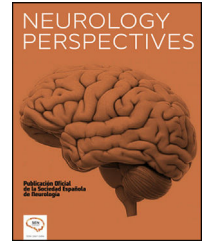




NEUROLOGY PERSPECTIVES

www.journals.elsevier.com/neurology-perspectives



ORIGINAL ARTICLE

Switching of monoclonal antibodies against the calcitonin gene-related peptide or its receptor in migraine. Results from a Spanish Cohort

J. Arzalluz-Luque^{a,*}, M. Millán Vázquez^a, R. Lamas Pérez^a, N. Sánchez Rodríguez^a, P. Gómez López^a, F.J. Gómez Fernández^a, J. Viguera Romero^b, C. Jurado Cobo^c, M. Fernández Recio^d, C. González Oria^a

^a Unidad de Cefaleas, Servicio de Neurología, Hospital Universitario Virgen del Rocío, Avenida Manuel Siurot s/n, 41013 Sevilla, Spain

^b Servicio de Neurología, Hospital Universitario Virgen Macarena, Av. Dr. Fedriani, 3, 41009 Sevilla, Spain

^c Servicio de Neurología, Hospital Universitario Reina Sofía, Av. Menéndez Pidal, s/n, 14004 Córdoba, Spain

^d Servicio de Neurología, Hospital Universitario Virgen de Valme, Ctra. de Cádiz Km. 548,9, 41014 Sevilla, Spain

Received 26 December 2023; accepted 2 April 2024

KEYWORDS

Migraine;
Switch;
CGRP;
Monoclonal antibodies;
Real-world evidence

Abstract

Background: Switching between calcitonin gene-related peptide (CGRP) and monoclonal antibodies (mAbs) may be a beneficial strategy after discontinuation. The aim of this study was to evaluate switching outcomes of effectiveness/tolerability.

Methods: Retrospective multicentric study of migraine patients who switched to another CGRP-mAb due to lack of tolerability or effectiveness (defined as <30% reduction of monthly headache days [MHD]). Assessment was performed before and 3 months after switch. The main outcome was the response rate of MHD. Secondary outcomes included other effectiveness/tolerability measures.

Results: 90 patients were included: 75 (83.3%) women, 72 (80%) chronic, and 18 (20%) episodic migraine. Mean age was 45.9 ± 11 years and mean duration of migraine was 29.2 ± 12.4 years. Mean time under first mAb prior to switch was 10.4 ± 4.9 months. Most frequent switches were erenumab-galcanezumab 38 (42.2%) and erenumab-fremanezumab 21 (23.3%). Lack of effectiveness (50/90, 55.6%) or tolerability (40/90, 44.4%) provoked switching. Most common adverse events (AEs) leading to discontinuation were constipation and flu-like syndrome in 16 (40%) patients each. Response rate (RR) of MHD 30%–50% occurred in 10 patients (11.1%), $\geq 50\%$ in 32 (35.6%) and <30% in 48 (53.3%) patients. Significant reduction was proved after switch in MHD (20 [IQR:15–29] vs 13 [IQR:7–23]; $p < .001$) and monthly migraine days (15 [IQR:12–20] vs 10 [IQR:7–16]; $p < .001$). After switching, 38 (42.2%) experienced AEs, but tolerability improved in

* Corresponding author at: Unidad de Cefaleas, Servicio de Neurología, Hospital Universitario Virgen del Rocío, Avenida Manuel Siurot s/n., 41013 Sevilla, Spain.

E-mail address: joaquin.arzalluz.sspa@juntadeandalucia.es (J. Arzalluz-Luque).

50% of patients who discontinued due to lack of tolerability. RR compared between switches to different CGRP-mAb classes showed no differences.

Conclusion: Switching may become an individualized strategy in migraine refractory patients who discontinue CGRP-mAbs due to lack of effectiveness/tolerability. In this study, supportive data are provided to the growing evidence of switch and future needs are highlighted.

© 2024 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

PALABRAS CLAVE

Migraña;
switch;
CGRP;
anticuerpos
monoclonales;
experiencia en vida
real

Experiencia del switch de anticuerpos monoclonales frente al péptido relacionado con el gen de la calcitonina o su receptor en migraña. Resultados de una cohorte española

Resumen

Introducción: El switch entre anticuerpos monoclonales (AMCs) frente al CGRP podría suponer una estrategia eficaz tras la discontinuación. El objetivo fue evaluar los resultados de efectividad/tolerabilidad del switch.

Métodos: Estudio retrospectivo multicéntrico incluyendo pacientes con migraña que realizaron switch a otro AMC-anti-CGRP debido a falta de tolerabilidad o efectividad (<30% reducción días cefalea mensual[DCM]). Fueron evaluados previamente y tres meses tras switch. La variable principal fue la tasa de respuesta en DCM. Los objetivos secundarios incluyeron otras medidas de efectividad/tolerabilidad.

Resultados: Se incluyeron 90pacientes: 75(83.3%) mujeres, 72(80%) con migraña crónica y 18 (20%) episódica. La edad media fue 45.9 ± 11 años, la duración media de migraña 29.2 ± 12.4 años. El tiempo medio con el primer AMC fue 10.4 ± 4.9 meses. Los switch más frecuentes fueron erenumab-galcanezumab 38(42.2%) y erenumab-fremanezumab 21(23.3%). La falta de efectividad (50/90, 55.6%) o tolerabilidad (40/90, 44.4%) causaron el switch. Los efectos adversos(EAs) más frecuentes fueron estreñimiento y síndrome pseudogripal en 16(40%) respectivamente. La reducción de DCM fue 30–50% en 10 pacientes(11.1%), $\geq 50\%$ en 32 (35.6%) y $< 30\%$ en 48(53.3%). Se demostró una reducción significativa de DCM tras el switch (20 [IQR:15–29] vs 13[IQR:7–23]; $p < 0,001$) y DMM (15[IQR:12–20] vs 10[IQR:7–16]; $p < 0,001$). Tras el switch, 38 pacientes(42.2%) experimentaron EAs, pero la tolerabilidad mejoró en 50% de pacientes que discontinuaron por ello. La reducción DCM comparada entre AMC con distinta diana(CGRP vs. ligando) no mostró diferencias.

