

CGRP Antagonists: The New Headache Frontier

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Introduction

The search for more effective migraine prevention stems from a greater recognition of the crippling impact migraines have on a significant portion of the global population. Migraine is the most prevalent neurologic affliction world-wide; the third most common disease world-wide [1] and the third leading global cause of disability in patients under 50 [2,3]. Yet, most of the 140 million people who suffer from chronic migraines (CM) world-wide do not receive preventive therapy [4]. Fourteen million Americans who could benefit from migraine prophylaxis have not had it suggested to them [5]. The cost of migraines to society is enormous, estimated at \$27 billion dollars in the U.S. annually [6,7].

Current recommendations are to consider preventive therapy with the occurrence of four or more migraines per month, when acute therapy does not confer adequate relief or has contraindication to its use or with overuse, and when quality of life or performance at work or school is hindered by the migraines [8-11]. Other indications for initiating preventive therapy are the characterization as an unusual migraine type occurring at any frequency, such as brainstem aura or hemiplegic migraines and previous migrainous infarction [8-11]. Unfortunately, until recently, available preventive therapy has been inadequate even when delivered optimally. When prophylactic therapy is introduced, greater than 80 percent of patients are non-compliant within a year [12]. Reasons for treatment failure include need for daily dosing, lack of efficacy, safety concerns, intolerance, drug-drug interactions, cost, and the development of Medication Overuse Headaches (MOH) in patients reaching too often for abortive medications in desperation for symptomatic relief.

Fortunately, the headache field is burgeoning with new and more effective options with medications developed specifically for migraine prevention. Also, the burden of migraines is receiving more notoriety, prompting an interest both in treating physicians and in patients to utilize migraine preventive therapies.

The Pathophysiology behind Migraine Prophylaxis

Until the development of CGRP antagonists, no migraine prophylactic agent was developed specifically to treat migraines. Rather, the choices of medications still in use today for migraine prophylaxis were based on the pathophysiologic theories of migraine genesis. The main theories include Chronic Spreading Depression (CSD), changes in Serotonin levels, Neurogenic Inflammation and the Vascular Theory. First described in 1950, CSD, characterized by cortical neuronal activation followed by a suppression of neuronal firing [13], was assumed to be the mechanism behind the migraine aura [14]. Detection of propagated waves of cortical activity, blood flow, metabolism and MRI signal during migraines attacks [15] seemed to mirror clinical symptoms. The flaw in this theory is that many migraineurs do not experience an aura, and those who do have aura do not have an aura with every migraine they develop. Additionally, premonitory symptoms such as confusion and yawning may occur hours before the aura [16] and involve different areas of the brain, such as the brainstem and hypothalamus [17]. Further, some abortive medications end only the aura while others only prevent the headache.

The merit of the other theories has also been debated. The role of 5-HT, a metabolic intermediate in the biosynthesis of the neurotransmitter serotonin, has been debated since the discovery of increased levels of 5-HIAA in urine during a migraine attack [1]. Indeed, the 5-HT based-triptans are the only medications developed specifically for migraine abortive therapy, though the exact mechanism of action is unknown [1]. The hypothesis that neurogenic inflammation in the dura alone initiates a migraine [18] is considered unlikely since multiple drugs known to block dural protein extravasation in animal models of neurogenic inflammation have failed to yield clinical benefit in clinical migraine trials [19].

The vascular theory of migraine genesis as originally proposed has lost favor as well. In 1940, stimulation of dural trigeminal afferents caused headaches in human subjects, giving rise to the notion that dilation of intracranial blood vessels was the initiating event in a migraine attack [20]. More recent studies

have failed to show dilation of cerebral and extracranial arteries during a migraine [1,21]. The current prevailing belief is that cerebral vessels do play a role in triggering migraine attacks but without vasodilation [1]. The story will continue in our discussion of CGRP.

