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Switching anti-CGRP monoclonal antibodies in chronic migraine – real-world observations of erenumab, fremanezumab and galcanezumab

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Abstract:

Objectives: The anti-CGRP monoclonal antibodies (anti-CGRP-mAb) are effective in migraine, however few studies have examined the benefit of switching from one anti-CGRP-mAb to another. In order to better inform clinical practice in this situation, we present our real-world findings of switching anti-CGRP-mAb in chronic migraine.

Methods: Individuals with chronic migraine that switched anti-CGRP-mAb treatment (erenumab, fremanezumab or galcanezumab) due to ineffectiveness or adverse effects were retrospectively identified. Headache diary data before, and up to six months after- anti-CGRP-mAb switch were analysed. Main outcome measures were monthly red days (days with headaches limiting activity or requiring triptans), headache days (days with any kind of headache), triptan use, other analgesic use and headache disability (HIT-6 score) at three months.

Results: The analysis included 66 instances of switching amongst 54 individuals. There were non-significant reductions of -1.2 [-2.7, 0.3] red days from baseline at three months, with ten individuals (15%) showing ≥50% improvement and twenty-two (33%) experiencing a ≥30% improvement. Improvements in headache days, triptan days, other painkiller use and HIT-6 score were non-significant. When individuals that switched due to side effects were excluded from the analysis, significant reductions in headache (Friedman p=.044) and a trend for improvement in red days (Friedman p=.083) were observed. With regard to side effects; on twelve occasions these improved or resolved on switching to a different anti-CGRP-mAb, whilst new symptoms were reported on eight occasions following a switch.

Conclusion: We recorded modest improvements in headache outcomes, although significant results were only observed in those that switched anti-CGRP-mAb due to ineffectiveness. Switching may therefore be a viable option for these individuals.

Key words: Switching, CGRP, Erenumab, Fremanezumab, Galcanezumab, Migraine.

Key messages:

What is already known on this topic?: A limited number of studies have suggested that switching to an alternative anti-CGRP-mAb medication may be beneficial for individuals that fail to respond to one drug, particularly across drug class (ligand- versus receptor-targeting) although overall evidence is lacking.

What this study adds: This observational study provides further data to the question of anti-CGRP-mAb switching in a cohort of 'hard-to-treat' chronic migraine patients. It examines headache outcomes in those that switched due to ineffectiveness as well as side effects, and explores subgroups that might hope to benefit from a switch.

How this study might affect research, practice or policy: Switching anti-CGRP-mAb represents a significantly under-researched topic yet an increasingly common scenario in an average headache clinic. This study hopes to inform clinical practice in this specific situation, for which no guidelines currently exist.

Introduction

The anti-CGRP monoclonal antibodies (anti-CGRP-mAb) represent one of the newest developments in the field of migraine therapies. Their benefit has been clearly demonstrated in placebo-controlled trials[1–8], and multiple centres have reported benefit in patients with severe migraine phenotypes with prior failure of multiple conventional therapies including onabotulinumtoxinA [9–15]. As highly-targeted therapies, modulating CGRP or its receptor, they also demonstrate good tolerability, especially when compared to standard preventive migraine therapies such as topiramate [16–18]. Despite this, those treated not infrequently fail to respond or derive limited benefit from an anti-CGRP-mAb drug or develop intolerable side effects necessitating discontinuation. Due to different targets of anti-CGRP-mAb drugs (ligand in the case of galcanezumab and fremanezumab; receptor in the case of erenumab), it has been suggested that those who fail to respond to one class may benefit from a switch to the other [19,20].

Relatively few studies on the subject of anti-CGRP-mAb switching exist in the available literature. Overeem et al examined the benefit in those that had switched from erenumab to an alternative, specifically galcanezumab or fremanezumab, due to ineffectiveness[21]. Of the 25 individuals included in the analysis, 32% experienced a ≥30% improvement in (combined migraine and non-migraine) headache days, providing evidence of modest benefit. An earlier analysis by Robbins et al. found that, of those that switched (for a range of reasons including ineffectiveness, adverse effects and financial reasons), 27% of thirty-seven individuals switching from erenumab to galcanezumab, and 32% of forty individuals switching from erenumab to fremanezumab responded positively (defined as ≥30% improvement in headache frequency) [22]. In addition to evidence from small case series[19,23], other published data includes a Spanish study of 26 patients, in whom 64% demonstrated improvement, and an Association of British Neurologists conference poster where around half (11/24) found the second anti-CGRP-mAb effective in reducing the frequency of migraine days [24]. More recently, Overeem and colleagues presented their

findings of 20 individuals that switched from a CGRP ligand mAb to erenumab due to ineffectiveness, noting a reduction of 4.1 headache days at three months, with 35% achieving ≥30% improvement in headache symptoms[25].

