Non-Opioids

Volume 21, Issue 3

Utilizing CGRP Antagonists for Non-Migraine Indications

The new class of CGRPs may also benefit patients living with chronic pain from trigeminal neuralgia, temporomandibular disorders, diabetic peripheral neuropathy, chemotherapy-induced neuropathy, and fibromyalgia. A review of the data to date.

CITE THIS ARTICLE
Limerick G, Doshi T. Utilizing CGRP Antagonists for Non-Migraine Indications. Pract Pain Manag. 2021;21(3).

May 5, 2021
Gerard Limerick, MD, PhD
Tina L. Doshi, MD, MHS, Assistant Professor of Pain Medicine

Calcitonin gene-related peptide (CGRP) antagonists have been a welcome addition to the armamentarium of physicians who treat migraine. At present, there are six CGRP antagonists FDA-approved for migraine therapy. These six medications fall into two groups: monoclonal antibodies (mAbs) and gepants.

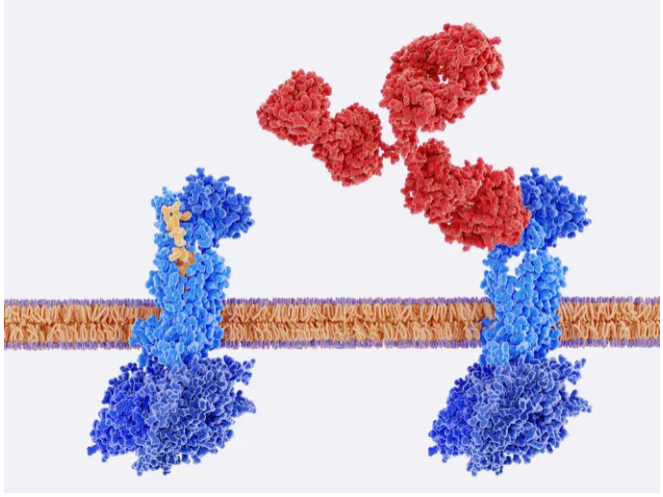
Background: Currently Available CGRP Antagonists for Migraine

The four anti-CGRP monoclonal antibodies are all prophylactic agents. Galcanezumab, fremanezumab, and eptinezumab prevent migraines by directly binding available CGRP molecules to inhibit docking to the CGRP receptor complex, while erenumab binds the CGRP receptor complex, thereby obstructing available CGRP binding sites on the receptor.

The two "-gepants" – rimegepant and ubrogepant – are small molecules that provide relief

from acute migraines by binding the CGRP receptor complex and occupying CGRP docking sites.

While CGRP antagonists act in different ways, the end result is the same: they treat migraine by disrupting CGRP signaling. It is presently thought that migraine formation begins in the central nervous system (CNS), perhaps in the dorsal pons, thalamus, and/or hypothalamus.[1] A wave of activation spreads to the trigeminal ganglion, where CGRP and its receptor are expressed. Bidirectional signaling occurs via second-order neurons between the trigeminovascular afferents thalamic and cortical areas, causing the perception of headache pain.[2] The trigeminal ganglion serves as an amplifier of migraine pain, mediated by persistently active CGRP circuits. Therefore, inhibition of CGRP activity likely suppresses the amplification activity that causes migraine pain.



While CGRP/CGRP receptor expression in the trigeminal ganglion is involved in migraine pathophysiology, CGRP and CGRP receptors have been found in other peripheral and CNS sites involved in pain signaling and may be useful in treating fibromyalgia, trigeminal neuralgia, diabetic peripheral neuropathy, and more. (Image: iStock)

Potential Targets for CGRP Antagonists

While CGRP/CGRP receptor expression in the trigeminal ganglion is involved in migraine pathophysiology, CGRP and CGRP receptors have been found in other peripheral and CNS sites involved in pain signaling, including the striatum, amygdala, hypothalamus, thalamus, and brainstem.[3-9] In particular, thalamic modulation has identified an inhibitory effect of CGRP antagonism on nociceptive signaling.[10] CGRP may also play a role in mediating pain signals from some Aδand C fibers.[11,12] Therefore, it stands to reason that antagonizing CGRP activity could be beneficial in managing pain states other than migraine.

Herein, we review some of the most promising non-migraine indications for CGRP antagonists.

Trigeminal Neuralgia

Trigeminal neuralgia is one of the most common etiologies of facial pain in the elderly population. The condition is characterized by recurrent, severe lancinating pains in the distribution of the trigeminal nerve, triggered by innocuous stimuli such as brushing teeth or talking. Episodes may last anywhere from a few seconds to several minutes.

