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# **Are Monoclonal Anti-CGRP Antibodies Effective in the Treatment of Adults with Migraines?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## Abstract

Objective: The objective of this selective EBM review is to determine whether or not “Are Monoclonal Anti-CGRP Antibodies Effective in the Treatment of Adults with Migraines?”

Study Design: A review of three randomized control trials (RCTs) written in English, published in 2014, 2015, and 2016.

Data Sources: Each study was published in a peer-reviewed journals found via the PubMed database. These studies measured the effectiveness of monoclonal anti-CGRP antibodies in relieving migraines in adults.

Outcomes Measured: The outcomes measured in these trials were by how much monoclonal anti-CGRP antibodies lead to a decrease from baseline in the frequency of migraine hours or days, as compared to a placebo. Migraine days were recorded by patients using an electronic headache diary, and defined by the International Classification of Headache Disorders II.

Results: Bigal (2016) and co-authors demonstrated significant improvement in number of headache hours at the end of the first week of treatment using 900-mg of TEV-48125 as compared to the placebo group. Bigal (2015) and co-authors found a higher decrease in number of headache days during weeks 9-12 in the group receiving 225 mg of TEV-48125 over the group receiving the placebo. Dodick et al also demonstrated a higher decrease in number of headache days by weeks 5-8 in the group receiving ALD403 compared to the placebo group.

Conclusion: The studies reviewed in this paper demonstrate that monoclonal anti-CGRP antibodies are an effective treatment for adults with migraines. Although this is a fairly novel therapy with further research still underway, this new drug class is a hopeful therapy option for adults suffering from migraine headaches.

Key Words: “migraine”, “monoclonal anti-CGRP antibodies”

## INTRODUCTION

Migraine headaches are a common and debilitating disorder. They are characterized as an acute, primary headache and can be accompanied by nausea, vomiting, photophobia, and phonophobia.<sup>2</sup> Migraines are described as a severe, throbbing pain on one side of the head, but they can also be bilateral.<sup>9</sup> On average, attacks last from 4 to 72 hours and can result in an accumulation of a large amount of missed days of work, school, activities, and productivity throughout a person's lifetime.<sup>9</sup> It should be noted that a migraine is not just a bad headache, but a neurological disorder accompanied by incapacitating symptoms.<sup>9</sup> Over 70% of those who suffer from migraines reported being disabled due to their condition, while 30% reported severe disability and reduction in quality of life.<sup>7</sup>

Migraine is the 3<sup>rd</sup> most common illness in the world with 18% of American women and 6% of American men suffering.<sup>9</sup> Over 4 million adults experience migraines daily.<sup>9</sup> Due to the staggering number of Americans suffering from migraines, healthcare costs and lost productivity associated with migraines add up to approximately \$36 billion annually in the US.<sup>9</sup> It is believed that about 1.2 million healthcare visits each year in the US are due to migraines.<sup>9</sup> Classically, General Practitioners have been the most common avenue for which individuals experiencing migraines seek treatment and care.<sup>7</sup> The large number of individuals suffering from migraines in conjunction with the rising number of midlevel providers means that Physician Assistants in a variety of specialties can expect to come in contact with, and often treat, patients afflicted by this condition.

The exact mechanism of migraine headaches is not proven, but it is believed that they are due to neurovascular dysfunction. This dysfunction happens when the dilation of blood vessels innervating the trigeminal nerve and release of neuropeptides cause peripheral sensitization and

headache.<sup>5</sup> Migraines are associated with a complex pattern of inheritance, and an autosomal dominant inheritance pattern is commonly seen.<sup>5</sup> They typically begin to affect individuals in their teens or twenties, and become less frequent in the forties and fifties.<sup>10</sup>

Unfortunately, there is no proven cure for migraine headaches, and treatment is based on abortive and preventative measures.<sup>10</sup> As with many other medical conditions, the treatment of migraines is often a trial and error process to determine what works best for each patient.

