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Emerging treatments for the primary headache disorders

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Abstract Migraine and cluster headache are common, episodic, often chronic and disabling disorders of the brain. Although there are many standard treatment techniques, none are ideal. This article reviews various novel pharmacologic and device-related treatments for migraine and cluster headache. Emphasis is given to recent advances in the development of monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) and its receptor, including promising results from phase 2 trials studying the safety and efficacy of LY2951742, ALD403 and TEV-48125, three anti-CGRP mAbs. Other new pharmacologic treatments discussed include the 5-HT1F receptor agonist lasmiditan and glial cell modulator ibudilast. Also reviewed is neuromodulation for migraine and cluster headache, including promising recent results of randomized controlled trials studying sphenopalatine ganglion stimulation, trigeminal nerve stimulation, transcutaneous vagus nerve stimulation, and transcranial magnetic stimulation. Finally, we discuss patch, inhaled, and intranasal methods of triptan and dihydroergotamine delivery.

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Introduction

The primary headache disorders are common, episodic, often chronic and disabling neurovascular disorders of the brain. Although there are many standard treatment techniques, none are ideal. We will review various novel pharmacologic and device-related treatments for migraine and cluster headache (CH), such as monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) and its receptor, neuromodulation for migraine and CH, and newer, improved delivery methods for older acute migraine treatment medications.

Calcitonin gene-related peptide (CGRP)-targeted therapies

CGRP is a 37-amino acid neuropeptide that plays an important role in migraine pathophysiology [1]. Small-molecule CGRP receptor antagonists showed promise as migraine treatments in several acute care trials as well as in one preventive trial. However, these results were overshadowed by hepatotoxicity concerns beginning with the first preventive trial [2]. No small-molecule CGRP receptor antagonists are being developed at this time.

Three monoclonal antibodies (mAbs) targeting CGRP and one targeting the CGRP receptor are currently in clinical trials. The first 3 to announce results from phase 2 studies were LY2951742, ALD403, and TEV-48125.

LY2951742 (Lilly & Co.) is a fully humanized anti-CGRP mAb with a half-life of 28 days. In a phase 2 trial, 218 patients with 4–14 migraine headache days per 28 days (MHD/28d) were randomized to LY2951742 150 mg or placebo administered subcutaneously (SC) every 2 weeks for 12 weeks. The primary outcome was change in MHD/28d from baseline to weeks 9–12. Patients in the LY2951742 group experienced a reduction of 4.2 MHD/28d (62.5 % decrease) compared to 3.0 MHD/28d (42.3 % decrease) in the placebo group ($p = .003$). The LY2951742 vs. placebo responder rates were as follows: 50 % responder rates were 70 % of verum-treated patients vs. 45 % for the placebo, the 75 % responder rates were 49 vs. 27 %, and the complete response rates (no migraines in the 3-month trial) were 32 vs. 17 %. The most common adverse event (AE) was upper respiratory tract infections (17 % in experimental group and 9 % in placebo group). Injection-site reactions occurred in 20 % of the experimental group and 6 % of the placebo group. The serious AEs in the trial were deemed unrelated to the study drug and there were no concerning changes on serum laboratory testing, electrocardiography, or vital signs. Neutralizing antibodies were detected in 8 patients at screening and 20 patients at the end of the study [3].

ALD403 (Alder BioPharmaceuticals) is a genetically engineered, desialylated, humanized anti-CGRP IgG1 antibody with a 31-day half-life. In a phase 2 trial, 163 patients with 5–14 MHD/28d were randomized to receive either a single dose of 1000 mg ALD403 or placebo administered intravenously (IV). The primary efficacy endpoint was change in MHD/28d from baseline to weeks 5–8. The mean reduction in MHD/28d was 5.6 in the ALD403 group and 4.6 in the placebo group, with a significant intergroup difference favoring the experimental group ($p = .0306$). A post hoc analysis revealed that 16 % of the patients in the experimental group had zero migraines during the 12 weeks of follow-up, while none of the patients in the placebo group had a complete response. There were no significant differences between the 2 groups in treatment-related AEs, no infusion reactions and serum laboratory testing and vital signs revealed no concerning changes [4]. Limitations of this study include that only a single dose was administered to patients and that the study was designed for 5 % one-sided significance. Results of phase 2b studies using IV ALD403 for chronic migraine (CM) and SC ALD403 for frequent episodic migraine (EM) are expected in 2015.

TEV-48125 (formerly known as LBR-101, Teva Pharmaceuticals, Ltd.), is a fully humanized anti-CGRP mAb with a half-life of 40–48 days depending on the dose. In February 2015, Teva announced that TEV-48125, administered SC monthly for 3 months, met its primary and secondary efficacy endpoints in a phase 2b trial for treatment of CM ($\geq$15 headache days and $\geq$8 migraine days/month), with numerical results forthcoming. This would represent the first evidence of anti-CGRP mAb efficacy in CM. There is also an ongoing phase 2 trial involving TEV-48125 for high-frequency EM (8–14 headache days/month), with results expected in 2nd quarter of 2015.

