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Medication underuse in real-life practice: the impact of galcanezumab towards achieving very low frequency episodic migraine in a southeast Asian middle-income nation

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Abstract

Background Migraine progression, particularly from episodic to chronic migraine (CM), increases disease burden and healthcare costs. Understanding the new concept of "Medication Underuse Headache" should encourage the health care provider to consider early intervention with calcitonin gene-related peptide (CGRP) monoclonal antibodies. Galcanezumab given early in the course of the disease, may prevent migraine chronification and have a robust response, moreso than when initiated in later stages of migraine. We aimed to determine the efficacy of galcanezumab in achieving very low-frequency episodic migraine (VLFEM) among patients with high-frequency episodic migraine (HFEM) and CM in a real world-setting in Thailand.

Methods A single-center, retrospective real-world, cohort study was conducted between 2023 and 2024. Adults aged 18 years or more who were diagnosed with HFEM or CM were included in this trial and categorized into two groups: galcanezumab and oral migraine preventive medication (OMPM). In the galcanezumab group, oral preventive medications were slowly tapered off within 3 months. The primary outcome was the differences in percentage of patients achieving VLFEM at months 3 and 6 between the two groups. Secondary outcomes included the differences in migraine class improvement, sustained response, and headache day reduction.

Results A total of 62 patients (31 in each group) were included: median age was 36.5 (IQR: 29.0–48.0) and 82% were female. There were no significant differences in the baseline demographic features between the two groups. The cumulative incidence of patients achieving VLFEM was significantly higher among the galcanezumab group compared to OMPM group (45.2% vs. 19.4% at month 3 and 52.9% vs. 32.4% at month 6, $p=0.03$). After 6 months of follow-up, patients with HFEM who received galcanezumab were significantly more likely to achieve any improvements in migraine class compared to those who received OMPM (92.9% vs. 46.7%, $p=0.01$). Among 15 patients who achieved VLFEM at month 3, 81.8% (9/11) of those who received galcanezumab and 50.0% (2/4) of those who received OMPM were able to sustain VLFEM at month 6.

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Conclusions This study emphasizes the benefit of early anti-CGRP therapy initiation, especially in patients with fewer headache days, and highlights the need for accessible migraine-specific treatments in low- to middle-income countries.

Keywords Medication underuse headache, Galcanezumab, Very low frequency episodic migraine, Preventive medication

Introduction

The chronification of episodic migraine leads to chronic migraine (CM) if it is not halted. This progression not only results in more headache days per month, but also substantially increases the overall burden of the disease, exacerbates the psychiatric and other comorbidities, and increases healthcare costs and consumption, all compared to episodic migraine (EM) [1–3]. Migraine is the second most common cause of disability, accounting for 45.1 million years lived with disability (YLD) globally, representing 5.6% of the global disease burden [4]. Additionally, CM incurs three times the direct and indirect costs in terms of economic loss compared to EM [5]. Among EM patients, those with high-frequency episodic migraine (HFEM: 8–14 headache days per month) carry a higher burden and a greater likelihood of progressing to CM than those with low-frequency episodic migraine (LFEM: 4–7 headache days per month). Furthermore, individuals with very low-frequency episodic migraine (VLFEM: fewer than 4 headache days per month) have the lowest risk of transforming from EM to CM [6]. Therefore, current treatment strategies emphasize intervention during the episodic stage of migraine to prevent chronification.

Recently, we published a review article on 'medication underuse headache', a term that underscores the importance of optimizing headache management to avoid inadequate control of headache frequency and severity. The concept suggests that inadequate dosing, inefficiency, incorrect timing, and intolerability of medication could potentially contribute to the chronification of migraine and probably medication overuse headache as well. Therefore, selecting the right medication at the right time is crucial. In preventive treatment strategies, we propose that early initiation of migraine-specific medication could help prevent the progression of the disease; however, there is still limited data to support this concept [7]. The term 'medication underuse headache' is introduced in this manuscript as a conceptual framework to highlight gaps in the adequacy of migraine treatment. It is not intended to represent a formal diagnostic entity or to promote any specific therapeutic approach.

Calcitonin gene-related peptide (CGRP) is a neuropeptide that plays a crucial role in the pathophysiology of migraine. Recently, in some countries, 4 monoclonal antibodies to either the CGRP ligand or receptor, have been approved for migraine prevention. Galcanezumab, a humanized immunoglobulin G4 monoclonal antibody that binds to CGRP, has shown strong evidence for migraine prevention, supported by randomized controlled trials and real-world studies from various countries. Post-hoc analyses from previous phase 3 clinical trials of galcanezumab have demonstrated evidence of early onset of efficacy, with a reduction in migraine headache days starting from the first week of treatment [8]. In 2022, the European Headache Federation and, in 2024, the American Headache Society endorsed CGRP monoclonal antibodies (mAbs) as first-line options for migraine prevention [9, 10]. The American Headache Society recommends that CGRP medications be considered as a first-line preventive treatment for patients experiencing 4 or more migraine days per month with at least moderate disability, defined by a MIDAS score of ≥11 or a HIT-6 score of >50 [10]. In Thailand, CGRP mAbs have been approved by the Thai Food and Drug Administration (FDA) for migraine prevention since 2019 [11]. However, the majority of Thai patients cannot receive reimbursement for CGRP-based treatments through either public coverage or private insurance, creating a significant barrier and contributing to the concept of medication underuse in the country. Additionally, the Thai Headache Society guidelines mandates that the initiation of such medication is allowed only after the patient experiences at least 8 headache days per month and has failed two or more classes of migraine preventive treatments. This has led to delayed preventive management.

Our primary objective was to determine the efficacy of galcanezumab in achieving VLFEM among patients with HFEM and CM in a real world-setting in Thailand. Other objectives include exploring the differences in migraine class improvement, sustained response, and headache day reduction between those who received galcanezumab and those who only received oral migraine preventive medication that is not gepants (OMPM). The findings from our study will serve as the first proof of concept in Thailand to shed light on the timing and efficacy of CGRP mAbs therapy in middle-income migraine patients, addressing the issue of medication underuse.

Method

Study design and setting

This analysis is a single-center, retrospective, real-world, cohort study. We conducted an electronic chart review study on migraine patients who attended the

comprehensive headache and orofacial pain (CHOP) clinic at King Chulalongkorn Memorial Hospital (KCMH), The Thai Red Cross Society, Bangkok, Thailand, between January 2019 and July 2024.

