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Original Article

Real-world comparison of the effects of injectable CGRPs on the headache impact test in an academic family medicine clinic: a pilot study

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Abstract

Background: Injectable anti-CGRP monoclonal antibodies (MABs) are increasingly used for migraine prevention. While trial data shows they reduce the average number of monthly migraine days, more real-world comparative evidence is needed to understand their impact on the Headache Impact Test (HIT-6).

Objective: Determine the efficacy of injectable anti-CGRP MABs on the HIT-6 scores in patients enrolled in the migraine clinic at multiple time intervals

Methods: This non-randomized, prospective case series involved a specific group of migraine patients who were started on injectable anti-CGRP MABs (erenumab-aaoe, fremanezumab-vfrm, and galcanezumab-gnlm), along with other recommended preventative therapies. The goal was to assess the average change in the HIT-6 score and the monthly number of migraine days compared to baseline.

Results: The primary outcome comparing the change in HIT-6 scores from baseline across the three groups showed no statistically significant differences in the mean scores at any time point (p-values of 0.8344, 0.1694, and 0.1301 for 3, 6, and 12 months, respectively). Similarly, the primary outcome comparing the change in average monthly migraine days from baseline among the three groups also revealed no significant differences in the mean at any time point (p-values of 0.5237, 0.1233, and 0.2115 for 3, 6, and 12 months, respectively).

Conclusion: Injectable anti-CGRP MABs improved HIT-6 scores and reduced the average number of monthly migraine days. However, no significant differences were observed between treatments at any time point. Despite these benefits, patients face cost-related challenges in continuing these therapies in real-world settings.

Keywords: migraine, chronic migraine, Headache Impact Test (HIT-6), anti-CGRP monoclonal antibodies, calcitonin gene-related peptide (CGRP)

Background

Migraines affect 15.4% of the population with higher prevalence in females, peaking between ages 18 and 44.[1,2] Individuals with migraines incur higher direct and indirect medical costs, including nine more lost workdays annually compared to individuals without migraines.[3,4] The International

Headache Society defines migraines without aura as headaches with specific features and associated symptoms. In contrast, migraines with aura have transient focal neurological symptoms that precede or accompany the headache.5,6 Migraines are classified as episodic (0 to 14 headache days per month) or chronic (greater than or equal to 15 headache days per month) for three or more months.[7]

The American Academy of Neurology (AAN) last updated the episodic migraine guidelines in 2012. Medications with established efficacy included antiepileptic drugs (divalproex sodium, sodium valproate, topiramate), beta-blockers (metoprolol, propranolol, timolol), and triptans (frovatriptan). Probably effective agents included antidepressants (venlafaxine, amitriptyline), beta-blockers (atenolol, nadolol), and triptans (naratriptan, zolmitriptan).[8] Of these, only divalproex sodium, valproate, topiramate, propranolol, and timolol are approved by the United States Food and Drug Administration (U.S. FDA) for migraine prevention. Other therapies not addressed by the AAN guidelines include onabotulinumtoxin A or nutraceuticals such as magnesium, coenzyme Q10, and/or riboflavin (vitamin B2). These preventative treatments may reduce headache frequency by 50%, although dose-related adverse effects often limit tolerability.[9]

Calcitonin gene-related peptide receptor antagonists (anti-CGRPs) are now available for migraine prevention. Three subcutaneous injectable anti-CGRP monoclonal antibodies (MABs) were approved by the U.S. FDA in 2018 for preventative treatment of migraines in adults: erenumab-aooe (Aimovig®), fremanezumab-vfrm (Ajovy®), and galcanezumab-gnlm (Emgality®).[10-12]

Elevated CGRP levels during migraines with or without aura promote vasodilation of blood vessels and cerebral inflammation. Therefore, blocking CGRP, reduces vasodilation and cerebral inflammation, thereby reducing migraine and headache frequency.[13] These agents significantly decreased mean monthly migraine days from baseline in both episodic migraines (average of around 4 fewer monthly migraine days vs. 2 with placebo) and chronic migraine (average of around 5 fewer monthly migraine days vs. 3 with placebo).[10-12] Injectable anti-CGRP MABs are effective as monotherapy, but they can also be used with other preventative and acute (abortive) therapies without the worrisome side effects of other treatments.[10-12]

