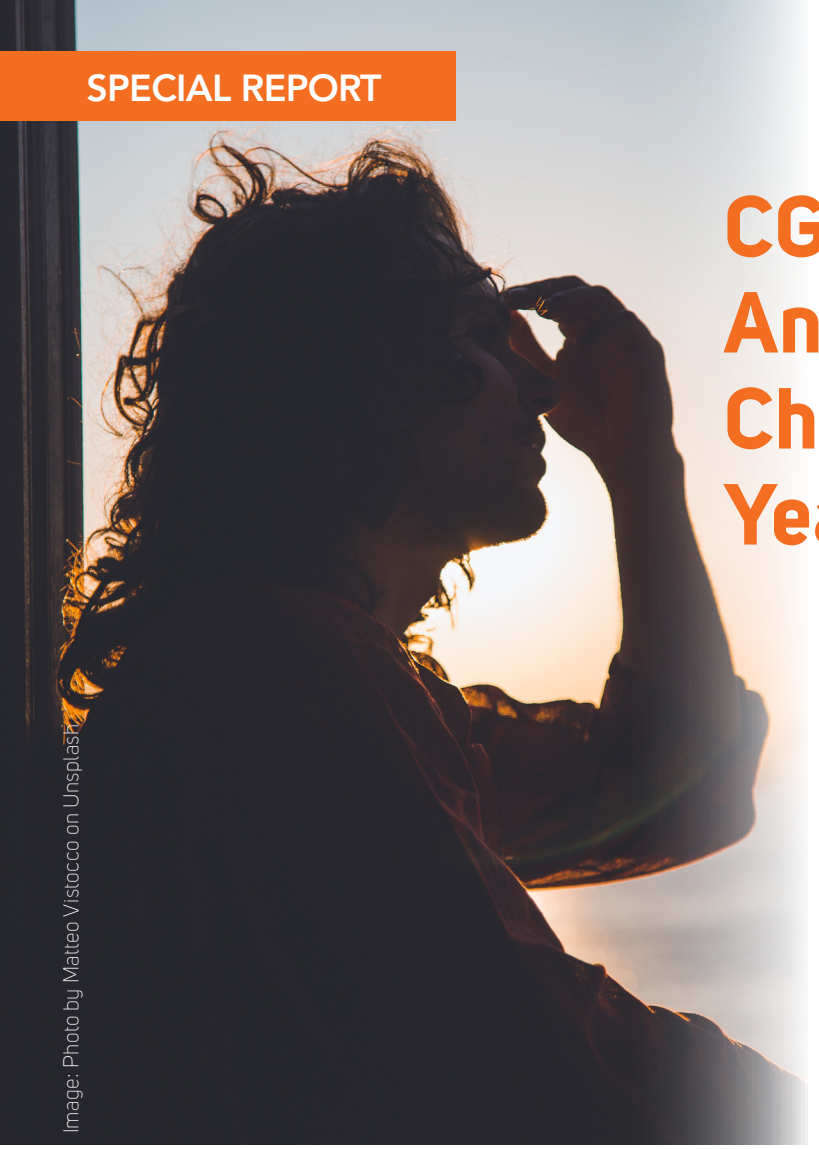
SPECIAL REPORT



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CGRP Monoclonal Antibodies for Chronic Migraine: Year 1 of Clinical Use

The author reports on early clinical experience with Emgality and Ajovy, including switching from one CGRP inhibitor to another and future considerations.