As prescriptions for these targeted migraine therapies continue to rise, prescribing clinicians will increasingly need to decide whether a switch is indicated in those individuals that fail to respond or develop intolerance to an anti-CGRP-mAb, whilst identifying those most likely to derive benefit. Clinical features such as vomiting, unilateral pain and photophobia have previously been associated with better response to anti-CGRP-mAb medication, whilst depression, medication overuse and presence of chronic migraine have predicted worse outcome[26]. In one study, those that reported improvement in depression and anxiety symptoms during the course of anti-CGRP-mAb treatment saw a corresponding and sustained response to treatment[27]. With specific regard to switching anti-CGRP-mAb, Overeem et al. observed that those suffering daily headache were less likely to respond to a switch[21].

In order to better understand clinical outcomes related to anti-CGRP-mAb switching, we present our own, real-world data of switching in individuals with chronic migraine in whom the initial anti-CGRP-mAb was ineffective or complicated by the presence of severe side effects. We report outcomes from headache diary scores, as well as describing adverse events and exploring outcomes in subgroups with different clinical features.

Methods

This retrospective cohort study was registered and approved locally by the hospital research and development department; ethics approval was deemed inapplicable as the data collection formed part of patients' routine care and study aims were in line with a service evaluation. All participants were under the care of the local headache/neurology service. Between February 2019 and August 2022 erenumab (Aimovig 70mg, usually increased to 140mg after 1-3 months) was offered under a commercial supply agreement to patients who

met the International Classification of Headache Disorders (ICHD) (2018)[28]definition of chronic migraine and had failed and/or had contraindications to ≥2 classes of preventative medications. It was subsequently approved for use in the UK National Health Service (NHS) at a dose of 140mg. Two other anti-CGRP-mAb treatments subsequently became available and were offered alongside erenumab - fremanezumab (Ajovy 225mg monthly - from 2020) and galcanezumab (Emgality 240mg first month, then 120mg monthly – from 2021) – and were provided to selected patients meeting the National Institute for Health and Care Excellence (NICE) criteria of either episodic or chronic migraine having failed or having contraindication to at least three migraine preventive drugs. In practice, all those selected for treatment suffered with chronic migraine. The choice of drug was made on the basis of several factors including cost, presence of latex allergy and individual preference. Participants either provided written or verbal consent for treatment, dependent on the source of funding (commercial supply agreement versus NHS, respectively). Maintaining a headache diary was a stipulated condition of treatment, and they were free to discontinue treatment at any point.

A number of those initially treated with anti-CGRP-mAb did not achieve satisfactory improvement in headaches (defined as <30% reduction of headache days after three months of treatment) or experienced adverse events necessitating discontinuation of the drug. Therefore a decision was made in selected patients to switch to another anti-CGRP-mAb. The duration of first anti-CGRP-mAb varied amongst participants, ranging from one month to over a year (mean 8.3 ± 5.9 months). Some experienced early side effects, worsening migraines or unequivocally poor immediate response, whilst others regressed to the mean after months of initial benefit, experienced mild but tolerable side effects or reported incomplete symptom control. Some switched after a cessation attempt, typically after a year of treatment. Whilst some individuals switched directly from one anti-CGRP-mAb drug to another, others underwent a variable treatment interval before switching when they

did not receive any anti-CGRP-mAb treatment (during which time non-CGRP-targeting migraine therapies could be administered, at the discretion of the managing physicians).

Participant identification and data collection

A local database of all patients commenced on anti-CGRP-mAb treatment, curated by the local headache service, was used to identify individuals for this study. Those that had received a minimum of two anti-CGRP-mAb drugs and submitted a minimum of one month's headache data on each drug were retrospectively identified. Submitted headache diaries constituted the outcome measures. Diaries employed a traffic-light system of 'red', 'amber' and 'green' days that enabled participants to self-categorise their headaches. Red days were defined as the number of days per month with headaches limiting activities of daily living or requiring use of triptans (used as a surrogate and more-easily self-categorised descriptor for migraine days). Amber days were defined as days with headaches but not limiting daily activities. Green days represented days completely free of headache. Outcome measures were monthly red days, 'headache' days (a summation of red and amber days), days requiring triptans, and days requiring painkillers (simple and/or opiate analgesia); monthly data was standardised to 28 days (calculated by dividing monthly data by the summation of red, amber and green days multiplied by 28). Participants also completed the validated headache disability questionnaire - 'Headache-impact test-6' (HIT-6)[29] - each month, whilst data relating to the incidence and nature of side effects was also collected.

