CGRP: A NEW ERA FOR MIGRAINE TREATMENT

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OBJECTIVES

• Review the underlying pathophysiology and etiology of migraine
• Examine the current therapeutic targets for treatment and prevention of migraine
• Describe the place of CGRP receptor antagonists in migraine treatment
CALCITONIN GENE-RELATED PROTEIN (CGRP) WHY SO EXCITED?

MIGRAINE
MIGRAINE PREVALENCE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>Low</td>
</tr>
<tr>
<td>RA</td>
<td>Low</td>
</tr>
<tr>
<td>Asthma</td>
<td>Low</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Moderate</td>
</tr>
<tr>
<td>OA</td>
<td>Moderate</td>
</tr>
<tr>
<td>Migraine</td>
<td>High</td>
</tr>
</tbody>
</table>

MIGRAINE: CLINICAL FEATURES

<table>
<thead>
<tr>
<th>Migraine Without Aura</th>
<th>Migraine With Aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>No aura or Prodrome</td>
<td>Aura or prodrome is present</td>
</tr>
<tr>
<td>Unilateral throbbing headache may be accompanied by nausea and vomiting</td>
<td>Unilateral throbbing headache and later becomes generalised</td>
</tr>
<tr>
<td>During headache, patient complains of phonophobia and photophobia</td>
<td>Patient complains of visual disturbances and may have mood variations</td>
</tr>
</tbody>
</table>

STRATEGIES FOR MIGRAINE TREATMENT

- Acute: Stop pain and progression
- Preempt: Known trigger slow timeline
- Prevent: Decrease the frequency
TRIGGERS AND AGGRAVATING FACTORS

- Fasting / foods
- Stress
- Circadian rhythm
- Medications
- Environment
- Hormones

PROPOSED MIGRAINE MECHANISM

Trigger → 5HT, NA → Vascular dilation ↑ Blood flow

- Trigeminal system
- Vomiting centre stimulated by 5HT
- More BV dilation
- Spinal cord

- Photo / phonophobia
- Hypothalamus
- Tightness / spasm neck / back
TREATMENT GOALS

<table>
<thead>
<tr>
<th>Acute attack</th>
<th>Preventative Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat attack rapidly and consistently</td>
<td>Reduce Attack: Frequency, Durations, Severity</td>
</tr>
<tr>
<td>Restore Patient ability to function</td>
<td>Improve: function and reduce disability</td>
</tr>
<tr>
<td>Minimise backup and rescue medications</td>
<td>Improve: Response to acute treatments</td>
</tr>
<tr>
<td>Minimal or no adverse effects</td>
<td>Minimal or no adverse effects</td>
</tr>
<tr>
<td>Involve and optimise self care</td>
<td>Involve and optimise self care</td>
</tr>
</tbody>
</table>

Prevalence of Common Migraine Symptoms (Fig. 1)

Prevalence of Migraine symptoms (Source: Migraine.com)
## CURRENT THERAPIES *

<table>
<thead>
<tr>
<th>Acute attack</th>
<th>Preventative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple Analgesics</strong></td>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td>E.g. Paracetamol / Aspirin / NSAID</td>
<td>E.g. SSRI, TCA</td>
</tr>
<tr>
<td><strong>Ergots</strong></td>
<td><strong>Anticonvulsants</strong></td>
</tr>
<tr>
<td>E.g. Dihydroergotamine</td>
<td>E.g. Valproate, Topiramate, Gabapentin</td>
</tr>
<tr>
<td><strong>Triptans</strong></td>
<td><strong>B-Blockers</strong></td>
</tr>
<tr>
<td>E.g. Sumatriptan, zolmitriptan; naratriptan</td>
<td>E.g. Propranolol</td>
</tr>
<tr>
<td></td>
<td><strong>Calcium Channel Blockers</strong></td>
</tr>
<tr>
<td></td>
<td>E.g. Verapamil</td>
</tr>
</tbody>
</table>

* Also various other agents e.g. Botox, magnesium, riboflavin ……

## LIMITATIONS OF CURRENT THERAPY?

- Not specifically designed as migraine treatments
- Directed to one part of the pathway e.g. vascular / neuro
- Drug interactions and tolerability concerns
- Limited effectiveness? (multiple trials of therapy)
WHY CGRP – WHAT IS ITS ROLE?

• Causal role in migraine pathophysiology

• Serum CGRP elevated during migraine attacks

• CGRP receptors:
  • pain pathways, intracranial arteries and mast cells

• Treatment with anti-migraine drugs normalizes CGRP concentrations
CGRP AS A DRUG TARGET?
What the antagonism does:

- At CGRP receptors located on mast cells it would inhibit inflammation caused by trigeminal nerve release of CGRP onto mast cells within the covering of the brain (meninges).

These include bradykinin, histamine, prostaglandins, tumour necrosis factor α (TNF-α), vascular endothelial growth factor and serotonin.


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What the antagonism does:

- At the CGRP receptors located in smooth muscle cells within vessel walls, it would inhibit the pathologic dilation of intracranial arteries without the unwanted effect of active vasoconstriction.
What the antagonism does:

* At the CGRP receptors it would suppress the transmission of pain by inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.


WHAT CGRP ANTAGONISTS ARE AVAILABLE?

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand</th>
<th>Dose Information / Frequency *</th>
<th>Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab</td>
<td>AIMOVIG</td>
<td>70 – 140 mg monthly</td>
<td>Receptor</td>
</tr>
<tr>
<td>Fremanezumab</td>
<td>AJOVY</td>
<td>225mg monthly 675mg Q 3 months</td>
<td>Protein</td>
</tr>
<tr>
<td>Galanezumab</td>
<td>EMGALITY</td>
<td>240mg first month 120mg monthly after</td>
<td>Protein</td>
</tr>
</tbody>
</table>

* Subcutaneous Injection – patient administered
WHAT DO WE KNOW ABOUT THEIR CLINICAL BENEFITS AND RISKS?

• Monoclonal – LARGE MOLECULES
• Do not cross the Blood Brain Barrier
• Must be given by injection
• Not metabolized in the liver (limit drug – drug reactions)
• Metabolized by proteolysis into peptides and amino acids
• Primarily SE = local injection site reactions

ERENUMAB

IBUPROFEN

C_{6472}H_{9964}N_{1728}O_{2018}S_{50}

C_{13}H_{18}O_{2}
WHAT DO WE KNOW ABOUT THEIR CLINICAL BENEFITS AND RISKS?

- Benefit in episodic, chronic, with / without aura and MOH
- Approx. 50% Reduction in HEADACHE FREQUENCY
  - Both >15 days per Month and in < 15 days per Month group
- Decrease Severity and Increase QOL
- No specific clinical data for >65 yr population or pediatrics
- Pregnancy – no data to support safety in pregnancy

AUSTRALIA:
ERENUMAB
ARTG (LATE 2018)

- 100% human monoclonal antibody - first in class
- Indication: prevention (prophylaxis) of migraine in adults
  - via neurologists and specialists
- Self-administered / subcutaneous injection
- 70 – 140mg monthly pre-filled pen
- $700-850 AUD / month
WHAT'S NEXT?

• Increasing range available
  • Targeting CGRP protein
  • Timeline for administration (monthly v quarterly …… years???)
  • E.g. Galanezumab (EMGALITY), Fremanezumab (AJOVY)

• Change in dose form
  • oral delivery?
  • IV infusion?

• Other ….