Migraine - what's on the horizon

Alok Tyagi
Consultant Neurologist
Glasgow
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Honoraria for giving lectures & attending advisory boards
Funding for attending medical conferences & a visiting Professorship
Hospitality in and out of hospital premises
Overview

- Oral acute & preventive treatments for migraine
- Injectable prophylactic treatments for migraine
- Non-invasive neuromodulation for migraine
The Migraine aura

Leao AAP; *J Neurophysiol* 1944; 7; 359-90

James et al; *J Physiol* 1999; 519; 415-5

Tusch & Dahlem; 2005
Pathophysiology of migraine;
Neurogenic inflammation

Modified from Moskowitz
Pathophysiology of migraine;
Trigeminal-autonomic reflex

Goadsby PJ, Lipton RB and Ferrari MD; NEJM; Jan 24 2002;4;346:257-270
Pathophysiology of migraine;
Dysfunction of brainstem control centres

Pain perception*
- Anterior cingulate cortex

‘Migraine generator’*
- Raphe nuclei
- Locus coeruleus
- Periaqueductal gray

Weiller et al. ; *Nat Med* 1995; 1; 658-60
Genetics of Migraine

Familial Hemiplegic Migraine - an ionopathy

- FHM-I
  - CACNA1A
  - P/Q voltage-gated Ca\textsuperscript{2+} channel chr 19

- FHM-II
  - ATP1A2
  - Na\textsuperscript{+}/K\textsuperscript{+} ATPase chr 1q23

- FHM-III
  - SCN1A
  - Voltage-gated Na\textsuperscript{+} channel chr 2

References:
- Ophoff et al. Cell 1996; 87:543
- De Fusco et al. Nat Gen 2003;33:192
- Dichgans et al., Lancet 2005;366:371
Pathophysiology of migraine;

Summary

del Rio, Linera; Functional Neuroimaging of headaches; *Lancet Neurol*; 2004 Nov; 3;11; 645-51
Headache and the neck; Convergence of trigeminal and cervical input

Bartsch et al, Brain 2002
Types of trials

- **Open label;**
  both researchers & participants know which treatment is being administered

- **Single blind;**
  participants are unaware which treatment is being administered but researchers are

- **Double blind;**
  both participants and researchers are unaware of which treatment is being administered

- **Randomised;**
  participants are randomly allocated to receive one or the other treatment under study

- **Randomised controlled;**
  participants are randomly allocated to receive the treatment under study or placebo
## Treatment goals in migraine

<table>
<thead>
<tr>
<th>Acute</th>
<th>Preventive</th>
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<tbody>
<tr>
<td>Goal: complete pain relief/improvement</td>
<td>Goal: to reduce the frequency and severity of</td>
</tr>
<tr>
<td>after 2 hours</td>
<td>attacks by at least 50%</td>
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<tr>
<td>Relief of associated symptoms</td>
<td>Reduce duration of attacks</td>
</tr>
<tr>
<td>Restoration of normal functioning</td>
<td>Improve responsiveness to acute therapy</td>
</tr>
<tr>
<td>Prevention of recurrence</td>
<td>Prevent medication overuse headache</td>
</tr>
<tr>
<td>Consistent efficacy in 2-3 attacks</td>
<td>Improve function and reduce disability</td>
</tr>
<tr>
<td>Sustained pain relief within 24 hours</td>
<td></td>
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</table>

Giamberardino MA & Martelletti P. *Expert Opin Emerg Drugs* 2015;20:137
Low adherence with current preventive therapy

- Retrospective claims analysis of a US claim database for 8,688 chronic migraine patients
- Regardless of medication used, adherence was low among oral migraine-preventive medications

Hepp Z et al. *Cephalalgia* 2015;35:478
Reasons for poor adherence

- Side-effects and lack of efficacy are the key drivers of suboptimal adherence

Blumenfeld AM et al. *Headache* 2013;53:644
Patient preference - efficacy or side effects?

