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Twelve-month efficacy of CGRP monoclonal antibodies and predictive value of short-term response: results of an Australian multicentre study

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ABSTRACT

Introduction Clinical trials show that calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) are effective preventative treatments for chronic migraine. Their efficacy over longer time periods and in cohorts originally excluded from trials remains uncertain. This study aims to explore the impact of CGRP mAbs in an Australian real-life setting.

Methods A multicentre cohort study was performed in the tertiary headache clinics of the Alfred and Austin Hospitals, Melbourne, Australia. Patients were commenced on a CGRP mAb for chronic migraine and asked to keep a headache diary, recorded at 3 monthly appointments for 12 months. Primary outcome was a ≥50% reduction in monthly headache days (MHD).

Results From a population of 105 patients, 90 patients commenced galcanezumab and 15 commenced fremanezumab. The ≥50% responder rate of the cohort was 52.4% after 3 months. Over 12 months follow-up, 25.7% of the cohort ceased due to a lack of efficacy and 16.2% ceased due to an adverse event. There was no difference in response or cessation between medications. There was poor agreement in 3-month and 12-month response rates (Cohen's κ=0.130; p=0.171). On subgroup analysis, continuous headache at baseline and number of trialled preventative treatments were the only factors associated with efficacy.

Conclusion CGRP mAbs were associated with sustained reductions in MHD over 12-month follow-up in patients with resistant migraine in Australia. Further studies are required to determine treatment options for patients with continuous headache. Poor agreement between outcomes at 3 and 12 months highlights the need to assess some patients at later timepoints.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) have been shown in clinical trials to be a safe and effective preventative treatment for chronic migraine.

WHAT THIS STUDY ADDS

⇒ This study confirms the efficacy of CGRP mAbs in a real-world population, including subgroups of patients not included in clinical trials.

⇒ It demonstrates the 12-month efficacy, tolerability and persistence of this class of therapies, and finds poor agreement in 3-month outcome measures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides further data on the efficacy of CGRP mAbs over longer time periods, and in patients excluded from clinical trials.

⇒ The poor agreement of 3-month and 12-month outcome has implications for local regulatory guidelines.

INTRODUCTION

The advent of calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) as an effective treatment for migraine represents the culmination of 40 years of preclinical research and clinical trials.[1] The generalisability of the phase II/III trials of CGRP mAbs is reduced, however, due to the exclusion of patients with continuous headache, recent treatment with other efficacious treatments such as onabotulinumtoxinA (onaB-A) or patients who had failed in excess of between two and four classes of preventative treatment, depending on the particular study.[1–3] Furthermore, most trials assessed efficacy at 3 months, which has been adopted by multiple local licensing bodies as an adequate trial to assess response. The predictive value of clinical response at 3 months and long-term response, however, remains unclear.

Within Australia, CGRP mAbs may be prescribed under the Pharmaceutical Benefits Scheme (PBS) for patients who meet the International Classification of Headache Disorders, third edition (ICHD-3) criteria for chronic migraine, where comorbid medication overuse headache (MOH) has been addressed, and, if patients have trialled at least three preventative treatments for

migraine.[4 5] At the time of this study, fremanezumab and galcanezumab were the only two CGRP mAbs available on the PBS in Australia. The aim of the study was to evaluate the efficacy of CGRP mAbs in patients excluded from the original trials and evaluate the predictive value of a 3-month clinical response.

METHODOLOGY

A multicentre prospective cohort study was performed in the tertiary headache clinics of the Alfred and Austin Health, two metropolitan hospitals in Melbourne, Australia. Patients with chronic migraine per ICHD-3 criteria[4] that were CGRP mAb naïve, and commenced on a CGRP mAb following local regulatory guidelines between June 2021 and March 2022 were enrolled in the study. Patients with continuous headache fulfilled the ICHD-3 criteria for chronic migraine, and did not fulfil ICHD-3 criteria for new daily persistent headache. No patients with MOH were commenced on a CGRP mAb.

