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Are quarterly fremanezumab injections as effective as monthly fremanezumab injections at reducing the number of migraine days per month in adults with chronic migraines?

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Are quarterly fremanezumab injections as effective as monthly fremanezumab injections at reducing the number of migraine days per month in adults with chronic migraines?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this systematic EBM review is to determine "Are quarterly fremanezumab injections as effective as monthly fremanezumab injections at reducing the number of migraine days per month in adults with chronic migraines?"

STUDY DESIGN: A systematic review of three randomized controlled trials (RCTs) that were peer reviewed and published in English after 2015 comparing quarterly versus monthly fremanezumab injections in adults 18-70 with chronic migraines.

DATA SOURCE: Three RCTs were obtained from PubMed and selected based on their relevance to the clinical question and if the RCTs addressed patient oriented outcomes.

OUTCOMES: The three selected RCTs for review, the outcome measured was the mean change from baseline in the average number of migraine days per month during the 12-week treatment period after the first dose of fremanezumab using self-reported electronic headache diary entries by study participants.

RESULTS: All three studies found that quarterly fremanezumab injections were less efficacious at reducing the mean number of migraine days per month than monthly injections. Silberstein et al. (2017) reported a reduction from baseline in monthly average migraine days of -4.9 (+/- 0.4) with quarterly injections and -5.0 (+/- 0.4) with monthly injections. Ferrari et al. (2019) reported a reduction from baseline in monthly average migraine days of -3.9 ± 0.3 with quarterly injections and -4.5 ± 0.3 with monthly injections. Goadsby et al. (2020) reported a reduction from baseline in monthly average migraine days of -6.0 ± 0.3 with quarterly injections -6.0 ± 0.3 with monthly injections.

CONCLUSIONS: The results of these three studies showed that quarterly fremanezumab is not as effective as monthly fremanezumab injections at reducing the number of migraine days per month for individuals with a diagnosis of chronic migraines. However, the difference in mean reduction of migraine days between the quarterly and monthly injections was less than one day in all three studies - Silberstein (2017): 0.1 days, Ferrari (2019): 0.6 days, Goadsby (2020): 0.5 days

Due to these results, a conversation with patients pursuing this treatment and shared decision making would be appropriate regarding whether a monthly or quarterly injection would be most beneficial on a case-by-case basis.

KEYWORDS: Fremanezumab, Migraines

INTRODUCTION:

Migraine is a primary headache syndrome which often includes a clinical presentation of recurrent, unilateral, pulsing, throbbing headache with nausea, photophobia, and phonophobia that lasts between 4-72 hours.[1] Chronic migraine (CM) is defined in individuals with at least 15 headache days per month lasting at least 4 hours per day.[1] Consideration for preventative therapy includes migraine headaches occuring 2-3 times per month or migraine headaches that result in significant disability.[1] CM affects a large number of patients worldwide and can impact the daily functionality of these individuals. Migraine is a leading cause of disability worldwide with a prevalence of 15-18%.[2,3] Chronic migraine has a prevalence of 2% of the population with individuals reporting a lower quality of life than those with other less frequent migraine types.[3]

With the frequency (≥15 days per month) and severity (≥4 hours per day) of symptoms that CM individuals experience, there is evidence of increased medical resource consumption, increased cost to the patients, and a significant loss in productivity. There is not an exact estimate available for the number of healthcare visits each year, however, an analysis of the International Burden Migraine Study revealed the following odds ratios for healthcare visits when comparing chronic migraine to episodic migraine: 2.32 (95%, CI 2.15-2.5) primary care physician visits, 3.23 (95%, CI 3.78-3.75) neurologist/headache specialist visits, 3.01 (95%, CI 2.56-3.55) emergency department visits, 2.84 (95%, CI 1.99-4.06) hospitalizations.[5]

In addition to the increased utilization of personnel resources, the mean annual cost in the USA per individual with CM is $8,243.00.[4] The direct medical costs, including pharmaceutical therapy, are reported at $4,943.00 while the indirect cost of lost productivity is reported at $3,300.00.[4] In other reviews, the mean total direct annual cost reported by the International Burden Migraine Study for individuals with CM in the US is $4,144.00[5] while the American

