Efficacy of fremanezumab in refractory chronic migraine patients: Real-world data from the Hull Migraine Clinic, UK

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Introduction

- Fremanezumab is an anti-calcitonin gene-related peptide (CGRP) monoclonal antibody found to be efficacious for episodic (EM) and chronic migraine (CM) prevention in the HALO trials (1, 2). It was approved in the UK for CM prophylaxis in patients unresponsive to ≥3 preventatives, with treatment cessation if <30% migraine frequency improvement after 12 weeks treatment (3).
- However, real-world fremanezumab efficacy data is sparse. Patients in existing clinical and real-world studies exhibited lower baseline monthly headache and migraine days than typically seen in many specialist headache centres (1, 4). Moreover, whilst anti-CGRP therapy efficacy in OnabotulinumtoxinA-refractory CM has been recently investigated for erenumab (5), real-world data on fremanezumab efficacy in this context is lacking.
- We report real-world fremanezumab efficacy in a CM cohort refractory to an average of >6 preventatives, including OnabotulinumtoxinA, in a prospective cohort study in the Hull Migraine Clinic, a large UK specialist headache centre.

Methods

- 289 CM patients refractory to an average of >6 preventatives (range 3–11, from amitriptyline, propranolol, topiramate, candesartan, flunarizine, pizotifen, sodium valproate, greater occipital nerve block, OnabotulinumtoxinA and others) commenced monthly subcutaneous fremanezumab 225mg between Nov 2020 – Apr 2021.
- Patients were asked to maintain a headache diary for ≥1 month prior to fremanezumab therapy and continuously thereafter. We measured monthly headache days (MHD), migraine days (MMD), headache-free days (HFD), acute analgesia medication days (AMD) and triptan days (TD), and monthly Headache Impact Test-6 (HIT-6) score to assess functional impact of headaches.
- At 3-month follow-up, data for each patient from the best month was extracted for analysis. We calculated cohort median and mean MHD and MMD, median HFD, AMD and TD, and mean HIT-6 scores, and change from baseline for each patient and median cohort change from baseline for each outcome. We compared post-treatment cohort outcomes to baseline using Wilcoxon signed rank test (categorical variables) or paired Student's t-test (continuous variables).
- At 3 months, we also assessed the proportion of patients achieving ≥30%, >50% and >75% reduction from baseline MHD and MMD, and ≥2-fold and ≥3-fold increase from baseline HFD. We also assessed the proportion of patients achieving MHD <15 days/month in any one month as an indicator of reversion to EM in any month.

Results

Baseline patient characteristics

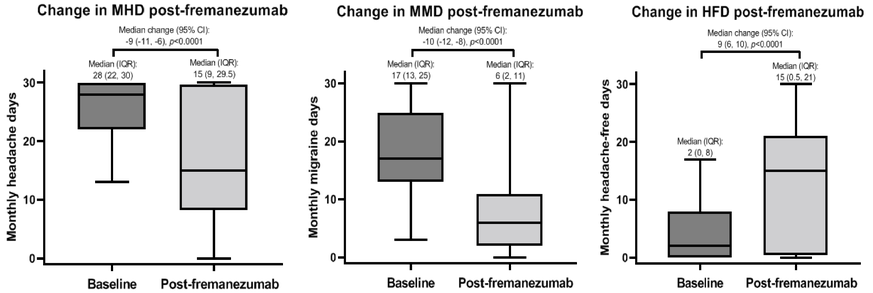
- At time of writing, 182 of 289 patients had completed 3 injections and 3-month follow-up. We report their outcomes.
- Gender: Male 63 (34.6%), Female 119 (65.4%). Mean age (years): 47.9 ± 13.7.
- 84 (46.2%) experienced 0 baseline HFD.
- Mean number of prophylactics failed per patient: 6.6. 165 (90.1%), 159 (87.4%) and 135 (74.2%) patients failed ≥5, ≥6 and ≥7 prophylactics . Commonest prophylactics tried: OnabotulinumtoxinA 166 (91.2%), amitriptyline 90.1%, propranolol 86.3%, candesartan 81.9%, topiramate 73.6%