Patients may first wish to pursue nonpharmacological options, such as acupuncture, massage, and rest and relaxation.<sup>7</sup> Simple analgesics like acetaminophen, Excedrin, and other NSAIDs are commonly used to treat migraines.<sup>3</sup> Triptans and Ergotamines are a mainstay of treatment for more moderate to severe attacks.<sup>3</sup> Antiemetics can be used to control symptoms.<sup>3</sup> Daily use of propranolol, topiramate, and verapamil may be considered for prevention in individuals suffering from frequent migraine attacks.<sup>10</sup>

Although there are several treatment options for migraines, many patients are still unable to find relief, whether it be due to medication side effects, or their lack of efficacy.<sup>7</sup> Recently, monoclonal antibodies against the calcitonin gene-related peptide (CGRP) have been evaluated for their effectiveness in the preventative treatment of adults with migraine.<sup>2</sup> CGRP is a neuropeptide widely distributed throughout the central and peripheral nervous system, and is associated with pain transmission and vasodilation.<sup>2</sup> During a migraine attack, serum levels of CGRP rise.<sup>2</sup> Antagonism of this pathway through monoclonal anti-CGRP antibodies is a new and hopeful method in the prevention and acute treatment of migraines.<sup>2</sup> This paper evaluates three randomized control trials comparing the efficacy of monoclonal anti-CGRP antibodies in the treatment of adults with migraines.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not monoclonal anti-CGRP antibodies are effective in the treatment of adults with migraines.

## **METHODS**

This systematic review utilized three randomized control trials (RCTs), all of which focused on adults greater than 18 years old diagnosed with migraine headaches, as per the *International Classification of Headache Disorders*. All trials used monoclonal anti-CGRP antibodies as the intervention, comparing it to a visually matched placebo. Outcomes measured included change from baseline in the frequency of headache hours and days compared to placebo. Each of the studies were randomized, double blind, placebo-controlled studies.

An extensive search of the PubMed database was completed by the author between November 2016 and February 2017 using the key words “migraine” and “monoclonal anti-CGRP antibodies”. Articles were published in English, and in peer-reviewed journals. They were selected based on their relevance to the clinical question, and if they included patient oriented outcomes. Inclusion criteria were randomized, double blind trials published after 2001, that compared monoclonal anti-CGRP antibodies to a placebo in patients diagnosed with migraine headaches. Exclusion criteria included patients under the age of 18, patients with history of any other type of headache not classified as a migraine, or if they had tried 3 or more preventative drugs without efficacy. Summary of statistics reported or used include change from baseline, p-value, ARR, and NNT. Table 1 displays the demographics and characteristics of these three articles.

D. Table 1- Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bigal <sup>1</sup> (2016)	Double Blind RTC	261	18-65	Patients 18-55 with history of chronic migraine and compliant with electronic headache diary	Received onabotulinumtoxin A during the 6 months before study entry and if 3 or more preventive medications failed because lack of efficacy	39	A subcutaneous injection of monoclonal anti-CGRP antibody TEV-48125 900mg, at the beginning of the study
Bigal <sup>2</sup> (2015)	Double Blind RTC	297	18-65	Patients 18 and older who had migraine headaches for 8-14 days per month and showed compliance with electronic headache diary	Patients with chronic migraine, those using opioids or barbiturates for more than 4 days during the run in phase, those who tried 3 or more preventative drugs without efficacy	28	Subcutaneous monoclonal anti-CGRP antibody, TEV-48125 225 mg, injected at the beginning of the treatment cycle
Dodick <sup>4</sup> (2014)	Double Blind RTC	174	18-55	Patients 18-55 with more than 12 months of migraines, diagnosed before age 50, who were compliant with the electronic headache diary for a 28 day trial	Regular and effective use of preventative drugs within 3 months, received Botox A within last 6 months, history of Chronic tension headache, hypnic headache, new daily persistent headache, basilar- type, sporadic or familial hemiplegic migraine	11	Subcutaneous dose of monoclonal anti-CGRP antibody ALD403 1000mg, injected at the beginning of the study

