CGRP Monoclonal Antibodies for Chronic Migraine

Early Clinical Experience with Erenumab: A Retrospective Review

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Migraine is a relatively common illness, known to affect 12% of the population. Chronic migraine (CM) is a frequently encountered subset of migraine, and presents certain difficulties in treatment. Those with CM often report at least 15 headache days per month, with at least 8 days being migrainous in nature; medication overuse headache (MOH) cannot be a major contributing factor to the headache pattern.

Many individuals suffering from CM do not do well with the usual preventive approaches. For instance, oral medications – such as antidepressants, anticonvulsants, and those used for hypertension – tend to have limited efficacy in patients with CM or come with too many side effects. In some cases, onabotulinumtoxinA (Botox) may be more effective than oral preventives and tends to have few side effects. As a result, many patients with CM end up with refractory chronic migraine (RCM), defined as failing on at least three types of prophylactic medications. Thus, new preventive approaches are needed for chronic migraineurs. The calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) may help to fill this role.

Enter the CGRPs Inhibitors

Calcitonin gene-related peptide is an important neuropeptide involved in the migraine process. CGRP receptors are ubiquitous in the sites that are involved in migraine pathogenesis. CGRP is involved in mast cell degranulation, neurogenic inflammation, and the subsequent vasodilation. During a migraine, CGRP levels usually rise. For those with migraine, infusions of CGRP may precipitate an attack.[1] During a migraine, trigeminal nerves that are activated may release CGRP, as well as other inflammatory compounds.[1] The mAbs that inhibit CGRP have been shown to be effective for a number of patients with chronic migraine.[2]

Erenumab-aooe (referred to as erenumab in this article) was the first CGRP mAb to become commercially available in May 2018. It is manufactured by Amgen and Novartis and branded as Aimovig. Erenumab is a subcutaneously administered once-per-month injection. There are currently two other mAbs available: fremanezumab (Teva Pharmaceuticals, Ajovy) and galcanezumab (Emgality, Eli Lilly). These are all large-molecule mAbs, with little penetration through the blood-brain barrier (BBB). Erenumab targets the CGRP receptor, while the others in this class affect the CGRP ligand. These large molecule mAbs have several major advantages, including little or no drug interactions. In addition, they are cleared through the reticuloendothelial system and do not irritate the liver or kidneys.[3] Demand for these newer preventives has been brisk, as there has been a paucity of effective therapies for those with chronic migraine.

Clinical Data on the First CGRP: Erenumab

The erenumab pivotal trial (n = 667) for chronic migraine resulted in reasonable efficacy over 3 months. The mean age was 40 years old. Patients received either placebo (70 mg or 140 mg) per month. A safety extension study was also conducted, in which approximately 40% of subjects achieved at least a 50% reduction in monthly migraine days, while placebo reduced migraine days only by 23%. The side effects in this pivotal trial were very few, with no serious adverse events reported.[4]

Erenumab was also studied in two Phase 3 pivotal trials for the prevention of episodic migraine. In the STRIVE trial (n = 955), a 50% or greater responder rate, for mean monthly migraine days per month, was achieved in 43.3% of the patients who received 70 mg monthly, and in 50% of those who received 140 mg monthly.[5] Few side effects were noted in both episodic trials. In the ARISE pivotal episodic trial with erenumab (efficacy analysis n = 570), 40% of those receiving 70 mg monthly reported 50% or greater relief.[6] The erenumab LIBERTY trial assessed episodic patients who had failed two to four previous preventive treatments. The erenumab 140 mg group had a 30.3% responder rate (50% or great response in monthly migraine days). A number of patients in the episodic migraine trials were able to continue erenumab for as long as 5 years. It was reported that 383 patients continued in the extension with reasonable and sustained efficacy.[7] There were scant side effects.

In addition, there was an erenumab and angina trial. Erenumab was used in patients with stable angina. No safety concerns were identified.[8] One further study of erenumab and blood pressure concluded that erenumab did not tend to increase blood pressure.[9]

Retrospective Evaluation: Use of Erenumab in Patients with Chronic Migraine

This paper provides an evaluation of the author's in-clinic experience using erenumab in patients with chronic migraine over a period of six months. Data were collected retrospectively and divided into three reports. In the first, efficacy and side effects were categorized for an initial 220 patients placed on erenumab. Results were assessed after three months of treatment. In the second report, the poor responders versus the excellent responders were compared. The third report focuses on patients who completed six months of treatment with erenumab.

