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A Comparison of Anti-Calcitonin Gene-Related Peptide Monoclonal Antibodies and Standard Migraine Prophylaxis in Those with Episodic Migraines

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by

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Abstract

The purpose of this research study is to determine if anti-calcitonin gene related peptide monoclonal antibodies (CGRP mAbs) more effective and tolerable in reducing the number of migraine days in comparison to conventional migraine prophylactic use of Propranolol, Amitriptyline, and Topiramate. Migraines are debilitating and a frequent reason for primary care visits interfering with an individual's work, school, and daily life. Standard of care treatment options for migraine prophylaxis are drugs initially developed for other diseases and can lead to unnecessary and unwanted side effects decreasing treatment adherence in the prevention of migraines. In this literature review, electronic search databases including PubMed and CINAHL were used to search for clinical trials and randomized controlled trials. A variety of keywords and mesh terms were used to define a set of the literature regarding the use of CGRP mAbs in the prevention of episodic migraines as compared to standard treatments. Literature chosen for review were published after 2004. Sources were excluded if published prior to 2004, addressed prevention of chronic migraines, included small-molecule CGRP receptor antagonists, were conducted on children/adolescents, or included any conventional treatments not being investigated, such as onabotulinumtoxinA. The research selected and reviewed for this project demonstrated that conventional migraine prophylaxis treatments are not well tolerated and have poor adherence rates. Calcitonin gene-related peptide monoclonal antibodies are proven effective in the prevention of episodic migraines and improvement of quality of life when compared to placebo. However, more research is needed with head-to head trials of CGRP mAbs in direct comparison to standard prophylactic migraine medications in order to determine which is more effective and tolerable.

Keywords: migraine prevention, episodic migraines, CGRP mAbs, Propranolol, Amitriptyline, Topiramate, Eptinezumab, Galcanzumab, Fremanezumab, Erenumab

Introduction

Calcitonin gene-related peptide (CGRP) is a neuropeptide that is known to cause potent arterial vasodilation. The role of CGRP in migraines is thought to be due to its influence on the trigeminovascular nociceptive system leading to sustained neurogenic inflammation and increased pain (Yuan et al., 2017). Studies have shown elevated levels of CGRP during migraine attacks; therefore, inhibition of this neuropeptide has been under study for the treatment and prevention of migraine headaches. The United States Food and Drug Administration (FDA) has approved of four CGRP-targeted monoclonal antibodies (mAbs) that hinder the function of CGRP (Cohen, Yuan, & Silberstein, 2022). These four CGRP mAbs will be investigated in this scholarly project for the safety and efficacy in prevention of migraines.

According to the International Classification of Headache Disorders 3rd ed. (ICHD-3), diagnostic criteria for migraines includes having at least five attacks lasting 4-72 hours with either nausea and/or vomiting, or photophobia and phonophobia. The headache must not be better accounted for by another ICHD-3 diagnosis. Migraines must have at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity.

The ICHD-3 classifies migraines based on frequency as either episodic or chronic. Migraines are considered episodic when they occur more than 4 but less than 15 days per month while chronic migraines occur over 15 days per month. Episodic migraines are more common than chronic migraines with about 2% of the total general population meeting the criteria for

chronic migraines. Episodic migraines also have the potential to progress to chronic, therefore the focus of this review is on the episodic migraine population (Pascual, 2015).

Statement of Problem

According to the American Migraine Foundation, migraines are the 2nd leading cause of disability in the United States affecting more than 36 million Americans and 1 billion people worldwide (American Migraine Foundation, 2023). This debilitating condition is a frequent reason for primary care visits as migraines interfere with an individual's work, school, and daily life. Standard of care treatment options for migraine prophylaxis are drugs initially developed for other diseases such as hypertension, epilepsy, and depression. Use of these medications can lead to unnecessary and unwanted side effects leading to decreased treatment adherence in the prevention of migraines. Research is needed to show the efficacy, safety, and tolerability of other treatment options including CGRP mAbs for those suffering from migraines.

Research Questions

In adults with episodic migraines with or without an aura, are anti-calcitonin gene related peptide monoclonal antibodies (CGRP mAbs) more effective in reducing the frequency/number of migraine days than conventional migraine prophylactic use of Propranolol, Amitriptyline, or Topiramate? Is there a statistically or clinically significant difference in tolerability or adherence of CGRP mAbs as compared to conventional migraine prophylaxis?

Methods

A literature review was conducted using electronic search databases including PubMed and CINAHL. Additional research articles were found via similar articles in PubMed. Keywords and mesh terms were used to define a set of the literature regarding the use of CGRP mAbs in the prevention of episodic migraines as compared to standard treatments resulting in 635 articles. The search was limited to clinical trials and randomized controlled trials in PubMed within the last nine years which resulted in 40 articles. The literature was further searched for specific

CGRP mAbs including erenumab, fremanezumab, eptinezumab, and galcanezumab for the prevention of episodic migraines with all searches narrowed to past 10 years, clinical trials, and randomized controlled trials. Galcanezumab for episodic migraine resulted in 44 studies, fremanezumab for episodic migraine resulted in 26 studies, eptinezumab for episodic migraine resulted in 11 studies, and erenumab for episode migraine resulted in 27 studies. Each of the CGRP mAbs were also searched versus standard migraine prevention resulting in 5 studies. Any studies that addressed prevention of chronic migraines, small-molecule CGRP receptor antagonists, conventional treatments not being investigated, systematic reviews, and studies on children/adolescents were excluded.

Research on the standard of care medications for migraine prevention was conducted through PubMed. Propranolol, Amitriptyline, and Topiramate were searched for the prevention of episodic migraines. Studies completed in the last 10 years were limited and search was widened to last 20 years. Those that included prevention treatments not included in this study, such as onabotulinumtoxinA, were excluded. This resulted in 8 articles.

Literature Review

Effectiveness, safety, and tolerability of Propranolol, Amitriptyline, and Topiramate in Migraine Prevention.

Diener et al. (2004) explored the efficacy and safety of Topiramate (TPM) in the prevention of migraines using a placebo and an active control of Propranolol (PROP). This was a double-blind, parallel-group study across 61 centers and 13 countries. Those ages 12-65 years with a diagnosis of episodic migraines with or without aura according to International Headache Society (IHS) criteria for at least one year qualified for the study. Eligible patients were randomized into one of four groups: placebo (n=143), TPM 100 mg (n=139), TPM 200 mg (n=143), or PROP 160 mg (n=143). The average age across all groups was just over 40 years

with ≥76% of patients being female. Patients in the study recorded their headache information including migraine and non-migraine characteristics. These characteristics in each of the groups were generally well-matched at baseline. Primary endpoint in the study by Diener et al. (2004) was comparison of TPM with placebo in change from baseline of mean monthly migraine frequency. Important secondary endpoints included: change in mean number of migraine days, change in average monthly rate of rescue medication use, and ≥50% reduction in monthly migraine frequency (responder rate). Safety was assessed by recorded treatment-emergent adverse events (TEAEs), clinical laboratory testing, and physical examinations including vital signs, body weight, and neurological examinations (Diener et al., 2004).

Diener et al. (2004) determined that the TPM 100 mg group met the primary endpoint, however the TPM 200 mg did not. For comparison between the TPM and PROP treatment groups, 95% confidence intervals were investigated. The TPM 100 mg group demonstrated a greater reduction in average monthly migraine frequency of -1.6 days (Standard Deviation (SD) 0.22, p =.011) as compared to placebo. The TPM 100 mg group also demonstrated a greater decrease than placebo in the following secondary endpoints: -1.8 mean migraine days (SD 0.25, p =.026), -1.5 days monthly rescue medication use (SD 0.21, p =.029), and 37% of patients achieving ≥50% responder rate (p =.010). The TPM 100 mg and PROP groups demonstrated similar results for the primary endpoint and all key secondary endpoints (Diener et al., 2004).