## OUTCOMES MEASURED

Outcomes were measured on the basis of patient reporting. Patients reported migraine information daily, using an electronic headache diary. A migraine day is defined as any day with migraine or probable migraine according to the *International Classification of Headache Disorders II*. In Bigal (2016) et al<sup>1</sup>, the change from baseline in the number of headache days during the first, second, and third weeks of treatment with monoclonal anti-CGRP antibodies, specifically TEV-48125, was evaluated.<sup>1</sup> This paper will focus on the change from baseline in number of headache hours in week 1, using the 900-mg dose. The study by Bigal (2015) et al<sup>2</sup> measured the mean decrease from baseline in the number of days fulfilling migraine criteria during the third treatment cycle, weeks 9-12, among other secondary endpoints not discussed in this paper. This paper focuses on the mean change from baseline in migraine days during weeks 9-12 in those receiving 225 mg of TEV-48125 vs placebo. Dodick et al<sup>4</sup> measured the change from baseline in the frequency of migraine days in placebo vs ALD403 at various time points, among other secondary endpoints.<sup>4</sup> This paper focuses on mean change from baseline in number of migraine days in placebo vs ALD403 during weeks 5-8.

## RESULTS

Bigal (2016) et al<sup>1</sup> included 261 men and women aged 18 to 65 in the trial. 39 patients did not complete the study, for reasons including lack of efficacy, lost to follow-up, nonfatal adverse events, protocol deviation, and withdrawal of consent. Patients were randomized to receiving a 900-mg injection of monoclonal anti-CGRP TEV-48125, a 675/225-mg injection, or a visually matched placebo, however this paper will focus on the results of the efficacy of the 900-mg injection compared to the placebo.<sup>1</sup> The 900-mg arm group consisted of 85 individuals receiving 4 active injections of 225 mg/1.5 mL once monthly.<sup>1</sup> The placebo group consisted of

89 individuals who received 4 placebo injections monthly.<sup>1</sup> The mean decrease in number of headache hours in the first week of treatment will be discussed in this paper. All patients in all groups were diagnosed with migraines and could continue to use up to two standard migraine preventive medications if they had been on a stable dose for at least 3 months before the onset of the study.<sup>1</sup> They had to show higher than an 80% compliance with an electronic headache diary during a 28-day trial period to be eligible for the study.<sup>1</sup> They were excluded if they had received onabotulinumtoxinA 6 months before the onset of the study, or if 3 or more preventative medications had already failed due to lack of efficacy, although the reasoning for this was not stated.<sup>1</sup> Patients were selected from 62 sites in the US, including headache centers, neurology clinics, and primary care sites.<sup>1</sup> Overall compliance for baseline and the first month post treatment was 92%, but methods of this evaluation were not discussed in the article.<sup>1</sup> All efficacy variables were analyzed by the intent-to-treat principle. By the end of week 1, the LSM change from baseline in number of headache hours for the placebo group was -2.85 (SD 2.21) as compared to a larger decrease of -11.37 (SD 2.26) for 900-mg of TEV-48125.<sup>1</sup> LSM difference between the two was -8.52 (95% CI: -14.27, -2.87, p=0.003).<sup>1</sup> The NNT to achieve a greater than 50% reduction from baseline in number of headache hours by the end of week one was 11.1%, meaning that for every 11 patients treated with monoclonal anti-CGRP antibodies over placebo, one additional patient will experience a reduction in migraine hours.<sup>1</sup> Specific adverse events of the studied treatment were not discussed. These results can be seen in Table 2.

**Table 2: Analysis of data comparing reduction of headache hours after week 1 using 900-mg TEV-48125 and placebo reported by Bigal et al.**

LSM from baseline, placebo	LSM from baseline, TEV-48125	LSM difference	95% Confidence Interval	ARR	% NNT
-2.85 (2.21)	-11.37 (2.26)	-8.52	-14.27, -2.87	9	11