Methods

Study Design: This retrospective study was conducted during November and December 2018. Data were collected exclusively for this study. The patients were seen at the Robbins Headache Clinic in Illinois. This clinic is an urban, tertiary, referral center featuring a socioeconomically diverse population. The study was designed to evaluate the early results with one CGRP monoclonal antibody: erenumab. IntegReview IRB approved the study protocol. All patients gave informed consent. As noted, this paper includes three distinct sets of data, described in the following sections.

Data Collection & Analysis: The two headache specialists in the clinic, Lawrence Robbins, MD, and Brooke Phenicie, NP-C, interviewed patients during their return office visits. Robbins also reviewed the patients' paper charts. Most, but not all, of the patients kept paper or electronic records of their headache days. The collected database was free of patient identifiers and names. Each mini study, or report, had its own set of data, including reported differences in age and gender. For reporting purposes, subjects were divided into three age groups: 18 to 40; 41 to 60; and 61 and over.

Frequency statistics were run on all categorical variables to describe the sample characteristics. Chi-square analysis was used to compare independent groups on categorical outcomes. Unadjusted odds ratios (OR) with 95% confidence intervals (95% CI) were used as measures of association. All analyses were conducted using SPSS Version 25 (Armonk, NY: IBM Corp) and statistical significance was assumed at an alpha value of 0.05.

Subjects and Headache Diagnosis, Study #1

The first 220 (171 women, 49 men) consecutive CM patients who received at least one dose of erenumab (70 mg or 140 mg) were included in this initial retrospective evaluation. Results were assessed for the first three months after erenumab was initiated. The patients' ages ranged from 19 to 79; the median age was 53.

All patients had the diagnosis of CM with or without aura. Diagnoses were made according to the International Classification of Headache Disorders.[10] In the past, patients had all tried at least three migraine preventive medications. Almost all of the patients had tried onabotulinumtoxinA as well. Along with the erenumab, many of the patients remained on daily preventives, which may have included onabotulinumtoxinA. One hundred thirty-two (132) of the 220 patients were considered to have RCM, as diagnosed per the European Headache Federation's definition.[11] Forty-eight (48) patients dropped off of the erenumab after one or two months for various reasons, primarily due to lack of efficacy and/or side effects, further described in the results below.

The primary data point was the degree of relief obtained during the initial three months. Relief was determined by the percentage decrease, versus baseline, in the number of

migraine days, combined with the number of moderate or severe headache days (even without features of migraine). Moderate or severe days were assessed via a 10-point visual analog scale. Zero represented no pain, while 10 indicated severe pain. Ratings 4 through 10 indicated moderate to severe headache. Relief was averaged for the entire first three months. If patients discontinued the erenumab prior to completing three months of treatment, relief was considered to be 0%. Side effects to the erenumab were also categorized.

Results of Study #1: Table I shows the range of chronic migraine improvement over 3 months of treatment in this group. Overall:

- 43% experienced 0 to 30% relief
- 34% experienced 30 to 70% relief
- 24% experienced 70 to 100% relief.

Those who experienced 0 to 30% relief included the patients who had dropped off of the erenumab prior to completing 3 months of treatment; others in the group reported being somewhat satisfied with the treatment and chose to continue on the erenumab.

Regarding efficacy in the female patients (171 total), there were no significant differences noted between the age groups. This was true for the men as well. When women were compared to the men, no statistical differences were found regarding efficacy, across all age groups. This was likely partially due to the low number of men in the study.

Table II denotes those who reported a high excellent (95 to 100%) response after 3 months of treatment; 10% of patients experienced an excellent response. No differences stood out between the age ranges. Women had approximately the same percentage of excellent response as observed in the men.

Adverse Effects: Table III describes the side effects reported by the 220 patients. Constipation was reported by 20% of the patients and, in some cases, required treatment. At least four patients discontinued the erenumab primarily due to constipation. Nausea (7%) was described as was increased headache (5%). The nausea usually resolved, but with an increase in headaches, the erenumab was usually discontinued. Fatigue (5%) was sometimes severe, requiring discontinuation of the medication. Joint pain (3%) sometimes accompanied the severe fatigue. Depression (3%) was sometimes exacerbated after erenumab was started. Anxiety (2%) also occurred. Diarrhea was seen in 2% of patients, and several patients experienced severe diarrhea. Injection site reactions (2%) were mild, not requiring discontinuation.

