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Research Article

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Efficacy of Fremanezumab In Resistant and Refractory Chronic Migraine Patients: Real-World Data from The Hull Migraine Clinic, Uk

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Abstract

Background

Fremanezumab is an anti-calcitonin gene-related peptide monoclonal antibody efficacious for chronic migraine prophylaxis. We evaluated real-world prophylactic efficacy of fremanezumab for refractory and resistant chronic migraine in a United Kingdom specialist headache centre (Hull Migraine Clinic).

Materials and Methods

289 adult patients with resistant and refractory chronic migraine commenced fremanezumab with prospective follow-up, maintaining headache diaries for ≥1-month pre-fremanezumab initiation and continuously thereafter. Patients failed 6 median previous prophylactics. We measured monthly headache days, migraine days, headache-free days, analgesia medication days, triptan days and Headache Impact Test-6 scores at baseline and during treatment.

Results

All outcomes significantly improved in results of 182 patients at 4-month follow-up ($p<0.0001$), with reduced median monthly headache days (by 9 days), migraine days (by 10 days) and Headache Impact Test-6 (by 14.5 points). 80% patients achieved ≥30% migraine reduction, whilst 68% and 42% patients achieved >50% and >75% reduction. 58%, 39% and 17% patients achieved ≥30%, >50% and >75% headache day reduction. OnabotulinumtoxinA-unresponsive patients exhibited substantial responses, with 78%, 66% and 39% patients achieving ≥30%, >50% and >75% migraine reduction. Medication-overuse did not affect responses. 45% patients achieved <15 headache days in any month, and 65% achieved <8 migraine days in any month. 37% achieved both outcomes. In multivariate analyses, baseline headache-freedom and lower Headache Impact Test-6 score associated with ≥30% migraine reduction ($p<0.05$), whilst baseline headache-freedom and lower migraine-days associated with achieving <15 headache days in any month ($p<0.01$).

Conclusion

Fremanezumab demonstrates real-world efficacy at 4 months in resistant and refractorychronic migraine, including in OnabotulinumtoxinA-unresponsive patients, irrespective of medication-overuse. Baseline headache-freedom, lower migraine-days and lower Headache Impact Test-6 score heralded superior responses.

Keywords: Fremanezumab, OnabotulinumtoxinA, Resistant, Refractory, Chronic Migraine, Headache-Freedom, Real-World

Introduction

Chronic migraine (CM), defined by the International Classification of Headache Disorders 3rd-Edition (ICHD3) as headaches occurring ≥15 days/month for >3 months with migrainous headaches on ≥8 days/month, is a disabling condition with significant morbidity affecting 1.4–2.2% of the population [1, 2]. Prophylaxis is the mainstay management strategy. However, oral prophylactics were not specifically designed totargetthe molecular pathophysiology of migraine, whilst patients are often unresponsive or intolerantof multiple oral treatments, incurring additional comorbidities in the process including medication-overuse headache (MOH), defined by ICHD3 as headaches occurring ≥15 days/month in patients with pre-existing headache disorder and regular overuse of ≥1 acute/symptomatic headache treatment medications for >3 months [1]. Moreover, oral prophylaxisadherence is inconsistent, ranging between 19–79% at 6 months [3]. In the UK, CMunresponsive to ≥3 oral prophylactics is eligible for OnabotulinumtoxinA [4]. However, despite these therapeutics, an estimated 5–31% of CM remains unresponsive to all existing preventatives [5].

Anti-calcitonin gene-related peptide (CGRP)andCGRP receptor-monoclonal antibodies constitute a novel preventative class specifically designed to target migraine pathophysiology.Fremanezumab is a humanised anti-CGRPmonoclonal antibodyefficacious for episodic migraine (EM) and CM prophylaxisin the Phase 3, randomised, double-blind, placebo-controlled HALO studies [6, 7]. Monthly and quarterly fremanezumabsignificantly reduced headache and migraine days and acute analgesia use at 12-weeks in the HALO CM trial and 12-months in a trial-extension study [6, 8]. Fremanezumab was approved by the US Food and Drug Administration foradult migraineprophylaxis (2018), by the European Medicines Agencyfor migraine prophylaxis in adults with ≥4 migraine days/month (2019), and by the UK National Institute of Health and Care Excellence (NICE)for prophylaxis of CM unresponsive to ≥3 prophylactics, with treatment cessation if <30% migraine frequency improvement after 12 weeks treatment(2020) [9-11].

However, whilst real-world data exist on efficacy of other anti-CGRP monoclonal therapies including erenumab and galcanezumab, real-world fremanezumab efficacy data is sparse. Existing studiesincorporated CM patients with lower baseline headache and migraine days than those typically encountered in specialist headache centres [6, 12]. Moreover, whilst erenumab demonstrated efficacy as an anti-CGRP therapy in OnabotulinumtoxinA-refractory CM, real-world fremanezumab data in this cohort is lacking [13]. Furthermore, novel HALO post-hoc analysis suggested>50%fremanezumab-treated CM patients reverted to EM at 3 months[14]. Reversion to EM is an important clinical landmark, as it potentially enables patients to safely self-medicate with abortive therapies only,without requiring specialist neurology input. Therefore, assessment of whether fremanezumab can reduce headache frequency to that of EM during any treatment months in the real-world is necessary and helpful.

In this prospective audit, we report real-world efficacy outcomes of monthly fremanezumab treatment in a CM cohort unresponsive to an average of >6 preventatives, including OnabotulinumtoxinA, in a large UK specialist headache centre (Hull Migraine Clinic).

Materials and Methods

Audit Participants

289adult patients fulfilling the ICHD3 CM diagnostic criteria from the Hull Migraine Clinic, a large UK tertiary headache centre, commenced fremanezumab according to NICE guidance between November 2020 and April 2021.All patients had failed ≥3 preventatives including amitriptyline, nortriptyline, propranolol, atenolol, topiramate, candesartan, venlafaxine, sodium valproate, flunarizine, pizotifen, gabapentin, pregabalin, greater occipital nerve block, external trigeminal nerve stimulation (Cefaly), external vagal nerve stimulation (gammaCore), and OnabotulinumtoxinA. TheEuropean Headache Federation consensusdefinedresistant migraine as migraine which remains significantly debilitating despite some treatment attempts, with failure of or contraindication to≥3 prophylactic classes and≥8 debilitating headache days/month for ≥3 consecutive months; whilst refractory migraine is defined as migraine which remains significantly debilitating despite maximal or near maximal numbers of treatment attempts, with ≥8 debilitating headache days/month for ≥6 consecutive months[15]. Therefore, accordingly, all our patients met the definition for resistant migraine, whilst those unresponsive to all of the following prophylactic classes, including anti-depressants, anti-epileptics, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and OnabotulinumtoxinA were considered to have refractory migraine. Medication failure was defined as treatment discontinuation due to absence of headache frequency, duration or severity reduction after ≥12 weeks, or intolerance. According to UK national guidelines, OnabotulinumtoxinA failure was defined as<30% sustained monthly headache-day reduction after ≥2cycles [4]. Unresponsive patients discontinued OnabotulinumtoxinA as stipulated bynational guideline, before commencingfremanezumab after a washout period of ≥3 months. Patientsfulfilling UK OnabotulinumtoxinA response criteria continued OnabotulinumtoxinA and were excluded from the study, since they were already on effective treatment. Oral prophylaxis continuation was at patient and clinician discretion, since there are no national stopping criteria for oral preventatives. Those using opioid analgesia and those withmedication-overuse (MO), namely non-opiate use ≥15 days/month or triptan use ≥10 days/month for >3 months, were included to accurately reflect the nature of real-world resistant and refractory patients[1].Fremanezumabwas offered after discussion of all available untried preventative strategies.All patients gave their consent to participate in our study. However, as an audit under national guidelines, formal research ethics committee review was not required (https://www.hra-decisiontools.org.uk/research).

Audit Design

We ascertained baseline demographics including migraine onset

age, CM duration,presence of aura and utilisation ofprevious prophylactics including OnabotulinumtoxinA. All patients self-administered monthly subcutaneous fremanezumab 225mg from prefilled autoinjector syringes after training, with first follow-up at 4 months post-study initiation(1 month after the third dose). Patients maintained a headache diary for ≥30 daysbefore fremanezumab initiation and continuously thereafter, recording monthly headache days (MHD), migraine days (MMD), headache-free days (HFD), acute analgesia medication (AMD) and triptan use days (TD), and Headache Impact Test-6 (HIT-6) score to assess migraine impact on quality-of-life [16]. Diary completion was mandatory for treatment continuation,as per our usual clinical practice.Headache-day was defined as a day with any headache of any severity; migraine-day was one with headaches fulfilling ICHD3 migraine criteria; and headache-free day was defined as a "crystal-clear" day without any head painsat all during the 24-hour period, as per Khalil *et al*[17]. Data from the 30 days immediately before first fremanezumab dose constituted baseline parameters for each patient, whilst experiencing ≥1 crystal-clear headache-free days during this period indicated baseline headache-freedom.

For each patient at 4-month follow-up, the data for all out comes (MHD, MMD, HFD, AMD, TD and HIT-6) from the treatment month containing their best MHD result served as their post-treatment data. For each outcome, we calculated pre- and post-fremanezumab cohort medians and the change median. We correlated baseline MHD and MMD with % MHD and MMD reductions for each patient. At 4-month follow-up, we calculated the proportions of patients achieving ≥30%, >50% and >75% reductions in MHD and MMD from baseline. We ascertained the proportion of patients who experiencedMHD <15 days in any treatment month,as early indication of reversion to the headache frequency of EM for at least one month. We ascertained the proportion of patients who experienced MMD<8 days in any treatment month,as indicative of migraine frequency reduction to a level manageable with acute analgesia and without incurring MO. We also ascertained the proportion of patients achieving both MHD <15 days in any treatment month, and MMD<8 days in any treatment month. Adverse events (AEs) during treatment were noted. Patients with<30% MMD reduction after 12-weeks treatment discontinued fremanezumab according to national guidance[11].

