Cluster headache: from neuromodulation to monoclonal antibodies

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## Disclosures

<table>
<thead>
<tr>
<th>Potential COI</th>
<th>Organisation</th>
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<tbody>
<tr>
<td>Advisory Boards</td>
<td>TEVA, Eli Lilly, Novartis</td>
</tr>
<tr>
<td>Speaker / Speakers Boards</td>
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<tr>
<td>Consultant</td>
<td></td>
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<tr>
<td>Grant support for research or education</td>
<td></td>
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<tr>
<td>Editorial Board</td>
<td>Cephalalgia (Associate Editor); Journal of Headache and Pain (Advisory Board); BioMed Research International (Editorial Board member); Frontiers in Neurology (Review Editor for Headache Medicine and Facial Pain); BMC Neurology – Pain section (Associate Editor); Behavioural Neurology (Academic Editor); Frontiers in Human Neuroscience (Associate Editor - Brain Imaging and Stimulation section)</td>
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<tr>
<td>Author royalties</td>
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<td>Other</td>
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</tbody>
</table>
Cluster headache

- Episodic (80%)
- Chronic (20%)
  - Cluster period lasts for more than one year without remissions or remissions <3 months

EVOLUTION OVER 10 YEARS

Episodic → Chronic 13%

Chronic → Episodic 47%

1-2% drug treatment-resistant?

(Manzoni GC et al. Cephalalgia. 1991)
NEUROSTIMULATION METHODS FOR CLUSTER HEADACHE

- deep brain stimulation – « hypothalamic »
- occipital nerve stimulation (ONS) - percutaneous
- sphenopalatine ganglion stimulation - pergingival
- vagus nerve stimulation (nVNS) - transcutaneous
- *transcranial* direct current stimulation (tDCS) (pilot)
38-year-old male suffering from chronic intractable CH.
- 2-5 CH attacks per day (30 min-4 hours) left or right- sided mainly during the night, accompanied by life-threatening hypertensive crises, massive oculo-facial phenomena (blind in the right eye for hemorrhage) and very aggressive behavior.
- 2 destructive operations on the right trigeminal nerve: right-sided attacks disappeared but left-sided worsened
- Hypothalamic stimulation to control left-sided CHs was performed. The left CHs gradually disappeared

Then, right CHs recurred: hypothalamic stimulation was successfully started also on the right side with only minor transitory side effects.
Hypothalamic DBS in CCH: synopsis of results

Deep brain stimulation in headache
Massimo Leone and Alberto Proietti Cecchi

TACs
n=73

- Chronic Cluster Headache  n=69
- SUNCT  n=3
- Paroxysmal hemicrania  n=1

- Pain-free  31.8%
- ≥ 50% improved  34.2%

Total treatment success  66%
(mean follow-up: 2.2 yrs)
Posterior Hypothalamus or midbrain activity?

Functional neuroimaging of headaches
Margarita Sánchez del Río and Juan Alvarez Linera

The Lancet, 2004

Deep Brain Stimulation in Cluster Headache: Hypothalamus or Midbrain Tegmentum?
Manjit S. Matharu · Ludvic Zrinzo

Curr Pain Headache, 2010

Note that the cluster headache activation lies in the midbrain posterior to the hypothalamus (Hyp) and medial to the red nucleus (RN). MB=mamillary bodies

“...However, it is possible, if not highly likely, that both the hypothalamus and midbrain tegmentum are activated in TACs, ...
Indeed, discrete activations of both the posterior hypothalamus and the ventral midbrain, straddling the red nucleus and the substantia nigra, have been observed in PH and HC...”
1. Before starting the procedures, 12 patients were recruited: while on the waiting list for 4 months, **10 went into remission**!
   → « refractory » chronic cluster may not be irreversibly refractory !!

2. The relevant target & mode of action are not certain
   → fiber tract stimulation ? (ventral tegmental area, posterior wall 3rd ventricle
   → neuromodulatory effect

3. Hypothalamic DBS is effective for intractable chronic cluster headache,
   → 1 sham-controlled trial: negative, but short FU
     **but recurrence with stimulator OFF**
   → it is not a benign, riskless procedure (**1 lethal intracerebral hemorrhage in our series**)  

4. Not recommended before **extracranial** invasive neurostimulation methods have failed
A paddle style stimulation electrode (Medtronic 3587A Resume II°) was implanted on the CCH side subcutaneously via a retromastoid C2–3 approach.