The only anti-CGRP receptor mAb currently being studied is AMG-334 (Amgen), with 2 phase 2 trials currently ongoing, 1 enrolling patients with 4–14 migraine days/month, and the other enrolling patients with CM.

Given that CGRP is a potent vasodilator, it is worth noting that no animal or human trials on antibodies to CGRP or its receptor have revealed cardiovascular or cerebrovascular AEs thus far. Further studies monitoring for these critical concerns are needed.

Other novel pharmaceuticals for treatment of migraine

Serotonin receptor agonists

The 5-HT_{1F} receptor is located throughout the peripheral and central trigeminovascular system. Unlike 5-$HT_{1B/1D}$ agonists ("triptans"), 5-HT_{1F} receptor agonists ("ditans") do not appear to cause vasoconstriction in in vitro experiments. The first 5-HT_{1F} receptor agonist, LY334370, showed efficacy in a phase 2 study, but development was discontinued due to liver toxicity in dogs [5]. Lasmiditan (CoLucid Pharmaceuticals, Inc.) has been studied for acute migraine treatment in 2 phase 2b studies. In the oral lasmiditan phase 2b study, the 2-h headache response rates at four studied doses of lasmiditan ranged from 34 to 52 %, all of which were superior to the 21 % 2-h response rate in the placebo group ($p \leq .025$). These studies have shown no evidence of drug-related cardiovascular adverse effects or chest symptoms, and the drug does not seem to constrict blood vessels. However, some patients have developed dose-dependent side effects such as paresthesia, dizziness, fatigue, and nausea. Notably, dizziness was experienced by 26 % of subjects receiving the 100 mg dose vs. 0 % of patients receiving placebo [6]. A phase 3 trial studying lasmiditan for acute migraine treatment is planned. This study will include patients with cardiovascular risk factors, which is significant given that cardiovascular disease is listed as a contraindication in the manufacturer's package inserts for all 7 available triptans.

Glial cell modulators

Satellite glial cells in the trigeminal ganglion may play a vital role in peripheral sensitization during migraine. Ibudilast (MediciNova, Inc.) is a non-specific

phosphodiesterase (PDE) inhibitor, most potent at PDE-3 and PDE-4, which suppresses glial cell activation. It has been used in Japan for treatment of post-stroke dizziness and asthma. Two phase 2 trials studying oral ibudilast are ongoing; the first is enrolling patients with CM, and the second is enrolling patients with medication overuse headache and chronic daily headache. These studies will include monitoring of proposed biomarkers serum glutamate, CGRP, glial fibrillary acidic protein and S100β. Ibudilast is also being studied for use in progressive multiple sclerosis, amyotrophic lateral sclerosis, and drug dependence.

Innovative neuromodulation devices

Sphenopalatine ganglion stimulator

The sphenopalatine ganglion (SPG) is a collection of neuronal cell bodies located in the pterygopalatine fossa containing synapsing parasympathetic nerves and post-synaptic sympathetic fibers that pass through it to their end organs. It appears to be involved in the pathogenesis of CH and likely also contributes to the autonomic dysfunction seen in migraine. The Pulsante SPG Neurostimulator (Autonomic Technologies, Inc.) is an on-demand, remote-controlled SPG stimulator that is placed over the SPG using a minimally invasive, trans-oral approach under general anesthesia. During a recently completed European study on chronic cluster headache (CCH), 566 cluster attacks were treated randomly with either full, sub-perception, or sham stimulation. Among the 28 patients who completed the experimental course, 68 % experienced either ≥50 % decrease in pain within 15 min during attacks, ≥50 % decrease in attack frequency, or both. Pain relief was achieved in 67 % of attacks treated with full stimulation, vs. 7 % of attacks treated with sham stimulation and 7 % of attacks treated with sub-perception stimulation. The study was well tolerated, with transient sensory disturbances and pain being the most common AEs [7]. An 18-month, long-term follow-up study has been reported and a larger, randomized, controlled trial (RCT) is currently enrolling up to 120 patients in the US. A CM study is ongoing in Europe.

Trigeminal (supraorbital nerve) stimulator

Transcutaneous electrical stimulation of the supraorbital branches of the trigeminal nerve using the Cefaly device (STX-Med) demonstrated efficacy in a multicenter, sham-controlled RCT enrolling 67 patients with at least 2 migraine attacks per month. Stimulation was applied bilaterally to the supraorbital and supratrochlear nerves. The treatment group outperformed the sham group significantly in reduction of headache days, migraine attacks, and use of abortive medications [8]. However, early consensus in clinical practice is that this treatment is less promising for migraine prevention than the results of the trial suggest; paresthesias produced are quite uncomfortable according to some patients who have tried the stimulator outside of the trial.

Transcutaneous vagal nerve stimulator

The gammaCore device (electroCore LLC) is a non-invasive vagal nerve stimulator (nVNS) which transcutaneously stimulates the cervical branch of the vagus nerve. It has shown promise for the treatment of CCH. In a RCT with 93 evaluable patients, nVNS plus standard of care (SoC) outperformed SoC alone in the acute and preventive treatment of CCH. Patients in the experimental group self-administered 3, 90-s stimulations twice daily for preventive treatment, as well as optional acute treatments for cluster attacks. A sham control was not used. The experimental group experienced a reduction of 7.6 cluster attacks/week vs. reduction of 2.0 attacks/week in the SoC group ($p = .002$). Patients used fewer sumatriptan injections and less oxygen therapy in the arm of the study that included nVNS [9]. The device is currently approved for use in the EU, UK, and Canada, with approval in the US anticipated this year.