The CSD, serotonin and vascular theories have each fallen out of favor to some degree. Yet, they all contribute to our understanding of the pathophysiology of migraine attacks and have inspired the largely fruitful use of anticonvulsants, antidepressants and antihypertensives which continue to be the mainstays of our migraine prophylactic approach with oral medications today.

This paper will focus on the more recently favored theory of the role of CGRP in migraine genesis and the newer treatments arising from this approach.

CGRP in Migraine

The Calcitonin gene-related peptide (CGRP), which is released from activated trigeminal sensory nerves, is thought to play a major role in the pathophysiology of migraine [22]. Neuropeptide found mostly in C unmyelinated sensory fibers CGRP acts as a potent vasodilator by decreasing intracellular concentration of free calcium ion concentration [18] which results in cell relaxation [4]. Significant quantities of neuropeptide, including CGRP, released from Trigeminal Ganglion (TG) neurons that innervate cranial vessels [24] are thought to precipitate the facial pain associated with migraine attacks [25]. Not only do the CGRP-containing nerves project from the TG to the dura, but CGRP receptors are also found at various sites involved in migraines, including the cortex, the thalamus, vagus nuclei and the dorsal root ganglia [26]. The intracranial effects of CGRP blockade that contribute to migraine prevention seem to be due to inhibition of CGRP release in the meninges which mediates vasodilation, neurogenic inflammation [27,28] and meningeal nociception [29-32]. Additionally, the projection of TG nerves expressing CGRP and CGRP receptors outside the blood-brain barrier facilitate feedback between the sensory and parasympathetic systems [33].

The blood vessel provides an endothelial cell-dependent signaling pathway for communication between the vasculature and the trigeminal nerves which occurs without obligatory change in vascular tone [1,34]. Additionally, the release of CGRP by endothelial cells may precipitate cortical neuronal excitability [35].

Clinical evidence for the role of CGRP in migraines has come from studies demonstrating that CGRP levels rise during a migraine and fall after resolution of migraine symptoms [36]. Further, CGRP levels rise in response to stimulation of the TG [37] and migraine attacks are triggered in patients infused with CGRP [36]. In fact, it has been shown that triptans abort migraines and Onabotulinumtoxin A prevents CM at least in part by preventing the release of CGRP [38-40]. Further, CGRP levels peak in people under age 40 and decline with age [41], mirror-

ing the demographics of migraineurs.

The TG does not have a blood-brain barrier, making it accessible to more molecules [42] and a potential site for therapeutic intervention. As Onabotulinumtoxin A does not cross the blood-brain-barrier, it is thought to prevent chronic migraine by blocking CGRP release from peripheral C fibers [39,40]. In 2018, three monoclonal antibodies (MABs) that either block CGRP or the CGRP receptor were approved by the FDA. These MABs are large molecules that, like Onabotulinumtoxin A, cannot cross the blood brain barrier [43]. As compared to natural antibodies that seek out and destroy foreign pathogens, therapeutic MABs can alter cell function without destroying it [44].

The CGRP Monoclonal Antibodies

Three monoclonal antibodies that act as CGRP antagonists for the prevention of both episodic (EM) and chronic migraines were approved by the FDA in 2018: Erenumab (Aimovig), Fremanezumab (Ajovy) and Galcanezumab (Emgality). These biologics are the first medications developed specifically to prevent migraine headaches. Their design was based on the recent advances in our understanding of migraine pathophysiology. Two block the CGRP ligand (Fremanezumab and Galcanezumab) and one blocks the CGRP receptor (Erenumab), theoretically neutralizing the action of CGRP released by perivascular TG sensory nerve fibers [22]. Data for EM and CM in all 3 MABs show a reduction of mean monthly migraine (MMDs) of 1-3 days compared to placebo, similar to data for Onabotulinumtoxin A in CM [45]. The profile of these three medications already on the market are quite similar, with rapid onset of action, minimal side effects, ability to initiate at therapeutic doses without a ramp up, and parenteral administration monthly via self-administered subcutaneous injection. All of these attributes will likely increase patient compliance. The responder rate is far greater than any oral prophylactic medications available, with previous preventives averaging a 50 percent responder rates and the anti-CGRP therapies achieving over 75 percent responder rates [8]. To date, there has been no direct comparison of the efficacy of Onabotulinumtoxin A with that of the MAB to the CGRP ligand or receptor. The roles these different methods of CGRP blockade will play will differ as the anti-CGRP therapies have been approved for the treatment of both EM and CM while Onabotulinumtoxin A has an indication only for CM. All three subcutaneous MABs to the CGRP ligand or CGRP receptor prevent EM, CM and MOH. All three decrease acute migraine abortive use, including triptans, and show an improvement in patient-reported disability and treatment satisfaction. All three promote conversion of CM to EM.