Conclusión: El switch podría suponer una estrategia terapéutica en pacientes refractarios tras discontinuación de AMC anti-CGRP por falta de efectividad/tolerabilidad. Este estudio aporta evidencia adicional del switch y plantea nuevas necesidades y futuras investigaciones.

© 2024 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Background

Migraine is a common primary headache disorder, affecting more than 4.5 million people in Spain, where its prevalence is 12% for episodic migraine (EM) and 2% for chronic migraine (CM).¹ It is considered one of the most disabling diseases by the World Health Organization^{2,3} and it is the second most disabling disease worldwide after low back pain.⁴ According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), migraine is defined as recurrent headaches lasting 4–72 h, of variable intensity, usually described as pulsating and unilateral, accompanied by nausea/vomiting, photophobia, and phonophobia.⁵ Regarding monthly headache days (MHD), it is classified in 2 major types: CM when ≥ 15 MHD for > 3 months, requiring at least 8 days with migraine features, and EM when < 15 MHD.⁵ This

disease includes not only headache but also disabling prodromal and postdromal symptoms and migraine aura. The association with other comorbidities has been stated, mostly neurological and psychiatric disorders.⁶

Recent advances in the understanding of migraine pathophysiology outlined the importance of neuronal circuits including cortical and subcortical structures and the relevant role of the calcitonin gene-related peptide (CGRP) pathway in modulation of central pain circuits and in the triggering of migraine.⁷ Similarly, CGRP antagonist proved to abort and prevent migraine attacks.⁷ These findings ultimately led to the development of monoclonal antibodies (mAbs) targeting CGRP ligand (galcanezumab, fremanezumab, and eptinezumab) or its receptor (erenumab). CGRP-mAbs proved to be effective, safe, and well tolerated for preventing migraine attacks.^{8–11} Indeed,

real-world evidence (RWE) studies, generally involving a more refractory population, confirmed efficacy, tolerability, and safety outcomes.^{12,13} To date, comparative head-to-head trials of CGRP-mAbs are lacking.

Nevertheless, the response may vary in real clinical practice. Actually, RWE shows that up to 30% of patients discontinued CGRP-mAbs, mostly due to lack of benefit.¹⁴ In addition, a recent multicenter prospective study of migraine patients treated with anti-CGRP-mAbs showed that around 40%–45% of patients did not achieve $\geq 50\%$ response rate (RR) at week 24 of follow-up.¹⁵ Same results were found in previous prospective studies after 3 and 6 months of follow-up.^{12,13} Interestingly, some non-responders might achieve a more effective response when switching to a different mAb, regarding monthly migraine days (MMD) reduction, improvement of quality of life parameters, and reduction of acute migraine medication use.¹⁶ Due to diverse therapeutic targets (CGRP ligand vs receptor), it is reasonable to question whether different action mechanisms may play a relevant role in the variability of efficacy found among patients. However, evidence regarding switch is lacking and clinical practice guidelines have not provided recommendations in this regard.¹⁷ The aim of this study was to evaluate whether switching CGRP-mAb is associated with clinical improvement in terms of effectiveness and tolerability outcomes.

Methods

An observational, longitudinal, retrospective, and multicenter study was conducted between January 2018 and June 2022. We included patients diagnosed with migraine according to ICHD-3 criteria, with or without aura, aged at least 18 years, who were treated with CGRP-mAbs and switched mAb for any reason: lack of effectiveness or lack of tolerability. Lack of effectiveness was considered when the reduction in MHD after the period with the first mAb was $< 30\%$ and lack of tolerability when adverse events (AEs) having a life impact occurred. There was no wash-out period before switching mAbs. All patients were evaluated before switch (after the period of treatment with first mAb, considered baseline) and then reevaluated 3 months after switching, when effectiveness and tolerability outcomes were assessed. No concomitant prophylactic medications were added or changed during this period, only discontinued at the request of patients.

Follow-up was performed at headache monographic neurology consultations. Electronic medical records were used to collect demographic data and clinical variables at baseline and after switching, including headache frequency (MHD and MMD), severity (measured by a 1–10 visual analogue scale [VAS]), use of acute and preventive migraine medication, disability, and anxiety-depression surveys. Medication overuse was considered if used ≥ 10 days per month for triptans and ≥ 15 days for non-steroidal anti-inflammatory drugs (NSAIDs). Disability questionnaires were those regularly used for headache: Migraine Disability Assessment Scale (MIDAS) and Headache Impact Test-6 (HIT6). Anxiety and depression surveys were Hospital Anxiety and Depression-Anxiety and Hospital Anxiety and Depression-Depression. Tolerability in terms of reported

AEs, the reason for discontinuation of first mAb (lack of effectiveness/lack of tolerability) and switch information were recorded.

The primary outcome of the study was to determine RR ($< 30\%$, 30% – 50% , $\geq 50\%$) of MHD. Secondary outcomes included measures of effectiveness (absolute changes in frequency of MHD/MMD, headache severity, disability scores, and use of acute migraine medication) and tolerability of switch. We analyzed other effectiveness outcomes such as mean reduction in VAS score and percentage of patients with VAS score reduction of at least 1 point. In addition, clinical variables of effectiveness were compared before and 3 months after switch. Differences in tolerability and reported AEs were also recorded. Lastly, we compared RR of MHD of switches performed to mAbs with same target to those performed to mAbs with different target (CGRP receptor vs ligand).

