Migraine Work in Translation

From discovery of CGRP to the monoclonal antibodies of today and -gepants of tomorrow, basic science has been translated to clinical progress over just 3 decades.

An Interview With Richard B. Lipton, MD

What's most important to you in the world of headache right now?

The revolutionary change in therapy that comes from a basic biologic insight into the role of calcitonin gene-related peptide (CGRP) and migraines. People talk about translational research going from bench to clinical trials to clinical practice and this is now a reality in headache medicine. The insight that CGRP played a crucial role in headache is approximately 30 years old; Lars Edvinsson first discovered the molecule as a sensory nerve transmitter in the nerves that supply the blood vessels of the head.[1] He demonstrated that it was a potent vasodilator and suspected it might play a role in migraine.[2] In 1988, Edvinsson and Peter Goadsby showed that CGRP levels were elevated in blood samples from the jugular vein taken from people experiencing migraine.[3] Jes Olesen and others showed that if you infuse CGRP into people with migraine, it triggers an attack.[4] We've known for a decade that CGRP-related therapies are effective treatment[5] and have been waiting eagerly for CGRP-therapies that are safe, tolerable, and effective to give us tools we can use in clinic on a day-to-day basis to help our patients with migraine. This makes the release of 3 monoclonal antibodies (MAbs) to CGRP or its receptor and the late-stage development of small-molecule CGRP antagonists, *-gepants*, truly the most exciting thing in the world of headache today.

We've made the leap from basic science to clinical trials to clinical use for not just one, but several, CGRP-related treatments, supporting the CGRP mechanistic hypothesis. In this way, translational medicine comes full circle. The hypothesis leads to treatments that strongly support the hypothesis, allowing us to study what can only be learned from actual clinical practice and experience with large numbers of patients.

How do monoclonal-antibody CGRP antagonists fit into the armamentarium of headache treatments?

In clinical trials, although there is a group of super-responders for whom the CGRP-MAbs are very effective, for most patients, the magnitude of effect is just a little better than the drugs we've been using (eg, antiepileptics, β-blockers, tricyclic antidepressants, or onabotulinum toxin). More importantly, the new CGRP-MAbs are more effective when you consider:

1) Of patients who started a preventive treatment, 75% discontinued it within a year because of side effects, low tolerability, or lack of efficacy and
2) Many patients could not use previously available treatments because of cardiovascular or other contraindications.

In contrast, in controlled clinical trials, the CGRP-MAbs have had high tolerability with almost no side effects and no cardiovascular contraindications. The real advantages, from my perspective, are that benefits begin quickly, dose titration is not required, side effects are low, and tolerability is high, all of which make it more likely patients will continue treatment.

What side effects do monoclonal antibody CGRP antagonists have?

The bottom line for all CGRP-related therapy is that patients don't feel like they are "medicated" and having to accept changes in their life that come from taking a medicine. In my experience with clinical trials and early clinical use, those who have discontinued a CGRP-MAb have been a tiny minority of people in late life (ie, in their 9th decade) taking erenumab who experienced constipation they couldn't tolerate; for most patients, constipation is very manageable. Both erenumab and -gepants target the CGRP receptor; the other MAbs target CGRP itself and do not have constipation as a side effect.

How might the the -gepants fit into the treatment armamentarium?

Efficacy

The -gepants and the MAbs are quite different (Table), and we can't make efficacy comparisons because clinical trials have tested very different hypotheses and different outcome measures. Trials for MAbs studied whether or not the drugs prevented migraine from occurring by measuring changes in the frequency of migraine. Recent clinical trials for the newest of the -gepants, rimegepant and ubrogepant, have tested whether or not the drug provides relief from migraine after it has begun; efficacy was measured as relief from pain and a patient's most bothersome symptom (MBS) (eg, photophobia, phonophobia, nausea).

Clinical trial data made publically available in press releases for rimegepant and ubrogepant show these have similar

TABLE. PROPERTIES OF -GEPANTS VS MONOCLONAL ANTIBODIES

	-gepants	Monoclonal Abs
Size	Small	Large
Route of administration	Oral	Injection/infusion
Indication	Acute treatment	Preventive treatment
Onset of effect	Hours	Days
Half-life	8-12 hours	3-6 weeks

efficacy for acute treatment of migraine as triptans, which are the most widely used acute treatments now available. In phase 3 clinical trials, 21.2% of people had relief from pain of a moderate to severe headache and 35.1% had relief from MBS within 2 hours of taking rimegepant, which was significantly better than the 10.9% and 26.8%, respectively, seen in people who took placebo ($P < .0001$) and comparable to efficacy of sumatriptan.[6,7] Data from a phase 3 study of ubrogepant for acute treatment of migraine presented at the 2018 American Academy of Neurology annual meeting showed 19.2% of patients who took 50 mg of ubrogepant and 21.2% of those who took 100 mg achieved freedom from pain compared with 11.8% of those who took a placebo (50 mg, $P = .0023$; 100 mg, $P = .0003$) and approximately 38% who took either dose of ubrogepant had resolution of MBS compared with 27.8% of those who took placebo ($P = .0023$).[8]

