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Review Article

Overview of Upcoming Treatments for Migraine. Too Much Enthusiasm?

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Abstract

Migraine is a burdensome disorder. Current treatments are far from desired. Recent knowledge has been indicating targets whose antagonism may improve efficacy. It is particularly true with CGRP and monoclonal antibodies can interfere with the CGRP pathway and decrease migraine frequency of attacks. Erenumab, galcanezumab and fremanezumab were recently approved and eptinezumab is likely to be soon.

Although efficacy figures were not spectacular, tolerability and potential higher adherence were noteworthy. However, caution must be exercised. The time frame after studies was limited in three years and dose administration was restricted to three monthly doses. CGRP is present thoroughly in human body and migraine is life-long disease, often requiring treatment for decades. It is not known whether this favorable profile can be maintained or will be observed with pregnant women or adolescents. In addition, there were deaths during studies, which may have happened without a clear relationship. New treatments are welcome, but caution is warranted.

Keywords: Migraine, Treatment, Future, Upcoming, Medications, Monoclonal Antibodies

Introduction

Migraine is a highly prevalent and incapacitating neurological disorder. It promotes substantial burden to the sufferers and the society [1]. Current available treatments, especially regarding prevention [2], were found useful by chance, when used to other pathological conditions [2]. Despite effectiveness, the drugs used up to now are far from the desired either by patients and treating physicians. In addition, low efficacy figures and unfavorable tolerability profiles make adherence poor and the treatment a real challenge [2,3].

Migraine pathophysiology knowledge has evolved during the last decades, but it is still incomplete [4,5]. Specific neuropeptides acting as mediators of the complex process involved in the headache attacks of migraine, such as calcitonin gene-related peptide (CGRP), have becoming protagonists of this disease that imposes huge costs to the humanity and its antagonism may lead to a clear improvement of patient's lives [4,5].

CGRP is a 37-amino acid peptide densely present in the thalamus, hypothalamus and cerebellum as well as in sensory neurons and fibers involved in pain transmission at dorsal root ganglia and trigeminal ganglia, either unmyelinated or myelinated. In addition, CGRP is also present in the peripheral nervous system [4,5]. It is a potent vasodilator encountered in joints, kidneys, adrenal glands, pancreas and throughout the arterial system in the smooth muscle cell layer as well [4,5].

The receptor to which CGRP binds has two subunits and is described as a G-protein coupled receptor, composed by a calcitonin receptor-like subunit (CLR) and an activity-modifying protein 1 subunit known as RAMP16. CGRP has been representing a core substance in migraine during the last two decades. Its serum levels are elevated in episodic migraine even interictally, the intravenous infusion of CGRP triggers attacks in migraineurs and CGRP concentrations in jugular veins blood rise during headache attacks of migraine. Additionally, CGRP serum level decreases with symptomatic relief of the headache [6,7].

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There are different molecules, which can antagonize the CGRP receptor or the peptide itself. During the last 20 years, potential agents for the acute treatment of migraine acting at the CGRP receptor have been studied [4,5,7,8]. The true efficacy of several compounds was demonstrated, but its clinical use revealed various degrees of hepatotoxicity. Unfortunately, it impeded the approval and resulted in the interruption of the release for upcoming agents such as telcagepant [8,9]. However, the concept of a drug antagonizing the CGRP and representing an useful tool for treating migraine attacks was never really abandoned. In addition, biological options such as monoclonal antibodies anti-CGRP or its receptor started to be developed and three were recently approved by the FDA [7,8,10].

These indisputable facts point indeed, to the usefulness and acceptable tolerability of this treatment path, initiated nearly 20 years ago.

Upcoming therapies

Three CGRP receptor antagonists and one anti-CGRP monoclonal antibody are close to be released. Erenumab, the only monoclonal antibody against the CGRP receptor and two monoclonal antibodies against the peptide CGRP itself, fremanezumab and galcanezumab, were approved in 2018 and will be discussed later [8].

