Migraine Update

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Disclosures
Speakers Bureau:
- Current: Amgen, ElectroCore, Lilly, Teva
- Relevant Products: Aimovig, Ajovy, GammaCore VNS, Emgality, Lasmiditan

Speakers Bureau:
- Past: Allergan, Avanir, GlaxoSmithKline, Pernix
- Relevant Products: Botox, Atogepant, Ubrogepant, Semprana, Onzetra-Xsail, Treximet

Advisory Board: Lilly
Dedication – Roger E. Farber, M.D.*

- U Penn Neurology Headache Center, Director
  - 1993-1996
- A Career filled with “Firsts”
  - U Penn Neurology & NIH with G. Milton Shy, M.D. & E. Arnold Carmichael
  - First studies in L-Dopa in Parkinson’s Disease
  - Pioneering research, 1969, Carotid and Transcranial Doppler, Carotid Endarterectomy & Stroke
  - First in-office MRI Machine, Minneapolis, MN
  - Director, American Society of Neuroradiology, 1983-87
  - Pioneering use of Chemotherapy agents in M.S.
- Notable and Quotable:
  - “Another patient? Oh, good!”
  - “Stop! Now, what did you see? What did you hear?”
  - “Your patients will teach you.”
  - “Do your best, and care a lot.”
  - “How sweet it is!”

(* In Loving Memory – Dr Alzheimer’s 2007, Died 2018)

Migraine Update

- Foundation
  - Secondary Causes of Headache
    - Migraine Diagnosis
- Migraine Pathophysiology - History lessons and Today
  - Vascular theory
  - Cortical Spreading Depression
  - Neurogenic Inflammation, Oligemia
  - Trigeminal-Vascular System
  - Sensitization (Central & Peripheral), Allodynia
  - CGRP
- New Migraine Treatment Options
  - Prevention - CGRP Monoclonal Antibodies
    - Devices – rFNS (Gammacore), sTMS, tSNS (Cefaly), Nerivio, Relivio
    - Pipeline – small molecule (GPT1-IV), GePants (CGRP receptor small molecule), Lasmiditan (5HT1-f)
Brain Tumor
Meningioma - Clivus

- Symptoms: Headache, imbalance, snoring, slight dysphagia.

Brain Aneurysm

Foundation
Secondary Causes First

Examples – Secondary, Extracranial:
- Carotid/Vertebral artery dissection
- Cervical spine disorders
- Dental disorders
- CSF leak
- Acute Angle Glaucoma
- “True” Sinusitis
Carotid Artery Dissection

True Sinusitis

Foundation
Secondary Causes First

Examples – Secondary, Systemic:
- Hypertensive urgency/emergency
- Altitude sickness
- OSA/Hypoxia/Hypercapnia
- Polycythemia vera
- SLE
- Temporal arteritis and other vasculidities
- Many, many others
Temporal Arteritis

Obstructive Sleep Apnea

Foundation
Secondary Causes First

Take home message:
1. Secondary Causes First
   a) Intracranial
   b) Extracranial
   c) Systemic
2. Then think primary headache disorder
   a) Migraine
   b) Cluster
   c) Etc.

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• New Migraine Treatment Options
  • Prevention - CGRP Monoclonal Antibodies
    - Design – rNDA (Genmab), JrNDA (G late), Nerivio, Relpax
  • Pipeline – eptinezumab (JPT-101), Zelphars (CGRP receptor small molecule), Lasmiditan (JPT-330)

Migraine Diagnosis

Diagnostic Criteria for Migraine (ICHD-3-beta)

- Headache is accompanied by at least 1 of:
  - Nausea and/or vomiting
  - Photophobia and/or phonophobia

- May be accompanied by aura:
  - Simple partial (sensory, motor, speech, visual)
  - Complex partial (focal seizures)

Chronic migraine:
- Headache on 15 days/month for at least 3 months
- Features of migraine on at least 8 days/month

Lipton R.B., et. al

Migraine Diagnosis

Simplified Migraine Criteria (2 out of 3):
1. Light sensitivity with headache
2. Nausea with headache
3. Decreased function with headache
   - Not attributable to other causes

Lipton R.B., et. al
The Understanding of Migraine Pathophysiology has Evolved

- Vasodilation
- CSD
- Oligemia
- CGRP
- PACAP

- Nerve Sensation
- Serotonin
- Neurogenic Inflammation
- Sensitization and Allodynia

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  • Prevention - CGRP Monoclonal Antibodies
  • Devices – nVNS (Gammacore), sTMS, tSNS (Cefaly), Nerivio, Relivion
  • Pipeline – eptinezumab (IgG1-IV), GePants (CGRP receptor small molecule), Lasmiditan (5HT1-f)

Trigeminal-Vascular System

Sensitization - Central & Peripheral
Clinical Result - Alodynia
CGRP
Role in Migraine

1. What is CGRP
2. Where is CGRP
3. What does CGRP modulate
4. Where are the CGRP receptors
5. What is the evidence

CGRP – What is it?
• 37-Amino Acid Signaling Neuropeptide
• Wide distribution in both PNS & CNS
• Expressed in ~50% of neurons in the trigeminal ganglia
• PNS - Released by Trigeminal Nerve during Migraine attacks
• CNS – Signals from Trigeminal Nerve to Trigeminal Nucleus Caudalis (TNC)

Thought to regulate
• Pain transmission, including meningeal nociception
• Neurogenic inflammation
• Vasodilation

Russo AF. Annu Rev Pharmacol Toxicol. 2015;55: 533-552

CGRP Receptors
What & Where?