Peres et al; *Headache*; 47(4); April 2007; 540-545
13 February 2017

**Advice**

following a resubmission:
botulinum toxin A (Botox®) is accepted for restricted use within NHS Scotland.

Indication under review: Prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

SMC restriction: use in adults with chronic migraine whose condition has failed to respond to \( \geq 3 \) prior oral prophylactic treatments, where medication overuse has been appropriately managed.
WoS criteria for Botox for chronic migraine

- Botox now approved by SMC for regular use on the NHS in Scotland for patients with a diagnosis of chronic migraine where medication overuse headaches have been appropriately addressed.

- Trials of the following drugs given in therapeutic doses for an adequate time period unless side effects or contraindications:
  - PIZOTIFEN
  - PROPRANOLOL
  - AMITRYPTALINE
  - TOPIRAMATE
  - CANDESARTAN
  - FLUNARIZINE

- Follow positive / negative stopping rules.
Neuromodulation
Non-invasive vagal nerve stimulation (n-VNS)

Gammacore device
n-VNS for cluster headaches

Goadsby PJ et al; Cephalalgia  Ahead of Print

Charly Gaul et al. Cephalalgia 2015
n-VNS for migraine

- Double blind, sham controlled, pilot study reported 38% of 27 patients completing 6 months open label phase as responders
  
  Silberstein et al; *Neurology*. 2016 Aug 2; 87(5); 529-38

- PROspectivE Study of nVNS for the Acute Treatment Of Migraine reported no difference compared to sham at 2 hours
  
  IHC, Vancouver Sep 2017

- Double blind randomised sham controlled trial in chronic migraine completed awaiting results (2017)
External trigeminal nerve stimulation (e-TNS)

- Double blind randomised sham controlled trial, 67 patients randomised

- The 50% responder rate was significantly greater (p=0.0023) in the treated arm (38.1%) than in the sham arm (12.1%)

- Treated group had a 29.7% patients reduction in migraine days compared to a 4.9% reduction in the sham group

Schoenen et al; Neurology; 2013 Feb 19; 80(8); 697-704
Transcranial magnetic stimulation
s-TMS

In a randomised, double blind study, patients were taught to apply the device to the occiput, just below the occipital bone, and to administer 2 pulses about 30 seconds apart. They were to begin treatment as soon as possible and within 1 hour of aura onset.

In the TMS group, 39% achieved a pain-free response 2 hours after treatment for the first attack compared with 22% in the sham stimulation group. According to the study authors, this represents a "therapeutic gain" of 17%

Lipton et al; Lancet Neurol 2010; 9(4); 373-380
Evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

- **NICE interventional procedures guidance [IPG477]: January 2014**

Current evidence on the safety of transcutaneous stimulation of the supraorbital nerve for treating and preventing migraine raises no major concerns. The evidence for efficacy is limited in quality and quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

- **NICE interventional procedures guidance [IPG559]: May 2016**

Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence for efficacy is limited in quality and quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

- **NICE interventional procedures guidance [IPG552]: March 2016**
Triptans – how do they work?

**Mechanism of action**

5HT1B & 1D receptor agonists

Vasoconstriction of dilated meningeal blood vessels

Inhibition of the release of vasoactive neuropeptides, CGRP, from perivascular trigeminal sensory neurons

Reduction of pain signal transmission in the trigeminal dorsal horn

Goadsby et al; *NEJM*; Feb 2002; 346(4); 257-70
Lasmitidan

- This drug is a highly selective 5HT1F receptor agonist unlike triptans (5HT1B & 1D agonists)

- Acts at the brainstem level and is devoid of vascular side effects

- In mouse models it blocks neurogenic inflammation but does not cause vasoconstriction

- May be particularly useful in patients with cardiovascular disease and migraine

- Four phase 1 and two phase 2 trials done between 2003 and 2015
Lasmitidan phase 3 clinical trials

- SAMURAI trial randomised 2231 patients into 3 arms
- 82% had cardiovascular risk factors
- Primary end point was proportion of patients headache pain free at 2 hours