The stimulator (Medtronic 7425 Itrel 3°) was switched on as soon as a typical attack occurred.
## ONS in DrCCH: very long term outcome

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yrs)</th>
<th>CH natural history</th>
<th>CCH duration (years)</th>
<th>Time under ONS (months)</th>
<th>Attack/day before ONS</th>
<th>Attack/day at last followup (mean)</th>
<th>% change in attack frequency</th>
<th>Preventive therapy at time of implantation</th>
<th>Preventive therapy at followup</th>
<th>Technical problems</th>
<th>IONS Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>E</td>
<td>9</td>
<td>4</td>
<td>0.20</td>
<td>N/A</td>
<td>N/A</td>
<td>Verapamil</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>2</td>
<td>53</td>
<td>E</td>
<td>3</td>
<td>103</td>
<td>4.7</td>
<td>0.043</td>
<td>0.33</td>
<td>Verapamil / Mequitine</td>
<td>Lithium carbonate / Verapamil</td>
<td>Empty battery 25</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>E</td>
<td>7</td>
<td>102</td>
<td>8.84</td>
<td>0.1</td>
<td>-97.40%</td>
<td>Lithium carbonate / Verapamil</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>E</td>
<td>4</td>
<td>52</td>
<td>1.61</td>
<td>0.33</td>
<td>-71.55%</td>
<td>Verapamil</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>5</td>
<td>57</td>
<td>E</td>
<td>4</td>
<td>38</td>
<td>0.16</td>
<td>N/A</td>
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<td>N/A</td>
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<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>C</td>
<td>6</td>
<td>95</td>
<td>0.16</td>
<td>Episodic</td>
<td>Episodic</td>
<td>Verapamil / Lithium carbonate</td>
<td>Verapamil / Tegretol / Topiramate</td>
<td>Empty battery x2</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>E</td>
<td>9</td>
<td>2</td>
<td>2.00</td>
<td>0.04</td>
<td>0.16</td>
<td>Episodic</td>
<td>Episodic</td>
<td>Empty battery x2</td>
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<tr>
<td>8</td>
<td>51</td>
<td>E</td>
<td>5</td>
<td>68</td>
<td>0.57</td>
<td>0.34</td>
<td>-5.36%</td>
<td>Lithium carbonate / Gabapentin</td>
<td>Lithium carbonate / Gabapentin</td>
<td>Delayed infection</td>
<td>OFF</td>
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<tr>
<td>9</td>
<td>34</td>
<td>E</td>
<td>8</td>
<td>na</td>
<td>na</td>
<td>N/A</td>
<td>N/A</td>
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<td>N/A</td>
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</tr>
<tr>
<td>10</td>
<td>67</td>
<td>C</td>
<td>5</td>
<td>58</td>
<td>3.5</td>
<td>0</td>
<td>-71.00%</td>
<td>Verapamil</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>11</td>
<td>55</td>
<td>C</td>
<td>2</td>
<td>52</td>
<td>5.5</td>
<td>0</td>
<td>-87.00%</td>
<td>Methysergide / Lithium carbonate</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>E</td>
<td>8</td>
<td>na</td>
<td>na</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>C</td>
<td>5</td>
<td>58</td>
<td>3.5</td>
<td>0</td>
<td>-71.00%</td>
<td>Verapamil</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>14</td>
<td>55</td>
<td>C</td>
<td>2</td>
<td>52</td>
<td>5.5</td>
<td>0</td>
<td>-87.00%</td>
<td>Methysergide / Lithium carbonate</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>C</td>
<td>14</td>
<td>54</td>
<td>3.00</td>
<td>0</td>
<td>-87.00%</td>
<td>GON injection / Verapamil</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Of the 3 patients with delayed infections requiring explantation, 1 was reimplanted 10 months later.

