Title

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CGRP Monoclonal Antibody use for the Preventive Treatment of Refractory Headache Disorders in Adolescents.

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Abstract

Background: Monoclonal antibodies (mAbs) to calcitonin gene-related peptide (CGRP) or its receptor have clinical trial evidence in adults with headache, but data are lacking in adolescents.

Objective: To describe the safety and efficacy of CGRP monoclonal antibody (mAb) treatment in adolescents with chronic headache disorders.

Methods: Retrospective multi-site cohort study of adolescents <18 years prescribed a CGRP mAb for headache prevention. Demographics, baseline headache characteristics, efficacy and side effect data was collected.

Results: n=112 adolescents received ≥1 dose of a CGRP mAb. Mean (SD; range) age at first dose was 15.9 years (1.4; 10.3 to 17.8). Ninety-four (83.9%) had chronic migraine, 12 (10.7%) had NDPH, and 6 (5.4%) had PPTH. At baseline, mean (SD) baseline headache days per month was 26.9 (6.1) (n=109) and headache was continuous in 75/111 (67.6%). At follow-up visit 1 there was a significant reduction in headache frequency compared to baseline (−2.0 days, 95% CI: −0.8 to −3.2). Significant benefit was perceived by 29.5% at follow-up visit 1 (n=33/112) and 30.1% (n=22/73) at visit 2. Significant functional improvement was perceived by 31% (n=31/94) at the 1st follow-up and 22.4% (n=15/67) at the 2nd follow-up. Most common side effects were injection site reactions in 17.0% (n=19) and constipation in 8.0% (n=9). Five patients (4.5%) discontinued due to side effects.

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Trial Registration: Not applicable

Conclusions: Side effects with CGRP mAb treatment in adolescents are similar to those reported in adult trials. CGRP monoclonal antibody treatment appears to benefit a proportion of adolescents with chronic refractory headache disorders

Keywords

Migraine; chronic migraine; daily and continuous headache; post-traumatic headache; new daily persistent headache; refractory headache; erenumab; galcanezumab; fremanezumab; CGRP monoclonal antibodies; pediatric; adolescent

Introduction:

Primary headache disorders are common in adolescents and can be a source of significant disability. The prevalence of migraine is estimated as 8% in pediatric patients overall[1], with chronic migraine seen in up to 2% of adolescents[2]. Among patients presenting to outpatient neurology clinics, up to 72% have chronic daily headache[3], which may include chronic migraine, New Daily Persistent Headache (NDPH) and Persistent Post-Traumatic Headache (PPTH)[4–6]. Higher headache frequency is associated with more functional disability as indexed by number of missed school days[7]. There is a need for preventive therapies that are safe and effective in adolescents, as evidence-based therapies remain limited[8,9]. This is particularly true for pediatric patients whose headache disorders have been refractory to treatment, including those with continuous headache and medication overuse headache, populations who have largely been excluded from clinical trials[10].

In adults, monoclonal antibodies (mAbs) to calcitonin gene-related peptide (CGRP) or its receptor have clinical trial evidence for efficacy and safety for the preventive treatment of episodic and chronic migraine[11–19]. Pediatric headache specialists have published advice on when to consider using CGRP monoclonal antibodies in children and adolescents[20]. However, while controlled studies of CGRP monoclonal antibodies in pediatric patients are currently underway, we are aware of no published data to date on the use of these treatments in adolescents.

Our pediatric headache specialty centers have been using these antibodies as off-label treatment for some of our adolescent patients with difficult to treat primary headache disorders. The aim of this multi-site U.S. retrospective cohort study was therefore to report on the efficacy and safety of CGRP monoclonal antibody treatment in children and adolescents, including those patients with difficult to treat and/or continuous headaches.

Methods:

This is a retrospective cohort study of adolescents aged less than 18 years seen at one of three U.S pediatric headache centers (University of California, San Francisco (UCSF), Children’s Hospital Colorado (CHCO), Children’s Hospital of Philadelphia (CHOP)) who were prescribed a CGRP monoclonal antibody for the preventive treatment of a chronic headache disorder.

Permissions:

This study was approved by IRBs at UCSF, CHCO and CHOP. Each institution approved sharing of de-identified data between institutions.