Three patients reported serious side effects. One occurred in a 21-year-old female with a history of hemiplegic migraine. She suffered a probable migraine-related stroke. Her cognitive symptoms have improved, but she was left with mild to moderate dysgraphia. She had a history of hemiplegic migraine (although none for 3 years), and had been using erenumab for 4 months. She was also on a low-dose birth control pill that contained estrogen.

The second involved a 31 year-old-woman who had severe neurologic symptoms, which began two weeks after her second erenumab injection. She also suffered from severe fatigue, with joint pains. Her symptoms did eventually resolve (but they recurred 3 months later, while off of the medication).

Table I: Results of Study #1 — Efficacy of Erenumab After Three (3) Months.

Group	0 to 30% Relief	30% to 70% Relief	70% to 100% Relief
All Patients (n = 220); Median age: 53	94 (43%)	74 (34%)	52 (24%)
Total Women (n = 171) Age range: 19 – 79; Median age: 50	74 (43%)	58 (34%)	39 (23%)
Women age 18 – 40 (n = 52)	21 (40%)	19 (37%)	12 (23%)
Women age 41 – 60 (n = 68)	31 (46%)	22 (32%)	15 (22%)
Women age 61+ (n = 51)	22 (43%)	17 (33%)	12 (24%)
Total Men (n = 49) Age range: 23 – 74; Median age: 63	20 (41%)	16 (33%)	13 (27%)
Men age 18 – 40 (n = 5)	2 (40%)	2 (40%)	1 (20%)
Men age 41 – 60 (n = 18)	8 (44%)	6 (33%)	4 (22%)
Men age 61+ (n = 26)	10 (38%)	8 (31%)	8 (31%)

When statistics were applied all of the differences remained nonsignificant.

Table II: Patients Who Experienced 95 - 100% Relief on Erenumab after Three (3) Months.

Total Patients	21 of 220 (10%)
Total Women	17 of 171 (10%)
Women age 18 - 40	6 of 52 (12%)
Women age 41 - 60	7 of 68 (10%)
Women age 61+	4 of 51 (8%)
Total Men	4 of 49 (8%)
Men age 18 - 40	1 of 5 (20%)
Men age 41 - 60	2 of 18 (11%)
Men age 61+	1of 26 (4%)

Table III: Patient-Reported Side Effects.

Side Effects	% of Patients (n = 220)
Constipation	20%
Nausea	7%
Increased Headache	5%
Fatigue	5%
Depression	3%
Joint Pain	3%
Injection Site Reaction	2%
Diarrhea	2%
Anxiety	2%

***In addition, 3 serious adverse events occurred, as described in the paper. **Discontinued erenumab treatment (at least partially) due to side effects: 7% of total patients (Note: It was not always possible to accurately determine if the reported side effect was actually an adverse drug reaction or due to another issue.)**

The third patient was a 65-year-old woman with a history of rheumatoid arthritis who reported suffering from severe fatigue and joint pains three weeks after receiving the erenumab. She had a history of rheumatoid arthritis, which had been in remission. She eventually improved with corticosteroid therapy. All three cases were reported to the FDA.

Subjects and Headache Diagnosis, Study #2

The second set of data was collected on the first 26 patients who were either non-responders (0 to 15% relief) or excellent responders (70 to 100% relief). Each group had 26 patients. These patients were drawn from the same population as in Study #1. All of the patients had a CM diagnosis; 16 of the poor responders had RCM, while 7 of the excellent responders suffered from RCM. Twelve of the poor responders dropped off of therapy after Months 1 or 2.

While 30% is often cited as "clinical meaningful pain relief," 15% was chosen as the upper limit for poor response. The reason for choosing 15% was that many of the patients with 20% (or greater) relief felt that they were satisfied with the response. For the excellent responders, 70 to 100% response was chosen because the patients felt that, at the 70% or higher level, their quality of life was greatly enhanced.