The mean of the last three months of headache data on preceding anti-CGRP-mAb treatment constituted 'baseline' data, and the first three months post-switching to a subsequent anti-CGRP-mAb 'treatment' data. A subset of participants that continued treatment beyond three months post-switch were also analysed up to six months. For those with missing data (either due to missing documentation or early discontinuation of treatment), the last observation within that treatment arm was carried forward ('last observation carried forwards' approach). This was done to minimise bias from drop-out

which might act to inflate a treatment effect by excluding individuals that stopped submitting diaries due to treatment ineffectiveness or cessation. Missing data amounted to two diaries at 1 month, eleven diaries at 2 months, and seventeen diaries at 3 months, with five incidences of data missing at both two and three months.

Data analysis

Statistical analysis was performed in R (version 4.2.1). As outcome data failed the statistical assumptions for normality (Shapiro-Wilk test $p<.05$ for red, headache, triptan, painkiller days, and HIT-6), the Friedman rank sum test (a non-parametric alternative to the repeated-measures ANOVA) was used to compare baseline red days, headache days, triptan days, painkiller days, and HIT-6 scores, to month 1, 2 and 3 data post- anti-CGRP-mAb switch. Significant results were explored using pairwise Wilcoxson signed-rank tests (Bonferroni-corrected for multiple comparisons). Thirty and fifty percent responder rates for red and headache days at three months were also calculated. In 38 instances, subjects continued the second anti-CGRP-mAb beyond three months, for whom red and headache day outcomes are reported up to 6 months. Subgroup analyses were performed in four groups; those that discontinued first anti-CGRP-mAb due to non-efficacy (excluding those that discontinued due to side effects); those that switched directly from one anti-CGRP-mAb onto another (with no intervening treatment break); those that switched twice and therefore received treatment with three anti-CGRP-mAb; and those with daily headache.

Results

Participants

Seventy-five instances of switching were identified amongst 63 individuals. In 9 instances, participants did not provide the minimum one month of baseline and one month of treatment data, therefore the final analysis included 66 instances of anti-CGRP-mAb switch in 54 individual patients (figure 1). Of these, there were 7 instances of participants switching from

fremanezumab to galcanezumab (mean interval between treatments; 3.1 ± 4 months), 10 instances from fremanezumab to erenumab (1.6 ± 2 months), 13 instances from erenumab to galcanezumab (1.8 ± 3 months), 33 instances from erenumab to fremanzeumab (6.5 ± 5 months), and 3 instances from galcanezumab to fremanezumab (1.0 ± 0 months). A total of 12 individuals received all three anti-CGRP-mAb drugs. In 53 instances, the reason for switch was on the basis of ineffectiveness, whilst 13 instances of switching were primarily due to the occurrence of clinically-significant side effects.

Table 1 shows the characteristics of the participants (recorded before first anti-CGRP-mAb treatment). The ages ranged between 21 to 73 years (mean = 48.9 ± 13.8 years, median = 51 years). Forty six of the 54 (85%) were female. Participants had suffered with migraine for between 2 and 48 years (mean = 18.2 ± 12.2 years, median = 14 years, unknown for 3 individuals), and reported trialling between one and nine prophylactic medications before receiving first anti-CGRP-mAb treatment (mean/median = 5, mode = 6) – this figure encompasses the total number of different medications belonging to the class of beta-blockers (propranolol, atenolol), tricyclics (amitriptyline, nortriptyline), anticonvulsants (topiramate, gabapentin, pregabalin, sodium valproate), angiotensin II receptor blockers (candesartan), calcium channels blockers (flunarizine), serotonin antagonists (pizotifen), and anti-depressants (venlafaxine, mirtazapine, duloxetine). Fifty-three individuals (98%) had previously received onabotulinumtoxinA. According to baseline scores, forty-five (70%) met the criteria for depression (Patient Health Questionnaire-9 (PHQ-9) score ≥10; mean score 13.7 ± 5.9), seventeen (27%) met the ICHD (2018) criteria[28] for triptan overuse (≥10 days requiring triptans per month), whilst twenty-two (35%) required non-triptan analgesics (including simple and opiate-based) on ≥15 days per month. Thirty (46%) reported daily headache at baseline.

Outcomes

Red and headache days

Participants suffered a mean of 13.1 ± 7.4 red days (headache limiting activities of daily living) at baseline, reduced to 11.9 ± 8.3 at three months post-switch (mean [95% CI] difference -1.2 [-2.7, 0.3] days). Ten individuals (15%) experienced a ≥50% improvement while twenty-two (33%) experienced a ≥30% improvement in red days at three months post-switch. Friedman rank sum test across four timepoints (baseline, month 1, 2 and 3) was significant (p=.043), although post-hoc tests only indicated significant differences between month 1 and month 3 (see supplementary materials). In 38 instances when anti-CGRP-mAb treatment continued beyond three months, eight participants (21%) achieved ≥50% and thirteen (34%) achieved ≥30% improvement at six months, with Friedman test indicating a significant result (p=.05)(figure 2).

