Monoclonal Antibodies and Migraine: What the Neurologist Needs to Know

As a new age in headache medicine is set to begin, it is incumbent upon neurologists to become better familiarized with and explore the implications of monoclonal antibodies in patient care.

By Peter McAllister, MD

In 1975, Georges Kohler and Cesar Milstein ushered in the modern era of monoclonal antibodies when they successfully fused myeloma cell lines with B cells to create hybridomas that could produce immortal cell lines, an effort for which they were awarded the Nobel Prize in Medicine and Physiology in 1984. Over the past 25 years, commercialization of therapeutic monoclonal antibodies (MAbs) has become a $95 Billion business. With an average of four new compounds approved by the Food and Drug Administration (FDA) annually, MAbs represent the fastest growing segment of the biopharmaceutical industry. Innovation and improvements in MAb production technologies have reduced manufacturing costs and increased yields, making MAbs available to a wider patient population. Increased understanding of the molecular biology of disease, coupled with a growing and aging world-wide population, have furthered the push for new MAbs to treat a wide variety of illness, from rare conditions, such as cryopyrin-associated periodic syndrome, to more common ailments such as asthma, rheumatoid arthritis, and cancer. Blockbusters such as Humira (adalimumab), Rituxan (rituximab), and Remicade (infliximab) are examples of MAbs well-known to physicians.

Monoclonal antibodies were introduced to neurologists in 2006 with the FDA approval of Tysabri (natalizumab) for multiple sclerosis. Since then, Lemtrada (alemtuzumab), Zinbryta (dacluzumab), and Ocrevus (ocrelizumab) were introduced in 2014, 2016, and 2017, respectively. Each of these moieties targets a specific T cell or B cell population to alter the immune system. In doing so, there is both reward (such as decrease in progression of disease, disability and MRI T2 lesions) and risk (including increased incidence of opportunistic infections, including the rare but often fatal progressive multifocal leukoencephalopathy (PML), malignancies, liver, renal, skin, and endocrinological disorders, and death). Indeed, each of these products carries a boxed warning, has a restricted delivery program requiring physician certification and patient registration, and a Risk Evaluation and Mitigation (REMS) Program.

Recently, there has been a great deal of excitement in the neurology and headache medicine communities as four companies race to complete registry trials of MAbs directed against calcitonin gene related peptide (CGRP) or its receptor for the preventive treatment of migraine and cluster headache. If approved, CGRP MAbs would represent a paradigm shift in headache medicine: the first time a class of drugs was commercialized specifically for primary headache prevention, rather than serendipitously discovered after approval for another indication. Importantly, and unlike MAbs used in multiple sclerosis, CGRP MAbs do not affect or alter the immune system, do not seem to have off-target toxicity, and so far appear safe and well-tolerated. As it is likely that one or more of these products will hit the market in the next 12 to 18 months (Amgen, for example, has publicly stated their intent to file with regulatory agencies in late 2017, hoping for a 2018
product launch), it is imperative that neurologists develop a working understanding of, and a comfort level with, both monoclonal antibodies and CGRP in the context of treating their headache patients.

The History of CGRP MAbs in Migraine

The CGRP story in migraine begins with its accidental discovery in 1982 by University of California, San Diego researchers Susan Amara and Michael Rosenfeld. In one of the earliest demonstrations of alternative gene splicing, Amara and Rosenfeld, while studying calcium regulation, found that the same gene encoding calcitonin in the thyroid gland can produce a different peptide in another organ, such as the brain. We now know CGRP as the polypeptide product from a tissue-specific alternative RNA splicing of the chromosome 11 p15.2 CALC1 gene, which also produces calcitonin and the calcium-lowering peptide katacalcin. But CGRP, which exists in both alpha and beta isoforms, plays no role in calcium homeostasis; rather, it has both vasodilatory and nociceptive properties. Present throughout the body, CGRP is widely expressed in both the peripheral and central nervous system (CNS), including important migraine sites, such as the dorsal root ganglia, trigeminal ganglion, and dorsal raphe nuclei, as well as the cerebellum.

In 1988, neuroscientist Lars Edvinsson, from Lund University in Sweden, found that stimulating the trigeminal ganglion increased CGRP in the cranial circulation. Following on this, in 1990 he and Peter Goadsby demonstrated that CGRP levels were elevated during migraine and that sumatriptan treatment returned CGRP to baseline levels. Interestingly, with substance P (thought at the time to be the major migraine nociceptive transmitter), they saw no such change. Further studies showed that infusion of CGRP into control subjects produced headache, and infusion into migraineurs produced migraine. More recent research has demonstrated that density of CGRP receptors on dural mechano-nociceptive neurons is down-regulated by onobotulinumtoxinA.