### Adverse Events

- **Battery replacement**: n=10
- **Surgery for lead migration**: n=2
- **Transient side shift**: n=3

Available open studies using iONS as add-on therapy have provided encouraging results in DrCCH, and iONS is now recommended before considering the more risky hDBS.
### ONS trials in drug-resistant Chronic Cluster Headache

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Patients with ≥ 50% improvement</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magis et al. 2007 &amp; 2011</td>
<td>15</td>
<td>36.8</td>
<td>11</td>
<td>Empty battery, infection…</td>
</tr>
<tr>
<td>Burns et al. 2007 &amp; 2009</td>
<td>14</td>
<td>17.5</td>
<td>5</td>
<td>Empty battery, lead migration, Infection…</td>
</tr>
<tr>
<td>Lara Lara et al. 2009 (A)</td>
<td>6</td>
<td>6-15</td>
<td>4</td>
<td>Infection</td>
</tr>
<tr>
<td>De Quintana et al. 2010</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Salomet al. 2010 (A)</td>
<td>14</td>
<td>?</td>
<td>7</td>
<td>Infection</td>
</tr>
<tr>
<td>Müller et al. 2010</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>Infection</td>
</tr>
<tr>
<td>Fontaine et al. 2011</td>
<td>13</td>
<td>14.6</td>
<td>10</td>
<td>Empty battery…</td>
</tr>
<tr>
<td>Strand et al. 2011</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Leone et al. 2015</td>
<td>35</td>
<td>72</td>
<td>20</td>
<td>Lead migration…</td>
</tr>
<tr>
<td>Leplus et al. 2021 (French ONS network)</td>
<td>95</td>
<td>43.8</td>
<td>64 (68.8%)</td>
<td>Local pain, lead migration, hardware dysfunction…</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>209</strong></td>
<td></td>
<td><strong>136 (65%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

ONS also effective in other TACs

![Graph showing response rates for different headache conditions](image)

- **Whole cohort**: 50% with 30% reduction, 77% with 50% reduction.
- **Migraine**: 38% with 30% reduction, 36% with 50% reduction.
- **Cluster headache**: 55% with 30% reduction, 53% with 50% reduction.
- **SUNCT/SUNA**: 77% with both 30% and 50% reduction.
- **Hemicrania continua**: 42% with 30% reduction, 26% with 50% reduction.
- **Other**: 21% with 30% reduction, 16% with 50% reduction.

Number (N):
- Whole cohort: 165
- Migraine: 76
- Cluster headache: 58
- SUNCT/SUNA: 31
- Hemicrania continua: 18
- Other: 18

(Matharu M et al 2015)
Fluoroscopy-guided subcutaneous implantation of bi-occipital leads

Safety and efficacy of occipital nerve stimulation for attack prevention in medically intractable chronic cluster headache (ICON): a randomised, double-blind, multicentre, phase 3, electrical dose-controlled trial

Lenczline A Wilkins1, Bao F de Coo1, Patty G G Doeben2, Wim M Mulleners3, Onno P M Toemstra2, Eveline C Bartels2, Katja Burger2, Frank Wille4, Robert T M van Dongen2, Erkko Kort5, Geert H. Spina6, Joost Haan5, Erik W van Zwet5, Frank J P M Huygen5, Michel D Ferrari1

for the ICON study group

Lancet Neurology 2021

Protocol

(n = 66, «verum»)

100% ONS

30% ONS

≥50% responders

44.6%

50%

44.6%

Protocol

Adverse events

Masked study phase

100% ONS stimulation

30% ONS stimulation

(n = 65, «sham»)

Number of events

Percentage of events

Serious adverse events

17

15 (22%)

7 (11%)

Hardware-related serious adverse events

Total

9

8 (12%)

5

4 (6%)

Lead migration

3

3 (5%)

3

3 (5%)

Replacement IPG

2

2 (3%)

0

0

Replacement lead or cable

4

3 (5%)

2

1 (2%)

Serious adverse events related to biological complications

Total

5

4 (6%)

2

2 (3%)

The abrupt, marked, and up to 2 years of sustained improvement in symptoms after ONS treatment following a highly stable, 12-week, pre-treatment baseline observation period in patients with an unremitting history of highly disabling MICCH over many years, strongly supports a therapeutic effect of ONS, rather than a placebo effect.
Occipital nerve stimulation (ONS)

The TRIGEMINOVASCULAR system:
the main pain-signaling system of the viscera brain
Study designed to investigate the **safety** and **efficacy** of the ATI Neurostimulation System™ for SPG stimulation for the treatment of chronic cluster headache.