Migraine Prevalence and Prevention study estimated annual productivity related losses at $5,392.03 for individuals with CM.[5]

Many of the preventative treatments for CM available were not developed specifically for migraines and their pathogenesis. Migraine is attributed to neurogenic inflammation, sensitization, and the resulting headache is attributed to neuronal dysfunction in the trigeminal system due to a release of vasoactive neuropeptides, of which calcitonin gene-related peptide (CGRP) is an example.[1,6] It can be difficult for patients to find an effective medication, often resulting in a trial period involving a variety of medications before migraine headaches are under control.[1] Current non-pharmaceutical preventative therapy for CM consists of the avoidance of triggers, regular sleep, regular meals, hydration, and acupuncture.[1] Pharmaceutical therapy for CM consists of antiepileptics (topiramate, valproic acid), cardiovascular medications (candesartan, guanfacine, propranolol, verapamil), antidepressants (amitriptyline, venlafaxine), and botulinum toxin A.[1]

Most recently, monoclonal antibodies against CGRP have been safely and successfully used for reducing the number of migraine days. The formulation of these agents targets the specific pathophysiology of vasoactive neuropeptides.[1] These monoclonal antibodies against CGRP include eptinezumab, erenumab, galcanezumab, and fremanezumab.[1] While monthly subcutaneous injections of fremanezumab, a fully humanized monoclonal antibody that selectively and effectively binds to CGRP, have proven to be efficacious at reducing migraine days in individuals with CM[2], adjusting to a less frequent dosing schedule may offer cost and time advantages to the patient. Therefore, this paper evaluates three randomized control trials (RCTs) comparing the efficacy of the monoclonal antibody, calcitonin gene-related peptide receptor antagonist, fremanezumab, as a quarterly subcutaneous injection verses its current

administration of a once monthly subcutaneous injection as preventative therapy for reducing the number of migraine days per month in individuals with CM.

OBJECTIVE:

The objective of this selective EBM review is to determine "Are quarterly fremanezumab injections as effective as monthly fremanezumab injections at reducing the number of migraine days per month in adults with chronic migraines?"

METHODS:

Resources and scholarly literature were selected by the author of this paper based on their ability to answer the question: Are quarterly fremanezumab injections as effective as monthly injections at reducing the number of migraine days per month in adults with chronic migraines? The trials were also selected based on their inclusion of patient-oriented outcomes (POEMs) related to CM. All trials were researched via PubMed, were published in in peer-reviewed journals in English, met exclusion criteria including headaches, case studies, and articles published prior to 2010. The three studies included in this selective EBM review are randomized, double-blind controlled clinical trials published in years 2017, 2019, and 2020 using the key words "fremanezumab" and "migraines" through the resource database PubMed.

Inclusion criteria included studies that were clinical trials, published from 2015-present, and in the English language. Statistics reported and used include mean change from baseline, standard error (SE), and p-values.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ferarri[2] 2019	RCT	509	18-70	18-70 yrs, Migraine onset <50 years, in good health, migraine ≥ 12 months, chronic migraine (CM) criteria. Patients with or without overuse of acute headache medicine, documented failure of 2-4 of the preventative treatments.	Current use of migraine preventative medications, onabotulinumtoxinA ≤ 3 months prior to screening, opioid or barbiturate containing treatments > 4 d/mo prior to screening, interventions or devices for migraine <2 months before screening of NSAIDs on almost daily basis for other indication, prior exposure to monoclonal antibody	15	Quarterly Vs Monthly fremanezumab SQ Injection
Silberstein[3] 2017	RCT	755	18-70	18-70 yrs, migraine ≥12 months, CM criteria, 30% of trial participants allowed stable dose of one migraine-preventative medications for at least 2 months prior to preintervention period	OnabotulinumtoxinA during 4 months prior to screening, use of interventions or devices for migraine (nerve blocks, transcranial magnetic stimulation during 2 months before screening), opiod or barbiturate medications >4 d/mo during preintervention period	20	Quarterly vs Monthly fremanezumab SQ Injection
Goadsby[6] 2020	RCT	1110	18-70	18-70 yrs, migraine ≥12 months, CM criteria*, max of 1 migraine preventative medication for rollover patients or 2 for new patients if dosage stable for ≥ 2 months.	OnabotulinumtoxinA during 4 months prior to screening, use of interventions or devises for migraine (nerve blocks, transcranial magnetic stimulation during 2 months before screening), opiod or barbiturate medications >4 d/mo during preintervention period, prior failure of ≥ 2 preventative medications after adequate therapeutic trial **only for rollover HALO patients*	237	Quarterly vs Monthly fremanezumab SQ Injection