CGRP Receptor Locations:
PNS
• Trigeminal Nerve A-delta fibers
• Meningeal vessels, smooth muscle cells
• Satellite glial cells
• Mast cells

CNS
• Second order neurons
• Trigeminal Nucleus Caudalis
• Spinal cord dorsal horn
• Thalamus

Russo AF. Annu Rev Pharmacol Toxicol. 2015;55: 533-552
CGRP
Role in Migraine

Evidence:
• During a Migraine attack, CGRP increased >2x in Jugular blood
• CGRP levels return to normal after effective migraine attack treatment
• CGRP infusion can induce a migraine attack in migraineurs
• Perivascular release of CGRP can induce plasma protein leakage from tissues


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Migraine Prevention – The Basics

Preventive treatment

- Goals
  • Reduce frequency, severity, disability
  • Prevent disease progression

- When to use
  • If >4 severe headache days per month
  • If <15 days/month head pain free

- How to pick (pre 2018)
  • No option designed specifically for migraine
  • Pick based on comorbid symptoms
    (AKA – the "Two for One" plan)
**Migraine Prevention, Pre 2018**

The “Two for One” Plan Options

Examples

- Amitriptyline
- Topiramate
- Propranolol
- Botulinum Toxin A
- Magnesium

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**Migraine Prevention, 2018 and beyond**

**CGRP Monoclonal Antibodies**

- **Rationale**
  - Interrupts CGRP Signaling pathway
  - Binds to either the ligand (CGRP) or its receptor
  - High specificity
  - Long duration - half-life approximately 1 month
  - Does not activate the host immune system
  - Does not cross the Blood-Brain Barrier
  - Cleared through reticulo-endothelial system
  - Not eliminated by the hepatic and renal pathways
  - Rate of cytochrome P450 metabolism is not a consideration
  - Not subject to interaction with other medications

- **Mechanism of action**
  - Targets scientifically proven disease-specific pathophysiology.

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**CGRP mAbs are FDA approved for Migraine Prevention in adults**

- The “First & Only” class of meds specifically designed for Migraine Prevention

- **Mechanism of action**
  - Targets scientifically proven disease-specific pathophysiology.
Migraine Prevention – 2018
CGRP Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Branding</th>
<th>Ajovy</th>
<th>Emgality</th>
<th>Aimovig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Teva</td>
<td>Amgen &amp; Novartis</td>
<td>Amgen &amp; Novartis</td>
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<tr>
<td>Approved For</td>
<td>Prevention of migraine in adults, chronic and episodic</td>
<td>Prevention of migraine in adults, chronic and episodic</td>
<td>Prevention of migraine in adults, chronic and episodic</td>
</tr>
<tr>
<td>Target</td>
<td>Attaches to CGRP peptide</td>
<td>Attaches to CGRP peptide</td>
<td>Attaches to CGRP peptide</td>
</tr>
<tr>
<td>Molecular Format</td>
<td>IgG2</td>
<td>Humanized</td>
<td>Humanized</td>
</tr>
<tr>
<td>Frequency</td>
<td>Monthly or quarterly</td>
<td>Monthly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Device</td>
<td>Prefilled syringe</td>
<td>Autoinjector</td>
<td>Autoinjector</td>
</tr>
<tr>
<td>Dose</td>
<td>70mg or 140mg</td>
<td>225mg (m) or 675mg (q)</td>
<td>240mg load &amp; 120mg thereafter</td>
</tr>
<tr>
<td>Listed Side Effects</td>
<td>Injection site pain/rxn - 6%</td>
<td>Injection site pain/rxn - 43%</td>
<td>Injection site pain/rxn - 18%</td>
</tr>
<tr>
<td>Cost</td>
<td>$575/month for both 70mg &amp; 140mg dosing</td>
<td>$575/month or $1,725/quarterly</td>
<td>$575/month</td>
</tr>
</tbody>
</table>

50% responder rate, episodic
- 43% @ 70mg
- 50% @ 140mg
50% responder rate, chronic
- 40% @ 70mg
- 41% @ 140mg

Migraine Pathophysiology - History lessons and Today
- Vascular theory
- Cortical Spreading Depression
- Neurogenic Inflammation, Oligemia
- Trigeminal-Vascular System
- Sensitization (Central & Peripherally), Abdominal
- CGRP

New Migraine Treatment Options
- Prevention - CGRP Monoclonal Antibodies
- Devices – nVNS (GammaCore), tTMS, sTMS (Cefaly), Nerivio, Relivio
- Pipeline – epitomumab (M1-10), GePants (CGRP receptor small molecule), Lasmiditan (5HT1f)