The TPM 200 mg group in the study by Diener et al. (2004) only showed a statistically significant improvement versus the placebo in responder rate, with 35% of patients achieving ≥50% reduction in average monthly migraine frequency (p =.028). The TPM 200 mg group did not reach statistical significance for the remaining measurements, most likely due to a high dropout rate of 54.5% (n =65). Of the 78 participants that dropped out of the TPM 200 mg group,

63 of them experienced TEAEs that led to discontinuation. Twenty-eight percent of patients in the TPM 100 mg group, 20% in the PROP group, and 10% in the placebo group discontinued treatment due to a TEAE. Most frequent reports of TEAEs in the TPM groups were paresthesia, difficulty concentrating, nausea, fatigue, insomnia, and anorexia. There were no clinically significant changes in laboratory tests, vital signs, or neurological exams. Patients in the placebo group showed an average 0.6% weight gain while patients in the TPM 100 mg group experienced an average decrease of -2.7% in weight. The TPM 200 mg group also showed an average decrease in weight of -3.4%. Patients in the PROP group demonstrated an average 2.3% weight gain (Diener et al., 2004).

Limitations of the study by Diener et al. (2004) include: high number patients dropping out of the TPM 200 mg group, no statistical comparison between TPM and PROP, potential conflicts of interest, and temporal domain. The large number of dropouts in the TPM 200 mg group may have resulted in the lack of statistical significance against placebo. There are potential conflicts of interest with authors receiving grants from pharmaceutical companies. Additionally, studies conducted on TPM and PROP in the last 10 years were limited, therefore this study was completed 18 years ago.

A study comparing the efficacy and tolerability of TPM and Amitriptyline (AMI) in the prevention of episodic migraine was conducted by Dodick et al. (2009). This was a 26-week, double-blind, double-dummy, parallel, noninferiority study conducted across 32 sites in the United States. Three hundred and forty-six eligible patients 18 years of age or older were randomized 1:1 into the TPM (*n*= 177) or AMI (*n*= 169) groups. Inclusion criteria were those with episodic migraine according IHS criteria, while exclusion criteria were: >2 failed migraine-preventive medications, failed trial of TPM or AMI, >15 days per month of abortive migraine

medication use, migraine without headache and aura only, history of cluster headaches, progressive neurological disorder, history of medical condition in which use of AMI is contraindicated, a major psychiatric disorder, history of an unstable medical condition within the past two years, history of drug or alcohol abuse within the past two years, history of liver dysfunction, or those who were pregnant. Patients across the two groups demonstrated similar baseline demographics and headache characteristics based on recorded migraine diaries. Both the TPM and AMI groups started with a dose of 25 mg titrating weekly, over a period of four weeks, to a maximum of 100 mg, or maximum tolerated dose. The titration schedule was the same for both the groups and a stable dose of 50 mg was required to continue onto the 22-week maintenance period (Dodick et al., 2009).

Data from headache records were used to analyze primary and key secondary efficacy variables. These records were kept by each patient and included headache duration, frequency, severity, and migraine symptoms including nausea, vomiting, photophobia, and phonophobia. The primary endpoint in the study completed by Dodick et al. (2009) was the change from baseline in mean number of monthly migraine episodes. Important secondary endpoints assessing mean monthly change from baseline to end of the double-blind phase included: rate of days with migraine, rate of abortive migraine medication use, migraine duration, migraine severity, as well as the duration and severity of migraine symptoms including nausea, vomiting, photophobia, and phonophobia. Subjective measurements including a single question functional disability survey, three domains of the Migraine-Specific Quality of Life Questionnaire (MSQ), the Migraine Disability Assessment Score (MIDAS), the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), and the Weight Satisfaction Scale Questionnaire (WSSQ) were all administered. Safety was measured by monitoring of TEAEs,

clinical laboratory tests, and physical examinations including neurological exams, vital signs, body weight, and electrocardiograms (EKGs).

Dodick et al. (2009) concluded that TPM was noninferior to AMI regarding the primary endpoint. There was no statistical significance between the two treatment groups with a mean reduction of -2.6 monthly migraine episodes in TPM group and -2.7 in the AMI group (95% CI -0.6 to 0.7; $p > .05$). There also was no statistically significant difference in any of the secondary endpoints between the TPM and AMI groups. The TPM group demonstrated a mean reduction of -3.2 in total migraine days and -3.1 in the AMI group (95% CI -0.9 to 0.7; $p > .05$). The rate of abortive medication use was measured in days with the TPM group demonstrating a mean reduction of -2.6 and -2.8 in the AMI group (95% CI -0.4 to 0.9; $p > .05$). A reduction of -1.0 days in migraine duration was seen in the TPM group and -1.1 in the AMI group (95% CI -0.1 to.4; $p > .05$). The reduction in severity of migraine characteristics including nausea, photophobia, and phonophobia was -0.3 in the TPM group and -0.2 in the AMI group (95% CI -0.2 to 0.1; $p > .05$). The frequency of vomiting was -0.3 in the TPM group and -0.4 in the AMI group (95% CI -0.3 to 0.4; $p > .05$).

Dodick et al. (2009) did discover statistically significant differences in the functional disability question, WSSQ, and the three domains of the MSQ. None of the remaining subjective measurements demonstrated statistically significant differences. The TPM group demonstrated a -0.33 change from baseline on the functional disability question compared to -0.19 in the AMI group (95% CI -0.3 to 0.0; $p = 0.04$). Those in the TPM treatment group recorded an overall improvement in weight satisfaction on the WSSQ with a score of 0.8, whereas the AMI group recorded an overall decrease with a score of 0.3 (95% CI 0.7-1.3; $p < .001$). The three domains of the MSQ assessed were the role function-restrictive (RR), emotional function (EF), and role

function-preventive (RP). RR measured the extent performance is limited by migraines, EF estimated the feelings of frustration and helplessness caused by migraines, and RP measured the degree to which performance of daily activities was restricted by migraines. The TPM treatment group demonstrated a mean change of 23.7 on the RR and 18.4 in the AMI group (95% CI 1.2-9.4; $p = .012$), 25.6 on the EF for the TMP group and 20.5 in the AMI group (95% CI 0.5-9.7; $p = .029$), and 16.7 on the RP for the TMP group and 12.5 in the AMI group (95% CI 0.8-7.5; $p = .014$).

Dodick et al. (2009) noted small changes from baseline in both groups in regard to BMI, blood pressure, and heart rate. No statistically significant changes in clinical laboratory tests and no deaths were reported. In the TPM group 85.9% experienced TEAEs and approximately 20% discontinued treatment due to these effects, while 88.8% in the AMI group experienced TEAEs and approximately 22.5% discontinued treatment due to TEAEs. The most common TEAEs leading to discontinuation in the TPM group were fatigue, confusion, dizziness, anxiety, and hypoesthesia. For the AMI group the most common were weight increase, fatigue, worsening of migraine, somnolence, and dry mouth.

While Dodick et al. (2009) demonstrated that TPM 100 mg was at least as effective as AMI 100 mg in decreasing mean monthly rate of migraines, weaknesses of the study include limited demographics with 84.9% of the participants being female and 84.6% being white. Another limitation of the study was the overall large number of exclusion criteria, which may make it difficult to infer the results to the general population. Dodick et al. (2009) did also discuss how use of the Q-LES-Q-SF and MIDAS could lead to limitations of the study as they may not adequately capture the full impact of migraines on an individual quality of life since the recall periods for these assessments are one week and three months respectively. Like the study

by Diener et al. (2004), recent studies conducted on TPM and AMI are limited therefore the study included here is 13 years old.