With regard to headache days, participants suffered a mean of 22.6 ± 7.1 days with headache of any kind (both limiting and non-limiting) at baseline, reducing to 21.5 ± 8.2 at month three post-switch (mean [95% CI] difference; -1.1 [-2.4, 0.3] days). Nine individuals (14%) experienced a ≥30% improvement in headache days, whilst six (9%) experienced a ≥50% improvement. Friedman test yielded a non-significant result (p=.54). For the 38 individuals that continued anti-CGRP-mAb beyond three months, two individuals (5%) achieved ≥50% and five (13%) achieved ≥30% improvement at six months. Friedman test did not indicate any significant differences in headache days between any timepoints (p=.45).

Triptan days, painkiller days, and headache disability

At baseline, participants required triptan medication on an average of 6.3 ± 7.7 days, reducing to 5.3 ± 7.1 days at three months following anti-CGRP-mAb switch (mean [95% CI] difference: -1.0 [-2.0, 0.2] days). There were no significant differences in triptan days across the four timepoints (p=.16). Nine (14%) achieved ≥50% and fifteen (23%) achieved ≥30% reduction in triptan days. With regard to painkiller use, participants required painkillers (simple and/or opiate analgesia) an average of 11.4 ± 9.6 days at baseline, reduced to 10.1

± 9.7 at month 3 post-switch (mean [95% CI] difference: -1.5 [-2.8, -0.2] days), with no significant differences across timepoints (*p*=.18). Nine (14%) achieved ≥50% and fourteen (21%) achieved ≥30% improvement in painkiller days. The mean HIT-6 score during subjects' last month of prior anti-CGRP-mAb treatment was 63.6 ± 10.7, reduced to 62.8 ± 9.1 at month three following switch (mean [95% CI] difference: -0.8 [-3.6, 2.0] points). Friedman test produced a non-significant result (*p*=.52).

Side effects

In 13 instances, the decision for anti-CGRP-mAb switch was made on the basis of intolerable side effects (Table 2). Amongst the most common side effects were constipation/gastrointestinal upset (four instances), cutaneous reaction (five instances), neuro-cognitive side effects (two instances), palpitations (one instance), and significant worsening of migraines (two instances). On twelve occasions, side effects spanning the range of symptoms described above were reported to have subjectively improved or resolved on switching to a different anti-CGRP-mAb. On eight occasions, new symptoms were reported following a switch.

Subgroup analysis

In order to control for the variability in inter-treatment intervals, we performed subgroup analysis by only examining individuals that switched directly from one anti-CGRP-mAb to another (i.e. with no intervening treatment break). Thirty-five subjects were included in this sub-analysis. These 'straight-switchers' had a lower group mean/median of red and headache days at all timepoints. Friedman test across four timepoints (baseline, month 1, 2, and 3) produced a significant result (*p*=.013) with post-hoc pairwise tests indicating significant differences between month 1 - 2 and month 1 - 3, although not between baseline - month 3 (see supplementary materials). There were no significant changes in headache days (*p*=.24).

Next, subgroup analysis were performed by excluding those who switched anti-CGRP-mAb due side effects, and therefore was composed exclusively of individuals that switched due to ineffectiveness ('non-responders'). This led to inclusion of 53 instances of switching. Friedman test showed a trend for improvement in red days (p=.083) and a significant improvement in headache days (p=.044), with post-hoc pairwise tests for headache days indicating significant differences between baseline - month 1 (Bonferroni-corrected p=.027), baseline - month 2 (p=.029), with baseline - month 3 just shy of statistical significance (p=.092). Responder rates for red days were less favourable in these individuals compared to the overall cohort, with nine (14%) showing ≥50% and seventeen (26%) showing ≥30% improvement in red days, while response for headache days were similar, with six (9%) showing ≥50% and nine (14%) showing a ≥30% improvement in headache days.

As individuals with daily headache have previously shown to exhibit poor treatment response following an anti-CGRP-mAb switch[21], outcomes for thirty individuals with daily headache were analysed. Friedman test produced a result approaching significance for red days (p=.096), although post-hoc tests indicated that this was primarily driven by differences between month 1 - 3 and month 2 - 3, owing to the red day burden increasing in the initial two months post-switch, with some improvement at month 3. Importantly, there was no difference between baseline - month 3 (p>1). Although change in headache days approached significance (p=.072), no timepoint survived post-hoc correction for multiple comparisons. Analysis with daily headache patients excluded did not produce a significant result for red (p=.18) or headache days (p=.95).