The efficacy and tolerability of ubrogepant, a small molecule acting as CGRP receptor antagonist was evaluated in a study with 834 participants. The design was double-blind treatment of one migraine attack either with placebo or 1 mg, 10 mg, 25 mg, 50 mg, 100 mg, in a 1:1 ratio [9]. Pain freedom and headache response at two hours were the primary endpoints and a total of 113 patients received placebo while 527 subjects received ubrogepant. A positive response trend in the proportion of participants achieving two-hour pain freedom was demonstrated ($p < 0.001$). Ubrogepant 100 mg was also significantly superior to placebo for the endpoint two-hour pain freedom (25.5% vs 8.9%), but not for two-hour headache response. Tolerability was similar between ubrogepant and placebo [11]. Despite the positive efficacy outcome, potential liver toxicity must be ruled out with further studies. There were patients with substantial alanine aminotransferase (ALT) increase reaching five to ten times the normal range [12].

Rimegepant is another small molecule acting as CGRP receptor antagonist. There is unpublished information regarding its phase 2/3 trials comparing different doses (75mg, 150mg and 300mg) with placebo. Pain free rates at 2 hours varied between 29.7% to 32.9%, while placebo rates reached 15.3% ($p<0.002$). Although it was comparable with 100mg sumatriptan regarding pain-free rates at 2h, its tolerability is better with no serious adverse events reported. Phase 3 data evaluated 1072 patients [8]. One study comparing Rimegepant and placebo demonstrated 2-hour pain freedom results of 19.6% versus 12% (P<.001) [8]. Another trial revealed the superiority of Rimegepant 75mg over placebo with similar results (19.2% versus 14.2%, P<.03).

Atogepant, previously designated Merck's MK-8031, is currently AGN-241689. It has been studied for the prevention of episodic migraine and not for the treatment of acute attacks. Different doses, ranging from 10mg, 30mg and 60mg in different posology were compared to placebo, but data is still unavailable [13]. So far, only personal communications report efficacy.

Monoclonal antibodies (mAb) represent attractive treatment options for migraine. All four mAb developed have very long half-life's, restricted tissue penetrance and highly selective affinity for the CGRP itself or its receptor. Therefore, it has become the center of the upcoming arsenal, although CGRP nerve endings are extra luminal in most tissues, which may impair and limit its efficacy [4,5]. Erenumab was the first mAb approved for the prevention of migraine. It is the only among the four mAb acting at the CGRP receptor and not at the CGRP itself [4,5]. Fremanezumab and galcanezumab were approved so far recently and act on the CGRP itself [8].

Erenumab was studied for patients with episodic migraine who were randomized to receive the doses of 7mg, 14mg, 70mg or placebo, in subcutaneous injections, every four weeks, for 12 weeks. The baseline headache frequency varied from 4 to 14 headache-days in 4 weeks. Change in number of migraine days during the weeks 9-12 compared to baseline was significantly superior for the 70mg dose (-3.4 versus -2.3 days, P=0.021) [14].

Erenumab was also studied for chronic migraine prevention. The phase 2 trial was carried out in various centers, with a randomized, double-blind, placebo-controlled involving 667 patients who received either 70mg, 140mg or placebo in two 1ml subcutaneous injections at the study centers on days 1, followed by 4 and 8 weeks later. The primary outcome was mean change in monthly migraine days from baseline to the last 4 weeks of the 12-week treatment phase. Both doses were significantly better than placebo reducing migraine days (-6.6 versus -4.2; P<.0001). It is noteworthy that this trial evaluated similar groups of patients who previously failed to 1 or 2 pharmacological agents for migraine prevention including either topiramate or onabotulinum toxin A [15].