- On-demand, patient-controlled therapy via Remote Controller
Pathway CH-I: RESPONDERS

Safety Analysis

32 enrolled / underwent implantation procedure

4 safety analysis only
1 failure to implant
2 explanted (lead migration)
1 skipped experimental period (pregnant)

Efficacy Analysis

28 completed experimental period

68% Responders

25% Acute Responders
7% Acute & Frequency Responders
36% Frequency Responders

32% Non-Responders

Pain relief at 15 minutes following SPG stimulation

1 year FU: 45%
(but 23% in very severe attacks)
(Jürgens et al. Cephalalgia 2017)

67% of attacks pain-free at 15min

1 year FU: 35%
(but no change in overall mean attack frequency)
(Jürgens et al. Cephalalgia 2017)

Adverse events:
Reversible sensory disturbances in maxillary division of the trigeminal nerve
(81% of patients)

Reversible sensory disturbances in maxillary division of the trigeminal nerve
(81% of patients)
Safety and efficacy of sphenopalatine ganglion stimulation for chronic cluster headache: a double-blind, randomised controlled trial

Peter J Gooding, Sameh Sahai-Srivastava, Eric J Kenisian, Anne H Colhoun, David C Matthews, Peter J McAllister, Peter D Costantino, Deborah J Friedman, John R Zuniga, Lasco L Machtler, Saurin R Popat, Ali R Rezaei, David W Dodick

Lancet Neurology 2019

Unadjusted analysis

<table>
<thead>
<tr>
<th></th>
<th>Sphenopalatine ganglion stimulation group (n=45)</th>
<th>Control group (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief at 15 min</td>
<td>189/410 (46%)</td>
<td>226/582 (39%)</td>
</tr>
<tr>
<td>Freedom from pain at 15 min</td>
<td>123/410 (30%)</td>
<td>125/582 (21%)</td>
</tr>
<tr>
<td>Sustained pain relief at 1 h</td>
<td>165/408 (40%)</td>
<td>175/576 (30%)</td>
</tr>
</tbody>
</table>

Adverse events (512 in 92 patients judged inadequately controlled)
- 378 related to study device/implantation - most associated with surgery
- The most common (within 30 days): numbness, pain, swelling, headache, paraesthesias, bruising, trismus, tenderness, taste alterations, and restricted jaw movement

<table>
<thead>
<tr>
<th></th>
<th>Sphenopalatine ganglion stimulation group</th>
<th>Control group</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from pain at 15 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% response</td>
<td>9/24 (38%)</td>
<td>3/28 (11%)</td>
<td>4.84 (1.00-32.20)</td>
<td>0.049</td>
</tr>
<tr>
<td>75% response</td>
<td>5/24 (21%)</td>
<td>1/28 (4%)</td>
<td>6.86 (0.69-34.82)</td>
<td>0.13</td>
</tr>
<tr>
<td>100% response</td>
<td>1/24 (4%)</td>
<td>1/28 (4%)</td>
<td>1.17 (0.01-95.52)</td>
<td>1.00</td>
</tr>
<tr>
<td>Weekly attack frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% response</td>
<td>28/45 (62%)</td>
<td>25/45 (56%)</td>
<td>1.31 (0.52-3.33)</td>
<td>0.67</td>
</tr>
<tr>
<td>75% response</td>
<td>22/45 (49%)</td>
<td>11/45 (24%)</td>
<td>2.92 (1.11-8.07)</td>
<td>0.03</td>
</tr>
<tr>
<td>100% response</td>
<td>7/45 (16%)</td>
<td>4/45 (9%)</td>
<td>1.88 (0.44-9.45)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

% pain-free responders 1st attack?
% response in severe attacks?
Transcutaneous Vagus Nerve Stimulation (tVNS)

Investigational Plan

Noninvasive Neurostimulation of the Vagus Nerve with the GammaCore™ Device
For the Relief of Pain, Nausea and Related Symptoms Associated with Migraine

Gammacore®
Transcutaneous cervical Vagus Nerve Stimulation (tVNS)

Neurovascular HEADACHE

V1 visc

pial / dural vessel

SPG

CGRP

BRAIN STEM

V1 som.

