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RESEARCH perspectives

The Role of CGRP as Targeted Treatment for Migraine

A CME Activity

Overview

Stewart J. Tepper, MD, provides his perspectives on the clinical impact of 4 recently published studies involving the management of patients with migraines.

Content Areas:

- Ubrogepant
- CGRP monoclonal antibodies
- AMG 334
- TEV-48125
- ALD403

Faculty

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Introduction and commentary on 4 studies

1. Introduction
   Tepper S.
2. A phase IIb, randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine
   Voss T, et al.
3. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled phase 2 trial
   Sun H, et al.
4. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled phase 2b study
   Bigal M, et al.
5. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide for the prevention of frequent episodic migraine: a randomised double-blind, placebo-controlled, exploratory phase 2 trial
   Dodick D, et al.

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CE/CME Information

Target Audience
This activity was developed for headache specialists, neurologists, primary care physicians and other health care professionals who have an interest in research and treatment advances in migraine.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the prevention and treatment of migraine
- Interpret the clinical implications of recent clinical data and ongoing trials involving CGRP as a targeted treatment option for migraine

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Stewart J. Tepper, MD

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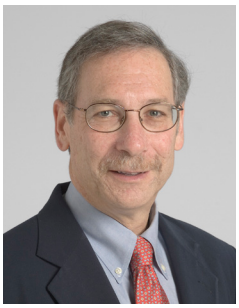
1 *Introduction*

Tepper S.



Stewart J. Tepper, MD

Hello. This is Dr. Stewart Tepper, professor of neurology at the Geisel School of Medicine and director of the Dartmouth Headache Clinic. Calcitonin gene-related peptide or CGRP is a peptide that's really found in every organ system, including the cerebral circulation. It comes in isoforms, the alpha which is primarily in the nervous system and usually in the peripheral nervous system, and the beta which is in the enteric nervous system. CGRP is the most potent endogenous vasodilator, although there are other vasodilators, such as nitric oxide. CGRP release results in not only vasodilation, but the initiation of neurogenic inflammation. The idea that CGRP might be at the top of the pyramid involved in migraine pathogenesis has led to the development of antagonists, or small molecules or gepants, to block CGRP, and monoclonal antibodies, or large molecules, to take out CGRP or its receptor in prevention.

The antagonists, or gepants, were developed initially for the acute treatment of episodic migraine. At least 7 gepants have been found to be effective in acute treatment of migraine. Although all have developed efficacy, many have been abandoned due to liver toxicity.

The first gepant to demonstrate effectiveness in acute treatment of migraine was olcegepant, which was intravenous, and, because of difficulty in developing an oral formulation, was not further developed. Telcagepant was an oral formulation of gepant with a slow onset, long duration of action, good tolerability. It stopped migraine effectively and consistently, and turned out to be hepatotoxic and was therefore abandoned. The next in line in that particular series of gepants was MK3207, which was more potent than telcagepant, and still liver toxic.

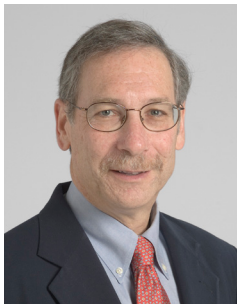
Numerous other gepants have been described as effective in phase 2 trials, none of them has progressed, until recently, to phase 3 trials. Ubrogepant, which was effective in a phase 2 trial in the acute treatment of migraine, has progressed to a phase 3 trial in 2016. Atogepant is a gepant that is planned to be used on a daily basis in prevention of episodic migraine.

Monoclonal antibodies have a long duration of action and were developed for the prophylaxis of frequent episodic or chronic migraine. They're not available orally, due to large molecular size. For the same reason, they don't cross the blood-brain barrier. Four monoclonal antibodies are in development for the prevention of migraine. All of them in one form or another target CGRP. ALD403, fremanezumab, and galcanezumab are monoclonal antibodies that target the CGRP peptide or ligand. Erenumab targets the CGRP receptor itself. All 4 of these monoclonal antibodies have been tested in phase 2, and efficacy and safety results appear promising.

The idea that one can target CGRP at the top of the pyramid, take it out, and either treat migraine acutely or preventively, is very attractive, and the tolerability of both the gepants and the monoclonal antibodies looks very good. There's a potential role for these CGRP-active medications in addressing unmet needs, and these include inadequate response to triptans or other acute medications, unacceptable adverse events with triptans, avoidance of the vasoconstrictive effect of triptans, and the adverse events associated with conventional migraine prevention.

