New CGRP treatments: “where will they fit in?”

LARS EDVINSSON
LUND UNIVERSITY, SWEDEN
Migraine in adults: 1-year prevalence

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
<th>studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>4.0</td>
<td>2</td>
</tr>
<tr>
<td>Asia</td>
<td>10.6</td>
<td>6</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>13.8</td>
<td>9</td>
</tr>
<tr>
<td>N. America</td>
<td>12.6</td>
<td>8</td>
</tr>
<tr>
<td>S. America</td>
<td>9.6</td>
<td>10</td>
</tr>
</tbody>
</table>

Population-based surveys up to 2007 of >500 participants covering ages 25-60 y, using IHS or modified IHS criteria

Mean: 11.2  
Median: 10.2
From the beginning, CGRP was hypothesized to play a role in migraine.
It has stood the test of time

- CGRP is found in perivascular nerves in intracranial blood vessel walls, cerebral and meningeal arteries/arterioles, and in neurons of the trigeminal ganglion\(^1\); with central projections into the trigeminal nuclear complex and at the spinal cord at C1–C3 levels\(^2\).
During migraine attacks (with or without aura) CGRP levels increase in external jugular but not cubital fossa blood.

Only CGRP elevated
No change in VIP, SP, NPY
Release of Perivascular Neuropeptides During Acute Primary Headache Attacks

<table>
<thead>
<tr>
<th></th>
<th>Neuropeptide Y</th>
<th>VIP</th>
<th>Substance P</th>
<th>CGRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine without aura</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>Yellow</td>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Chronic paroxysmal headache</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Green</td>
</tr>
</tbody>
</table>

- **Yellow**: No change from before headache
- **Green**: Significant increase in neuropeptide level

CGRP receptor antagonists
- New class of antimigraine drug

- Block the action of CGRP on the CGRP-receptor complex
  - CLR
  - RAMP1
  - RCP
  - $\text{G}_s$-protein-coupled receptor
- Increase cAMP

- Calcitonin receptor-like receptor (CLR)
- Receptor activity-modifying protein 1 (RAMP1)
- Receptor component protein (RCP)
Sites of effects of specific anti-migraine drugs

Edvinsson et al 2018 Nat Rev Neurol.
Acute treatment with CGRP receptor blockers provides relief of migraine headache

Pain free at 2 hrs (% Patients)

- Olcegepant (1-10 mg, i.v.)
- Placebo

Sustained Pain free at 24 hrs (% Patients)

- Olcegepant (1-10 mg, i.v.)
- Placebo

Olesen et al, NEJM 2004
Edvinsson & Linde, Lancet 2010
Telcagepant is Effective in the Treatment of Acute Migraine: double-blind, parallel-group, randomized controlled trial.

2 hour pain free

% Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>T-150</th>
<th>T-300</th>
<th>Z5</th>
<th>Z2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho et al. Lancet 2008</td>
<td>9.6</td>
<td>17.2</td>
<td>26.9</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Ferrari et al. Lancet 2001</td>
<td></td>
<td></td>
<td></td>
<td>32.4</td>
<td>29.1</td>
</tr>
</tbody>
</table>
Telcagepant - phase 3 clinical data

Primary outcomes @ 2h

Pain Relief

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Telcagepant 150 mg</th>
<th>Telcagepant 300 mg</th>
<th>Zolmitriptan 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Relief</td>
<td>27.7</td>
<td>49.8</td>
<td>55.0</td>
<td>56.4</td>
</tr>
</tbody>
</table>

Pain Freedom

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Telcagepant 150 mg</th>
<th>Telcagepant 300 mg</th>
<th>Zolmitriptan 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Freedom</td>
<td>9.6</td>
<td>17.2</td>
<td>26.9</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Associated Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Telcagepant 150 mg</th>
<th>Telcagepant 300 mg</th>
<th>Zolmitriptan 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phonophobia</td>
<td>36.8</td>
<td>53.8</td>
<td>57.8</td>
<td>55.3</td>
</tr>
<tr>
<td>Photophobia</td>
<td>28.9</td>
<td>45.0</td>
<td>51.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>67.0</td>
<td>65.1</td>
<td>71.3</td>
<td></td>
</tr>
</tbody>
</table>

p<0.010, ***p<0.001 for telcagepant-placebo pairwise comparison.