Inclusion criteria:

Patients were included if they met the following criteria: 1) diagnosis of chronic migraine (with or without aura), New Daily Persistent Headache (NDPH) or persistent post-traumatic headache (PPTH) by a pediatric neurologist or nurse practitioner with experience in pediatric headache; 2) prescribed and initiated treatment with a CGRP monoclonal antibody for the prevention of headache after June 2018; 3) age <18 at the time of first injection; 4) at least one follow-up visit within 12 months following initiation of treatment with the CGRP monoclonal. There were no exclusions for aura, daily and/and continuous headache or mediation overuse.

Data Collection:

Data were collected using a standardized data collection form in REDCap (Research Electronic Data Capture)[21]. Baseline data collected included patient demographics, headache characteristics, presence of comorbid psychiatric or pain disorders severe enough to be documented in notes, and level of functional impairment (including PedMIDAS[22] scores if available and a baseline functioning determination by the research team as defined below). Number of prior preventives included all preventive exposures documented under past medications, regardless of whether it was an ‘adequate trial’. Efficacy, functional outcomes and side effect data were collected for up to two follow-up visits after the CGRP monoclonal antibody was prescribed.

Outcome measures:

Measures of efficacy were defined *a priori*. “Significant benefit” was defined as having at least one of: 1) decrease in headache frequency by at least one third for at least one month, 2) decrease in headache intensity by at least one third for at least one month, 3) decrease in headache duration by at least one third for at least one month, or 4) notes document a “significant” or “substantial” improvement in headache for at least one month. Patients were considered to have “some benefit” if some degree of improvement was documented in the notes, but criteria for “significant benefit” were not met, and “no benefit” if there was documented lack of improvement or above criteria for “significant” or “some” benefit were not met. Finally, patients were considered to have “worsened” if there was documented worsening of headaches.

Change in functional status was also defined *a priori*. “Significant functional improvement” was defined by having ≥one of the following: 1) notes document return to school; 2) notes document return to activities; 3) notes document a “significant” or “substantial” improvement in function. Patients were considered to have “some functional improvement” if some degree of functional improvement was documented in the notes, but criteria for “significant functional improvement” was not met, and “no functional improvement” if there was documented lack of functional improvement or above criteria for “significant” or

"some" functional improvement were not met. Patients were considered to have "worsening function" if there was documented worsening of function.

In addition to reporting PedMIDAS scores at baseline, baseline functioning was also determined by the study team as follows: "No concerns with functioning" was documented if the notes outlined no concern about function and/or attending school regularly, and/or no impact of headaches on activities or sports. "Some functional limitation" was documented if the notes outlined attendance at regular school, but occasionally missing school or activities. "Moderate functional limitation" was noted if there were problematic absences or missed activities. "Significant functional limitation" was indicated if documentation showed significant functional limitation and/or school change (e.g. home hospital instruction, independent study or dropping out) and/or if patient had to stop sports/activities. "Not document or other" was used if there was some other level of functioning noted or if functioning level could not be determined. If baseline assessment wad during summer, the prior school year was used to make the determination.

Side Effect Data:

Any side effects documented in patient charts were recorded and reported.

Statistical analysis & plan:

Descriptive statistics for continuous variables included mean and standard deviation, median with interquartile range, and mode depending on the distribution of the variable. Proportions are reported for categorical variables. Wilcoxon rank sum tests were used for analysis of continuous measures and to compare changes in median values. Chi-square tests were used to compare proportions for categorical measures. McNemar's tests were used to compare changes in proportions from visit to visit. All missing data was reported in the Tables.

Results:

The study population consistent of n=112 patients who received ≥1 dose of a CGRP monoclonal antibody treatment. Baseline data are shown in Table 1. The difficult nature of the chronic headache disorders in our patient population is highlighted by the high mean (SD) baseline headache frequency of 26.9 (6.1) days/month (n=109), the median baseline PedMIDAS score of 120 (interquartile range 48–182) (n=57) indicating severe disability, and the classification of "significantly limited" baseline function in 46/92 (43.4%). Headache was continuous in 75/111 (67.6%) at baseline. Mean (SD; range) number of preventives tried prior to CGRP monoclonal antibody use was 9.5 (5; 2–27). At least 13.4% (n=15) had previously tried onabotulunium toxin A injections. Seventy-one patients (63.4%) had previously been admitted to the hospital for treatment of headache, and the mean (SD) number of admissions were 2.30 (1.6). A co-morbid mental health disorder was seen in 68/111 (61.3%) and another chronic pain condition was seen in 30/111 (27.0%).

