New treatments for migraine

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outline
ACUTE PREVENTION
What is happening in the brain during migraine?

Activation of trigeminal system

Cortical spreading depression
  Explains aura

Vasodilation
  Activation of trigeminal ganglion leads to increase in extracerebral blood flow
  Local release of CGRP and substance P

Inflammatory response
  Mast cell degranulation/release of histamine, changes in post capillary venules, platelet aggregation
20 years from the laboratory bench to bedside

Drugs that block CGRP
- Monoclonal antibodies (mAbs)
- Small molecules ("gepants")
NEW ACUTE TREATMENTS for Migraine

“Gepants”
“Ditans”

What does a patient that is having a migraine want?

Complete freedom from pain
FAST!
Minimal or NO side effects
No headache recurrence
Rapid return to normal function
“Gepants”

small molecules that block the CGRP receptor

Ubrogepant (Ubrelvy)
  50 & 100 mg tablet
Rimegepant (Nurtec ODT)
  75 mg orally disintegrating tablet
Ubrogepant (Ubrelvy)

- At 2 hrs, odds of reporting return to normal function were 2X as high in patients treated with either 50/100 mg Ubrelvy vs placebo

- At 24 hrs, patient reported satisfaction and improved change was 61% treated vs 37% placebo

**Rimegepant (Nurtec ODT)**

**Pain freedom at 2 hrs**
- 21% vs 11% placebo

**Free most bothersome symptom**
- 35% vs 27% placebo

Both parameters sustained through 48 hours

86% pts treated with Nurtec did not use any rescue medication 24 hrs post-dose

“Ditans”

**Lasmiditan** *(Reyvow)*

- 5-HT1F serotonin receptor agonist
- receptor activation is linked to the inhibition of CGRP release
- NOT vasoconstrictive
Lasmiditan (Reyvow)

Data from 100 mg dose

Pain freedom at 2 hrs

25% vs 11% placebo (UP)
31% vs 20% placebo (NUP)

Free most bothersome symptom

34% vs 24% placebo (UP)
33% vs 44% placebo (NUP)

Sustained pain freedom at 24 hours

14/17 % vs 5.6% placebo

Patient perceived outcomes +

NEW PREVENTIVE TREATMENTS for Migraine

CGRP monoclonal Antibodies
- link to CGRP receptor
- link to CGRP peptide

Erenumab (Aimovig)
Galcanezumab (Emgality)
Fremanezumab (Ajovy)
Eptinezumab (Vyepti)
Who benefits from starting a CGRP preventive?

- > 1-2 migraines a week
- Long disabling duration of attacks
- Intolerance or contraindication to oral preventive drugs
- Not planning pregnancy, not breastfeeding
How to decide which CGRP mAb to choose?

• Fast onset of effect
• High efficacy in all
• 1/3 of patients achieve >75% reduction in frequency of migraines in first 1-3 months
• Well tolerated and minimal side effects
Facts to keep in mind when making a choice...

- mode
  - ...3 are self-injections
  - ...1 is an intravenous infusion

- counteract potential side effects
  - constipation and muscle spasms would make Erenumab less favored

- coverage/cost
  - likely limiting factor, depends if included in your insurance’s formulary and their pre-authorization requirements
Frequently asked questions...

• How long is an adequate trial?
  • 4-6 months
• If a patient does not respond to 1 CGRP mAb, will another work?
  • probably
• Will the CGRP mAb stop working?
  • low risk
• Will the CGRP mAb work if there is medication overuse headache (MOH)?
  • Yes they can
• Do CGRP mAbs help in chronic migraine?
  • All 4 have evidence
• Can you take CGRP mAbs and “gepants”?
  • Yes, but would like more studies
Do CGRP mAbs help Chronic Migraine (CM)?

Botulinum toxin injection treatments every 3 months had been the only FDA approved treatment in CM from 2010 to 2017.

Data from the clinical trial
Fremanezumab (Ajovy)

- 50% reduction in average of headache days per month
- 38% pts quarterly use
- 41% pts monthly use
- 18% pts placebo

Fremanezumab for the Preventive Treatment of Chronic Migraine
List of authors.Stephen D. Silberstein, M.D., David W. Dodick, et al.
November 30, 2017
Do CGRP mAbs help Chronic Migraine (CM)?

- Data from the clinical trials
  - Galcanezumab (Emgality)
    - Included pts with MOH
  - Erenumab (Aimovig)
    - Included pts with MOH


Do CGRP mAbs help Chronic Migraine (CM)?

- Data from the clinical trials
  - Eptinezumab (Vyepti), Promise 2 trial specifically looked at CM
  - 40% pts had MOH

Efficacy and safety of eptinezumab in patients with chronic migraine
PROMISE-2
Richard B. Lipton, Peter J. Goadsby, Jeff Smith, Barbara A. Schaeffler, David M. Biondi, Joe Hirman, Susan Pederson, Brent Allan, Roger Cady
Neurology Mar 2020, 94 (13) e1365-e1377
Treatments in the horizon…

Other “gepants”
• Atogepant- in trials for prevention of migraine
• Vazegepant- nasal spray in trial for acute treatment
• Rimegepant- completed trial for preventive use, awaiting FDA review

Other novel mechanisms…
• Pit adenyl cyclase-activating polypeptide mAb
Thank you!