Role, effectiveness, and safety of CGRP-mAbs in migraine prevention.

Eptinezumab

Ashina et al. (2020) conducted a phase 3 study known as The Prevention of Migraine via Intravenous ALD403 Safety and Efficacy 1 (PROMISE-1). This study was on the efficacy and safety of eptinezumab for preventive treatment of those with episodic migraines. It was a randomized, double-blind, placebo-controlled trial that included adults ages 18-75 years with a diagnosis of episodic migraines according to the International Classification of Headache Disorders, 3rd ed. (ICHD-3) criteria at or before the age of 50 years.

The primary endpoint in the study by Ashina et al. (2020) was the change from baseline monthly migraine days (MMDs) over weeks 1-12 with key secondary endpoints being ≥75% migraine reduction rate over weeks 1-4, ≥75% migraine reduction rate over weeks 1-12, ≥50% migraine reduction rate over weeks 1-12, and percentage of those with migraine the day following dosing. Eight-hundred and eighty-eight eligible patients were randomly placed into one of four groups in a 1:1:1:1 ratio. The groups included 30 mg eptinezumab, 100 mg eptinezumab, 300 mg eptinezumab, or placebo. Patients in each group received up to four treatments via IV day 0, week 12, week 24, and week 36. Of the 888, 835 patients remained in Ashina et al. (2020) study until week 12 and 77.8% of the patients were given all four doses (300 mg (*n*=213), 100 mg (*n*=212), 30 mg (*n*=205), and placebo (*n*=205). Efficacy of treatment was assessed by patient's electronic diary entries which included migraine characteristics, severity, duration, and use of any abortive migraine medications. Safety was evaluated by adverse event monitoring, measuring vital signs, physical examinations, 12-lead EKGs, clinical laboratory

testing, related medication use, and the Columbia-Suicide Severity Rating Scale (C-SSRS) (Ashina et al., 2020).

There was a statistically significant decrease in MMDs from baseline frequency during weeks 1-12 in the 300 mg and 100 mg groups as compared to the placebo group. The eptinezumab 30 mg group was not considered statistically significant in relation to the placebo. Monthly migraine days at baseline for all groups including placebo were similar. During weeks 1-12 mean MMDs for the 100 mg group was reduced by -3.9 days (95% CI -4.25 to -3.47; p=0.0182), -4.3 days (95% CI -4.70 to -3.90; p=0.0001) for the 300mg group, and -3.2 days (95% CI -3.60 to -2.79) for the placebo group. At the end of week four, 30.8% (n= 68) of patients in the 100 mg group experienced ≥75% reduction in migraines (95% CI 2.4% - 18.6%; p= 0.0112) and 31.5% (n= 70) of those in the 300 mg group (95% CI 3.2% - 19.3%; p=0.0066) compared to 20.3% (n= 45) in the placebo. Additionally, the 300 mg group experienced statistical significance compared to placebo for the secondary endpoints of ≥75% migraine responder rate in weeks 1-12 and ≥50% responder rate in weeks 1-12. Sixty-six patients (29.7%) experienced ≥75% reduction in migraines (95% CI 5.8% - 21.2%; p= 0.0007) and 125 (56.3%) experienced ≥50% reduction in migraines (95% CI 9.8% - 28%; p= 0.0001) through week 12. Regarding safety, the authors concluded 59.7% of patients experiencing at least one treatment-emergent adverse event (TEAE) and the percentage of patients with any TEAE was similar among eptinezumab and placebo groups. A total of 29 patients withdrew due to a TEAE, 12 in the 30 mg group, six in the 100 mg group, five in the 300 mg group, and six in the placebo group (Ashina et al., 2020).

Major limitations of the study conducted by Ashina et al. (2020) were limited geographic diversity, low number of non-Caucasians, and decreased number of men. Additionally, the

overall response to placebo was high. The study was conducted across two countries with a mean patient age of 39.8 years with 61.4% over 35. Just over 84% of the patients were female and white.

While Ashina et al. (2020) assessed the results of the PROMISE-1 study over the course of the first 12 weeks, Smith et al. (2020) analyzed the safety and efficacy of eptinezumab over one year. The study design, patients, and demographics in the study by Smith et al. (2020) remain the same as Ashina et al. (2020). In the study conducted by Smith et al. (2020), outcomes assessed via patient electronic diary included: MMDs from weeks 1-48 and during each 12-week dosing interval, responder rates (≥50%, ≥75%, 100%), and abortive migraine medication use. Additionally, the Medical Outcomes Study Short-Form Health Survey (SF-36, version 2.0) was used to assess efficacy of eptinezumab. Smith et al. (2020) measured tolerability and safety of eptinezumab in the same manner as Ashina et al. (2020) measuring physical and laboratory exams, monitoring TEAEs, and recording concomitant medication use.

Of the 888 patients treated during PROMISE-1, 77.8% received all four doses through week 48 of treatment, 167 in the 30 mg group, 177 in the 100 mg group, 180 in the 300 mg group, and 167 in the placebo group. Since eptinezumab at 30 mg was found to be statistically insignificant during Ashina et al. (2020) study, Smith et al. (2020) did not further investigate this dosage. Smith et al. (2020) examined 95% confidence intervals for the comparison of the eptinezumab and placebo groups. The mean reduction in MMDs during weeks 13-24 was -4.5 days in the 100 mg group and -4.8 days in the 300 mg group compared to -3.8 day in the placebo. During weeks 25-36 the mean reduction in MMDs was -4.7 for the 100 mg group and -5.1 for the 300 mg group compared to -4.0 in the placebo. The mean reduction in MMDs during

weeks 37-48 was -4.5 for the 100 mg group and -5.3 for the 300 mg group compared to -4.1 in the placebo group.

Smith et al. (2020) also found that the percentage of patients with ≥50% and ≥75% response rate in weeks 1-48 was persistently higher in the eptinezumab 100 mg and 300 mg groups as compared to placebo. One-hundred and forty-three (64.7%) of those within the 100 mg group experienced ≥50% reduction in MMDs and 155 (69.8%) in the 300 mg group compared to 123 (55.4%) in the placebo group through week 48. Regarding abortive headache medication use, patients were placed into two categories at baseline, 1-9 days per month or ≥10 days per month. Those in the 1-9 days per month experienced -0.8 and -2.6 less days of abortive medication use in the 100 mg and 300 mg eptinezumab groups respectively as compared to –1.3 in the placebo. In the ≥10 days per month -8.9 and -11.1 less days of abortive medication use were seen in the 100 mg and 300 mg groups respectively in contrast to -7.9 days in the placebo group. By the end of the study, patients in the eptinezumab groups experienced improvements of 3.1-5.2 points on the bodily pain domain of the SF-36 in comparison to 2.1 in the placebo group. Additionally, patients in the eptinezumab groups experienced 2.1-2.9 point improvement on the physical role-functioning domain of the SF-36 versus 1.5 in the placebo group. In the eptinezumab 100 mg group TEAEs dropped from 33.2% with the first dose to 18.5% with the last dose and 32.6% after dose one in the eptinezumab 300 mg group to 21.2% with the last dose.

Limitations of this yearlong PROMISE-1 study conducted by Smith et al. (2020) was similar to those mentioned by Ashina et al. (2020) including limited geographic diversity, low number of non-Caucasians, decreased number of men and an overall high response to the placebo. Additionally, patients were not fully adherent with their electronic diary for one year and nearly 25% of patients ended the study early.

