What's New in Migraine Research?

Highlights from the recent AAN meeting

Highlights from the American Academy of Neurology annual scientific meeting

The annual scientific meeting of the American Academy of Neurology (AAN) ended on April 22, and as is typical of that huge and prestigious meeting a torrent of new information was presented. Since the advent of the Triptan Era 30 years ago, the headache section of the AAN meeting has assumed progressively greater importance, and this year was no exception. There were presented the results from a number of interesting research studies related to migraine, and a sampling of those with particular relevance for this magazine's readership are described below.

Another new treatment for migraine prevention

If migraine is thought to result from a genetically hypersensitive biologic circuit within the nervous system, and if the conduction of head pain signal within that circuit results from electrochemical transmission, the two most important "chemicals" in the circuit are the proteins serotonin and calcitonin gene related peptide (CGRP).

The triptans, sumatriptan/Imitrex being the prototype, exert their therapeutic effect by stimulating receptors to serotonin located within the migraine circuitry. The long search for a therapy which would block the action of CGRP culminated in the emergence of erenumab (Aimovig) in May 2018. Erenumab/Aimovig is a "designer drug" for migraine prevention, an anti-CGRP monoclonal antibody that blocks the receptor to CGRP in the migraine circuit and is self-injected subcutaneously (under the skin) once-monthly.

The arrival of erenumab/Aimovig rapidly was followed by the addition of two more subcutaneously self- injected anti-CGRP monoclonal antibodies and one that is infused intravenously every three months. All are indicated for migraine prevention. In addition to these "Mabs" (monoclonal antibodies), two anti-CGRP "gepants" are available for clinical use: rimegepant

(Nurtec) and ubrogepant (Ubrelvy). These "gepants" are smaller molecule medications than the Mabs and may be administered orally. Both currently are indicated only for acute migraine treatment.

This soon may change. An experimental "gepant", atogepant, is under investigation for its safety, tolerability and effectiveness as an oral medication for migraine prevention, and the results of a large-scale clinical research trial evaluating atogepant for prevention of episodic migraine were presented at the AAN meeting. This oral medication administered on a daily basis was significantly more effective than placebo in reducing monthly migraine days. A similar trial evaluating atogepant for the suppression of chronic migraine is currently in progress.

If atogepant receives FDA approval, migraineurs who require prevention therapy will have an oral alternative to the injectable monoclonal antibodies for blocking the action of CGRP and thus preventing migraine.

Acute treatment, preventive treatment or both?

Clinical investigators involved in migraine research long have asked: what makes one therapy a prevention therapy and another therapy for acute headache treatment only? Certain medications in fact may be effective for both purposes, and rimegepant (Nurtec) may be one of those medications.

At present rimegepant (Nurtec) is indicated for the acute treatment of migraine only. The clinical research trials that earned rimegepant its FDA indication for acute migraine treatment were followed by a more extended trial investigating the drug's long-term safety and effectiveness. Regarding effectiveness, the investigators were concerned primarily with the question of whether rimegepant would continue to treat acute migraine episodes in a satisfactory manner when taken over an extended period. Interestingly, the study not only demonstrated that rimegepant was safe and that it retained its effectiveness with repeated use; it also demonstrated that migraineurs participating in the study who consistently used rimegepant for their acute migraine headache s experienced a progressive reduction in the frequency of migraine episodes.

Clinicians and clinical scientists long have suspected that aggressive and effective acute migraine treatment might exert a prophylactic effect. In other words, not only does the acute treatment help the headache that you are currently having; it also may reduce the likelihood of your having another migraine headache within the coming days, weeks or even months.

Because this appeared to be happening with rimegepant, scientists involved with its development decided to conduct a prospective and large-scale study investigating the medication as a migraine prevention therapy. Results of that study were presented at the AAN meeting, and they indicated that in patients with episodic migraine rimegepant taken every other day was significantly more effective than placebo in reducing monthly migraine days. If the FDA approves rimegepant (Nurtec) for migraine prevention, it will become the first medication with a dual indication: acute migraine treatment *and* migraine prevention.

Coming from a somewhat different direction but along the same line, in the clinical research which earned intravenously administered epitenzumab (Vyepti) its indication for migraine prevention, the investigators involved noted that patients receiving epitenzumab were more likely to exhibit an early response to treatment than were patients randomized to receive placebo. This difference was evident as early as the first 24 hours following initiation of the initial infusion and was yet more pronounced by 1 week.