Study participants

In the galcanezumab group, we included all participants, ages 18 years or above, who were diagnosed with migraine by headache-specialized neurologists according to the diagnostic criteria of the ICHD-3; each was treated with galcanezumab for at least 6 months. The CGRP mAb therapy was applied following the Thai migraine guideline, which recommends CGRP mAbs for patients with migraine who have at least 8 migraine days per month and show insufficient effectiveness or intolerance to at least two classes of conventional oral migraine preventives for at least 6 weeks; this could include tricyclic antidepressants, antiseizure medication, beta-blockers, or calcium channel blockers [11]. Patients whose data were unavailable for at least 6 months of CGRP mAb treatment were excluded. Galcanezumab was administered with a loading dose of 240 mg subcutaneously in the first month, followed by a monthly maintenance dose of 120 mg. In the galcanezumab group, oral preventive medications were slowly tapered off within 3 months.

In the reference group (OMPM), we included age-, sex-, and migraine class-matched participants aged 18 years or above who were diagnosed with migraine by headache-specialized neurologists according to the diagnostic criteria of the ICHD-3 and had not received anti-CGRP therapy during the initial 6 months follow-up period. Patients with less than 6 months of available follow-up data were excluded. Preventive medications were administered at the maximum tolerable dose.

Both groups of patients included in the study had to follow up monthly or at least trimonthly with a headache specialist at our clinic to evaluate the clinical data and refill the medications.

Definition of migraine class

In this study, we defined the migraine class according to the following range: 1. Very low-frequency episodic migraine (VLFEM) - having 0–3 headache days per month; Low-frequency episodic migraine (LFEM) - having 4–7 headache days per month; High-frequency episodic migraine (HFEM) - having 8–14 headache days per month and Chronic migraine (CM) - having ≥ 15 headache days per month [12, 13].

Clinical evaluation and outcomes

We retrospectively collected information on demographic characteristics, comorbidities, headache characteristics, baseline migraine days, and both prior and current acute care and preventive drugs, including the type and number of pills at baseline. Patients were instructed to fill out a paper-based daily headache diary to record the duration and intensity of pain, associated symptoms, and the type and number of acute medication pills used. All headache diaries were submitted to the physicians at each visit and uploaded into the electronic medical record (EMR) for review. Patients were also asked to complete the Thai version of the Migraine Disability Assessment (MIDAS) questionnaire [34] at the initiation of galcanezumab, as well as at the 3rd and 6th months following the start of therapy. For those on OMPM, patients were asked to complete the MIDAS questionnaire at the beginning of the consultation and every three months thereafter. The baseline period in this study is defined as follows: for the galcanezumab group, it is the date of initiation of galcanezumab, and for the OMPM group, it is the date of initiation of preventive medication. The primary outcome was to investigate the percentage of patients achieving VLFEM at the 3rd and 6th months comparing patients in the galcanezumab group and the OMPM group. Our secondary outcomes included: (1) the percentage differences between the galcanezumab and the OMPM group in achieving a different migraine class; (2) the percentage difference in achieving VLFEM between HFEM and CM between the two groups; (3) the trend in reduction of headache days between the two groups; (4) the percentage difference in sustaining VLFEM between the two groups.

Ethical approval

This study was approved by the Institutional Review Board Research Ethics Committee (IRBREC) of the Faculty of Medicine, Chulalongkorn University, Bangkok, and KCMH in October 2023 (IRB number 706/2023). The approval of retrieving retrospective data from electronic medical records (EMR) was made and informed consent was waived by IRBREC. All methods were carried out following relevant guidelines and regulations.

Statistical analysis

Demographic characteristics, comorbidities, headache features, and medication use were summarized using the median with interquartile range (IQR) for continuous variables and number with percentage for categorical variables. Comparisons between galcanezumab and OMPM groups were conducted using the Wilcoxon rank-sum test and Chi-square or Fisher's exact test as appropriate. Kaplan-Meier plots were used to show the proportion of participants achieving VLFEM, with the log-rank test used to determine the differences between the two groups. A multivariable Cox proportional hazard model, adjusted for age, sex assigned at birth (male/female), and comorbidities (yes/no), and baseline migraine class (HFEM/CM), was used to assess

the association between galcanezumab use and the primary outcome. Sankey diagrams were used to illustrate changes in migraine class from baseline to months 3 and 6. Statistical significance was defined as $p = < 0.05$. All analyses were performed using Stata 17.0 (Stata Corp, College Station, TX).

Results

A total of 62 patients (31 in the galcanezumab group and 31 in the OMPM group) were included in the study. The baseline characteristics are displayed in Table 1. The median age among all participants was 36.6 years (IQR: 29.0–48.0), and 51 (82%) were female. Mean monthly migraine days were 12.5. Myofascial pain syndrome was the most common comorbidity (24%), followed by depression (23%) and anxiety (9%). The overall median MIDAS score was 27.5 (IQR: 13–60). The most common acute medication used were NSAID (46.8%), acetaminophen (25.8%) and triptan (22.6%), respectively. The most commonly used preventive medications were tricyclic antidepressants (29%), beta-blockers (18%), and antiseizure medications (15%), respectively. In terms of headache classification, 47% of patients had HFEM, while 53% had CM. There were no statistically significant differences in baseline characteristics between the two groups.

Responder rate in achieving VLFEM

The cumulative incidence of participants achieving VLFEM increased over time in both the OMPM and galcanezumab groups (Fig. 1). Kaplan-Meier analysis showed that patients initiating galcanezumab had significantly higher conversion rates to VLFEM compared to OMPM: 29.0% vs. 6.5% at month 1, 45.2% vs. 19.4% at month 3, and 52.9% vs. 32.4% at month 6 ($p = 0.03$). In a subgroup analysis by baseline migraine class, patients with HFEM receiving galcanezumab had significantly higher rates of achieving VLFEM compared to OMPM: 50.0% vs. 6.7% at month 1, 78.6% vs. 33.3% vs. month 3, and 85.7% vs. 40.0% at month 6 ($p < 0.001$) (Fig. 2A). There were no significant differences among patients