Patients who were commenced on a CGRP mAb were instructed to prospectively complete a headache diary, which was recorded at 3 monthly clinical appointments. Patient demographic data were collected from the electronic medical record. Monthly headache days (MHD) were measured at baseline in the month prior to initiation of CGRP mAb, and measured in the month prior to each appointment (ie, week 9–12, week 32–36, etc). The primary outcome was a ≥50% reduction in MHD. The primary outcome is distinct from local regulatory requirements evaluating efficacy, which requires a ≥50% reduction in monthly migraine days (MMD) at 3 months to continue therapy.

Statistical analysis was performed using SPSS V.28.0. Population characteristics were summarised with descriptive statistics. Longitudinal change was assessed with paired samples t-test for normally distributed data. A multivariant analysis was undertaken with a Kruskal-Wallis test for non-normally distributed ordinal data (MHD, age and number of failed preventative therapies). A Wilcoxon signed-rank test was used for non-normally distributed categorical groups. Pearson's correlation was used to assess correlation. Survival analysis was undertaken by Kaplan-Meier method. The concordance of binary variables (responders vs non-responders at 3 and 12 months) was assessed with Cohen's kappa of agreement. Test results were considered significant when $p<0.05$.

RESULTS

A total of 110 patients were commenced on a CGRP mAb over the study period, with five patients subsequently lost to follow-up and not included in the analysis. The population demographics are summarised in table 1. The

Table 1 Cohort demographics

	Total cohort (n=105)	Fremanezumab (n=15)	Galcanezumab (n=90)	P value
Age Mean (SD)	42.2 (12.0)	46.3 (9.3)	41.5 (12.4)	0.118
Female n (%)	7 (73.3)	12 (80)	65 (72.2)	0.508
Previous preventers Median (IQR)	5 (4)	6 (4)	5 (3)	0.375
Previous preventers n (%)				
3–4	37 (35.2)	4 (26.7)	33 (36.7)	
5–6	31 (29.5)	5 (33.3)	26 (28.9)	
7–8	20 (19.0)	4 (46.7)	16 (17.8)	
9–10	9 (8.6)	0 (0.0)	9 (10.0)	
11–12	5 (4.8)	1 (6.7)	4 (4.4)	
13–14	1 (1.0)	0 (0.0)	1 (1.1)	
15–16	2 (1.9)	1 (6.7)	1 (1.1)	
Previous onabotulinumtoxinA N (%)	36 (34.3)	3 (20)	33 (36.7)	
Baseline MHD Median (IQR)	30 (10)	30 (12)	30 (10)	0.856
Three-month change in MHD Median (IQR)	10 (18)	3 (15)	10 (18)	0.385
Three-month ≥50% response n (%)	55 (52.4)	5 (33.3)	50 (55.6)	0.094

≥50% response—the proportion of the population who have a ≥50% reduction in the number of headache days from baseline.
MHD, monthly headache days.

Table 2 Reported AEs and life events in study cohort

Event/Reported AE	N (%)
Ceased due to planned pregnancy	2 (1.9)
Anxiety	2 (1.9)
Constipation	2 (1.9)
Fatigue	2 (1.9)
Rash	1 (1.0)
Alopecia	1 (1.0)
Weight gain	1 (1.0)
Chest pain	1 (1.0)
Depression	1 (1.0)
Dizziness	1 (1.0)
Bloating	1 (1.0)
Insomnia	1 (1.0)
Multiple myeloma	1 (1.0)

AE, adverse events.

mean age of the cohort was 42.2 years (SD 12.0) and had failed a median of 5 (IQR 4) previous preventative treatments for migraine, with a baseline MHD of 30 (IQR 10) prior to commencing a CGRP mAb. A total of 90 patients commenced galcanezumab, and 15 patients commenced fremanezumab over the study period. Significantly fewer patients were commenced on fremanezumab, however the groups were otherwise well matched for age, gender, previously trialled preventative medications and baseline MHD frequency.