Post treatment outcomes at follow-up visits 1 and 2 are shown in Table 2. Erenumab was the most commonly prescribed treatment (97/112, 86.6% at visit 1 and 65/74, 87.5% at visit 2). Mean (SD) time to 1st follow-up was 2.7 (2.3) months and to 2nd follow-up was 4.6 (1.9) months. There was a significant decrease in mean headache frequency from baseline to visit

one (mean difference: −2.0 days; 95% CI: −0.8 to −3.2; p=0.001). Significant benefit was perceived by 29.5% at visit 1 (33/112) and 30.1% (22/73) at visit 2. Significant functional improvement was perceived by 33.0% (31/94) at the 1st follow-up and 22.4% (15/67) at the 2nd follow-up. Of those who had continuous headache at baseline, 9/74 (12.0%) reported resolution of continuous headache at follow-up visit 1 and 8/48 (16.7%) had resolution of continuous headache at follow-up visit 2. Significant or some benefit was noted in 68.0% (51/75) (95% CI: 0.56 to 0.78) of those with continuous headache vs. 77.8% (28/36) (95% CI: 0.61 to 0.90) of those without continuous headache at the first follow-up (p=0.287). Significant functional improvement was noted in 57.1% (36/63) (95% CI: 0.44 to 0.70) of those with continuous headache vs. 71.0% (22/31), (95% CI 0.52 to 0.86 in those without continuous headache at the first follow-up (p=0.196). The most common facet of headache described as improved was severity, described by 50.9% (57/112) at visit 1 and 47.3% (35/74) at visit 2.

Additional clinical events occurring around the time of CGRP monoclonal antibody use were also collected. Twenty-four percent of patients (n=27) started another medication in addition to the CGRP mAb between visit 1 and visit 2, while 14.3% (n=16) stopped another medication. Hospital admission for headache treatment occurred in 19.7% (n=15) immediately prior to starting the mAb (e.g. between the baseline visit when treatment was recommended and the date of first injection) and in 6.5% (n=7) while already using the mAb. Sixty-eight percent of patients (n=76) reported “another interval event” during their treatment with the CGRP mAb. These events included: starting of the school year or school stress (n=20; 17.9%); stressful life event (n=15; 13.4%); other injury, surgery, infection (n=9; 8.0%); head trauma or concussion (n=7; 6.2%); illness (n=7; 6.2%); menarche or problem with menstruation (n=2; 1.8%) or other (n=16; 14.3%).

Side effects are reported in Table 3. Of the n=112 patients, n=36 experienced a side effect (32.1%). Injection site reactions occurred in 17.0% (n=19), constipation in 8% (n=9), fatigue in 7.1% (n=8), dizziness in 4.5% (n=5) and both nausea and worsening headache in 3.6% (n=4). One patient each reported: arthralgia, nasopharyngitis, alopecia, decreased appetite, memory/awareness difficulties, flu-like illness, eye twitching, stomach-ache, sore leg. Five patients (4.5%) discontinued due to side effects. Reasons cited for discontinuation included: worsening constipation (n=1), event concerning for seizure (n=1), dizziness and hair loss (n=2), dizziness and an episode of syncope with worsening headache (n=1). The event concerning for seizure involved a convulsion with associated dizziness and confusion with loss of consciousness, jerking, and bladder/bowel incontinence that occurred 9 hours after using the 140 mg dose of erenumab. It is not clear if the convulsion was syncopal or epileptic in nature.

Discussion:

To our knowledge, this is the first study to report on the safety and efficacy of CGRP monoclonal antibody use in adolescents. It is important to note that the patient population in this study differs substantially from the patient population most often studied in migraine preventive trials[10,23]. All of the adolescents in this study had a chronic headache disorder (chronic migraine, NDPH, or persistent post-traumatic headache) and two-thirds

experienced continuous headache at baseline. Their condition was significant enough to require care at a subspecialty pediatric headache clinic, and 63.4% had previously been hospitalized for headache treatment. Most had been dealing with a significant headache problem for years, and on average they had been treated with 9.5 preventives prior to trying a CGRP pathway monoclonal antibody. While there is no universally accepted definition as to what constitutes a “treatment refractory” headache disorder, it is hard to imagine that these adolescents would not meet any reasonable definition that could be set forth. In this historically understudied population of adolescents, it is difficult to know what kind of treatment response rates should be considered a therapeutic success. Clinically, our collective opinion is that any degree of improvement in this historically difficult to treat population should be considered to be encouraging and a hopeful sign. The results of this chart review study suggest that CGRP monoclonal antibodies may be a safe and effective option for at least a proportion of adolescents who have difficult to treat, chronic headache disorders.