Table 1 Baseline characteristics of all 62 participants

	Overall (*N* = 62)	Galcanezumab (*N* = 31)	OMPM (*N* = 31)	*P*
Age (years)	36.5 (29.0–48.0)	35.5 (28.8–50.4)	37.2 (29.0–45.7)	0.87
Sex				0.74
Female	51 (82%)	26 (84%)	25 (81%)	
Male	11 (18%)	5 (16%)	6 (19%)	
Comorbidities				
Depression	14 (23%)	7 (23%)	7 (23%)	> 0.99
Anxiety	9 (15%)	4 (13%)	5 (16%)	> 0.99
Myofascial pain syndrome	24 (39%)	12 (39%)	12 (39%)	> 0.99
Fibromyalgia	3 (5%)	2 (6%)	1 (3%)	> 0.99
Obstructive sleep apnea	2 (3%)	0 (0%)	2 (6%)	0.49
Headache frequency per month	12.5 (10.0–21.0)	12.0 (8.0–21.0)	15.0 (10.0–22.0)	0.32
MIDAS	27.5 (13.0–60.0)	30.0 (14.0–79.0)	25.0 (13.0–50.0)	0.30
Acute medications at baseline				
Acetaminophen	16 (25.8%)	8 (25.8%)	8 (25.8%)	> 0.99
NSAID	29 (46.8%)	18 (58.1%)	11 (35.5%)	0.08
Tramadol	2 (3.2%)	1 (3.2%)	1 (3.2%)	> 0.99
Triptan	14 (22.6%)	5 (16.1%)	9 (29.0%)	0.22
Ergot	5 (8.1%)	3 (9.7%)	2 (6.5%)	> 0.99
Preventive medications at baseline				
Tricyclic antidepressants	18 (29%)	7 (23%)	11 (35%)	0.26
Beta-blockers	11 (18%)	4 (13%)	7 (23%)	0.32
Antiseizure medications	9 (15%)	6 (19%)	3 (10%)	0.47
Calcium-channel blocker	4 (6.5%)	0 (0%)	4 (12.9%)	0.11
Migraine Class				> 0.99
HFEM	29 (47%)	14 (45%)	15 (48%)	
CM	33 (53%)	17 (55%)	16 (52%)	

All continuous variables are displayed as median (IQR)

Abbreviations: CM: chronic migraine; HFEM: high-frequency episodic migraine; MIDAS: Migraine Disability Assessment; OMPM: oral migraine preventive medication

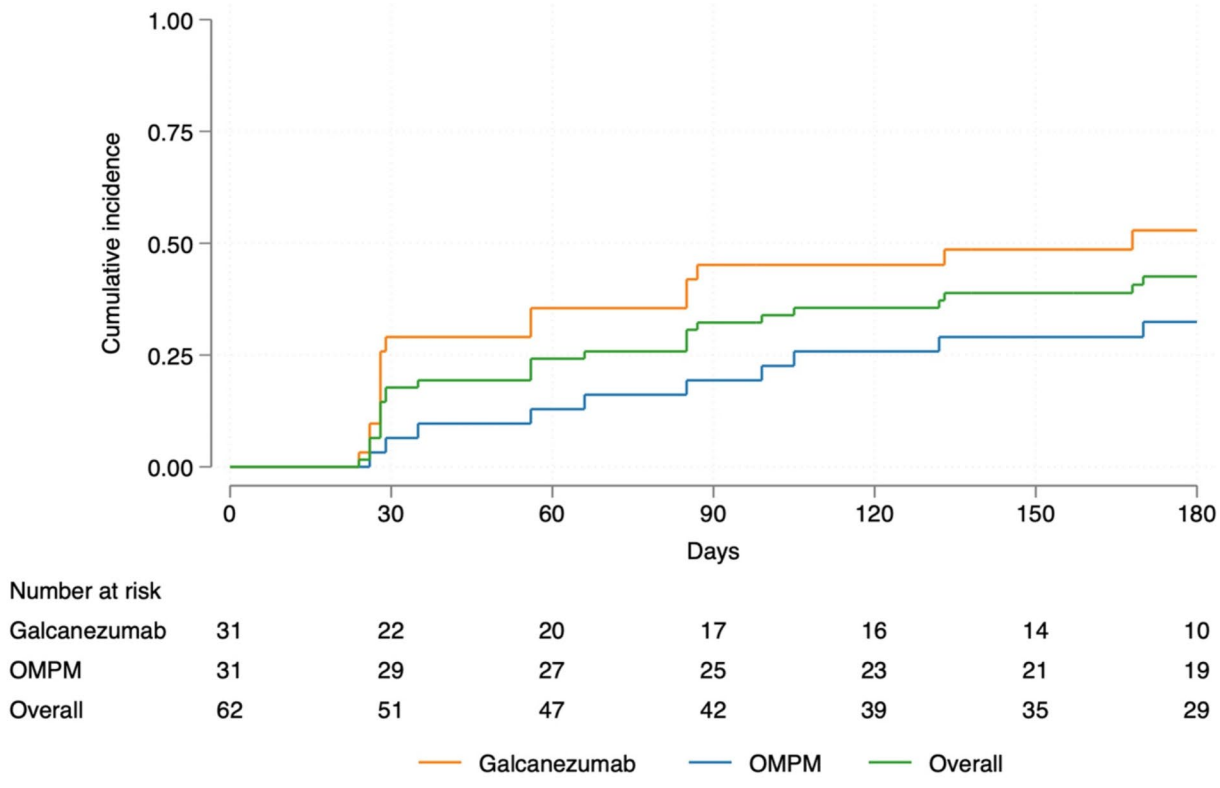

Fig. 1 Kaplan-Meier plots showing the cumulative incidence of patients achieving VLFEM among galcanezumab group (orange line), OMPM group (blue line), and overall (green line) over 6 months follow-up period
Abbreviation: OMPM: oral migraine preventive medication; VLFEM: very low-frequency episodic migraine

with CM at baseline (Fig. 2B). A multivariable Cox proportional hazards model showed galcanezumab use was significantly associated with higher rates of achieving VLFEM (adjusted odds ratio [aOR] 3.55; 95%CI 1.56–8.04, $p = 0.002$).

Improvements in migraine classes categorized by baseline diagnosis

Patients with CM in both the galcanezumab and OMPM groups had similar proportion achieving VLFEM at month 3 (11.8% [2/17] vs. 12.5% [2/16]). However, the difference was more pronounced among those with HFEM (64.3% [9/14] vs.13.3% [2/15]) (Fig. 3). A similar trend was observed at 6 months, with 23.5% [4/17] of galcanezumab group with CM and 25% [4/16] of OMPM group with CM at baseline achieving VLFEM, and 64.3% [9/14] of the galcanezumab group with HFEM and 20.0% [3/15] of OMPM group with HFEM at baseline achieving VLFEM.

Importantly, the galcanezumab group showed a higher proportion of patients with improvement in their migraine classes from baseline compared to OMPM group at both 3 and 6 months. At month 3, 64.5% [20/31] of patients receiving galcanezumab had improvements, including 85.7% [12/14] of those with HFEM and 47.1% [8/17] of those with CM, compared to 51.6% [16/31] of patients receiving OMPM, with 60.0% [9/15] of those with HFEM and 43.8% [7/16] of those with CM. At month 6, 77.4% [24/31] of the galcanezumab group had improvements in their migraine class, with 92.9% [13/14] of HFEM and 64.7% [11/17] of CM, compared to 58.1% [18/31] in the OMPM group, with 46.7% [7/15] of HFEM and 68.8% [11/16] of CM (Table 2).