The first CGRP blocking agents used in migraine were not monoclonal antibodies but rather small molecules. Olcegepant (Boehringer Ingelheim GmbH), an intravenous formulation, and Telcagepant (Merck & Co.), an oral preparation, both demonstrated efficacy in randomized, placebo-controlled trials. However, issues with formulation in the former, and off-site (liver) toxicity in the latter prevented commercialization. Newer small molecule oral CGRP receptor antagonists (hopefully without significant toxicity) are in development. These include Allergan’s Ubrokegapt, which recently began Phase 3 studies for acute treatment in episodic migraine (EM), and atocegapt, as an EM preventive.

While the CGRP MAbs have numerous advantages, it is still early, and questions remain. Safety in long-term use, in pregnancy, and in special populations, such as children and the elderly, remains unknown. Post-marketing surveillance will be essential.

A paradigm shift occurred in the early 2000s when scientists at Rinat, a spin-off of Genentech (a company with significant expertise in the monoclonal antibody arena) turned their attention to migraine with the development of an anti-CGRP MAb. As is often the case in the world of biopharma, however, Rinat was acquired by a larger company, Pfizer, who decided in 2011 that migraine was not a business direction they wished to pursue. Thus, they sold the Rinat CGRP MAb to a small upstart called Labrys Biologics, who chaperoned the drug through Phase 2 studies before being acquired themselves by Israel-based generic giant Teva Pharmaceutical Industries. Meanwhile Amgen, the world’s largest biotech company, was busy working on it’s own MAb product that would bind to the heterodimer CGRP receptor (called CRL/Ramp), thus separating itself from the Teva MAb, which binds to the CGPR ligand itself. Following completion of phase 2 studies, Amgen entered into an agreement with Novartis International AG in which Amgen retained marketing rights in the United States, Canada, and Japan, while Novartis got Europe and the rest of the world. Around the same time, Eli Lilly & Company had its own candidate MAb in the works, but rather than pursue early phase human studies themselves, they outsourced it to a “virtual” or “pop-up” biotechnology company, called Arteaus, which consisted of a handful of scientists brought together in Cambridge, MA, solely for the purpose of getting their compound through early phase development. When Lilly saw a positive signal in Arteaus’ data, they optioned the compound back in-house for later phase development and commercialization, and Arteaus, its work completed, closed its doors. The last of the four, Alder, a small clinical-stage biopharmaceutical company located near Seattle, developed its ligand-binding MAb in an unconventional manner: using diploid Pichia Pastoris yeast strains and their patented MabXpress technology, designed to simply the antibody formatting process. Thus, the monoclonal antibody era in migraine was born, and the race was on.
MAbs for Migraine

MAb therapy carries several key advantages over traditional small molecule compounds. Exquisite “lock-and-key” target specificity, long half-life (generally weeks to months), low risk of drug-drug interactions, and limited potential for off-site toxicity make MAbs attractive therapeutic agents.14 Due to their large size and hydrophilicity, MAbs are administered parenterally. Avoiding oral administration (of particular importance in migraineurs, many of whom have gastroparesis during or even between migraine attacks) is another advantage. Lastly, dosing of MAbs monthly or even quarterly is likely to increase patient compliance versus daily oral preventive medicines.

Monoclonal antibodies are large (average weight 150 kDa) glycopeptides shaped like the letter Y. They are composed of light chains and heavy chains held together with disulfide bonds. Each chain is further divided into domains. Light chains contain one variable region (the end of which contains a hypervariable, or CDR, sub-region) and one constant region. The variable region binds to the CGRP ligand or receptor. Heavy chains, consisting of one variable and three to four constant regions, determine antibody class. Two types of light chains are designated kappa and lambda, encoded on chromosomes 22 and 2, respectively. Of the five classes of antibodies (IgM, IgG, IgA, IgE, IgD), therapeutic commercial MAbs are mainly produced against immunoglobulin class G (and specifically subclasses IgG1 and IgG2), the most abundant immunoglobulin class and subclasses in natural human serum. Of the approximately 70 FDA approved MAbs, the vast majority are derived from mammalian (murine) cells, while a small portion are made in bacteria or yeast using recombinant DNA technology.15