Over two-thirds of patients in this study had benefit (“significant” or “some” benefit combined) from treatment with the CGRP monoclonal antibodies. Specifically, 71.5% of patients had benefit at 2.7 months after initiation of treatment (first follow-up visit); and 69.8% had benefit by 4.6 months after initiation of treatment (second follow-up visit). This early response to treatment has previously been shown in the phase 2 trial of erenumab for prevention of chronic migraine in adults, though statistically significant superiority of erenumab over placebo was not demonstrated until 12 week follow-up[19]. In addition to the early and sustained subjective benefit and functional improvement reported by patients in our cohort, headache frequency also significantly decreased from baseline to follow-up visit 1, which was unexpected in this highly refractory patient population. However, the most commonly reported benefit was decrease in headache severity. Over half of the patients reported functional improvement with CGRP monoclonal antibody treatment; again, this was largely seen within 2 months of starting treatment, with 61.7% reporting significant or some functional improvement at first follow up and 53.7% reporting functional improvement at the second follow up.

Importantly, benefit and functional improvements were seen in both patients with and without continuous headache at baseline, and some even had a break in their continuous headache after starting the CGRP monoclonal antibody (12% at follow-up visit 1, 17% at follow-up visit 2). Patients with continuous headache have largely been excluded from clinical trials including the phase 2 clinical trial of erenumab for chronic migraine.[19] This is perhaps due to concern that treatment efficacy may not be reflected in standard primary outcome measures, such as the commonly reported ≥50% reduction in headache frequency outcome. Our findings suggest that these patients may still benefit from CGRP monoclonal antibody use.

Side effects with CGRP monoclonal antibody use in adolescents appear to be similar to those reported in the adult clinical trials[11–13,19]. The most commonly reported side effects were injection site reactions (17.0%), constipation (8.0%) and fatigue (7.1%). Discontinuation rate due to side effects was 4.5%. Of note, pediatric headache specialists have highlighted potential effects of CGRP mAbs that may be specific to children and

adolescents, including impact on bone growth and linear growth due to CGRP's role in bone formation and ossification[20], and, in those with a comorbid condition that disrupts the blood-brain barrier, potential for impact on central nervous system development. Unfortunately, assessment of CNS development and impact on bone development were beyond the scope of this study, and it remains important to be aware of these potential effects of CGRP monoclonal antibodies in the pediatric population.

Strengths of this study include inclusion of patients from multiple sites, use of a standardized data abstraction form, and *a priori* definition of what constitutes efficacy and functional benefit. An additional strength of this study is that it informs our understanding of outcome measures in adolescents who have continuous headache and/or "treatment refractory" headache disorders. For example, if researchers wish to design a trial in adolescent patients with continuous headache using a primary outcome measure of "proportion achieving cessation of continuous headache", our study suggests that approximately 12% can be expected to achieve this outcome by the 3-month mark.

Limitations include those intrinsic to retrospective chart review research, such as reliance on patient recall as documented in the chart, inability to control for other interval events that may have impacted headache frequency during the course of treatment with the CGRP monoclonal antibody, lack of a comparison group and the drop out of patients from visit 1 to visit 2 for various reasons. Despite the lack of a placebo group, we think this particular patient population is unlikely to have much of a placebo response after having had multiple outpatient and inpatient treatments.

Rigorous controlled trials of CGRP monoclonal antibody use for the preventive treatment of headache disorders in adolescents are needed.