Changes in migraine classes categorized by baseline diagnosis

For patients with HFEM at baseline, a higher proportion of the galcanezumab group transitioned to VLFEM at month 3 (64.3% vs. 13.3% in the OMPM group). Fewer patients in the galcanezumab group shifted to LFEM (21.4% vs. 46.7%) or remained in HFEM (14.3% vs. 20%). By month 6, this trend continued, with more patients in the galcanezumab group achieving VLFEM (64.3% vs. 20% in the OMPM group). Transitions to LFEM were more balanced (28.6% for galcanezumab vs. 26.7% for OMPM), while fewer patients receiving galcanezumab remained in HFEM (7.1% vs. 26.7%). Notably, none of the patients with HFEM at baseline who received

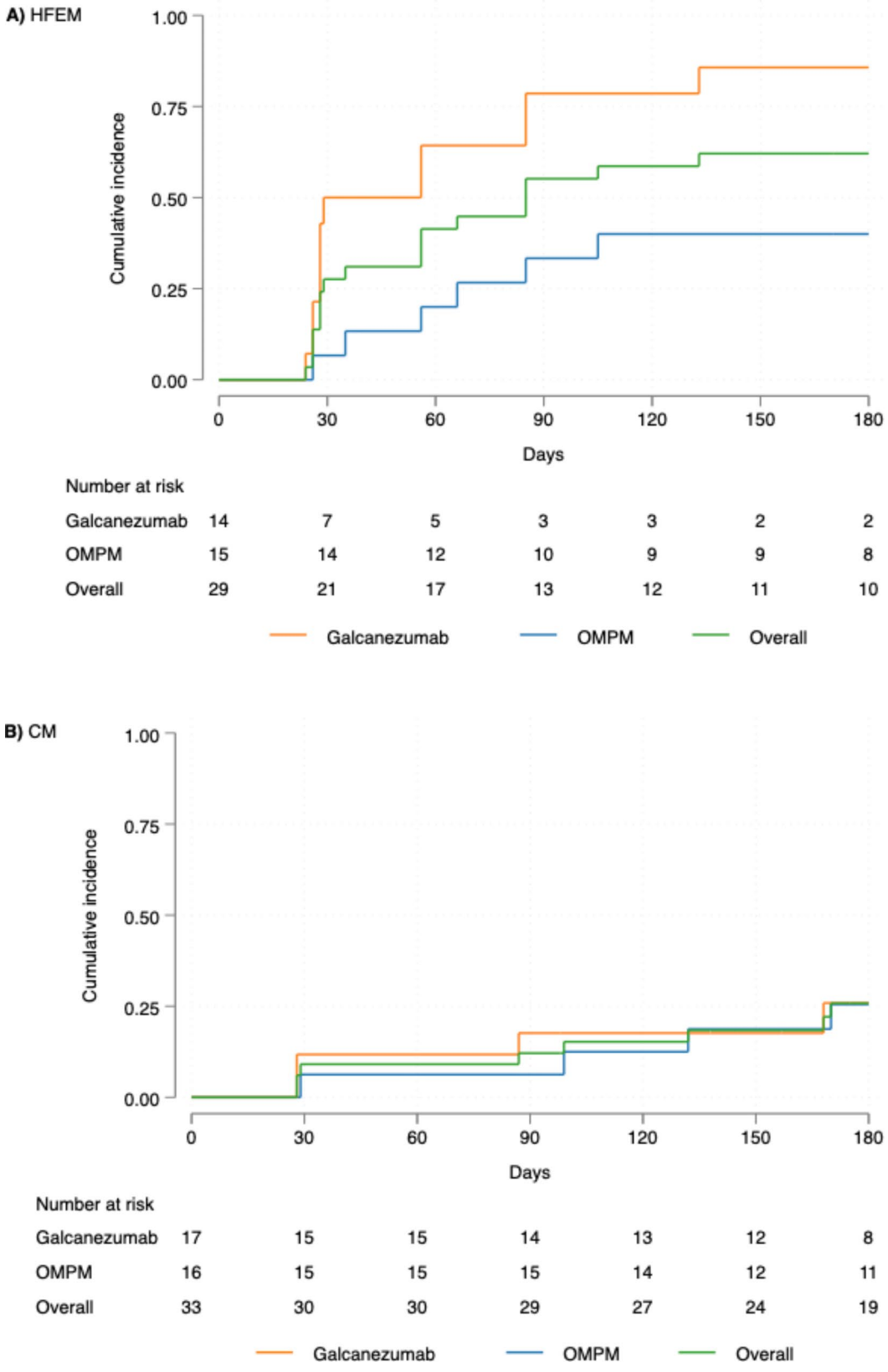

Fig. 2 Kaplan-Meier plots showing the cumulative incidence of participants achieving VLFEM among galcanezumab group (orange line), OMPM group (blue line), and overall (green line) over 6 months follow-up period categorized by baseline migraine class: (**A**) HFEM; (**B**) CM
Abbreviation: CM: chronic migraine; HFEM: high-frequency episodic migraine; OMPM: oral migraine preventive medication; VLFEM: very low frequency episodic migraine

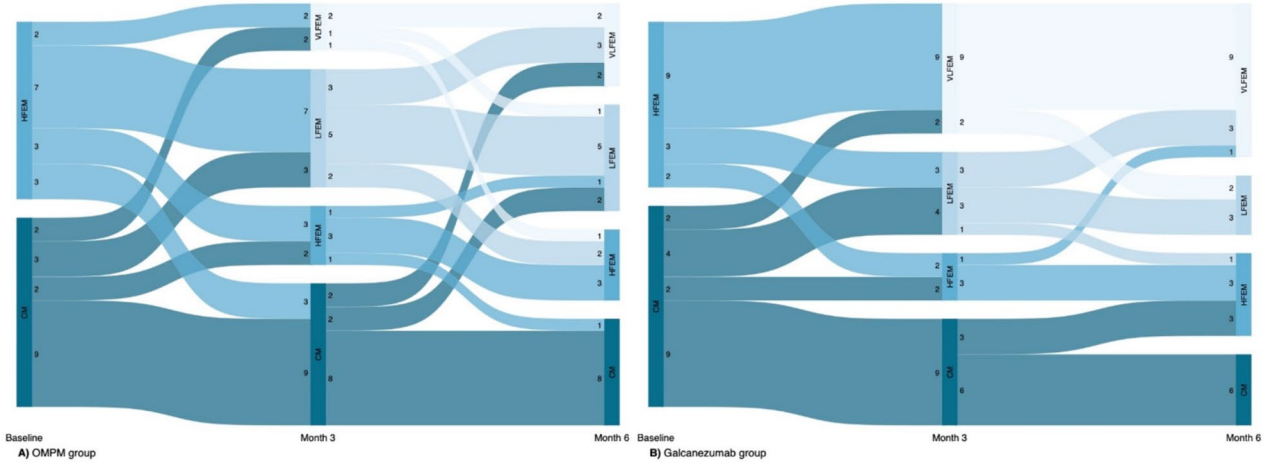

Fig. 3 Sankey diagrams illustrating changes in migraine class from baseline to months 3 and 6: (**A**) Galcanezumab group; (**B**) OMPM group
Abbreviation: CM: chronic migraine; HFEM: high-frequency episodic migraine; LFEM: low-frequency episodic migraine; OMPM: oral migraine preventive medication; VLFEM: very low-frequency episodic migraine