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In the March 2019 issue of Practical Pain Management, *the author shared his retrospective clinical and anecdotal experience with the new class of calcitonin gene-related peptide (CGRP) inhibitors, specifically, Aimovig (Amgen/Novartis, approved by FDA in May 2018) as a preventive for chronic migraine. That report included data over a period of six months at the author's headache clinic in Illinois. In this follow-up report, the author recaps six months of Aimovig use as well as three months of use with two other CGRP-inhibiting products, both approved in September 2018: Emgality (Eli Lilly) and Ajovy (Teva Pharmaceuticals), including results seen when switching among the three available products.*

Calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) are the first pharmacological treatments developed explicitly for the prevention of migraine.[1-3] There are currently three antibodies available, Aimovig, Emgality, and Ajovy, all administered as a subcutaneous injection. A fourth compound (intravenous) is under development (eptinezumab, ALD403, Alder BioPharmaceuticals). This paper summarizes use of the three available medications in an outpatient headache clinic over approximately one year, based on when each mAb entered the market. All patients had a diagnosis of chronic migraine. Many of these patients were refractory to standard preventive therapies. In addition, potential challenges surrounding long-term use of these important migraine preventives are discussed.

Emgality and Ajovy: Early Results

Population and Approach

Patients diagnosed with chronic migraine were assessed after 3 months of therapy (that is, three monthly injections) of either Emgality (n = 70) or Ajovy (n = 79) in the author's outpatient headache clinic. The patients' ages ranged from 19 to 74. Virtually all of these patients had previously utilized a number of preventive medications, including onabotulinumtoxinA (Botox), with inadequate relief. Along with the mAb, many of the patients remained on a daily preventive medication, or on Botox injections. Approximately 60% of the patients were considered to have refractory chronic mi-

Table I: Efficacy of Ajovy or Emgality Over 3 Months.

Participants	AJOVY 79 patients (68 female, 11 male)	EMGALITY 70 patients (56 female, 14 male)
Percentage reporting 0 to 30% relief	50%	40%
Percentage reporting 31 to 70% relief	33%	46%
Percentage reporting 71 to 100% relief	18%	14%
Combined subset: Percentage reporting 31 to 100% relief	51%	60%
Subset: Percentage reporting 95 to 100% relief	8%	3%

Table II: Side Effects Reported by Patients Utilizing Ajovy or Emgality Over 3 Months.

Patient-Reported Side Effects	AJOVY 79 patients (68 female, 11 male)	EMGALITY 70 patients (56 female, 14 male)
Alopecia	3%	3%
Anxiety	4%	3%
Constipation	6%	10%
Depression	6%	6%
Diarrhea	1%	NA
Fatigue	4%	4%
Increased headache	5%	6%
Injection site reaction	3%	4%
Irritability	3%	NA
Insomnia	NA	1%
Muscle pain or cramps in skeletal muscles	5%	3%
Nausea	6%	4%
Rash (usually on the trunk)	4%	3%
Shingles (recurrent)	1%	NA
Weight loss	1%	1%
Weight gain	4%	3%

Note: To qualify as a side effect, or an adverse effect, the patient and/or the treating physician had to feel that, more likely than not, the reported effect was due to the drug.

graine according to the standard definition by the European Headache Federation.[4]

The primary data point was the degree of relief obtained during the initial 3 months of mAb therapy. Relief was determined by either the percentage decrease (versus baseline) in the number of migraine days per month, or by the number of moderate or severe headache days per month. Moderate or severe days were assessed using a 10-point visual analog scale (VAS). Relief was averaged for the 3-month period. If patients discontinued the mAb prior to completing 3 months of treatment, relief was considered to be 0%. All patients provided informed consent and IRB approval was obtained for this retrospective review. See Table I for specific data.

Discussion

The efficacy for Ajovy and Emgality in this small outpatient clinic patient population was reasonable from a clinical perspective, with 50 to 60% of patients reporting at least a 31% improvement at the end of 3 months of therapeutic use and with similar results to those found with Aimovig (see Part I of this article).[5] The difference in efficacy between the two mAbs was not considered to be significant. Ajovy was frequently prescribed for those who had failed on a trial of Aimovig in the prior months (October and November 2018.) The timing of those Ajovy prescriptions may have artificially lowered the efficacy results, as most of the patients trialing Ajovy had already failed on Aimovig.