Over the first 3-month treatment period, 52.4% (55/105) of the cohort achieved a ≥50% reduction in frequency of their MHD, corresponding with a median reduction of 10 (IQR 18) MHD. There was no difference in treatment outcome between fremanezumab and galcanezumab (table 1). During the 12-month follow-up period, 58.1% (61/105) of the cohort continued treatment, 25.7% (27/105) ceased due to a lack of efficacy and 16.2% (17/105) ceased due to an adverse emergent event or change in circumstance (table 2). There was no significant difference in the rate of continuation between therapies (χ^2=0.252, p=0.615), represented in figure 1.

The efficacy of CGRP mAbs over the 12-month treatment period is summarised in figure 2. After 12 months, the ≥50% responder rate for patients continuing treatment was 80% (40/50), corresponding to a median reduction of 18 MHD (IQR 12) compared with baseline. The utility of the ≥50% responder rates at 3 months was evaluated by Cohen's κ. A total of 50 patients completed 12 months of therapy, of whom 39 had been responders at 3 months, or 37.1% of the original cohort commenced on therapy, on an intention-to-treat basis. There was no statistical agreement between the 3-month and 12-month ≥50% response rates (κ=0.130, p=0.171).

A subgroup analysis was conducted to explore the efficacy of CGRP mAbs in groups not included in clinical trials. In patients who had failed >4 preventative therapies, the 3-month 50% responder rate was 41.2%, compared with 73% in patients who had failed four or fewer. In patients who reported no headache-free days per month at baseline, the 50% responder rate was 43.1% compared with 63.8% in those who did not.

A Kruskal-Wallis H test showed that there was a statistically significant difference in the 50% responder rate at 3 months in patients who had failed multiple preventative treatments (χ^2=10.54, p=0.001), mean rank for responders of 43.20 and non-responders of 62.08. There was no significant difference in clinical response with regard to baseline MHD (χ^2=2.471, p=0.116) or age

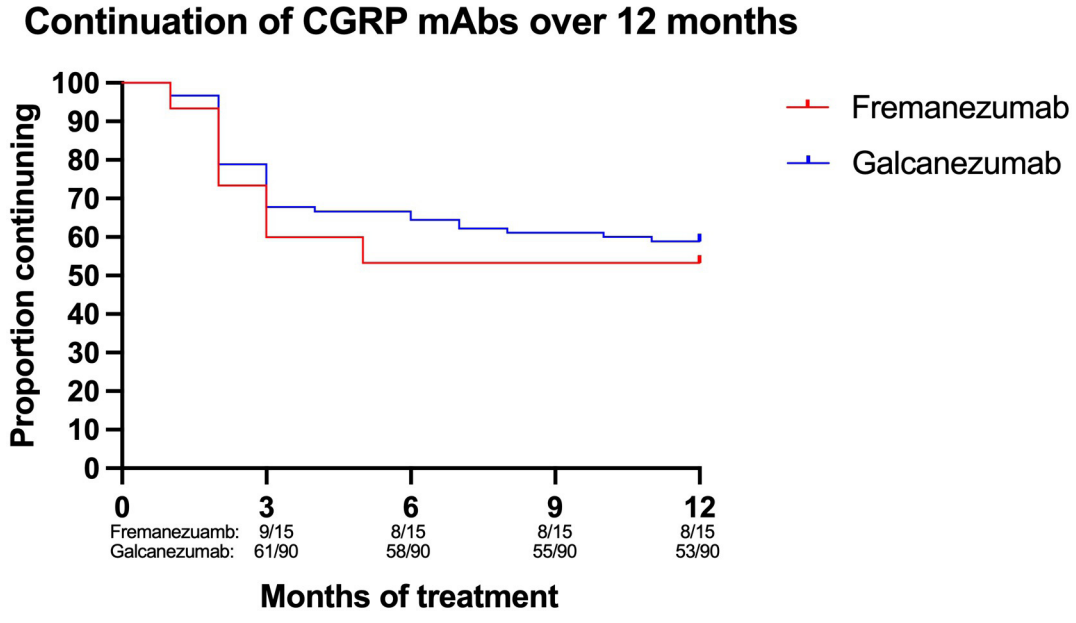

Figure 1 Kaplan-Meier survival curve demonstrating continuation of treatment over 12-month follow-up. CGRP, calcitonin gene-related peptide; mABs, monoclonal antibodies.

