

Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy

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Abstract

Objective

To provide the first clinical report that 2 calcitonin gene-related peptide (CGRP) therapies, a small molecule CGRP receptor antagonist and an anti-CGRP receptor antibody, can be used concomitantly to treat refractory migraine.

Methods

Case reports are presented of 2 patients participating in a long-term safety study of rimegepant 75 mg oral tablets for acute treatment (NCT03266588). After Food and Drug Administration approval of erenumab, both patients started subcutaneous erenumab monthly as allowed per protocol.

Results

Patients were women 44 and 36 years of age with ≥ 2 decades of self-reported suboptimal response to multiple migraine medications. Patient 1 used rimegepant for 6 months and then started erenumab 70 mg subcutaneous monthly. Despite a response to preventive treatment with erenumab, she experienced substantial relief treating 7 of 7 acute attacks with rimegepant and eliminated regular, frequent use of ibuprofen and a caffeinated analgesic. Patient 2 used rimegepant for 60 days before starting erenumab 140 mg subcutaneously monthly. While on erenumab, 9 of 9 attacks treated with rimegepant responded. She stopped near-daily use of injectable ketorolac and diphenhydramine. While using rimegepant alone or together with erenumab, patients reported no related adverse events.

Conclusions

Rimegepant 75 mg may be effective for acute treatment during concomitant erenumab preventive administration. The mechanism underlying the benefits of concomitant use of a small molecule CGRP receptor antagonist and an anti-CGRP receptor antibody is unknown and requires further study.

ClinicalTrials.gov identifier

NCT03266588.

Classification of evidence

This study provides Class IV evidence that for patients with migraine using erenumab, rimegepant is effective for acute treatment.

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Criteria for rating therapeutic and diagnostic studies

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Glossary

cAMP = cyclic adenosine monophosphate; **CGRP** = calcitonin gene-related peptide; **mAb** = monoclonal antibody; **MMD** = monthly migraine day; **ONS** = occipital nerve stimulator.

Calcitonin gene-related peptide (CGRP) plays a crucial role in migraine pathophysiology and is now established as an important target for both preventive and acute treatments.^{1,2} The current approved preventive CGRP-targeting treatments are monoclonal antibodies (mAbs) that bind either the CGRP receptor or the CGRP ligand. Small molecule CGRP receptor antagonists, known as gepants, are in development for acute and preventive treatment. In anticipation of approval of the gepants, questions have arisen about their combined use in patients on mAbs. If the CGRP signaling pathway is already blocked, will gepants be effective on top of mAbs? We recently observed 2 patients enrolled in a long-term safety study of rimegepant who started treatment with erenumab, a CGRP receptor–targeted mAb. These 2 patients provide preliminary observations that gepants may be effective for migraine attacks occurring during preventive CGRP mAb therapy and that mAbs remain effective for migraine prevention during the coadministration of gepants for acute treatment.

Methods

This article summarizes the cases of 2 patients with migraine who were participating in a long-term safety study of rimegepant 75 mg oral tablets for acute treatment (ClinicalTrials.gov identifier: NCT03266588). While use of investigational biological agents was prohibited by the protocol, after erenumab approval by the US Food and Drug Administration (May 2018), both patients started subcutaneous monthly preventive therapy. The long-term safety study protocol was approved by independent institutional review boards and/or ethics committees at each trial center. No statistical analyses were performed on the results reported herein; they are based on patient report and investigator observation.

Patient 1

The first patient is a 44 year-old white woman with a history of migraine without aura since 1995. Before enrollment in a trial of rimegepant, she reported an average of 8 attacks with pain of moderate to severe intensity per month during the preceding 3 months. She treated acutely with sumatriptan 100 mg oral tablets or a fixed combination of acetaminophen, acetylsalicylic acid, and caffeine. Ibuprofen was used as needed for dysmenorrhea and migraine.

During a 30-day lead-in phase of the clinical trial, the patient used sumatriptan to treat 10 migraine attacks of moderate to severe pain intensity. After the lead-in phase, she entered the treatment phase of the long-term safety trial and received rimegepant 75 mg as needed, up to once daily, for the acute

treatment of migraine. Within 1 week, she discontinued ibuprofen for migraine, and she stopped the caffeine-containing analgesic 5 weeks after entering into treatment with rimegepant 75 mg.

