## Cases

Super responder
Delayed responder
Combined benefit
mAb plus gepant

# Move the needle – Clinician perspective

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## Disclosures

- ***Consultant:*** Acorda, Alder, Allergan, Amgen, Avanir, Depomed, electroCore, Lilly, Novartis, Pernix, Promius, Supernus, Teva, Upsher-Smith
- ***Grant/research support:*** Alder, Allergan, Amgen, electroCore, Lilly, Teva
- ***Speaker:*** Acorda, Allergan, Amgen, Avanir, Depomed, electroCore, Lilly, Novartis, Pernix, Promius, Supernus, Teva, Upsher-Smith

## Moving the needle

- What do patients want?
- What is good enough?
- Identify super-responders
- Rational co-pharmacy

## Case 1

- 23-year-old female grade school teacher
- Developed headaches around age 12
- Feels dizzy, has frequent yawning, urination prior to headache; no aura
- Pain is L > R, stabbing and severe
- Lasts 2 days, worse with menses, when lasts 5 days
- Reports “I can not tolerate the noise and lights in the classroom”
- Misses work 1-3 x per month

## Case 1

Estimates headache up to 24 days per month

- VS: BP 120/70, P 72, R 12; complete medical and neurologic exams are normal

Acutely, she gets relief with sumatriptan 100 mg PO but usually has recurrence that requires retreatment

For prevention, she has tried amitriptyline, which caused excessive sedation, and topiramate, which caused word-finding difficulty

## What Is Her Diagnosis?

**International Classification of Headache Disorders (ICHD-3)**
**Diagnostic Criteria for Chronic Migraine Without Aura**

- **Description:**
- Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.
- **Diagnostic criteria:**
- Headache (migraine-like or tension-type-like[1]) on ≥15 days/month for >3 months, and fulfilling criteria B and C
- Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
- On ≥8 days/month for >3 months, fulfilling any of the following[2]:
  - criteria C and D for 1.1 *Migraine without aura*
  - criteria B and C for 1.2 *Migraine with aura*
  - believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- Not better accounted for by another ICHD-3 diagnosis

*Cephalalgia*. 2018;38(1):1-211.

## Proposed new CM criteria

- ICHD-3 criteria for chronic migraine (CM) include mixture of migraine and tension-type-like headaches
- Does not account for patients with high frequency of migraine but no other headaches.
- Study results:
- Patients with migraine on eight or more days but not 15 days with headache a month are as disabled as patients with ICHD-3 defined CM.
- Should be included in revised diagnostic criteria for chronic migraine

Proposed new diagnostic criteria for chronic migraine. Chalmer MA et al. Cephalalgia. (2019)

## Options: Classification of Migraine Preventive Therapies AAN AHS Guidelines, 2012

**Level A:**
**(≥2 Class I trials)**

**Antiepileptic drugs**
VPA*
Topiramate*
**β-blockers**
Metoprolol
Propranolol*
Timolol*

**All of the MABs have Level A as of 2018:**
Erenumab*
Fremanezumab*
Galcanezumab*

**Level B:**
**Probably effective**
**(1 class I or 2 class II studies)**

**Antidepressants**
Amitriptyline
Venlafaxine
**β-blockers**
Atenolol
Nadolol

**Level C:**
**Possibly effective**
**(1 class II study)**

**ACE inhibitors**
Lisinopril
**β-blockers**
Nebivolol
Pindolol
**ARBs**
Candesartan†
**Antihistamines**
Cyproheptadine
**Old data/meds**
Clonidine, Guanfacine, CBZ

**Level U:**
**Inadequate or conflicting data to support or refute use**

**Carbonic inhibitors**—acetazolamide
**Antithrombotics**—warfarin
**SSRIs**—fluoxetine, fluvoxamine
**β-blockers**—bisoprolol
**TCAs**—protriptyline
**AEDs**—GBP
**CCBs**
Verapamil, nicardipine, nimodipine, nifedipine
**Muscle relaxants**—cyclandelate

**Possibly or probably ineffective**

Established as not effective
**AEDs**—LTG

Probably not effective
**TCAs**—clomipramine

Possibly not effective
**AEDs**—OXCB
**BZDs**—clonazepam
**β-blockers**—acebutolol
**NSAIDs**—nabumetone
**ARBs**—telmisartan

*FDA-approved for migraine prevention.
†New evidence puts candesartan Level A or B.
VPA=valproate. MRM=menstrually-related migraine. ACE=angiotensin converting enzyme. ARBs=angiotensin receptor blockers. CBZ=carbamazepine. SSRIs=selective serotonin reuptake inhibitors. AEDs=antiepileptic drugs. GBP=gabapentin. CCB=calcium channel blocker. LTG=lamotrigine. TCAs=tricyclic antidepressants. OXCB=oxcarbazepine. BZD=benzodiazepine. NSAIDs=nonsteroidal anti-inflammatory drugs.
Silberstein SD, et al. *Neurology*. 2012;78(17):1337-1345.

