Headache
© 2018 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.13408
Published by Wiley Periodicals, Inc.

Letter to the Editor

CGRP Antagonists: Physiologic Effects and Serious Side Effects

The article by Depre and colleagues demonstrated that the new migraine preventive erenumab may be safe for stable angina patients.[1] While this is reassuring, many questions remain. The monoclonal antibodies (mAbs) targeting CGRP are effective and well tolerated. Short-term side effects are few. CGRP affects many body systems and, unfortunately, long-term effects are unknown. There are a number of issues, therefore, that must be addressed.

This letter summarizes many of the clinically relevant physiologic effects of CGRP. It is important to note that much of what is published is in animal (primarily rat) studies; human studies have begun to contradict some of these results. However the human CGRP physiologic studies have not yet been published.

CGRP plays a role in preventing hypertension. Once HTN occurs, CGRP is released. This release diminishes over time. CGRP may be helpful in preventing cardiovascular disease. A reduction in CGRP may become clinically relevant primarily in the face of vascular pathology. CGRP is a strong vasodilator. Loss of CGRP may enhance stress in the aorta. For those with cardiac disease, infusions of CGRP improve circulation. CGRP also facilitates angiogenesis. When the protective effects of CGRP are diminished, it is possible that cardiac or cerebral infarcts may become more severe. CGRP helps to protect against vascular inflammation, cell death, and ischemia in various organs. CGRP also plays a protective role in those with heart failure. CGRP is possibly an inhibitor of platelet aggregation, through cAMP activation. This effect has not been demonstrated in humans. Inhibiting CGRP could conceivably lead to embolic cardiac or cerebral events. Patients with diabetes and advanced CAD may be at more risk from CGRP antagonism.[2-4]

CGRP is also found abundantly in the lungs. CGRP may be beneficial for those who suffer from pulmonary hypertension, and by lowering levels we could harm pulmonary function.

Within the blood-brain barrier (BBB), there is slight penetration (0.1% to 1%) of these large molecule mAbs into the CNS, but this be clinically relevant. Outside of the BBB, there are critical areas that may be affected by the antagonists. These include the anterior pituitary, choroid plexus, median eminence, area postrema, and the circumventricular organs. The anterior pituitary hormones (GH, TSH, FSH, LH, ACTH, MSTH, Prolactin) may be affected by lowering CGRP. Choroid plexus CGRP may play a role in CSF production, and also in maintaining CSF inflammatory homeostasis. CGRP antagonism effects on the median eminence may influence hypothalamic hormone (CRF, TRF, DA, GHRH, GnRH) release. The CGRP in the area postrema may be involved in nausea and vomiting. Other circumventricular organs are involved in homeostasis of cardiovascular or immune functions, fluid regulation, and thirst or feeding.[5] The loss of CGRP may possibly affect these vital functions.

Beta CGRP is present throughout the GI system. CGRP is possibly important in gastric mucosal protection, although this has not yet been determined with evidence. Those with GI ulcers or inflammatory bowel disease may be at higher risk for these mAbs. CGRP also affects GI motility.[2,3] While constipation is a more likely side effect, diarrhea is also possible.

In the skin, CGRP is involved with thermoregulation, blushing, flushing, cold hypersensitivity, skin edema, and itch. CGRP is very important for tissue repair, wound healing, and regeneration of the skin. For those with burns, CGRP plays a role in healing.[2,4]

CGRP is involved in bone metabolism and repair.[6] We are not sure, in humans, of the clinical significance. In the presence of certain pathological conditions, CGRP may protect against renal damage. CGRP levels are raised during dialysis. With septic patients, CGRP helps with inflammation, and also in regulating BP.

Within the pancreas, CGRP may reduce insulin levels. Antagonizing CGRP could conceivably have a positive effect on diabetes. However, those with diabetes plus coronary artery disease may be at a higher risk if CGRP is diminished. With aging, CGRP levels usually decline, but there may be a bimodal effect. At times there may be an increased release of CGRP with advancing age.[2,4] If CGRP is increased with advancing age, this effect is probably not sustained.

Early in pregnancy fetal CGRP levels are minimal. There may be more risk of CGRP antagonism later in pregnancy. It may not be possible to determine the true pregnancy risk, but preliminary animal studies have not revealed major problems. A CGRP pregnancy registry is being organized.