Although her acute attacks responded well to treatment with rimegepant 75 mg, attacks were frequent, and after 6 months in the rimegepant long-term safety study, she was started on erenumab 70 mg subcutaneous monthly as a preventive therapy. After starting erenumab, her monthly migraine days (MMDs) declined by 46% over the first 4 weeks from 13 to 7 MMDs of any pain intensity, but she continued to experience migraine attacks. Over the subsequent month, she treated 7 breakthrough migraine attacks that occurred while on erenumab with rimegepant 75 mg oral tablet. Attacks were relieved each time. No other acute migraine medications were needed to resolve the rimegepant-treated attacks. While receiving rimegepant alone, she experienced 1 adverse event of streptococcal pharyngitis that was considered by the investigator to be unrelated to rimegepant. While receiving rimegepant alone or concomitantly with erenumab, she experienced no adverse events related to treatment. At the end-of-study visit, she reported that she was very satisfied with rimegepant and rated it “much better” than previous treatments.

Patient 2

The second patient is a 36 year-old white woman with a 19-year history of migraine without aura. She reported an average of 11 MMDs with pain of moderate to severe intensity. Her treatment history involved subcutaneous sumatriptan, intranasal zolmitriptan, and oral tablets of rizatriptan, eletriptan, naratriptan, and almotriptan, all of which were suboptimal (e.g., relief took too long, did not last, was inconsistent). She also had a 6-year history of treatment with an implanted occipital nerve stimulator (ONS). At enrollment, her migraine treatments included oral sumatriptan 100 mg, IM ketorolac tromethamine 30 mg, IM diphenhydramine 100 mg, oral methadone 80 mg, oral ondansetron 8 mg, oral zonisamide 250 mg, and ONS. Before enrollment, she stopped using methadone, a prohibited medication for the trial.

During a 30-day run-in to the long-term safety trial, the patient experienced 22 attacks of moderate to severe pain intensity. On entry into the treatment phase, she received 30 tablets of rimegepant 75 mg and was instructed to take rimegepant 75 mg up to once per calendar day, as needed, for the acute treatment of migraine attacks of any pain intensity. In the first 30 days of treatment, she used 16 doses of rimegepant; in the second 30 days, she used 11 doses of

rimegepant and stopped ondansetron, ketorolac, and diphenhydramine. Because of high headache frequency, she was subsequently started on a monthly dose of erenumab 140 mg. Over the first 30 days after starting erenumab, she experienced 9 attacks, all of which were treated successfully with rimegepant. While using rimegepant alone or together with erenumab, she experienced no adverse events.

Discussion

Rimegepant 75 mg oral tablet and erenumab 70 mg and 140 mg subcutaneous injection have demonstrated efficacy in separate randomized controlled clinical trials for acute and preventive treatment of migraine, respectively.^{3–5} The response to erenumab in these patients appears typical. However, with histories of long-term polypharmacy with acute medications, both patients were at risk of failing preventive treatment. While the initiation of erenumab reduced MMDs, the onset of treatment with rimegepant enabled the first patient to end 22 years of acute treatment with a caffeine-containing combination analgesic. The second patient eliminated near-daily use of 2 injectable medications: an IM nonsteroidal anti-inflammatory drug and an IM antiemetic. In the long term, the reduction of attack frequency and the elimination of regular, frequent use of multiple acute medications are likely to be of substantial clinical import to these patients.

The profile of benefit seen in clinical trials and experiences with rimegepant and erenumab tend to be similar to those described herein and suggest that both compounds will have a meaningful role in the migraine armamentarium. The benefits of their concomitant use may involve additive effects and may be generalizable to other combinations of anti-CGRP agents with distinct molecular targets. Because it is a small case series, this study provides Class IV evidence that combining rimegepant with erenumab may provide effective and safe treatment of patients with a history of refractory migraine.