Descriptive statistics were developed. Categorical variables were reported as frequencies and percentages, and quantitative variables were expressed as measures of central tendency and dispersion. Median and interquartile range (IQR) were used for variables with asymmetric and abnormal distributions. Bivariate analysis was then performed. Normality tests were used, which defined non-parametric statistical hypothesis tests. In order to analyze matched samples before and after switching mAb, Wilcoxon test was chosen. Differences in RR between switches to same and different class were studied with Mann–Whitney *U* test. Results were analyzed with the SPSS 28.0.1.0. statistical package and R software. Results considered statistically significant when $p < .05$.

We conducted this study according to the declaration of Helsinki. The local ethics committee approved the study (1720-N-22). All patients received written and verbal information.

Results

Our study included 90 patients. Baseline demographics and clinical characteristics prior to switch are summarized in Table 1. Of the 90 patients included, 75 (83.3%) were women. The mean age of the cohort at baseline was 45.9 ± 11 years and the mean duration of migraine was 29.2 ± 12.4 years. Diagnosis were CM in 72 patients (80%) and EM in 18 patients (20%), including 75 (83.3%) without aura and 15 (16.7%) with aura. Time under first mAb prior to switch was 10.4 ± 4.9 months. The median MHD was 20 (IQR: 15–29) days. Among headache days, patients had a median MMD of 15 (IQR: 12–20). The median VAS was 8 (IQR: 7–8). Regarding concomitant treatment, median monthly days of NSAIDs use was 9 (IQR: 4–13) and median monthly days of triptans use was 6 (IQR: 2–10). NSAIDs overuse happened in 15/84 (17.9%) and triptans overuse in 18/73 (24.7%). Forty-four patients (48.9%) received concomitant oral prophylaxis, and 9 (10%) received regular onabotulinumtoxinA at the same time.

Switch information is summarized in Fig. 1. Initial mAbs were erenumab in 59 patients (65.6%), galcanezumab in 29 (32.2%), and fremanezumab in 2 (2.2%). After discontinuation, all 90 patients switched to a different CGRP-mAb and the main switches were: 38 (42.2%) erenumab–

Table 1 Demographic and clinical characteristics of the overall cohort prior to switch.

	n=90
Female sex, n (%)	75 (83.3)
Age, mean±SD	45.9±11
Diagnosis	
Chronic migraine, n (%)	72 (80)
Episodic migraine, n (%)	18 (20)
Aura, n (%)	15 (16.7)
Duration of migraine (y), mean±SD	29.2±12.4
Time under first mAb prior to switch (m), mean±SD	10.4±4.9
MHD, median (IQR)	20 (15–29)
MMD, median (IQR)	15 (12–20)
VAS, median (IQR)	8 (7–8)
Acute monthly NSAIDs use (days), median (IQR)	9 (4–13)
Acute monthly triptans use (days), median (IQR)	6 (2–10)
NSAIDs overuse, n (%)	15/84 (17.9)
Triptans overuse, n (%)	18/73 (24.7)
Oral preventive treatment, n (%)	44 (48.9)
OnabotulinumtoxinA, n (%)	9 (10)
MIDAS, median (IQR)	52 (30–92)
HIT-6, median (IQR)	66 (63–70)
HAD-A, median (IQR)	15 (10–21)
HAD-D, median (IQR)	7.5 (7–8)

HAD-A: Hospital Anxiety and Depression-Anxiety, HAD-D: Hospital Anxiety and Depression-Depression, HIT-6: headache impact test-6, IQR: interquartile range, mAb: monoclonal antibody, m: months, MHD: monthly headache days, MIDAS: migraine disability assessment scale, MMD: monthly migraine days, NSAIDs: non-steroidal anti-inflammatory drugs, SD: standard deviation, VAS: visual analogue scale, y: years.

galcanezumab, 21 (23.3%) erenumab–fremanezumab, and 20 (22.2%) galcanezumab–erenumab. Two consecutive switches were reported in 6 patients. After switch, 5/9 (55.6%) were still receiving onabotulinumtoxinA and 35/44 (79.5%) had stable oral preventive medication. The remaining patients discontinued the concomitant treatment during the study at their request. The reasons for switch were lack of effectiveness in 50 patients (55.6%) and lack of tolerability due to AEs in 40 patients (44.4%). The most common AEs were constipation in 16 (40%) patients and flu-like syndrome in 16 (40%) patients. Other AEs were injection site related symptoms in 5 (5.6%), hair loss in 2 (2.2%) and weight gain in 1 (1.1%).

Regarding effectiveness outcomes of switch, 30%–50% RR was achieved in 10 patients (11.1%) and $\geq 50\%$ was seen in 32 patients (35.6%), whereas $<30\%$ RR was observed in 48 patients (53.3%) (Fig. 2). The mean VAS score reduction was 0.24 ± 1.83 (range of reduction from -7 to $+6$) and VAS score reduction of ≥ 1 was reported in 29 patients (32.2%). Assessment of clinical characteristics before and after switch is shown in Table 2. This analysis showed a significant reduction in MHD and MMD after switch (Fig. 3). Median MHD with the first CGRP-mAb was 20 (IQR: 15–29) vs 13 (IQR: 7–23) after switch ($p < .001$). Median MMD was 15 (IQR:

12–20) before vs 10 (IQR: 7–16) after switch ($p < .001$). No significant differences were found in headache severity, acute medication days, or disability, anxiety or depression scores.

Most of the patients switched to a mAb with different mechanism of action: 79 (87.8%). In this group, RR were: 42 patients (53.2%) $<30\%$, 10 (12.7%) 30%–50%, and 27 (34.2%) $\geq 50\%$. Eleven patients (12.2%) switched to a mAb with similar mechanism of action; in this group, 6 patients had RR $<30\%$ and 5 patients $\geq 50\%$. RR were compared between both groups and no significant differences were found. The group who switched to a different class mAb and to a same class mAb showed a mean reduction of 23.61% (SD ± 45.67) and 30.78% (SD ± 41.2) in MHD, respectively, whereas the overall cohort had a 24.4% mean reduction in MHD after switch. In Fig. 4, the distribution of reduction of MHD among groups is displayed.