Finally, switching outcomes were analysed in the 12 individuals that switched anti-CGRP-mAb twice, and therefore received erenumab, fremanezumab and galcanezumab. Change in red and headache days were analysed separately for the first and second switch. For the first switch, there were no significant differences for red and headache days between any timepoints (Red days; p=.83; Headache days; p=.22). For the second switch, there was a significant difference in red days (p=.028), with post-hoc pairwise tests indicating significant

differences between month 1 - 3 (Bonferroni-corrected *p*=.035). Headache days demonstrated non-significant improvements (*p*=.13).

Discussion

We observed modest improvement for the outcome 'red' days – more severe headaches limiting activities of daily living – across the entire cohort of participants. On average, individuals saw reductions of -1.2 red days from baseline three months following anti-CGRP-mAb switch, although statistically-significant differences were only observed between month 1 and month 3, seemingly due to a worsening of red days in the first month post-switch; in particular an increased incidence of participants experiencing daily red days, accounting for a greater proportion of higher ranked scores at this timepoint. Although improvement between baseline and month 3, which was the primary outcome of interest, failed to achieve a significant result, around a third of participants achieved ≥30% improvement in the most severe and disabling headaches at three months, while a not-insignificant proportion (15%) achieved ≥50%-response. This observation in such a highly treatment-resistant group is encouraging and in line with what sufferers of chronic pain state to be the overriding objective in pain management – a large reduction in symptoms[30]. While outcomes for headache days (days with any headache, limiting or non-limiting), as well as secondary outcomes - days requiring triptans, painkillers and monthly headache disability scores – were less pronounced than that seen for red days, interestingly, when individuals that switched due to side effects were excluded from the analysis, a significant reduction in overall (disabling and non-disabling) headache symptoms from baseline was demonstrated.

Our study therefore provides evidence of moderate benefit in individuals switching anti-CGRP-mAb treatment, although primarily in those switching due to ineffectiveness. Although our decision to include those switching due to side effects was well-reasoned, given that many individuals reported these in conjunction with poor treatment response (with severe

worsening of migraines constituting an adverse event for two participants), inclusion of these individuals appears to have skewed the analysis towards a less favourable treatment response, possibly with underestimation of the true treatment effect (although, conversely, our results may be more representative of the real-world outcomes to be expected in severe and treatment-resistant migraine sufferers). As evidenced by the 38 participants that continued anti-CGRP-mAb beyond three months, in whom the greatest reductions in red days were observed beyond three months post-switch, it is also possible that a longer observation phase may be necessary to adequately gauge effectiveness following anti-CGRP-mAb switch, an assertion further supported by Overeem et al.'s recent analysis, in which six months outcomes saw an improvement over those recorded at three months[25], and that of Barbanti and colleagues, who reported that half of non-responders to anti-CGRP-mAbs at 12 weeks were in fact late responders[31].

Our results for red days are not dissimilar to those of Overeem et al.'s 2021 analysis, which measured a ≥30% improvement in monthly headache days in 32%, and a ≥50% response in 12% of individuals[21]. Similar to ours, their cohort contained a high proportion of chronic migraine sufferers with an extensive history of treatment failure. Unlike Overeem's group, we used a traffic-light scoring system of 'red', 'amber' and 'green' days in our study design in order for participants to self-categorise their migraine symptoms more easily, using subjective limitation to activities of daily living or need for triptan medication as a surrogate for the most severe headache category ('red days'). Whilst this categorisation differs from the conventional approach of defining migraine and headache days on the basis of specific clinical symptoms, we and others[32] have found the approach enables easier and more consistent self-reporting of headache symptoms. This is especially relevant in real-world observational studies and an issue notably encountered in Overeem's analysis, in which reliable differentiation between headache and migraine days from headache diary documentation was not possible[21]. Nevertheless it is possible that our descriptors do not

generalise fully to the conventional classifications, limiting comparisons between other studies.

In contrast to Overeem's study who excluded participants that submitted less than two months of data in any cycle, we widened our inclusion criteria to include individuals that submitted a minimum of one's month data . In our experience, patients with early poor response to treatment, side effects or severe worsening of migraine symptoms are less likely to continue submitting headache diaries, and such an approach might therefore act to overestimate a treatment effect. Similar to Overeem's group, when data was missing, we used a 'last observation carried forward approach' to minimise the risk of attrition bias. Whilst this statistical approach has received criticism, particularly when data is presumed not to be missing at random[33], we felt that the propensity for an inflated treatment effect due to drop-out justified its use, and that our results provide a reliable, conservative estimate in a challenging, real-world setting.

