Calcitonin Gene-Related Peptide Monoclonal Antibodies

A new treatment for managing migraine in the clinic is on the horizon.

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Migraine is a recurrent headache disorder that poses a significant burden on public health.[1,2] One-year prevalence of migraine is estimated at 16%, and the condition has a substantial socioeconomic impact, ranking among the top 20 causes of global disability.[1]

Patients with frequent headache days or function-impairing headache should be offered preventive pharmacologic therapy.[3,4] However, epidemiologic studies have shown that fewer than half of candidates for migraine-preventive treatment actually use preventive therapy.[3] Adverse side effects, lack of efficacy, and contraindications, such as cardiovascular limitations precluding triptan use, can limit utilization of preventive options.[5] Some of these issues may be attributable to a lack of migraine-specific preventive agents. Current preventive management guidelines are taken from medication classes originally developed to treat seizures, mood disorders, and hypertension.[4,5] Monoclonal antibodies to calcitonin gene-related peptide (CGRP) offer migraine-specific preventive medication.

Calcitonin Gene-Related Peptide Monoclonal Antibodies and Migraine

Clinical use of CGRP monoclonal antibodies as a migraine-specific preventive treatment is in phase 3 clinical trials. CGRP is a 37-amino acid neuropeptide first described in 1983[6] and found in neural tissue, where it plays a role in nociception. CGRP has two major isoforms: α-CGRP and β-CGRP, which have distinct physiological functions. α-CGRP is the primary neuronal isoform, found both centrally and peripherally.[7] A therapeutic implication for CGRP in migraine was suggested when CGRP plasma levels in the external jugular vein were found to be increased during thermocoagulation of the trigeminal ganglion in patients with trigeminal neuralgia and facial flushing.[8] Subsequent experiments found elevated CGRP levels in the external jugular vein, but not the cubital fossa, in individuals experiencing migraine. Importantly, other known nociceptive neuropeptides were not altered, suggesting a unique significance for CGRP in pathophysiology of migraine.[9] Experiments have shown increased CGRP plasma levels in patients with migraine, but not in control subjects without migraine, following nitric oxide–induced headache.[10,11] Sumatriptan, a first-line agent in acute migraine treatment, reduces CGRP release via activation of 5-HT1D and 5-HT1F receptor subtypes.[12] CGRP infusion has been shown to trigger migraine in patients with migraine with and without aura.[13,14]

The neurophysiology of CGRP has been described. Nociceptive C-fibers in the trigeminal ganglion and at the trigeminal nucleus caudalis carry high concentrations of CGRP.[15] It is uncertain if Aδ fibers contain CGRP. CGRP is involved in pathways of peripheral sensitization and hyperalgesia and central sensitization. The primary site of action for CGRP is thought to be the trigeminovascular system, located outside the blood–brain barrier, where CGRP interacts with trigeminal afferents and meningeal vasculature to propagate ongoing synthesis and release of nociceptive peptides, including nitric oxide and CGRP.[15,16] Monoclonal antibodies to CGRP may disrupt this cycle, thus preventing migraine-associated pain.

Clinical Trials

The 4 monoclonal antibodies that target CGRP or the CGRP receptor and have been studied in the prevention of episodic and chronic migraine are: eptinezumab (ALD403), erenumab (AMG 334), fremanezumab (TEV-48125), and galcanezumab (LY2951742).

Phase 2 and phase 3 placebo-controlled trials evaluating the safety and efficacy of the CGRP and CGRP-receptor monoclonal antibodies for patients with episodic or chronic migraine have shown a significant decrease in the average number of monthly headache days compared to patients treated with placebo, and no safety concerns related to treatment have been noted.[17-26]

Eptinezumab

Eptinezumab is a humanized monoclonal antibody targeting CGRP and developed as an intravenous formulation to produce a more immediate therapeutic response. In a phase 2 clinical trial, patients with episodic migraine (5 to 14 days/28-day period) had efficacy (reduction in number of migraine days from baseline) and safety outcomes measured at weeks 5 through 8.[17] Patients received a one-time intravenous dose of 1,000 mg of eptinezumab. The most common adverse events were upper respiratory tract and urinary tract infections; other adverse events included nausea and vomiting, fatigue, back pain, and arthralgia. Results suggested a 1 day/month difference in migraine frequency reduction compared to placebo.

