A Migraine Revolution!

Understanding the new migraine therapies

There is currently occurring nothing short of a revolution in migraine therapeutics. Little had emerged in the way of new migraine medications since onabotulinumtoxinA (Botox) became available for the treatment of chronic migraine in 2010. Suddenly, starting with the appearance of erenumab (Aimovig) in May 2018, new therapies for migraine prevention and acute migraine treatment have been dropping in our laps like eggs from an especially ambitious hen.

What with their number, variety, and often unpronounceable names, even a headache subspecialist can have difficulty keeping all these newcomers straight. What follows is a simple overview intended to give you some idea of the new migraine therapies already available for general clinical use and those likely to soon become available.

Mabs, Gepants and Ditans

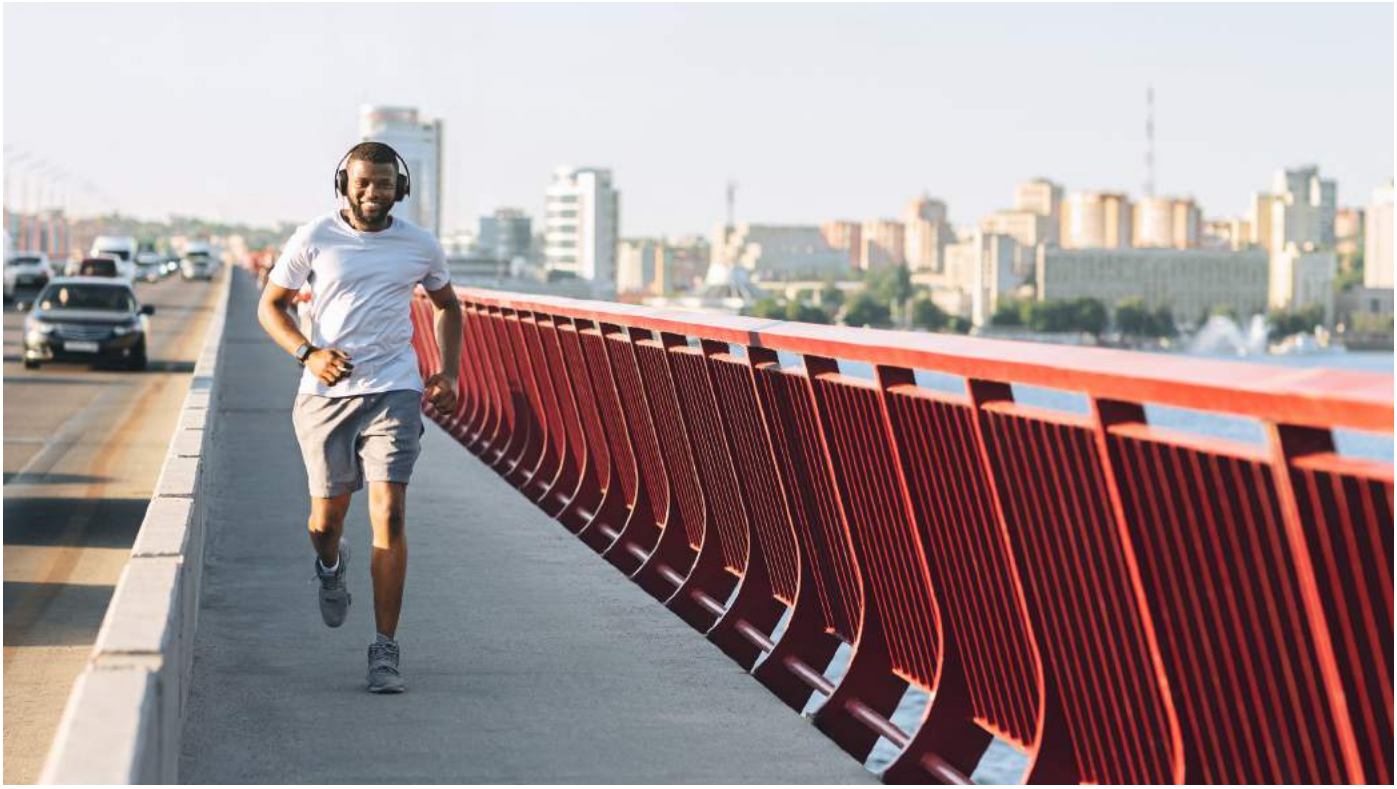
THE AVAILABLE ANTI-CGRP MONOCLONAL ANTIBODIES ("MABS")