By conducting subgroup analysis, we addressed the main potential sources of bias in the study, as well as attempting to identify those groups most likely to benefit from anti-CGRP-mAb switch. Arguably the most serious limitation of the study related to the significant variability in time between anti-CGRP-mAb treatments, with some individuals switching directly from one anti-CGRP-mAb to another, and others undergoing a treatment pause of variable duration during which no anti-CGRP-mAb was administered. This means that pre- and post- switching observations were not 'time-locked', and therefore any natural evolution of migraine symptoms, during which headache frequency may have naturally improved or worsened, or changes to regular medications might act to introduce bias, limiting comparisons. Whilst this was a shortcoming in the study design, the evolving availability of anti-CGRP-mAb drugs over time (in addition to the stipulation for a three-month treatment break after 1 year of treatment in a subset of patients) made this unfeasible to achieve in our retrospective, observational study. Nevertheless, we aimed to address this potential source of bias by studying only those individuals that switched directly from one anti-CGRP-mAb to

another with no intervening break. This showed that the subgroup of ‘straight-switchers’ had an overall milder migraine phenotype (reflected by lower baseline red and headache days) but exhibited similar levels of improvement compared to the group as a whole. Analysis of those that underwent two switches, despite inclusion of only twelve individuals, indicated that the second switch showed a trend towards improvement in the more severe ‘red’ days, suggesting that failure of one anti-CGRP-mAb switch should not necessarily preclude a further switch attempt. We also explored the impact of daily headache on switching outcomes, with our data neither providing strong evidence for or against previous findings that those with daily headache are less likely to respond to anti-CGRP-mAb switch[21]. Although individuals with daily headache did not experience significant reductions in red or headache days from baseline after three months following anti-CGRP-mAb switch, exclusion of these daily headache sufferers did not result in significantly improved outcomes for the remaining cohort.

As discussed, we made a decision not to exclude participants who discontinued anti-CGRP-mAb treatment due to adverse effects, not only on the basis that these accompanied a poor treatment response for many individuals, but also because we felt this data would provide useful and relevant information for clinicians. Accordingly we found that many individuals experienced side effects on one but not another anti-CGRP-mAb drug. Interestingly, in several individuals, improvement in side effects occurred when switching across the same drug class (that is to say, switching to another anti-CGRP-mAb drug targeting the CGRP ligand rather than receptor. i.e. fremanzeumab to/from galcanezumab), although due to the small number of participants switching between drugs, it is hard to draw firm conclusions.

As with similar real-world studies in individuals with resistant migraine phenotypes, missing data remains a significant problem and risks overestimating a treatment response by non-inclusion of individuals that fail to submit headache diaries after a null or negative treatment response. Whilst we did our best to minimise attrition bias by employing a ‘last observation carried forward’ approach, the non-inclusion of nine individuals that failed to submit a single

headache diary in one or more treatment arm may have biased our sample, and by extension overestimated a treatment effect, however as previously described, this approach may conversely have led to an overly conservative estimate of the effect size.

Conclusion

Our results suggest that anti-CGRP-mAb switch may be beneficial in reducing migraine, particularly in individuals that switch due to ineffectiveness. Whilst subgroup analyses did not clearly indicate those groups more or less likely to benefit, they suggest that the presence of daily headache or a previous unsuccessful attempt at anti-CGRP-mAb switch should not necessarily preclude a switch attempt.

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Competing interests

SW has attended conferences and received speaker's fees from Novartis

Ethics approval statement

This study was approved by the hospital Research and Development team. Following discussion of the study aims and methodology, formal approval by Ethics Committee was deemed unnecessary.

Contributorship statement

Below outlines specific contributions of the authors:

JT - data collection, analysis, manuscript preparation.

RS - data collection.

NW - data collection.

AG - analysis, manuscript preparation.

GC - data collection, manuscript preparation.

SW - manuscript preparation, oversight.

References

1 Dodick DW, Ashina M, Brandes JL, *et al.* ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia* 2018;**38**:1026–37. doi:10.1177/0333102418759786

2 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**:1999–2008. doi:10.1001/jama.2018.4853

3 Stauffer VL, Dodick DW, Zhang Q, *et al.* Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. *JAMA Neurol* 2018;**75**:1080–8. doi:10.1001/jamaneurol.2018.1212

4 Silberstein SD, Dodick DW, Bigal ME, *et al.* Fremanezumab for the Preventive Treatment of Chronic Migraine. *N Engl J Med* 2017;**377**:2113–22. doi:10.1056/NEJMoa1709038

5 Detke HC, Goadsby PJ, Wang S, *et al.* Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology* 2018;**91**:e2211–21. doi:10.1212/WNL.0000000000006640

6 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**:425–34. doi:10.1016/S1474-4422(17)30083-2

7 Bigal ME, Edvinsson L, Rapoport AM, *et al.* Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. *Lancet Neurol* 2015;**14**:1091–100. doi:10.1016/S1474-4422(15)00245-8

8 Bigal ME, Dodick DW, Krymchantowski AV, *et al.* TEV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points. *Neurology* 2016;**87**:41–8. doi:10.1212/WNL.0000000000002801

9 Kanaan S, Hettie G, Loder E, *et al.* Real-world effectiveness and tolerability of erenumab: a retrospective cohort study. *Cephalalgia* 2020;**40**:1511–22.