Summary of post-fremanezumab changes in headache efficacy outcomes

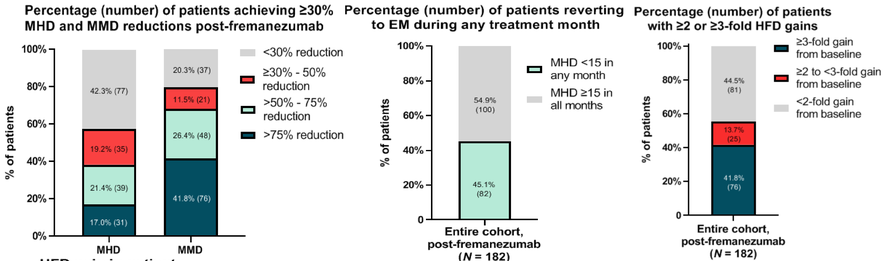
Outcome (*N* = 182)	Pre-treatment	Post-treatment	Median or mean change (95% CI)	*P* value
MHD (days), median (IQR)	28 (22. 30)	15 (9, 29.5)	-9 (-11, -6)	<0.0001
MHD (days), mean (SD)	25.8 (4.9)	16.7 (10.0)	-9.1 (-10.3, -7.8), -37.5%	<0.0001
MMD (days), median (IQR)	17 (13, 25)	6 (2, 11)	-10 (-12, -8)	<0.0001
MMD (days), mean (SD)	18.8 (7.4)	8.4 (8.2)	-10.5 (-11.6, -9.3), -56.8%	<0.0001
HFD (days), median (IQR)	2 (0, 8)	15 (0.5, 21)	9 (6, 10)	<0.0001
AMD (days), median (IQR)	10 (4.5, 20)	4 (0, 7)	-5 (-7, -3)	<0.0001
TD (days), median (IQR)	1.5 (0, 9)	0 (0, 3)	0 (-1, 0)	<0.0001
HIT-6 score, mean (SD)	68.5 (5.9)	54.0 (9.5)	-14.5 (-15.9, -13.1)	<0.0001

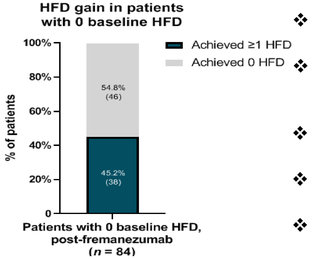
CI confidence interval, IQR interquartile range, SD standard deviation

Results- MHD, MMD and HFD improvement



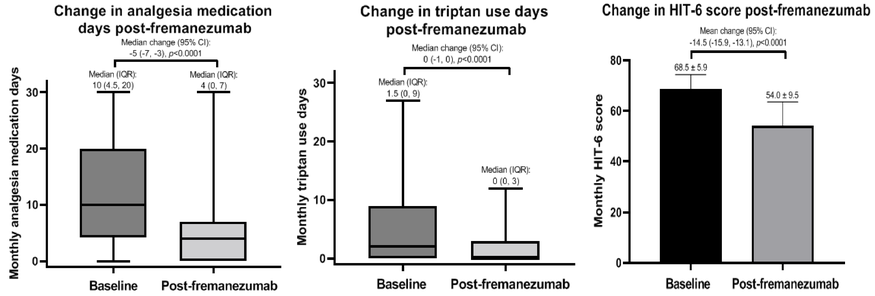
- Median MHD decreased from 28 at baseline to 15 days (median reduction: 9 days, *p*<0.0001). Mean MHD decreased from 25.8 at baseline to 16.7 days (mean reduction: 37.5%, 9.1 days, *p*<0.0001).
- Median MMD decreased from 17 at baseline to 6 days (median reduction: 10 days, *p*<0.0001). Mean MMD decreased from 18.8 at baseline to 8.4 days (mean reduction: 56.8%, 10.5 days, *p*<0.0001).
- Median HFD increased from 2 at baseline to 15 days (median gain: 9 days, *p*<0.0001).