Two phase 3 pivotal registration trials were published recently [16,17]. The STRIVE (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention) trial evaluated subjects presenting 4 to 14 migraine days/month during 6 months with 3 arms. Among the 955 randomized patients, 319 received 140mg, 317 received 70mg and 319 received placebo in monthly subcutaneous injections. In the primary endpoint of reduction in mean migraine days per month, compared to the previous 3-month baseline period, the 140mg group had a higher reduction of 3.7 days. The 70mg dose group reduced headache frequency by 3.2 days and placebo group of 1.8 days (P <.001 for each dose vs. placebo). In the secondary endpoints of ≥ 50% responder rate in mean monthly migraine days, days with use of migraine-specific medications and changes of score for everyday activities and general physical impairment, both doses were significantly better than placebo [16].

The other phase 3 pivotal study included 570 patients who were treated for 3 months either with the dose of 70mg or placebo. The change of mean monthly migraine days from weeks 9-12 comparing with baseline was also the primary endpoint. The mAb promoted a mean reduction of 2.9 days vs. 1.8 days of the placebo group (P<.001). In both pivotal phase 3 studies, there were no serious adverse events related to the study medications, but injection-site reactions or local pain were presented by 3.2% to 6% of those having used erenumab. Some degree of non-

incapacitating arthralgia and constipation were also observed with erenumab in the STRIVE study [17].

Fremanezumab or LBR-101 or TEV-48215 from TEVA, was the second mAb for migraine treatment approved by the FDA. The trials with fremanezumab were designed for episodic migraineurs, high-frequency episodic migraineurs and chronic migraineurs. The study for high-frequency episodic migraine used different doses and patients with 8 to 14 headache days during a 4-week baseline period. The subjects were randomized to receive 675mg (followed by two placebo doses) or 225mg or placebo every 4 weeks during the study timeframe of 12 weeks [18]. The study medications were administered in subcutaneous injections. Efficacy endpoint was measured in thru the changing number of migraine days during the weeks 9-12 or the third 4-week treatment period compared to frequency baseline. The use of both doses revealed a significantly greater reduction compared to placebo. Monthly doses of 225mg demonstrated a reduction of -6.27 vs -3.46 of the placebo; difference 2.81 days (P<.0001) while 675mg resulted in a reduction of 6.09 vs 3.46 days of the placebo; difference 2.64 days (P<.0001). This trial did not exclude the concomitant use of preventive medications, which had to be in stable doses for the previous 2 months prior to the inclusion [18].

In a pivotal phase 3 registration trial, the HALO study, the mean change in number of migraine days and not only on headache days, was compared among 875 patients (742 women; 133 men) with mean age of 41.8 years. Those patients who received 225mg per month (3 doses) had a reduction from 8.9 days to 4.9 days versus 9.2 days to 5.3 days in patients who received a single dose of 675mg. The placebo group presented a reduction in migraine days from 9.1 days to 6.5 days. The difference between monthly dosing vs. placebo was -1.5 days (P<.001) and between a single higher dose vs. placebo was -1.3 days (P<.001) [19].

Tolerability issues were not troublesome or different between placebo and treatment groups. Erythema and induration at injection sites (n=3 and 2), depression, anxiety and diarrhea (respectively, n=2, n=2 and n=2) were the adverse events presented by the studied patients. However, nearly 2% of the patients in each of the groups discontinued treatment because of Liver function abnormalities observed in 2 subjects with the monthly doses, 1 patient with the quarterly dose and 1 placebo subject. Although one death occurred with a patient having received the higher dose of fremanezumab, apparently it was caused by diphenhydramine overdose and suicide [19].

Fremanezumab was also evaluated for the prevention of chronic migraine [20]. The patients were randomized to receive the initial loading dose of 675mg followed by two monthly doses of 225mg or three-monthly doses of 900mg or placebo. The doses were administered every 4 weeks for 12 weeks. The mean reduction in headache hours of any intensity during the weeks 9-12 was significantly greater compared to placebo either for the highest dose as for the 675mg/225mg and 225mg subjects. The patients who received three doses of 900mg presented less 67.5 hours vs -37.1 h; difference 30.4 h, P=.0057. The difference between the patients who received 675mg/225mg and 225mg was – 59.8 h vs 37.1 h; difference 22.7 h, P=.038. Interestingly, these patients could be using up to two preventive agents simultaneously, but without dose adjustments during the previous three months. It is noteworthy that the mean number of headache days per month at baseline was 16 for all groups which can't allow definitive comparisons with daily or near-daily headache sufferers [20].