The ease of administration and rapid onset of action of these MABs is beneficial in several respects. These MABs have a serum half-life of 20-50 days [33], allowing for once a month or quarterly injections, which translates to increased patient compliance over oral prophylactic medications. Second, the parenteral delivery route bypasses the issue of decreased gastrointestinal absorption that often accompanies migraine, re-

sulting in greater bioavailability than the oral agents. As with most subcutaneous injections, the bioavailability of the CGRP antagonists ranges 40-74% [46,47]. While all oral preventive medications in use require up to three months to attain therapeutic doses and maximal efficacy and Onabotulinumtoxin A requires at least three cycles or 6 months to demonstrate benefit, all three antibodies show superior effect as compared to placebo in one week and meaningful migraine reduction within one month [43].

The safety profile of all three anti-CGRP/CGRP receptor MABs is close to placebo. All three MABs have injection site reactions, and Erenumab at the 140 mg dose has been associated with increased constipation as compared to placebo. As CGRP is involved in maintaining homeostasis in the cardiovascular system, glomerular filtration [48], bone metabolism [49] and the gastrointestinal mucosa [50], there needs to be close monitoring of reports of adverse effects. One particular concern is whether the chronic blockade of CGRP, a potent vasodilatory agent, results in hypertension and cardiac dysfunction [51,52] and impedes its safeguard action in the face of cardiac and cerebral ischemia. The Erenumab Angina Study performed Exercise Tolerance Tests on patients receiving Erenumab 140 mg or placebo; there was no change from baseline in exercise duration, time to onset of ST-segment depression, and time to onset of exercise induced angina, interpreted as a likelihood of 97.6% safety [53]. Only a low percentage of patients using these CGRP antagonists develop antidrug Ab (1-18%) [4], which may explain why no immunoallergic hypersensitivity reactions have been seen [54]. The significance of the antidrug Ab remains unclear, and longitudinal monitoring will be necessary to determine if they reduce therapeutic effectiveness. One possible explanation for why there have been no serious immune-mediated adverse interactions is that all three of these MABs are either partially or fully humanized MABs with few to no non-human amino acids. Also, because these MABs are eliminated by the reticuloendothelial system and not metabolized by the liver or the kidney, there are fewer potential drug-drug interactions, and, therefore, may be used safely in conjunction with other oral or injectable migraine prophylactic agents [37]. Further, without the breakdown into peptides and amino acids, no toxic metabolites are produced [44].

The differences between Erenumab, Fremanezumab and Galcanezumab are largely in terms of dosages and intervals of administration. Erenumab has been shown to work equally well in CM sufferers who have and who do not have concomitant MOH [4] as compared to Topamax which did not perform as well in patients with migraine plus MOH [43]. Erenumab may resolve medication overuse in CM sufferers [4]. Galcanezumab is the only anti-CGRP therapy with an indication for episodic cluster.