V1 som.

Trigeminal nucleus caudalis

Nucleus tractus solitarius

NO

(Ach)

VIP

Aδ, C

(Aδ)

Gammacore®

(Visceral) vagal afferents

NO (Visceral) vagal afferents

GSP SPG SP

V1 som.

V1 som.
**gammaCore™ studies in Cluster Headache**

<table>
<thead>
<tr>
<th>Study</th>
<th>Size (N)</th>
<th>CH type ; Type of Treatment</th>
<th>Format</th>
<th>Status</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU Cluster Headache (Royal Free)</td>
<td>19 patients</td>
<td>cCH and eCH</td>
<td>Open-label case series</td>
<td>Nesbitt et al. Neurology 2015.</td>
<td>15 patients improved 47% attacks aborted 42% reduction of daily attacks</td>
</tr>
<tr>
<td>PREVA</td>
<td>97 patients</td>
<td>cCH</td>
<td>Open-label, SoC vs SoC + tVNS comparator study</td>
<td>Gaul et al. JHP 2017</td>
<td>40% decrease in attack frequency 50% responder rate: 49% (vs 9% Soc)</td>
</tr>
<tr>
<td>ACT 1</td>
<td>133 patients</td>
<td>cCH (n=48) and eCH (n=85)</td>
<td>Double-blind, RCT, active sham study</td>
<td>Silberstein et al. Headache 2016</td>
<td>Pain relief at 15min: 26.7% (vs 15.1% sham) (ns)</td>
</tr>
<tr>
<td>ACT 2</td>
<td>92 patients</td>
<td>cCH (n=65) and eCH (n=27)</td>
<td>Double-blind, RCT, active sham study</td>
<td>Goadsby et al. Cephalalgia 2017</td>
<td>Pain-free at 15min allacks: 14% (vs 12% sham) (ns)</td>
</tr>
<tr>
<td>Real World UK</td>
<td>30 patients</td>
<td>29 drcCH</td>
<td>Retrospective</td>
<td>Marin et al. JHP 2018</td>
<td>64% decrease in weekly attack frequency</td>
</tr>
</tbody>
</table>
CCH patients: nVNS stimulations were twice daily and as needed for acute

PREVA Study Overview

Study protocol

Baseline Phase

Randomised Phase

Open-label Phase

Standard of Care
Plus nVNS
(N=48)

Standard of Care
(N=49)

Standard of Care
Plus nVNS
(N=90)

Standard of Care
(N=114)

2 weeks

4 weeks

4 weeks

PREVA Study Overview (Gaul et al. Cephalalgia 2016, JHP2017)

% Change From Baseline in Weekly Attack Frequency (Mean ± 95% CI)

SoC Alone (n=47)

nVNS+SoC (n=37)

PREVA Study Overview (Gaul et al. Cephalalgia 2016, JHP2017)

No. of Attacks per Week (Mean ± 95% CI)

SoC Alone

nVNS+SoC

Randomised Phase

Extension Phase

SoC Alone (n=47)

nVNS+SoC (n=37)

PREVA Study Overview (Gaul et al. Cephalalgia 2016, JHP2017)

Patients (%)

Attack Frequency Reduction From Baseline to the End of the Randomised Phase

>25%  76%  P<0.001b

>50%  49%  P<0.001b

>75%  22%  P<0.001b

100%  8%
gammaCore™ for acute treatment in episodic & chronic CH
(pooled data from ACT1 an ACT2)

(De Coo et al. Cephalalgia 2019)

225 participants (112 episodic, 113 chronic; N=108 nVNS, N=117 sham)

% of all attacks with pain freedom at 15 min

% of patients pain-free at 15 min in ≥50% of attacks

nVNS was superior to sham in episodic but not chronic cluster headache
Transcranial neurostimulation methods

Transcranial direct current stimulation
- tDCS

Repetitive transcranial magnetic stimulation
- rTMS

ACTIVATION
- high frequency
- low frequency

INHIBITION
This work was supported by a grant from the King Baudouin Foundation-Belgium.