Another phase 3 pivotal registration trial of fremanezumab for the prevention of chronic migraine enrolled 1130 patients who were randomized to receive 675mg as loading dose at baseline followed by two doses of placebo at weeks 4 and 8 (376 patients) or 675mg as loading dose at baseline and 225mg at weeks 4 and 8 (379 patients) or placebo (375 patients) in 132 specialty centers [21]. The change in headache days reaching a peak severity or the change in headache days in which migraine-specific medications were used was the primary endpoints [21].

Baseline frequency of migraine days among studied groups were 16.4 days for the placebo group, 16.2 days for the quarterly dose group and 16 days for the monthly dose group. The patients who received fremanezumab every month presented a reduction in migraine headache days of 4.6 ± 0.3. The ones receiving fremanezumab quarterly showed a reduction of 4.3 ± 0.3 days and the 375 placebo patients demonstrated a 2.5 ± 0.3 reduction in headache days (P<.001 for both comparisons with placebo).

All secondary endpoints were also significantly better for the patients who received the mAb. Disability, for example, was evaluated thru the Headache Impact Test (HIT-6), and revealed reductions of -4.5 for the placebo patients versus -6.8 and -6.4, respectively for the monthly and quarterly patients (P<.001 for both doses vs placebo). The endpoint ≥ 50% responder rate for the reduction in monthly migraine days was, respectively, 18% for the placebo users, 41% for the monthly dose subjects and 38% for the quarterly dose patients, (P<.001 for both doses vs placebo) [21].

Injection-site reactions were the most observed adverse event for the mAb users. However, although no differences were encountered among active antibodies and placebo with regard to the elevation of liver function tests, 10 patients (5 in each dose group) versus 3 placebo patients (not statistically significant) demonstrated some degree of alanine transaminase or aspartate aminotransferase increasing levels [21].

The third approved mAb, galcanezumab or LY2951742 from Lilly, was studied in two phase 3 trials (EVOLVE1 and EVOLVE2) for the preventive treatment of migraine [22,23]. The EVOLVE1 trial was a randomized (2:1:1), double-blind, placebo-controlled comparison between galcanezumab 120mg, galcanezumab 240mg or placebo. The patients received one subcutaneous dose every month for 6 months. In addition, they were followed up for other 5 months after their last injection. Ninety centers in North America were involved in the study, which had a clinic-based design. The patients (18-65 years) had a minimum of 1-year history of migraine and 4 to 14 migraine headache days per month. A total of 858 patients were included in the intention-to-treat population. Contrarily to other mAbs studies, no other preventive medications were allowed during the study [22].

Primary outcome was the mean change in number of monthly migraine headache days during the treatment period. Secondary endpoints were a frequency reduction of at least 50%, of at least 75%, and of 100%. In addition, migraine headache days with acute medication utilization, scores from the Migraine-Specific

Quality of Life questionnaire and Patient Global Impression of Severity as well as Migraine Disability Assessment were also compared between groups [22].

Among the 858 patients included (mean age, 40.7 years; 718 women [83.7%]), the primary endpoint was achieved for both galcanezumab doses. The number of patients who completed the trial was 718 (81.9%). Active treatment significantly reduced monthly migraine headache days by 4.7 days (120 mg) and by 4.6 days (240 mg) compared with placebo (2.8 days) (for both P<.001). Regarding the secondary endpoints, galcanezumab 120mg and 240mg had similar results, which were significantly superior to placebo [22].

