Headache in the CGRP Era

There are knowns, unknowns, and bogeymen.

By Peter McAllister, MD

Years ago, when calcitonin gene-related peptide (CGRP) antagonists for headache treatment were but a glimmer in a researcher's eye, former Secretary of Defense Donald Rumsfeld, known for pithy *bon mots*, said, "*There are known knowns; those are things we know we know. There are known unknowns; those things we know we do not know. But there are also unknown unknowns—the ones we don't know we don't know.*" This puzzling pronouncement provided plenty of fodder for late-night talk show hosts and is also relevant to clinical medicine.

As clinicians, we strive to slide as many of the unknowns (both known and unknown kinds, if you follow) as possible across a metaphorical ledger into the known known column. With pharmacotherapy, we eliminate unknowns, designing large thoughtful studies and tracking safety and efficacy through years of postmarketing surveillance. Eventually, we get to know a drug, and when we do, even if it is saddled with numerous side effects, it seems okay. Time and experience decrease fear and anxiety for patients and practitioners alike.

In contrast, uncertainty is magnified when a highly anticipated novel class of blockbuster drugs hits the market as we experienced in 2018, when erenumab (Aimovig; Amgen, Thousand Oaks, CA), fremanezumab (Ajovy; Teva, North Wales, PA), and galcanezumab (Emgality; Eli Lilly and Company, Indianapolis, IN) received FDA approval for preventing migraine.[1] A fourth, eptinezumab (Alder Pharmaceuticals, Bothell, WA) is due out in about 6 months. Although each of these monoclonal antibodies (MAbs) to CGRP or its receptor seemed efficacious, safe, and well-tolerated in trials, since launch, the reception has been mixed. This feedback has come primarily via social media as patients and physicians wonder if these drugs may not be as effective, safe, and well-tolerated as studies led us to believe. Concerned folk, worriers, and nay-sayers sprung up like mushrooms after spring rain. So, as we close in on a year of CGRP-related treatment availability, let's review what we know, think we know, may not know, definitely don't know, and fear.

The Known Knowns

The first known known needs to be kept top of mind; migraine, for the most part, is awful and most patients who need preventive treatment are not receiving it.[2] Thus, we also know that we need to identify better the patients who will benefit from prevention and help them adhere to treatment. There is also an unmet need for safe, well-tolerated, efficacious prevention. Our current rag-tag group of oral preventives simply isn't cutting it for many of our patients. In the war against migraine, we need more, and better, ammunition.

The Known Unknowns

These are heady, early days in a new era, and unknowns, like nighttime monsters in a child's bedroom, lurk in the shadows. We must remember that studies are artificial in a number of ways. Not everything found (or not) in clinical trials applies to the broader group of people we see in clinical practice. In trials, CGRP MAbs appeared as efficacious as other available preventives and also wonderfully devoid of both annoying and dangerous side effects. Monthly or quarterly dosing schedules seemed ideal from a patient adherence perspective. Add to this the reality that, for commercially insured patients, these agents are virtually free (or nearly free) for at least the rest of 2019, and it would appear we have ample reason to celebrate.

As of this writing, more than 200,000 patients have injected a CGRP MAb. This known known is a huge number, considering the time since approval. We've amassed amazing breadth (numbers), but little depth (time) of exposure. We know that in the studies the adverse event profile was similar to placebo, with only injection site reactions for fremanezumab and galcanezumab, and that plus a very small percentage of constipation (3% on the higher dose) with erenumab.

What we know we don't know yet includes the effect of blocking CGRP on fetal development. Converting this unknown to a known is crucial, considering women of childbearing age are the most likely to be prescribed a CGRP Mab.

We also know that we don't know how to switch among MAbs—we simply have no guidance. Should we wait a month, or 5 months/5 half-lives? Does it matter if we're switching due to an adverse event or lack of efficacy?