The 2015 Bigal et al<sup>2</sup> study included 297 men and women ages 18 to 65 who had migraine headaches 8-14 days per month. Patients were randomly assigned to groups, with 104 receiving a placebo, 95 received 225mg of TEV-48125, and 96 received 675 mg of TEV-48125.<sup>2</sup> All were given subcutaneous injections once every 28 days for 3 months.<sup>2</sup> Inclusion criteria is as follows: patients with at least 8-14 headache days per month, may have used stable doses of one migraine preventative drug for at least two months before screening, and may have used acute migraine drugs up to 14 days a month.<sup>2</sup> They had to demonstrate at least 80% compliance with an electronic headache diary during this 28-day run in phase.<sup>2</sup> Exclusion criteria is: patients fulfilling criteria for chronic migraines, used opioids or barbiturates for more than 4 days during the run-in phase, or had tried 3 or more preventative drugs without efficacy.<sup>2</sup> Patients were selected from 62 sites in the US, including headache centers, neurology clinics, and primary care sites.<sup>2</sup> 28 withdrew from the treatment whether from lack of efficacy, lost to follow up, protocol deviation, non-fatal adverse events, or withdrawal of consent.<sup>2</sup> 23% of patients in the placebo group and 27% of patients in the 225 mg group reported treatment related adverse events, which include minor injection site reactions and pain.<sup>2</sup> Intention to treat analysis was used.<sup>2</sup> This paper will focus on the mean change from baseline in migraine days during weeks 9-12 in those receiving 225 mg of TEV-48125 vs placebo.<sup>2</sup> The least square mean change in number of migraine-days in the third treatment cycle (weeks 9-12) relative to baseline was -3.46 migraine

days (SD 5.40) in the placebo group vs a larger decrease of -6.27 migraine-days (5.38) in the 225 mg group.<sup>2</sup> The LSM difference was -2.81 (95% CI:-4.07, -1.55, p<0.0001).<sup>2</sup>

NNT and NNH were not calculated because the study did not provide the number of patients that achieved reduction in headache days.

**Table 3: Analysis of data comparing LSM change from baseline in number of migraine days using placebo or 225mg TEV-48125 at weeks 9-12 reported by Bigal (2015) et al**

LSM change from baseline, placebo	LSM change from baseline, 900 mg TEV-48125	LSM difference placebo vs 225mg
-3.46 (5.40)	-6.27 (5.38)	-2.81 (-4.07, -1.55)

p<0.0001, CI 95%

The 2014 study by Dodick et al<sup>4</sup> included patients age 18-55 years suffering from migraines. Specific location sites for patient selection were not discussed. Inclusion criteria is as follows: patients with more than 12 months of migraine, diagnosed before age 50, frequency of 5-14 migraines per 28 day period in each of the 3 months before screening, and showed compliance with electronic headache diary in 25 out of the 28 day run in period.<sup>4</sup> During the 28-day screening, patients had to have experienced at least 5 and up to 15 migraines to be included.<sup>4</sup> Patients could use acute migraine drugs for 14 days or less per 28 day period in the 3 months before and during the initial screening period.<sup>4</sup> Exclusion criteria is: history of regular use of any headache preventative drug with evidence of efficacy from a placebo-controlled trial within 3 months of the initial screening, received botulinum A toxin within 6 months before screening, or had a history of any other type of headache.<sup>4</sup> 174 patients were randomly assigned to groups, with 82 receiving the placebo, and 81 received an infusion of ALD403.<sup>4</sup> 11 of the assigned individuals did not receive the allocated injection due to withdrawal of consent, ineligibility, or

scheduling issues.<sup>4</sup> Adverse events were experienced by 52% of patients in the placebo group and 57% in the ALD403 group, including URI, UTI, fatigue, nausea, vomiting, and arthralgia.<sup>4</sup> Intention to treat analysis was utilized. The study measured the mean change in migraine days from baseline in patients receiving placebo vs ALD403 at different time points.<sup>4</sup> This paper will focus on mean change from baseline in weeks 5-8. The mean change in migraine days from baseline between weeks 5-8 was -4.6 (3.6) for placebo as compared to a larger decrease of -5.6 (SD 3.0) for the ALD403 group.<sup>4</sup> The difference is -1.0, (95% CI: -2.0, 0.1, p=0.0306).<sup>4</sup>

**Table 4: Analysis of data comparing change from baseline in number of migraine days during weeks 5-8 using placebo vs ALD403 reported by Dodick et al**