Galcanezumab

The efficacy and safety of galcanezumab in the prophylactic treatment of episodic migraines was studied by Skljarevski et al. (2018) in a phase 3, double-blind, placebo-controlled study over a period of six months across 109 study sites and 11 different countries. Those eligible for the study included individuals 18-65 years of age with a diagnosis of episodic migraine with or without aura per the ICHD-3. Patients were not included if they failed treatment with three or more migraine prevention drugs in the past, if they were currently using opioids or barbiturates more than two times per month, had been exposed to galcanezumab or another CGRP mAb within the past 30 days, had a known hypersensitivity to several drugs, or had any medical or psychiatric illnesses that would prevent engagement in the study.

The primary purpose of Skljarevski et al. (2018) study was to assess the mean change from baseline in number of monthly migraine headache days (MHDs) during the six months of treatment comparing galcanezumab to a placebo. The following key secondary endpoints were included in the study comparing baseline to the six-month treatment duration: mean percent of patients with a decrease of ≥50%, ≥75%, and 100% in monthly MHDs, mean change in monthly MHDs with abortive migraine medication use, mean change of the Patient Global Impression of Severity (PGI-S) rating, and mean change in the RR domain score of the MSQ. Skljarevski et al. (2018) assessed safety by monitoring TEAEs, discontinuation rates due to AEs, vital signs, body weight, and deaths. Nine-hundred and fifteen patients were randomized in a 2:1:1 ratio into the placebo (*n*=461), galcanezumab 120 mg (*n*=231), or galcanezumab 240 mg (*n*=223) groups with over 83% of patients completing treatment in each group. Demographics and baseline scores were similar across all groups with 85% females and over 68% Caucasian in each group.

The outcome of the study conducted by Skljarevski et al. (2018) demonstrated a statistically significant difference in the overall mean reduction of monthly MHDs by 4.3 (SD 0.27) for the galcanezumab 120 mg group (CI 95% -4.8 to -3.8; $p < .001$) and 4.2 (SD 0.27) for 240 mg group (95% CI -4.7 to -3.7; $p< .001$) as compared to 2.3 (SD 0.2) in the placebo. Skljarevski et al. (2018) also found that both doses of galcanezumab met all key secondary endpoints. Fifty-nine percent of patients in the galcanezumab 120 mg group experienced ≥50% reduction in MHDs (95% CI 55 to 64; $p <.001$), 34% experienced ≥75% reduction (95% CI 29 to 38; $p <.001$), and 12% experienced 100% reduction in MHDs (95% CI 9 to 15; p <.001). Fifty-seven percent of patients in the galcanezumab 240 mg group attained ≥50% reduction in MHDs (95% CI 52 to 61; $p <.001$), 34% experienced ≥75% reduction (95% CI 30 to 39; $p <.001$), and 14% attained 100% reduction in MHDs (95% CI 11 to 17; $p <.001$). This was compared to the placebo in which 36% experienced ≥50% reduction, 18% with ≥75% reduction, and 6% with 100% reduction in MHDs.

Patients in the galcanezumab 120 mg group used abortive migraine medication 3.7 days less than baseline (95% CI -4.1 to -3.2; $p<.001$) and 3.6 days in the 240 mg group (95% CI -4.1 to -3.2; $p <.001$) as compared to 1.9 in the placebo. Statistical improvements were seen in the MSQ and the PGI-S of both galcanezumab dosing groups as compared to placebo. Those within the 120 mg treatment group demonstrated a mean change of 28.5 points (95% CI 26.2 to 30.7; $p <.001$) and 27 points (95% CI 24.7 to 29.3; $p <.001$) on the MSQ RR in comparison to 19.7 points for those within the placebo. A mean change of -1.2 points (95% CI -1.4 to -1.1; $p=.002$) was seen in the 120 mg group and as well as the 240 mg group (95% CI -1.3 to -1.0; $p =.012$) in the PGI-S compared to -0.9 for those in the placebo group.

TEAEs were reported in 65% of the 120 mg and 71.5% of the 240 mg galcanezumab groups as compared to 62.3% in the placebo. Of those who discontinued the study due to AEs 1.7% were from the placebo group, 2.2% from the 120 mg group, and 4.0% from the 240 mg galcanezumab group. There were no statistically significant differences in vital signs and body weight. No deaths were reported in the study by Skljarevski et al. (2018).

Limitations of the conducted by Skljarevski et al. (2018) were low number of non-Caucasians, decreased number of men, and several authors of the study are employees and minor shareholders of the company who funded the study while others report they have received grants, support, and fees from publishing and pharmaceutical companies.

Fremanezumab

A 12-week study on the effectiveness and tolerability of fremanezumab for prevention of episodic migraines was completed by Dodick et al. (2018). This was a phase 3, double-blind, parallel-group study across 123 sites in nine different countries. A total of 874 patients between the ages of 18-70 years were included based on ICHD-3 criteria for episodic migraines for at least 12 months prior to screening. Patients in this study were excluded if they used onabotulinumtoxinA four months or less before the screening, used barbiturates or opioids for more than four days during screening, or failed two or more migraine prevention treatments with at least three months of treatment. Patients who in the two months prior to screening had used an intervention or device like nerve blocks were not included in this study. The patients were randomized in a 1:1:1 fashion into either the fremanezumab monthly treatment group (*n*=289), the single-higher dose of fremanezumab (*n*=291), or the placebo (*n*=294). Patients in the monthly treatment group received one 225 mg/1.5 mL injection of fremanezumab and two placebo injections at baseline, week four, and week eight. Those in the single-higher dose treatment

group received three injections of 225 mg/1.5mL fremanezumab (for a total of 675 mg) at baseline with placebo only injections at weeks four and eight (Dodick et al., 2018). Baseline demographics and clinical characteristics were similar among all treatment groups.

The primary endpoint for Dodick et al. (2018) study was the mean difference from baseline in the number of MMDs during the 12-week treatment period after first injection. Secondary endpoints included: ≥50% decrease in mean number of MMDs from baseline to week 12, mean change from baseline to week four in number of MMDs, change from baseline to week 12 in mean monthly days with use of abortive migraine medications, and mean change in the MIDAS. Dodick et al. (2018) measured safety with physical examinations, clinical laboratory tests, vital signs, EKGs, reported AEs, and medication use.

The mean reduction of MMDs during the 12-week period after the first dose was -3.7 days (95% CI -4.15 to -3.18; p <.001) for the monthly fremanezumab group and -3.4 days (95% CI -3.94 to -2.96; p <.001) for the single-higher dose group as compared to -2.2 days for the placebo group. Key secondary endpoints were investigated using 95% confidence intervals. The secondary endpoints were met with 47.7% (n= 137) of patients in the monthly dosing group attaining ≥50% decrease in mean number of MMDs (p <.001) and 44.4% (n= 128) in the single-higher dose group (p <.001) compared to 27.9% (n= 81) in the placebo group. The monthly fremanezumab group experienced a decrease of -3.0 (p<.001) in mean monthly days with any abortive medication use and -2.9 days in the single-higher dose group (p<.001) as compared to -1.6 days in the placebo group. The secondary endpoint of mean change from baseline to week four in number of MMDs was statistically significant (p <.001) for each of the fremanezumab groups with -3.5 days for the monthly group and -3.3 days for the single-higher dose group as compared to -1.7 days in the placebo group. Dodick et al. (2018) also found a significant

difference in the MIDA score for the fremanezumab monthly dosing group of -24.6 (p <.001) and -23.0 for the single-higher dosing group (p <.002) as compared to -17.5 for the placebo.

Regarding safety, Dodick et al. (2018) concluded that 66% of patients in the fremanezumab monthly group and 66% in the single higher group experienced at least one AE as compared to 58% in the placebo group. Serious AEs and AEs leading to discontinuation were similar across all groups with 2% or less. There were no pertinent changes in vital signs, EKG findings, laboratory tests, or physical exam measures. One reported death occurred over 100 days after fremanezumab single-higher dose was given, but this death was determined to be unrelated to the study.