Table 2 Proportion of participants with any improvements in migraine class from the baseline diagnosis at months 3 and 6

	Galcanezumab	OMPM	*p*
Overall	*N* = 31	*N* = 31	
Month 3	20 (64.5%)	16 (51.6%)	0.30
Month 6	24 (77.4%)	18 (58.1%)	0.10
HFEM	*N* = 14	*N* = 15	
Month 3	12 (85.7%)	9 (60.0%)	0.22
Month 6	13 (92.9%)	7 (46.7%)	0.01*
CM	*N* = 17	*N* = 16	
Month 3	8 (47.1%)	7 (43.8%)	> 0.99
Month 6	11 (64.7%)	11 (68.8%)	> 0.99

* $p < 0.05$

Abbreviations: CM: chronic migraine; HFEM: high-frequency episodic migraine; OMPM: oral migraine preventive medication

galcanezumab progressed to CM (0% vs. 20.0% at month 3; 0% vs. 26.7% at month 6) (Fig. 4A and B).

For patients with CM at baseline, both groups showed similar patterns of transitioning to different migraine classes at month 3: 11.8% of the galcanezumab group and. 12.5% of the OMPM group transitioned to VLFEM; 23.5% and 18.8% transitioned to LFEM; 11.8% and 12.5% transitioned to HFEM; while 52.9% and 56.2% remained in CM, respectively. By month 6, a higher proportion of patients with CM at baseline in both groups transitioned to VLFEM (23.5% for galcanezumab vs. 25% for OMPM). However, fewer patients in the galcanezumab group shifted to LFEM (5.9% vs. 31.2% for OMPM), while more shifted to HFEM (35.3% vs. 12.5% for OMPM). Both groups showed a similar percentage of those remaining in CM (35.3% vs. 31.2% for OMPM) (Fig. 5A and B).

The trend in reduction of headache days between OMPM and galcanezumab group

Figure 6 shows a comparison of the trend in the reduction of migraine headache days between the OMPM and galcanezumab groups. The key finding is the slope of the graph. In the galcanezumab group, a linear decrease in the number of headache days was observed, with a sustained reduction in migraine headache days. In contrast, the OMPM group exhibited a more fluctuating response without sustained improvement.

Sustaining VLFEM between OMPM and galcanezumab group

A total of 15 patients achieved VLFEM at month 3: 11 from the galcanezumab group and 4 from the OMPM group. Among the galcanezumab group, 9 patients (81.8%) were able to sustain VLFEM through month 6. In contrast, only 2 patients (50.0%) in the OMPM group maintained VLFEM from month 3 to month 6.

Comparison in achieving VLFEM between HFEM and CM in the Galcanezumab group

In the galcanezumab group, patients with HFEM were more likely to achieve VLFEM than those with CM at both month 3 and month 6 (78.6% vs. 17.8% and 85.7% vs. 25.9%, respectively, $p < 0.001$). These findings strongly support the notion that early initiation of galcanezumab could lead to better outcomes (Fig. 7).

Discussion

To the best of our knowledge, this paper is the first to compare anti-CGRP therapy with OMPM in low- to middle-income countries. It is also the first to illustrate the concept of "medication underuse headache,"