Anodal frontal tDCS for chronic cluster headache treatment: a proof-of-concept trial targeting the anterior cingulate cortex and searching for nociceptive correlates

Delphine Magis, Kevin D'Ottilio, Marco Lisicki, Chany Lee and Jean Schoenen

FDG-PET before and after pONS
(Magis et al. BMC Neurology 2011)

Electrical field (COMETS) with anodal Fz tDCS

Ipsilateral perigenual anterior cingulate cortex

Area hypermetabolic after pONS in responders vs non-responders
Anodal tDCS targeting ACC in CCH

- 31 patients enrolled, 8 drop-outs (compliance 20%) during the 1st week, 23 patients in intention-to-treat:
- 21 completed a 4-week period of daily 20-min tDCS (20min, 2mA), 10 of them during 8 weeks (compliance: 91%), 2 drop-outs.
- Mean weekly attack frequency decreased by 40% after 4 weeks of daily stimulation; 50% responder rate was 50% at 8 weeks.
Conclusions

Episodic CH is disabling, but most often amenable to available drug treatments

Chronic CH is extremely disabling and difficult to treat

1. **Hypothalamic DBS** is effective in *CCH* (±60%), but not riskless

2. **Percutaneous ONS** has comparable efficacy (50-60% of responders) and is less risky

3. **Sphenopalatine ganglion stimulation** aborts attacks in 35% of *CCH* patients, and might reduce frequency in 45% (no RCT)

4. **Cervical transcutaneous vagus nerve stimulation** aborts attacks in 35% of *ECH* patient, but not in *CCH*; it might reduce frequency in 49% of *CCH* patients (no RCT)

5. **Anodal tDCS targeting the ACC** might have a preventive effect in *CCH* (no RCT)
The TRIGEMINOVASCULAR SYSTEM: the main pain-signaling system of the viscera brain

Ictal pathophysiology: targets of acute CCH drugs

MIGRAINE HEADACHE

TRIGEMINAL NUCLEUS CAUDALIS

CGRP

PAG

5-HT1F

5-HT1B/D

C2 som

C1 som

V1 som.

V1 visc

Neck

BRAIN STEM

Ditans

Gepants

Triptans

CGRP (Edvinsson & Goadsby Cephalalgia 2004)
Humanized monoclonal antibodies

Humanized anti-CGRP Mabs

**ALD 403** (Alder Biopharmaceuticals)
- **EPTINEZUMAB** (iv)

**LY2951742** (Eli Lilly)

---

**Table 2. Attributes of emerging a-CGRP monoclonal antibodies.**

<table>
<thead>
<tr>
<th></th>
<th>Eptinezumab</th>
<th>Erenumab</th>
<th>Galcanezumab</th>
<th>Fremanezumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody-IgG</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2a</td>
</tr>
<tr>
<td>Type</td>
<td>Humanized</td>
<td>Human</td>
<td>Humanized</td>
<td>Humanized</td>
</tr>
<tr>
<td>Target</td>
<td>CGRP</td>
<td>CLR/RAMPI</td>
<td>CGRP</td>
<td>CGRP</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>40-74%</td>
<td>40%</td>
<td>?</td>
</tr>
<tr>
<td>T1/2 (days)</td>
<td>28</td>
<td>21</td>
<td>25–30</td>
<td>45</td>
</tr>
<tr>
<td>Production cell line</td>
<td>Yeast</td>
<td>Mammalian</td>
<td>Mammalian</td>
<td>Mammalian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Chinese hamster ovary)</td>
<td>(Chinese hamster ovary)</td>
<td>(Chinese hamster ovary)</td>
</tr>
<tr>
<td>Route frequency</td>
<td>IV/quarterly</td>
<td>SQ/monthly</td>
<td>SQ/monthly</td>
<td>SQ/monthly or quarterly</td>
</tr>
</tbody>
</table>

- **ERENUMAB** (subcut)
Humanized anti-CGRP Mabs

- They have high target specificity with minimal potential for off-target toxicity,
- Are degraded and cleared within the reticuloendothelial system,
- do not undergo hepatic metabolism or renal clearance, and
- do not compete for binding sites

As a result, the potential for drug interactions is minimal.
Humanized anti-CGRP Mabs

- As large molecules, they require parenteral administration since they are proteins and would be catabolized by peptidases in the gastrointestinal tract.