Demographics were collected for both groups (as they were for the other two studies described herein). In addition, various medical and psychological conditions were included in the analysis. With regard to specific diagnoses, New Onset Daily Persistent Headache (NDPH) and post-traumatic headache were diagnosed according to the International Classification of Headache Disorders;[10] neck pain was considered positive if it was persistent and significant; central sensitization disorders included any of the following—temporomandibular dysfunction, irritable bowel syndrome, chronic pelvic pain, fibromyalgia, and complex regional pain syndrome; medical conditions included immune illnesses; psychiatric conditions were evaluated according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[12] In addition, all patients completed the Psychiatric Health Questionnaire (PHQ-9).

Previous responses to different migraine treatments were also assessed. These included responses to onabotulinumtoxinA treatment for CM, which was considered positive if the patient experienced at least a 30% improvement. A response to triptans, opioids, and butalbital compounds was considered positive if the patient stated that the drug was beneficial enough to remain on the medication without significant side effects.

Results of Study #2: After three months of erenumab therapy, the poor responders (0 to 15% relief, n = 26; median age: 58) were compared to the excellent responders (70 to 100% relief, n = 26; median age: 57). These patients were drawn from the same population as in Study #1.

In the poor responder group, 12 of the 26 patients dropped off of the erenumab after Months 1 or 2, due to lack of efficacy and/or side effects. Almost all of the poor responders were women (24 out of 26). The majority of patients described the headache location as both anterior and posterior. Only one patient in each group reported primarily posterior pain. Years of headache averaged 28. Relatively few patients (two in the poor response group, four in the excellent response group) reported an aura with their migraines. NDPH and post-traumatic headaches were also uncommon.

The majority of patients had transformed migraine, meaning their chronic migraine headaches came about over a

Table IV: Poor Responders vs Excellent Responders.

Response	Poor Respnders (0 - 15% Relief)	Excellent Responders (70 - 100% Relief)
Age Range	23 - 71	21 - 68
Median Age	58	57
	# Patients out of 26	**# Patients out of 26**
Women/Men	24 / 2	21 / 5
Headache Pain: Anterior	10	7
Headache Pain: Posterior	1	1
Headache Pain: Anterior and Posterior	15	18
Years of Headaches: Range	4 - 50	5 - 60
Years of Headaches: Average	28	28
Headache with Aura	2	4
New onset daily persistent headache	3	1
Post-Traumatic Chronic Migraine	3	2
Neck Pain	16	10
Central Sensitization	5	11
Immune Conditions	6	2
Anxiety	20	22
Depression	15	17
Bipolar Spectrum	5	4
Personality Disorder	2	1
Insomnia	14	18
Refractory Chronic Migraine Total:	n = 16	n = 7
Mild Refractory	4	4
Moderate Refractory	6	2
Severe Refractory	6	1
Prior Positive Response to:		
OnabotulinumtoxinA	8	12
Triptans	22	21
Opioids	18	8
Butalbital	12	10

*Assessment completed after 3 months of treatment. The first 26 patients in each group were included. Statistical calculation: neck pain (16 vs 10): OR 2.56, 95% CI, 0.84 – 7.83, nonsignificant. Refractory chronic migraine did rise to the level of statistical significance. The opioid differences were also statistically significant. The other differences were not statisically significant.

number of years. Neck pain, either independently or as a feature of migraine, was often present. Neck pain was described by 16 of the poor responders and 10 responders in the excellent response group. Despite this difference between the poor responders (16 with neck pain) and the excellent responders (10 reporting neck pain), these differences did not rise to the level of statistical significance. However, the small sample size likely limited the statistical power.

The presence of at least one other central sensitization syndrome was observed in 5 of the poor responders and in 11 of the excellent response group. Autoimmune illness was comorbid in 5 of the poor responders, and in 11 with an excellent response. Anxiety was almost ubiquitous, diagnosed in 20 with a poor response and in 22 with an excellent response. Depression was commonly observed, although not as frequently as with anxiety. Fifteen (15) of the poor responders, and 17 in the excellent response group, had been diagnosed with depression. The bipolar spectrum was diagnosed in five of the poor responders, and four with an excellent response. Two patients in the poor response group, and only one in the excellent response group, had been diagnosed as having a personality disorder. Insomnia was frequently encountered, with 14 of the poor response group having a diagnosis of insomnia, and 18 in the excellent response group.