The selected studies, detailed in Table 1, include a population of patients diagnosed with CM who were treated with the intervention of quarterly fremanezumab subcutaneous injections of 675 mg at month 1, 225 mg placebo month 2, and 225 mg placebo month 3 and compared to patients with CM that were treated with monthly fremanezumab subcutaneous injections of 675 mg at month one, 225 mg fremanezumab month 2, and 225 mg fremanezumab month 3. Inclusion and exclusion criteria varied slightly between each study but were largely similar. The measured outcome was the mean change from baseline in the number of migraine days per month.

OUTCOMES:

In all three RCTs, patient data was collected using daily, participant self-reported electronic headache diary and outcome measured was the mean change from baseline in the average number of migraine days per month during the 12-week treatment period after the first administered dose of fremanezumab. Silberstein et al., Ferrari et al., and Goadsby et al. defined migraine days as a calendar day with ≥ 4 hours of consecutive headache pain or calendar day with migraine-specific medication use (triptan or ergot) for headache treatment.[2.3.6]

RESULTS:

The Silberstein et al. (2017) study was a randomized, double-blind, parallel-group trial that took place in nine countries at 132 clinics that treated individuals with headaches. Patients were 18-70 years old, had at least a 12-month history of migraine, and met the criteria for chronic migraine during the 28-day preintervention period.[3] CM criteria was defined as "…headache of any duration or severity on ≥15 days and headache meeting ICHD-3 beta criteria for migraine on ≥8 days."[3]

Of note for this study, 30% of patients on a stable-dose of migraine-preventative medication were allowed to continue these medications if they had been on a stable dose ≥2 months prior to the preintervention period. [3] Randomized allocation concealment was achieved at a 1:1 ratio via "electronic interactive-response technology, with stratification according to sex, country, and baseline use of preventative medication (yes or no)."[3]

Patients in the intervention group received a baseline fremanezumab dose of 675 mg administered followed by a single placebo injection at weeks 4 and 8.[3] In the comparison group, participants received a baseline fremanezumab dose of 675 mg followed by one, 225 mg injection of fremanezumab at weeks 4 and 8.[3] Data were collected daily through a participant, self-reported headache diary with a final evaluation of the mean change in the average number of migraine days from the baseline 28 day preintervention period occuring at week 12.

Table 2 demonstrates the mean (±SE) change from baseline in the average number of migraine days per month in the intervention group of quarterly fremanezumab (-4.9 ± 0.4) and in the comparison group of monthly fremanezumab (-5.0 ± 0.4).[3] The p-value is reported at $p<0.001$ with a CI of 95% for both groups (numeric range not provided), indicating that the reduction in migraine days between quarterly and monthly fremanezumab was statistically significant and the treatments were not as effective in the quarterly fremanezumab group.[3] Discontinuation rates were low in both groups: 1% of quarterly and 2% of monthly patients.