Triptans have about a 2-hour half life and many who achieve pain relief with triptans still have the migraine return or recur after 2 hours. Drugs with longer half-lives, such as the -gepants are more likely to be effective for the duration of an attack. In clinical trials for rimegepant, treatment effects began as early as 15 minutes and 85% of the patients who took rimegepant did not need rescue medications. Benefits of treatment were evident through 48 hours, including measures of freedom from pain ($P < .0001$), pain relief ($P < .0001$), freedom from the MBS ($P = .0018$), and freedom from functional disability ($P < .0001$). This suggests not only that the longer half-life may provide longer-lasting effects but also that rimegepant may have some preventive effect.[9] Studies to test that hypothesis are underway. A third -gepant, atogepant, is also being studied as a potential preventive treatment.

Other Potential Benefits of -Gepants

In the US, it is estimated that 15% of adults (ie, 1 in 7) have migraine, and whether this is chronic or episodic, acute treatment is needed by all who experience migraine. Triptan medications account for over 80% of the prescribed medications for acute treatment but are contraindicated in individuals with cardiovascular risk factors. My estimate is that there are 3 million people with migraine who have contraindications to triptans. The -gepants will be very important for these individuals because there are no contraindications to them for people with cardiovascular risk factors.

Many of the acute treatments in use today actually make headache worse on a long-term basis; this is the phenomenon of medication-overuse headache or rebound headache. Because there is evidence from open-label extension studies that rimegepant reduces the number of headache days per month (ie, may be preventive), there is reason to believe that treatment with -gepants will not result in medication-associated headaches.

The different half-lives of -gepants and MAbs are also important because migraine is most prevalent in women of child-bearing age who may want to become pregnant at some point. We don't know yet if the MAbs have any negative effect on a developing fetus, but we do know that the MAbs cross the placenta. Similarly, we don't know the effects of the -gepants on the developing fetus or if the drug crosses the placenta. However, the long half-life of the MAbs means a woman might have to wait months to reach 95% MAb clearance, whereas with the -gepants, she would only have to wait 2.5 days for the drug to be out of her system.

What side-effect and safety concerns are there for -gepants?

The -gepants were developed before the MAbs to CGRP. The first of the -gepants was olcegepant, which was shown to work as an intravenously delivered treatment for acute treatment of migraine.[5] This product really died on the vine because the intravenous administration isn't as useful for acute treatment and the manufacturers were unable to create any other formulation.

The next -gepant studied was tolcagepant, which had efficacy similar to the triptans and completed phase 3 trials. In a safety study, very high doses (more than would ever reasonably be given) caused elevation of liver enzymes and development was stopped.[10,11] The safety study with tolcagepant not only kept that drug from coming to market, it also created concern about liver safety for all subsequently developed -gepants. Data from MAbs and newer -gepant treatments that also block the CGRP cascade, however, suggest that the liver toxicity of tolcagepant was off-target toxicity, that is, not an effect of blocking CGRP in and of itself. These findings further suggest that not all small-molecule CGRP blockers will have liver toxicity.

Pooled results from 3,556 people in clinical trials of rimegepant showed it was similar to placebo with regard to elevated liver enzymes and other adverse events.[9]

Similarly, for ubrogepant, in studies comprising a total of 21,454 migraine attacks treated with 31,968 doses over a 1-year period, no hepatic safety concerns or significant adverse events

were seen. This was also true in a study of 500 healthy control subjects who took ubrogepant over an 8-week period.[12]

Summary

The MAbs approved for preventive treatment of migraine and still in development are an example of scientific research resulting in clinically applicable treatment—translational medicine. These treatments have much higher tolerability, fewer side effects, and similar efficacy to currently available preventive treatments.

The next translational medicine advances on the horizon are the small-molecule CGRP antagonists, rimegepant and ubrogepant. These are both in late-stage clinical trials and have shown similar efficacy to available acute treatments also with much better tolerability and lower side effects. There is also some preliminary evidence that these molecules may serve as both acute and preventive treatments, which could be advantageous for patients given the oral administration and shorter half-life of the -gepants compared with the MAbs.

This work is creating great hope that people with migraine will have effective and tolerable treatments that may improve quality of life and decrease migraine-related disability. ■

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