Sixteen of the poor responders had been diagnosed as RCM, while only 7 in the excellent responder group were considered to have RCM. This author has previously published on categorizing RCM as mild, moderate, or severe.[13] Four in each group were considered to have mild RCM; six of the poor responders and two in the excellent response group were diagnosed as having moderate RCM; six in the poor response group were considered to have severe RCM, while only one in the excellent response group suffered from severe RCM. Despite these differences, for the individual refractory groups they

Table Va: Patients Who Completed Six (6) Months of Erenumab Treatment – Results.

Month #	Relief (Average)
1	36%
2	35%
3	32%
4	27%
5	29%
6	27%

Table Vb: Patients Who Averaged 0 to 15% Relief ("Poor Responders") after the First 2 Months of Treatment (avg. relief during Months 5 and 6 is reported).

Patients (n = 15)	% Relief During Months 5 and 6
9	0%
2	10%
2	15%
1	20%
1	50%

did not rise to the level of statistical significance, again, primarily due to the small sample size. However, for the total refractory group (16 versus 7), the results did rise to the level of statistical significance (OR 1.34, 95% CI, 1.34 - 14.03).

In looking at prior medication response, eight patients in the poor response group, and 12 in the excellent response group, had previously had a positive response to onabotulinumtoxinA. A number of patients continued with onabotulinumtoxinA therapy during erenumab treatment. The majority of patients (22 in the poor response group and 21 in the excellent response group) described a previous positive response to triptans; therefore, most of the patients (20 in the poor response group, 19 in the excellent response group) continued to utilize triptans as abortive medications during erenumab treatment. With regard to opioids, 18 in the poor response group and eight in the excellent response group reported prior positive responses for migraine. These patients continued prescribed opioids while on the erenumab. For this opioid group, the differences did rise to the level of statistical significance (OR 5.06, 95% CI, 1.56 - 16.44). Twelve (12) of the poor responders, and 10 in the excellent response group, described a prior positive response to butalbital medications. These patients continued taking the butalbital compounds. See Table IV for details.

Subjects and Headache Diagnosis: Study #3

The third set of data focused on the first 50 patients to complete six months of treatment. These patients were drawn from the same population as Study #1. Ages ranged from 26 to 68. Subjects were assessed for the percentage of relief obtained during each consecutive month. The same criteria for relief that was previously listed for the data collection on 220 patients was used. Many patients in the clinic, for various reasons, had decided to discontinue the erenumab. The patients in this third study, therefore, only included those who injected the erenumab for the full six consecutive months.

Results of Study #3: Table Va shows the average relief reported by the 50 subjects using erenumab for six months, with percentages ranging from 27 to 36%. A total of 15 patients described poor relief (0 to 15%) for the average of the first two months. Among these 15, their average relief for Months 5 and 6 is shown in Table Vb, ranging from 0% to 50%. For the nine excellent responders after Month 2 (ie, average of Months 1 and 2 = 70 to 100% relief), the relief was also evaluated after Months 5 and 6. Three of these patients experienced excellent relief (95%) during Months 5 and 6. See Table Vc for full details.

Discussion

The Unknowns

The two main issues tied to CGRP mAbs for migraine prevention are: Will they remain reasonably effective over time, and, What is the true side effect profile? The efficacy question may only be answered after several more years of treatment. Regarding side effects, the author has major concerns about the various risks that could arise due to blocking of CGRP on a chronic basis, as described in the previously published "At Stake: The Possible Long-Term Side Effects of CGRP Antagonists."[14]

CGRP most likely is an inhibitor of platelet aggregation. Blocking this effect may increase the chance for cardiac or cerebrovascular effects.[15] As of September 30, 2018, there were at least six cerebrovascular events listed on the FDA Medwatch site.[16] This author has put in a Freedom of Information Request for details on those events and, anecdotally, has heard about several other erenumab-related strokes, yet to be officially reported, in addition to the one reported in this retrospective review.

On the other hand, CGRP plays some role in the prevention of hypertension and may be somewhat protective for cardiovascular disease; it is a powerful vasodilator, particularly in the meningeal and cerebral arteries. Blocking CGRP may lead, under certain circumstances, to intrace-

Table Vc: Patients Who Averaged 70 to 100% Relief ("Excellent Responders") after the First 2 Months of Treatment (avg. relief during Months 5 and 6 is reported).