New Migraine Treatment Options
Devices * – Gammacore nVNS

Non-Invasive Vagal Nerve Stimulator
(gammaCore, nVNS)
- Handheld, patient-controlled device, which preferentially activates afferent A and large B fibers, not C or efferent pathways that mediate bradycardia and bronchoconstriction
- Multiple possible MOAs related to headache/pain
  - Inhibits CSD
  - Decrease in Glutamate
  - Suppresses Neuronal firing in TCC
  - Modulates Trigeminal/Autonomic Reflex

- CE Mark for Primary Headache
- FDA Approved
- Acute treatment of episodic, cluster (ACT1 & ACT2 RCTs)
- Prevention of Cluster (PRESTO RCT, Class I Evidence)
- Acute treatment of migraine (PRESTO RCT, Class II Evidence)

* Device Section gratefully adapted from Alan M. Rapoport, M.D. Past-President, IHS; Founder, NEHC. Presented at HCOP 12th Annual Meeting, Jan 2019
New Migraine Treatment Options
Devices – Gammacore nVNS

PRESTO: 50% Responder Rates at 120 Minutes in EM

New Migraine Treatment Options
Devices – Single Pulse Transcranial Magnetic Stimulation (sTMS)
New Migraine Treatment Options
Devices – Cefaly
Transcutaneous Supraorbital Neurostimulation (tSNS)

Primary Outcome Measure: Change in Pain Score on VAS at 1 hour Compared to Baseline (n=99)

New Migraine Treatment Options
Devices – Cefaly
Transcutaneous Supraorbital Neurostimulation (tSNS)

3 Types of tSNS

New Migraine Treatment Options
Devices – Nerivio Migra*
Remote Neuromodulation – Upper Arm

Nerivio Migra for the Acute Treatment of Migraine

* A novel remote neuromodulation device controlled by an app (Theranica Bio-Electronics Ltd., Israel)
* Under FDA review
* Peripheral nerves of the upper arm are stimulated to induce conditioned pain modulation (CPM) – a descending endogenous analgesic “pain inhibits pain” mechanism
* Peripheral nociceptive information just below the perceived pain threshold can activate the descending pain inhibitory pathway and inhibit the headache

* Under FDA Review
New Migraine Treatment Options
Devices – Nerivio Migra*
Remote Neuromodulation – Upper Arm

Nerivio Migra
*Under FDA Review

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Signaling</th>
<th>Spatial effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain inhibition</td>
<td>Noradrenalin</td>
<td>Global</td>
<td>A few minutes after stimulus exposure</td>
</tr>
<tr>
<td>Touch inhibition</td>
<td>Serotonin</td>
<td>Local</td>
<td>Only during stimulus exposure</td>
</tr>
</tbody>
</table>

* Under FDA Review

New Migraine Treatment Options
Devices – Relivion*
Combined Occipital & Trigeminal Neuromodulation

* Neuromodulation technology delivers precise modulated pulses simultaneously to six branches of the occipital & trigeminal nerves, via 3 adaptive output channels.
* The occipital & trigeminal nerves conduct the signals directly to the brainstem for maximal synergistic effect.

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### New Migraine Treatment Options

**In the Pipeline – Eptinezumab (ALD403)**

**CGRP Monoclonal Antibody for Migraine Prevention**

<table>
<thead>
<tr>
<th><strong>Parameter</strong></th>
<th><strong>Eptinezumab (ALD403)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name</strong></td>
<td>Alder BioPharmaceuticals</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>Prevention of migraine in adults, chronic and episodic</td>
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<td><strong>Target</strong></td>
<td>Attaches to CGRP peptide</td>
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<tr>
<td><strong>Molecular Format</strong></td>
<td>IgG1 Humanized</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Quarterly</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Intravenous</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>300mg &amp; 100mg</td>
</tr>
<tr>
<td><strong>Studies</strong></td>
<td>Phase 3 - Promise 1 &amp; 2, open label safety study</td>
</tr>
</tbody>
</table>

### New Migraine Treatment Options

**In the Pipeline – “Ge-Pants”**

**Acute Migraine Treatment**

**“Ge-pants” Class for Migraine Treatment**

<table>
<thead>
<tr>
<th><strong>Medication</strong></th>
<th><strong>CGRP Inhibition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ubrogepant</td>
<td>Binds to the CGRP receptor</td>
</tr>
<tr>
<td>Atogepant</td>
<td>Competes with CGRP for the CGRP receptor</td>
</tr>
<tr>
<td>Rimegepant</td>
<td>Small Molecule</td>
</tr>
</tbody>
</table>

**Lasmiditan**

**“The Un-Triptan”**

- 5-HT1F receptor agonist, (rather than a 5-HT1B,D receptor agonist)
- Acts centrally, and not peripherally
- Route – Oral / Pill
- Non-vasoconstrictive acute anti-migraine therapy
- Phase 3 Trials – SAMURU & SPARTAN
- Doses – 50mg, 100mg & 200mg
- Results - pain relief 59% @ 2hrs
- Side effects - dizziness, paresthesia, somnolence
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• Questions

THANK YOU!