Table 2. Mean Change from Baseline in Average Number of Migraine Days Per Month in Silberstein et al. 2017 Study

Fremanezumab	**Migraine days during 28-day preintervention period**	**Mean change from baseline in Average # of Migraine days per month post 12-week treatment period**	**P-value**
Quarterly (n=375)	16.2 ± 4.9	-4.9 ± 0.4	<0.001
Monthly (n=375)	16.0 ± 5.2	-5.0 ± 0.4	<0.001

Ferrari et al. (2019) was a randomized, double-blind, parallel group trial where participants were assigned at random in a 1:1 ratio to quarterly and monthly fremanezumab injections via "electronic interactive response technology."[2] This clinical trial included 104 sites spanning 14 countries and patients that met the CM criteria that were between the ages of 18-70. Failure of 2-4 classes of migraine preventive medications within past decade was a notable inclusion criterion for the trial participants which differs from the 2017 Silberstein et al. study. Exclusion criterion included use of migraine preventative medication, which is another difference between Ferrari et al. (2019) and Silberstein et al. (2017).[2] Data was similarly collected via daily electronic self-reported headache diary entries.

This 2019 trial used the same intervention and comparison medication dosage and administration as the previously discussed trial. The quarterly group received a 675 mg dose of fremanezumab at baseline followed by single placebo injections at weeks 4 and 8 and the monthly group received a 675 mg dose at baseline followed by a single subcutaneous injection of 225 mg fremanezumab at weeks 4 and 8.[2]

Patients in the intervention group of quarterly fremanezumab had a mean (±SE) change from baseline in the average number of migraine days per month of -3.9 ± 0.3 and patients in the comparison group of monthly fremanezumab had a mean change from baseline in the average number of migraine days per month of -4.5 ± 0.3 (Table 3).[2] The p-value is reported at $p<0.0001$ with a CI of 95% for both groups (numeric range not provided), indicating that the reduction in migraine days between quarterly and monthly fremanezumab was statistically significant and the treatments were not as effective in patients with CM receiving quarterly fremanezumab, resulting in a small treatment effect.[2] Additionally, this study also reported the mean percentage change from baseline among quarterly (-34.9% (31.7)), and monthly (-36.8% (32.1)) fremanezumab

groups for monthly average migraine days, indicating quarterly injections were not as effective as monthly injections.[2] More than 97% of the participants completed the study (544/559).[2]

Table 3. Mean Change from Baseline in Average Number of Migraine Days Per Month in Ferrari et al. 2019 Study

Fremanezumab	**Monthly Migraine days at baseline (Standard Deviation)**	**Mean change from baseline in Average # of Migraine days per month post 12-week treatment period**	**P-value**
Quarterly (n=276)	14.1 (5.6)	-3.9 ± 0.3	<0.0001
Monthly (n=283)	14.1 (5.6)	-4.5 ± 0.3	<0.0001

The final study for this review, Goadsby et al. (2020), was another randomized, double-blind, parallel-group study where participants who met CM criteria were randomized in a 1:1 ratio into quarterly and monthly fremanezumab groups utilizing "interactive response technology, with patients stratified by sex, country, and preventive medication use at baseline (yes/no)."[6] This study consisted of 135 sites across 9 countries and included participants from the HALO efficacy studies as well as new participants.[6] Data was, once again, collected through a daily, electronic self-reported headache diary. Additional inclusion criteria for this RCT consisted of the following: 18-70 years of age, ≥12 months history of migraine prior to screening, and using no greater than 2 migraine preventative medications for new patients or a maximum of 1 migraine preventative medication in rollover HALO patients.[6] Unlike the two previous trials (Silberstein et al. 2017, Ferrari et al. 2019), patient use of onabotulinumtoxinA, opioids, barbiturates, previous failure of ≥ 2 preventive medications or use of an intervention or device did not apply to new patients.[6]

Quarterly group participants received a baseline 675 mg dose of fremanezumab and a single placebo at months 2 and 3.[6] Monthly group participants received a baseline 675 mg dose followed by a single 225 mg dose of fremanezumab at months 2 and 3.[6]

Patients in the intervention group of quarterly fremanezumab had a mean (±SE) change from baseline in the average number of migraine days per month of -6.0 ± 0.3 and patients in the comparison group of monthly fremanezumab had a mean change from baseline in the average number of migraine days per month of -6.5 ± 0.3 (Table 4).[6] There were no reported p-values or confidence intervals. However, this study did report the percentage of patients with at least a 50% reduction from baseline in the average monthly number of migraine days from quarterly fremanezumab (42%) and monthly fremanezumab (48%), which resulted a NNT of 16. This indicates that quarterly injections were not as effective as monthly injections. The discontinuation rate in this study was the highest among the three RCTs reviewed with 21.4% of study participants halting treatment.[6] The top three reported reasons were withdrawing consent (78/1110 patients), lack of efficacy (64/1110 patients), and adverse event (38/1110 patients).[6] This trial length was longer in duration (12 months) than the two previously discussed 12 week trials, which could explain the higher number of participants who discontinued the study. The data from the week 12 evaluation was used for this EBM.