Weassessed MHD, MMD, HFD and HIT-6 outcomes,the proportions of patients achieving ≥30%, >50% and >75% MHD and MMD reductions, and the proportions achieving MHD <15 in any treatment month,MMD<8 in any treatment monthand both outcomesin threesub-analyses in:

1. patients with and without baseline headache-freedom, to elucidate possible efficacy differences;
2. OnabotulinumtoxinA-refractory patients, to establish fremanezumab efficacy in this important cohort; and
3. patients with and without baseline MO, to ascertainits possible impact on fremanezumab efficacy.

Statistical Analysis

We compared baseline and post-fremanezumabMHD, MMD, HFD, AMD, TDand HIT-6 outcomes for thecohort and within eachsubanalysis groupusing Wilcoxon's signed-rank test, since all pre- and post-treatment outcomes significantly deviated from normal distributionin the Kolmogorov-Smirnov goodness-of-fit test (p<0.05). MHD, MMD, HFD, AMD, TD, HIT-6were presented as median and interquartile ranges (IQR), and age, migraine onset age and duration of chronic migraine as mean ± standard deviation (SD). Spearman's rank correlation coefficient assessed correlations between baseline MHD and MMD and% MHD and MMD reductions, with R^2 goodness-of-fit calculation. In sub-analyses, inter-group comparisons of median changes for non-normally distributed variables were performed using the Mann-Whitney U test. Continuous variables were compared using unpaired Student's t-test. Dichotomous variables between groups were compared using Fisher's two-tailed exact test.Bonferroni correction of the p value for multiple comparisons was applied as indicated.

Univariate logistic regression was performed to identify all variables significantly associated with two key treatment outcomes: ≥30% MMD reduction(enabling fremanezumab continuation),and MHD<15 days in any treatment months (early indicator of reversion to EM), respectively, with further analysis using multivariate logistic regression. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. For each variable, p<0.05 indicated statistical significance. Statistical analysis was performed using GraphPad Prism (Version 9.2.0, GraphPad Software, San Diego, California, USA).

Results

Patient Demographic Characteristics

Table 1: Baseline clinical characteristics of study patients who completed 4-month follow-up

Baseline characteristics (*n* = 182)	
Gender- Male, *n* (%) Female, *n* (%)	63 (35%) 119 (65%)
Age (years), mean (SD)	47.9 (13.7)
Aura, *n* (%)	82 (45%)
Migraine onset age (years), mean (SD)	26.2 (15.2)
Duration of chronic migraine (years), mean (SD)	12.3 (5.4)
Patients with medication overuse, *n* (%)	71 (39%)
Baseline MHD (days), median (IQR)	28 (22, 30)
Baseline MMD (days), median (IQR)	17 (13, 25)
Baseline HFD (days), median (IQR)	2 (0, 8)
Patients with 0 baseline HFD, *n* (%) Patients with ≥1 baseline HFD, *n* (%)	84 (46%) 98 (54%)
Number of previous prophylactic treatments failed per patient, median (IQR), range	6 (6, 7) 3 – 11
Previous prophylactic treatments failures, *n* (%) ≥5 ≥6 ≥7	165 (90%) 159 (87%) 135 (74%)
Patients with resistant migraine, *n* (%) Patients with refractory migraine, *n* (%)	182 (100%) 43 (24%)
Patients with onabotulinumtoxinA failure, *n* (%) Number of treatment cycles, median (IQR), range	166 (91%) 6 (5, 7), 3 – 9
Patients by each failed prior prophylactic, *n* (%)	
- OnabotulinumtoxinA	166 (91%)
- Amitriptyline	164 (90%)
- Nortriptyline	15 (8%)
- Venlafaxine	22 (12%)
- Propanolol	157 (86%)
- Atenolol	5 (3%)
- Sodium valproate	41 (23%)
- Topiramate	134 (74%)
- Candesartan	149 (82%)
- Flunarizine	9 (5%)
- Pizotifen	54 (30%)
- Gabapentin	42 (23%)
- Pregabalin	24 (13%)
- Greater occipital nerve block (GONB)	26 (14%)
- External trigeminal nerve stimulation (Cefaly)	3 (2%)
- External vagal nerve stimulation (GammaCore)	3 (2%)

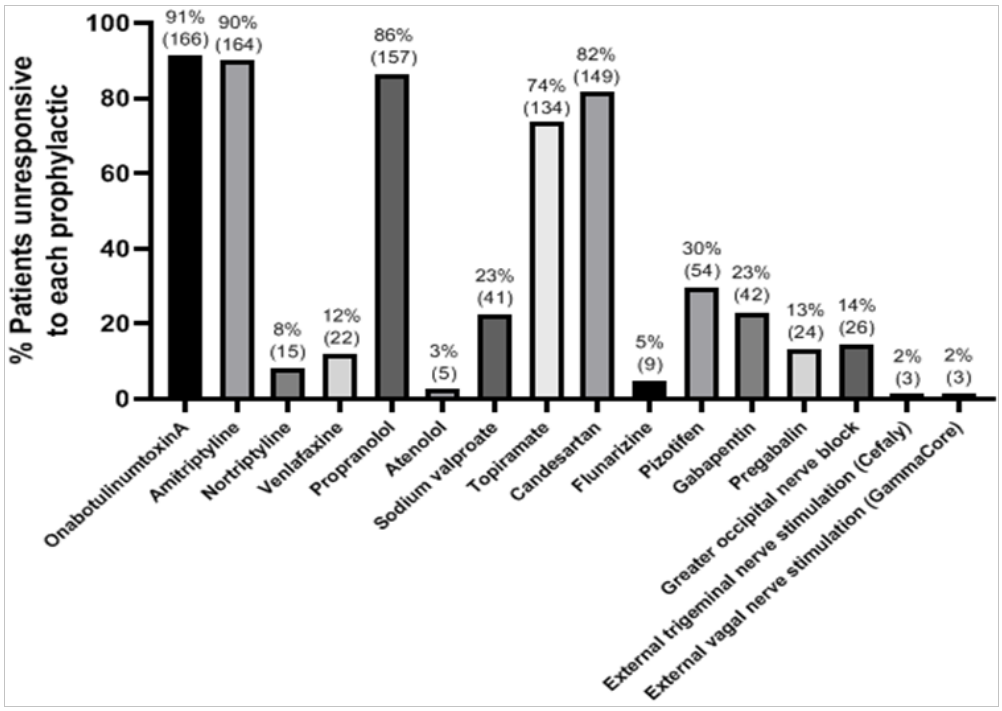


Figure 1: Cohort use of previous migraine prophylactics. Percentage and number (in parentheses) of patients who tried and were unresponsive to each migraine prophylactic.

Of 289 total patients, we report the outcomes of 182 patients who completed 3 injections and 4-month follow-up. Baseline characteristicsof these patients and prior prophylactics used are summarised [Table 1, Figure 1]. 182 (100%) patients had resistant migraine, whilst 43 (24%) satisfied the criteria for refractory migraine.

Cohort fremanezumab efficacy outcomes

Table 2a: Changes in monthly headache days, monthly migraine days, crystal-clear headache-free days, analgesia use and HIT-6 score post-fremanezumab treatment

Outcome (n = 182)	Baseline	Post-fremanezumab	Change median	*P value*(<0.008)
MHD (days), median (IQR)	28 (22, 30)	15 (9, 29.5)	-9	<0.0001*
MMD (days), median (IQR)	17 (13, 25)	6 (2, 11)	-10	<0.0001*
HFD (days), median (IQR)	2 (0, 8)	15 (0.5, 21)	9	<0.0001*
AMD (days), median (IQR)	10 (4.5, 20)	4 (0, 7)	-5	<0.0001*
TD (days), median (IQR)	1.5 (0, 9)	0 (0, 3)	0	<0.0001*
HIT 6 score, median (IQR)	68 (65, 72)	55 (48, 61)	-14.5	<0.0001*

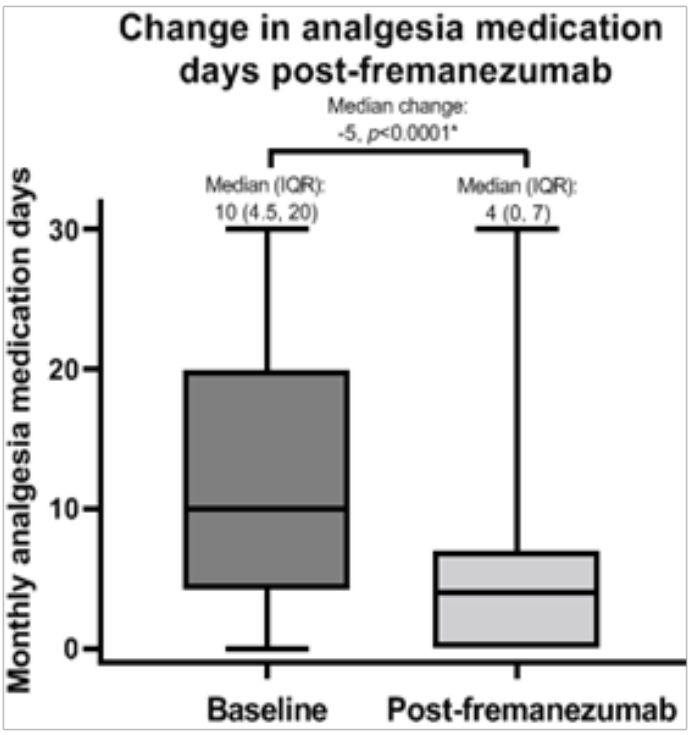
Median change in MHD, MMD, HFD, AMD, TD and HIT-6 compared using Wilcoxon signed-rank test. Bonferroni correction for multiple comparisons set at $p< 0.05/6 = 0.008$ for statistical significance. * denotes $p<0.008$.