Infusing a pure murine MAb into a human is likely to elicit an immune response, and the formation of human-against-mouse-antibodies (HAMA), which markedly shortens circulating half-life and produces symptoms ranging from pruritus and hives to life-threatening anaphylaxis.16 To combat this immune response, human antibody sequences may be spliced onto murine MAbs. Chimeric antibodies, then, in which the constant region is replaced with human sequences, are typically 70 percent human, and elicit less of an immune reaction than pure murine MAbs. Humanized MAbs, a further improvement, contain 85 to 90 percent human sequences (only the hypervariable region is murine), while human MAbs are 100 percent human and are not derived in the typical fashion. Rather human MAbs are the product of recombinant technology using transgenic mice and/or phage display libraries.17

MAb nomenclature can be confusing, but an understanding of the scheme of nonproprietary MAb naming brings with it some valuable information about what the antibody is, where it came from, and what it does. All MAbs have a prefix, followed by sub-stem A, sub-stem B, and a suffix, which is always -mab. The prefix carries no special meaning, serving only to impart uniqueness (much like -ono, -abo and -inco are prefixes for the botulinum type A neurotoxins, and have no particular meaning). Sub-stem A references the MAb target. Examples include

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EM=episodic migraine, HFEM= high frequency episodic migraine, CM= chronic migraine, EC= episodic cluster, CC= chronic cluster, CPTH= chronic post-traumatic headache
-b for bacterial, -t (or -tu) for tumor, and -n for neural targets. Sub-stem B denotes the source, with -o for mouse (murine), -xi for chimeric, -zu for humanized and -u for human. Thus, olaratumab (prefix olara, sub-stem A -t for tumor, sub-stem B -u for human and suffix -mab) is a human monoclonal antibody acting against tumors, while rituximab (ri-tu-xi-mab) is a chimeric MAb also directed against tumors.

A Closer Look at the Four Agents Under Study

The four CGRP MAbs currently competing for FDA approval for migraine are erenumab (co-developed by Amgen and Novartis), fremenezumab (Teva), galcanezumab (Eli Lilly) and eptinezumab (Alder Biopharmaceuticals). As is readily deducible from the nomenclature, erenumab is a fully human MAb, while the others are humanized. Erenumab is also the only one of the four to bind the CGRP receptor; the others bind the CGRP ligand itself. (See Table 1).

Amgen/Novartis’ erenumab, in a phase 2 study of episodic migraine (EM), showed mean reduction in migraine days/month (MDM) at week 12 compared to baseline of -3.4 (70mg dose), compared to -2.3 for placebo.19 Their chronic migraine (CM) Phase 2 study demonstrated -6.6 MDM reduction (at 70mg and 140mg) vs. -4.2 for placebo.20 Arise, their phase 3 EM study showed a week 12 reduction in MDM of -2.9 versus -1.8 for placebo, while Strive, a six-month double-blind placebo-controlled trial in EM demonstrated a -3.7 MDM decrease in the 140mg dose, -3.2 in the 70mg dose, and -1.8 in the placebo group.21

Teva published two Phase 2 studies of their fremenezumab at 675mg and 225mg versus placebo in high frequency episodic migraine (HFEM, 8-14 days/month). Twelve week MDM reduction was -6.1, -6.3 and -3.5, respectively.22 In their CM phase 2 trial they used a unique primary outcome measure: change from baseline in headache hours during third of three treatment cycles. Using three doses (900mg, a loading-dose of 675mg followed by 225mg in months two and three, and placebo), they found -67.5 hours in the 900mg group, -60 hours in the 675/225mg group, and -37.1 hours in the placebo group.23 Unlike all FDA-approved preventive migraine medications (such as topiramate, divalproate sodium and propranolol), fremenezumab was shown to work fast, splitting from placebo in as early as three days. Phase 3 studies are ongoing and, per FDA decree, MDM reduction at week 12, rather that headache hours, will be the primary outcome measure.