> **Expanding the herapeutic horizon**

In contrast to the situation with rimegepant, where the results of an acute treatment trial led to a migraine prevention trial, the epitenzumab investigators decided to follow their prevention study with an acute treatment study: RELIEF. In the RELIEF study, epitenzumab administered within 6 hours of onset of an acute migraine episode was significantly more effective than placebo in providing early pain relief AND prolonged the time until the patient's next migraine episode. As similarly suggested from the rimegepant research, this therapy—epitenzumab—was beneficial for an acute migraine headache and had a "downstream" prevention effect.

While it appears likely that epitenzumab (Vyepti) will remain indicated for migraine prevention only, the results from this research would seem to imply that if one is destined to respond to the medication as a prevention therapy, that response is likely to become evident relatively soon after initiation of treatment. For patients who are understandably anxious to experience a reduction in migraine burden and who struggle to remain compliant with prevention therapies that may not declare their benefit (or lack thereof) for many weeks, such relative rapidity would be most welcome.

Revolutionary therapies? Yes...but at what cost?

To decode the biologic circuitry of migraine, to design therapies that "fit" that circuitry and to find that these therapies are safe, tolerable and effective is undeniably exciting, but can we afford the new therapies? Reducing a patient's average number of monthly migraine days is nice, but does the cost involved justify the clinical improvement obtained? Rest assured, these new therapies for acute migraine treatment and migraine prevention are not cheap. Are they worth the price?

Using an American claims database, Tepper and his colleagues compared erenumab/

Aimovig and typically much cheaper oral migraine prevention medications for their effect on healthcare resource utilization (HRU) and use of acute/symptomatic medication. To assess HRU, they specifically recorded migraine–related ER visits, hospitalizations and other visits to a healthcare provider.

To summarize, the investigators found that HRU and use of acute/symptomatic medication were significantly less in patients receiving erenumab compared to patients receiving oral medication intended for migraine prevention.

Can these exciting new therapies for migraine pay their own way? In other words, taking a hard-eyed view at cost versus benefit and even ignoring the *indirect* costs associated with migraine (physical, emotional, social, work-related), can these therapies offset their expense by reducing the substantial *direct* costs associated with HRU? If the results obtained by these investigators can be extrapolated from erenumab/Aimovig to its brethren, so it would seem.

Migraine Prevention: Are 2 Therapies Better Than 1?

When a migraine patient's response to a prevention medication is positive but incomplete, should the clinician continue *monotherapy* and simply switch the patient to a different medication, or should the initial medication be continued and a second and hopefully complementary medication be added (*polytherapy*)?

This question has persisted for years, and dampening the enthusiasm for polytherapy have been two major factors: first, given the uncertainty as to how the older medications used for migraine prevention exert their therapeutic effect, it has been difficult to determine which medication might be complementary to another; second, the older medications typically possess a number of potential side effects, and with *polytherapy* the risk of side effects emerging naturally increases.

But the playing field has changed. Now there are a number of medications intended for migraine prevention which are far easier for patients to tolerate and whose mechanisms of action are better understood. For the treatment of chronic migraine, onabotulinumtoxinA (BotoxA) and the anti-CGRP monoclonal antibodies are notable for their high degree of tolerability and their well-demonstrated ability to reduce migraine burden. If a patient with chronic migraine experiences a meaningful reduction in headache burden following initiation of treatment with BotoxA but still is experiencing multiple migraine episodes each month, might it be useful to continue BotoxA but add, say, erenumab (Aimovig)?

With their at the colleagues at Abbvie and the Headache Center of Southern California, Drs. Jack Schim and Andrew Blumenfeld set out to address this very question. In a retrospective chart review they examined clinical outcome in a large series of patients with chronic migraine who had been receiving serial BotoxA injection therapy for at least 6 months (many for 2 years or more), had experienced a partial positive therapeutic response and then were prescribed a self-injected anti-CGRP monoclonal antibody as well.

The results of their study were presented at the AAN meeting, and those results indicated that the addition of an anti-CGRP monoclonal antibody to patients receiving BotoxA led to yet further success in reducing migraine burden.

At least for these two particular types of therapies and in the setting of chronic migraine where the positive therapeutic response to BotoxA has plateaued, 2 seems to be more effective than 1.

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