The most prevalent side effects reported by the author's patients when using Ajovy included: nausea, constipation, depression, and increased headache. The most reported side effects with Emgality were: constipation, depression, and increased headache. No serious side effects were encountered with either medication. The percentage of side effects, however, seem to be considerably higher than those described in both products' Phase 2 and 3 studies.[1-3] In Phase 2 and 3 trials, constipation was relatively common and appeared to be more prevalent with the use of Aimovig. Nausea, fatigue, joint pain, hair thinning or hair loss, and increased headache were also all encountered with some frequency. Anxiety and depression were reported as well. The true occurrence of the relatively minor side effects is unknown.[6,7] In the author's view, some reasons for this discrepancy may include:

- The patients in the "real life" study presented here may be generally more refractory to treatment than were those participating in Phase 2 and 3 studies; a common occurrence in migraine research.
- The patients in the presented retrospective study may have an increased number of medical and psychological comorbidities compared to those included in the Phase 2 and 3 studies.

- The Phase 2 and 3 studies did not appear to include a checklist of various symptoms, to be asked after each treatment visit; instead, the patients were asked general questions by the study personnel, which may have led to the undercounting of side effects.
- In general, side effects may be disaggregated in studies, which can decrease the percentage of a particular side effect. For example, fatigue may be described by different patients as "tiredness" or "malaise."
- The Phase 3 study numbers may have been underpowered with regard to picking up significant side effects.
- The studies did not last long enough to evaluate longer-term side effects. After data collection is completed, it is possible to "re-aggregate" the side effects, but this is not ideal.[8] In addition, side effects are not always clearly defined as mild, moderate, or severe.

All of these design flaws, many of which occur with the development and testing of any new drug or product, may lead to missing potentially significant side effects, which is why clinical and anecdotal data is important when introducing new products to the patient population.

Comparable Early Results to Aimovig

For comparative purposes, the following is a recap of early results found with the author's outpatient clinic use of Aimovig for the prevention of chronic migraine.[5]

In that evaluation, the author assessed 220 chronic migraine patients (171 women, 49 men) who had been prescribed Aimovig. Efficacy and side effects were evaluated after 3 months. Slightly less than 60% of the patients reported at least 30% relief. Approximately 24% of the patients reported 70 to 100% relief. The response after 2 months generally was predictive of response after 6 months of treatment. Most (but not all) of the patients who utilized frequent opioids at baseline did not do well with the Aimovig. If patients had moderate or severely refractory chronic migraine, they generally did not do well with the Aimovig. The most common side effects reported were: constipation (20%), nausea (7%), increased headache (5%), and fatigue (5%).

Switching Among the CGRP Monoclonal Antibodies for Migraine Prevention

In the author's experience, refractory migraine patients often do not do well on their initial CGRP monoclonal antibody. If a patient does not do well when trialing a CGRP mAb for the first time, a clinician may consider whether to switch the patient to another similar medication. The author assessed this option using retrospective data from refractory migraine patients over the period of October 2018 through May 2019. These patients, all of whom had a diagnosis of chronic migraine, ranged in age from 22 to 72. In all, 121 patients (96 women and 25 men) were included in the analysis.

A "positive" response was considered to be at least a 30% improvement in headache frequency (days per month) over baseline. Less than 30% improvement was considered to be a "poor" response. When switching 37 patients from Aimovig to Emgality, 27% responded positively. When switching 40 patients from Aimovig to Ajovy, 32% responded positively. See Table III, as well as Tables IV-VII for additional switching outcomes.

Lessons Learned

When switching a patient from one CGRP inhibitor to another for the prevention of chronic migraine, the results shown here are generally not encouraging. However, there were a number of patients who did well with the change. When switching from one mAb to another due to lack of efficacy, just over one in four patients did well. The outcomes were slightly better if the medication was changed due to side effects. When patients were doing well on a CGRP-inhibitor for migraine and had to change medications due to financial or insurance concerns, the results were found to be largely positive. This outcome may be due to the fact that the first mAb was effective, without significant side effects, and because switching was not due to medical reasons. In the author's clinical experience, patients who fail on one mAb often request to switch to another; however, they often then fail on the second mAb as well, due to lack of efficacy or side effects.