While these agents in clinical trials appear to improve mean monthly migraine days, trials did not utilize newer validated tools for measuring migraine response, such as the Migraine Disability Assessment (MIDAS) or the Headache Impact Test (HIT-6). The HIT-6 is a six-item self-administered questionnaire that can help measure adverse headache impacts on social functioning, role functioning, vitality, cognitive functioning, psychological stress, and headache pain.[14] The scores for HIT-6 range from 36 to 78 with four headache impact severity categories: little or no impact less than or equal to 49, some impact 50-55, substantial impact 56-69, and severe impact 60-78. The HIT-6 questionnaire has also been shown to discriminate well between chronic, episodic, and non-migraine patients. An American Headache Society (AHS) Consensus Statement defines the

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meaningful improvement in HIT-6 as a reduction from a baseline of ≥ 5 points.[15] The HIT-6 assessment is convenient and easier to administer than the MIDAS, making it more practical for clinical use. To date, trials have assessed HIT-6 scores for 1 or 2 of the injectable anti-CGRP MABs but not a comparison of all 3 simultaneously.

Objective

This study aimed to compare the effects of injectable anti-CGRP MABs on the HIT-6 scores and mean monthly migraine days in patients enrolled in the migraine clinic at multiple time intervals.

Methods

Design

This study was approved by the Texas Tech University Health Sciences Center (TTUHSC) Amarillo Institutional Review Board #A20-4171. This study is a non-randomized, prospective case series that involved a defined group of migraine patients followed over time to examine associations between erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm and subsequent outcomes on mean change from baseline in the HIT-6 scores and monthly average number of migraine days. This research involved a time-series design without randomization to treatment groups due to potential insurance formulary issues. In this study design, each participant had measurements done before and after receiving an injectable anti-CGRP MAB at pre-specified intervals, including an initial visit, 3 months, 6 months, and 12 months.

Inclusion criteria

Male or female, any ethnicity, ages 18 to 70 years old, able to speak and read English, diagnosis of episodic or chronic migraine with or without aura, prescribed an injectable anti-CGRP MAB therapy. Patients must have been prescribed two separate or combination preventative therapies over 3 months without adequate response, which was determined based on subjective symptom reporting on migraine scales and objective migraine findings before injectable anti-CGRP MAB were initiated. Patients may have concurrent prescriptions of other acute (abortive) migraine therapies (i.e., triptans, ergotamine derivatives, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or butalbital/acetaminophen/caffeine). Patients may also be prescribed magnesium, Coenzyme Q10, and/or riboflavin (vitamin B2) at any time before the initiation of injectable anti-CGRP MAB.

Exclusion criteria

<18 years old or > 70 years old, diagnosis of medication overuse headache or episodic cluster headaches, concurrent use of opiates, pregnancy, myocardial infarction, stroke, transient ischemic attacks, unstable angina, coronary artery bypass graft surgery or percutaneous coronary intervention within 6 months of screening, venous thromboembolism including deep vein thrombosis and/or pulmonary embolism within 6 months of screening, uncontrolled systolic blood pressure over 140 mm Hg or diastolic blood pressure over 90 mm Hg.

Recruitment

Subjects were recruited by word-of-mouth discussions during clinic visits at the Texas Tech Physicians (TTP) Headache Clinic located in an academic family medicine clinic at the TTUHSC School of Medicine in Amarillo, Texas. Individuals who had established caregiver relationships in Texas Tech Physicians (TTP) Headache Clinic were approached about involvement in the study and new patients. The screening script approved by the IRB was used for word-of-mouth discussions on patient recruitment.

Subjects screened but meeting the exclusion criteria (screening failure) will be replaced one-for-one with additional candidates with a goal of 60 subjects (20 per group).

Interventions

Migraines were managed according to the standard medical recommendations for individuals receiving injectable anti-CGRP MABs, and selection depended largely on insurance versus the availability of first-dose sampling. Erenumab-aaoe is available in 70 to 140 mg pre-filled syringes (PFS) and is injected subcutaneously (SubQ) every 1 month. Fremanezumab-vfrm is available in a 225 mg autoinjector or PFS and may be administered at 225 mg subQ every 1 month or 675 mg subQ every 3 months. Galcanezumab-gnlm is available in a 120 mg autoinjector or PFS and is typically administered as 240 mg subQ once and then 120 mg subQ every 1 month. Individuals who met the screening criteria and consented to be in the study had to complete the Headache Impact Test (HIT-6) questionnaire. Subjects were required to complete this questionnaire at baseline before or in temporal relationship to the first injectable anti-CGRP MAB therapy dose. This questionnaire was required to be filled out at baseline, 3 months, 6 months, and 12 months. Individuals were required to complete an initial face-to-face visit in the headache clinic and could also have subsequent face-to-face visits. If the subject's preference changed to telehealth, they could complete their follow-up appointment via telehealth. The HIT-6 questionnaire was completed either in person or by telehealth.