Conflict of Interest and Financial Disclosures:

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Abbreviations

CGRP	Calcitonin gene-related peptide
NDPH	New Daily Persistent Headache
PTTH	Persistent Post-Traumatic Headache

REFERENCES

1. Abu-Arafeh I, Russell G. Prevalence and clinical features of abdominal migraine compared with those of migraine headache. Arch Dis Child. 1995;72(5):413–417. [PubMed: 7618907]
2. Lipton RB, Manack A, Ricci JA, Chee E, Turkel CC, Winner P. Prevalence and burden of chronic migraine in adolescents: results of the chronic daily headache in adolescents study (C-dAS). Headache. 2011;51(5):693–706. [PubMed: 21521206]
3. Wiendels NJ, van der Geest MC, Neven AK, Ferrari MD, Laan LA. Chronic daily headache in children and adolescents. Headache. 2005;45(6):678–683. [PubMed: 15953300]
4. Bigal ME, Lipton RB, Tepper SJ, Rapoport AM, Sheftell FD. Primary chronic daily headache and its subtypes in adolescents and adults. Neurology. 2004;63(5):843–847. [PubMed: 15365134]
5. Shaw L, Morozova M, Abu-Arafeh I. Chronic post-traumatic headache in children and adolescents: systematic review of prevalence and headache features. Pain Manag. 2018;8(1):57–64. [PubMed: 29192541]
6. Kuczynski A, Crawford S, Bodell L, Dewey D, Barlow KM. Characteristics of post-traumatic headaches in children following mild traumatic brain injury and their response to treatment: a prospective cohort. Dev Med Child Neurol. 2013;55(7):636–641. [PubMed: 23560811]
7. Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: association with school performance. Neurology. 2012;79(18):1881–1888. [PubMed: 23109652]
8. Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary:Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Headache. 2019;59(8):1144–1157. [PubMed: 31529477]
9. Locher C, Kossowsky J, Koechlin H, et al. Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2020.
10. Hershey AD, Powers SW, Coffey CS, et al. Childhood and Adolescent Migraine Prevention (CHAMP) study: a double-blinded, placebo-controlled, comparative effectiveness study of amitriptyline, topiramate, and placebo in the prevention of childhood and adolescent migraine. Headache. 2013;53(5):799–816. [PubMed: 23594025]
11. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018;38(6):1026–1037. [PubMed: 29471679]
12. Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017;377(22):2123–2132. [PubMed: 29171821]
13. Ashina M, Goadsby P, Reuter U, al. e. Long-term safety and tolerability of erenumab: three-plus year results from an ongoing open-label extension study in episodic migraine. Paper presented at: 2018 American Headache Society Annual Scientific Meeting June 28-July 1, 20182018; San Francisco, CA.
14. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018:333102418779543.
15. Aurora SK. Efficacy of Galcanezumab in Patients who Failed to Respond to Preventives Previously: Results from EVOLVE-1, EVOLVE-2, and REGAIN Studies. Paper presented at: American Academy of Neurology Annual Scientific Meeting2018; Los Angeles, CA.

16. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018.
17. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018;319(19):1999–2008. [PubMed: 29800211]
18. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017;377(22):2113–2122. [PubMed: 29171818]
19. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425–434. [PubMed: 28460892]
20. Szperka CL, VanderPluym J, Orr SL, et al. Recommendations on the Use of Anti-CGRP Monoclonal Antibodies in Children and Adolescents. Headache. 2018;58(10):1658–1669. [PubMed: 30324723]
21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–381. [PubMed: 18929686]
22. Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche MA, Maynard MK. PedMIDAS: development of a questionnaire to assess disability of migraines in children. Neurology. 2001;57(11):2034–2039. [PubMed: 11739822]
23. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics. 2009;123(3):924–934. [PubMed: 19255022]

Key Findings:

- The side effects of using CGRP mAb treatment in adolescents are similar to those reported in adult trials.
- CGRP monoclonal antibody treatment appears to benefit a proportion of adolescents with chronic refractory headache disorders, including those with continuous headache.

Table 1:

Demographic and Baseline Data for *n*=112 adolescents treated with at least one dose of CGRP pathway monoclonal antibody.