Patients (n = 9)	% Relief During Months 5 and 6
3	95%
2	90%
1	80%
1	35%
2	0%

rebral vasoconstriction.[17] It is possible that other related compounds, such as amylin or adrenomedullin, may help to compensate for the loss of CGRP. In addition, various vasodilators may also help to mitigate negative effects from CGRP antagonism. These include, for instance, nitrous oxide and vasoactive intestinal peptide. CGRP also is important in neovascularization.[18] The neuropeptide may enhance recovery from ischemia by stimulating angiogenesis and has been reported to help prevent secondary lymph edema. CGRP may enhance lymphangiogenesis.[18] The adverse health consequences on the above systems, by blocking CGRP, are unknown.

The effects of CGRP mAbs on hormones has not been studied. The hypothalamus and pituitary are not, for the most part, protected by the blood-brain barrier (BBB). CGRP is present in these areas. In theory, CGRP antagonism could result in various hormonal effects. The choroid plexus, involved in cerebrospinal fluid production, is not protected by the BBB, nor is the area postrema, involved in nausea and vomiting. Circumventricular organs, important in homeostasis of various functions, are also not protected. In addition, a number of patients have reported severe fatigue from erenumab. Additionally, joint pain has been an issue for some patients. It is possible that the hypothalamic-pituitary-adrenal (HPA) axis may be involved with these side effects as the HPA axis is not protected by the BBB. Studies have yet to be conducted regarding the effects of CGRP mAbs on these areas.

CGRP has been associated with skin blushing, flushing, cold sensitivity, itch, edema, and thermoregulation.[19] After surgery, or after a serious burn, healing may be impaired by the CGRP mAbs. Since CGRP plays a role in the metabolism of bone, it is involved with bone healing.

In diabetics, by antagonizing CGRP, there may be a higher risk for coronary artery disease. In the GI tract, CGRP has myriad functions. CGRP is involved in motility, and in protecting the gastric mucosa.[20] Constipation may occur with CGRP antagonism, and to a lesser degree, diarrhea. Again, these effects have not yet been studied with regard to the CGRP mAbs.

Finally, it is not advised that these medications be used during pregnancy as there may be more risk to the CGRP mAbs in later stages. Preliminary studies in animals have not revealed major issues with a newborn.[21]

As of December 31, 2018, there were 7,211 adverse events reported to the FDA.[16] Of these, 803 were deemed to be serious, with multiple hospitalizations. Only a fraction of side effects are officially reported to the FDA.[16] Only a fraction of side effects are officially reported to the FDA. It is very concerning that there is a paucity of studies on the serious consequences of blocking CGRP for long periods of time.

Until more is known, therefore, it would be prudent to screen patients for risk. Informed consent should be obtained. Those who may be at increased risk for adverse effects from erenumab include patients with: risk factors for stroke; clotting abnormalities; hemiplegic migraine; recent surgeries or fractures; active GI ulcers; inflammatory disease of the GI tract; hormonal issues. Finally, those on certain birth control medications may be at higher risk, although this area is controversial.

Study Limitations

There were major limitations to the retrospective reviews provided herein, including the small number of patients involved. The evaluations were based on observation, with no control group. The subjects included were relatively refractory as compared to most migraineurs. Data collection relied on patient diaries and calendars, as well as patients' self-reported histories, which are not always accurate. The team was unable to ascertain whether each of the reported side effects was due to the erenumab or another issue(s).

The major strength of this study is that the patients were not selected for any purpose other than migraine treatment. They represented a "real life" group of migraineurs, albeit relatively refractory, making analysis of poor responders versus excellent responders possible. The six-month results may be helpful in understanding the efficacy of erenumab on preventing chronic migraine over longer periods of time.

Conclusions and Forward Thoughts

This observational, retrospective review of relatively refractory chronic migraineurs found that patients using erenumab over three months experienced reasonable and acceptable efficacy. Just under 60% of subjects reported at least 30% relief. In those patients taking erenumab for six months, efficacy drifted down slightly. If patients did poorly for the first 2 months, they generally did not improve afterward. However, most of the patients with excellent initial relief continued to do well.

There were no major efficacy differences between men and women, and efficacy was similar for all age groups (ranging from 18 to over 60). Side effects were frequently reported, with constipation being the most common (20%). Three serious side effects were reported.

