**CGRP INHIBITORS(MABS): A NEW CLASS FOR MIGRAINE PREVENTION**

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 **Calcitonin Gene-Related Peptide(CGRP) is a vasoactive peptide. It is part of the “inflammatory soup” that is involved in dilation of cerebral and dural blood vessels. CGRP is widely distributed throughout the body. CGRP levels in serum are increased during migraine or cluster headache. Triptans partly work on migraine via modulation of CGRP.**

 **Four companies have developed CGRP antagonists that are large molecule monoclonal antibodies(mAbs). MAbs have been used for a number of conditions. They work both indirectly, by activating host immune systems, and directly by binding to ligands or receptors. The migraine mAbs are subclasses of IgG. MAbs have very little potential for drug-drug interactions, as they are metabolized thru the reticuloendothelial system. MAbs are unlikely to cause liver or kidney irritations. MAbs should not be confused with the CGRP meds called “gepants”, which are small molecule drugs being developed as migraine abortives. Gepants are metabolized thru the liver.**

 **After injection, mAbs are distributed in many tissues. The highest concentrations are in lung, kidneys, heart and spleen; very little crosses into the brain.**

 **There are 4 mAbs: erenumab(Amgen/Novartis), fremanezumab(Teva), galcanezumab(Lilly), and eptinezumab(Alder). All have been successful in Phase 3 studies. Erenumab is a receptor antagonist(unique among these), with a half-life of 21 days, to be given SQ once per month(at home). Fremanezumab is a ligand antagonist, with a half-life of 45 days, to be given SQ every month, or every quarter. Galcanezumab is a ligand antagonist, with a half-life of 25 to 30 days, to be given SQ every month. Eptinezumab is a ligand antagonist, with a half-life of 32 days, to be given IV every quarter.**

 **The mAbs will have indications for chronic migraine, and/or episodic migraine. One or two may have a cluster indication, and for post-traumatic headache as well.**

 **The phase 3 results for all 4 mAbs have yielded similar results. Many patients saw their migraine days decrease by 2 to 5 per month. For up to 1/3 of patients, headaches improve 75% or more. A smaller minority (20% in the intravenous trial) experienced almost 100% improvement. There are similarities between these mAb results, and those achieved by the administration of Botox for migraine. Many patients will have little (or very modest) relief, while others may see their headaches drastically reduced.**

 **Migraine preventive medications often lose effectiveness over time. We do not know if this will occur with mAbs. Botox has been surprising in this regard; most patients who find Botox to be helpful do not experience a significant decline in efficacy. Hopefully mAbs will yield similar sustained benefits.**

 **Side effects have been minimal, for the short-term. Outside of local injection reactions, the mAbs have been surprisingly well tolerated. No cardiovascular or liver concerns have been raised. For the long-term, we are particularly worried about cardiovascular risk. CGRP plays a role in cardiovascular homeostasis during ischemic events. It has vasodilatory effects, and is important in the regulation of blood pressure. CGRP also is involved in wound healing; blocking it could, in theory, interfere. While the mAbs do not cross the blood brain barrier(BBB), the pituitary gland lies outside of the BBB. CGRP and it’s receptor are found in the anterior pituitary. CGRP is also present in the GI tract. In theory, blocking CGRP could contribute to inflammatory bowel disease. CGRP also plays a role in GI motility.**

 **Because we do not know long-term effects, I will be cautious in prescribing. I will have patients do a “drug holiday”, with time off. Patients will be screened for cardiovascular risk. We will require informed consent.**

 **Many migraineurs experience declining efficacy to preventives over time. One notable exception has been with Botox. While some do exhibit tolerance to Botox, more patients see a long-term reduction in their headaches. Time will tell as to the long-term efficacy of the mAbs.**

 **Cost and insurance will be one of the barriers to prescribing CGRP. Since Botox is FDA indicated for chronic migraine, it is possible that some insurers may require the use of Botox as one step, prior to prescribing the CGRP drugs. The fact that these require either SQ or IV administration will present some barrier to use.**

 **Over time, the patients who have an excellent response to the mAbs will continue for the long-term. This may be only 20% of patients, but for those migraineurs, the mAbs will be life changing. As our current preventives have limited efficacy, and carry significant side effects, the mAbs provide hope for many migraine sufferers.**