- Because of their large size, they do not cross the bloodbrain barrier in appreciable quantities and therefore central nervous system side effects and toxicity should be minimal.

- The long half-life of mAbs (3–6 weeks) results in less frequent administration (monthly or quarterly) compared to oral preventive drugs which invariably require daily dosing.
Humanized anti-CGRP Mabs

- Unlike oral preventive drugs, mAbs have the potential for immunogenicity, the development of neutralizing antibodies, and the potential for hypersensitivity injection site reactions.
- However, a-CGRP mAbs have been engineered to minimize immune system activation.
- In addition, these mAbs are not considered to be associated with immune suppression, opportunistic infections or malignancies.
Galcanezumab in patients with **episodic cluster headache**

**Clinical Trial**

- **Objective:** Prevention of episodic cluster headache
- **Participants:** 314 patients assessed for eligibility, 106 underwent randomization, 57 received placebo and 49 received 300 mg of galcanezumab.
- **Completion:** 45 (79%) completed the trial, 45 (92%) completed the trial.
- **Adverse Events:**
  - Discontinued due to adverse event:
    - Placebo: 12 (21%)
    - Galcanezumab: 4 (8%)
  - Withdrawn:
    - Placebo: 12 (21%)
    - Galcanezumab: 4 (8%)

**Trial of Galcanezumab in Prevention of Episodic Cluster Headache**

**Table 2. Primary and Key Secondary End Points.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (N=57)</th>
<th>Galcanezumab (N=49)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least-squares mean change from baseline in weekly frequency of cluster headache attacks across wk 1–3</td>
<td>(-5.2\pm1.3)</td>
<td>(-8.7\pm1.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Percentage of patients with a response at wk 3†</td>
<td>53</td>
<td>71</td>
<td>0.046</td>
</tr>
</tbody>
</table>

**Table 4. Safety Analyses.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=57)</th>
<th>Galcanezumab (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse event — no. (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to adverse event — no. (%)</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>All adverse event during the trial — no. (%)</td>
<td>19 (33)</td>
<td>21 (43)</td>
</tr>
</tbody>
</table>

**Mean weekly total pain burden & PGI-I**

Galcanezumab in patients with chronic cluster headache

Weekly cluster headache attack frequency

- **Primary endpoint**
  - BL mean: 18.5
  - LS mean change from BL: -4.6
  - GMB: 19.2
  - LS mean change from BL: -5.4
  - p-value: 0.334

Sustained response through week 12

- **PBO (N = 120)**
  - % Achieving sustained response: 17.5

- **GMB 300-mg (N = 117)**
  - % Achieving sustained response: 16.2

**Response of 50% reduction**

Participants randomized 1:1 to galcanezumab or placebo
Galcanezumab in real-world conditions (cCH)

N = 22

Treatment started with
- Galcanezumab 240 mg
- Erenumab 70 mg
- Erenumab 140 mg

Months under treatment until now: 4.6 ± 4.3 (range: 1–16)
Observation period under treatment within present study:
- Month 1: 22 patients
- Month 2: 14 patients
- Month 3: 10 patients

Days between first and second treatment: 31.0 ± 4.3
Days between second and third treatment: 30.9 ± 2.8

*Was reduced to 120 mg in subsequent months in two patients.
**Was increased to 140 mg in subsequent months in all patients and changed to galcanezumab 240 mg in the third month in one patient.

\[ \text{Attacks per week} \]

\[ \text{Acute medication uses} \]

\[ \text{Pain intensity during attacks [0–10]} \]

\[ \text{CGRP (R) antibody} \]