Erenumab

Erenumab is a human monoclonal antibody targeting the CGRP receptor formulated as a subcutaneous injection. In the phase 3 study to evaluate the efficacy and safety of erenumab in migraine prevention (STRIVE) trial, patients with episodic migraine received monthly doses of subcutaneous placebo or erenumab at a dose of 70 mg or 140 mg for 6 months.[18] Results from months 4 through 6 showed a mean reduction of 1.4 headache days per month and 1.9 headache days per month at the erenumab 70 mg and 140 mg doses, respectively, compared to placebo. Although injection-site pain was observed, the overall safety profile of erenumab was similar to that of placebo. In the phase 3 ARISE trial, patients received monthly doses of subcutaneous placebo or 70 mg erenumab. Preliminary results from weeks 9 through 12 showed a mean reduction of 1.1 headache days/month with erenumab 70 mg compared to placebo.[19] An open-label extension of the phase 2 clinical trial studying patients with episodic migraine (4 to 14 days/month) showed that at week 64, 65% of participants receiving 70 mg of subcutaneous erenumab every 4 weeks had more than a 50% reduction in migraine days per month.[20,21]

In a phase 2 clinical trial for patients with chronic migraine (15 or more headache days per month, of which 8 or more were migraine days), placebo or erenumab, at doses of 70 mg and 140 mg, was given subcutaneously every 4 weeks for 12 weeks. Patients had a mean reduction of 2.5 headache days per month compared to placebo.[22] The most common adverse events were injection site pain, upper respiratory tract infection, and nausea.

Fremanezumab

Fremanezumab is a humanized monoclonal antibody targeting CGRP in a subcutaneous injectable formulation. In a phase 3 clinical trial, patients with chronic migraine (15 or more headache days per month, of which 8 or more are migraine days) received placebo or fremanezumab quarterly (a single dose of 675 mg at baseline and placebo at weeks 4 and 8) or fremanezumab monthly (675 mg at baseline and 225 mg at weeks 4 and 8). Patients experienced a mean reduction of 1.8 headache days per month and 2.1 headache days per month with the quarterly and monthly doses, respectively, compared to placebo.[23] The most common adverse event was injection site pain.

Fremanezumab was also studied in patients with high-frequency episodic migraine (8 to 14 headache days per month). In a phase 2 clinical trial, patients received placebo or fremanezumab at doses of 225 mg or 675 mg subcutaneously every 28 days for 3 months. Patients had a mean reduction of 2.8 headache days per month and 2.6 headache days per month with 225 mg and 675 mg doses, respectively, compared to placebo.[24] The most common adverse events were injection site pain, pruritus, or erythema.

Galcanezumab

Galcanezumab is a humanized monoclonal antibody targeting CGRP, available as a subcutaneous injectable formulation. In a phase 2b clinical trial, patients with episodic migraine (4 to14 headache days per 28-day period) received placebo or 5 mg, 50 mg, 120 mg, or 300 mg of galcanezumab by subcutaneous injection once per month for 3 months and experienced a mean reduction of 1.1 headache days per month with 120 mg of galcanezumab compared to placebo. The most common adverse events were injection site pain, upper respiratory tract infections, and nasopharyngitis.[25,26]

Clinical Use of Calcitonin Gene-Related Peptide Antibodies

Patient Population

Based on results of recent studies, CGRP antibodies would be beneficial as preventive treatment for patients with episodic or chronic migraine, either as monotherapy or an adjunct therapy.[27,28] Of note, the mean age of patients studied was approximately 40 years, and none had any underlying cardiovascular, gastrointestinal, or renal impairment. CGRP antibodies have not been tested during pregnancy.