Limitations of the study include potential financial conflicts, short-term follow up, and no comparison of fremanezumab against other preventative medications. Additionally, the study did not include patients with more than two failed preventive drugs in the past, those with a continuous headache, and certain populations like those who were pregnant or had a history of acute coronary syndrome, ischemic stroke, or a compromised blood-brain barrier.

Goadsby, Silberstein, et al. (2020) expanded the study by Dodick et al. (2018) to assess the long-term tolerability, safety, and efficacy of fremanezumab. Patients who completed the study by Dodick et al. (2018) had the option to enroll in Goadsby, Silberstein, et al. (2020) study; these individuals are known as the rollover patients. Goadsby, Silberstein, et al. (2020) additionally recruited new patients who met the inclusion criteria of 18-70 years of age with migraine according to the ICHD-3 for ≥ 12 months prior to screening. The exclusion criteria set by Dodick et al. (2018) was not used by Goadsby, Silberstein, et al. (2020) for new patients. Goadsby, Silberstein, et al. (2020) study was a double-blind, parallel-group, phase 3 study that was completed over 135 sites. The screening period was completed only by the new patients

followed by 12-months of treatment for rollover and new patients. Six hundred and sixty-one rollover patients from Dodick et al. (2018) study continued with the same dosing regimen (monthly treatment group receiving one 225 mg/1.5 mL injection of fremanezumab plus two placebo injections and single-higher dose treatment group receiving three injections of 225 mg/1.5mL fremanezumab [total of 675mg] every three months with placebo injections between). Additionally, 119 new patients were randomized into the fremanezumab monthly or single-higher dose (quarterly) groups for a total of 386 monthly and 394 quarterly. Baseline demographics and clinical characteristics were alike across the two treatment groups.

The purpose of the study by Goadsby, Silberstein, et al. (2020) was to assess the long-term safety and tolerability of fremanezumab for prophylactic use in migraines. Goadsby, Silberstein, et al. (2020) evaluated safety by physical examinations, reported AEs, clinical laboratory tests, vital signs, EKGs, and suicidality via the C-SSRS. Injection-site monitoring was of special interest to Goadsby, Silberstein, et al. (2020), therefore monitoring immediately following injection and one hour after administration for any signs of reaction including induration, redness, bruising, and pain was completed. Measurements of redness, induration, and bruising were completed, and a 5-point pain scale was used. If the patient presented with a severe injection-site reaction one hour after injection the patient was reassessed three hours later and every hour after until the reaction or pain was less severe.

Additionally, Goadsby, Silberstein, et al. (2020) used the patient's electronic diary to assess the mean difference from baseline in number of MMDs, headache days, days with any abortive headache medication use at months three, six, and 12, and the percent of patients with ≥ 50% decrease from baseline in mean number of MMDs at months six and 12. Goadsby,

Silberstein, et al. (2020) used the MIDAS to assess average change from baseline in headache-related disability at months six and 12.

Of the 780 total patients with episodic migraine treatment included in the Goadsby, Silberstein, et al. (2020) study, over 79% completed treatment. Only 5% of AEs in each treatment group led to study withdrawal. Injection-site reactions remained the most common AE with 30-32% of those within either fremanezumab treatment group experiencing injection-site pain and 29-38% injection-site induration. Serious cardiovascular related AEs and suicidal ideation were determined to be unrelated to the study drug. One death occurred during the study about 300 days after fremanezumab dose and was determined unrelated to the study drug as the patient had a history of atrioventricular block and hypertension. Liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were monitored with no serious elevations needing treatment. No severe hypersensitivity reactions occurred during the study. There were also no clinically significant differences in changes from baseline for any physical examinations, vital signs, clinical laboratory tests, or EKGs (Goadsby, Silberstein, et al., 2020).

In Goadsby, Silberstein, et al. (2020) study both fremanezumab treatment groups demonstrated a decrease in number of MMDs from baseline to month 12 (-5.2 quarterly and -5.1 monthly). Also, fremanezumab treatment groups demonstrated decreases in number of monthly headache days (-4.9 quarterly and -4.8 monthly), monthly number of days with any abortive headache medication use (-4.6 quarterly and -4.3 monthly), and ≥ 50% response rate from baseline to month 12 (66% quarterly and 68% monthly). Those in the fremanezumab quarterly treatment group demonstrated an average 26.0 improvement on the MIDAS and 27.4 for the monthly treatment group from baseline to month 12.

The study by Goadsby, Silberstein, et al. (2020) did not include a placebo group as it was determined with other studies, such as Dodick et al. (2018) study that fremanezumab is effective in treatment of episodic migraines. This study was not based on any statistical analysis and all primary and secondary variables were summarized with descriptive statistics. Other limitations discussed in Dodick et al. (2018) study was similar to Goadsby, Silberstein, et al. (2020) study including no comparison of fremanezumab against other preventative medications, not including patients with more than two failed preventive drugs in the past and those who had a continuous headache.

Erenumab

Erenumab was assessed in the prevention of episodic migraines by Goadsby et al. (2017) in a double-blind, placebo-controlled study across 121 sites. Goadsby et al. (2017) study included a 24-week treatment phase in which 955 patients were randomized in 1:1:1 into the 70 mg erenumab (*n*= 317), 140 mg erenumab (*n*= 319), or placebo (*n*=319) groups. All groups were well-balanced in regard to baseline demographics and clinical characteristics. Treatment injections occurred at day one and then weeks four, eight, 12, 16, and 20. Patients ages 18-65 years old with a diagnosis of migraine according to the ICHD-3 for at least one year before screening were eligible for inclusion. Those who received botulinum toxin within the prior four months, had a history of hemiplegic migraine or cluster headache, used devices or procedures in the prior two months for migraine prevention, or had no response with two or more migraine preventive treatments were excluded from the study.

The primary objective in Goadsby et al. (2017) study was to assess the average change from baseline in number of MMDs to months 4-6 of treatment. Key secondary endpoints included average number of days abortive migraine medication was used, mean change in

physical impairment and everyday activity domains of the Migraine Physical Function Impact Diary (MPFID), and at least 50% reduction from baseline in mean number of MMDs. All of these secondary endpoints were evaluated from baseline to the final three months of treatment. An electronic diary was used to keep data on migraine and headache characteristics. Safety was evaluated by clinical laboratory tests, EKGs, and vital signs.

A 95% confidence interval was examined in comparing the erenumab treatment groups to the placebo. The 70 mg group demonstrated a decrease in mean MMDs by -3.2 days (SD 0.2) (p <.001) and -3.7 in the 140 mg group (p <.001) in comparison to -1.8 days in the placebo group meeting the primary endpoint. Secondary endpoints were also met.

There was at least a 50% reduction in mean MMDs from baseline to the final three months for 43.3% of those in the 70 mg group (p <.001) and 50% in the 140 mg group (p <.001) as compared to 26.6% in the placebo. Average number of days in which abortive medication was used was 1.1 days less in the 70 mg group (p <.001) and 1.6 days in the 140 mg group (p <.001) in comparison to 0.2 days for those in the placebo group. Everyday activity impairment on the MPFID assessment demonstrated improvements by 5.5 in the 70 mg group (p <.001) and 5.9 in the 140 mg group (p <.001) as compared to 3.3 in the placebo. The physical impairment domain of the MPFID also demonstrated improvements by 4.2 in the 70 mg group (p <.001) and 4.8 in the 140 mg group (p <.001) in comparison to the 2.4 score improvement in the placebo group.

Discontinuation of treatment due to AEs were similar between all groups with 2.5% in the placebo, 2.2% in the 70 mg group, and 2.2% in the 140 mg group. There were no clinically significant differences between the placebo and erenumab groups regarding clinical laboratory tests, vital signs, or EKGs. There were no reported deaths. A limitation of the study by Goadsby et al. (2017) was the exclusion of patients who did not have a response to two or more

preventative migraine medications in the past. Additionally, over 84% of those in each group were female and over 49% were located in North America.