Table 2b: Numbers and proportions of patients achieving ≥30%, >50% and >75% reductions from baseline monthly headache days and baseline monthly migraine days post-fremanezumab treatment

Outcome (*n* = 182)	MHD, *n* (%)	MMD, *n* (%)
≥30% reduction from baseline	105 (58%)	145 (80%)
>50% reduction from baseline	70 (39%)	124 (68%)
>75% reduction from baseline	31 (17%)	76 (42%)

Table 2c: Numbers and proportions of patients achieving MHD <15 in any month, MMD <8 in any month, MHD <15 in any month and MMD <8 in any month, and number and proportion of patients with 0 baseline headache-free days achieving ≥1 headache-free days post-fremanezumab treatment

Outcome	*n* (%)
Patients with 0 baseline HFD who achieved ≥1 HFD (*n* = 84)	38 (45%)
MHD <15 in any month (*n* = 182)	82 (45%)
MMD <8 in any month (*n* = 182)	119 (65%)
MHD <15 in any month and MMD <8 in any month (*n* = 182)	67 (37%)



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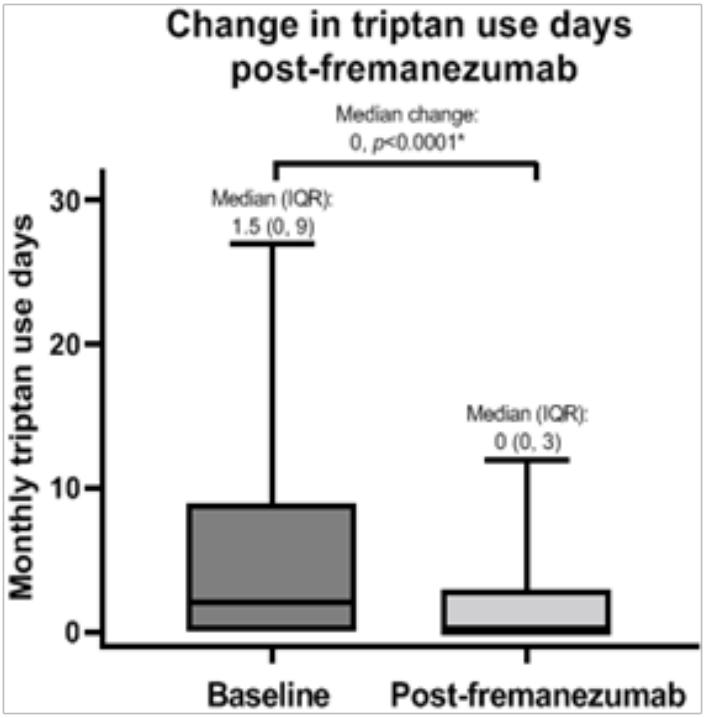

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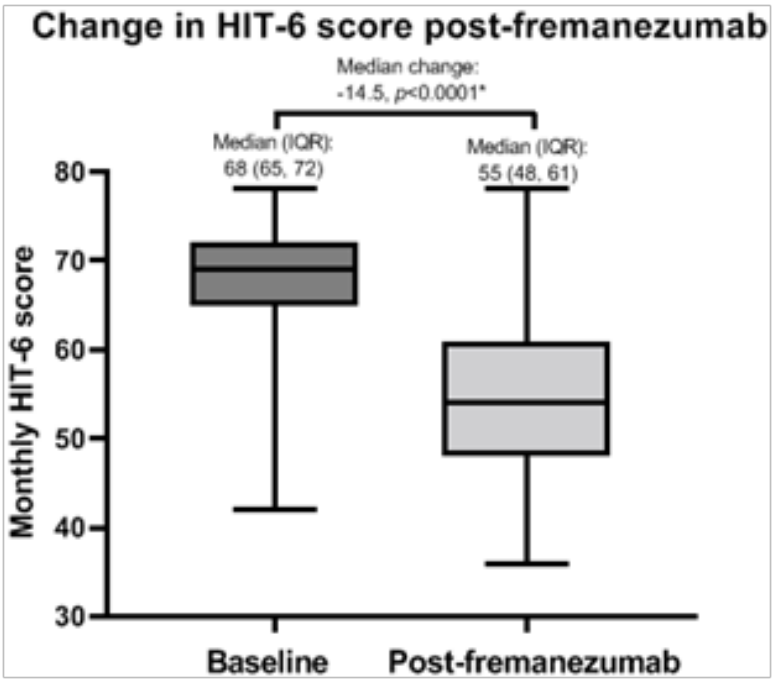


(c)

Figure 3: Changes in analgesia use and HIT-6 post-fremanezumab treatment. (a – c) Change in acute analgesia medication use days (a), triptan use days (b) and HIT-6 score (Wilcoxon signed-rank test). Bonferroni correction for multiple comparisons set at p< 0.05/6 = 0.008 for statistical significance. * denotes p<0.008.

At 4-month follow-up, median MHD reduction from baseline was 9 days, MMD reduction was 10 daysand HFD increase was9 days (all p<0.0001) (Table 2a, Figure2a–c).38 (45%) of 84 patients without baseline headache-freedom achieved ≥1 HFD post-fremanezumab[Table 2c, Figure 2d]. These indicatedsignificant MHD, MMD and HFDimprovements after 3 fremanezumab doses.

We assessed correlation between baseline MHD and MMD and individual patient response magnitudes. Baseline MHD negatively correlated with % MHD reduction(r = -0.410, R^2 = 17%, p<0.0001)and % MMD reduction (r = -0.155, R^2 = 2%, p=0.0416) [Figure2e, f]. Baseline MMD demonstrated no correlation with % MMD reduction (r = -0.119, p=0.13, data not shown).Therefore, fewer baseline headache daysassociated with superiorMHD and MMD reduction responses statistically, but with limited clinical significance. Baseline MMD bore no correlation with the magnitude of MMD responses.

We evaluated ≥30%, >50% and >75% MHD and MMD reductions from baseline to quantify the proportion of patients experiencing significant fremanezumab responses and those meeting the UK fremanezumab continuation criteria (Table 2b, Figure 2g). 105 (58%), 70 (39%) and 31(17%) patients achieved ≥30%, >50% and >75% MHD reduction. 145(80%)patients achieved ≥30% MMD reduction, thereby meeting the UK fremanezumab continuation criteria. 124 (68%) and 76 (42%) achieved >50% and >75% MMD reduction. 46 (25%) achieved ≥30% MMD reduction without achieving ≥30% MHD reduction (not shown). Overall,sizeable proportions ofpatients experiencedlarge-magnitude MHD and MMDimprovements, particularly MMD improvement, with80% patientsqualifying for fremanezumab continuation beyond 3 months.

To contextualise real-world fremanezumab utility, we evaluated the proportion of patients achieving MHD <15 days or MMD<8 daysin any treatment month[Table 2c, Figure2h]. 82 (45%) patients achieved MHD <15 days in any treatment month. 119 (65%) achieved MMD <8 days in any treatment month.67 (37%) achieved both outcomes.Therefore, within 3 months of fremanezumab initiation, substantial proportions of our cohort demonstratedearly headache improvement towards EM reversion and migraine frequency reduction to one safely manageable with abortive therapies without risking MO.

Post-fremanezumab, median AMD reduction was 5 days, TD reduction was 0 daysand HIT-6 reduction were 14.5 (all p<0.0001) [Table 2a, Figures3a-c].These demonstrated significantly reduced acute analgesia and triptan use to a frequency below that which predisposes to MO,alongside significantly improved quality-of-life.

Fremanezumab Efficacy in Patients with And Without Baseline Headache-Freedom

Table 3a: Baseline clinical characteristics of patients with and without baseline headache-freedom

Baseline characteristics	Patients with 0 baseline HFD (*n* = 84)	Patients with ≥1 baseline HFD (*n* = 98)	*P value*(<0.003)
Gender- Male, *n* (%) Female, *n* (%)	30 (36%)	32 (33%)	0.7540
	54 (64%)	66 (67%)	
Age (years), mean (SD)	47.1 (13.8)	48.9 (12.6)	0.3591
Aura, *n* (%)	38 (45%)	45 (46%)	1.0000
Duration of migraine (years), mean (SD)	25.3 (15.8)	27.0 (14.2)	0.4484
Duration of chronic migraine (years), mean (SD)	12.9 (5.1)	11.8 (5.5)	0.1660
Baseline MHD (days), median (IQR)	30 (30, 30)	23 (19, 25)	<0.0001*
Baseline MMD (days), median (IQR)	24 (16, 30)	15 (10, 19)	<0.0001*
Baseline HFD (days), median (IQR)	0 (0, 0)	7 (5, 11)	<0.0001*
Number of previous prophylactic treatments failed per patient, median (IQR)	6 (6, 7)	6 (6, 7)	0.7782
Previous prophylactic treatments failures, *n* (%) ≥5 ≥6 ≥7			
	80 (95.2%)	85 (86.7%)	0.0720
	77 (91.7%)	82 (83.7%)	0.1215
	64 (76.2%)	71 (72.4%)	0.6128
Patients with onabotulinumtoxinA failure, *n* (%)	74 (88%)	92 (94%)	0.1963
Number of treatment cycles, median (IQR)	6 (6, 7)	6 (6, 7)	0.3923
Baseline medication-overuse, *n* (%)	38 (45%)	33 (34%)	0.1285
Baseline HIT-6 score, median (IQR)	70 (66, 72)	68 (65, 71)	0.0311

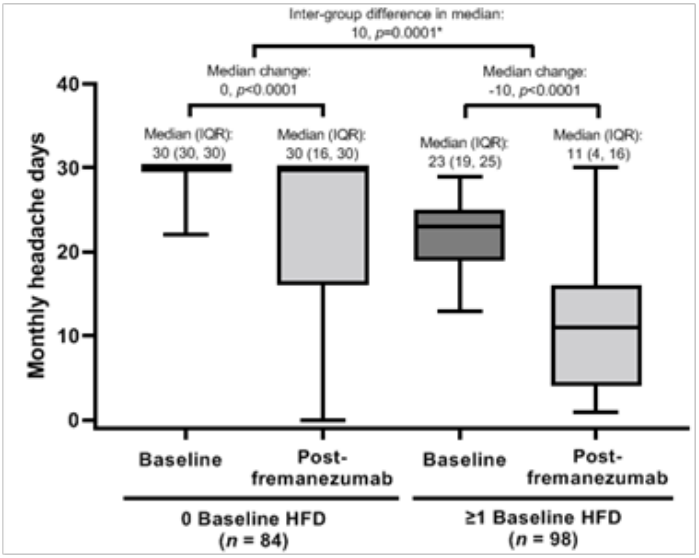
Inter-group MHD, MMD, HFD and HIT-6 compared using Mann-Whitney U test, continuous variables compared using unpaired Student's t-test, and dichotomous variables compared using Fisher's two-tailed exact test. Bonferroni correction for multiple comparisons set at $p < 0.05/16 = 0.003$ for statistical significance. * denotes $p<0.003$.