CGRP antagonism may conceivably help with certain pain syndromes, such as arthritis and fibromyalgia. Arthritis patients have increased levels of CGRP in plasma and synovial fluid.[2,3] It is possible that the CGRP migraine mAbs may decrease other chronic pains as well.

Amylin (AMY) and adrenomedullin (ADM) ligands, and receptors, may help to compensate for the loss of CGRP. Regarding vasodilation, there are a number of compounds (NO, VIP, and others) that are also strong vasodilators, that may compensate. The CGRP ligand has some affinity for these AMY and ADM receptors. If the CGRP receptor is antagonized, the ligand may still attach to the other receptors. However, if CGRP attaches to the other receptors, the effect will be as if AMY or ADM attached, not a CGRP effect. CGRP antagonists may affect ADM levels. The overlapping and complex pharmacology among CGRP, AMY, and ADM raises some questions.[7]

There may be a difference in long-term safety between the receptor antagonist and the mAbs that target the CGRP ligand. Also, the question of taking a "drug holiday" arises. Should we consider discontinuing the mAb for a period of time every 6 months, as we did with methysergide? To achieve an effect it may be necessary to discontinue the CGRP antagonist for at least 3 months. This approach may possibly enhance safety, but it may also bring about more antibody-antibody production.

It is prudent for physicians to obtain informed consent. We should strongly encourage active reporting of adverse events. The FDA database for adverse events will be vital in assessing risk. In addition, it may be possible for the companies to coordinate on a combined "CGRP mAb Adverse Event Center." For the planned pregnancy registry, it will be ideal if the 4 companies involved are able to coordinate efforts.

It would be helpful to develop a "CGRP Antagonist Risk Scale."[3] For this scale we would include the issues and conditions raised in this letter. For instance, a 40-year-old patient with mild HTN, and a past history of a gastric ulcer, may present only a slight (theoretical) increased risk. A 60-year-old with CAD and DM, with an active GI ulcer, may be at higher risk. Adolescents are being prescribed the CGRP mAb, which is off-label under age 18. Some older adolescents suffer from frequent severe migraines, refractory to all approaches. For these adolescent patients, it may be reasonable to prescribe the CGRP mAb. However, there are a number of potential problems for younger patients. CGRP is important in bone formation, at least in animal studies. In addition, we do not yet have studies that measure hormone levels. For young people, the most important would be growth hormone, ideally measured before and after administration of the CGRP mAb. There are many other clinical scenarios that may pose an increased theoretical risk. Over time our risk assessment will become much more accurate.

Early clinical use with Aimovig has resulted in a number of patients with moderate or severe fatigue. Several patients have also experienced diffuse muscle or joint pains. The hypothalamic-pituitary-adrenal (HPA) axis may be a culprit, as it is not protected by the blood brain barrier. It will be helpful to have studies assessing hormonal effects, both before and after treatment.

These monoclonal antibodies have been remarkably safe for up to 3 years. Over 10,000 patients have been studied, between the 4 companies. All of the various migraine medications have possible side effects. For many patients the CGRP mAbs may be a safer alternative. The decision whether to use a CGRP mAb includes the patient's clinical headache profile, history of response to headache medications, medical comorbidities, risk versus benefit, and quality of life issues. In 5 years we will know much more about possible long-term adverse effects.

Lawrence Robbins, MD
Robbins Headache Clinic – Neurology,
2610 Lake Cook Road, Suite 160, Riverwoods, IL 60015, USA
email: lrobb98@aol.com

REFERENCES

1. Depre C, Lubomir A, Starling A, et al. A randomized double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina. *Headache*. 2018;58:715-723.
2. Russell F, King R, Smillie S, et al. Calcitonin gene-related peptide: Physiology and pathophysiology. *Physiol Rev*. 2014;94:1099-1142.
3. Robbins L. At stake: The possible long-term side effects of CGRP antagonists. June 2018;1-4. Available at: practicalpainmanagement.com.
4. Iyengar S, Ossipov M, Johnson K. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. *Pain*. 2017;158:543-559.
5. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients-a review of pros and cons. *J Headache Pain*. 2017;18:96. doi: https://doi.org/10.1186/s10194-017-0807-1.
6. He H, Chai J, Zhang S, et al. CGRP may regulate bone metabolism through stimulating osteoblast differentiation and inhibiting osteoclast formation. *Mol Med Rep*. 2016;13:3977-3984.
7. Brain S, Grant A. Vascular actions of calcitonin gene-related peptide and adrenomedullin. *Physiol Rev*. 2014;84:903-934.