Because both of these antimigraine agents target the CGRP receptor, it is unknown what mechanism(s) underlie the acute and preventive treatment benefits seen during concomitant treatment. It is unlikely that differences in affinity are a factor, because both molecules exhibit similar high (20–30 pmol/L) affinity for the human CGRP receptor.^{6,7} In contrast, given the disparate physical size of these 2 agents, it is conceivable that the therapeutic benefits of coadministration may involve functional antagonism of a pool of CGRP receptors that are more readily available to the 280× smaller rimegepant (0.53 kDa) than to the biologic antagonist erenumab (≈150 kDa). For example, membrane-bound CGRP receptors are known to internalize into endosomes after CGRP agonist stimulation.^{8,9} Mechanistic studies in cellular and animal behavior assays have shown that these internalized CGRP receptors can continue to actively

drive CGRP-mediated pain signals.¹⁰ Given that the truncated peptide antagonist CGRP (8–37), conjugated to cholesterol for endosome-specific targeting, can suppress CGRP-mediated endosomal signaling and inhibit both cellular signals and animal pain responses,¹⁰ it is possible that a differential ability for small molecules vs mAbs to enter cells and engage endosomal CGRP receptors may be a factor. The lipophilicity (logD 2.08) and inherent membrane permeability of rimegepant⁶ would provide for potential ready access to endosome-bound CGRP receptors, regardless of whether the neuropeptide CGRP is present or absent. In contrast, neither receptor-targeted nor ligand-targeted CGRP mAbs are localized with internalized CGRP receptors in the presence of CGRP.⁹ This may present a situation during migraine attacks (when CGRP levels are most elevated¹¹) in which the 2 agents have differential access to an endosome-bound CGRP-mediated pain signaling pathway and rimegepant might provide additional benefits to ongoing mAb therapy.

Additional evidence of differential intracellular action comes from functional antagonism studies of CGRP-mediated signaling via cyclic adenosine monophosphate (cAMP). Despite their comparable binding affinity for the human CGRP receptor, erenumab is 16× less potent than rimegepant at antagonism of cAMP signaling in whole-cell assays.^{6,7} Consequently, an additive benefit of combination therapy may derive from enhanced inhibition of CGRP-mediated intracellular cAMP signaling cascades.

Alternatively, the observed therapeutic actions may be related to differential receptor kinetics of CGRP small molecules and CGRP mAbs. Rimegepant has demonstrated the ability to maintain CGRP receptor antagonism *in vivo* in primates even when repeatedly challenged by IV CGRP bolus delivery,⁶ whereas the ability of CGRP mAbs to withstand displacement by repeated waves of CGRP release is unknown. Differences in CGRP receptor turnover or CGRP receptor internalization in the presence of small molecule binding vs large antibody binding may also be involved.^{8,9}

Because rimegepant has 65× higher affinity for the human CGRP receptor vs the amylin-1 (CTR/RAMP1) receptor, the potential involvement of the amylin-1 receptor may seem less likely, because any engagement would be much less than for CGRP receptor inhibition. Nevertheless, this is a potential point of difference between the 2 molecules; erenumab is reported not to inhibit amylin-1,⁷ although a definitive causal link between amylin-1 receptor inhibition and migraine has yet to emerge.

Additional studies will be needed to determine whether these or other differences are the primary drivers of the effectiveness of combination therapy with rimegepant and erenumab.

This is the first clinical report describing concomitant use of anti-CGRP therapies for acute and preventive treatment in

patients with migraine. While CGRP antagonist antibodies have demonstrated efficacy in reducing attack frequency, most individuals who respond experience breakthrough attacks and continue to require acute treatment. Rimegepant 75 mg oral tablet appears to offer utility as an acute treatment for migraine attacks that occur during preventive treatment with CGRP antagonist antibodies. The potential mechanisms underlying these benefits remain unknown. This question and others should be explored in future research.

Biohaven Pharmaceuticals will provide access to deidentified patient-level data that underlie the results in this article in response to scientifically valid research proposals. Data from this study, including the study protocol, will be made available beginning 9 months and ending 24 months after the publication of this article. Biohaven will consider requests from qualified researchers for access to the data. Proposals should be directed to the corresponding author. Biohaven will review the request using an internal committee composed of Biohaven colleagues who are responsible for the program, including a clinician, a statistician, and a data-sharing professional. Biohaven will make reasonable efforts to fulfill all data requests for legitimate research purposes, but there might be instances in which retrieval or delivery of data is not feasible such as those involving, for example, patient privacy, requirements for permissions, contractual obligations, and conflicts of interest. All those receiving access to data will be required to enter into a data use agreement provided by Biohaven, which will contain the terms under which the data will be provided.

Author contributions

K. Mullin and D.B. Kudrow: drafting/revising the manuscript, data acquisition, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding. R. Croop: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding. M. Lovegren: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. C.M. Conway: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision. V. Coric: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. R.B. Lipton: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval.

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