Table 3b: Treatment outcomes post-fremanezumab in patients with and without baseline headache-freedom

Outcome (*n* = 182)	Patients with 0 baseline HFD (*n* = 84)	Patients with ≥1 baseline HFD (*n* = 98)	Inter-group difference	*P value*(<0.004)
MHD, median (IQR)				
- Baseline:	30 (30, 30)	23 (19, 25)	Reduction in median: 10	0.0001*
- Post-fremanezumab:	30 (16, 30)	11 (4, 16)		
- Intra-group median change, *p value:*	0, p<0.0001	-10, p<0.0001		
MMD, median (IQR)				
- Baseline:	24 (16, 30)	15 (10, 19)	Reduction in median: -4	0.1478
- Post-fremanezumab:	9 (4, 16)	4 (2, 8)		
- Intra-group median change, *p value:*	-12, p<0.0001	-8, p<0.0001		
HFD, median (IQR)				
- Baseline:	0 (0, 0)	7 (5, 11)	Reduction in median: -10	<0.0001*
- Post-fremanezumab:	0 (0, 13)	19 (14, 25)		
- Intra-group median change, p value:	0, p<0.0001	10, p<0.0001		
HIT-6, median (IQR)				
- Baseline:	70 (66, 72)	68 (65, 71)	Reduction in median: 4	0.0048
- Post-fremanezumab:	57 (50, 64)	52 (48, 56)		
- Intra-group median change, p value:	-12, p<0.0001	-16, p<0.0001		
Patients with baseline MO achieving MO cessation, *n* (%)	n = 38 28 (74%)	n = 33 30 (91%)	17%	0.0730
Patients achieving: *n* (%)				
- MHD < 15 in any month	19 (23%)	63 (64%)	41%	<0.0001*
- MMD<8 in any month				
- MHD < 15 in any month	36 (43%)	83 (85%)	42%	<0.0001*
and MMD<8 in any month	11 (13%)	56 (57%)	44%	<0.0001*
Patients achieving MHD reduction of: *n* (%) ≥30% >50% >75%	 34 (40.5%) 21 (25.0%) 5 (6.0%)	 71 (72.4%) 49 (50%) 26 (26.5%)	 32.0% 25.0% 20.5%	 <0.0001* 0.0007* 0.0003*

Patients achieving MMD reduction of: *n* (%)				
≥30%	61 (72.6%)	84 (85.7%)	13.1%	0.0413
>50%	50 (59.5%)	74 (75.5%)	16.0%	0.0256
>75%	26 (31.0%)	50 (51.0%)	20.0%	0.0069

Treatment outcomes in patients with or without baseline headache-freedom. Intra-group and inter-group MHD, MMD, HFD and HIT-6 comparisons made using Wilcoxon signed-rank test and Mann Whitney U test, respectively. Inter-group comparisons of dichotomous variables made using Fisher's two-tailed exact test. Bonferroni correction for multiple comparisons set at $p < 0.05/14 = 0.004$ for statistical significance. * denotes $p<0.004$.



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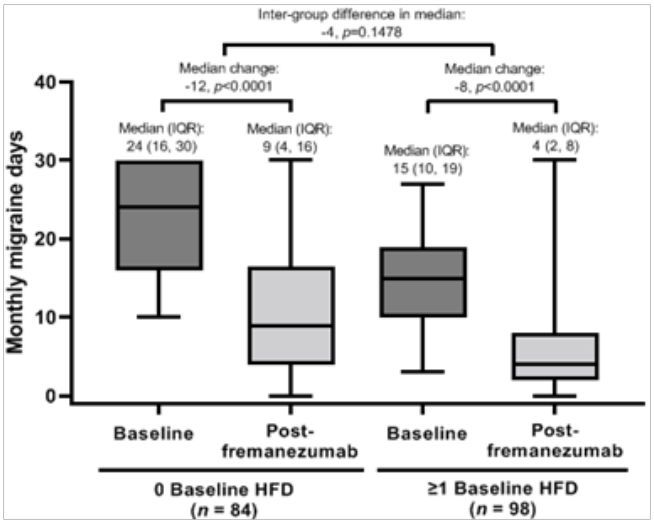

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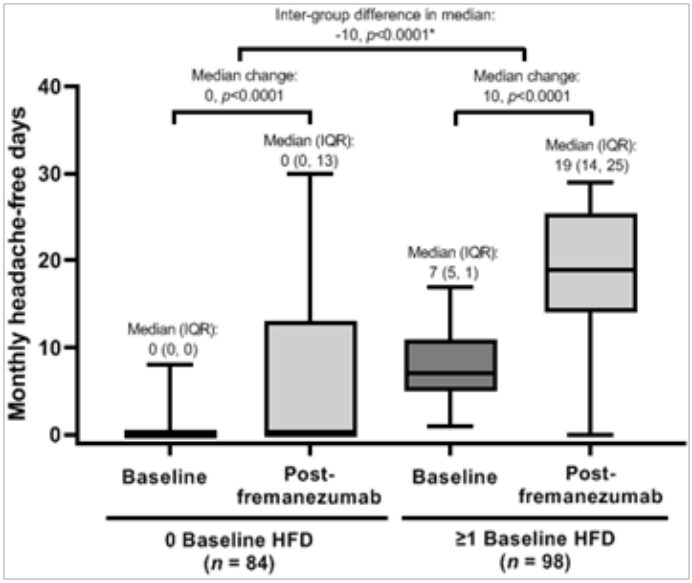

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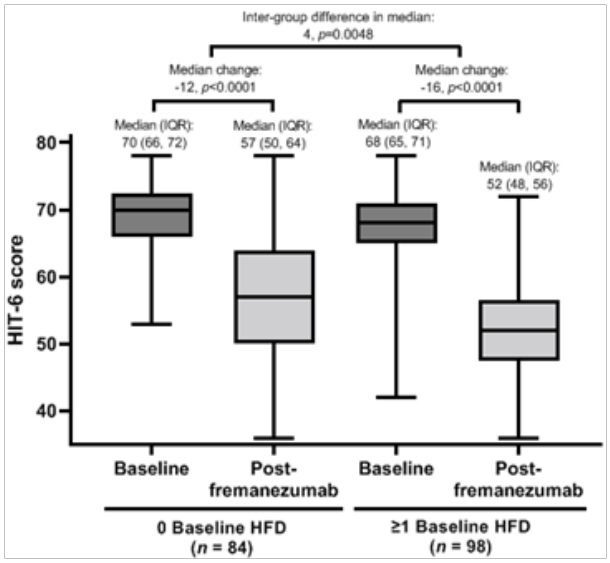

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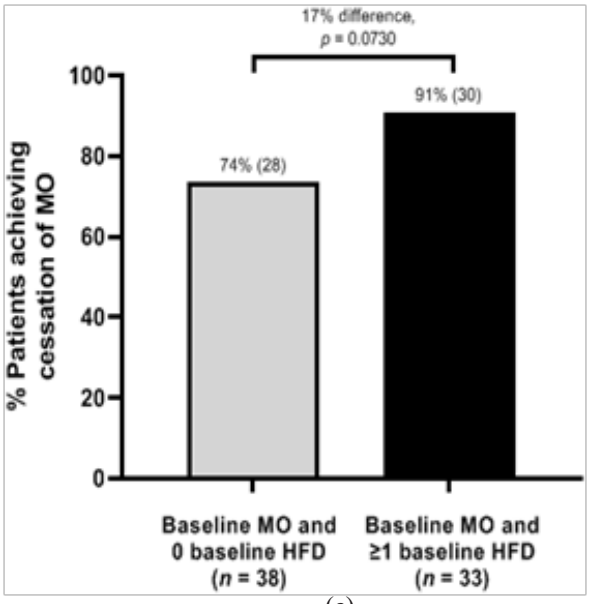
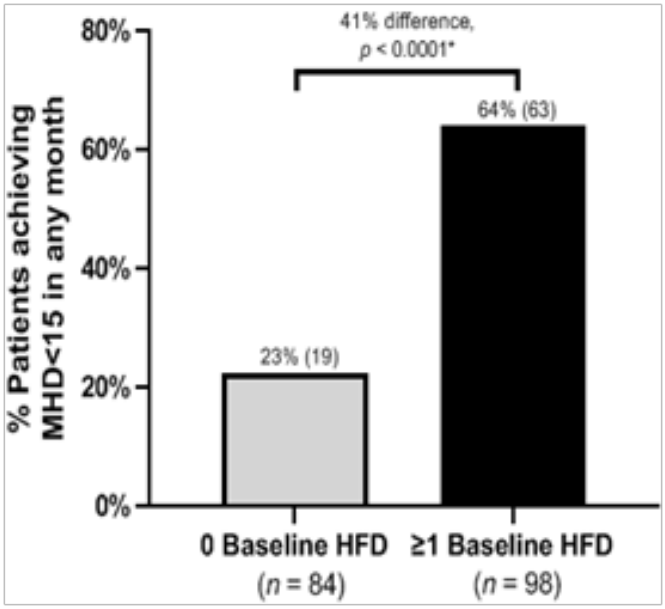
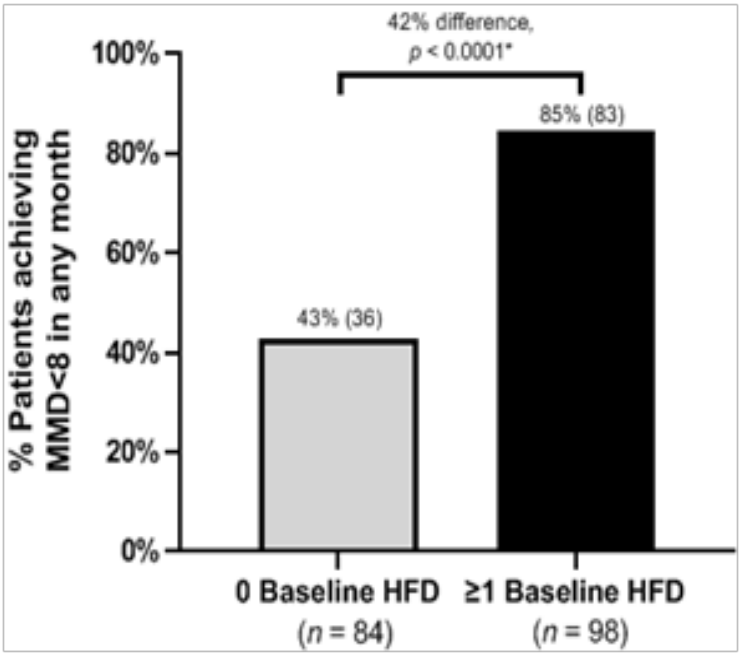