Mean change from baseline, placebo	Mean change from baseline, ALD403	Difference in mean change from baseline
-4.6 (3.6)	-5.6 (3.0)	-1.0 (-2.0, 0.1)

p=0.0306, CI 95%

During weeks 5-8, patients who showed at least a 50% response was 50% of placebo patients (43/80), 75% of ALD403 patients (58/77), with the difference being 22% (95% CI: 7, 35).<sup>4</sup> Using this information, the Relative Risk Reduction (RRR) of 0.3888, Absolute Risk Reduction (ARR) of 0.21, and Number Needed to Treat (NNT) of 4.76 was calculated, meaning that for every 5 patients treated with ALD403 over placebo, one additional patient will experience reduction in migraine days than the placebo group.<sup>4</sup>

**Table 5: Analyzation of data for 50% responders during weeks 5-8 in placebo vs ALD403 treatment, as reported by Dodick et al**

CER (placebo)	EER (ALD403)	RRR	ARR	NNT
0.54	0.75	0.388888	0.21	4.76

## **DISCUSSION**

The three studies discussed in this review suggest that monoclonal anti-CGRP antibodies are effective in the treatment and prevention of migraine headaches in adults. All studies showed monoclonal anti-CGRP antibodies to be superior to the placebo in decreasing frequency of migraine headaches. The statistical significance in all three studies was  $p < 0.05$ , supporting monoclonal anti-CGRP antibodies in the treatment of migraine headaches.

The review has multiple limitations that are worth mentioning. Firstly, two studies included adults 18-65, while another focused on adults 18-55; however migraine headaches still affect both young and the elderly. Another limitation to this review is that no studies had an extensive follow up period to determine the efficacy of these treatments on a long-term basis. It is believed that the intravenous administration in these studies could have contributed to a higher rate of placebo response, as well as expectation in light of the novelty of the monoclonal anti-CGRP drug class. Another point to note is that all studies observed the efficacy of monoclonal anti-CGRP drugs on a scheduled, and not as needed or symptomatic basis.

The most significant aspect of this review to discuss is the novelty of this drug class. Monoclonal anti-CGRP drugs are still in clinical trials, and have not yet been approved by the FDA as a treatment for migraine headaches.<sup>6</sup> Unfortunately, once this drug does become available for public use, treatments are expected to begin at a cost of \$8,000, and insurance coverage is unclear.<sup>6</sup> However, it is encouraging to note that all trials in progress as well as completed, including the three mentioned in this review, have shown no major or concerning side effects of this new drug class. The class will hopefully be on the market in early 2018.<sup>6</sup>

## CONCLUSION

Monoclonal anti-CGRP antibodies are effective in the treatment of adults with migraines. The three randomized control trials discussed in this review showed improvement in outcomes measured after the use of monoclonal anti-CGRP antibodies. Based on these results, monoclonal anti-CGRP antibodies should be used as a new medication for the prevention and treatment of migraine headaches in adults.

Despite this convincing evidence, further research should be done in order to determine if long lasting relief can be achieved through the use of this treatment, potential long-term side effects of the medication, and their effectiveness and safety in children, the elderly, and pregnant women. Currently, there are four specific monoclonal anti-CGRP antibodies that are expected to be on the market within the next year or sooner. These are Alder, Amgen, Lilly, and Teva.<sup>8</sup> All but one of these medications requires administration by a physician, which introduces a burden to providers who will have to obtain approval for administration of the new drug.<sup>8</sup> Further research into more practical and independent administration methods for this migraine treatment will be beneficial to both patients and providers alike. All studies in this review investigated the effectiveness of monoclonal anti-CGRP antibodies in the treatment of migraines as compared to a placebo, so there is little information regarding their efficacy in comparison to the standard migraine treatments of today. However, there are currently several recently completed or ongoing Phase 3 trials underway, which are expected to shed some light on the efficacy of this treatment in comparison to the standard, treatment of choice, migraine medications.<sup>8</sup> Although the three studies discussed in this review answered the question that monoclonal anti-CGRP antibodies are effective in the treatment of adults with migraines, there are still many questions to be answered and much to be discovered on this new and promising treatment option.

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