2 *A phase IIb, randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine*

Voss T, et al.



Stewart J. Tepper, MD

Hello. This is Dr. Stewart Tepper, professor of neurology at the Geisel School of Medicine and director of the Dartmouth Headache Clinic. I'll be discussing the publication of "A phase IIb, randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine," by Tiffini Voss and colleagues. This study report was published in *Cephalalgia*. I selected this article to discuss because many of our patients with migraine experience incomplete pain relief and ongoing disability despite the use of acute treatment including triptans. Many of our patients have vascular disease, and so cannot use triptans or dihydroergotamine.

Ubrogepant is a calcitonin gene-related peptide, CGRP, receptor antagonist or gepant, for the acute treatment of migraine and therefore has no vasoconstrictive effects. Other medications in the gepant class have shown significant benefits for acute treatment of migraine, but often at the expense of major liver toxicity. This study was intended to assess the efficacy, safety, and tolerability of ubrogepant for a single attack of migraine, with or without aura, in adults.

The methods of the study were: this was a phase 2b randomized, double-blind, placebo-controlled, dose-ranging, multicenter study involving adults with a 1-year history or more of episodic migraine, with or without aura. Eligible patients experienced 2 to 8 moderate-to-severe migraine attacks per month in each of the 2 months prior to screening.

Randomization was stratified based on the participant's self-reported usual response to triptan therapy. Patients were allocated in a one-to-one ratio to one of the following treatment groups: 1, 10, 25, 50 or 100 mg of ubrogepant or placebo. Patients were provided a single dose of study medication and were instructed to treat a qualifying migraine with key features including moderate or severe intensity, onset within 4 hours, not previously treated for that attack, and not a recurrence.

Key findings of the study were: 640 patients administered the study treatment, of whom 627 or 98% completed the study. The mean age was 40.8 years; 87% of the patients were female; 30.2% experienced migraine with aura; and 31.3% experienced severe impairment of daily activities due to migraine.

The usual migraine treatment was a nonsteroidal anti-inflammatory drug in 71.6% and an oral triptan in 40.6%. There was a positive response trend across ubrogepant doses as measured by the percentage of patients who achieved 2-hour pain freedom, moving a patient from moderate-to-severe pain to 0 pain at 2 hours. The 25 and 50 mg doses of ubrogepant demonstrated nominal significance over placebo for 2-hour pain freedom as measured by the proportion of patients who achieved 2-hour pain freedom. Ubrogepant 100 mg was significantly superior to placebo for 2-hour pain freedom; 25.5% for the active vs 8.9% for the placebo.

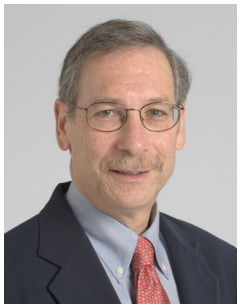
None of the ubrogepant dose groups demonstrated superiority to placebo for the 2-hour headache response, which is defined as moving a patient from moderate-to-severe pain down to either 0 or mild pain. Nausea and dizziness were more common for the active ubrogepant groups across doses than for placebo. Somnolence was more common with placebo. Otherwise, adverse events were similar between ubrogepant and placebo.

Here are my thoughts and analysis of this study. Migraine is now considered a major risk factor for vascular disease as shown in the study published by Tobias Kurth and colleagues in the *BMJ* early in 2016. A search is underway for migraine-specific acute medication beyond NSAIDs that does not have vasoactive properties. One potential class for this holy grail would be the CGRP receptor antagonist small molecules or gepants. This phase 2 study demonstrates efficacy and tolerability of ubrogepant, a non-vasoactive acute medication that looks like it might fit this need. Ubrogepant met the primary endpoint of pain freedom at 2 hours when patients treated a migraine at moderate-to-severe levels of pain. Tolerability appeared good, and so far, safety has been acceptable.

The dose that appeared to work best was 100 mg. Clinicians are now in a waiting game for whether this gepant will succeed in pivotal registration studies to include randomized controls and open-label safety extension. At this point, with this investigational medication, clinicians need to monitor developments and await regulatory evaluation and, if appropriate, approval. Then we may have the opportunity to use safer acute medications in our migraine patients. At this point, larger randomized controlled trials need to confirm efficacy, and a large, open-label extension trial needs to be completed to prove safety, before ubrogepant can be submitted to regulatory authorities for evaluation and approval. That's where we stand at this time.

