What is CGRP?

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Outline

- CGRP
- Role in migraine
- How medications act on CGRP
- Q&A (definitely Q, maybe some A)
CGRP: Calcitonin Gene Related Peptide

• Neuropeptides: signaling molecules in the brain
• CGRP involved in regulating blood flow in the brain
• Acts to relax blood vessels
History of CGRP in Migraine

- **1983**: CGRP is discovered
- **1988**: Trigeminal nerve stimulations provoke CGRP release
- **1990**: CGRP elevated in blood during migraine
- **2008**: Telcagepant shows promise as acute treatment
- **2010**: IV Infusion of CGRP provokes migraine-like HA
- **2014**: Preventive trial of telcagepant terminated due to adverse effects
- **2018**: CGRP targeted mAbs approved for prevention
- **2020**: Gepants approved for acute treatment
- **2022**: Gepants likely to be approved for preventive treatment
CGRP in Migraine

- CGRP levels increase during acute migraine
- Triptans reduce CGRP levels during acute migraine
  - Decrease corresponds with migraine relief
- CGRP increased between migraines in persons with CM
- Degree of CGRP elevation predicts positive response to onabotA

Cernuda-Morollón et al. Neurology 2013, 81 (14) 1191-1196
How do the meds work?

**Triptans** act on serotonin receptors 5HT1b/d

**Ditans** act on serotonin receptor 5HT1f

**Gepants** are small molecules that bind to and block the CGRP receptor, without causing any vasoconstrictive effects

**Anti-CGRP monoclonal antibodies** bind the CGRP receptor or CGRP itself

**Onabotulinum** toxin binds to docking proteins and inhibits vesicle release.

CGRP-R, calcitonin gene-related peptide-receptor; 5-HT, 5-hydroxytryptamine; mAb, monoclonal antibody.

## CGRP Monoclonal Antibodies (mAbs)

<table>
<thead>
<tr>
<th></th>
<th>Erenumab (Aimovig)</th>
<th>Galcanezumab (Emgality)</th>
<th>Fremanezumab (Ajovy)</th>
<th>Eptinezumab (Vypeti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding site</td>
<td>Receptor</td>
<td>Ligand</td>
<td>Ligand</td>
<td>Ligand</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Device</td>
<td>Autoinjector</td>
<td>Autoinjector Prefilled syringe</td>
<td>Autoinjector Prefilled syringe</td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>70mg or 140mg monthly</td>
<td>240mg x1, then 120mg monthly</td>
<td>225mg monthly 675mg quarterly</td>
<td>100mg or 300mg monthly</td>
</tr>
<tr>
<td>Side effects</td>
<td>Injection site reaction Constipation Hypersensitivity reactions Constipation w complications* Hypertension*</td>
<td>Injection site reaction Hypersensitivity reactions</td>
<td>Injection site reaction</td>
<td>Nasopharyngitis Hypersensitivity reactions</td>
</tr>
</tbody>
</table>

*postmarket
## Gepants: Acute treatment

<table>
<thead>
<tr>
<th></th>
<th>Ubrogepant</th>
<th>Rimegepant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>50, 100mg</td>
<td>75mg</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Oral tablet</td>
<td>Oral disintegrating tablet</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>1 tab at onset, can repeat in 2 hrs</td>
<td>1 tab at onset, can repeat in 24 hrs</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>CYP3A4 inhibitors (antifungals, antibiotics, verapamil, barbiturates)</td>
<td>CYP3A4 inhibitors or inducers</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Nausea, sleepiness</td>
<td>Nausea</td>
</tr>
</tbody>
</table>
Q&A

• Can I just get my CGRP levels tested?
  • Oh, if it were only that easy
  • Half life is 7 minutes
  • No commercially available test

• What else does CGRP do in the body?
Q&A

• Side effects
  • How are side effects determined?
    • On label
    • Postmarketing report
  • What if I have a side effect that’s not listed?
    • Tell your doctor.
    • Report negative side effects of prescription drugs to the FDA [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.
Q&A

• If I’ve tried one CGRP antibody, should I consider trying another?
  • Lack of benefit? Yes, the medications are different
  • Side effects? Maybe

• Why don’t these medications help me?
  • Clinical trials often represent an “idealized” patient population
  • Migraine is complicated, CGRP is not the whole story.
It's hormonal!

It's inflammation!

It's cortical spreading depression!

It's diet!

It's CGRP!

It's vascular!

Credit: Joe Sutliff
The future in bright!