## Case 1

- Prescribed erenumab in July 2018
- Had 2 days of migraine in the week after treatment
- In following month, her headaches dropped to 11
- Subsequent months, dropped further to 1-2/month, milder, able to treat with OTC meds

## Onset of response


## Efficacy seen from Week 1[1]

Post-hoc analysis – Chronic Migraine

At Week 1, 25% of patients taking erenumab achieved a ≥50% reduction in weekly migraine days from baseline vs 16% taking placebo


*p≤0.02 for each group vs placebo. P-values are not adjusted for multiplicity.
Chronic migraine defined as 15 or more headache days per month, of which 8 or more of those days were migraine days.
OR, odds ratio.
Weekly migraine days at baseline: placebo 4.6, erenumab 70mg 4.5, erenumab 140mg 4.5.

References: 1. Tepper S, et al. Poster EP3070. EAN, Amsterdam, June 24–27, 2017

## Case 2

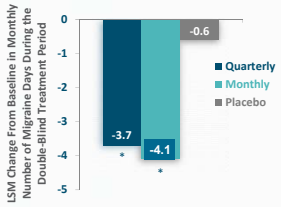
- 32 year old woman with migraine with aura since 12 y/o, runs a daycare center
- History of asthma, fibromyalgia
- Reports 4-5 migraine attacks monthly, lasting up to 2 days
- With other HAs, up to 25 days per month
- Uses rizatriptan for relief, but is tired after using it

## Case 2

- Prior failed trials of propranolol, amitriptyline
- Presently taking topiramate 50 mg BID x 3 months
- Reports some headache improvement, but cognitively slowed “I feel as dumb as a rock”

## Change in Monthly Migraine Days During FOCUS Phase 3b Study

838 participants with episodic (329 [39%]) or chronic (509 [61%]) migraine were randomly assigned to placebo (n=279), quarterly fremanezumab (n=276), or monthly fremanezumab (n=283).




*P<0.0001 vs placebo.

- Ferrari et al. Lancet. 2019 Sep 21;394(10203):1030-1040

## Case 3

- 63-year-old woman with chronic migraine
- Headaches date back to her teens.
- Has had headache every single day for at least 11 years, in bed an average of 20 days per month
- Has been on at least 15 different preventives, all of which were either ineffective, or had excessive side effects.
- Treated 5 months ago with 70 mg erenumab. She noted mild tenderness at the injection site the next day which then resolved.

## Case 3

- The following month, she had 7 headache free days.
- Dose increased at that time to 140 mg
- After 2 months of similar headache pattern, said she wants to switch meds
- Switched to fremanezumab with return of daily headache pattern
- After 2 months, switched to galcanezumab
- In following months, she had 6-7 headache free days.

Should have continued therapy

## How long to treat

- Early onset of benefit does not mean no additional benefit with longer treatment
- Episodic migraine clinical trial data from OLE out to 64 weeks showed some patients had sustained benefit
- 52 weeks sustained efficacy shown in chronic migraine (Tepper AHS 2018)
- Safety data available for 4½ years in episodic migraine

## Case 4

45 year old MD with migraines since medical school

Evolved to chronic, started on onabotulinum toxin A

Headaches decreased from 20-25 days per month to 6-8 monthly over 4-5 cycles (12 weeks each)

Uses sumatriptan PO or SQ as abortive

Gets headache pain gone, but feels "washed out", has to lay down for a while

When seen in September 2018, notes she is still missing clinic at times, fremanezumab started

## Case 4

At next BTX treatment, is asked "how is it going

- *"I have a mouth so dry it feels like cotton, and have heartburn"*

And the treatment results?

- *The 1st month, it was better, the 2nd, only had 1 headache, acetaminophen was sufficient*
- *"I am no longer anxious about my headache control, and my family is happier also"*

## Case 4

At 7 week follow-up

- *I have not had a single symptom, even if perhaps I might have deserved it"*
- *1 year follow-up – no migraines, no headaches*
- *Continuing on onabotulinumtoxin-A and fremanezumab*

## Use with other preventives

- mAbs generally studied as monotherapy.
- In the STRIVE and ARISE episodic migraine studies, a small number of patients were receiving concurrent prophylactic therapy
- No drug-drug interactions are expected
- Considerable clinic experience with concurrent onabotulinumtoxin-A
- ~ 400 patients who had ≥ 50% benefit with onabot-A, with a migraine mAb as add-on
- Criteria ≥ 4mo migraine days at baseline

## Case 5

50 year old woman with 11 migraine days monthly, some with aura, and 28/30 headache days

2 prior oral preventives, as well as onabotulinumtoxin-A in past

Did well with onabotulinumtoxin-A for 11 years, then benefit ceased

Started erenumab 140mg monthly in September 2018

## Case 5

Follow-up in November 2018
"I generally feel better, perhaps by about 20%"
Still with near daily headaches

Discussed other mAbs, decided to continue erenumab

At revisit in March 2019, reduced to 1 per month
Still gets occasional aura, without headache pain

## mAb plus gepant

mAbs not available at study onset

Small number of "protocol violators" in long term rimegepant study used it as abortive in addition to erenumab with good benefit

Postulated that rimegepant may access receptors that are incompletely blocked, different receptor kinetics, or differential displacement of antibodies by CGRP

Mullin, K, Kudrow, D et al. Poster presentation AHS July 2019

## Other cases:

*Neuromodulation options*
*Lasmitidan*
*Gepants blur acute/preventive distinction*

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# Thank you!

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