As for tolerability after switch, 38 patients (42.2%) experienced AEs. The distribution of AEs after switch was: constipation 17 (44.7%), flu-like syndrome 13 (34.2%), injection site-related symptoms 6 (15.8%), hair loss 1 (2.6%), and weight gain 1 (2.6%). A comparative graph of tolerability before and after switch is shown in Fig. 5. In the group of patients who discontinued the first mAb due to AEs (Fig. 6), 50% (20/40) improved tolerability with resolution of the AEs that motivated discontinuation. The 20 patients who still had AEs described: constipation 12 (60%), flu-like syndrome 4 (20%), injection site-related symptoms 3 (15%), and hair loss 1 (5%).

Discussion

This RWE study shows that migraine refractory patients who discontinue anti-CGRP mAbs (including non-responders and those with intolerance) may benefit from switching to another mAb, mainly in terms of effectiveness. We report absolute significant reductions in median MHD and MMD compared to baseline. In addition, a $\geq 50\%$ RR occurred in more than one-third of the patients and a $\geq 30\%$ RR was observed in 36.7% of the patients. Although the proportion of AEs was similar after switching, we report an improvement in tolerability in those patients whose switch was motivated by lack of tolerability with the first treatment. In fact, resolution of the AEs that prompted the switch was observed in half of the patients in this group.

In previous literature about switch, the first mAb is usually erenumab and switch is mostly to galcanezumab or fremanezumab^{18–20} when ineffectiveness of erenumab is stated. This is similar to our study and is probably due to the earlier approval of erenumab. In general, there is a lack of consensus on the definition of first CGRP mAb ineffectiveness. In most cases, RR of MHD is the main outcome when assessing switch.²¹ Although there is a general tendency to consider lack of efficacy when $<30\%$ reduction in headache frequency is achieved,^{19,22} most studies are retrospective and influenced by different clinical practice protocols. Given the retrospective and multicenter nature of our study, the same limitations may apply, but based on previous literature, lack of effectiveness was considered when at least 30% reduction in MHD was not achieved. However, what is considered effective may differ among

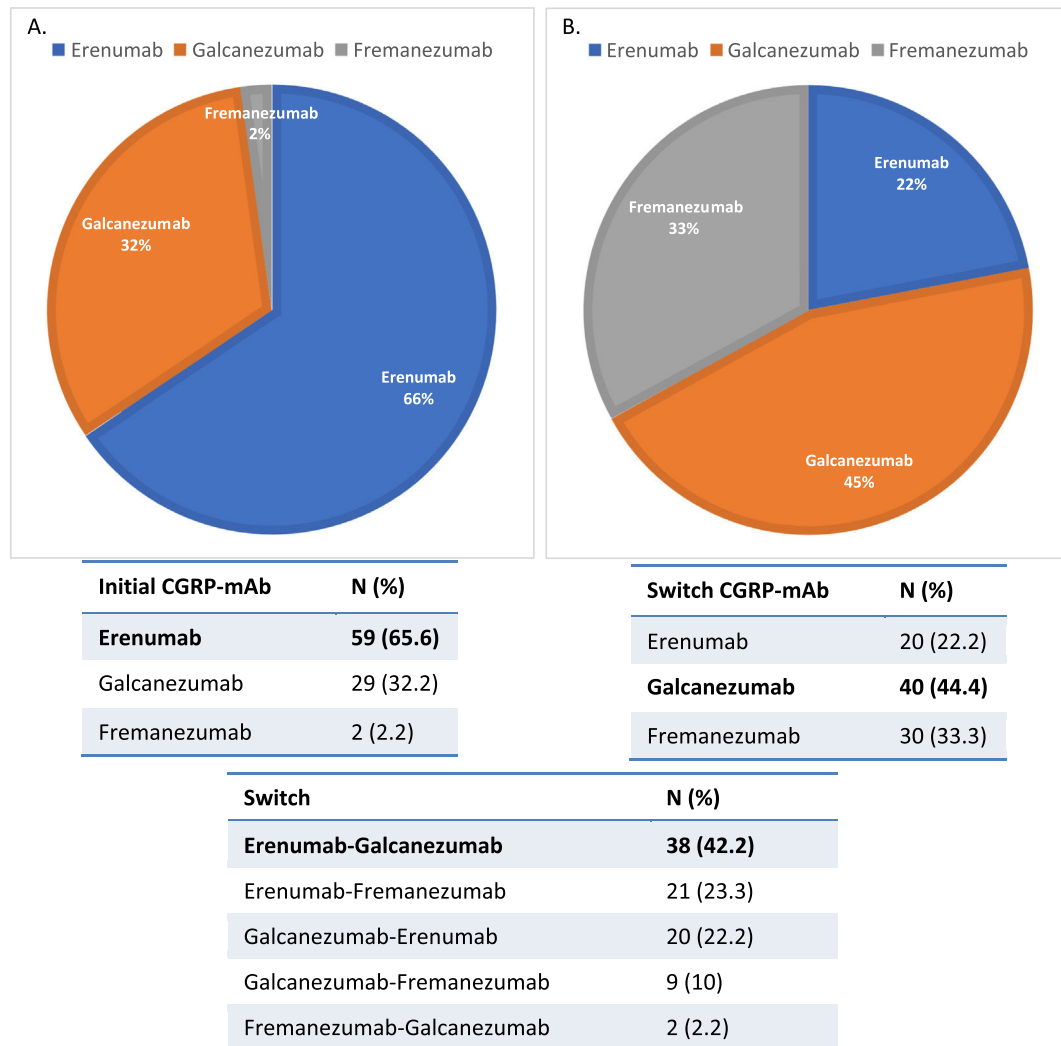


Fig. 1 Switch information. Initial (A) and switch (B) CGRP-mAbs are represented in this figure. Tables show distribution of initial CGRP-mAb, switch CGRP-mAb, and a summary of switches performed. CGRP-mAb: Calcitonin gene related-peptide monoclonal antibody.