10 Giorgio L, Hill B, Murphy M, *et al.* A prospective real-world analysis of erenumab in refractory chronic migraine. *J Headache Pain* 2020;**21**.

11 Vernieri F, Altamura C, Brunelli N, *et al.* Galcanezumab for the prevention of high frequency episodic and chronic migraine in real life in Italy: a multicenter prospective cohort study (the GARLIT study). *J Headache Pain* 2021;**22**:1–10.

12 Cohen JM, Thompson S, Patterson-Lomba O, *et al.* Real-world Reductions in Migraine and Headache Days for Patients With Chronic and Episodic Migraine Initiating Fremanezumab in the US (4171). 2021.

13 Faust E, Pivneva I, Yang K, *et al.* Real-World Treatment Profiles, Clinical Outcomes, and Healthcare Resource Utilization of Patients with Migraine Prescribed Erenumab: A Multicenter Chart-Review Study of US Headache Centers. *Neurol Ther* 2021;:1–14.

14 Kudrow D, Cady RK, Allan B, *et al.* Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. *BMC Neurol* 2021;**21**:1–12.

15 Talbot J, Stuckey R, Crawford L, *et al.* Improvements in pain, medication use and quality of life in onabotulinumtoxinA-resistant chronic migraine patients following erenumab treatment–real world outcomes. *J Headache Pain* 2021;**22**:1–10.

16 Overeem LH, Raffaelli B, Mecklenburg J, *et al.* Indirect Comparison of Topiramate and Monoclonal Antibodies Against CGRP or Its Receptor for the Prophylaxis of Episodic Migraine: A Systematic Review with Meta-Analysis. *CNS Drugs* 2021;**35**:805–20. doi:10.1007/s40263-021-00834-9

17 Shi M, Guo J, Li Z, *et al.* Network meta-analysis on efficacy and safety of different anti-CGRP monoclonal antibody regimens for prophylaxis and treatment of episodic migraine. *Neurol Res* 2021;**43**:932–49. doi:10.1080/01616412.2021.1940672

18 Reuter U, Ehrlich M, Gendolla A, *et al.* Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia Int J Headache* 2022;**42**:108–18. doi:10.1177/03331024211053571

19 Porta-Etessam J, González-García N, Guerrero ÁL, *et al.* Failure of monoclonal antibodies against CGRP or its receptor does not imply lack of efficacy of other drugs from the same class. *Neurol Engl Ed* 2021;**36**:638–40. doi:10.1016/j.nrleng.2020.10.008

20 Ziegeler C, May A. Non-Responders to Treatment With Antibodies to the CGRP-Receptor May Profit From a Switch of Antibody Class. *Headache J Head Face Pain* 2020;**60**:469–70. doi:10.1111/head.13729

21 Overeem LH, Peikert A, Hofacker MD, *et al.* Effect of antibody switch in non-responders to a CGRP receptor antibody treatment in migraine: A multi-center retrospective cohort study. *Cephalalgia* 2021;:03331024211048765.

22 Robbins L. CGRP Monoclonal Antibodies for Chronic Migraine: Year 1 of Clinical Use. 2019;:6.

23 Briceño-Casado MDP, Gil-Sierra MD, De-La-Calle-Riaguas B. Switching of monoclonal antibodies against calcitonin gene-related peptide in chronic migraine in clinical practice: a case series. *Eur J Hosp Pharm* Published Online First: 14 September 2021. doi:10.1136/ejhpharm-2021-002946

24 Weatherall M, Matharu M. 059 Switching CGRP monoclonal antibodies for chronic migraine: real-world outcomes of 37 episodes. *J Neurol Neurosurg Psychiatry* 2022;**93**:A119.1-A119. doi:10.1136/jnnp-2022-ABN.384

25 Overeem LH, Lange KS, Fitzek MP, *et al.* Effect of switching to erenumab in non-responders to a CGRP ligand antibody treatment in migraine: A real-world cohort study. *Front Neurol* 2023;**14**.https://www.frontiersin.org/articles/10.3389/fneur.2023.1154420 (accessed 7 Jul 2023).