#p<0.001 for telcagepant 150 mg-zolmitriptan pairwise comparison

Telcagepant also worked in Randomized Controlled Trial for Migraine Prevention

Telcagepant 140 mg BID (n=248)
Telcagepant 280 mg BID (n=247)
Placebo (n=125)

-2.7*  
-3.0***

Mean monthly migraine days

-0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0

% Patients with ≥50% reduction in headache days

Telcagepant 140 mg BID (n=248) 36.3%**
Telcagepant 280 mg BID (n=247) 35.6%***
Placebo (n=125) 20.8%

Efficacy and Safety of telcagepant (MK-0974), a Novel Oral CGRP Receptor Antagonist, for Acute Migraine Attacks

Kathryn M. Connor,1 Robert E. Shapiro,2 Ernst Christoph Diener,3 Sylvia Lucas,4 James Kost,1 Xiaoyin Fan,2 Christopher Assaid,1 Tony W. Ho1

1Merck Research Laboratories, North Wales, PA, USA, 2University of Vermont College of Medicine, Burlington, VT, USA, 3University of Essen, Essen, Germany, 4University of Washington Medical Center, Seattle, WA, USA

UBROGEPANT Proportion of 2 h pain freedom and proportion of 2 h headache response

Tiffini Voss et al. Cephalalgia 2016;36:887-898
Summary results of gepants – they all show good effects

Pain freedom rate at 2 hrs (% of patients)

- **olcegepant**
- **telcagepant**
- **MK-0974**
- **MK-3207**
- **BI443701A**
- **Rimegepant**
- **BMS-927711**
- **Ubrogepant**
- **MK-1602**

Edvinsson et al 2018 Nat Rev Neurol
Today - gepants

1. Ubrogepant (MK-1602 now Allergan) – for acute therapy – phase III have been completed (n=2).

2. Rimegepant (BMS now Biohaven) – semi-acute – phase III reported

3. Aterogepant (Allergan) – for prophylaxis - ?

4. Other; a derivatives of telcagepant (MK-2918) are explored, and an intra-anti-CGRP receptor antagonist is developed (BMS-742413).

Overall: the gepants are superior over placebo in pain freedom at 2 h, sustained response over 24 h and in improving migraine associated symptoms.

Place in therapy: (i) acute attacks, (ii) with or without triptans or NSAID, (iii) Some are tested for longer effects (Rimegepant) and some for prophylaxis (Aterogepant).
## New CGRP Antibody Antagonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Development notes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD403</td>
<td>Humanized (rabbit) IgG1 to CGRP ligand</td>
<td></td>
</tr>
<tr>
<td>Erenumab (AMG334)</td>
<td>Human IgG2 to CGRP receptor</td>
<td>= Aimovig (16/5-18)</td>
</tr>
<tr>
<td>Galcanezumab (LY2951742)</td>
<td>Humanized IgG4 to CGRP ligand</td>
<td></td>
</tr>
<tr>
<td>TEV48125 (LBR-101)</td>
<td>Humanized (murine) IgG2a to CGRP ligand</td>
<td></td>
</tr>
</tbody>
</table>

Evolution of monoclonal antibodies and immunogenicity potential. Monoclonal antibodies have evolved to include fewer nonhuman sequences, which are recognized as foreign. Murine sequences are depicted in green and human sequences are depicted in blue. As antibodies become more human, the potential for immunogenicity is decreased.

Evolution of monoclonal antibodies and immunogenicity potential. Monoclonal antibodies have evolved to include fewer nonhuman sequences, which are recognized as foreign. Murine sequences are depicted in green and human sequences are depicted in blue. As antibodies become more human, the potential for immunogenicity is decreased.
mAb Metabolism and Elimination

- Not filtered by kidney or excreted into urine intact
- Catabolized into peptides and amino acids by reticuloendothelial system, consisting of phagocytes (i.e., macrophages and monocytes)
- Antibody transport from mother to fetus, due to the neonatal Fc receptor
- FcRn transports IgG across placental barrier
- Long half-life of IgG due to binding to FcRn receptor, which is also present in reticuloendothelial cells