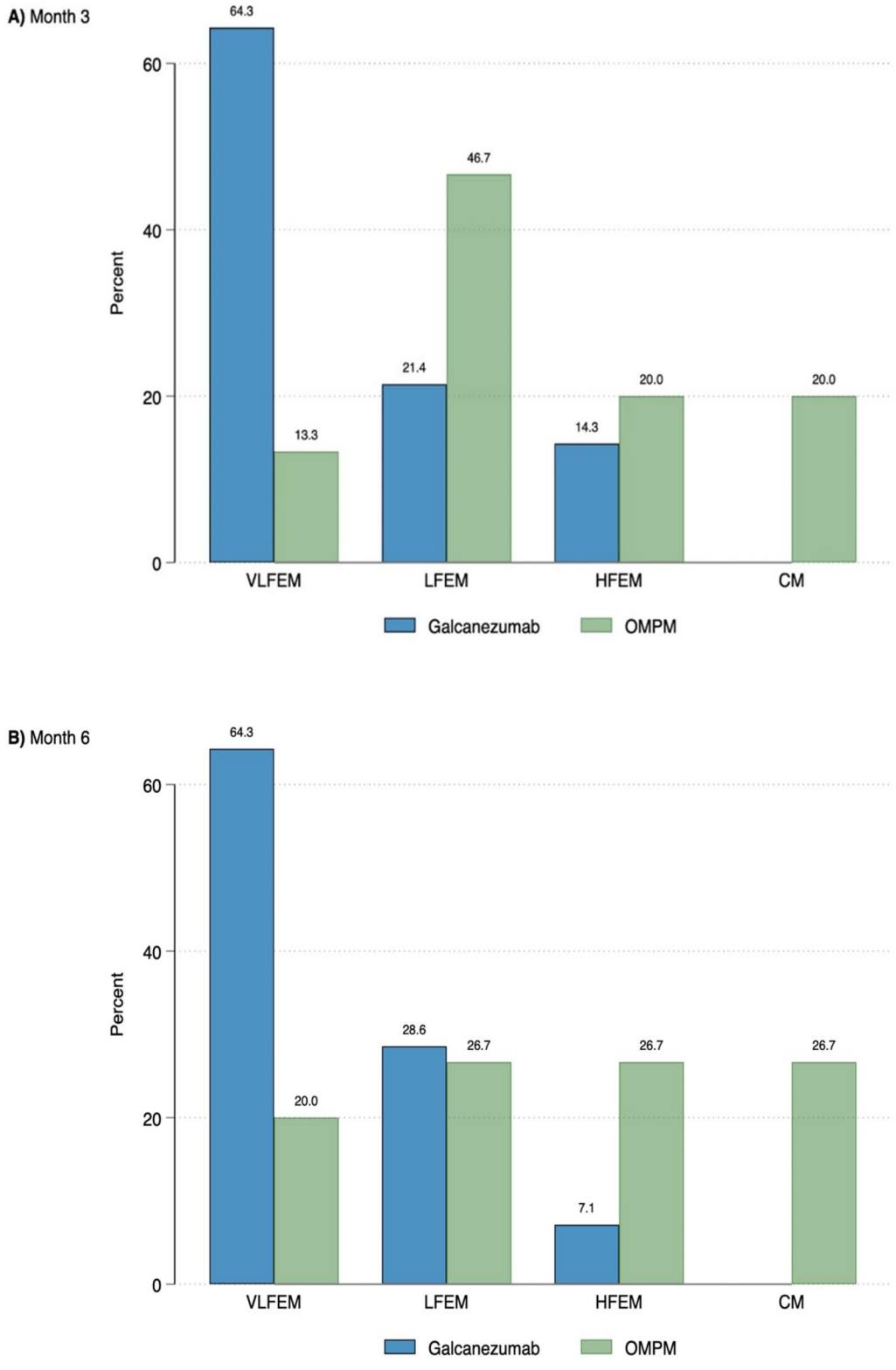

Fig. 4 Migraine class among those with HFEM at baseline at month 3 (**A**) and month 6 (**B**) after follow-up
Abbreviations: CM: chronic migraine; HFEM: high-frequency episodic migraine; LFEM: low-frequency episodic migraine; OMPM: oral migraine preventive medication; VLFEM: very low-frequency episodic migraine

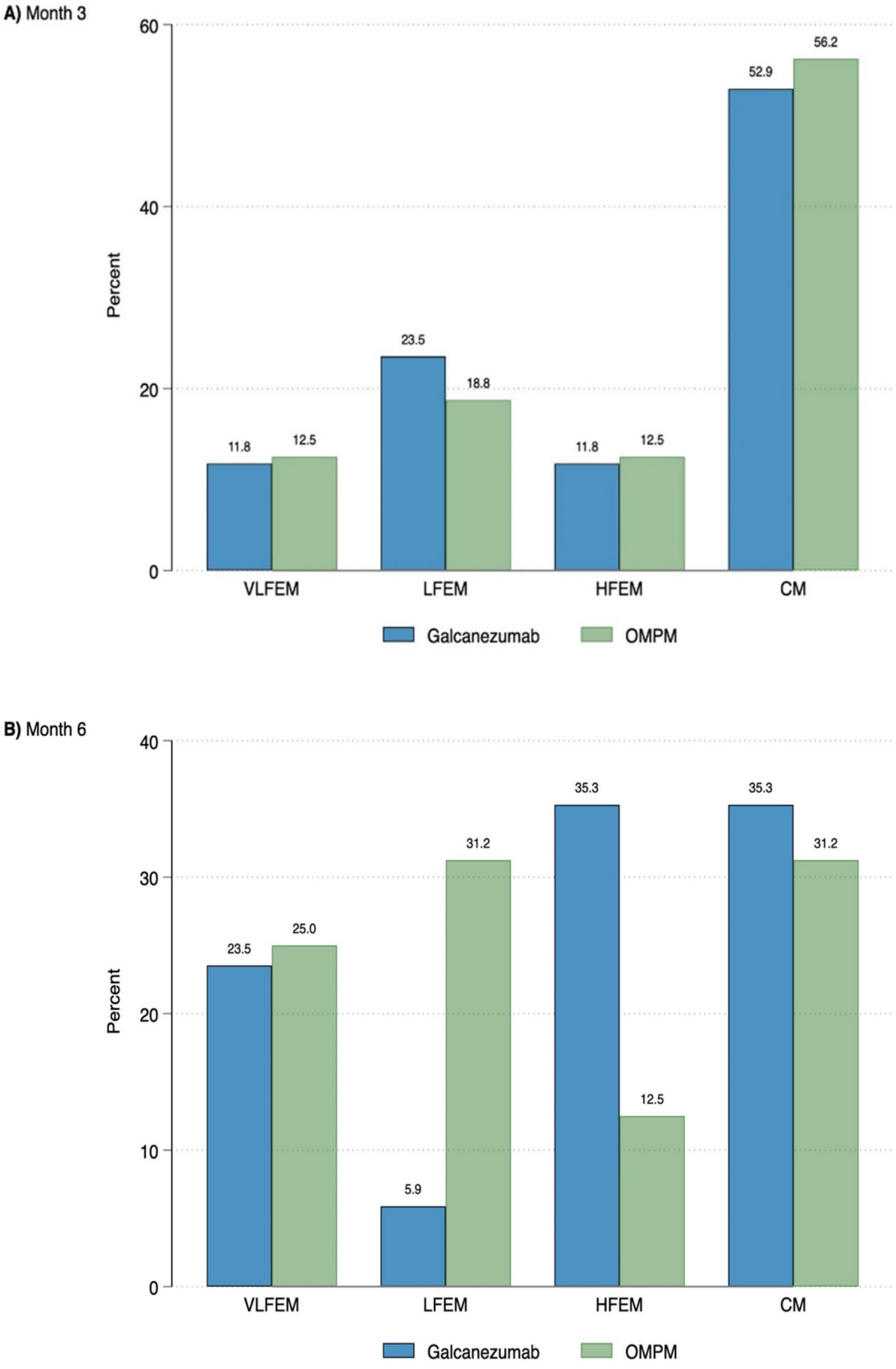

Fig. 5 Migraine class among those with CM at baseline at month 3 (**A**) and month 6 (**B**) after follow-up
Abbreviations: CM: chronic migraine; HFEM: high-frequency episodic migraine; LFEM: low-frequency episodic migraine; OMPM: oral migraine preventive medication; VLFEM: very low-frequency episodic migraine