17% difference,
p = 0.0730
91% (30)
74% (28)
% Patients achieving cessation of MO
100
80
60
40
20
0
Baseline MO and 0 baseline HFD (n = 38)
Baseline MO and ≥1 baseline HFD (n = 33)

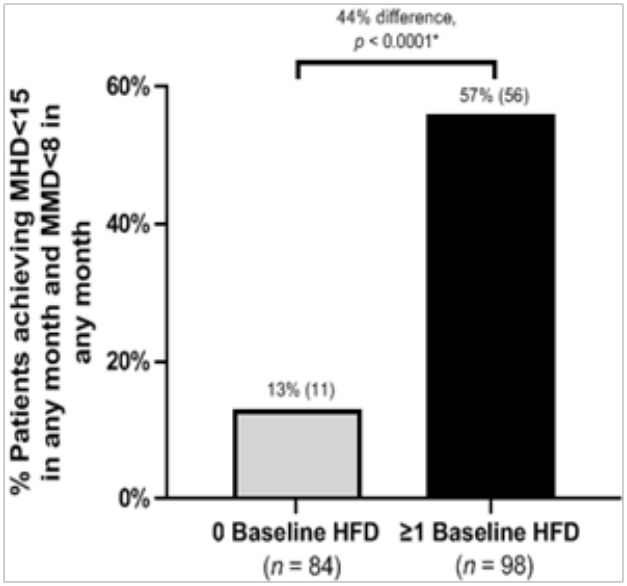
(e)


41% difference,
p < 0.0001*
64% (63)
23% (19)
% Patients achieving MHD<15 in any month
80%
60%
40%
20%
0%
0 Baseline HFD (n = 84)
≥1 Baseline HFD (n = 98)

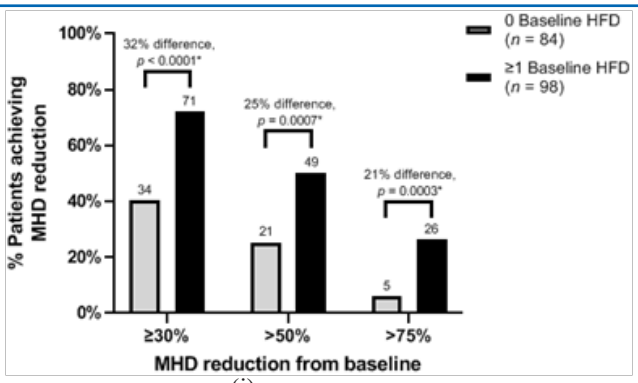
(f)


42% difference,
p < 0.0001*
85% (83)
43% (36)
% Patients achieving MMD<8 in any month
100%
80%
60%
40%
20%
0%
0 Baseline HFD (n = 84)
≥1 Baseline HFD (n = 98)

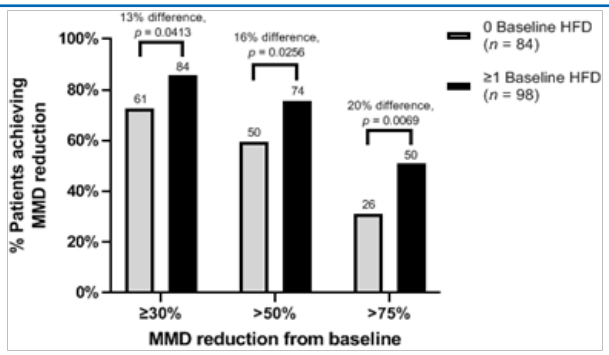
(g)


44% difference,
p < 0.0001*
57% (56)
13% (11)
% Patients achieving MHD<15 in any month and MMD<8 in any month
60%
40%
20%
0%
0 Baseline HFD (n = 84)
≥1 Baseline HFD (n = 98)

(h)



(i)



(j)

Figure 4: Treatment outcomes in patients with or without baseline headache-freedom. (a–d) Change in MHD (a), MMD (b), HFD (c) and HIT-6 score (d). Intra-group and inter-group MHD, MMD, HFD and HIT-6 comparisons made using Wilcoxon signed-rank test and Mann Whitney U test, respectively. e) Percentage and number (in parentheses) of patients with baseline medication-overuse (MO) achieving cessation of MO post-fremanezumab. (f–j) Percentage and number (in parentheses) of patients achieving MHD<15 in any treatment month (f), MMD<8 in any treatment month (g), and both outcomes (h), and ≥30%, >50% and >75% reduction of baseline MHD (i) and MMD (j). Inter-group comparisons of dichotomous variables made using Fisher's two-tailed exact test. Bonferroni correction for multiple comparisons set at $p< 0.05/14 = 0.004$ for statistical significance. * denotes $p<0.004$.

We compared treatment outcomes between patients with and without baseline headache-freedom. Patients without baseline headache-freedom exhibited significantly greater baseline MHD, MMD and HFD but similar other baseline characteristics, including HIT-6 score and the proportion of patientswith baseline MO (Table 3a). Both groups achieved significant post-fremanezumab-MHD, MMD, HFD and HIT-6 improvements (all $p<0.0001$). Patients with baseline headache-freedom experienced significantly greater median MHDreductionand HFD gain compared to those without, with significantly greater percentages achieving ≥30%, >50% and >75%MHD reductions, MHD <15 days in any month, MMD <8 days in any month,and both outcomes. There were no significant inter-group differences in median MMD reduction orpercentages of patients achieving significant MMD reductions. Similar percentages of patients stopped medication-overuse post-fremanezumabin both groups [Table 3b, Figure 4a-j].Therefore, those with baseline headache-freedom demonstratedgreater headache improvement,independent of reduced medication-overuse, suggesting baseline headache-freedomas a potential response prognosticator.

Fremanezumab Efficacy in OnabotulinumtoxinA-Unresponsive Patients

Table 4a: Baseline clinical characteristics of OnabotulinumtoxinA-unresponsive patients

Baseline characteristics (n = 166)	
Gender- Male, *n* (%) Female, *n* (%)	59 (35%) 107 (65%)
Age (years), mean (SD)	48.6 (13.6)
Aura, *n* (%)	73 (44%)
Duration of migraine (years), mean (SD)	26.0 (15.3)
Duration of chronic migraine (years), mean (SD)	12.1 (5.4)
Number of previous prophylactic treatments failed per patient, median (IQR)	6 (6, 7)
Previous prophylactic treatments failures, *n* (%) ≥5 ≥6 ≥7	 53 (92%) 141 (85%) 126 (76%)
Number of onabotulinumtoxinA treatment cycles, median (IQR)	6 (6, 7)

Baseline clinical characteristics of OnabotulinumtoxinA-unresponsive patients.

Table 4b: Treatment outcomes in OnabotulinumtoxinA-unresponsive patients

Outcome (*n* = 166)	Baseline	Post-fremanezumab	Change median	*P value* (<0.0125)
MHD (days), median (IQR)	28 (23, 30)	16 (9, 30)	-8	<0.0001*
MMD (days), median (IQR)	18 (14, 25)	7 (2, 11)	-9	<0.0001*
HFD (days), median (IQR)	1 (0, 7)	14 (0.75, 20.25)	8	<0.0001*
HIT-6 score, median (IQR)	68 (65, 72)	56 (48, 61)	-12	<0.0001*
Patients achieving MHD reduction of: *n* (%) ≥30% >50% >75%		 94 (57%) 60 (36%) 24 (15%)		
Patients achieving MMD reduction of: *n* (%) ≥30% >50% >75%		 129 (78%) 109 (66%) 65 (39%)		
Patients achieving MHD < 15 in any treatment months, *n* (%) Patients achieving MMD<8 in any treatment months, *n* (%)		72 (43%) 104 (63%)		

Median change in MHD, MMD, HFD and HIT-6 compared using Wilcoxon signed-rank test. Bonferroni correction for multiple comparisons set at $p< 0.05/4 = 0.0125$ for statistical significance. * denotes $p<0.0125$.

In 166 OnabotulinumtoxinA-unresponsive patients, fremanezumab induced significant headache, migraine, headache-free days and HIT-6improvements, demonstrating high treatment efficacy in this cohort [Table 4a, 4b].