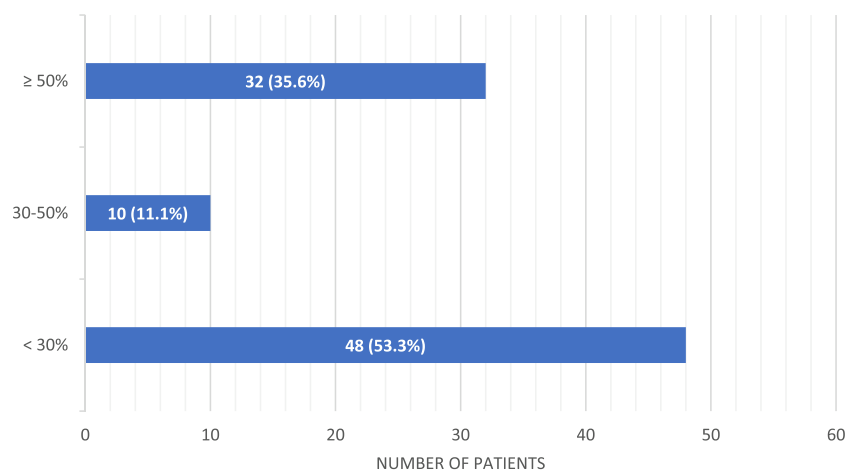


Fig. 2 RR of MHD after switch to a different anti-CGRP mAb. CGRP: calcitonin gene-related peptide, mAb: monoclonal antibody, MHD: monthly headache days, RR: response rate.

Table 2 Statistical analysis of efficacy outcomes before and after switch.

	Before switch	After switch	<i>p</i> -value
MHD, median (IQR)	20 (15–29)	13 (7–23)	<.001
MMD, median (IQR)	15 (12–20)	10 (7–16)	<.001
VAS score, median (IQR)	8 (7–8)	7.5 (7–8.5)	NS
Acute monthly NSAIDs use (days), median (IQR)	9 (4–13)	7 (3–12)	NS
Acute monthly triptans use (days), median (IQR)	6 (2–10)	3 (3–9)	NS
MIDAS, median (IQR)	52 (30–92)	53 (25.5–90)	NS
HIT-6 score, median (IQR)	66 (63–70)	65 (61–68)	NS
HAD-A, median (IQR)	15 (10–21)	15.5 (9–21)	NS
HAD-D, median (IQR)	7.5 (7–8)	5.5 (2–9)	NS

HAD-A: Hospital Anxiety and Depression-Anxiety, HAD-D: Hospital Anxiety and Depression-Depression, HIT-6: headache impact test-6, IQR: interquartile range, MHD: monthly headache days, MIDAS: migraine disability assessment scale, MMD: monthly migraine days, NSAIDs: non-steroidal anti-inflammatory drugs, VAS: visual analogue scale.

patients depending on the impact on their quality of life and their previous clinical situation. Thus, <30% MHD reduction may represent effectiveness in some refractory patients. In addition, effectiveness definitions should include not only headache frequency but also additional clinical parameters, such as severity, use of abortive treatments, or impact on quality of life. Interestingly, a recent retrospective study defined ineffectiveness for the first mAb by combining several variables simultaneously,²³ including reduction in headache days, disability scores, and abortive medication use. These new strategies provide guidance for future work in establishing consistent definitions of switching outcomes.

Limited real-world data are available regarding the effectiveness of switching, including case series and retrospective studies. No interventional clinical trial has evaluated the effect of switching to another anti-CGRP mAb. A retrospective real-world study of 78 switching patients reported that approximately one-third of erenumab non-responders had a $\geq 30\%$ RR of MHD at 3 months after switching to galcanezumab/fremanezumab.¹⁹ Previous small case reports demonstrated clinically meaningful reductions in MMD and headache intensity.^{18,20,24,25} Another recent retrospective cohort study with 22 patients and

several variables as main outcomes reported that nearly 50% of patients achieved $\geq 30\%$ RR in MHD, but also sustained reductions over time in abortive medication use and MIDAS/HIT-6 score at 3-month follow-up.²³ In this regard, our results provide additional evidence for switch as a beneficial tool for migraine refractory patients, as we report $\geq 50\%$ RR of MHD in more than one-third of patients at 3-month follow-up. Although this improvement in effectiveness can be considered discrete (with about half of the patients improving <30%), it should not be underestimated due to the refractoriness of our population. RWE studies tend to enroll more refractory patients than clinical trials,²⁶ and this can greatly influence effectiveness results. In fact, refractoriness is one of the main characteristics of our cohort, since failure of three previous prophylactic treatments is required to meet the financial conditions of CGRP mAbs in Spain, and our patients also had undergone a mAb discontinuation. In addition to the aforementioned improvement in RR, we also found significant reductions in median MHD (20 vs 13 days) and MMD (15 vs 10 days). Similarly, a subgroup analysis of the Finesse study shows that MMD decreased from 13.6 at baseline to 7.2 at month 3, and this decrease was greater in CM than in EM.¹⁶ In any case, the fact that an