26 Raffaelli B, Fitzek M, Overeem LH, *et al.* Clinical evaluation of super-responders vs. non-responders to CGRP(-receptor) monoclonal antibodies: a real-world experience. *J Headache Pain* 2023;**24**:16. doi:10.1186/s10194-023-01552-x

27 Torres-Ferrus M, Gallardo VJ, Alpuente A, *et al.* Patterns of response to anti-calcitonin gene-related peptide monoclonal antibodies during first 6 months of treatment in resistant migraine patients: Impact on outcome. *Eur J Neurol* 2023;**30**:1937–44. doi:10.1111/ene.15816

28 Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia Int J Headache* 2018;**38**:1–211. doi:10.1177/0333102417738202

29 Kosinski M, Bayliss MS, Bjorner JB, *et al.* A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2003;**12**:963–74. doi:10.1023/a:1026119331193

30 Moore RA, Straube S, Aldington D. Pain measures and cut-offs – 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;**68**:400–12. doi:10.1111/anae.12148

31 Barbanti P, Aurilia C, Egeo G, *et al.* Late Response to Anti-CGRP Monoclonal Antibodies in Migraine: A Multicenter, Prospective, Observational Study. *Neurology* Published Online First: 18 April 2023. doi:10.1212/WNL.0000000000207292

32 Marissa Lagman-Bartolome A, Lay C. The Traffic Light of Headache: Simplifying Acute Migraine Management for Physicians and Patients Using the Canadian Headache Society Guidelines. *Headache J Head Face Pain* 2019;**59**:250–2. doi:10.1111/head.13428

33 Lachin JM. Fallacies of Last Observation Carried Forward. *Clin Trials Lond Engl* 2016;**13**:161–8. doi:10.1177/1740774515602688

Tables

Table 1: Participant characteristics for all individuals included in the final analysis

Participant characteristics	n=54
Age (mean ±SD (range))	48.9 ± 13.8 (21 – 73)
Female (n (%))	46 (85.2%)
Numbers of years suffering migraine (mean ± SD (range))	18.2 ± 12.2 (2 – 48)
Number of previously-trialled oral prophylactics (mean ± SD (range))	5.2 ± 2.5 (1 – 9)
Previous onabotulinumtoxinA (n (%))	53 (98.1%)

Table 2: Details of adverse events in study participants. $^{*}/^{\dagger}/^{\Delta}$ represents same patient

Participants experiencing side effects on first anti-CGRP-mAb

Participant	CGRP-mAb	Details of side effect	Switched to	Outcome
1 *	Fremanezumab	Severe worsening of migraines and neuro-cognitive (memory and word-finding) symptoms	Galcanezumab	Improvement
2	Fremanezumab	Severe skin reaction at injection site	Erenumab	Improvement
3	Fremanezumab	Severe worsening of migraines	Erenumab	Improvement
4	Erenumab	Severe skin reaction at injection site on 140mg dose	Galcanezumab	Improvement
5	Erenumab	Severe constipation	Galcanezumab	Improvement
6	Erenumab	Palpitations	Galcanezumab	Improvement
7	Erenumab	Constipation	Fremanezumab	Improvement
8 Δ	Erenumab	Constipation	Fremanezumab	Improvement
9	Erenumab	Visual disturbances, nausea, dizziness, gastrointestinal upset, tremulousness).	Fremanezumab	Same side effects occurred.
10	Erenumab	Rash and vertigo	Fremanezumab	Rash improved but increased bruising. Vertigo improved somewhat.
11	Erenumab	Severe itching and swelling at injection site	Fremanezumab	Improvement
12	Erenumab	Chest pain resulting in discontinuation and referral to cardiology (ischaemic cause later excluded)	Fremanezumab	No recurrence of chest pain
13 †	Galcanezumab	Painul swelling on foot	Fremanezumab	Improvement

Participants experiencing new side effects on second anti-CGRP-mAb

1 †	Erenumab	No side effects	Galcanezumab	Painful swelling on foot
2	Erenumab	No side effects	Fremanezumab	Joint pain and insomnia
3	Erenumab	No side effects	Fremanezumab	Body aches and fatigue
4 *	Erenumab	No side effects	Fremanezumab	Worsening of migraines, memory and word-finding problems

5	Erenumab	No side effects	Fremanezumab	Bloating, constipation, nausea, spaced out feeling, vertigo
6	Erenumab	No side effects	Fremanezumab	Insomnia, constipation, weight gain.
7	Erenumab	No side effects	Fremanezumab	Localised itching (mild enough to continue drug)
8[Δ]	Fremanezumab	Moderate constipation	Galcanezumab	Hypertension. Severe worsening of constipation.