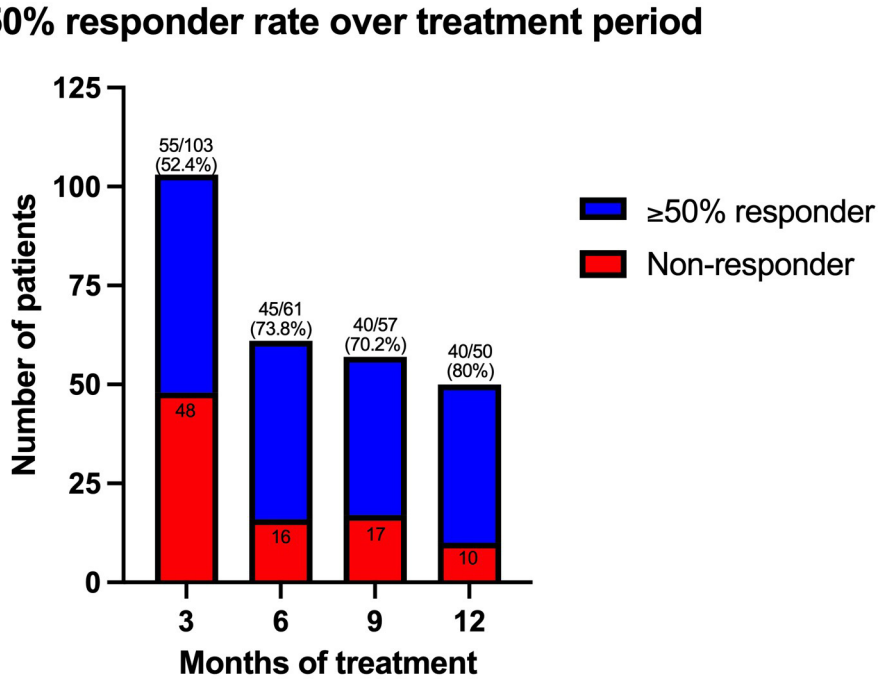

Figure 2 Efficacy of calcitonin gene-related peptide monoclonal antibody over 12-month period, represented as the proportion of patients with ≥50% reduction in monthly headache days.

(χ^2=0.822, p=0.365). On a Wilcoxon signed-rank test, there was no significant difference in patients who had previously failed onaB-A and percentage reduction in MHD (z=−0.590, p=0.555). One patient over the age of 70 years was commenced on a CGRP mAb and ceased the medication after 3 months due to lack of efficacy.

DISCUSSION

This study provides real-world evidence of the efficacy of ligand-targeting CGRP mAbs in the treatment of chronic migraine in Australia. The clinical response observed is comparable to clinical trials, and other groups worldwide.[1 2 6] Over a 12-month period of treatment, approximately one-quarter of patients ceased the medication due to a lack of efficacy, with the remainder maintaining a clinical response over the follow-up period.

Patients with continual headaches were excluded from phase II to phase III study, presumably due to concern of reduced response to primary end points, limiting generalisability and data for these patients.[7 8] Within our cohort, a significant difference was seen in the clinical efficacy of CGRP mAbs in patients who reported no headache-free days at baseline, and with the number of previously trialled preventative medications, highlighting the need for further treatment options in this cohort. In keeping with the work of Alpuente *et al*,[9] age and previous exposure to onaB-A had no association with efficacy. This may relate to the differential mechanism of action of the two therapies, with onaB-A preventing activation of unmyelinated C-fibres, and CGRP mAbs acting via thinly myelinated Aδ-fibres.[10] The clinical data on adults over the age of 70 years remain sparse, however.