Questions and Potential Challenges in Managing Migraine with CGRP mAbs

There are a number of potential management issues surrounding these new preventives. The following commentary is solely the author's opinion.

Patient and Medication Selection

Choosing a preventive medication, no matter the target, always involves many factors. Comorbidities, both medical and psychiatric, drive clinician decision-making when it comes to medication choice, as do the patient's age, medical history, sleep patterns, GI system, job requirements, and finances.[9] When it comes to CGRP mAbs, the long-term side effects are not yet known, so in this author's experience, Botox, which tends to result in far fewer adverse effects, may be a better choice when selecting medication options for certain refractory migraine patients.

Switching Among Available Products; Ending a Medication Trial

The results from the retrospective analysis provided here-

Table III: Patient Response When Switching from Aimovig to Emgality or Ajovy, Sustained Over 3 Months.

Response	Reason for switching		
	Lack of efficacy	Side effects	Financial burden
Positive response from Aimovig to Emgality (n = 37)	4/20 (20%)	3/11 (27%)	3/6 (50%)
Positive response from Aimovig to Ajovy (n = 40)	5/17 (30%)	3/15 (20%)	5/8 (60%)
Positive response from Aimovig to Emgality or Ajovy, combined (n = 77)	9/37 (24%)	6/26 (23%)	8/14 (57%)

Total positive response: 27% to Emgality and 32% to Ajovy.

Table IV: Patient Response When Switching from Ajovy to Emgality or Emgality to Ajovy, Sustained Over 3 Months.

Response	Reason for switching		
	Lack of efficacy	Side effects	Financial burden
Positive response from Ajovy to Emgality (n = 14)	1/6 (17%)	1/3 (33%)	3/5 (60%)
Positive response from Emgality to Ajovy (n = 11)	1/5 (20%)	0/2 (0%)	2/4 (50%)
Positive response from Emgality to Ajovy or Ajovy to Emgality, combined (n = 25)	2/9 (22%)	1/5 (20%)	5/9 (56%)

Total positive response: 36% to Emgality, 27% to Ajovy.

Table V: Patient Response When Switching from Emgality to Aimovig (n = 19), Sustained Over 3 Months.

Response	Reason for switching		
	Lack of efficacy	Side effects	Financial burden
Positive response from Emgality to Aimovig (n = 19)	3/7 (43%)	1/3 (33%)	4/7 (57%)

Total positive response to Aimovig: 42%.

Table VI: Patient Response When Switching from Aimovig to Emgality or Ajovy, and then Back to Aimovig (n = 13).

Response	Reason for switching		
	Lack of efficacy	Side effects	Financial burden
Positive response from Aimovig to Emgality or Ajovy, and back to Aimovig	2/4 (50%)	4/6 (66%)	2/3 (66%)

Total positive response to back-and-forth switch: 62%.

Table VII: Patient Response Switching from 1 CGRP mAb to Another Overall (n = 121), Sustained Over 3 Months

Response	Reason for switching		
	Lack of efficacy	Side effects	Financial burden
Positive response to Aimovig	27%	33%	58%

in are somewhat discouraging. When patients are switched due to lack of efficacy or side effects, approximately one-third do well on the second mAb. While this is not a robust response, for those 30% of patients, a switch may be worthwhile. By the time individuals are placed on a CGRP mAb, they typically have failed a number of other preventive medications. Thus, if the patient wishes to attempt another CGRP inhibitor, it may be reasonable to agree. However, if the second mAb fails, it is questionable whether it is in the best interest of the patient to trial a third mAb.

If switching is needed due to finances or insurance, and the patient did well on the first mAb, it is likely that he or she may improve after switching to a second similar product, however, at the present time, there is not sufficient data on switching overall.

In the author's clinical experience, if a patient does well on a particular medication for at least three months, he/she will continue to benefit. However, the positive effects may wane over time. If the first two to three months on a new medication do not go well, it is the author's opinion that the drug be removed from the treatment plan.