The gammaCore device is also being studied for treatment of migraine. In an open-label, single-arm, multiple-attack pilot study, 27 patients with EM treated 80 migraine attacks acutely with 2, 90-s nVNS treatments [10]. In double-blind, sham-controlled pilot RCT using nVNS to prevent CM, 59 patients received 2, 90-s stimulations 3 times a day for 2 months, followed by a 6-month open-label phase [11]. These pilot studies suggested that nVNS was safe and well tolerated for acute and preventive treatment for migraine. Further studies are warranted.

Occipital nerve stimulator

Occipital nerve stimulation (ONS) has demonstrated promising preliminary results in CCH. Fifty-nine patients across 6 open-label studies have experienced a decrease in attack frequency >50 % in 75 % of patients, and 63 % of patients would recommend the procedure [12]. ONS has also been studied for intractable CM, with promising open-label studies leading to the ONSTIM trial (Medtronic). This multicenter, blinded, feasibility RCT missed its primary endpoint by achieving a 3-month 50 % responder rate of 39 %, although greater than half of the participants achieved a ≥30 % reduction in headache severity or frequency with ONS [13]. The OPTIMISE trial, testing the Boston Scientific Corporation Precision System in the management of intractable CM, is ongoing.

Transcranial magnetic stimulator

Transcranial magnetic stimulation (TMS) creates fluctuating magnetic fields applied externally to the scalp to induce a current in the underlying cerebral cortex. Single-pulse TMS (sTMS) has been studied as an abortive treatment for migraine with aura, while repetitive TMS (rTMS) is being studied for preventive treatment of migraine.

A portable sTMS device, SpringTMS (eNeura Inc.), was approved by the FDA in December 2013 for patient-administered acute treatment of migraine with aura. In a phase 3 trial, 267 participants were randomized to administer 2 pulses about 30 s apart of either sTMS or sham stimulation to the occiput within 1 h of aura onset. The pain-free response at 2 h after treatment was 39 % in the sTMS group and 22 % in the sham group ($p \leq .02$) [14]. A new model that will be marketed in the US is being developed.

New delivery methods for old migraine acute care medications

In an attempt to outrace cutaneous allodynia, to bypass migraine-induced nausea, vomiting, and gastroparesis, or to extend duration of delivery in patients prone to recurrence of migraine, reformulations of existing migraine acute care treatments have been developed. Examples that are already commercially available include diclofenac potassium powder for solution that dissolves in water (Cambia in the US, Voltfast in Europe) and intranasal formulations of sumatriptan, zolmitriptan and dihydroergotamine (DHE).

The Zecuity battery-powered, transdermal sumatriptan patch (Teva Pharmaceuticals, Ltd.) uses an electrical current to deliver sumatriptan across the skin into the SC space, bypassing the gastrointestinal system. It maintains therapeutic drug levels twice as long as a 50 mg tablet of sumatriptan and four times as long as the 6 mg injection, but is slower to become effective. It outperformed placebo for the primary endpoint of 2-h headache freedom (18 vs. 9 %, $p = .0092$); this superiority was maintained at all time points up to 12 h post-patch administration (all $p = \leq .01$) [15]. As of February 2015, Teva is advertising that the Zecuity patch will be available soon.

The Semprana Tempo inhaler (Allergan), an orally inhaled DHE formulation, was superior to placebo in its 4 co-primary endpoints including 2-h pain relief (58.7 vs. 34.5 %, $p \leq .0001$) and it demonstrated equal efficacy in patients with and without allodynia in its phase 3 trial [16]. However, FDA approval has been delayed by technical obstacles in manufacturing and filling the canisters.

The OptiNose (AVP-825) breath-powered intranasal delivery system (Avanir Pharmaceuticals) improves the nasal absorption compared to liquid nasal sprays. Blowing against resistance elevates the soft palate, preventing the powder from entering the nasopharynx. This technique coats a large surface area of mucous membranes in both nostrils leading to rapid absorption. A phase 3 trial studied 11 mg sumatriptan powder delivered via the OptiNose device. The 2-h pain relief primary endpoint was superior to placebo (67.7 vs. 45.2 %, $p = .02$) and to historical rates of response to oral sumatriptan. Its rate of onset appeared to be faster than oral sumatriptan's but less quick than that of SC sumatriptan. It also demonstrated a lower rate of side effects than the oral and SC formulations, which is probably attributable to the lower peak serum concentration [17]. In November 2014, the FDA requested that Avanir perform a new human factors validation study, delaying release of the product until later in 2015.

Conclusion

Results from recent clinical trials create optimism that new pharmaceutical and device-assisted neuromodulation treatments will expand our armamentarium of effective, well-tolerated treatments for patients with migraine and CH.

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