In the current hypothesis of how trigeminal neuralgia occurs, known as the ignition hypothesis, demyelination of the trigeminal nerve root (typically by microvascular compression) leads to abnormal discharges. This ectopic firing may then lead to amplification of pain signals, such that mild stimuli provoke severe pain.[13] Clinical studies indicate that CGRP signaling may play a role in trigeminal neuralgia. Blood samples taken from 20 patients with trigeminal neuralgia demonstrated significantly elevated levels of CGRP when compared to controls.[14]

In another recent study of 47 patients with trigeminal neuralgia treated with botulinum toxin type A injections to the painful area, plasma concentrations in trigeminal neuralgia patients were higher than in healthy controls. In the patients who responded positively to the injections, there was a significant drop in CGRP blood concentrations, when compared to non-responders.[15]

While the exact mechanism of CGRP in trigeminal neuralgia has not been elucidated, there are animal studies that support these clinical findings. It is important to recognize that most animal studies reporting on trigeminal neuralgia actually use models that more closely resemble trigeminal neuropathy (a separate, but related clinical condition);[16] however, studies of injury to the trigeminal ganglion can still yield important insights about pain mechanisms in both trigeminal neuralgia and neuropathy.

In one animal model study, rats underwent constriction injury of the infraorbital branch of the trigeminal nerve (CCI-ION model) to simulate trigeminal neuralgia. At 14 days after injury, CGRP was found to be elevated in sections of the affected trigeminal ganglion when compared to control rats.[17] These findings also replicated in another study that assessed CGRP levels in CCI-ION rats at 15 days post-injury and found that they were elevated in comparison to control rats.[18] In a third study utilizing CCI-ION rats, administration of MK-8825, a CGRP receptor antagonist, was able to reduce mechanical allodynia.[19]

Practical Takeaway on CGRP for Trigeminal Neuralgia: Collectively, these data support a role for CGRP in the pathophysiology of trigeminal neuralgia and suggest CGRP antagonism as a potential therapy. Currently, a multicenter double-blind, placebo-controlled crossover trial of rimegepant for treatment refractory for trigeminal neuralgia is being led (Biohaven Pharmaceuticals, NCT03941834). A similar study to assess the efficacy and safety of

erenumab in trigeminal neuralgia is underway (Denmark, NCT04054024).

Temporomandibular Disorders

Temporomandibular disorders (TMD) are a family of orofacial pain disorders linked by pain stemming from the temporomandibular joint and/or muscles of mastication. TMD and migraine are well-documented as comorbid disorders,[20-23] and CGRP is also involved in the pathogenesis of TMD. Therefore, it is reasonable to consider that CGRP may be a potential target for TMD treatment.[24-26]

Animal models of TMD often employ complete Freund's adjuvant (CFA), a suspension of desiccated mycobacterium in paraffin oil and mannide monooleate which, when injected, induces inflammation, tissue necrosis, and ulceration.[27] When injected into mouse masseter, it causes significant spontaneous TMD-like orofacial pain behavior, as well as neuronal activation in the trigeminal nucleus. In mice pre-treated with MK-8825, there is a significant reduction in the development of these spontaneous pain behaviors following injection of CFA.[25] These findings have been corroborated in other similar studies.[28]

Additionally, mouse masseter muscle tendon ligation produces a myogenic TMD, which may be augmented by injection of nitroglycerin to induce a migraine-like hypersensitivity. In mouse models that have undergone this injury with subsequent nitroglycerin injection, CGRP levels have been found to be upregulated in the spinal trigeminal nucleus caudalis.[26]

Practical Takeaway on CGRP for Temporomandibular Disorder: Given these animal model data, clinical studies are needed to investigate whether CGRP antagonists may be beneficial in treating TMD in humans.

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is the most common neurologic complication of diabetes, affecting as many as 50% of diabetes patients.[29] While the pathophysiology is not completely understood, it is thought to be the result of some combination of the presence of increased reactive oxygen species, oxidative stress, and mitochondrial dysfunction in peripheral tissues and Schwann cells, which leads to degeneration of peripheral nerve fibers and impairment of the DRG neurons.[30-32] Although not always present in diabetic neuropathy, pain is a common occurrence, typically symmetric in both lower extremities, and frequently described as "burning" or "stabbing."

Lower levels of CGRP have been found in the serum of patients with diabetes[33] but most of the literature examining the role of CGRP in chronic neuropathic pain, including painful diabetic neuropathy, is limited to animal models. Capsaicin has been found to preserve CGRP

in the DRG neurons of diabetic mice.[34] A recently published study found that administering capsaicin to diabetic mice helped preserve nociceptive sensation.[32]

Concordantly, decreased sensation of noxious thermal stimuli has been associated with significant reductions of CGRP in mouse DRG neurons.[35] Thus, it appears that CGRP plays a role in the preservation of nociceptive signaling in peripheral neuropathic pain. Interestingly, in another study, delivering CGRP8-37 (a CGRP antagonist) via a dissolvable microneedle patch provided local analgesic benefit in mouse models of peripheral nerve injury and diabetic neuropathy without disturbing normal nociceptive signaling.[36] This assumption fits with clinical observations that patients being treated with CGRP antagonists do not typically have any alterations in pain sensation.