Another vexing known unknown: what is the true constipation rate? Significant chatter at meetings and on the blogosphere suggests constipation may be more frequent than seen in trials—by a little bit or by a lot, depending who is commenting. A review of 68 published studies suggests the background constipation rate in the general population is

16%,[3] likely higher in persons with migraine, women, and those in late-life. Although with erenumab, constipation appears dose-dependent and resolved with time, there are likely to be more intransigent cases in the real world, particularly among those who, due to some medical condition, would have been excluded from studies. On the FDA Medwatch Adverse Event Reporting Dashboard (where anyone can report any adverse event—causally related or not), constipation accounted for 11% of the 7000-plus postings for erenumab but also over 3% of postings for fremanezumab and galcanezumab.[4]

Last, although data from the clinical trials are reassuring, we do not yet know the risk of cardio- or cerebrovascular events in at-risk individuals who would have been excluded from trial participation. After all, CGRP is a potent vasodilator these treatments block. A tiny number of reported strokes (0.27%, or 23 cases) have appeared on the Medwatch site—whether those are causal or coincidental is anyone's guess.

The Unknown Unknowns

Have we considered all potential pitfalls of CGRP MAbs, or are there some we don't know we don't know? Given the ubiquitous nature of CGRP, it does give thoughtful clinicians some pause. Perusing the medical and scientific literature until my head pounded, I found other areas of potential concern: there is emerging literature on the role of CGRP in angiogenesis (on the bright side, I suppose, inhibiting angiogenesis may halt vascular tumors).[5] In a test tube, CGRP inhibits platelet aggregation; might it in humans? How about bone growth and healing, given the role CGRP on osteoblasts and osteoclasts? At risk of sounding like a broken record: we just don't know yet.

Trouble may increase as clinical experience does, or not. But I think physicians in the "sky-is-falling" camp (you know who you are) might want to review the original package insert for our trusted old friend amitriptyline, the second-most prescribed migraine preventive. Adverse effects included constipation, paralytic ileus, urinary retention, seizures, coma, hallucinations, sedation, tardive dyskinesia, cardiac arrythmia, increased intraocular pressure, testicular swelling, and black tongue (*black tongue!*). And, lest we forget, a black box warning of increased suicidality.

Considering topiramate, the FDA Medwatch site lists 12,500 adverse event reports, (69% serious), with many deaths reported. My strong suspicion is that if amitriptyline and topiramate were studied in the modern era, they likely would not have been approved (would aspirin, for that matter?). If they squeaked through FDA approval, there would have been a ground swell of leading headache specialists clamoring about limited efficacy (likely about the same as the CGRP MAbs) and a smorgasbord of objectionable threats, real and hypothetical.

It is good that social media wasn't around when amitriptyline and topiramate were launched. The blogosphere, I'm quite certain, would have erupted like a volcano. I could envision #Elavilkills, #Dope-a-max, and #Idratherhaveamigraine trending on our collective social media feeds.

Of course, now we have depth and breadth of experience with amitryptiline and topiramate and are comfortable. The dangers are known knowns, so we prescribe them frequently, warts and all. The unknown bogeyman long ago vanished for these, but remains a sinister presence with the newer CGRP MAbs. Hopefully the old adage, "Use new medicines early, while they're still safe," won't come back to haunt us.

The Future

Like it or not, the CGRP era is not only here to stay, it is expanding, with new indications for CGRP MAbs (including cluster headache, pediatric migraine, and posttraumatic headache) and possible second-generation oral CGRP antagonists for acute treatment and prevention. Unknowns (known and unknown) will continue to plague us. Should a patient take an oral CGRP antagonist as acute treatment while on a CGRP Mab for prevention? I can't get my head around whether that would be smart, useless, or outright dangerous. It may be none of the above, but I'm eager to find out. The scary nature of new medicines is also, at least to me, intellectually exciting.

Donald Rumsfeld is also known for saying, "*You don't go to war with the army you want, you go with the army you have.*" In our war against migraine, this chronic, dreadful, disabling condition, we'd love to have a treatment that is 100% safe and effective, but we'll never have that. The new CGRP MAbs are not perfect soldiers, and certainly not battle tested, but they've reported for duty and so far, seem to be a valuable addition to the army we have. We should encourage our patients to report side effects, and we need a pregnancy registry. Although we must try to answer as many unknowns as we can, until they become knowns and the bogeyman recedes into the shadows, in the meantime, CGRP MAbs are here for use. Our patients need them, and we should carefully, thoughtfully, (and perhaps even frequently) use them. ■

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