3 *Safety and efficacy of AMG 334 for prevention of episodic migraine: A randomised, double-blind, placebo-controlled phase 2 trial*

Sun H, et al.



Stewart J. Tepper, MD

Hello, this is Dr. Stewart Tepper, professor of neurology at the Geisel School of Medicine and director of the Dartmouth Headache Clinic. I'll be discussing the publication "Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled phase 2 trial," by Hong Sun and colleagues. This study was published in *Lancet Neurology*.

I selected this article to discuss because preventive medications commonly used for migraine—such as topiramate, valproate, beta-blockers, and amitriptyline—have limited efficacy and are associated with adverse events that contribute to poor adherence. Monoclonal antibodies that bind either the ligand calcitonin gene-related peptide, CGRP, or to its receptor, have shown clinical benefit for migraine prevention with good reported safety. This study assessed the safety and efficacy of the anti-CGRP receptor monoclonal antibody erenumab, AMG 334, for the prevention of episodic migraine.

Methods of this study were: this was a phase 2 randomized, double-blind, placebo-controlled, multicenter study involving adults with a history of episodic migraine, with or without aura, for 12 months or longer. Patients were randomized in a 3 to 2 to 2 to 2 ratio to monthly subcutaneous placebo or erenumab at a dose of 7, 21, or 70 mg for 12 weeks. The study involved 4 phases, of which only the 7-week screening phase and the 12-week double-blind treatment phase have been completed.

Key findings of the study were: 483 patients with a mean age of 41 years were randomized; 81% were women. Patients experienced an average of 9 migraine days per month. Fifty-eight percent had not been previously treated with preventive therapy. A third of patients had failed previous preventive therapy due to lack of efficacy or adverse events. At week 12, reductions in monthly migraine days were not significantly different for the 7 and 21 mg doses of erenumab vs placebo. However, the mean reduction in monthly migraine days from baseline to week 12 was 3.4 days with the 70 mg of erenumab, which was significant greater than the 2.3 days with placebo.

Reduction in monthly migraine attacks was similar for each of the 3 erenumab dose groups and placebo. Adverse event was experienced by 54% of patients who received placebo and 52% of patients who received erenumab. The most frequently reported adverse events in patients treated with erenumab were nasopharyngitis in 7%, fatigue in 4%, and headache in 3%.

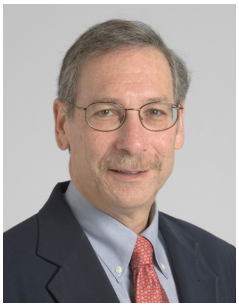
Here are my thoughts and analysis of this study: erenumab is the only anti-CGRP monoclonal antibody that targets the CGRP receptor, and not the peptide or ligand itself. Prior to this study, it was unknown whether the strategy would work in migraine prevention. This phase 2 randomized, controlled trial demonstrated that erenumab injected subcutaneously, and monthly for 3 months, prevents episodic migraine in comparison to placebo. This is only a phase 2 trial, so current treatment will not change for the providers. This biologic will next be tested in the phase 3 pivotal randomized controlled trial with the safety extension arm. If safety and efficacy are confirmed, it will be submitted to regulatory authorities for evaluation, and if appropriate, approval.

The anti-CGRP monoclonal antibodies may change the face of migraine prevention, in that they appear to be extremely effective, and so far, safe and well-tolerated. As was seen in this study, the adverse events for the 2 groups, active and placebo, were basically the same. The opportunity to prevent migraine with a monthly injection will be a paradigm shift for clinicians and patients alike. As after any phase 2 trial, larger phase 3 trials of efficacy and safety need to be completed. Also unanswered is the question of whether the antibody to a CGRP receptor will offer any advantage or disadvantage over an antibody to the CGRP peptide itself.

4

Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine, a multicentre, randomised, double-blind, placebo-controlled phase 2b study

Bigal M, et al.



Stewart J. Tepper, MD

Hello. This is Dr. Stewart Tepper, professor of neurology at the Geisel School of Medicine and director of the Dartmouth Headache Clinic. I'll be discussing the publication "Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine, a multicentre, randomised, double-blind, placebo-controlled phase 2b study," by Marcelo Bigal and colleagues. This study report was published in *Lancet Neurology*. I selected this article to discuss because chronic migraine is one of the most disabling disorders, as it has a substantial impact on daily functioning, even more so than episodic migraine. Nonetheless, patients are often undertreated. The importance of calcitonin gene-related peptide or CGRP in the pathogenesis of migraine is well characterized, and agents that act against CGRP have been shown to reduce symptom severity. This study assessed the safety, tolerability, and efficacy of the anti-CGRP monoclonal antibody fremanezumab, or TEV-48125, for the prevention of chronic migraine.