Goadsby, Reuter, et al. (2020) continued the previous study by assessing the efficacy and tolerability of erenumab over the course of one year. Patients were re-randomized into either erenumab 70 mg or 140 mg with once monthly injection over a 28-week period. Of the 955 patients who were included in Goadsby et al. (2017) study, 845 patients entered the long-term study conducted by Goadsby et al. (2020). There were 421 in the 70 mg erenumab group and 424 in the 140 mg group with similar baseline characteristics.

The purpose of the study by Goadsby, Reuter, et al. (2020) was to assess if erenumab decreased MMDs and improved patient-reported outcomes over one year. Endpoints explored in the study were assessed from baseline to week 52 and included: change in MMDs, abortive migraine medication use per day, achievement of ≥ 50%, ≥75%, or 100% decrease in MMDs, and change in the physical impairment and everyday activities domains of the MPFID. Long-term safety was assessed in the same manner as Goadsby et al. (2017) including monitoring AEs, clinical laboratory tests, EKGs, and vital signs.

The mean change in MMDs during the 52-week treatment period was -1.1 in the 70 mg group and -1.8 in the 140 mg group. Goadsby, Reuter, et al. (2020) also assessed from the previous study baseline, never having received an injection of erenumab, to week 52 with -4.2 days in the 70 mg group and -4.6 days for those in the 140 mg erenumab group. The mean change in abortive medication use over the 52-week treatment phase was -0.7 in the 70 mg group and -1.0 days in the 140 mg group. Previous study baseline to week 52 demonstrated a reduction of -1.8 days in the 70 mg group and -2.0 in the 140 mg group. Patients in the 70 mg group demonstrated an improvement on the physical impairment domain of the MPFID of 1.3 and 1.9

in the 140 mg group. The everyday impairment domain of the MPFID also demonstrated improvements of 1.8 in the 70 mg group and 2.3 in the 140 mg group. Sixty one percent of patients in the 70 mg group achieved ≥ 50% reduction in MMD, 38.5% achieved ≥75%, and 19.8% achieved 100% reduction in MMDs. Over 64% of those in the 140 mg group achieved ≥50% reduction in MMDs, 40.8% achieved ≥75%, and 21.2% achieved 100% reduction in MMDs during the 52-week study by Goadsby, Reuter, et al. (2020).

Goadsby, Reuter, et al. (2020) reported that across the erenumab groups, 57.2% of patients reported AEs in the 70 mg group and 55% in the 140 mg group. Discontinuation of treatment due to AEs occurred in six patients in the 70 mg group and 10 in the 140 mg group. There were no significant changes in clinical laboratory tests or vital signs for either erenumab group. There was one cardiac-related death reported during this study, however it was found that the patient had a genetic heart condition known to cause sudden cardiac death, therefore, it was ruled unrelated to erenumab treatment.

Limitations of the study by Goadsby, Reuter, et al. (2020) include: there was no placebo, comparison between the groups was completed in a descriptive fashion versus statistical analysis, potential financial conflicts of interest, exclusion of patients who did not respond to two or more preventative migraine medications in the past, and limited demographics of the patients.

CGRP-mAbs versus current standard of care for prevention of migraines.

A randomized, double-blind, active-controlled phase IV study was conducted at 82 sites in Germany by Reuter et al. (2022) to compare the efficacy and tolerability of erenumab to TPM. A double dummy technique was used to match the placebo dummies as TPM was tablet form and erenumab was subcutaneous injection. Patients, staff, investigators, and those performing assessments were all blinded to the treatments. Patients were eligible for the study if they were

18-65 years of age with a history of migraines with or without aura for at least 12 months prior to screening and who had not been treated previously with TPM or a monoclonal antibody targeting calcitonin gene-related peptide. Patients were eligible if they had at least four migraine days per month as defined by the ICHD-3. Patients were excluded from the study if they were over 50 years of age at the time of onset of migraines, had a history of hemiplegic or cluster headaches, or were unable to distinguish a migraine from other headaches. Those who were eligible were randomly assigned using interactive response technology and stratification according to MMDs in a 1:1 ratio to the TPM or erenumab groups.

The study conducted by Reuter et al. (2022) included a two-week screening period, a 24-week treatment phase, and a four week safety follow up. Eligibility was assessed during the screening period in which patients had to record headache information daily in an electronic diary with greater than or equal to 80% compliance during the screening phase. During the 24-week treatment phase there was six weeks of up-titration with weekly visits and then maintenance with visits at eight, 12, 16, 20, and 24 weeks. During the up-titration phase the goal was to increase the weekly dose of TPM or matching placebo in 25 mg increments to reach 100 mg per day in accordance with the United States prescribing information and European summary of product characteristics. Erenumab or the matching placebo was given subcutaneous injection every four weeks starting at 70 mg or 140 mg. Those receiving 70mg could be increased to 140 mg at any time during the 24-week treatment phase as deemed appropriate by the investigators. During this treatment time patients logged duration and severity of migraine/non-migraine headache and any use of rescue medication in their electronic diary. They also completed outcome questionnaires including the headache impact test (HIT-6), medical outcome short form health survey version 2 (SF-36v2), treatment satisfaction questionnaire for medication, Beck

Depression Inventory or C-SSRS. Physical exams, clinical laboratory testing, vitals, review of electronic diary compliance, documentation of adverse events and use of other medications, and ECGs were completed at regular visits to assess safety.

The primary endpoint was the number of patients who stopped erenumab or topiramate due to an adverse event during the 24-week treatment phase. The main reason for stopping was assessed in each patient. The secondary endpoint was the number of patients in each group who achieved ≥50% decrease from baseline MMDs over the fourth, fifth, and sixth months of the treatment phase. Seven hundred and seventy-seven patients were deemed eligible and randomly placed into the erenumab or the topiramate group. One patient did not receive medication making the groups equal of 388 patients per group. Of the 777 eligible patients 739 or 95.1% completed the study until week 24.

The results concluded the proportion of patients who stopped their medication due to adverse events during the 24-week treatment phase was 10.6% (n= 41) in the erenumab group and 38.9% (n= 151) in the topiramate group with an odds ratio (OR) of 0.19 (95% CI 0.13 to 0.27; p<0.001) and a relative risk (RR) of 0.27 (95% CI 0.20 to 0.37; p<0.001). According to Reuter et al. (2022) only one patient in the erenumab group stopped medication due to lack of efficacy. Within the last three months of the treatment phase 55.4% (n= 215) of the patients in the erenumab group attained a 50% or more reduction in MMDs from baseline as compared to 31.2% (n= 121) of the topiramate group with OR of 2.76 (95% CI 2.06 to 3.71; p<0.001) and RR of 1.78 (95% CI 1.50 to 2.11; p<0.001).

During months four through six, patients in the erenumab group demonstrated a reduction of -5.86 (SD 0.24) in average MMDs compared to -4.02 (SD 0.24) in the topiramate group (p <0.001). Additionally, the erenumab group recorded a significantly larger decrease for both the

HIT-6 and SF-36v2 questionnaires. A reduction of -10.9 (SD 0.4) in the erenumab group and -7.7 (SD 0.4) in the topiramate group were seen on the HIT-6 (p <0.001). An improvement of 5.5 (SD 0.4) points on the physical component SF-36v2 was seen in the erenumab group as compared to 3.6 (SD 0.4) points in the TPM group (p <0.001). Those in the erenumab group experienced an improvement of 1.0 on the mental component of the SF-36v2 compared to a negative experience -1.2 for those in the TPM group (p <0.001).