Using OnabotulinumtoxinA and a CGRP Inhibitor Together

In the author's practice, 23 patients have been able to manage their chronic migraine with a combination of Botox and a CGRP mAb. Typically, these patients improve 40 to 80% over baseline, with each therapy contributing to the improvement. Our clinic has observed no interactions or problems with this combination. However, insurance companies will usually pay for only one or the other.

Possible Serious Side Effects

FDA's Adverse Event Reporting system (FAERS) website, as of June 30, 2019, listed 16,625 adverse events in connection with all three antibodies in total. A noted 2,207 of these events were deemed to be serious, with some identified as life-threatening. The majority of adverse events, 13,557, were reported from the use of Aimovig, which has been on the market for a longer period. Most (approximately 65%)

of the patients on a CGRP mAb were utilizing Aimovig. It may be several years before the medical community is able to conclude that one of the antibodies carries an increased risk over another. Hypersensitivity reactions have also been reported, and it will take some time before the true percentage of serious side effects is known, including which ones are most prevalent.

Lasting Effects and Dosage

A number of patients within the author's clinic have reported that the mAb effect only lasts 2 to 3 weeks. Since the half-life of the CGRP mAbs is around 30 days, it is difficult to explain this phenomenon. However, this occurrence may demonstrate the reality that the medical community may not know the true physiologic effects of these medications for some time. It would be possible, off-label, to use an injection more frequently than once per month. However, the safety of this approach is unknown, and insurance will not usually cover the mAbs more than once per month.

Separately, some patients may respond well to the mAb but are unable to tolerate the treatment. In the author's practice, we have, in certain cases, used a 70-mg dose of Aimovig instead of a higher 140-mg dose. Emgality and Ajovy are only available in one dose for migraine prevention. It may be possible to use half of a dose of a mAb that is available as a pre-filled syringe (such as Ajovy) but this is untested and off-label. Higher doses than are listed in the package insert may be possible as well, but again, would be off-label, and insurance companies will usually not cover higher amounts. Of note, Emgality is FDA indicated at 120 mg for migraine prevention but is also approved for 300 mg if used for episodic cluster headache.

Conclusions and Forward Thoughts

For those with chronic migraine, the usual preventive approaches often result in failure due to a lack of efficacy and/or intolerable side effects. The calcitonin gene-related peptide monoclonal antibodies have been very effective for many chronic migraineurs who previously failed the standard treatments. This paper summarizes early results from all three currently available mAbs. While side effects may limit use, the pain management community may be able to assess the true side effect profile in the coming years. •

Author Bio: ***Lawrence Robbins, MD,*** *is a neurologist specializing in headache and psychopharmacology. He has published four books and has written or contributed to at least 350 articles or abstracts. Dr. Robbins was awarded the Travell Pain Physician award by the American Academy of Pain Management in 2008 and has been in America's Top Doctors since 2002.*

Disclosure: Dr. Robbins is on the speaker's bureaus of Amgen, Teva, and Lilly. These are the primary companies involved in this article.

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Can CGRP Help Clarify Why Migraine Is More Common in Women?

An animal study explored how males and females may respond differently to calcitonin gene-related peptide.

Reported by Dan Brubaker, with Gregory Dussor, PhD

A leading cause of disability worldwide,[1] migraine is two to three times more prevalent among women than men.[2,3] Past research has shown us that one major piece of the migraine pathophysiology puzzle is calcitonin gene-related peptide (CGRP), a common and potent vasodilator. While many treatments for migraine work by blocking CGRP activity,[4,5] there is still much to learn regarding both the greater female prevalence and how and where CGRP activates the pain fibers associated with migraine. "The meninges that cover the brain are a fairly important location for headaches," said Gregory Dussor, PhD, associate professor at the Center for Advanced Pain Studies within the University of Texas at Dallas. "We think that CGRP can, and should, work there."