Administration

Eptinezumab is administered intravenously, whereas erenumab, fremanezumab, and galcanezumab are administered subcutaneously. The studied frequency of subcutaneous injections varied from monthly to quarterly. In studies, therapy with CGRP monoclonal antibodies has a significant

effect within 1 to 4 weeks of treatment.[29] A post hoc analysis showed a fremanezumab dose-dependent therapeutic response within the first week of treatment.[30]

Safety Considerations

Phase 2 and phase 3 clinical trials have shown CGRP monoclonal antibodies are well-tolerated. However, the clinical use of CGRP and CGRP receptor antibodies must take into account safety-related concerns. CGRP and CGRP receptors are present in the peripheral, enteric, and central nervous systems and the cardiovascular system and active in wound healing and other physiologic functions.[5,7,26,31-34]

The β-CGRP isomer is active in the gastrointestinal tract. In animal models administered CGRP antibodies, there was mucosal damage, suggesting that CGRP antibodies could contribute to loss of gastrointestinal mucosal integrity and predispose patients to inflammatory bowel disease.[31] Concerns for hepatotoxicity arose from the -gepant class of small-molecule CGRP receptor antagonists.[27,31] However, there is no evidence of treatment-related hepatotoxic adverse events from studies on the safety profile of the CGRP antagonists that are not metabolized primarily by the liver.[17-26,29]

CGRP has been shown to play a protective role in the vascular system; as a potent vasodilator, CGRP can buffer the effects of cerebral and cardiac ischemia.[31-33] Thus, CGRP blockade may carry a risk of escalating mild ischemic events into permanent infarcts.[31,32] Upregulation of CGRP may also be protective against hypertension and aortic vascular hypertrophy and fibrosis; α-CGRP knockout mice models were found to have increased hypertension and aortic hypertrophy.[33] Although no treatment-related vascular adverse events have occurred in randomized controlled trials for CGRP monoclonal antibodies,[17-26,29] long-term effects are not yet known.

The importance of CGRP relative to other vasodilatory mediators released during myocardial ischemia has not been established. Depre et al studied whether erenumab impairs stress-induced myocardial ischemia in patients with stable angina.[35] This was assessed by comparing changes in total exercise time during an exercise treadmill test in patients given erenumab versus patients given a placebo. Erenumab, given intravenously, did not reduce exercise capacity, a surrogate of underlying myocardial ischemia. No difference was observed in the time to onset of ≥1 mm ST-segment depression. No difference was observed in the time to onset of exercise-induced angina. No difference in adverse events was reported. These results support the hypothesis that inhibition of the CGRP receptor does not aggravate myocardial ischemia in an at-risk population of patients with stable angina.

CGRP, along with substance P, is involved in wound healing in aged rat models.[34] Although not demonstrated in clinical trials, disruptions in CGRP activity could theoretically lead to poor wound healing.[7,31]

CGRP may also play a role in other disease states including arthritis, diabetes, obesity, and skin conditions, although to what extent is not known.[7] In the brain, there are areas that express CGRP but do not have a protective blood–brain barrier, including the pituitary gland. CGRP antibodies may therefore have an effect on hypothalamo-hypophyseal tract function.[7,31]

Long-Term Perspective for Calcitonin Gene-Related Peptide Antibody Therapy

Studies are still needed to elucidate the long-term safety and efficacy of CGRP monoclonal antibodies. The development of tachyphylaxis from the reflexive production of drug-neutralizing antibodies as a response to CGRP monoclonal antibodies is a possibility but has not been seen in clinical trials. In addition, the costs and availability of CGRP antibodies have not yet been determined.

There are several benefits to CGRP monoclonal antibodies in the clinical setting. They appear to be well-tolerated, with mild injection site reaction as the most common adverse event. To date, neurocognitive or hepatotoxic side effects, commonly associated with current migraine preventive treatments, have not been found, most likely because CGRP monoclonal antibodies are too large to penetrate the blood–brain barrier and metabolism of CGRP monoclonal antibodies occurs outside the liver. Short-term efficacy of CGRP monoclonal antibodies has been demonstrated in phase 2 and phase 3 clinical trials and appears to have rapid onset, allowing patients and providers to determine quickly the presence of a therapeutic response. The halflife of CGRP monoclonal antibodies is long, and monthly to quarterly administrations would ease the treatment burden associated with daily preventive medications.

CGRP monoclonal antibodies signify the development of a new class of migraine-specific preventive treatment, and depending on long-term outcomes, could revolutionize treatment approaches in headache medicine. ■

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