## mAbs vs Small Molecules

<table>
<thead>
<tr>
<th></th>
<th>mAbs</th>
<th>Small Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>~150 kD</td>
<td>&lt;1 kD</td>
</tr>
<tr>
<td><strong>Injection</strong></td>
<td>Must be injected</td>
<td>Orally administered</td>
</tr>
<tr>
<td><strong>Cell Entry</strong></td>
<td>Do not enter cells or cross BBB</td>
<td>Many enter cells and cross BBB</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Half-life of 1-4 weeks</td>
<td>Half-life of minutes to hours</td>
</tr>
<tr>
<td><strong>Manufacture</strong></td>
<td>Manufactured in tissue culture</td>
<td>Chemically synthesized</td>
</tr>
</tbody>
</table>
Antibody Binding to Receptor Complex

mAb

CGRP receptor complex

RAMP1

CLR

Trigeminal nerve

CGRP

Primary endpoint: Least squares mean change from baseline in migraine days per month in the double-blind phase

Secondary endpoint: percentage of patients with a 50% or greater reduction from baseline in mean migraine days per month over the final 3 months

(Months 4, 5, 6: P<0.001 vs placebo)

Erenumab Phase III study of the prevention of episodic migraine

STRIVE (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention)

Primary end point: Change from baseline in average number of headache days per month (12-week period after the first dose of study treatment)

Secondary end point: Change from baseline in the average number of migraine days per month (12-week period after the first dose of study treatment)

mAbs: early onset of actions

Fremenezumab (CM):

Eptinezumab (EM; Day 1):

Erenumab (EM):

Patients With ≥50% Reduction in Weekly Migraine Days (%)

- Week 1
  - Placebo: 1.34%
  - 675/225 mg: 1.96%
  - 900 mg: 1.84%
- Week 2
  - Placebo: 2.05%
  - 675/225 mg: 2.51%
  - 900 mg: 2.05%
- Week 3
  - Placebo: 2.13%
  - 675/225 mg: 50.0%
  - 900 mg: 47.2%

Baseline | Week 1 | Week 2 | Week 3
---------|--------|--------|--------
Placebo  | 1.34%  | 2.05%  | 2.13%
675/225 mg | 1.96%  | 2.51%  | **
900 mg   | 1.84%  | **     | **
CM: Reduction of mean monthly migraine days according to prior treatment

No prior treatment failures

≥1 prior treatment failures

≥2 prior treatment failures

Data are LSM (95% CI) change from baseline at Month 3

Number of subjects in the efficacy analysis set: No prior treatment failures, n=210; ≥1 prior treatment failures, n=446; ≥2 prior treatment failures, n=323

Adjusted analysis utilizes a linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and baseline value as covariates and assuming a first-order autoregressive covariance structure. The overall baseline values were usually ~18 monthly migraine days CI, confidence interval; LSM, least squares mean.
## Differences of mAbs to current preventive migraine medications

<table>
<thead>
<tr>
<th></th>
<th>mAbs for episodic and chronic migraine(^1)</th>
<th>Currently available medications (episodic migraine)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Formulation</td>
<td>SC / IV solution</td>
<td>Oral / tablet</td>
</tr>
<tr>
<td>Dose titration</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Frequency of intake</td>
<td>Monthly / every 3rd month</td>
<td>Daily</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Fast (days)</td>
<td>Slow (weeks)</td>
</tr>
<tr>
<td><strong>Side effects (AEs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Effect on weight</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>- Mood change</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>- Drowsiness / fatigue</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>- Cognitive dysfunction</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>- Dizziness</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Monoclonal antibodies show good effects with minor AEs

Edvinsson et al 2018 Nat Rev Neurol
Calcitonin Gene-Related Peptide (CGRP): The facts

- That CGRP is involved in the pathogenesis of migraine headache is established.

- That CGRP and its receptor are located throughout peripheral and central trigeminal pathways, and other central sites involved in pain regulation, is also established.

- That investigational drug therapy targeting CGRP and/or its receptor is effective for acute migraine treatment and in prevention is established.

- That the BBB is intact during migraine attacks is likely

- Where do CGRP therapeutics act and what does this tell us about the pathogenesis of migraine headache?
Place of CGRP Abs in therapy?
My view

1. Prophylaxis – they are given sc or iv once per month or less.
2. Type of disease – frequent episodic migraine and chronic migraine.
3. How about cluster headache? – trials are ongoing (positive vibes).
4. Efficacy; 20% superresponders, >50% effective, 25% no effect.
5. AEs – very few and mild. Long half-life and not metabolized.
6. Prize will be a limitation.
7. TLV will likely ask us to have documented testing currently available medications with poor outcome.
Thanks for the attention