What Might the Migraine Landscape Look Like Post-CGRP?

Will CGRP do for prevention what triptans have for acute treatment?

By Robert P. Cowan, MD, FAAN

I have been asked to reprise, in written form, a largely editorial talk I presented at the Headache Cooperative of New England meeting in Boston in early 2017. It is not intended as a review of calcitonin gene-related peptide (CGRP) antibodies or antagonists. Nor is it meant as a commentary on the pharmaceutical industry or those headache specialists who speak for them. Rather, it is an effort that will, I hope, encourage the reader to consider not only the scientific merit of developments presented within our field, but also the practical implications of those developments.

Introduction

After nearly 30 years without a significant change in the pharmacopeia, everyone is talking about the new class of medications for migraine. There has not been this much excitement in the headache community since the triptans came to the United States in the early 1990s. Even the venerable *New England Journal of Medicine*, which largely ignores headache, saw fit to print not one but two articles in the same issue about the new calcitonin gene-related peptide (CGRP) agents coming to market.[1,2] One would think that a sea change was upon us.

Why, one might ask, was there not more enthusiasm when functional and structural imaging studies started to appear demonstrating that there were actual markers for differentiating patients with chronic migraine (CM) from those with episodic migraine? Where was the media when articles suggested that comorbidities and other patient characteristics seemed to identify populations that could be at greater risk for chronification or that behavioral therapies are just as effective as pharmacologics in prevention? Surely, these are discoveries with enormous potential to change the migraine landscape. Why is it that a new class of drugs that appears to be marginally (if that) more efficacious than currently available medications has caused such a stir?[3]

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Could it be because the tremendous financial and promotional resources of pharma have been brought to bear on a neglected, but potentially profitable corner of health care—an untapped market? Could it simply be that we are so desperate for better treatments for our patients that we are ready to swear the emperor has new clothes?

To be fair, the new CGRP antibodies have an attractive side effect profile, which in itself is a significant step forward. Monthly or quarterly administration can be an attractive tool for improving compliance. However, major questions remain unanswered and are only infrequently addressed. The questions are not trivial. How likely are these drugs to be available to the majority of patients who could benefit from a gentler preventive?

Indications are that the monoclonals will be priced in the range of the currently available onabotulinumtoxinA 4—a biologic that requires two and sometimes three adequate trials of less expensive medications that have no FDA indication for CM, in addition to a diagnosis of CM, before being authorized by insurers.

Other questions remain: What will be the effect of circulating anti-CGRP antibodies on patients experiencing stroke or myocardial infarction?[4] Fewer than 8,000 trial study participants have received this new class of drugs, and, other

than migraine, participants have all been healthy. Until numbers include a more representative sampling of the general migraine population, we will not know the answers to this, but animal studies suggest it is an issue worth further exploration.[5,6]

Even if we assume the gepants and enzumabs are as good as their manufacturers claim, and that there are no postlaunch surprises, and that they are as accessible as baby aspirin, what would it mean to the 30+ million migraine patients in the United States? Could this be life-changing for some segments of the migraine population?

It appears that about 20% of CM patients receiving CGRP antibodies have gone 30 days or more without a migraine. Certainly, if replicated, this is astonishing. However, at this time, we do not know the characteristics of this subpopulation, but perhaps with larger numbers and some large data analytics, that will come.

The better side effect profile is not trivial. Individuals who might benefit from a preventive but have been unable to tolerate any of the preventives currently in use will welcome the arrival of the CGRP agents.

Finally, parenteral delivery systems may have a significant effect on compliance, presumably decreasing breakthrough attacks arising from skipped or missed doses.

Remember: this is all based on the notion that these drugs are effective, safe, and accessible. Let us consider each of these assumptions separately.