The second study, EVOLVE 2, was also randomized, double-blind involving 915 intention-to-treat patients. They either received monthly subcutaneous injections of placebo (n = 461), galcanezumab 120 mg (n = 231) or 240 mg (n = 223) during 6 months23. The primary endpoint was the mean change from baseline in monthly migraine headache days. Other key secondary endpoints were response rates of ≥ 50%, ≥ 75%, and 100% in addition to reduction of monthly migraine headache days with acute medication use. The Role Function-Restrictive score of the Migraine-Specific Quality of Life Questionnaire and The Patient Global Impression of Severity rating were assessed and compared as well [23].

The studied population was largely female (85.4%), caucasian (70.3%), and North American (48.7%) or European (26.3%) with a mean age of 41.9 years. At baseline, 66.9% of patients had ≥8 migraine headache days/month. Interestingly in this trial, most of the subjects (65.5%) had prior experience with migraine preventive medications, whereas 14.3% had previously failed to two or more pharmacological agents [23].

Monthly migraine headache days were reduced by 4.3 and by 4.2 days with galcanezumab 120mg and 240mg, while placebo reduced headache days by 2.3 and group differences (95% CIs) versus placebo were 2.0 (-2.6, -1.5) and 1.9 (-2.4, -1.4), respectively. Both doses were superior to placebo for all key secondary endpoints and the occurrence of injection site reactions was the most common adverse event. Both galcanezumab doses had significantly more injection site reactions and injection site pruritus, but 240 mg group had significantly more injection site erythema versus placebo [23].

Eptinezumab or ALD-403 from Alder is the only mAb in intravenous injections. It was initially studied in a single dose of 1000mg as a proof of concept. It is also for the prevention of episodic migraine and was compared to placebo in a randomized, double-blind, phase 2 trial. In the study, 163 patients (18-55 years) received, at 26 centers, either ALD403 (n=81) or placebo (n=82). The baseline frequency of headache was 5 to 14 migraine days per month. The primary objective was to assess safety at 12 weeks after infusion, but the primary efficacy endpoint was the change in the frequency of migraine days comparing baseline with the weeks 5-8. Patients were followed up until 24 weeks for exploratory safety and efficacy analyses, and the evaluation was performed by intention to treat [24].

The mean observed change in migraine days was -5.6 for the ALD403 group compared with -4·6 for the placebo group (difference -1.0, 95% CI -2.0 to 0.1; P=.0306). Adverse events were experienced by 46 (57%) of 81 patients in the ALD403 group and by 43 (52%) of 82 in the placebo group. Fatigue (3 [4%] vs 3 [4%]) was the most frequent adverse event and upper respiratory tract infection (placebo 6 (7%) patients vs ALD403 7 (9%) patients), arthralgia (4 [5%] vs 1 [1%]), urinary tract and back pain (4 [5%] vs 3 [4%]) were also reported. There were no differences in laboratory safety data or in vital signs between the two treatment groups [24].

PROMISE 1 and 2 were the two phase 3 pivotal trials for migraine prevention. It stands for "Prevention of Migraine via Intravenous eptinezumab Safety and Efficacy". The first trial evaluated 888 migraineurs with 4-14 migraine days per 30-days, who were randomized to receive quarterly intravenous infusions of either eptinezumab doses of 30mg, 100mg or 300mg or placebo. The primary endpoint was the reduction in migraine days over weeks 1-12. Baseline frequency among groups was similar reaching 8.4 to 8.7 days. The 300mg dose reduced migraine days by -4.3 compared to -3.2 of the placebo group and -4 and -3.9, respectively for 30mg and 100mg doses (P<.0001 for 300mg vs placebo; .0046 for 30mg vs placebo and .0182 for 100mg vs placebo) [25].

Responder rates of ≥ 75% and ≥ 50% were secondary endpoints also evaluated and compared between groups for the weeks 1-4 and 1-12. As for the weeks 1-4, 31.5% of the 300mg patients versus 20.3% of the placebo group revealed a responder rate of higher than 75% (P=.0066). Additionally, 51% of those having received 300mg achieved ≥ 75% reduction in days of migraine after the 3rd and 4th infusions [25].