CGRP Exposure and Sex Differences

Dr. Dussor noted a previous study[6] which showed that, when applied to the meninges of rats, CGRPs did not alter pain fibers. He and his team of researchers at the Center for Advanced Pain Studies at the University of Texas at Dallas set out to challenge the notion that CGRP may trigger migraine pain in the menin-

ges. While the previous study only involved male rats, Dr. Dussor's team studied rodents of both sexes—a design change that led to an unexpected result.[7] "The response to application of CGRP in the meninges of females and males is dramatically different," said Dr. Dussor. "We got a very robust response in the female and essentially nothing in the male."

The study involved injecting CGRP into rats (sample sizes ranged from six to 21 across all experiments) as well as mice (sample sizes ranged from four to 12 across all experiments). Behavioral responses were recorded via von Frey testing, a common method that measures withdrawal from tactile stimulation.[8] Dr. Dosser explained that von Frey testing allowed his team to assess hypersensitivity in CGRP-injected rodents, with hypersensitivity serving as a proxy for migraine pain. "It's known that 60 to 80% of migraine patients get this hypersensitivity of their skin during their headaches," Dr. Dussor said.

Using sets of von Frey filaments — a nylon fishing line-like material that ranges in diameter — Dr. Dussor's team poked the rodents' foreheads. They then swapped out thinner filaments for thicker ones in stepwise fashion until each subject withdrew from the contact before enough force could be applied to bend the filament. With this approach, they established a baseline measure of the tactile force required to prompt a withdrawal response. Following injection of CGRP into the meninges, the researchers repeated the procedure on the same individuals to check for changes in facial sensitivity. Echoing the greater prevalence of migraine among women, only the female rodents showed hypersensitivity during von Frey testing after CGRP, withdrawing from significantly reduced tactile force.

Dr. Dussor's team used an initial dose of 3.8 µg CGRP, which proved insufficient in eliciting a response from males. But, following the positive finding in females, they lowered the dose in 10-fold increments and established that female rats continued to respond with hypersensitivity to a dose of CGRP as low as 1 pg. Testing 1 pg CGRP on mice yielded similar results. In addition, mice and rats together allowed the team to record pain signals spontaneously produced by the animals, namely grimaces.

"Measuring a threshold in response to poking is great, but it's not headache; it's hypersensitivity of the skin," explained Dr. Dussor. "We can't say with 100% certainty that the animal is grimacing because it has a headache, but it's another endpoint that is suggestive of headache."

Using a previously established 3-point scale (no grimace, moderate grimace, and obvious grimace),[9] the team then collected grimace scores that ultimately mirrored their hypersensitivity results: only females responded to the CGRP with behaviors indicative of pain.

Are Females Primed for Migraine?

Further testing revealed that injecting rats with 0.1 ng interleukin-6 (IL-6) primed females to respond to an even smaller dose (0.1 pg) of CGRP. Here, IL-6 also produced tactile hypersensitivity, but the CGRP wasn't administered until each rat's behavior returned to baseline. The researchers found similar results by injecting human recombinant brain-derived neurotrophic factor (BDNF) in place of IL-6. Even further testing revealed that CGRP itself primed rats to respond to sodium nitroprusside (SNP) at a dose that does not normally elicit pain.

These experiments may help to explain how a variety of noxious stimuli (CGRP, IL-6, BDNF, SNP) may collectively trigger migraines, with one stimulus priming a pain response to even the slightest exposure of a second stimulus. "You can do something to the animal that clearly causes a response, and it will recover," said Dr. Dussor. "But there's something about the animal that is different, that now has made it sensitive to all these things that wouldn't normally cause a problem."

Implications for Treatment Choice

These findings may not lead to any substantial change to migraine pharmacotherapies among human patients just yet. According to Dr. Dussor, the medications currently available for migraine clearly work for both women and men. However, there may be subtle differences between the sexes in terms of how effective the medications are at different doses. For Dr. Dussor, the more important consequence of his study is that CGRP is now implicated in migraine's greater prevalence among women.

"Why is migraine more common in females? We don't know, and there's probably not one answer, [but] 20 answers," said Dr. Dussor. "[It] could be that CGRP contributes something very important to the migraine process, and you don't need as much CGRP for that to happen in females as you do males."

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