Table 1. Demographics and baseline characteristics

Characteristic	erenumab-aaoe 140 mg (n=6)	fremanezumab-vfrm 225 mg (n=11)	galcanezumab-gnlm 120 mg (n=11)
Age	32.1 ± 11.3 (18-54)	39.9 ± 12.2 (18-60)	40.0 ± 12.9 (18-60)
Sex, Female	6 (100%)	10 (90.9%)	11 (100%)
Race, white	6 (100%)	11 (100%)	11 (100%)
Chronic migraine diagnosis	5 (83.3%)	10 (90.9%)	9 (81.8%)
Baseline monthly migraine days	16.5 ± 7.0 (10-30)	18.3 ± 7.5 (5-30)	16.1 ± 7.0 (5-30)
Baseline HIT-6 score	68 ± 5.0 (65-78)	66 ± 6.1 (53-78)	66 ± 6.4 (53-78)
Combination preventative treatment with injectable anti-CGRP MAB	3 (50%)	6 (54.5%)	6 (54.5%)
Prior Medication use			
Antiepileptics	6/6 (100%)	9/11 (81%)	10/11 (90.9%)
Tricyclic antidepressants	3/6 (50%)	3/11 (27.2%)	3/11 (27.2%)
SSRI or SNRI	2/6 (33.3%)	4/11 (36.4%)	7/11 (63.6%)
Beta-blockers	1/6 (16.7%)	4/11 (36.4%)	2/11 (18.2%)
OnabotulinumtoxinA	1/6 (16.7%)	4/11 (36.4%)	1/11 (9%)
Current Acute Treatments			
Triptan	5/6 (83.3%)	6/11 (54.5%)	6/11 (54.5%)
Dihydroergotamine	0/6 (0%)	0/11 (0%)	0/11 (0%)
Oral gepant	1/6 (16.7%)	0/11 (0%)	1/11 (9%)
NSAID	5/6 (83.3%)	8/11 (72.7%)	6/11 (54.5%)
Acetaminophen	1/6 (16.7%)	4/11 (36.4%)	3/11 (27.2%)
Butalbital/acetaminophen	1/6 (16.7%)	1/11 (9%)	0/11 (0%)
Concurrent preventative therapies	3/6 (50%)	6/11 (54.5%)	6/11 (54.5%)

Statistical Analysis

No formal statistical power calculations were performed for this pilot study. Continuous variables are summarized with descriptive statistics, including number, mean, median, standard deviation (SD), minimum, and maximum, and categorical variables were summarized with counts and percentages as appropriate. For the primary outcomes, a one-way ANOVA was performed to compare the change in HIT-6 and change in average monthly migraine days from baseline from 3 months, 6 months, and 12 months between the three different groups (erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm). The statistical analyses were conducted using SAS 9.4.

Results

Recruitment occurred from February 2020 until March 2021 during which 28 patients met the inclusion criteria (6 erenumab-aooe, 11-fremanezumab-vfrm,and11galcan-ezumab-gnlm). The average age was 39 years, 96% were women, 92% had a diagnosis of chronic migraines, the baseline average monthly migraine days was 17, and the average HIT-6 score at baseline was 66 (severe impact). The most commonly used preventative migraine medications included topiramate, amitriptyline, venlafaxine, fluoxetine, propranolol, and onabotulinumtoxin A, while sumatriptan or sumatriptan/naproxen were the most frequent acute treatments. Acetaminophen and ibuprofen were also frequently reported. Additional patient demographics and baseline characteristics are reported in

Table 1. For graphical representations of the data, please refer to the box plots in Figures 1 and 2 which highlight central tendency, spread, and potential outliers in the data set. All 28 patients had baseline and 3-month

Table 2. Change in HIT-6 score from baseline

Time	Anti-CGRP MAB	Obs	N	Miss	Mean	Std Dev	Median	Min	Max	P-value
3 months	erenumab-aaoe	6	6	0	-6.2	4.4	-6.5	-13.0	0.0	0.8344
	fremanezumab-vfrm	11	11	0	-7.3	9.1	-4.0	-21.0	7.0	
	galcanezumab-gnlm	11	11	0	-5.0	10.1	-6.0	-22.0	18.0	
6 months	erenumab-aaoe	6	5	1	-14.2	10.7	-15.0	-25.0	-1.0	0.1694
	fremanezumab-vfrm	11	9	2	-12.1	9.9	-8.0	-32.0	-2.0	
	galcanezumab-gnlm	11	8	3	-3.1	12.9	-3.0	-23.0	22.0	
12 months	erenumab-aaoe	6	4	2	-25.3	8.2	-29.0	-30.0	-13.0	0.1301
	fremanezumab-vfrm	11	6	5	-19.0	11.9	-18.0	-38.0	-7.0	
	galcanezumab-gnlm	11	6	5	-12.7	5.2	-12.5	-21.0	-7.0	