There was no statistically significant difference in the response rate, or continuation of fremanezumab and galcanezumab, however there was significantly fewer patients commenced on fremanezumab in the study period. We found poor agreement between the ≥50% responder rate at 3 and 12 months, suggesting that further studies with later response assessments and evaluation of the positive/negative predictive value of 3-month efficacy assessments are required.

Our study highlights the limitation of assessing clinical response at 3 months, which has also been reported recently by Barbanti *et al*, who reported that half of CGRP mAb non-responders at 12 weeks were in fact late responders.[11] Within our cohort, due to regulatory requirements which required patients that did not achieve a ≥50% reduction in MMD to cease therapy, we were unable to accurately assess the true proportion of patients who may have been late-responders. Similarly, the 12-month responder rate is difficult to interpret due to the proportion of patients who are discontinued due to either lack of efficacy at 3 months or for other factors (eg, pregnancy).

The efficacy of a receptor-targeting CGRP mAb (erenumab) was not assessed due to local availability. The relative efficacy of CGRP mAbs is of interest to treating clinicians, and in our study, we found no difference between fremanezumab and galcanezumab. In an open-label study, Overeem *et al* reported efficacy of erenumab in patients who had not responded to fremanezumab or galcanezumab after 3 months.[12] Whether there is a differential response in some patients to receptor-targeting therapy, or whether the findings by Overeem *et al* are a

further example of late response to CGRP mAbs, requires specific study.

The adverse event rate leading to cessation of treatment in this cohort was 16%. While higher than reported in shorter phase II–phase III studies, similar rates of discontinuation have been reported by other groups over similar time frames.[13 14] Cullum *et al* reported a cohort of 300 patients treated with erenumab from the Danish Headache Centre, and found a discontinuation rate of 13.7%.[13] Other groups however, have reported lower rates.[15] The reason for such variability in continuation rates is not clear.

The majority of reported adverse events were not out of keeping with the mechanism of action or previously reported side-effect profiles of CGRP mAbs,[1 16] further highlighting the need for informed and shared clinical decision making. The reported side effect of worsened depression and anxiety, although rare, warrants careful observation given patients with significant mental health disorders were excluded from the clinical trials.

This study compares favourably with similar studies in other academic centres. Argyriou *et al*, who also reported a cohort of patients with at least three preventative treatment failures, reported a ≥50% reducation in MHD at 3 months of 62.6%, with similar reports by Cullum *et al*.[17 18] Iannone *et al* reported lower rates of treatment continuation at 12 months compared with our cohort.[19] The reported adverse event rate varies in the literature between 19.5% and 73.3%,[2 13 20] with similar reported events.

There are several limitations to this study. First, as patients are required by local regulators to achieve a 50% reduction in MMD at 3 months to continue treatment,[5] this may have biased reporting. Furthermore, evaluation of MHD rather than MMD limits the assessment of efficacy in patients who improve their migraine days but continue to experience background headaches, clinically, this is of particular relevance in patients who experience migraine with continuous headache. Also, as non-responders are transitioned to other therapies, this falsely inflates the response rate of those continuing treatment. Previously trialled preventative treatments, which was associated with reduced clinical response, is likely a surrogate marker for duration of disease which was not recorded; this has previously been reported as a predictor of response in onaB-A[3] and requires further consideration with respect to CGRP mAbs. Finally, differentiation between failure of previous preventative treatment due to efficacy or tolerability was not possible.

CONCLUSION

CGRP mAbs were associated with significant and sustained reductions in MHD over 12-month follow-up in patients with chronic migraine. There was poor agreement between 3-month and 12-month clinical response, highlighting the need for further evaluation of this as the determinant of efficacy by regulators. Further clinical studies are required to explore the utility of 3-month outcome measures, and the efficacy and safety of CGRP mAbs in select subgroups.

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Patient consent for publication Not applicable.

Ethics approval This study received institutional review board approval (HREC Alfred: 727/21, Austin: 22/Austin/08).

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