Erenumab (Aimovig) is highly selective for the CGRP receptor complex. This is important because theoretically a less selective drug might be more likely to cause adverse side effects [55]. The medication was evaluated in patients who had failed two or more prophylactic agents [43], and proved to be beneficial in

the more refractory migraine sufferers. It is the only one of the three MABs that is fully humanized [55]. It is administered in one or two 70 mg doses monthly via an autoinjector [56]. There has been demonstrated increased efficacy of a 140 mg dose over a 70 mg dose, with a 10.5 day decrease in headache at 52 weeks with the 140 mg dose and a -8.5 day decrease in headache at 52 weeks with the 70 mg dose as compared to baseline [57]. At week 64 of the Open Label Extension (OLE) trial for EM, as compared to placebo, 65% of patients experienced a 50% or greater reduction in headache days, 42% experienced a 75% or greater reduction in headache days, and 26% experienced a 100% reduction in headache days [3]. In the pivotal trial of Erenumab use in CM, at one year in the OLE, there was a reduction of 10.5 migraines per month which translates to a 4 month drop in migraines per year [58]. The most frequent adverse side effects were injection site reactions and constipation [59]. Long-term safety data is complete in CM after one year of open-label treatment and long-term safety data in EM over three years is ongoing. At the time of publication, there had been one fatality attributed to arteriosclerosis in a patient with a history of hypertension and left anterior hemiblock on EKG; based on autopsy findings, this death was deemed not related to the investigational drug by the investigator.

Fremanezumab (Ajovy) is a 95% fully humanized MAB (remainder 5% is murine) which binds to the CGRP ligand. This medication was also studied in migraine patients who had had previous medication failure. It is administered either monthly via a pre-filled 225 mg syringe or quarterly with the injection of three syringes (total 675 mg). This flexibility may be desirable in treating a needle-phobic or a non-compliant patient whose quarterly injections can be more conveniently administered in the physician's office. In a placebo-controlled add-on trial of EM and CM, when Fremanezumab was used in combination with other migraine prophylactic agents, such as anticonvulsants, antidepressants and beta blockers, a close 50% reduction in the number of headache days was demonstrated [60]. In an OLE trial, the Migraine Disability Assessment scale (MIDAS) scores continued to drop in the monthly injection group over 6 months [61]. The most common adverse reaction was injection site reactions.

Galcanezumab (Emgality), a 90% fully humanized MAB (remainder 10% is murine) which blocks the CGRP ligand MAB. Like the other two MAB, it has an indication for EM and CM, but it is the only one of the three MAB indicated for episodic (not chronic) cluster headaches. (EVOLVE trial) There is a loading dose of two 120 mg injections followed by monthly single 120 mg subcutaneous injections.

There remain many unanswered questions regarding the use of these anti-CGRP therapies for the prevention of EM and CM. First, practitioners are anxious to learn if these MABs can be safely combined with Onabotulinumtoxin A injections. While both work via the CGRP pathway, they have distinct mechanisms of actions which many believe will result in a beneficial synergism. Not surprising, insurance coverage may drive how

these drugs fit into our treatment paradigm. Given the safety and efficacy of the anti-CGRP and anti-CGRP receptor antibodies, they could be used as first-line treatment. However, they are expensive, and many insurance companies are requiring documentation of treatment failure of two or three oral prophylactic agents before approving the MABs. Further, some insurance companies will not approve this therapy for four months after the last set of Onabotulinumtoxin A injections. Such a hurdle will likely result in the patient returning to a baseline of increased headache frequency before making the switch. There is increased burden on the practitioner as more staff effort is required to obtain pre-approval. Other outstanding issues include the appropriate interval to wait when switching between the MABs, the safety of these drugs during pregnancy and lactation, and the recommendations for how long to stay off these MABs when planning to conceive.

Conclusion

The significant headache reduction and improved quality of life afforded to many of the patients treated with the anti-CGRP ligand and anti-CGRP receptor MABs is heretofore unprecedented. Additionally, there are other promising agents on the horizon, including the intravenous anti-CGRP MAB Eptinezumab and the gepants. With greater numbers of patients treated with these agents, we will learn more about their long-term safety, the individuation between the available therapeutic MAB's, and the feasibility of combining them with established treatment modalities such as Onabotulinumtoxin A and the soon-to-be released gepant group of medications.

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