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>100 mgm (n=503)</th>
<th>200 mgm (n=518)</th>
<th>Placebo (n=524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of subjects pain free at 2 hrs</td>
<td>28.2%</td>
<td>32.2%</td>
<td>15.3%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
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- 2 hour pain freedom rates appear very similar to triptans
- Also available as an iv preparation
- Side effects include dizziness, somnolence, nausea, fatigue, vertigo & paresthesia

EHMTIC Glasgow Sep 2016
Calcitonin Gene-Related Peptide (CGRP)

- **CGRP** is a 37-amino acid neuropeptide derived from the gene encoding calcitonin.

**CGRP exists in two forms in humans**

- **α-CGRP** is the predominant form
  - Found in the peripheral and central nervous systems.
  - Formed from alternative splicing of the calcitonin/CGRP gene on chromosome 11.

**CGRP receptor**


**Potential concerns with CGRP antagonism;**

- Inhibit vasodilatation
- Cause vasoconstriction
- Inhibit compensatory vasodilatation


In the periphery CGRP mediates vasodilatation and centrally it mediates the transmission of pain and is also involved in regulatory mechanisms. CGRP acts on the second order neurons in the trigemino-cervical complex

CGRP and migraine

During migraine attacks (with or without aura) CGRP levels increase in the extracerebral circulation (external jugular blood).

Sumatriptan acts via presynaptic 5-HT1B/D receptors to suppress CGRP release from trigeminal nerves.

Treatment with sumatriptan normalized the increase in CGRP levels seen in acute migraine, with relief of headache pain.

Acute treatment with CGRP receptor blockers provides relief of migraine headache

Olcegepant, the first potent and selective non-peptide antagonist of the CGRP receptor, was shown to be effective in treating acute migraine.

However, as some of agents had a number of issues, including liver toxicity, new approaches that target CGRP or its receptor were needed.

Pain free at 2 hrs (% Patients)

Sustained Pain free at 24 hrs (% Patients)

What are monoclonal antibodies?

Monoclonal antibodies (mAbs)
Are from a single B-cell line and recognize one antigen epitope

Polyclonal antibodies (pAbs)
Are from multiple B-cells that recognize multiple antigen epitopes

Human or “fully human” monoclonal antibodies (mAbs) have been developed to reduce immunogenicity
Nomenclature for therapeutic monoclonal antibodies

Source (% human protein)
- Mouse (0% human)
- Chimeric (65% human)
- Humanized (> 90% human)
- Human (100% human)

Generic suffix: -omab -ximab -zumab -umab

Mechanism of action of therapeutic monoclonal antibodies

- Destroy target cells or alter target-cell function without cell destruction
• Therapeutic monoclonal antibodies have been developed that inhibit the activity of CGRP at the CGRP receptor.

• **Monoclonal antibodies to the CGRP receptor** only inhibit function at the CGRP receptor, leaving other calcitonin-family receptors functionally intact.

  There is one monoclonal antibody that targets the CGRP receptor:

  Erenumab (AMG 334)

• **Monoclonal antibodies to the CGRP ligand** inhibit the function of CGRP at all calcitonin-family receptors.

  There are 3 monoclonal antibodies to the CGRP ligand in development:

  Eptinezumab (ALD403)
  Galcanezumab (LY2951742)
  Fremanezumab (TEV-48125)
Trials summary

• Complex trial design

• Trials in episodic migraine, high frequency episodic migraine, chronic migraine, episodic & chronic cluster headaches

• A number of follow on open label studies

• Most trials in migraine include patients who have tried up to 3 preventive treatments

• Some trials allow patients to continue on preventive treatment

• Most (but not all) trials allowed medication overuse
Fremanezumab for prevention of episodic migraine; Study design

- Randomized, double-blind, phase 2b study in 297 patients with 8–14 headache days per month

- Randomization 1:1:1; stratified by sex and use of concomitant preventive therapy

