After the Revolution

What Do We Know? What Do We Not Know?

How have the new migraine therapies performed?

In the Winter 2020 issue of this magazine we described the revolution in migraine therapeutics resulting from the advent of three new therapies for acute migraine treatment and four for migraine prevention. The first of these, erenumab (Aimovig), became available for general clinical use in May 2018, and the last, rimegepant (Nurtec), in March 2020 of this year.

How has this unprecedented bounty affected migraine's therapeutic landscape? What have we learned from implementation of these new therapies, and what still remains unclear?

Well, first and foremost we have learned once again that in the setting of migraine treatment it's best not to pitch one's expectations too high. These therapies have not eradicated migraine nor removed migraine's ability to erode quality of life. None is a "magic bullet". Each appears to have its niche, but none is a "one size fits all" therapy.

That said, let's begin by reviewing the most important observations that have arisen from large-scale clinical use of the new therapies.

How do the new medications for acute migraine treatment stack up against one another, the triptans and other competitors?

Rimegepant (*Nurtec*), ubrogepant (*Ubrelvy*) and lasmiditan (*Reyvow*) all possess a primary mechanism of action for migraine treatment which differs from that of the triptans. For patients who have not responded to the triptans or have found the triptans difficult to tolerate and in the subpopulation of migraine patients for whom the triptans are contraindicated (typically individuals considered to be at high risk for cardiovascular or cerebrovascular complications potentially resulting from triptan-related constriction of arteries), all three of these newcomers represent safe and attractive options.

1. Safety issues aside, in regards to these newcomers, the triptans or other symptomatic medications intended for acute migraine treatment, it is impossible to claim with any degree of certainty that one therapy is superior to another. We lack data from well-conducted clinical research studies pitting one active therapy against another, and neither promotional materials from pharmaceutical companies nor anecdotal reports from healthcare providers can substitute for such data.

2. Suffice it to say that clinical experience to date with the three new acute migraine treatments seems to parallel what we observed as one new oral triptan followed another into clinical practice: some patients will respond beautifully to all three, some will prefer one over the other and some will find all three essentially useless.

i. Ubrogepant and rimigepant have a similar mechanism of action which is quite distinct from that of lasmiditan. Does failure to respond to ubrogepant predict failure to respond to rimigepant, and vice versa? Again, there are no meaningful data to assist in answering this question, but from clinical practice it seems clear that some patients will report a positive experience with one after having not done well with the other.

ii. We know from clinical trials that lasmiditan can cause dizziness and - more problematic consequent to the cautionary warning related to driving - sedation. These side effects are a major problem for some patients and non-existent for others. Regardless, *all patients new to the drug should be aware of these potential side effects*.

3. Consistent with their performance in the clinical research trials which earned the three newcomers their FDA approvals, all three appear safe and are usually well-tolerated. Even so, not all patients find these medications easy to take. Some patients will report a variety of unpleasant symptoms that they consider to be side effects of the relevant drug, and in some cases those symptoms will not duplicate what was reported from the clinical research trials.

How do the new medications for migraine prevention stack up against their competitors?

Erenumab (*Aimovig*), galcanezumab (*Emgality*), fremanezumab (*Ajovy*) and eptinezumab (*Vyepti*) all are anti-CGRP monoclonal antibodies ("Mabs") which act to disable or block calcitonin gene related peptide, a protein that plays a major role in the nervous system circuitry which generates migraine headache. The first three are injected by the patient subcutaneously (under the skin) via autoinjectors which are similar to an epinephrine pen; for fremanezumab there is the option of injecting every three months rather than monthly.

Epitenzumab is administered intravenously every three months for migraine prevention, and because it was the last of the four to become available for general clinical use and did so as the pandemic was developing, there has been too little use of the drug to offer any meaningful observations.

1. All three of the self-injected anti-CGRP Mabs possess a solid evidence base for use as prevention therapy in both episodic migraine and chronic migraine. In regards to the prevention/suppression of chronic migraine, the same claim can be made for only two other therapies: topiramate and onabotulinumtoxinA. For chronic migraine patients who fail to respond to those therapies or find them difficult to tolerate, any of the three self-injected Mabs represents an attractive option.

2. Are these anti-CGRP Mabs "better" than their competitors for treating patients with episodic or chronic migraine? Is any one of the Mabs superior to the other two? Again, as with the new oral medications for acute migraine treatment, we simply do not have the data available to support a clear answer. About the best that can be said is that all 3 offer the convenience of once-monthly dosing rather than the daily dosing required of all oral medications commonly used for migraine prevention. In addition, both from the placebo-controlled clinical trials that earned them their FDA indications and from subsequent clinical practice, all three tend to be well-tolerated, and judging from their performance in those trials and now in clinical practice, no one of the three has emerged to rank as being "the best".

3. Galcanezumab and fremanezumab act to disable CGRP by attacking that protein directly, whereas erenumab acts by preventing CGRP from "docking" with its receptor in the migraine circuitry. Given this difference, should patients who fail to respond to galcanezumab or fremanezumab try erenumab, or vice versa? While very preliminary data suggest that at least some patients who fail either erenumab or galcanezumab may experience a positive treatment response when switched from one medication to the other, there is simply not sufficient evidence to recommend that such management be incorporated into routine clinical practice.

4. When erenumab first became available for general clinical use, many clinicians chose to prescribe the new medication as "add-on therapy" for chronic migraine patients who had experienced a partial positive response to serial onabotulinumtoxinA injection therapy but whose response appeared to have "plateaued". When galcanezumab and fremanezumab became available,

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each was used in the same manner. Are onabotulinumtoxinA and the Mabs synergistic in suppressing chronic migraine (i.e., work better when administered together than when used independent of one another)? or are we simply wasting time and money by simultaneous use of two therapies which appear to exert their effect at approximately the same location within the migraine circuitry? While simultaneous treatment with the onabotulinumtoxinA and a Mab is not producing reports which would give rise to safety concerns, the effectiveness of such treatment remains unproven.

5. In regards to tolerability, the same can be said for the anti-CGRP Mabs as was said for the new oral medications used to treat acute migraine headache: consistent with their performance in the clinical trials which earned the three self-injected Mabs their FDA approvals, all three appear safe and generally well-tolerated. This is not to say that all patients will be comfortable with these the Mabs even when they are effective in substantially reducing headache burden. The constipation which was reported by patients in clinical trials involving the higher of the two doses of erenumab (140 mg) also may be reported by patients receiving the lower dose (70 mg) or either of the other two Mabs. The constipation associated with the anti-CGRP Mabs may be severe and even clinically serious.

Some patients will report other unpleasant symptoms that they consider to be Mab side effects, and in many cases this will involve symptoms not reported by patients who participated in the clinical research trials.

With more data provided from ongoing and future clinical trials and with yet more clinical experience, many of the uncertainties listed here will be put to rest. Other questions may never be answered, and, inevitably, new questions will arise. Such is the nature of science.

So how should we rate the impact of this recent migraine revolution? Perhaps it would be most realistic to assess that impact from the glass half-full perspective: while migraine remains a major detriment to public health and a chronic drain on quality of life for millions of migraineurs, progress has been made. A minority of patients have been super-responders to one or more of the new therapies, and every day in a busy clinic headache subspecialists hear patients refer to these therapies as "life-changing" or "miraculous". A second group may not have experienced the same dramatic improvement but nevertheless report a welcome reduction in headache burden. It is the third group, that sizable proportion of migraineurs who have tried and failed the new therapies, who will stimulate research investigators to ignite yet another "migraine revolution".