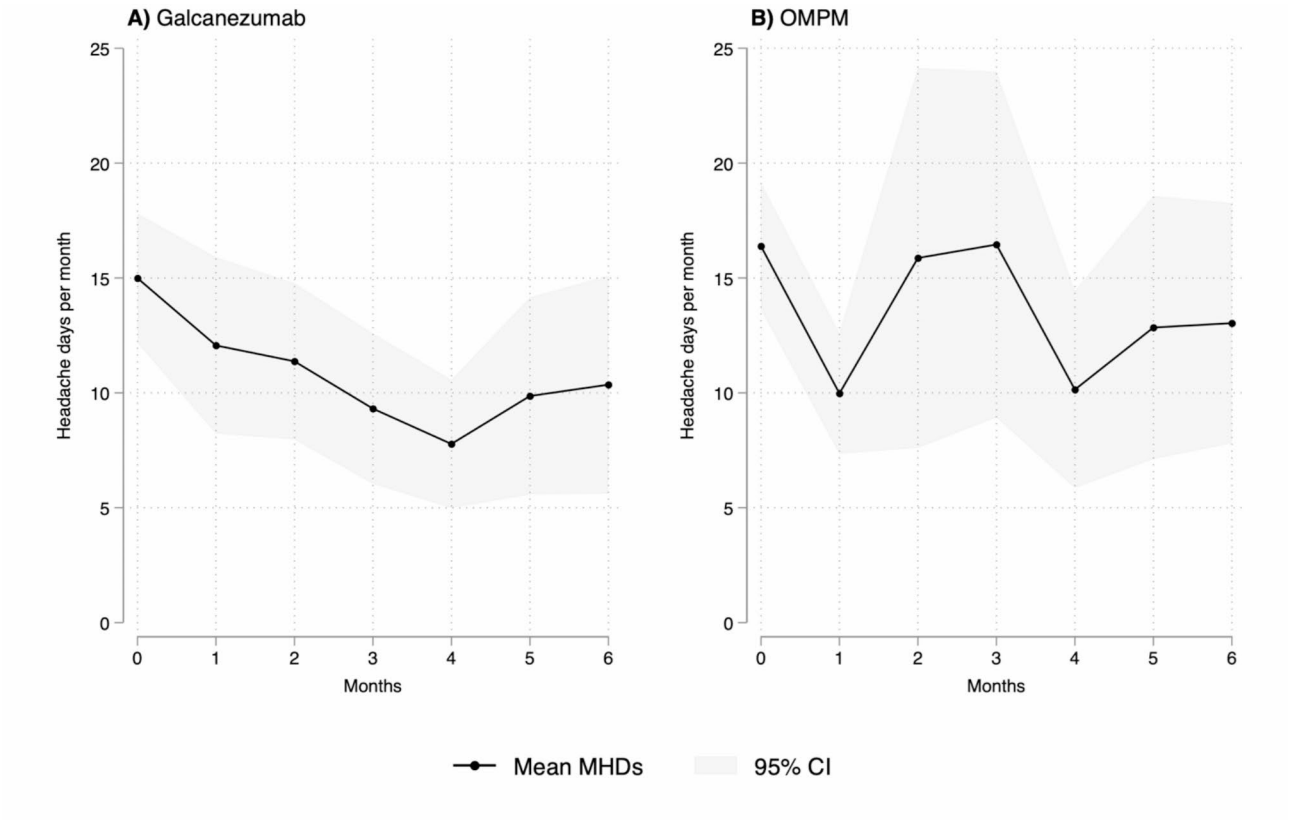

Fig. 6 Mean changes in monthly headache days with 95%CI categorized by the two groups: (**A**) Galcanezumab; (**B**) OMPM
Abbreviation: MHDs: monthly headachy days; OMPM: oral migraine preventive medication

demonstrating that initiating treatment early is more beneficial than waiting until the headache becomes chronic [7]. Our key findings are as follows: (1) Patients who initiated galcanezumab had significantly higher rates of achieving VLFEM compared to those on OMPM. (2) Among patients using galcanezumab, those with HFEM had a significantly higher rate of achieving VLFEM compared to those with CM. (3) In patients with CM, both treatment groups showed poor outcomes in achieving VLFEM. (4) Galcanezumab resulted in a more sustained decrease in migraine headache days compared to the fluctuating pattern observed with OMPM. However, it is important to note that "medication underuse headache" is presented as a conceptual tool to underscore the clinical importance of ensuring optimal migraine treatments. This concept is not formally defined as a diagnostic entity and is solely intended to enhance clinical awareness and encourage improved management strategies.

Current findings suggest that patients experiencing HFEM and CM have a higher disease burden compared to those with LFEM and VLFEM [14–17]. In this context, we believe that reporting the decrease in the number of headache days may not fully capture the true disability and pain experienced by patients, as most studies have indicated. Although the criteria for classifying EM have not yet been firmly established, we suggest the benefit of such classification. Nonetheless, reaching LFEM or even VLFEM for a certain period might be beneficial when deciding to stop the medication [18, 19]. This process might be due to the reverse process of hyperexcitability and brain changes caused by preventive medications [20–23].

Our study supports the use of migraine-specific medications such as anti-CGRP therapy (e.g. galcanezumab) as the treatment of choice for migraine patients. While OMPM has shown some improvement, galcanezumab demonstrated a more substantial reduction in achieving VLFEM. Our findings align with previous studies comparing anti-CGRP therapies to OMPM. For example, in the HER-MES study, erenumab significantly reduced migraine headache days compared with topiramate [24, 25]. The proposed mechanism is attributed to its high affinity for the CGRP receptor and its specificity to migraine pathophysiology, which leads to a greater therapeutic response. However, due to its high cost and lack of affordability, particularly in low- to middle-income countries, this has become an unmet need and has led to medication underuse in our regions [26]. Additionally, economic analysis looking at direct and indirect costs is lacking in this region.