Practical Takeaway on CGRP for Diabetic Neuropathy: Further work is needed to elucidate the role of CGRP in nociceptive signaling and diabetic neuropathy. However, given the ability of CGRP8-37 to produce localized analgesia in mouse models of diabetic neuropathy while preserving nociceptive signaling, it may be worthwhile to consider clinical trials of CGRP antagonists in treating diabetic peripheral neuropathy.

Chemotherapy-Induced Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer therapy. Chemotherapy agents widely known to cause CIPN include the platinum drugs, taxanes, vinca alkaloids, and bortezomib, and their neurotoxic effects are believed to be mediated by impairing mitochondrial function.[37] Like diabetic neuropathy, CIPN is not always painful, but pain is a frequent occurrence and can often be extremely challenging to treat.

Unsurprisingly, also like diabetic neuropathy, there are conflicts in the literature evaluating the role of CGRP in CIPN. A recent study of neuronal changes in patients with bortezomib-induced painful peripheral neuropathy found that it may be partially due to impaired regeneration of CGRP fibers in the subepidermal layer.[38]

Additionally, in rat models of cisplatin-induced neuropathy and neurogenic bronchoconstriction, there is a decrease in the electrically induced release of CGRP in the trachea fluid, suggesting an association between CGRP alterations and peripheral neuropathy.[39] This data affirms the findings in the aforementioned studies of diabetic peripheral neuropathy that suggest an important role for CGRP in maintaining normal nociceptive signaling.

Flavonoids are molecules that have shown some anti-neuropathic properties. In a recent study, the flavonoid 3-hydroxyflavone (3HF) was found to alleviate nociceptive pain, paw edema, development of tactile and cold allodynia, and hyperalgesia in mice that had been

treated with paclitaxel. A computational analysis of 3HF signaling found that the anti-neuropathic effects of 3HF were at least partially mediated through binding of the CGRP receptor (in addition to binding of the nuclear factor-kappa B and substance P receptors).[40]

Practical Takeaway on CGRP for Chemotherapy-Induced Neuropathy: Although recent evidence is weak, the data do indicate that CGRP signaling may play a role in paclitaxel-induced neuropathy, and that modulation of CGRP signaling pathways could provide benefit in patients with CIPN.

Fibromyalgia

Fibromyalgia is a pain disorder that is notoriously difficult to treat. It is characterized by diffuse hyperalgesia and/or allodynia, fatigue, memory difficulties, psychiatric symptoms, and somatic complaints.[41,42] There are likely multiple underlying derangements in fibromyalgia, but based on most evidence, the core pathology is likely an alteration in central neural processing in nociceptive pathways.[43] Importantly, like migraine, stressors have been linked to the subsequent development of fibromyalgia and similar chronic pain conditions.[44]

While there is very little literature on CGRP in the role of fibromyalgia, this is a point worth noting, as stress-induced hyperalgesia is reduced by spinal blockade of CGRP.[45]

Practical Takeaway on CGRP for Fibromyalgia: CGRP antagonists could potentially help mitigate the diffuse hyperalgesia that is a hallmark of fibromyalgia. Presently, there is a multicenter, randomized, double-blind, placebo-controlled study underway to investigate the efficacy and safety of fremanezumab in patients with fibromyalgia (Teva Pharmaceutical Industries (NCT03965091).

Conclusion and Practical Takeaways

CGRP antagonists have proved to be effective options for the management of migraines. However, given the wide-ranging expression of CGRP, CGRP antagonists may be useful for treating many other pain disorders. An important step toward making this reality is working toward a clearer understanding of the role of CGRP in nociceptive signaling. This would help clinicians better evaluate the safety of utilizing these medications in non-migraine indications and help physicians and patients anticipate possible adverse effects.

In addition, the effective doses for non-migraine pain conditions may be different than those used for migraine, and different CGRP antagonist types may be more or less effective for specific indications. Thus, there is also a need for more clinical trials to provide proof-of-concept, standardize dosing regimens, and identify the most effective therapeutic

mechanisms of action.

Additional Resources

- CGRP Monoclonal Antibodies for Chronic Migraine
- CGRP Monoclonal Antibodies for Chronic Migraine: Year 1 of Clinical Use
- At Stake: The Possible Long-Term Side Effects of CGRP Antagonists
- See also how CGRP inhibitors may compare to ASIC inhibitors and insulin growth factor (IGF) for pain
- Case Chat: Treating Chronic Headache and Migraine with New Agents

Disclosures: Dr. Doshi discloses that she is a volunteer co-investigator for the Biohaven study of rimegepant for trigeminal neuralgia.

SEE OUR REFERENCES

Notes: This article was originally published April 28, 2021 and most recently updated May 5, 2021.