Fremanezumab Efficacy in Patients with and Without Baseline Analgesia Medication Overuse

Table 5a: Clinical characteristics of patients with and without baseline analgesia MO

Baseline characteristics	Patients with MO (*n* = 71)	Patients without MO (*n* = 111)	*P value* (<0.0045)
Gender- Male, *n* (%)	18 (25%)	28 (25%)	1.0000
Female, *n* (%)	53 (75%)	83 (75%)	
Age (years), mean (SD)	48.4 (12.9)	47.6 (13.5)	0.6920
Aura, *n* (%)	30 (42%)	52 (46%)	0.6470
Duration of migraine (years), mean (SD)	26.8 (15.7)	25.8 (14.8)	0.6647
Duration of chronic migraine (years), mean (SD)	13.0 (5.8)	11.9 (5.1)	0.1804
Baseline MHD (days), median (IQR)	28 (24, 30)	28 (22, 30)	0.5646
Baseline MMD (days), median (IQR)	20 (15, 25.5)	17 (12, 24)	0.0753
Baseline HFD (days), median (IQR)	2 (0, 6)	2 (0, 8)	0.4859
Number of previous prophylactic treatments failed per patient, median (IQR)	6.5 (5, 7)	6 (6, 7)	0.3174
Patients with onabotulinumtoxinA failure, *n* (%)	64 (90%)	102 (92%)	0.7899
Baseline HIT-6 score, median (IQR)	69 (66, 72)	68 (63, 72)	0.1012

Inter-group MHD, MMD and HFD compared using Mann-Whitney U test, continuous variables compared using unpaired Student's t-test and dichotomous variables compared using Fisher's two-tailed exact test. Bonferroni correction for multiple comparisons set at $p< 0.05/11 = 0.0045$ for statistical significance.

Table 5b: Treatment outcomes in patients with baseline MO

Outcome (*n* = 71)	Baseline	Post-fremanezumab	Change median	*P value*(<0.0125)
MHD (days), median (IQR)	28 (24, 30)	15 (6.5, 26.5)	-11.5	<0.0001*
MMD (days), median (IQR)	20 (15, 26.5)	6.5 (2, 11)	-13	<0.0001*
HFD (days), median (IQR)	2 (0, 6)	15 (3, 22)	11	<0.0001*
HIT-6 score, median (IQR)	69 (66, 72)	54 (48, 61)	-15	<0.0001*
Patients achieving MHD reduction of: *n* (%) ≥30% >50% >75%		 45 (63%) 30 (42%) 15 (21%)		
Patients achieving MMD reduction of: *n* (%) ≥30% >50% >75%		 61 (86%) 53 (75%) 33 (47%)		
Patients achieving MHD < 15 in any treatment months, *n* (%)		34 (48 %)		
Patients achieving MMD<8 in any treatment months, *n* (%)		54 (76%)		
Patients with baseline MO reverting to non-MO, *n* (%)		58 (82%)		

Median change in MHD, MMD, HFD and HIT-6 compared using Wilcoxon signed-rank test. Bonferroni correction for multiple comparisons set at $p < 0.05/4 = 0.0125$ for statistical significance. * denotes $p<0.0125$.

Table 5c: Treatment outcomes in patients without baseline MO

Outcome (*n* = 111)	Baseline	Post-fremanezumab	Change median	*P value*(<0.0125)
MHD (days), median (IQR)	28 (22, 30)	15 (9, 30)	-8	<0.0001*
MMD (days), median (IQR)	17 (12, 24)	6 (2, 11)	-8	<0.0001*
HFD (days), median (IQR)	2 (0, 8)	14 (0, 20.5)	8	<0.0001*
HIT-6 score, median (IQR)	68 (63, 72)	56 (48, 63)	-11	<0.0001*
Patients achieving MHD reduction of: *n* (%) ≥30% >50% >75%		 60 (54%) 40 (36%) 16 (14%)		
Patients achieving MMD reduction of: *n* (%) ≥30% >50% >75%		 84 (76%) 71 (64%) 43 (39%)		
Patients achieving MHD < 15 in any treatment months, *n* (%)		48 (43%)		
Patients achieving MMD<8 in any treatment months, *n* (%)		65 (59%)		

Median change in MHD, MMD, HFD and HIT-6 compared using Wilcoxon signed-rank test. Bonferroni correction for multiple comparisons set at $p < 0.05/4 = 0.0125$ for statistical significance. * denotes $p<0.0125$.

Table 5d: Treatment outcome comparisons in patients with and without MO

Outcome	Patients with MO (*n* = 71), Change median	Patients without MO (*n* = 111), Change median	*P value* (<0.004)
MHD (days)	-11.5	-8	0.0744
MMD (days)	-13	-8	0.0152
HFD (days)	11	8	0.0604
HIT 6 score	-15	-11	0.0951
Patients achieving MHD reduction of: *n* (%) ≥30% >50% >75%	 45 (63%) 30 (42%) 15 (21%)	 60 (54%) 40 (36%) 16 (14%)	 0.2232 0.4368 0.3122
Patients achieving MMD reduction of: *n* (%) ≥30% >50% >75%	 61 (86%) 53 (75%) 33 (47%)	 84 (76%) 71 (64%) 43 (39%)	 0.1303 0.1450 0.3557
Patients achieving MHD < 15 in any treatment months, *n* (%)	34 (48%)	48 (43%)	0.5457
Patients achieving MMD<8 in any treatment months, *n* (%)	48 (68%)	71 (64%)	0.6356

Inter-group MHD, MMD, HFD and HIT-6 comparisons made using Mann-Whitney U test. Inter-group comparisons for percentages and numbers of patients achieving MHD<15 in any treatment month, MMD<8 in any treatment month, and ≥30%, 50% and 75% MHD and MMD reduction from baseline made using Fisher's two-tailed exact test. Bonferroni correction for multiple comparisons set at $p < 0.05/12 = 0.004$ for statistical significance.

We next compared treatment outcomes between patients with and without baseline MO, who exhibited similar baseline characteristics (Table 5a). Post-fremanezumab, both groups achieved significant improvement in all outcomes, with no significant inter-group differences in median improvement for any outcomes. 58 (82%) with baseline MO reverted to non-MO, with cessation of non-opioid and triptan overuse. [Tables 5b, c, d].Overall, fremanezumab demonstrated similar efficacy in patients with and without baseline MO.

Factors associated with fremanezumab response

Table 6a: Univariate and multivariate logistic regression analysis of patient factorsassociated with achieving ≥30% MMD reductionfrom baseline post-treatment and fremanezumab continuation

Patient factor	OR in univariate analysis (95% CI)	*P value* (<0.05)	OR in multivariate analysis (95% CI)	*P value*(<0.05)
Female gender	1.384 (0.600 – 3.056)	0.4299	-	-
Age (as continuous variable)	1.012 (0.985 – 1.041)	0.3849	-	-
Migraine onset age (as continuous variable)	0.998 (0.971 – 1.028)	0.9094	-	-
Total migraine duration (as continuous variable)	1.106 (0.988 – 1.048)	0.2889	-	-
Chronic migraine duration (as continuous variable)	0.967 (0.906 – 1.036)	0.3186	-	-
Baseline HFD ≥1	4.697 (2.110 – 11.32)	0.0003*	2.789 (1.032 – 7.883)	0.0461*
Baseline MMD (as continuous variable)	0.913 (0.864 – 0.959)	0.0006*	0.972 (0.908 – 1.037)	0.3971

≥1 previous prophylactics	0.963 (0.714 – 1.312)	0.8059	-	-
Previous OnabotulinumtoxinA use	1.805 (0.476 – 11.81)	0.4481	-	-
Medication overuse	0.4725 (0.197 – 1.049)	0.0761	-	-
Baseline AMD (as continuous variable)	1.042 (1.000 – 1.090)	0.0655	-	-
Baseline TD (as continuous variable)	1.024 (0.967 – 1.093)	0.4365	-	-
Baseline HIT-6 (as continuous variable)	0.886 (0.823 – 0.947)	0.0007*	0.918 (0.848 – 0.989)	0.0282*

* denotes $p<0.05$.

Table 6b: Univariate and multivariate logistic regression analysis of patient factors associated with achieving MHD <15 days/ month in any treatment month post-fremanezumab

Patient factor	OR in univariate analysis (95% CI)	*P value*	OR in multivariate analysis (95% CI)	*P value*
Female gender	1.465 (0.756 – 2.890)	0.2628	-	-
Age (as continuous variable)	1.028 (1.005 – 1.052)	0.0168*	1.024 (0.998 – 1.051)	0.0798
Migraine onset age (as continuous variable)	1.021 (0.998 – 1.045)	0.0733	-	-
Total migraine duration (as continuous variable)	1.009 (0.988 – 1.032)	0.4048	-	-
Chronic migraine duration (as continuous variable)	1.016 (0.962 – 1.074)	0.5674	-	-
Baseline HFD ≥1	9.857 (4.963 – 20.68)	<0.0001*	4.564 (2.032 – 10.67)	0.0003*
Baseline MMD (as continuous variable)	0.889 (0.849 – 0.926)	<0.0001*	0.923 (0.868 – 0.978)	0.008*
≥1 previous prophylactics	0.891 (0.697 – 1.132)	0.3492	-	
Previous onabotulinumtoxinA use	1.383 (0.505 – 3.855)	0.5249	-	
Medication overuse	0.9368 (0.516 – 1.701)	0.8296	-	
Baseline AMD (as continuous variable)	1.015 (0.985 – 1.048)	0.3311	-	
Baseline TD (as continuous variable)	1.076 (1.027 – 1.131)	0.0028*	1.051 (0.997 – 1.111)	0.068
Baseline HIT-6 (as continuous variable)	0.924 (0.880 – 0.967)	0.001*	0.982 (0.923 – 1.044)	0.5687

* denotes $p<0.05$.