Age at first dose (years): mean (SD); range	15.9 (1.4); 10.3 to 17.8
Female sex assigned at birth: *n* (%)	91 (81.3%)
Weight (kg): mean (SD)	67.1 (18.0); *n*=110
Headache Diagnosis: *n* (%)	
Chronic migraine; Migraine with aura.	94 (83.9%); 22 (24.7%)
New daily persistent headache (NDPH)	12 (10.7%)
Persistent post-traumatic headache (PPTH)	6 (5.4%)
Duration of any headache (years): mean (SD)	6.0 (3.2)
Duration of significant headaches (years): median (IQR)	3.0 (2.0–5.0)
Continuous headache at time of first prescription: *n* (%)	
Yes	75 (67.6%)
No	36 (32.4%)
Duration of continuous headache at baseline (years): mean (SD); n	2.6 (1.6); *n*=64
Comorbid mental health disorder: *n* (%)	68 (61.3%); *n*=111
Comorbid other chronic pain condition: *n* (%)	30 (27.0%); *n*=111
Baseline headache frequency, days per month:	*n*=109
Mean (SD)	26.9 (6.1)
Median (IQR)	30 (27–30)
Baseline PedMIDAS score: median (IQR); *n*	120 (48 to 182); *n*=57
Baseline functioning as determined by study team: *n* (%)	*n*=92
No concerns with function	2 (2.2%)
Some functional limitation	21 (22.8%)
Moderate functional limitations	23 (25.0%)
Significant functional limitations	46 (50.0%)
Not documented in chart or missing data	20
Number of preventives tried prior to CGRP mAb: mean (SD); range	9.5 (5.1); 2–27
Number of hospital admissions for headache management prior to CGRP mAb use:	
Proportion of patients with a prior admission: *n* (%)	71 (63.4%)
Mean number of admissions (SD)	2.30 (1.6)

* n (participants) reported if missing data present

* IQR=interquartile range (Q1–Q3); SD=standard deviation

Table 2:

Efficacy and functional status outcomes after mAb treatment.

	First Follow Up *Mean (SD) time: 2.7 (2.3) months*	**Second Follow Up** *Mean (SD) time: 4.6 (1.9) months*
Prescribed mAb: *n* (%)	*n*=112	*n*=74
Erenumab	97 (86.6%)	65 (87.8%)
Galcanezumab	8 (7.7%)	4 (5.4%)
Fremanezumab	7 (6.2%)	5 (6.8%)
Missing data	0	38
Mean headache frequency (days/month):	*n*=110	*n*=66
Mean (SD)	24.6 (9.0);	25.3 (8.2)
Median (IQR)	30 (20–30)	30 (24–30)
Mean difference from baseline (95% CI)	−2.0 (−0.8 to −3.2) *	−1.4 (−0.03 to −2.8)
	p=0.001 *	*p*=0.045 *
Reported Benefit	*n*=112	*n*=73
Significant benefit	33 (29.5%)	22 (30.1%)
Some benefit	47 (42.0%)	29 (39.7%)
No benefit	27 (24.1%)	17 (23.3%)
Worsened	5 (4.5%)	5 (6.8%)
Not documented in chart or missing data	0	1
Reported Functional Status	*n*=94	*n*=67
Significant improvement	31 (33.0%)	15 (22.4%)
Some improvement	27 (28.7%)	21 (31.3%)
No improvement	31 (33.0%)	22 (32.8%)
Worsened	5 (5.3%)	9 (13.4%)
Not documented in chart or missing data	18	7
PedMIDAS score:	*n*=19	*n*=11
Median (IQR); *n*	47 (10–197);	34 (25–126)
Mean difference from baseline (95% CI)	−17 (−21 to 55)	−14; (−61 to 88)
Participants reporting resolution of continuous headache after treatment: *n* (%)	9/74 (12%)	8/48 (17%)
Most common facet of improvement noted:		
"Less severe": *n* (%)	*n*=57/112 (50.9%)	*n*=35/74 (47.3%)

* Indicates significance of p=<0.05

P values reported are for the Wilcoxon signed rank test on the median.

Table 3:

Side effects reported by those receiving at least one dose of a CGRP mAb (*n*=112).

Side Effect	**Number reporting a side effect: *n (%)***
Any side effect	36 (32.1%)
Injection Site Reaction	19 (17.0%)
Constipation	9 (8.0%)
Fatigue *(+ "sleepiness"x2; 'washedout'x1)*	8 (7.1%)
Dizziness or syncope	5 (4.5%)
Nausea	4 (3.6%)
Worsening headache	4 (3.6%)
Other *(each was reported by n=1, 0.9%)*	Arthralgia, nasopharyngitis, alopecia, decreased appetite, memory/awareness difficulties, flu-like illness, eye twitching, stomach-ache, sore leg.
Discontinued CGRP mAb due to side effects	5 (4.5%)
Reasons for discontinuation cited:	Episode of syncope and worsening headache (*n*=1), worsening constipation (*n*=1), dizziness and hair loss (*n*=2), convulsion (undetermined if syncopal or epileptic) (*n*=1).

*Some individuals reported more than one side effect