- Treatment with 3 x 28-day treatment cycles of SC 225mg TEV-48125, 675mg TEV-48125, or placebo (4 SC injections - double dummy)

- Patients allowed to use 1 preventive medication for at least 2 months before screening visit, and acute migraine drugs up to 14 days per month

- Exclusions: > 4 days/month of opioid or butalbital use; failed ≥3 preventive medications

- **Primary endpoint**: Change from baseline in migraine days (migraine/probable migraine >4 hours OR treated with migraine-specific drug) during the 3rd treatment cycle (weeks 9–12)

Fremanezumab for prevention of episodic migraine: Primary endpoint analysis (Weeks 9-12)

Baseline mean migraine days: 11.5 (placebo), 11.5 (225mg), 11.3 (675mg)

### Fremanezumab for prevention of episodic migraine: Responder rates (Weeks 9-12), post-hoc analysis

<table>
<thead>
<tr>
<th>TEV-48125</th>
<th>50% Responder rate</th>
<th>75% Responder rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28%</td>
<td>11%</td>
</tr>
<tr>
<td>225mg</td>
<td>53%</td>
<td>34%</td>
</tr>
<tr>
<td>675mg</td>
<td>59%</td>
<td>31%</td>
</tr>
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</table>

The most common treatment-emergent adverse events (AEs) were mild injection site pain or erythema; these were similar in all groups.

There were 3 serious AEs (fibular fracture and migraine with hypertensive crisis in the 225mg dose group; 1 antiphospholipid antibody and tremor in the 675mg dose group).

2 subjects had anti-drug antibodies before and after drug administration.

Framenezumab for prevention of chronic migraine: Study design

• Randomized, double-blind, phase 3 study in 1130 patients

• Randomization 1:1:1 to Framazenumab quarterly (a single dose of 675 mgm at baseline and placebo at weeks 4 and 8), framanezumab monthly (675 mgm at baseline and 225 mgm at weeks 4 and 8) or matching placebo.

• Patients were excluded if onabotulinumtoxinA was used 6 months before screening, or they had used >4 days opioids / butalbital during the run-in phase, or had failed ≥3 preventive medications

• No upper limit on acute drug use and patients with continuous (unremitting) headache were not excluded

• Primary endpoint: Mean change from baseline in the average number of headache days.

Silberstein et al; *N Engl J Med*; 2017 Nov 30; 377 (22); 2113-2122
Framenezumab (TEV-48125) for prevention of chronic migraine: Study design

Silberstein et al; *N Engl J Med*; 2017 Nov 30; 377 (22); 2113-2122
CGRP monoclonal antibodies; 50% responder rates at 12 weeks in phase 2 studies
CGRP monoclonal antibodies; 50% responder rates at 12 weeks in phase 2 studies-comparison
## CGRP Therapeutic Monoclonal Antibodies: Summary

<table>
<thead>
<tr>
<th>Target</th>
<th>Erenumab (AMG 334)</th>
<th>Eptinezumab (ALD403)</th>
<th>Galcanezumab LY2951742</th>
<th>Fremanezumab (TEV-48125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine types studied</td>
<td>Episodic Chronic</td>
<td>Episodic Chronic</td>
<td>Episodic Chronic Cluster headache</td>
<td>Episodic Chronic Cluster headache</td>
</tr>
<tr>
<td>Route of administration</td>
<td>SC (monthly)</td>
<td>IV</td>
<td>SC (2-weekly or monthly)</td>
<td>SC (monthly)</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td>21</td>
<td>31</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>Current development phase</td>
<td>Phase 3 complete</td>
<td>Phase 3 complete (Episodic Migraine)</td>
<td>Phase 3 complete (Chronic Migraine)</td>
<td>Phase 3 complete</td>
</tr>
</tbody>
</table>
If interested in participating in clinical research please email –
the research co-ordinator in Clinical Research Facility, QEUH, Glasgow

Anissa.Benciheub@ggc.scot.nhs.uk