- 57.7%, 38.5% and 17.0% achieved ≥30%, >50% and >75% MHD reduction from baseline.
- 79.7% achieved ≥30% MMD reduction from baseline, thereby meeting the UK fremanezumab continuation criteria. 68.1% and 41.8% achieved >50% and >75% MMD reduction from baseline.
- 45.1% achieved MHD <15 days/month in any treatment month, indicating reversion of headache frequency to that of EM for ≥1 months.
- 55.5% and 41.8% achieved ≥2-fold and ≥3-fold HFD increase from baseline.
- 45.2% of those without baseline headache-freedom achieved ≥1 HFD post-fremanezumab, with mean HFD gain of 14.7 days.

Results- Analgesia use and HIT-6 improvement



- Median AMD decreased from 10 at baseline to 4 days (median reduction: 5 days, *p*<0.0001).
- Median TD decreased from 1.5 at baseline to 0 days (median reduction: 0 days, *p*<0.0001).
- Mean HIT-6 score decreased from 68.5 at baseline to 54.0 (mean reduction: 14.5, *p*<0.0001).

Discussion

- Fremanezumab significantly improved headache and migraine day frequency, headache-freedom, analgesia use, and reduced headache impact on functioning in a highly-refractory CM population in the real-world within 3 months.
- Our median MHD and MMD reduction of 9 and 10 days, and mean MHD and MMD reduction of 37.5% and 56.8%, exceeds the 4.3–4.6 days of MHD reduction at 12 weeks in HALO CM (1). Our data corroborates the 7.9 and 8.0 days of MHD and MMD reduction at 3 months in a recent real-world study of 587 CM patients by Cohen *et al* (4), and the 8.7–9.1 days of MMD reduction in responders in a HALO CM post-hoc analysis (6). However, other studies generally included less refractory patients. At baseline, HALO CM patients randomised to monthly fremanezumab had 20.3 days/month with any headache and 12.8 designated "headache days" (day with headache ≥4 hours of at least moderate severity, or requiring triptan/ergot use) and MMD of 16.2, whilst MHD and MMD were 16.4 and 14.7 days in Cohen *et al* (1, 4). Furthermore, HALO CM included only patients who have used ≤1 preventative while those who failed ≥2 different classes of preventatives were excluded (1). Therefore, we observed significant efficacy in a more refractory cohort.
- Overall, 79.7% patients achieved ≥30% MMD reduction within 12 weeks, thus meeting the UK continuation criteria. 38.5% and 68.1% achieved >50% MHD and MMD reduction in our cohort, consistent with 38-41% achieving >50% MHD reduction in HALO CM, and 52.8-59% achieving >50% MMD reduction in HALO CM responders (1, 6).
- Significant headache, analgesia use and functional improvements in our cohort, where >90% were OnabotulinumtoxinA-refractory, suggests fremanezumab has high-efficacy in OnabotulinumtoxinA-refractory CM. Similarly, in CM patients who failed a mean of 8.4 preventatives with 91% refractory to OnabotulinumtoxinA and baseline MHD of 23.4 and MMD of 19.7, Lambru *et al* showed at 3 months, erenumab reduced MHD by 6.3 days, MMD by 6.0 days and increased HFD by 4.2 days, and 49%, 35% and 13% achieved ≥30%, ≥50% and ≥75% MMD reduction (7). Moreover, Talbot *et al* assessed red days (headache days limiting daily activity), green days (headache-free days), analgesia and triptan use and HIT6 score in OnabotulinumtoxinA-refractory patients treated with erenumab (5). Patients were refractory to ≥3 preventative classes and a mean of 5.5 preventatives. At 3 months post-treatment, red days reduced by 6.4 to 9.3 days, green days increased by 5.7 to 9.3 days, analgesia and triptan days reduced by 2.2 and 3.4 days and HIT6 reduced by 7.1. Therefore, anti-CGRP therapies are likely to be highly efficacious in OnabotulinumtoxinA-refractory CM patients.
- 45.1% of our cohort experienced MHD <15 in any treatment month, compared with 34-54% experiencing reversion to EM (average MHD <15 over 3 months, or MHD <15 in all 3 months) with monthly fremanezumab in a HALO CM post-hoc analysis (8). However, given severer baseline features, longer treatment durations are likely required for our patients to revert to EM over 3 consecutive months.

Conclusion

- We report significant improvement in headache severity and frequency, analgesic use and quality of life in a highly refractory CM cohort of patients with fremanezumab.

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