Migraine is generated by a circuit that relies on naturally occurring proteins as well as electricity for transmission of a head pain signal circuit. Calcitonin gene-related peptide (CGRP) is one of those proteins, and its activity appears to be critical to producing migraine headache. It follows that inactivating or blocking CGRP would "short-circuit the circuit", calming down that biologically sensitized circuit and resulting in headache reduction.

The anti-CGRP monoclonal antibodies (Mabs) are human or "humanized" proteins that are too large to pass from the bloodstream into the brain easily and thus may exert their primary action in migraine within the meninges, the covering of the brain, where head pain receptors are located. Four Mabs are now available for prevention of headache in patients with episodic or chronic migraine: **erenumab** (Aimovig), **galcanezumab** (Emgality), **fremanezumab** (Ajovy) and **epitenzumab** (Vyepti).

Three of these therapies appear to exert their anti-migraine effect by acting upon CGRP, their mechanisms of action differ slightly. Erenumab blocks the receptor in the migraine circuitry which CGRP is attempting to activate, and the other 3 Mabs attach directly to the CGRP molecule to render it ineffective.

All three are administered via subcutaneous (under the skin) self-injection, which most patients find easy to manage. Injections are administered every month; in the case of Ajovy, there is the option of administration every three months. Epitenzumab is administered intravenously (IV) every three months in a facility that is set up to administer IV medications. The clinical trials which earned each of these Mabs its FDA approval demonstrated more or less identical results when the Mab involved was



compared to placebo (a "dummy solution"). Lacking any results from studies comparing one Mab to another, at this point, it's impossible to make any claim for which one is "best." In the clinical trials, all the Mabs appeared to be safe and extremely well-tolerated. At the higher of the two doses available for erenumab (140 mg versus 70 mg), however, a small percentage of patients may experience constipation which in rare cases can have severe clinical consequences. There are warnings about constipation in the US erenumab prescribing information and the European Union galcanezumab prescribing information, implying that this side effect could occur with all of these Mabs. These are new therapies, and it's consequently impossible to make any absolute claims about their long-term safety. Given what we know about these antibodies—their chemical structure and metabolism—along with results from safety studies extending out for up to five years, there is no compelling reason to anticipate that issues related to long-term safety will emerge.

All three reduce headache burden by at least 50% in a reasonably high percentage of patients with either episodic or chronic migraine, and headache reduction may occur as early as two weeks following the first treatment. There is evidence that higher and higher number of people will obtain 75% or greater reduction of migraine days with longer treatment periods, with up to five years now reported. This provides more encouragement to stay with treatment and give it a chance to work.

As discussed previously, **epitenzumab** is administered intravenously, and its onset of therapeutic action is so rapid that it is being tested as a therapy for acute, severe migraine headache even while it already has been approved for migraine prevention. If epitenzumab is highly effective for acute migraine, it conceivably could come to serve as the treatment of choice for patients presenting to an ER or urgent care center for management of severe headache. Along with its fast onset, epitenzumab has an extended therapeutic effect.

THE GEPANTS

As with erenumab, gepants block the CGRP receptor within the migraine circuitry, but they are smaller than the Mabs and thus are able to pass from the bloodstream into the brain itself. **Ubrogepant** (Ubrevly) recently was approved by the FDA for the acute treatment of migraine and is now available for general clinical use. It comes in tablet form, and unlike the triptans its label includes no precautions regarding the possibility of the drug causing heart attack, stroke

or other vascular complications. Ubrogepant may represent a particularly attractive acute treatment option for migraine patients felt to be at high risk for vascular complications, for patients who have tolerated the triptans poorly and for patients for whom the triptans have been ineffective.