Adverse events were more common in the topiramate group (81.2%) compared to the erenumab group (55.4%) with most common cause of discontinuation for the study in the topiramate group being disruption in attention, nausea, paresthesia, and fatigue. The most common adverse events in the erenumab group were fatigue, nausea, and disruption in attention. In conclusion, Reuter et al. (2022) demonstrated with this study that erenumab, compared to topiramate, increased treatment acceptance and had good efficacy for prevention of episodic and chronic migraines.

Limitations of the study include lack of a placebo group. Discontinuation rates in both treatment groups due to adverse events in Reuter et al. (2022) study was higher than placebo-controlled studies. Reuter et al. (2022) support their hypothesis that this is due to a nocebo effect where a patient experiences an adverse reaction because he or she expects a treatment will cause harm. Another limitation was partial unblinding due to typical adverse reactions of topiramate. All patients of the study were made aware of the possible adverse events of both study drugs before partaking in the study. To try to reduce this limitation the study was blinded and used a double-dummy design. Patients were also not given a list of side effects to mark but were to freely report their adverse reactions to personnel at the onsite visits.

A final limitation reported by Reuter et al. (2022) was that patients in their study could not reduce the dose of topiramate in order to comply with the United States prescribing information and European summary of product characteristics. Reduction of dosage in clinic does occur meaning that discontinuation of topiramate in this study may be higher than in real life situations where the dosage can be reduced instead of stopped. Although Reuter et al. (2022) did not identify this as a limitation, the overall diversity of the patients in this study were limited. Just over 85% of the patients were female and 99.2% were Caucasian. Some potential conflicts of interest include two of the authors had received grants, support, and fees from Amgen, Abbvie, Allergan, Alder, Eli Lilly, Medscape, StreaMedUp, Teva Pharmaceutical as well as Novartis, which funded this study. Eight of the authors work for Novartis and four of them have stock in Novartis.

A retrospective, observational cohort study was completed by Varnado et al. (2022). In this study, CGRP mAbs including erenumab, fremanezumab, and galcanezumab were compared to standard of care (SOC) migraine prevention treatments including antiepileptics, beta-blockers, antidepressants, and onabotulinumtoxinA. Varnado et al. (2022) used information from IBM MarketScan and Medicare Supplemental Databases to assess treatment patterns, including treatment adherence, persistence, and discontinuation, of adults ≥ 18 years of age at diagnosis of migraine with ≥ 1 claim for CGRP mAb or SOC preventative treatments.

The study included a 12-month baseline, six-month follow-up, and 12-month follow-up phase. Patients were included in the study if they were recently started on a CGRP mAb or SOC preventative treatment but not during the 12-month baseline phase. Patients were excluded if they had a history of epilepsy, cancer, cluster headaches or were pregnant. One to one propensity score matching was used to control for selection bias and 3,082 patients were included in both of

the two groups. Baseline characteristics were similar after matching. Over 85% of the patients within each of the groups was female with an average age of 43.2-44.4 years. Treatment adherence was assessed by calculating the proportion of days covered (PDC) and medication possession ratio (MPR). Patients were considered treatment adherent with a PDC or MPR of ≥ 80%. Persistence was defined as the number of days of continuous therapy from the first day of treatment use until the end of the 12-month follow-up period allowing for a 60-day gap between refills whereas discontinuation was defined as failure to refill the drug within that 60-day gap (Varnado et al., 2022).

Varnado et al. (2022) found patients on a CGRP mAb had greater treatment adherence, persistence, and were less likely to discontinue their treatment over six and 12 month follow up as compared to those on a SOC preventative treatment. It was also discovered that a significantly greater number of those in the CGRP mAb group received acute medications including triptans (71.7%) and antiemetics (24.7%) compared to acute use with those in the SOC group (triptans 56.2% and antiemetics 18.7%) (p <.001). At 12-months, CGRP mAb patients had significantly greater adherence than SOC treatment patients with mean PDC 55.1% versus 35.2% (p <.001) and 32.7% versus 18.7% having a PDC ≥ 80% (p <.001). The mean MPR for the CGRP mAb group was 57.8% versus 36.9% of the SOC treatment group (p <.001) with 36.7% in the CGRP mAb group achieving an MPR ≥ 80%, as compared to 21% of the SOC treatment group (p<.001).

According to Varnado et al. (2022), those in the CGRP mAb group were nearly twice as likely to refill their drug as compared to the SOC group (7.0 vs 4.1; p <.001). The CGRP group demonstrated a significantly greater persistence than SOC (212.5 vs 131.9 days; p <.001) during 12-month follow-up. Lastly, the CGRP group was significantly less likely to discontinue

treatment than SOC group throughout the follow up period. Within one month 16% of those in the CGRP group discontinued their treatment as compared to almost half of the SOC group. At the end of the 12-month follow-up, significantly less patients discontinued CGRP compared with SOC (58.8% vs 77.6%; p <.001).

Since this study by Varnado et al. (2022) used the specific databases for inclusion, the study sample only includes those with commercial health or private Medicare supplemental insurances. This limitation and the potential for mistakes due to data coding and/or data entry error could decrease inferences of the results to the general population. Additionally, there may be potential financial conflicts with some of the authors and funding company of the study.

Discussion

Recurrent migraines are disabling and debilitating for the large number of people who suffer from them. Migraines can interfere with an individual's work, school, and overall daily life. Current standard of care medications for prophylaxis are not specific to migraines, therefore pose the risk of unwanted/unnecessary side effects. This literature review helps explore the research questions posed providing an awareness of the effectiveness, safety, and tolerability of CGRP mAbs and how this compares to the standard medications currently being used within the clinic setting.

The first area to be explored is the effectiveness of conventional treatment and CGRP mAbs in the reduction of monthly migraine days (MMDs). A few of the more common conventional treatments used in the prevention of migraines include topiramate, amitriptyline, and propranolol. Diener et al. (2004) and Dodick et al. (2009) were able to conclude that topiramate, amitriptyline, and propranolol are all effective in reducing migraine frequency and decreasing the frequency in which individuals need to use abortive migraine medications. Diener

et al. (2004) demonstrated that 100 mg of either topiramate or propranolol reduced monthly migraine frequency by at least 50% while Dodick et al. (2009) concluded that those treated with amitriptyline or topiramate demonstrated decreased migraine severity with decreased nausea, vomiting, photophobia, and phonophobia. There was no statistically significant difference in the effectiveness of topiramate and amitriptyline or topiramate and propranolol in reducing MMDs, however topiramate did demonstrate improvements in some quality-of-life areas and weight loss (Diener et al., 2004; Dodick et al., 2009). Patients within the topiramate group felt an overall improvement in the performance of daily activities that were previously restricted by migraines and had reduced feelings of frustration and helplessness caused by migraines in comparison to the amitriptyline group (Dodick et al., 2009).

Regarding the effectiveness of eptinezumab, galcanezumab, fremanezumab, and erenumab, all were determined to be effective medications in the reduction of MMDs compared to a placebo. Similar to amitriptyline, propranolol, and topiramate, all CGRP mAbs demonstrated a statistically significant decrease in the need for abortive medication use (Dodick et al., 2018; Goadsby et al., 2017; Skljarevski et al., 2018; Smith et al., 2020). Eptinezumab and galcanezumab were found to reduce monthly migraine frequency by at least 75% (Ashina et al., 2020; Skljarevski et al., 2018). A 75% reduction rate was not explored in the studies for erenumab and fremanezumab, however they were each found to demonstrate at least 50% reduction (Dodick et al., 2018; Goadsby et al., 2017). Many different subjective outcomes were used to assess CGRP mAbs effectiveness on decreasing impairment of function and improving migraine disability. Those receiving fremanezumab and erenumab demonstrated a decrease in activity impairment due to migraines while those receiving eptinezumab demonstrated improvements in bodily pain and social functioning (Dodick et al., 2018; Goadsby et al., 2017;

Smith et al., 2020). Erenumab and eptinezumab groups also demonstrated improvements in physical health (Goadsby et al., 2017; Smith et al., 2020). Galcanezumab was even found to decrease the overall severity of the migraine itself (Skljarevski et al., 2018). These subjective measures are associated with meaningful improvements in the quality of life of those who suffer from migraines.