Efficacy

In terms of decrement in the number of headache days per month, the CGRP antibodies are roughly in line with the number we saw in the PREEMPT trials a decade ago.[7,8] Although no patient or headache specialist would argue that this is the only, or even the best, measure of the value of a migraine treatment, at least for the present, it is the gold standard. At the time of this writing, there do not exist subclassifications of migraine that would allow for the argument that certain patients may see dramatically greater improvement in their headaches with CGRP antibodies or any other treatment modality, outside specific contraindications. At the same time, a great deal of comment has focused on so-called super-responders—trial participants who have had absence of migraine for periods of 30 days and longer. There have been some innovative statistical manipulations and subtle turns of phrase in reporting these findings that hint at a cure. But it is difficult to ignore the slightly more sinister view that the marketing value of dangling a cure in front of millions of patients with headache has far more value than doing the difficult (but less profitable) work of identifying the characteristics of the super-responder population. Perhaps these studies are being undertaken as we speak. But certainly, if this new drug class can effectively eliminate migraine in 20% of patients, then all other things (access, availability, untoward consequences) being equal, this would have an enormous effect, particularly since CM accounts for as much as 85% of all migraine-related costs.[9]

Side Effect Profile

Whereas overall efficacy measures have been modest, it seems clear that the side effect profile is significantly better than that of other agents currently available for prevention of either episodic migraine or CM. Ignoring the obvious comment that there is strong evidence for the efficacy of nonpharmacologic treatments (which carry their own baggage in terms of coverage by insurance and time commitment on the part of patients), having a pharmaceutical that is noninferior to existing treatments but with a more favorable side-effect profile would seem, on the surface, to be a wonderful advance. However, given the non-life-threatening nature of the side effect profile for the current standard of care, it seems unlikely that insurers will be persuaded to authorize a better tolerated drug over a less expensive one. Thus, although the side effect profile is attractive to patients and providers, it is likely to be trumped by accessibility issues. While the approval criteria used in the insurance industry are a closely guarded secret and vary from insurer to insurer, without a legislative mandate for transparency in this process, a more favorable side effect profile is unlikely to change the landscape after CGRP agents enter the market.

Accessibility

Numbers floating around the financial market suggest that the migraine antibodies will represent a $4.5 billion product.[10] This is anticipated to occur largely without significant market expansion. This means that, much like we saw in the 1990s with the triptan wars, the strategy will be to draw patients away from the population currently on existing preventives, with less focus on migraineurs not currently using a preventive. If this is, indeed, the strategy to be adopted by the marketers in pharma, it may be a hard sell if their products are priced at or above existing therapies. There has been no indication that any of the CGRP companies are considering pricing significantly below onabotulinumtoxinA, the only FDA-approved agent for CM. Moreover, like onabotulinumtoxinA, the monoclonal antibodies are licensed as biologics, making the emergence of generics unlikely in the foreseeable future. Accessibility remains the greatest unknown as these molecules come to market. Until the FDA issues approved indications for the package insert, and the insurers respond with criteria for approval, it is impossible to predict accessibility. Ultimately, it is accessibility that will determine the effect of this new class of drugs on the field.

Delivery Systems

When sumatriptan first came out in the early 1990s, it was only available as an injectable. To this day, injectable sumatriptan is the fastest acting formulation of any triptan. For reasons unknown (presumably a marketing decision), as soon as an oral formulation became available, the manufacturer shifted most of their promotional efforts to the orals, which were very successful. As a consequence, subsequent triptans also focused on oral formulations, for the most part. The lesson learned (rightly or wrongly) was that, in the migraine space, injectables were not the way to go. This, of course, predated the success of injectables for multiple sclerosis. Has the attitude (real or perceived) changed among manufacturers, providers, and patients? How providers and patients will embrace an injectable alternative to oral medication or onabotulinumtoxinA is unclear. It will also be interesting to see how providers and patients respond to the choice of an infusion, presumably in the office or at an infusion center versus a self-administered injectable, and whether patient convenience and compliance will be improved by monthly or quarterly injections. In the meantime, pharma is actively pursuing oral formulations of CGRP antagonists and antibodies.

Indications

Indications for a new medication are determined by the FDA. Whether the CGRP agents will receive indications for CM, high-frequency episodic migraine, episodic or chronic cluster, or posttraumatic headache remains to be seen. At this point, all indications seem to be on the table, and manufacturers are collecting data for all of these indications. However, indication is only one barrier to access. Step edits—the requirements imposed by a given insurer—may be a significantly greater obstacle to access than FDA indications. It is likely that high-risk (and expensive) patients may have an easier time accessing these new agents. Of course, off-label use of medications is a bastion of treatment in headache medicine, and once the new class has any indication, proactive patients and providers will seek access to these drugs. However, it is likely that off-label access will not significantly move the needle in terms of effect on the migraine landscape as a whole.