In terms of comparing poor responders to excellent responders (Study 2), neck pain was frequently observed among both groups, although more commonly in the poor responders. Central sensitization syndromes were observed more frequently among those with an excellent response. Anxiety was very frequently diagnosed in both groups; to a lesser degree, depression was also a common comorbidity. Insomnia was present in many of the patients. The poor responders were more likely to be diagnosed with refractory chronic migraine, with moderate or severe refractoriness much more prevalent among the poor responders. Regarding prior chronic migraine prevention, many patients in both groups had found onabotulinumtoxinA to be helpful, and most patients had found triptans to be useful as well. A prior positive response to opioids was encountered much more frequently among the poor responders. Many patients had previously reported good results from butalbital compounds.

Overall, the CGRP monoclonal antibodies for the prevention of chronic migraine represent a major therapeutic advance for medicine and the pain management community. For many patients, the efficacy may be moderate or excellent. For some CM patients, these preventives may be life-changing. Side effects remain a major concern. More discussion and studies regarding safety issues are needed. Time will tell as to long-term efficacy and safety. •

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References

1. Lassen LH, Haderslev PA, et al. CGRP may play a causative role in migraine. *Cephalalgia*. 2002; 22(1):54-61.
2. Tepper, S. Anti-Calcitonin Gene-Related Peptide(CGRP) Therapies: Update on a previous review after the American Headache Society 60th Scientific Meeting, San Francisco, June 2018. *Headache*. 2018;58:276-290
3. Reuter U. Anti-CGRP antibodies: a new approach to migraine prevention. *Lancet Neurol*. 2014;13(9):857-859.
4. Tepper SJ, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: A randomized, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* 2017;16(6):425-434.
5. Goadsby PJ, Reuter,U, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017;377(22):2123-2132.
6. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. May 2018 (ePub).
7. Reuter U, Goadsby PJ, et al. Efficacy and Safety of Erenumab in Episodic Migraine Patients with 2-4 Prior Preventive Treatment Failures: Results from the Phase 3b LIBERTY Study. Poster Presented at: American Academy of Neurology meeting, Los Angeles, California, April 2018.
8. Depre C, Antalik L, Starling A, et al. A randomized, double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina. *Headache*. 2017;58(5):715-723.
9. Tepper SJ, Pascual J, et al. Analysis of blood pressure following short-term and long-term treatment with erenumab. Poster Presented at: American Academy of Neurology meeting, Los Angeles, California, April 2018.
10. IHS. Headache classification committee. The International Classification of Headache Disorders, 3rd edition (beta); ICHD-3. London, United Kingdom, 2018.
11. Matelletti P, et al. Refractory chronic migraine: a consensus statement on clinical definition from the European Headache Federation. *J Headache Pain.* 2014;15:47.
12. APA. Diagnostic and Statistical Manual of Mental Disorders (5th edition), Washington, DC, 2013.
13. Robbins L. Refractory chronic migraine: long-term follow-up using a refractory rating scale. *J Headache Pain*. 2012;13(3):225-229.
14. Robbins, L. At Stake: The Possible Long-Term Side Effects of CGRP Antagonists. Pract Pain Manage. September 2018 (ePub). Available at: www.practicalpainmanagement.com/pain/headache/stake-possible-long-term-side-effects-cgrp-antagonists.
15. Matsumato Y, Ueda S, Matsushita S, et al. Calcitonin gene-related peptide inhibits human platelet aggregation. *Jpn Circ J.* 1996;60(10):797-804.
16. FDA Medwatch adverse drug site: www.fda.gov/safety/medwatch (erenumab-aooe). Accessed February 24, 2019.
17. Russell FA, King R, Smillie SJ, et al. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev.* 2014;94(4):1099-1142.
18. Majima M, Ito Y, Hosono K, Amano H. CGRP/CGRP receptor antibodies: potential adverse effects due to blockade of neovascularization? *Trends Pharmacol Sci.* 2019;40(1):11-21.
19. Brain SD, Grant AD. Vascular actions of calcitonin gene-related peptide and adrenomedullin. *Physiol Rev*. 2004;84(3):903-934.
20. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients-a review of pros and cons. *J Headache Pain*. 2017;18(1):96.
21. Gangula PR, Zhao H, Supowit S, et al. Pregnancy and steroid hormones enhance the vasodilation responses to CGRP in rats. *Am J of Physiol.* 1999;276(1):H284-H288.