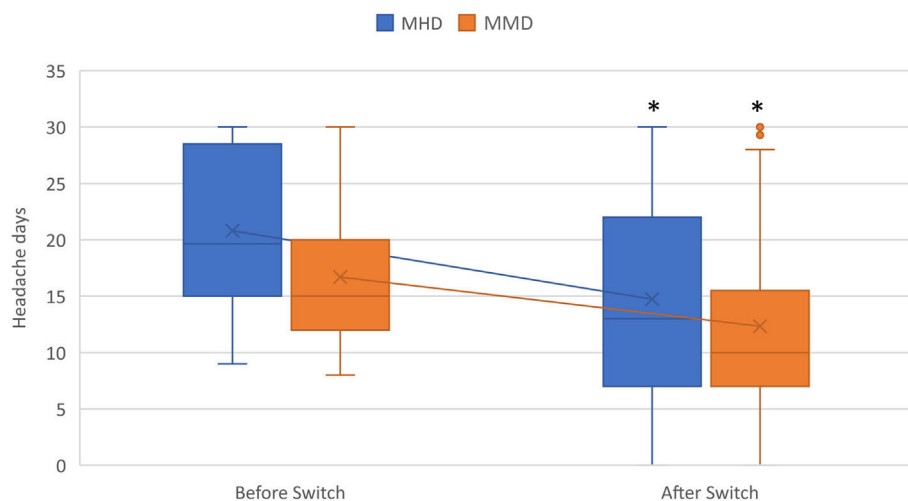


Fig. 3 MHD and MMD evolution before and after switch. MHD: monthly headache days, MMD: monthly migraine days. *Statistical significance $p < .001$.

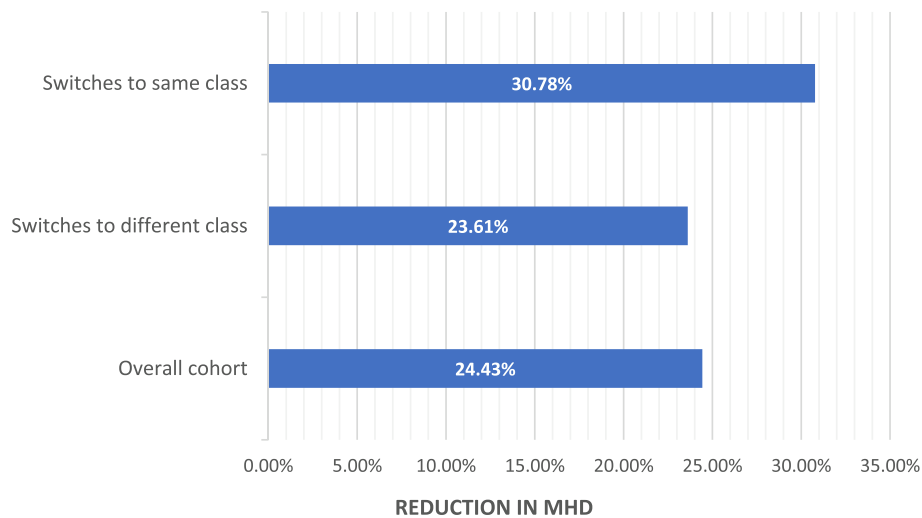


Fig. 4 Reduction in MHD after switch in different groups. No statistical differences were found between switches to same vs different class. MHD: monthly headache days.

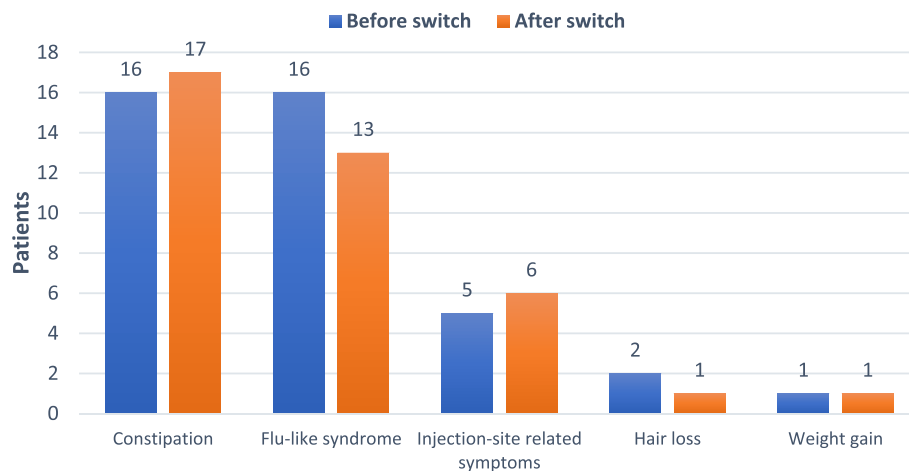


Fig. 5 Tolerability before and after switch. AEs distribution is shown before and after switch in absolute numbers. AEs: adverse events.

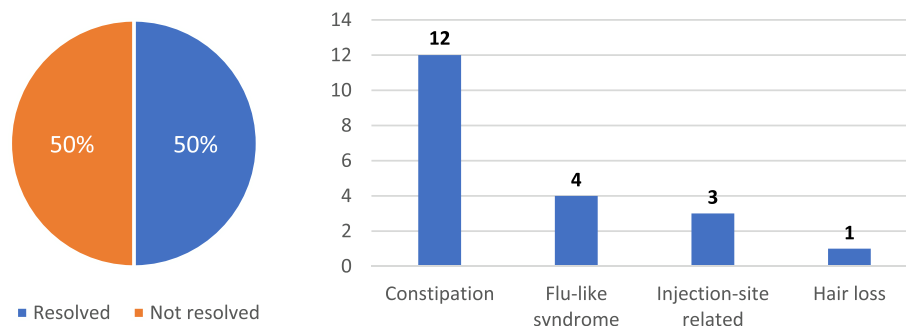


Fig. 6 AEs among patients who discontinued first mAb because of lack of tolerability and their distribution. In 50% (20/40) of patients, there was a resolution of the AE that motivated discontinuation. The distribution of AEs among patients who still had lack of tolerability is shown. AEs: adverse events, mAb: monoclonal antibody.

improvement in headache frequency was observed in a refractory cohort suggests that these data can be considered representative of the real-world population and can therefore be extrapolated to clinical practice.