HIT-6 scores and mean monthly migraine days reported. However, at 6 months, 6 patients were lost to follow-up, and by 12 months, 6 additional patients were lost to follow-up. Reasons included loss/change of insurance (6/12), preference for onabotulinumtoxinA and atogepant (3/12), pregnancy (1/12), and unspecified reasons (2/12). As shown in Table 2, the primary outcome change in HIT-6 from baseline demonstrated no statistically significant difference between the three treatment groups at 3, 6, or 12 months (p = 0.8344, 0.1694, and 0.1301, respectively). Similarly, Table 3 summarizes the secondary outcome of change in mean monthly migraine days which also showed no significant difference between the three treatment groups at 3, 6, or 12 months (p = 0.5237, 0.1233, and 0.2115, respectively).

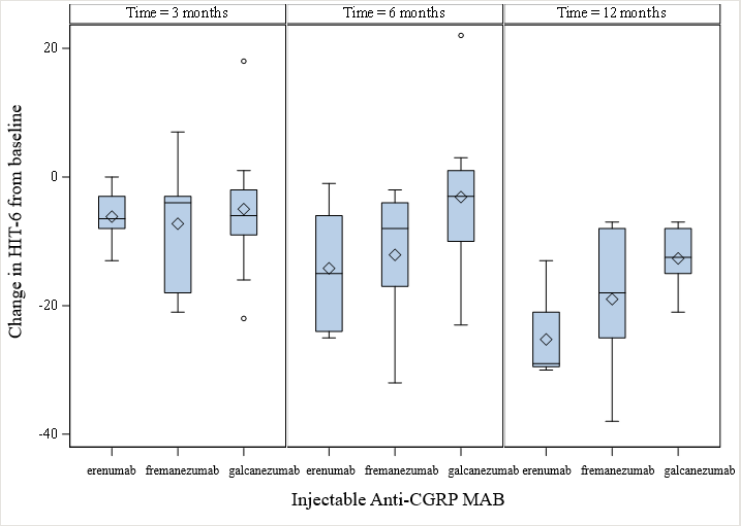

Figure 1. Box Plot change in HIT-6 Score from

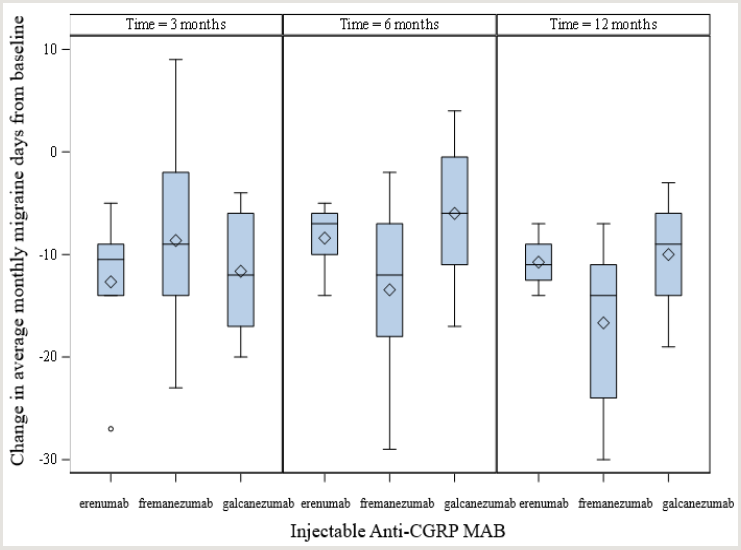

Figure 2. Box Plot change in average monthly migraine days from baseline

Discussion

In this study comparing injectable anti-CGRP MABs impact on HIT-6 and mean monthly migraine days, no differences were observed between the different treatment options. Although this study was not powered to assess clinical outcomes, patients were followed for up to 12 months, and it does appear that each anti-CGRP MAB does improve HIT-6 scores and mean monthly migraine days. In clinical trials, patients on injectable anti-CGRP MABs experienced around 5 fewer monthly migraine days on average compared to 3 with a placebo. In this study, at 3 months, 100% of erenumab-aaoe, 72.7% of fremanezumab-vfrm, and 90.9% of galcanezumab-gnlm experienced ≥ 5 fewer monthly migraine days on average at 3 months. The AHS consensus statement defines a meaningful improvement in HIT-6 as a reduction from baseline of ≥ 5 points within patients. In a systematic review and meta-analysis with erenumab, HIT-6 scores improved by -6.97 at 3 months.[16] A fremanezumab trial in 559 patients with chronic migraines found that at 6 months the HIT-6 scores improved by -8.1.[17] A galcanezumab trial in 87 patients with mostly chronic migraines found that at 3 months the HIT-6 scores improved by -4.4.[18] In this study, at 3 months, 66.6% of erenumab-aaoe, 45.5% of fremanezumab-vfrm, and 54.5% of galcanezumab-gnlm experienced ≥ 5 point improvement from baseline on their HIT-6 scores.