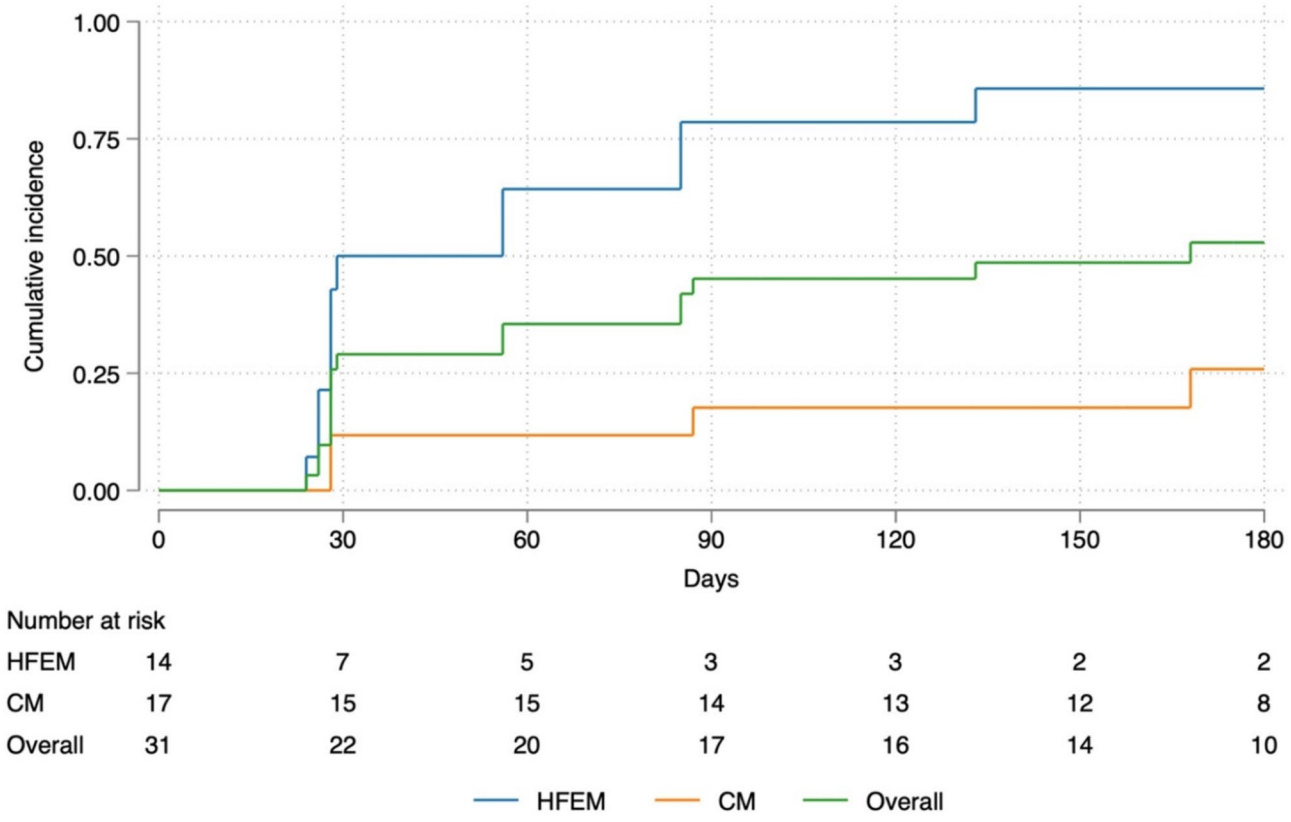

Fig. 7 Kaplan-Meier plots showing the cumulative incidence of participants achieving VLFEM among galcanezumab group, categorized by baseline migraine class: HFEM (blue line), CM (orange line), and overall (green line) over 6 months follow-up period
Abbreviation: CM: chronic migraine; HFEM: high-frequency episodic migraine; VLFEM: very low-frequency episodic migraine

Another key perspective of this study is that initiating anti-CGRP therapy when patients have a lower number of migraine headache days leads to a greater likelihood of achieving VLFEM compared to those with CM. In line with previous studies, growing evidence suggests that early initiation of anti-CGRP therapy, when headache days are fewer, could result in better treatment outcomes [27–29]. Although the eligibility criteria for initiating anti-CGRP therapy in Thailand are currently limited to patients with HFEM and CM, we believe that starting treatment in those with LFEM would offer greater benefits, better control, and sustained outcomes for patients [30]. We therefore call for a change in the Thai guideline and the reimbursement issues in Thailand. Interestingly, our findings show that in the CM group, achieving VLFEM is challenging, even with anti-CGRP therapy, and appears to be slightly more difficult compared to the OMPM group. This may be explained by multiple factors. Patients with CM may exhibit a longer history of headaches and a higher baseline disease burden, encompassing pronounced central sensitization and established pain pathways, which could reduce the relative efficacy of any preventive treatment, including CGRP antibodies [31]. The small sample size and retrospective nature of the study may also have reduced the statistical power to detect significant differences in outcomes for the CM group. In the Thai population, anti-CGRP therapy is typically prescribed only when migraine attack are very severe, which may contribute to these findings. This further emphasizes the potential benefit of early initiation of anti-CGRP therapy for better quality of care.

Sustained response is also a crucial outcome for patients with migraine. In our study, we demonstrated that patients receiving anti-CGRP therapy experienced a more sustained decrease in migraine headache days compared to those on OMPM. Similarly, a post-hoc analysis of the EVOLVE-1 and EVOLVE-2 trials found that 80% of patients who achieved VLFEM at month 3 were able to maintain it through month 6 [12]. Our findings are consistent with this result. Interestingly, the OMPM group shows a fluctuation in the number of headache days. This implies varying treatment responses without sustainability.

There are several limitations to our study. First, the small number of participants is a constraint; but given the low- to middle-income socioeconomic context of our country, we believe this is one of the few studies providing such data. Second, the retrospective nature of this

study may result in some missing parameters. We used the matched case-control retrospective study design to reduce the selection bias resulting in similar baseline characteristics between both groups. Third, due to the retrospective nature of the study and the limited follow-up duration, we were unable to demonstrate evidence supporting the role of early treatment in preventing migraine progression or chronification. A prospective study with a larger population and longer follow-up is needed to confirm the potential benefits of early intervention in reducing the risk of migraine chronification. Lastly, there is a potential for selection bias in treatment allocation due to patient preferences or financial barriers to accessing CGRP therapies. Poor socioeconomic status is a potential risk factor for migraine progression [32, 33], and this may have introduced some confounding effects in our results. However, it is worth noting that most patients receiving CGRP mAb in our study were eligible for direct medical cost reimbursement through their employee benefits, regardless of their position or rank within the organization. This likely mitigates the potential bias associated with individual socioeconomic status.

Conclusion

This is the first study in a low- to middle-income country comparing galcanezumab with OMPM. Our study underscores the importance of addressing "medication underuse headache," demonstrating that migraine-specific therapy and early initiation of preventive treatment, when the number of headache days is still low, can lead to better treatment outcomes.

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Author contributions
All authors designed the study, conceptualized the study, and acquired the data. WR, PA, AH, and ST drafted the manuscript for intellectual content, created the figures, analyzed data, and interpreted of data. TP, AT and AR revised the manuscript for intellectual content. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board Research Ethics Committee (IRBREC) of the Faculty of Medicine, Chulalongkorn University, Bangkok, and KCMH in October 2023 (IRB number 706/2023). The approval of retrieving retrospective data from electronic medical records (EMR) was made and informed consent was waived by IRBREC. All methods were carried out following relevant guidelines and regulations.

Competing interests
Wanakorn Rattanawong receives speaker and advisory board honorarium from ZP therapeutics, DKSH Thailand, Pfizer Thailand, BL HUA, Viatris Thailand and Lundbeck; Prakit Anukoolwittaya receives speaker and advisory board honorarium from ZP therapeutics, DKSH Thailand, Pfizer Thailand, BL HUA, Akarin Hiransuthikul has no conflict of interest, Thanakit Pongpitakmetha receives speaker and advisory board honorarium from ZP therapeutics, Pfizer Thailand, and BL HUA, Auranee Trisataya is currently an employee at ZP therapeutics at the time of submission, Sekh Thanprasertsuk receives speaker and advisory board honorarium from ZP therapeutics, DKSH Thailand, Pfizer Thailand, BL HUA, Alan M. Rapoport serves as an advisor for AbbVie, Doctor Reddy's, Satsuma; he is on the Speakers Bureau of AbbVie, Doctor Reddy's and Teva Pharmaceutical Industries; he is Editor-in-Chief of Neurology Reviews and on the Editorial Board of CNS Drugs.

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