We investigated potential predictive factors for achieving≥30% baseline MMD reduction,and MHD<15 in any treatment month, respectively[Table 6a, b]. ≥30% baseline MMD reduction associated with baseline HFD (OR 2.789, p=0.0461) and HIT-6 score (OR 0.918, p=0.0282) in multivariate regression analysis, indicating baseline headache-freedom and lower HIT-6 scores independently associated with ≥30% MMD response.Achieving MHD <15 in any monthassociated with baseline HFD ≥1 (OR 4.564, p=0.0003) and MMD (OR 0.923, p=0.008) in multivariate analysis, signifying baseline HFD ≥1 and lower baseline MMD independently associated with headache frequency reversion to that of EM in any treatment month. Other characteristics including migraine duration, medication-overuse, previous prophylactics orOnabotulinumtoxinA were not associated with either outcome.

Safety and Tolerability

37 (20%) patients discontinued fremanezumab due to inefficacy. Injection site irritation and rash was the only AE reported in 5 (3%) patients. No patients discontinued fremanezumab due to AEs (data not shown).

	Hull experience (n = 182)	HALO CM, monthly fremanezumab Silberstein *et al* [6, 17] (n = 379)	HALO CM, quarterly fremanezumab [6, 17] (n = 376)	FOCUS, monthly fremanezumab Ferrari *et al* [19], Ashinaet *al* Ashina [24] (n = 283)	CONQUER, Mulleners *et al* [20], Reuter et *al* [25] (n = 95)	REGAIN, Detke *et al* [21] (n = 555)

Discussion

Table 7a: Comparison between Hull experience and salient randomised-controlled studies of anti-CGRP monoclonal antibodies in chronic migraine

Study type	Real-world	RCT vs placebo (DB phase)		RCT vs placebo (DB phase)	RCT (3months DB phase)	RCT (3months DB phase)
Migraine type	CM	CM		Mixed (61% CM, 39% EM)	CM	CM
Anti-CGRP therapy	Fremanezumab	Fremanezumab		Fremanezumab	Galcanezumab	Galcanezumab: 120mg monthly (n = 278) 240mg monthly (n = 277)
No. of prior prophylactic agents failed	Median 6 (≥3)	≤1		2–4	2–4	≤3
Onabotulinumtoxin A failure, %	91%	-		25%	-	-
Follow-up duration	4 months	12 weeks post-first dose		12 weeks post-first dose	3 months post-first dose (DB)	3 months post-first dose (DB)
Baseline MHD, days	28	20.3	20.4	Headache days of ≥ moderate severity: 12.7	21.5	120mg : 21.2 240mg: 21.4
Baseline MMD, days	17	16.0	16.2	14.1	19.2	120mg: 19.4 240mg: 19.2
MHD reduction, days	9	4.6	4.3	3.6 vs placebo	3m: 6.7	-
MMD reduction, days	10	5.0	4.9	4.5 (3.5 vs placebo) CM subgroup analysis: 3.8 vs placebo	3m: 6.6	120mg: 4.8 240mg: 4.6
AMD reduction, days	5	4.2	3.7	4.2	3m: 6.1	120mg: 4.7 240mg: 4.3
HIT-6 reduction	14.5	6.8	6.4	6.4	-	-
>30% MHD responders, %	58%	-	-	-	-	-
>50% MHD responders, %	39%	41%	38%	-	-	-
>75% MHD responders, %	17%	-	-	-	-	-

>30% MMD responders, %	80%	-	-	-	-	-
>50% MMD responders, %	68%	Post-hoc: 59%	Post-hoc: 53%	34%	3m: 36%	120mg: 28% 240mg: 28%
>75% MMD responders, %	42%	Post-hoc: 22%	Post-hoc: 17%	12%	3m: 12%	120mg: 7% 240mg: 9%

CM- chronic migraine; DB- double blind; EM- episodic migraine; OLE- open-label extension; RCT- randomised controlled trial.

Table 7b: Comparison between Hull experience and other salient real-world or open-label extension studies of anti-CGRP monoclonal antibodies in chronic migraine

	Hull experience (*n* = 182)	Cohen et al [12]- abstract data, CM patients (*n* = 587)	FOCUS, OLE phase, Ashinaet *al* [24] (*n* = 274)	Lambruet *al* [22] (*n* = 164)	GARLIT, Vernieriet *al* [23] (*n* = 130)	CONQUER, OLE, Reuter *et al* Reuter [25], CM patients (*n* = 193)	REGAIN, Detkeet *al* [26]- abstract data, CM patients (*n* = 1022)
Study type	Real-world	Real-world	RCT- 3 months OLE	Real-world	Real-world	RCT- 3 months OLE	RCT- 9 months OLE
Migraine type	CM	CM	Mixed (61% CM, 39% EM)	CM	CM	CM	CM
Anti-CGRP therapy	Fremanezumab	Fremanezumab	Fremanezumab	Erenumab	Galcanezumab	Galcanezumab	Galcanezumab: 120mg or 240mg monthly flexible dosing
No. of prior prophylactic agents failed	Median 6 (≥3)	-	2–4	Mean 8.4 (≥3)	≤5	2–4	≤3
OnabotulinumtoxinA failure, %	91%	-	-	91%	-	-	-
Follow-up duration	4 months	6 months	24 weeks post-first dose	6 months	6 months post-first dose	6 months post-first dose (OLE)	12 months post-first dose (OLE)
Baseline MHD, days	28	16.4	Headache days of ≥ moderate severity: 12.7	23.4	21	20.4–21.5	19.4 overall
Baseline MMD, days	17	14.7	14.2	19.7	20	18.1–19.2	-
MHD reduction, days	9	8.0	4.5–5.2	3m: 6.3 6m: 6.8	-	6m: 6.6–8.3	6m: 6.5–7.3 12m: 8.0–9.0
MMD reduction, days	10	7.9	4.7–5.5	3m: 6.0 6m: 7.5	3m: 12 6m: 14	6m: 6.5–8.2	-
AMD reduction, days	5	-	32.0	3m: 3.3 6m: 4.0	-	6m: 5.1–7.0	-
HIT-6 reduction	14.5	-	-	3m: 7.7 6m: 7.5	3m: 12 6m: 13	-	-

>30% MHD responders, %	58%	-	-	-	-	-	-
>50% MHD responders, %	39%	-	-	-	-	-	6m: 45–46% 12m:53–57%
>75% MHD responders, %	17%	-	-	-	-	-	-
>30% MMD responders, %	80%	-	-	3m: 49%			
6m: 60%	-	-	-				
>50% MMD responders, %	68%	-	38–46%	3m: 35% 6m: 38%	3m: 67% 6m: 64%	6m: 39–48%	-
>75% MMD responders, %	42%	-	16–20%	3m: 13% 6m: 22%	3m: 33% 6m: 38%	6m: 19–25%	-

CM- chronic migraine; DB- double blind; m- months; OLE- open-label extension; RCT- randomised controlled trial.

Cohort Fremanezumab Efficacy Outcomes

Whilst real-world efficacy data on anti-CGRP the rapies are available for erenumab and galcanezumab, weprovidethe first real-world evidence off remanezumab efficacy in improving headache out comes with in 3-months of treatment initiation in-resistant, refractory andOnabotulinumtoxinA-unresponsiveCM patients, regardless of medication-overuse. Those with baseline headache-freedom exhibited greaterresponses than those without, whilst baseline headache-freedom, lower MMD and lower HIT-6 associated with superior responses.

Compared to randomised-controlled trials [Table 7a], our results corroborate the 12-week HALO trial of fremanezumabefficacy in CM (6). Our median MHD reduction of 9 days, MMD reduction of 10 days, AMD reduction of 5 days and 14.5-point HIT-6 reductionexceeded the 4.6 and 4.3 days of headache reduction, 5.0 and 4.9 days of migraine reduction,4.2 and 3.9 days of analgesia use reduction and 6.8 and 6.4-point HIT-6 reduction in the HALO monthly and quarterly fremanezumab groups. Similar proportions achieved >50% MHD reduction (39% in our cohort, versus41% and 38% in bothHALO groups). Post-hoc analysisdemonstrated that 59% and 22% of HALO responders achieved>50% and>75% MMD reduction with monthly fremanezumab at 3 months, compared to 68% and 42% in our cohort. Monthly fremanezumab also reduced analgesia use by 6.7 days and HIT-6 by 8.2 points[18]. However, HALO patients were less refractory than ours, exhibiting 20.3 days/month with any headache, 12.8 designated “headache days” (day with moderate-to-severe headaches lasting ≥4 hours, or requiring triptan/ergot use) and 16.2 monthly migraine days at baseline and with ≤1 previous preventatives used. In a mixed cohort (61% CM) unresponsive to 2–4 prophylactics, the FOCUS studydemonstrated 3.5 days MMD reduction and 3.6 days moderate-to-severe headache day reduction compared to placebo at 12weeks, with34% and 12% achieving>50% and >75% MMD reductions. Sub-analysis in CM patients demonstrated 3.8 days MMD reduction [19]. However, unlike our study, FOCUS studied CM and EM patients as a mixed cohort, with the CM sub-analysis providing the most direct comparisons with our results.For other anti-CGRP therapeutics, the Phase 3b CONQUER trial of CM patients unresponsive to 2–4 preventative classes showed galcanezumab reduced MHD by 6.7and MMD by 6.6 days at 3 months (end of double-blind phase)[20]. In the REGAIN trial in CM unresponsive to ≤3 prophylactics, monthly galcanezumab at 120mg and 240mg reduced monthly migraine days by 4.8 and 4.6 days, respectively, with 28% and 7–9% achieving >50% and >75% MMD reductions [21]. However, REGAIN excluded OnabotulinumtoxinA-refractory patients. Overall, compared to trials with less-refractory patients who tried fewer previous preventatives, we observedgreater outcome improvements in our more refractory cohort.