Table 4. Mean Change from Baseline in Average Number of Migraine Days Per Month in Goadsby et al. 2020 Study

Fremanezumab	**Monthly Migraine days at baseline (Standard Deviation)**	**Mean (SE) change from baseline in Average # of Migraine days per month post 12-week treatment period**
Quarterly (n=551)	16.4 (5.1)	-6.0 ± 0.3
Monthly (n=559)	16.4 (5.3)	-6.5 ± 0.3

DISCUSSION:

Chronic migraine can be a debilitating condition where monoclonal antibodies against CGRP, like fremanezumab, have been recently utilized successfully as preventative therapy to decrease the number of migraine days per month and to improve patient quality of life.

Traditionally, fremanezumab has been delivered as a once monthly subcutaneous injection. The goal of this systematic review was to determine if quarterly fremanezumab was as effective as the current practice of monthly fremanezumab in reducing the number of migraine days per month in patients with CM so that patients could possibly benefit from decreased number of injections, healthcare visits, and associated medical costs while effectively controlling their condition.

All three selected studies had the comparison benefit of utilizing the same dosage, frequency of administration, and route of administration. The studies also included the generalizability benefit of being conducted in a large number of countries and facilities. The Goadsby et al. 2020, Ferrari et al. 2019, and Silberstein et al. 2017 studies demonstrated a difference in the reduction of migraine days from baseline between quarterly and monthly fremanezumab administration with the outcomes favoring the monthly dosage. However, when treating patients, it is also important to consider clinical significance. The differences between the change from baseline in average number of migraine days per month between both groups in all three studies are: 0.5 (Goadsby et. al 2020), 0.6 (Ferrari et al. 2019), and 0.1 (Silberstein et al. 2017). With the outcomes reporting about half a day or less difference between quarterly and fremanezumab groups, treatment frequency warrants a shared decision-making discussion with patients where this data is presented.

Research on this topic was limited by the solitary use of PubMed as the source for clinical trials. Generalizability was limited in all three studies due to the high number of female participants and the inclusion criteria of relatively healthy individuals. These trial outcomes may not be generalizable to individuals with additional comorbidities. The Silberstein et al. study allowed up to 30% of the trial participants to utilize a migraine -preventative drug and was the

only study to report a very close mean change from baseline in the number of migraine days between the quarterly (-4.9 ± 0.4) and monthly (-5.0 ± 0.4) injections and may have altered the outcome of the study. Another consideration when interpreting the data provided is that P-values and confidence intervals were not provided for the Goadsby et al. study, which makes it difficult to evaluate if the data provided was statistically significant. Additionally, Teva Pharmaceuticals provided funding for all three studies and employees participated in the data analysis and authoring of the trials. This limited the validity of the study results due to the possibility of bias.

CONCLUSION:

According to the results of this systematic review, quarterly fremanezumab is not as effective as monthly administered fremanezumab at reducing the number of migraine days per month individuals with chronic migraine. Statistically significant differences between both groups were reported in the Ferrari et al. and Silberstein et al. studies with quarterly fremanezumab having a lower reduction in the number of migraine days compared to monthly fremanezumab. Similar results were found in the Goadsby et al. trial without reported p-value and confidence interval precision measurements.

Further studies on fremanezumab should include varying doses, varying, frequency of administration, and dual therapy with other preventative medications that have different pharmacokinetics to cut down on the number of injections and cost associated with monthly injections in patients with chronic migraine. An additional consideration is longer trial lengths (>1 year). Future studies may also find it beneficial to evaluate of the use of fremanezumab in populations with comorbidities.

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