While all these studies conclude that both CGRP mAbs and conventional treatments are effective in reducing monthly migraine days as compared to a placebo, there is only one head-to-head trial comparing the effectiveness of the two groups to one another. In the study by Reuter et al. (2022) CGRP mAbs demonstrated superiority over a standard treatment. Reuter et al. (2022) reported that erenumab decreased MMDs by 5.86 days compared to 4.02 days for those taking topiramate ($p < 0.001$). Additionally, those receiving erenumab recorded a significantly greater decrease in the impact of migraines on social and cognitive functioning, psychological and physical health, and energy level following treatment compared to those receiving topiramate (Reuter et al., 2022). Though the literature is promising regarding the effectiveness of CGRP mAbs, more studies are needed in order to draw conclusions of whether they are more effective than standard migraine prevention medications.

A few studies included in the literature review looked at the effectiveness of the CGRP mAbs over a prolonged period of time. While these studies did continue to show effectiveness in reducing migraine days, most of the studies did not compare to a placebo group and therefore do not demonstrate statistical analysis. The importance of these studies was to assess the safety and tolerability or adherence of CGRP mAbs over a year.

As previously determined, standard of care migraine prevention medications are effective, however many come with several side effects and subsequently demonstrate poor

adherence (Varnado et al., 2022). Therefore, the next and potentially most important area to be explored is the safety and tolerability of migraine prevention medications. As Reuter et al. (2022) stated in their article, "Tolerability is a major contributing factor to therapeutic success of migraine prevention."

Diener et al. (2004) and Dodick et al. (2009) demonstrated similar side effect profiles for 100 mg topiramate, 100 mg amitriptyline, and 160 mg propranolol. Many individuals experienced paresthesia, difficulty concentrating, nausea, fatigue, insomnia, anorexia, dry mouth, somnolence, and dizziness. Those receiving propranolol or amitriptyline experienced a clinically significant increase in weight, while those receiving topiramate experienced a decrease (Diener et al., 2004; Dodick et al., 2009). While there were no statistically significant changes in clinical laboratory studies between these three drugs, a decrease in blood pressure and heart rate was noted in those taking topiramate with an increase in blood pressure and heart rate for those taking amitriptyline (Diener et al., 2004; Dodick et al., 2009). Diener et al. (2004) did investigate 200 mg topiramate which did not meet statistical significance for most of the measurements due to 44% of the patients withdrawing from the study as a result of adverse reactions. Twenty-eight percent of those receiving 100 mg topiramate and 20% of those receiving 160 mg propranolol discontinued due to adverse reactions to these medications (Diener et al., 2004). In the study by Dodick et al. (2009) 85.9% of those in the 100 mg topiramate group experienced adverse reactions leading to about 20% discontinuing treatment. Dodick et al. (2009) reported that 88.8% of those receiving 100 mg amitriptyline experienced adverse reactions leading to approximately 22.5% discontinuing treatment.

Regarding safety and tolerability of CGRP mAbs, there were no statistically significant differences in vital signs, weight, EKG findings, laboratory tests, or physical exam measures in

comparison to a placebo (Ashina et al., 2020; Dodick et al., 2018; Goadsby et al., 2017; Skljarevski et al., 2018). Injection site pain and reaction were the most common adverse reactions for those receiving galcanezumab or fremanezumab (Dodick et al., 2018; Skljarevski et al., 2018). Nasopharyngitis and upper respiratory infection were common adverse events for those in the erenumab and galcanezumab groups (Goadsby et al., 2017; Skljarevski et al., 2018). Majority of the adverse reactions experienced by those receiving eptinezumab included nausea and fatigue (Ashina et al., 2020).

Adverse events leading to treatment discontinuation were similar across all groups including placebo in the study on fremanezumab with 2% or less discontinuing from each group (Dodick et al., 2018). In the one-year study on fremanezumab over 79% of patients completed treatment with only 5% of adverse reactions in each group leading to study withdrawal (Goadsby, Silberstein, et al., 2020). Erenumab also demonstrated similar discontinuation rates due to adverse reactions across all groups with 2.5% in the placebo and 2.2% in the 70 mg and 140 mg groups (Goadsby et al., 2017). The year-long study of erenumab also demonstrated fewer than 3% discontinuation rate in each group (Goadsby, Reuter, et al., 2020).

Of those who discontinued galcanezumab due to adverse events, 2.2% were from the 120 mg group and 4% were from the 240 mg group (Skljarevski et al., 2018). Just over 5% of individuals receiving 30 mg eptinezumab, 2.7% receiving 100 mg, and 2.2% receiving 300 mg discontinued treatment due to adverse reactions (Ashina et al., 2020). Smith et al. (2020) determined that adverse reactions decreased with dosing intervals. For example, in the eptinezumab 100 mg group 33.2% of individuals experienced an adverse reaction after the first dose whereas 18.5% experienced an adverse reaction following the last dose (Smith et al., 2020).

Two articles included in the literature review discuss a direct comparison of CGRP mAbs to conventional treatments. In the head-to-head trial of erenumab versus topiramate, erenumab demonstrated a greater tolerability in addition to improved efficacy (Reuter et al., 2022). Reuter et al. (2022) found that over 81% of those receiving topiramate demonstrated adverse reactions and nearly 40% discontinued treatment due to this, whereas just over 10% experienced an adverse event that led to discontinuation for those receiving erenumab. Varnado et al. (2022) supports this finding as their study demonstrates higher treatment adherence for those receiving a CGRP mAb over any of the standard of care prophylactic treatments. Discontinuation rates for those in the standard of care group was 80% whereas those in the CGRP mAb group was 59%. Varnado et al. (2020) discovered that approximately 50% of patients discontinued their conventional migraine prophylactic treatment within one month of initiation, while less than 20% discontinued their CGRP mAb.

Conclusion

In conclusion, the literature supports CGRP mAbs effectiveness in the prevention of episodic migraines and improvement of quality of life when compared against placebo. However, more evidence is needed with head-to-head trials of CGRP mAbs in direct comparison to standard prophylactic migraine medications in order to determine which is more effective and tolerable. Results of one large head-to-head study across many sites is promising with statistically significant decreased MMDs for those receiving erenumab in comparison to topiramate, however there were potential conflicts of interest with grants, support, and fees (Reuter et al., 2022). Additionally, results of one retrospective, observational study is encouraging regarding the tolerability and adherence profiles of CGRP mAbs in comparison to standard migraine prophylaxis treatments, however this type of study is not as high of level of

evidence as a randomized control trial would be and there are potential financial conflicts of interest (Varnado et al., 2020). Through continued research and evidence of support, CGRP mAbs may change the current standard of care in the prevention of episodic migraine treatments.

Application to clinical practice

In clinical practice, patients who suffer from migraines will be encountered frequently. Current standard of care medications come with unwanted side effects leading to decreased compliance. With FDA approval of CGRP mAbs future research may help change the treatment hierarchy of migraine prevention. As there is a significant impact on quality of life for patients who suffer from migraines, providers must be educated on possible treatment options and their possible side effects. With this research, it was found that CGRP mAbs may be a viable treatment option with increased tolerability, safety, and efficacy. However, providers must also be aware of other aspects not explored in this research such as drug-drug interactions and cost effectiveness of the CGRP mAbs.

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