding CGRP itself.

Thus, blocks events leading to migraine.
# CGRP MABs for Migraine Prevention

<table>
<thead>
<tr>
<th></th>
<th>Erenumab (Aimovig)</th>
<th>Fremanezumab (Ajovy)</th>
<th>Galanezumab (Emgality)</th>
<th>Eptinezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>EM/CM</td>
<td>EM/CM</td>
<td>EM/CM (Cluster)</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>70 or <strong>140mg</strong> SC monthly</td>
<td>240mg load, 120mg SC monthly</td>
<td>225mg monthly 675mg quarterly</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>CGRP receptor</td>
<td>peptide or ligand</td>
<td>peptide or ligand</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Available</td>
<td>Available</td>
<td>Available</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Contraindication</strong></td>
<td>Hypersensitivity to Erenumab or excipients</td>
<td>Hypersensitivity to Fremanuzamab or excipients</td>
<td>Hypersensitivity to Galanuzamab or excipients</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Most common AE</strong></td>
<td>Constipation 3%, (Placebo 3%)</td>
<td>Inj site reac 18% (Plac 15%)</td>
<td>Inj site reac 45% (Plac 38%)</td>
<td>Pending</td>
</tr>
</tbody>
</table>
Erenumab
Erenumab Clinical Trials

Erenumab
Efficacy and safety investigated in multiple clinical trials for both episodic and chronic migraine.

Episodic migraine (trial STRIVE)
24-weeks; Phase III RCT, double-blind
955 adult patients (38.7% no previous benefit from migraine preventives)
3 arms: 70 mg (n=317) or 140 mg (n=319) erenumab, or placebo (n=319)

Episodic migraine further investigated (ARISE trial)
3-month; Phase III RCT double-blind
577 adult patients
2 arms: 70 mg erenumab or placebo

Chronic migraine
3 month; RCT, double-blind
667 patients
3 arms: Erenumab 70 mg (n=191) or 140 mg (n=190), or placebo (n=286)
Erenumab CM - MSQ

Change in Migraine-Specific Quality-of-Life Questionnaire (MSQ) scores from baseline over 3 months

A. MSQ-RFR

B. MSQ-RFP

C. MSQ-EF

Placebo (n = 281)
Erenumab 70 mg (n = 188)
Erenumab 140 mg (n = 187)

Erenumab CM - HIT
Change in Headache Impact Test–6 (HIT-6) total score from baseline over 3 months

For 140mg:
HIT-6 score
Decreased below 2.3 points
(minimal for meaningful improvement)
By end of first month.

Erenumab CM - MIDAS

Change in Migraine Disability Assessment (MIDAS) scores from baseline to month 3

A. Total score

B. Absenteeism score

C. Presenteeism score

Least-squares (LS) mean changes from baseline in (A) MIDAS total, (B) absenteeism, and (C) presenteeism scores among participants with chronic migraine who were assigned to receive erenumab 70 mg, erenumab 140 mg, or placebo every month. The error bars represent 95% confidence intervals (CIs). Figure based on the efficacy analysis set. All p values ≤0.05.

2018 Danish Clinical CGRP Infusion Study

Subset migraine patients infused with CGRP do not get HA

Fig. 5 Headache intensity after CGRP and placebo. Individual headache intensity scores on the CGRP day (a) and placebo day (b). Black lines: Median intensity at each time point. The median headache intensity was 0 for all time points after placebo. The median time (range) to onset of migraine was 30 min (20–152.5) after CGRP.
Anti-CGRP and Vasoconstriction

**Gepants in patients with stable angina**
treadmill exercise time vs placebo - no effect

**Erenumab tested in patients with stable angina**
treadmill exercise time vs placebo - no effect

**Conclusion:**
CGRP appears to have no direct vasoconstriction effects.

However, stay tuned:
Open-label [long-term clinical trial](#) with erenumab for 5 years (end of 2019, 383 patients).
CONCLUSIONS:

Migraine is common; affects about 15% of the US population
Considered a complex neurovascular disorder
Central and peripheral mechanisms
CGRP Monoclonal Antibodies
**Minimal** side effects, monthly injections, can be highly effective
These help a subset of migraine patients; sub-population that do not respond
QUESTIONS???
QUESTIONS?
International Headache Society Diagnostic Criteria:
Migraine with Aura

A. At least 2 attacks fulfilling criteria B-D.
B. One or more of the following fully reversible aura symptoms:
   1. Visual
   2. Sensory
   3. Speech and/or language
   4. Motor
   5. Brainstem
   6. Retinal
C. At least 2 of the following
   1. At least 1 aura symptom spreads gradually over ≥ 5 minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5 to 60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by a headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack is excluded.