Eli Lilly’s Galcanezumab Phase 2 EM study demonstrated week 12 MDM reduction of -4.2 versus -3.0 in placebo. Two Phase 3 studies in the works, an EM trial called Evolve-2, and a CM trial called Regain. Eptinezumab, the Alder product, is the only intravenous MAb, and is also unique in its every three month dosing schedule. A phase 2 EM study demonstrated (at weeks 5-8, versus baseline), -5.6 MDM reduction (1000mg) versus -4.6 for placebo.25 Their single-dose phase 2 CM trial used another novel primary outcome measure: a 75 percent responder rate, which was 33 percent and 31 percent in the 300mg and 100mg doses, respectively.26 (Interestingly, the other CGRP MAbs report 75 percent responder rates (as secondary outcomes or post-hoc analyses) of between 31 to 60 percent, and 100 percent responders (that is, no migraine at all) of 15 to 32 percent. These so-called “super-responders” have generated a great deal of excitement in the neuroscience community and clearly warrant further analysis). Alder’s Phase 3 trials (Promise 1 for EM and Promise 2 for CM) are underway, and should wrap up in late 2017.

In addition to migraine, Teva and Lilly are studying their CGRP MAbs in episodic and chronic cluster headache. No results are available. At least two companies are contemplating proof-of-concept studies of CGRP MAbs in chronic post-traumatic headache (CPTH). Amgen and Alder are in early phase development of new MAbs directed against PACAP-38 (pituitary adenylate cyclase-activating peptide), another endogenous neuropeptide with autonomic and nociceptive properties.27

Across multiple indications, no significant safety signals have been identified. Side-effects, generally rated as mild-to-moderate, vary slightly between compounds and include injection site pain and erythema, upper respiratory and urinary tract infections, nausea, dizziness and abdominal pain. Unlike small molecule oral CGRP antagonists, no liver function abnormalities or other off-site safety signals have been detected. Despite CGRP’s vasodilatory properties, no cardio- or cerebrovascular signals have emerged. Unlike MAbs directed against components of the immune system, no changes in white blood count have been seen. It is highly unlikely that CGRP MAbs, once approved, will require blood monitoring, have restricted access or require a REMS program.

Monoclonal Antibodies: Here to Stay

As is the case in other areas of medicine, MAbs have arrived in neurology, first in multiple sclerosis, soon
migraine and perhaps other headache disorders, and following shortly thereafter in Alzheimer’s disease, Parkinson’s disease, neuropathy and other conditions of interest to neurologists. While the CGRP MAbs have numerous advantages, we must also remind ourselves that is still early and questions remain. Safety in long-term use, in pregnancy, and in special populations such as children and the elderly remains unknown. Post-marketing surveillance will be essential. CGRP facilitates wound healing, prevents apoptosis, and increases anti-oxidant enzymes, all of which may theoretically be disrupted by blocking the CGRP ligand or receptor, although complete lack of significant safety signals in human studies are thus far quite reassuring.

Additionally, it remains entirely unclear who the so-called “super-responders” are, and why, (excluding these super-responders), the CGRP MAb data are good (a drop of several headache days per month), but not extraordinary. In other words, given the large role CGRP is purported to play in migraine pathophysiology, why aren’t more people getting a lot better? A better understanding of pharmacogenomics (correlating efficacy, safety, side-effects and pharmacokinetics with genotypes) and identification of specific and reliable biomarkers will prove useful. There is also a suggestion that CGRP MAbs have a beneficial effect on interictal (between headache) days in migraine patients in terms of quality of life and ability to perform activities of daily living, and this too needs to be fleshed-out.

Cost may also prove a roadblock and hinder widespread use of these agents. Although all four companies are tight-lipped on price structure, industry analysts estimate the CGRP MAb price tag will “not be inconsequential.” Given that all four products seem similar in efficacy, with fewer safety signals in humans, patients will likely play one company against the other, extracting deep discounts in price in return for formulary exclusivity. Additionally, payers will almost certainly require step-edits of the CGRP MAb or any other treatment for migraine. For a medicine that she/he does not stand to financially gain from in the form of an office visit and/or injection fee.

Despite these unanswered questions, CGRP MAbs are on their way. As migraine is the third most prevalent and seventh most disabling medical condition worldwide, new treatments, particularly those that are targeted, safe, fast and well-tolerated, are welcome. And with an estimated 36 million migraine sufferers in the US alone, there is a massive potential market for CGRP MAbs (estimated at five billion dollars annually), giving biopharmaceutical companies more than ample impetus to push ahead to the finish line. An interesting era is approaching in neurology and headache medicine, harkening back to the heady days of the introduction of triptans a generation ago.

Get ready. The next 12–24 months promise to be an exciting time.

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