Our results substantiatethose ofreal-world and open-label extension (OLE) studies of anti-CGRPmigraine prophylactic agents[Table 7b]. A real-world study of 587 fremanezumab-treated CM patients (baseline MHD 16.4 days, MMD 14.7 days) reported MHD and MMD reductions of 8.0 (49%) and 7.9 (54%) days at 3 months, and 10.8 (66%) and 10.1 (69%) days at 6 months, consistent with our results (abstract data) [12].In a real-world study of CM patients unresponsive to 8.4 prophylactics on average (91% OnabotulinumtoxinA-refractory), erenumab reducedMHD and MMD by 6.3 and 6.0 days at 3 months,and 6.8 and 7.5 days at 6 months. 49%, 35% and 18% patients achieved ≥30%, ≥50% and ≥75% MMD reductionat 3 months, lower than the 80%, 68% and 42% in our cohort [22].In GARLIT, a real-world study of CM unresponsive to a median of 5 prophylactics, galcanezumab reduced baseline MHD by 12 days to 8 days and HIT-6 by 12 points to 58 at 3months, with 67% and 33% achieving >50% and >75% MHD reduction. After 6 months of fremanezumab, there were 14 days MHD reduction, 13 points HIT-6 reduction and 64% and 38% achieving >50% and >75% MHD reductions[23]. The OLE phase of FOCUS to 24-weeks demonstrated 4.5–5.2 days of moderate-to-severe headache day reduction and 4.7–5.5 days of MMD reduction, with 38–46% and 16–20% achieving >50% and >75% MMD reductions [24]. In the OLE phase of CONQUER, galcanezumab reduced MHD by 6.6–8.3 and MMD by 6.5–8.2 days at 6 months in CM unresponsive to 2–4 preventative classes [25]. In

OLE phase of REGAIN, monthly galcanezumab reduced MHD by 6.5–7.3 days at 6 months and 8.0–9.0 days at 12 months, with 45–46% and 53–57% achieving >50% MHD reduction (abstract data) [26].Overall, our more-refractory cohort demonstrated slightly greater improvements to these studies.Our consistent observation of better response in patients more refractory than those in RCT and OLE studies raises the possibility of deploying fremanezumab as a first or second-line prophylactic agent, health economicand funding constraints notwithstanding.

Real-world fremanezumab EM reversion data is lacking. We assessed MHD<15 days/month responses as early indication of EM reversion. 45% achievedMHD<15 in any month, whilst 37% achieved both MHD<15 in any month and MMD<8 in any month. Defining EM reversion as either average MHD<15 days over 3 months or MHD<15 days in all 3 months, both HALO post-hoc analysisand FOCUS demonstrated53–54%and 34% EM reversionwith monthly fremanezumab according to either definition[14, 27]. Apost-hoc erenumab trial extension study that defined EM conversion as <45 headache days during each of multiple 12-week periods during the64-week study durationdemonstrated 53.1% EM conversion after 12 weeks treatment [28].Similarly, GARLIT demonstrated EM conversions of 74% at 3 months and 77% at 6 months with galcanezumab in the real-world [23]. However, our more refractory cohort will likely require longer treatment durations than other studies to achieve EM reversion over 3 consecutive months.

Fremanezumab Efficacy in Patients with and Without Baseline Headache-Freedom

We are the first to demonstrate better outcomes in patients with baseline headache-freedom compared to those without, with no previous studies evaluating the impact of headache-freedom on anti-CGRP therapeutic outcomes. We show significantly greater MHD reduction (+10 days) and percentages achieving ≥30%, >50% and >75% MHD reduction (+32%, +25%, +21%), MHD <15 in any month (+41%), MMD <8 in any month (+42%), and both MHD <15 in any month and MMD <8 in any month (+44%)in those with baseline headache-freedom, suggesting baseline headache-freedom may predict superior anti-CGRP therapy response. Given migraines often co-exist with other cephalalgias, patients without headache-freedom may harbour both a fremanezumab-responsive migraine and a second, less-responsive, chronic daily headache, as illustrated by 25% of our cohort exhibiting ≥30% migraine response without headache-day reduction. Chronic daily headaches may further predispose to MOH, complicating management. Alternatively, psychosocial factors may affect perception of headache improvement and subsequent reporting.

Fremanezumab Efficacy in OnabotulinumtoxinA-Unresponsive Patients

We demonstrated significant fremanezumab efficacy in OnabotulinumtoxinA-unresponsive patients, with median MHD and MMD reductions of 8 and 9 days, 12-point HIT-6 improvement, and 78% achieving ≥30% MMD reduction. In a real-world study ofOnabotulinumtoxinA-unresponsive patients refractory to 5.5preventatives on average, 3 months of erenumab reduced the number of headache days limiting daily activity by 6.4 days, triptan use by 3.4 days and HIT-6 by 7.1 points, and improved headache-free days by 5.7 days [13]. Although lacking head-to-head comparisons, these suggest anti-CGRP therapies may be highly-efficacious in OnabotulinumtoxinA-unresponsive CM. Consequently, one might consider anti-CGRP antibodies before OnabotulinumtoxinA for CM prophylaxis on efficacy grounds, with additional advantage of self-administration minimising face-to-face interactions duringpandemics. Recent studies further suggest anti-CGRP therapies and OnabotulinumtoxinA yield greater efficacy in combination than either alone[29, 30]. Therefore, anti-CGRP therapies and OnabotulinumtoxinA may hold a complementary and synergistic future relationship, with each potentially useful for treating patients unresponsive to the other, with combination therapy for highly resistant or refractory patients. However, future direct efficacy and safety comparisons in trialsare necessary to define their precise relationship.

Fremanezumab Efficacy in Patients with And Without Baseline Medication-Overuse

We provide the first real-world evidence of similar fremanezumab efficacyacross all outcomes measured in patients with and without MO, with 82% of those with MO reverting to non-MO. These corroborateclinical trial sub-analysis results for fremanezumab (HALO), galcanezumab (REGAIN) and erenumabdemonstrating similar headache, migraine and HIT-6 improvements, and real-world results showing similar proportions achieving ≥50% MHD or MMD reduction after 6 months of erenumab or galcanezumab, in those with and without MO[31-34].Therefore, current evidence suggests anti-CGRP therapies are similarly efficacious in patients with and without MO.

Determinants of Fremanezumab Response

We identified that baseline headache-freedom,lower MMD and lower HIT-6 scoreassociated with fremanezumab response and reversion to the headache frequency of EM for ≥1 months.Two real-world studies demonstrated lower baseline analgesia use, MMD and HIT-6 predicted >50% MMD response post-erenumab, partially corroborating our results[35, 36].In comparison, HALO post-hoc analysisfound greater acute analgesia, oral preventative and previous topiramate and OnabotulinumtoxinA usage in non-reverters compared to EM reverterspost-fremanezumab [14]. Other studies identified MOH duration, number of previous prophylactics, CM duration and psychological factors associating with negative erenumab response[37, 38]. Previous use of preventativesdid not constitutea treatment response discriminator in our cohort, likelydue to numerous previous preventatives (including OnabotulinumtoxinA) tried by most of our patients. Our results suggest baseline headache-freedom as key predictor of anti-CGRP therapy response and EM reversion, alongside lower baseline MMD and HIT-6 scores.

Fremanezumab Safety and Tolerability

Our cohort tolerated fremanezumab well, with 5 patients reporting injection-site reactions as the only AE and no AE-related treatment discontinuations, compared to 71% developing AEs (96% mild), 41% developing injection-site reactions and 2% discontinuing treatment due to AEs at 12 weeks in the HALO monthly fremanezumab group [6]. Our patients reported no symptoms raising concerns for liver function derangements, cardiovascular/cerebrovascular AEs or infections, as observed in the 12-month HALO extension study[8]. Therefore, fremanezumab demonstrates high safety and tolerability in our cohort.

Strengths and Limitations of Our Audit

Our main strengths are a sizeablereal-world population of highly resistant and refractory CM patientsunresponsive to an average of 6 prophylactics,including 91% unresponsive toOnabotulinumtoxinA, with detailed follow-up enabling comprehensive and multidimensional clinical data capture. Limitations include non-randomisation and reliance on subjective reporting with potential for reporting/attrition bias. Since we studied patients with resistant and refractory CM, it is possible that regression toward the mean may partially account for some observed improvement. Similarly, other interventions associated with attending a specialist headache centre, including betterpatient education and lifestyle modifications, may also benefit patient outcome. Furthermore, although baseline MHD negatively correlated with % MHD and MMD reductions statistically, R2 goodness-of-fit analysis indicated poor clinical predictive value. Nevertheless, our study is important in demonstrating real-world fremanezumab efficacy in resistant and refractory CM, including OnabotulinumtoxinA-unresponsive patients, with or without MO, and in identifying baseline headache-freedom as a treatment-response determinant warranting validation in future studies.

Conclusion

We reportreal-world fremanezumab efficacy in improving headache and quality-of-life outcomes at 4monthsin resistant and refractory CM, includingin OnabotulinumtoxinA-unresponsive patients, with or without MO. Patients with baseline headache-freedom exhibited greater responses than those without. Headache-freedom, lower MMD and lower HIT-6 at baseline may predict superior responses.

Study Highlights

1. Fremanezumab improves all major headache outcomes at 4months inreal-world chronic migraine patients unresponsive to 6 prophylactics on average, with 80% achieving ≥30% migraine reduction.
2. Fremanezumab significantly improves outcomes in OnabotulinumtoxinA-unresponsive patients, with 78% achieving ≥30% migraine reduction.
3. Headache-freedom, lower monthly migraine days and lower HIT-6 score at baseline associated with superior responses.
4. Fremanezumab maintains similar efficacy,irrespective of baseline medication-overuse.

Declarations

Ethics Approval and Consent to Participate

All patients gave their consent to participate in our study. However, as an audit under national guidelines, formal research ethics committee review was not required (https://www.hra-decision-tools.org.uk/research).

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

Fan Cheng- none.
Qinyao Wu- none.
Mariam Hussain- none.
Victoria Wilkinson- none.
Lisa Wilson- none.
Modar Khalil- none.

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Authors' Contributions

FC contributed to patient evaluation, data collection, database maintenance, data analysis and interpretation and wrote the manuscript. QW contributed to data collection, extraction and database maintenance. MH, VW and LW contributed to patient evaluation and data collection. FA, MK, VW and LW contributed to data collection and database maintenance. FA and MK contributed to critical revision of the manuscript and for important intellectual concepts.

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