Before beginning my analysis, let's hear about some of the study highlights form the lead authors' perspective. What are the 3 most important highlights or findings of the study? This study validated CGRP as an important target for chronic migraine. It provided proof of concept. Other studies have demonstrated the role of CGRP in episodic migraine, but this is the first that demonstrated a role in chronic migraine. This study validated the usefulness of antibody therapy for chronic migraine by demonstrating that a large biological protein can be useful for the treatment of migraine. This study demonstrated the efficacy and safety and tolerability of multiple doses of fremanezumab, TEV-48125, in the prophylactic treatment of chronic migraine.

What impact do you think this study will have on the management of patients with migraine? This is the first modern class of preventive medication for episodic of chronic migraine that was actually developed for migraine, based on the understanding of the science behind the disease. The other preventive medications for migraine were found to be somewhat effective in migraine prevention serendipitously. For example, topiramate was developed for seizures. Botulinum toxin was first used for wrinkles and dystonia, and so forth. If the safety and tolerability seen in phase 2 are replicated in ongoing phase 3 trials, and the drug is approved, several important gains will be brought to the clinic.

Migraine may be managed by infrequent injections instead of daily medications. Onset of action of fremanezumab was the fastest ever seen in a migraine trial, as it separated from placebo in only 3 or 7 days, depending on the dose. This was for chronic migraine, not episodic migraine. That's a harder disorder to treat. Since the drug does not penetrate the CNS, the rate of CNS adverse events, such as dizziness and sleepiness, is actually similar to placebo.

Methods for the study were: this was a phase 2b randomized, double-blind, double-dummy, placebo-controlled multicenter study involving adults with a history of chronic migraine. Patients were permitted to have used stable doses of up to 2 different migraine preventive medications for at least 3 months prior to study entry, except that onabotulinumtoxinA could not have been used for 6 months prior to study entry. Patients had to demonstrate at least 80% adherence to their acute migraine treatment. Following a 28-day screening period, patients were randomized 1-to-1 to 1-to-placebo or 2 different doses of fremanezumab.

Randomization was stratified by gender and use of concomitant preventive medication. Study medication was administered as 4 subcutaneous injections in the abdomen at the beginning of each 28-day treatment cycle for 3 cycles. Patients in the 900 mg fremanezumab group received 4 active injections of 225 mg each. Patients in the 675/225 mg fremanezumab group received 3 active injections and 1 placebo injection at the beginning of the first treatment cycle, followed by 1 active injection, and 3 placebo injections at the beginning of the second and third cycles.

Key findings of the study were: 264 adults were randomized with a mean age of 41 years; 86% were women. The mean number of headache hours of any severity per month ranged from 157.7 to 169.1 hours across the different groups. Sixty percent of patients were not using preventive therapy. An adverse event occurred in 53% and 47% of patients in the 675/225 mg and 900 mg groups, respectively, and 40% in the placebo group. A treatment-related adverse event occurred in 29% and 32% of the 675/225 mg and 900 mg participants, respectively, and 17% of placebo patients. None of the adverse events were judged to be serious.

Mild injection pain was the most common treatment-related adverse event occurring in 7% to 9% of the 675/225 mg and 900 mg patients, respectively, and 3% of placebo patients. Injection site pruritus occurred in 5%, 2%, and 0% of patients, respectively.

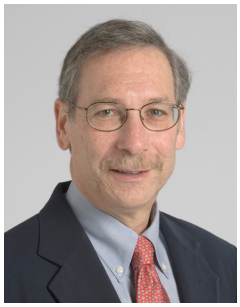
The mean reduction from baseline in number of headache hours during weeks 9 through 12 was 59.84 hours in the 675/225 mg group, and 67.51 hours in the 900 mg group, both of which were significantly greater reductions compared with 37.1 hours in the placebo group.

Here are my thoughts and analysis of this study. This phase 2 trial demonstrates that the anti-CGRP monoclonal antibody fremanezumab, administered subcutaneously and monthly for 3 months, prevents chronic migraine with remarkable speed, good tolerability, and high efficacy. The chronic migraine patients selected in this particular study were more refractory than those who participated in earlier studies on onabotulinumtoxinA and topiramate. The biologic appeared to work in both primary chronic migraine and medication overuse headache patients. This is only a phase 2 trial, so current treatment does not change. This biologic will next be tested in a phase 2 pivotal randomized control trial with a safety extension arm. If efficacy and safety are confirmed, it will be submitted to regulatory authorities for evaluation, and if appropriate, approval.