Other effectiveness outcomes have also been evaluated in studies. Significant reductions in disability scores (MIDAS and HIT-6) and acute migraine medication have been reported at 3 months after switching.^{16,23} It is important to emphasize that most studies focus on headache frequency^{21,27} and do not always include other clinical parameters such as disability and anxiety/depression scores, which can be very illustrative of the impact on daily life. This may be due to the difficulty in interpreting their subjective component and the time required to complete these questionnaires. However, disability and mood disorders are important clinical factors to consider when assessing patients with refractory migraine. They were included in our study, but no significant differences were found after switching. This needs further analysis with larger cohorts.

Most switch analyses focus on non-responders to prior CGRP mAbs. Therefore, given the global paucity of information on switching due to lack of tolerability, the data reported in our cohort may be relevant. Tolerability rates of current RWE are variable.^{14,28} As for AEs, their distribution was unchanged after switching in our cohort and was also consistent with the distribution in previous studies.^{22,27,28} Interestingly, although it was only subjectively assessed and no formal questionnaires were administered, tolerability improved in 50% of patients whose switch was motivated by AEs in our study. It may be reasonable to consider the possibility that safety profiles may be heterogeneous among CGRP-mAbs, even more given that it is unknown how their variable targets may have an impact on efficacy and tolerability. Further research in this area may have future implications so that switching may become a therapeutic strategy not only to improve efficacy but also to address tolerability issues.

As aforementioned, the different mechanisms of action of anti-CGRP mAbs may differentially affect effectiveness, safety, and tolerability in migraine patients. Therefore, it is reasonable to ask whether patients who did not respond to one anti-CGRP pathway mAb class might benefit from switching to the other class. However, in our series, no differences in RR were found between patients who switched to a mAb with a different mechanism of action. This is largely influenced by the size of our cohort and the asymmetry of the switches we report. Most patients switched from a CGRP receptor-targeting mAb to another CGRP ligand-binding mAb, with the consequent challenge of stating differences in this setting.

The main limitations of this study are the retrospective design and the lack of longer follow-up after switching, which was limited to 3 months. Longer follow-up from this event would provide long-term effectiveness and tolerability data, which would be of interest to evaluate the benefits of switching. These data would also provide a more accurate picture compared to real-world practice, where discontinuation is usually considered after at least 6–12 months of treatment with a mAb.¹⁷ Therefore, we highlight the current need to perform prospective studies that can assess the long-term outcome of switching after at least 6 months.

Although there is currently a growing body of evidence on benefits of switch, we believe our study provides additional supportive data and highlights future research directions and needs. Nevertheless, there is a lack of prospective studies with larger cohorts and longer follow-up periods. Determining the specific group of patients who could truly benefit from switching in terms of effectiveness and tolerability would be one of the major challenges in the future perspective of CGRP-mAb research.

Conclusion

This RWE cohort study suggests that some migraine refractory patients may benefit from switching to another mAb after discontinuation, particularly in terms of reduction of MHD. Partial improvement in AEs is also reported in patients who discontinued due to lack of tolerability. In our experience, switching may be an individualized treatment strategy in refractory patients. However, larger studies with long-term follow-up are needed to reach conclusive results. Our findings add new information to the current evidence on CGRP-mAbs switching and encourage future research in this area.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Patient consent

All patients received written and verbal information.

Ethical considerations

We conducted this study according to the declaration of Helsinki. The local ethics committee approved the study (1720-N-22).

Declaration of competing interest

The Authors declare that there is no conflict of interest.

Acknowledgments

The authors acknowledge Fundación Pública Andaluza para la Gestión de la Investigación en Salud (FISEVI) of Hospital Universitario Virgen del Rocío for statistical and methodological support on this manuscript.

References

1. Matías-Guiú J, Porta-Etessam J, Mateos V, Díaz-Insa S, Lopez-Gil A, Fernández C, Scientific Committee of the PALM Program. One-year prevalence of migraine in Spain: a nationwide population-based survey. *Cephalalgia*. 2011 Mar;31(4):463–70. <https://doi.org/10.1177/0333102410382794>.
2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence,

- prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017 Sep 16;390(10100):1211–59. [https://doi.org/10.1016/S0140-6736\(17\)32154-2](https://doi.org/10.1016/S0140-6736(17)32154-2).
3. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018 Nov;17(11):954–76. [https://doi.org/10.1016/S1474-4422\(18\)30322-3](https://doi.org/10.1016/S1474-4422(18)30322-3).
 4. Burch RC, Buse DC, Lipton RB. Migraine: epidemiology, burden, and comorbidity. *Neurol Clin*. 2019 Nov;37(4):631–49. <https://doi.org/10.1016/j.ncl.2019.06.001>.
 5. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan;38(1):1–211. <https://doi.org/10.1177/0333102417738202>.
 6. Pelzer N, de Boer I, van den Maagdenberg AMJM, Terwindt GM. Neurological and psychiatric comorbidities of migraine: concepts and future perspectives. *Cephalalgia*. 2023 Jun;43(6):3331024231180564. <https://doi.org/10.1177/03331024231180564>.
 7. Ho TW, Edvinsson L, Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol*. 2010 Oct;6(10):573–82. <https://doi.org/10.1038/nrneurol.2010.127>.
 8. Tepper S, Ashina M, Reuter U, Brandes JL, Doležil D, Silberstein S, 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 Jun;16(6):425–34. [https://doi.org/10.1016/S1474-4422\(17\)30083-2](https://doi.org/10.1016/S1474-4422(17)30083-2).
 9. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018 Dec 11;91(24):e2211–21. <https://doi.org/10.1212/WNL.0000000000006640>.
 10. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA*. 2018 May 15;319(19):1999–2008. <https://doi.org/10.1001/jama.2018.4853>.
 11. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020 Mar;40(3):241–54. <https://doi.org/10.1177/0333102420905132>.
 12. Barbanti P, Aurilia C, Egeo G, Fofi L, Cevoli S, Colombo B, et al. Erenumab in the prevention of high-frequency episodic and chronic migraine: Erenumab in Real Life in Italy (EARLY), the first Italian multicenter, prospective real-life study. *Headache*. 2021 Feb;61(2):363–72. <https://doi.org/10.1111/head.14032>.
 13. Caronna E, Gallardo VJ, Alpuente A, Torres-Ferrus M, Pozo-Rosich P. Anti-CGRP monoclonal antibodies in chronic migraine with medication overuse: real-life effectiveness and predictors of response at 6 months. *J Headache Pain*. 2021 Oct 7;22(1):120. <https://doi.org/10.1186/s10194-021-01328-1>.
 14. Kanaan S, Hettie G, Loder E, Burch R. Real-world effectiveness and tolerability of erenumab: a retrospective cohort study. *Cephalalgia*. 2020 Nov;40(13):1511–22. <https://doi.org/10.1177/0333102420946725>.
 15. Barbanti P, Egeo G, Aurilia C, Altamura C, d'Onofrio F, Finocchi C, et al. Italian Migraine Registry study group. Predictors of response to anti-CGRP monoclonal antibodies: a 24-week, multicenter, prospective study on 864 migraine patients. *J Headache Pain*. 2022 Nov 1;23(1):138. <https://doi.org/10.1186/s10194-022-01498-6>.
 16. Straube A, Broessner G, Gaul C, Hamann X, Hipp J, Kraya T, et al. Real-world effectiveness of fremanezumab in patients with migraine switching from another mAb targeting the CGRP pathway: a subgroup analysis of the Finesse Study. *J Headache Pain*. 2023 May 23;24(1):59. <https://doi.org/10.1186/s10194-023-01593-2>.
 17. Sacco S, Amin FM, Ashina M, Bendtsen L, Deligianni CI, Gil-Gouveia R, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *J Headache Pain*. 2022 Jun 11;23(1):67. <https://doi.org/10.1186/s10194-022-01431-x>.
 18. Patier Ruiz I, Sánchez-Rubio Ferrández J, Cárcamo Fonfria A, Molina García T. Early experiences in switching between monoclonal antibodies in patients with nonresponsive migraine in Spain: a case series. *Eur Neurol*. 2022;85(2):132–5. <https://doi.org/10.1159/000518899>.
 19. Overeem LH, Peikert A, Hofacker MD, Kamm K, Ruscheweyh R, Gendolla A, et al. Effect of antibody switch in non-responders to a CGRP receptor antibody treatment in migraine: a multi-center retrospective cohort study. *Cephalalgia*. 2022 Apr;42(4–5):291–301. <https://doi.org/10.1177/03331024211048765>.
 20. Ziegeler C, May A. Non-responders to treatment with antibodies to the CGRP-receptor may profit from a switch of antibody class. *Headache*. 2020 Feb;60(2):469–70. <https://doi.org/10.1111/head.13729>.
 21. Kaltseis K, Filippi V, Frank F, Eckhardt C, Schiefficker A, Broessner G. Monoclonal antibodies against CGRP (R): non-responders and switchers: real world data from an austrian case series. *BMC Neurol*. 2023 Apr 28;23(1):174. <https://doi.org/10.1186/s12883-023-03203-9>.
 22. Lambru G, Caponnetto V, Hill B, Ratti S, Sacco S, Murphy M, et al. Long-term effect of switching from an anti-CGRP receptor to an anti-CGRP ligand antibody in treatment-refractory chronic migraine: a prospective real-world analysis. *Neurotherapeutics*. 2023 Sep;20(5):1284–93. <https://doi.org/10.1007/s13311-023-01394-0>.
 23. Iannone LF, Burgalassi A, Vigani G, Tabasso G, De Cesaris F, Chiarugi A, et al. Switching anti-CGRP(R) monoclonal antibodies in multi-assessed non-responder patients and implications for ineffectiveness criteria: a retrospective cohort study. *Cephalalgia*. 2023 Apr;43(4):3331024231160519. <https://doi.org/10.1177/03331024231160519>.
 24. Porta-Etessam J, González-García N, Guerrero ÁL, García-Azorín D. Failure of monoclonal antibodies against CGRP or its receptor does not imply lack of efficacy of other drugs from the same class. *Neurologia (Engl Ed)*. 2021 Oct;36(8):638–40. <https://doi.org/10.1016/j.nrleng.2020.10.008>.
 25. 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*. 2023 Jul;30(4):e19. <https://doi.org/10.1136/ejhpharm-2021-002946>.
 26. Cullum CK, Do TP, Ashina M, Bendtsen L, Hugger SS, Iljazi A, et al. Real-world long-term efficacy and safety of erenumab in adults with chronic migraine: a 52-week, single-center, prospective, observational study. *J Headache Pain*. 2022 Jun 2;23(1):61. <https://doi.org/10.1186/s10194-022-01433-9>.
 27. Ihara K, Ohtani S, Watanabe N, Takahashi N, Miyazaki N, Takemura R, et al. Switching between anti-calcitonin gene-related peptide monoclonal antibodies: a comparison of monthly and quarterly dosing. *J Neurol Sci*. 2023 Oct 15;453:120811. <https://doi.org/10.1016/j.jns.2023.120811>.
 28. Pavelic AR, Wöber C, Riederer F, Zeberholz K. Monoclonal antibodies against calcitonin gene-related peptide for migraine prophylaxis: a systematic review of real-world data. *Cells*. 2022 Dec 29;12(1):143. <https://doi.org/10.3390/cells12010143>.