Tolerability profile was similar among groups. Upper respiratory infection occurred in 11% of the 30-mg, 10% in the 100-mg, 10% in 300-mg and 7% of the placebo groups.

The PROMISE-2 study was designed to evaluate the efficacy in the prevention of chronic migraine [26]. The patients had ≥ 15 to 26 headache days per month with at least 8 migraine days. They either received placebo or epitnezumab in the doses of 100mg and 300mg in intravenous quarterly injections. Baseline migraine frequency was 16.2 for the placebo group and 16.1 days for the active antibody groups. Changes in mean migraine days per month during weeks 1-12 was the primary endpoint. Reductions were, respectively, -8.2 days for 300-mg group, -7.7 for the 100-mg group and -5.6 days for the placebo group (P<.0001 for both doses versus placebo) [26].

Nasopharyngitis was the commonest adverse event, reported in 6% of those receiving 300 mg and in 4% of those receiving placebo and 100-mg eptinezumab. No deaths were reported in any eptinezumab study [26].

Comments

Migraine headache frequency or headache days decreasing of at least 50% are the clinical trial endpoint recommended by the International Headache Society (Clinical Trials Subcommittee) [27]. It is definitely below the expected or desired by patients or their treating physicians, who struggle to get or provide headache relief [27]. Nevertheless, even the currently FDA approved pharmacological agents for migraine prevention, such as propranolol, topiramate and sodium divalproex are capable of providing this degree of headache frequency reduction to higher than half of the patients2. In addition, when doing

so, poor tolerability is commonly seen even with the use of rational combination of drugs [2,28]. The recently approved antibody treatments are clearly better in terms of comfort for administering once-a-month treatments as well as regarding adverse events profile, but with limited efficacy to promote at least 50% reduction in migraine frequency is an undisputable limitation perhaps with much higher costs [4,8,10].

In addition, one might argue on long-term safety of these treatments especially because CGRP is widely distributed in the human body and migraine is a life-long disease, which may require treatment during decades [10]. Moreover, crucial doubts regarding whether repetitive use thru the lifespan will be necessary as well as whether patients who become pregnant during or after treatment will perform safely. Although the four monoclonal antibodies revealed an attractive profile of tolerability in phases 2/3 trials, one can't forget the three deaths during the studies with fremanezumab and erenumab. One patient committed suicide 109 days after receiving 675mg of fremanezumab for episodic migraine, another subject perished due to a chronic obstructive pulmonary disease 69 days after receiving 675mg of fremanezumab in a trial for chronic migraine prevention and a third patient died of a so called arteriosclerosis event after receiving 70mg of erenumab for the prevention of episodic migraine. Despite the lack of clear relationship between mAb and the fatal events one can't deny the possibility of cardiovascular ischemia and even myocardial infarction when CGRP is suppressed, despite recent evidence of safety even in a stable angina patient [29].

In addition, the airway homeostasis and the proper activity of the adrenal glands and the pancreas are also related to CGRP presence throughout the human tissues. These facts may bring back the frustration with setbacks as with telcagepant, a promising near-launched CGRP receptor antagonist [9].

No doubt those patients are anxiously waiting for mechanism-based or precision-designed therapies for migraine, which could provide better treatment outcomes and fewer disturbing effects. We particularly believe that the combination between the already available pharmacological agents with one or two monoclonal antibodies will represent the most efficacious approach, despite the lack of evidence that will remain until pharmaceutical industries forget a little bit their tireless quest for profits and remember patient's needs. Either way, caution must be exercised at this time since further studies are required to evidence the adverse side effects potential as well as long term safety of these upcoming treatments. The new era of migraine treatment is at the door and very welcome, but enthusiasm and parsimony have always to hang on safety.

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