Again, the future appears bright if the efficacy, safety, and tolerability of these biologics are confirmed in registration studies with safety arms. The ability to treat refractory patients with migraine-specific prophylaxis could completely change our management of patients. Larger phase 3 trials of efficacy and safety need to be completed. In the case of fremanezumab, the phase 3 safety extension trial includes one group of patients who will be injected subcutaneously, monthly, with active medication, and one group who will be injected every 3 months with active medication, and then—in between—with placebo, to see if less frequent injections of active medication will maintain efficacy.

5 *Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide for the prevention of frequent episodic migraine: a randomised double-blind, placebo-controlled, exploratory phase 2 trial*

Dodick D, et al.



Stewart J. Tepper, MD

Hello. This is Dr. Stewart Tepper, professor of neurology at the Geisel School of Medicine and director of the Dartmouth Headache Clinic. I'll be discussing the publication "Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide for the prevention of frequent episodic migraine: a randomised double-blind, placebo-controlled, exploratory phase 2 trial," by David Dodick and colleagues. This study report was published in *Lancet Neurology*.

I selected this article to discuss because episodic migraine is a common and disabling disorder that is ineffectively treated in many patients. Calcitonin gene-related peptide or CGRP is an important neurotransmitter in the pathogenesis of migraine, which has led to the clinical development of several CGRP antagonists or gepants, and anti-CGRP monoclonal antibodies. ALD403 is a monoclonal antibody that potently and selectively binds to both alpha and beta forms of human CGRP. The goal of the present study was to assess the safety, tolerability, and efficacy of ALD403 for the prevention of episodic migraine in adults.

Methods of the study were: this was a phase 2, randomized, double-blind, placebo-controlled multicenter proof-of-concept study involving adults with a 12-month or more history of episodic migraine. Patients were allowed to use acute migraine treatment for up to 14 days per month, up to 10 days of triptan use. Patients could not have used standard preventive treatment for more than 7 days during the 3 months prior to the study, and were not allowed to have used onabotulinumtoxinA for the previous 6 months. Patients were randomized 1-to-1 to a single dose of ALD403 1000 mg or placebo via an intravenous infusion. Randomization was stratified by baseline number of migraine days per 28 days.

Key findings of the study were: 174 patients were randomized, of whom 163 received study treatment. Patient mean age was 39 years; 82% were women. At baseline, patients experienced 8.4 to 8.8 migraine days per 28 days. The Headache Impact Test-6 score was 63.8 to 64.5, indicating severe disability. An adverse event was experienced by 57% of ALD403 patients and 52% of placebo patients. An upper respiratory tract infection was the only adverse event that occurred in 5% or more of patients, and more frequently in the ALD403 group than the placebo group. A URI occurred in 9% of ALD403 patients and 7% of placebo patients. No treatment-related serious adverse events occurred in either group. The mean reduction in migraine days between baseline and weeks 5 through 8 was 5.6 in the ALD403 group and 4.6 days in the placebo group, and the difference was statistically significant. Similar results were observed during weeks 9 through 12.

Here are my thoughts and analysis of this study. This phase 2 trial found that 1 single infusion of the anti-CGRP monoclonal antibody ALD403 prevented episodic migraine with good efficacy, safety and tolerability. Because this is an experimental medication in an exploratory phase 2 trial, no change in current patient management will occur yet. ALD403 and the other 2 anti-CGRP monoclonal antibodies, fremanezumab and galcanezumab, as well as the anti-CGRP receptor monoclonal antibody, erenumab, all prevented episodic migraine in phase 2 trials. ALD403 is the only 1 of the 4 which was given intravenously in a single dose. As was noted, larger phase 3 trials of efficacy and safety need to be completed. Should these trials confirm the phase 2 results, there'll be an intravenous option for administering a preventive biologic in migraine prophylaxis.

Several unanswered questions remain on ALD403, assuming efficacy, safety, and tolerability are confirmed. First, is there any advantage to an intravenous formulation for patients, over subcutaneous injections? Second, how long will the therapeutic effect of the single infusion last? This latter question is being studied in a longer trial of ALD403 underway at the time of this recording.