On February 27, **rimegepant**, (Nurtec), another orally administered gepant, received FDA approval for acute migraine treatment is available in pharmacies as an oral disintegrating tablet (ODT) formulation. Rimegepant currently is indicated only for acute migraine treatment, but because of its extended duration of action it also is being studied for its usefulness in migraine prevention.

Atogepant, an orally administered Gepant which in clinical trials as demonstrated safety, tolerability and effectiveness as a prevention therapy for both episodic and chronic migraine. Unlike the 3 subcutaneously self-administered Mabs currently available (administered monthly) and epitenzumab (administered every 3 months), atogepant will need to be taken on a daily basis.

For a month or two, If history holds, these new therapies should enable yet more migraineurs to "to live well despite migraine."

Finally, there is ongoing research involving an intranasally administered gepant, **vazegepant**, for acute migraine treatment.

THE DITANS

Serotonin (5-HT; 5-hydroxytryptamine) plays a significant role in the migraine circuitry, and medications that mimic serotonin at certain of its receptors are effective in blocking the transmission of a head pain signal. The triptans and ergotamines can accomplish this by acting at the 5-HT1D receptor. Still, they also are active at the 1B receptor, which promotes blood vessel constriction. Hence the warning that the triptans are at least relatively contraindicated for patients at risk for heart attack, stroke, or other vascular complications.

In reality, there is very little evidence that the triptans pose a significant risk of causing vascular complications in any patient, including those who have symptomatic cardiovascular disease, cerebrovascular disease, or an unfavorable atherosclerotic risk profile. Be that as it may, fearing a vascular complication, medical providers remain hesitant to prescribe triptans for many of their migraine patients.

As with the 1D receptor, stimulation of the 5-HT 1F receptor blocks transmission affecting the signal and does so without causing any vascular blood vessel constriction. In October of last year, the FDA approved **lasmiditan** (Reyvow), a medication active at the 5-HT 1F, and lacking affinity for the 1B receptor. As with ubrogepant mentioned previously, lasmiditan

represents an excellent option for migraineurs who are not felt to be good candidates for triptan therapy or have had difficulty tolerating the triptans. Whether lasmiditan will prove to be useful for patients who have failed to respond to the triptans is as yet unknown. Use of lasmiditan for acute migraine headache may cause dizziness, sedation or both.

An Embarrassment of Riches?

Erenumab, galcanezumab, fremanezumab, epitenzumab, ubrogepant, atogepant, rimegepant, vazegepant, and lasmiditan: nine new medications for migraine, seven of which are already available, one recently FDA-approved and soon to appear in pharmacies and atogepant anticipated to become available for general clinical use later in 2020. Such rapid emergence of multiple new therapies is without precedent in modern medicine. But what does it mean for you, the individual migraineur?

If you are well-satisfied with your current degree of migraine control, then these breakthroughs may be interesting but not particularly relevant to your needs. If you are having migraine episodes infrequently and can terminate those episodes rapidly and without significant side effects using your current acute treatment regimen, then newer his not necessarily better.

On the other hand, recently published data from the CaMEO Study indicate that a majority of migraineurs are not satisfied with their current degree of migraine control. If you are within that majority, it may be time to explore these new options with a knowledgeable medical provider.

To take a broader view, how effective will these new therapies prove to be in reducing the massive public health burden imposed by migraine? Will their emergence attract more attention to migraine as being a common and treatable medical disorder, in turn compelling more citizens to seek and receive enlightened medical care for their migraine? Or will these new therapies simply increase the cost of treating migraine without significantly reducing the emotional and financial toll the disorder exacts?

The author of this article has no crystal ball. Still, all involved in the field understand it is merely the nature of medicine - and science generally - that each new answer leads to yet more questions and that rarely does any one therapy or group of therapies represent the final answer to treating a physical disorder...especially a disorder as common as migraine.

That said, 30 years ago the author participated in the first American research study investigating the experimental drug that became injectable sumatriptan (Imitrex), observed firsthand the near-magical affect its administration produced in his research patients and over the ensuing years watched as migraine emerged from its shadowy nook to take its place in the spotlight of clinical medicine and research. If history holds, these new therapies should enable yet more migraineurs to "to live well despite migraine."