In 2024, the American Headache Society published a position statement that CGRP therapies are first-line options for the prevention of migraines and indicated, “initiation of these therapies should not require trial and failure of non-specific migraine preventative medication approaches.”[19] Though other experts from the American College of Physicians which recently published an update on migraine prevention reserved the use of CGRP medications for, “nonpregnant adults in outpatient settings who do not tolerate or inadequately respond to a trial or trials of a beta-adrenergic blocker (metoprolol or propranolol), the antiseizure medication valproate, the serotonin and norepinephrine reuptake inhibitor venlafaxine, or the tricyclic antidepressant amitriptyline.”[20]

In real-world practice, the treatment plan depends largely on patient preference, comorbidities, and the insurance plan, with many insurance plans requiring past medication failures with ≥60 to 90-day trial on other agents. In addition to injectable anti-CGRP MABS, there are widely available oral anti-CGRP medications. At the beginning of this study, rimegepant and ubrogepant were approved for acute migraine management. Now, rimegepant and atogepant are approved for chronic migraine prevention. Many patients may prefer oral gepants over injectable anti-CGRP MABs based on ease of oral administration. However, some patients may prefer the injectable anti-CGRP MAB if they have problems with nausea/vomiting or a preference for continuous CGRP inhibition. Each agent carries risks and benefits, and selection will still largely be driven by patient preference, comorbidities, and insurance plans.

This study had several strengths in comparing the 3 most common injectable anti-CGRP MABs in a real-world setting with a selection of agents based on patient characteristics and formulary restrictions. This patient population was representative of a typical migraine population, and this study design allowed each participant to serve as their own control to eliminate potential confounding characteristics. This study also reveals that many patients respond to and tolerate injectable anti-CGRP MABs but, unfortunately, are unable to continue therapy mainly due to insurance and formulary preference changes. This study also allowed other preventative therapies to be used with injectable anti-CGRP MABs, a distinct limitation of the currently available literature. This study also had several limitations: it was a single-center, small sample size, non-randomized, non-blinded, had a high drop-out rate, lacked a formal power analysis, and lacked a proper control group or randomization to individual treatment groups, posing a potential risk of selection bias.

Conclusions

This study reveals that while injectable anti-CGRP MABs (erenumab-aaoe, fremanezumab-vfrm, and galcanezumab-gnlm) showed improvements in HIT-6 scores and reduction in mean monthly migraine days, there were no significant differences between treatments. Real-world evidence supports their efficacy, and the response seen in this trial aligns with clinical trials showing that these agents do impact HIT-6 and monthly migraine days. Though the anti-CGRP agents are recommended as first-line therapy for migraines by some organizations, including AHS, our study suggests that insurance-related challenges limit long-term continuation. Future research should address ways to mitigate insurance-related coverage issues with injectable anti-CGRP MABS.

Table 3. Change in average monthly migraine days from baseline

Time	Injectable Anti-CGRP MAB	N Obs	N	N Miss	Mean	Std Dev	Median	Min	Max	P-value
3 months	erenumab-aaoe	6	6	0	-12.7	7.6	-10.5	-27.0	-5.0	0.5237
	fremanezumab-vfrm	11	11	0	-8.6	9.3	-9.0	-23.0	9.0	
	galcanezumab-gnlm	11	11	0	-11.6	5.9	-12.0	-20.0	-4.0	
6 months	erenumab-aaoe	6	5	1	-8.4	3.6	-7.0	-14.0	-5.0	0.1233
	fremanezumab-vfrm	11	9	2	-13.4	8.6	-12.0	-29.0	-2.0	
	galcanezumab-gnlm	11	8	3	-6.0	7.0	-6.0	-17.0	4.0	
12 months	erenumab-aaoe	6	4	2	-10.8	2.9	-11.0	-14.0	-7.0	0.2115
	fremanezumab-vfrm	11	6	5	-16.7	8.6	-14.0	-30.0	-7.0	
	galcanezumab-gnlm	11	6	5	-10.0	5.9	-9.0	-19.0	-3.0	

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