Postapproval Monitoring

To date, the most compelling argument for the CGRP antibodies has been the favorable side effect profile. It is important to keep in mind the somewhat artificial environment of the clinical trial. Subjects with comorbid conditions are excluded from these studies, and it is not until the medication is in general use that unexpected consequences may come to light in specific populations. Often, these consequences emerge when patients with cardiac conditions or other acute and chronic diseases utilize the medication. Couple this with the awareness that CGRP is found throughout the body, and in addition to modulating pain, it has anti-inflammatory action and a role in energy metabolism, among other functions, and the risks compound. The list of drugs found to be unsafe following release is long and includes medications such as Vioxx, Accutane, Cylert, Permax, and Propulsid, to name a few. The risks associated with these drugs did not come to light until a wider distribution revealed them. Without a major restructuring of drug trial design or wider and more sophisticated use of computer modeling, it is impossible to predict these unforeseen outcomes. However, the effect of circulating antibodies in patients with unanticipated breakdown of the blood–brain barrier due to injury or stroke and the effect on healing in patients with circulating antibodies and cardiac events or inflammatory disease remains unknown. Should this prove an issue following access, the field could be greatly affected.

Other Unknowns

The CGRP agents, like all expensive medications, and health care in general, are subject to regulation at the state and federal levels. Changes to the Affordable Care Act, such as reversal of coverage for preexisting illness, could have a dramatic effect, not only on CGRP access, but also on the entire field of headache medicine, because most headache syndromes begin prior to adulthood and individual coverage. Similarly, a move to the single payor system could dramatically alter the coverage landscape, as could complete privatization of health care. The implications of such major shifts in coverage are well beyond the scope of this article.

The list of drugs in the pipeline is long and impressive, ranging from modulators of various ion channels to targets identified from genetic mutations to other neuropeptides and nonpharmacologic neuromodulation and immune cell modulators. Any one of these could potentially eclipse the field. The migraine market is enormous, funding is increasing (albeit slowly), and advocacy is raising the public visibility of headache and migraine. The effect of these elements could shift the landscape in ways we can only imagine.

I would be remiss were I not to point out that adoption of new care models, independent of pharma, and currently known but not widely available have the potential to change headache medicine dramatically, with or without new drug discovery. These also have important obstacles in terms of access and reimbursement, not the least of which is the incorporation of biobehavioral therapies in headache care.

The data on biofeedback, cognitive-behavioral therapy, and mindfulness therapy are as strong as the data coming out from pharma. However, without the resources of pharma, they rarely rise to the level of public awareness. Moreover, the implementation of these therapies does not mesh well with current practice models, and multidisciplinary programs are few and far between. This may change

as performance measures become tied to revenue.

Lifestyle and self-efficacy continue to emerge as key elements in migraine management, but counseling is time-consuming and poorly reimbursed. The current culture in health care is weighted toward pharmacologic solutions and acute treatments. Changes in these behaviors could alter the landscape beyond and before a new class of drugs can realize a significant effect on the field as a whole.

A better understanding of headache subtypes, particularly with respect to medication response and behavioral therapy response, could improve both diagnosis and treatment strategies. Broader utilization of computer-based diagnostic tools and real-time data collection through apps will undoubtedly benefit the field by improving access to accurate diagnosis, building larger databases, and improving monitoring between interventions.

Conclusion

Will the CGRP agents do for prevention what the triptans have done for acute treatments? Hopefully. Will they single-handedly change the landscape for the majority of migraineurs? Unlikely. But taken along with changes in health care policy, biobehavioral medicine, new drug development, restructuring of insurance approval based on outcomes measures, and adoption of big data analytics, computer modeling, and real-time data collection, the future looks bright for a sea change in the diagnosis and treatment of migraine and other headache syndromes. ■

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