Dear Editor:

Calcitonin gene-related peptide monoclonal antibodies (CGRP-mAb: galcanezumab, erenumab, and fremanezumab) have recently been implemented as a preventive treatment for migraine. All these drugs have been shown to be efficacious and safe in reducing the number of days with headache or migraine per month in controlled clinical trials lasting 12 weeks. They are funded as a fourth-line treatment in patients with at least 8 migraine days per month after failure of 3 or more previous preventive treatments, including botulinum toxin in the case of chronic migraine.¹

However, uncertainty remains regarding their long-term effectiveness and safety, the optimal duration of treatment and the management of patients with refractory disease. Regarding the latter point, the latest "Clinical Practice Guidelines for Headache"² of the Spanish Society of Neurology’s Headache Study Group (GECSEN) proposes the possible use of a different CGRP-mAb in the event that the first CGRP-mAb is ineffective. Case series have been published¹,³ reporting that switching to a CGRP-mAb with a different action mechanism (anti-ligand/anti-receptor) effectively decreases the number of days with migraine per month in a significant percentage of patients. As this evidence is limited, we would like to report our experience analysing the effectiveness and safety after 3 months of treatment with a second CGRP-mAb due to a partial response or intolerance to a first antibody.

The main efficacy variable in clinical trials is the decrease in the number of headache or migraine days per month. However, in the clinical setting, patients are satisfied when treatment improves their quality of life, whether due to a reduction in the number of migraine or headache days or in pain intensity, or due to an increase in the number of pain-free days. Thus, we consider a treatment to be effective if it reduces the number of headache or migraine days per month by at least 50% compared to baseline and/or if it leads to significant improvements in the Headache Impact Test and Migraine Disability Assessment quality of life scales. Treatment response is considered partial if the decrease in headache frequency is less than 50% and null if treatment is ineffective. Our hospital’s protocol suggests switching to a second CGRP-mAb only in the event of partial response or intolerance after the first three doses of treatment, and this treatment should be administered 1 month after the last dose of the first monoclonal antibody.

We analysed treatment status at 3 months in 190 patients treated between December 2019 and March 2021, reviewing
the reasons for continuation, switching, and discontinuation of treatment reported in patient medical records.

One hundred and thirty patients (68%) continued with the initial treatment due to effectiveness and tolerance; treatment was suspended in 22 (12%) due to ineffectiveness or intolerance; and 38 (20%) switched to a second-line CGRP-mAb. Of these 38 patients, 28 completed 3 months of treatment and were reassessed, with the treatment being continued in 18 (64%) and suspended in 10 (36%). Table 1 presents the characteristics and progression of patients treated with a second monoclonal antibody.

We reassessed the response and tolerance to the second CGRP-mAb of the 28 patients who completed the 3 months of treatment and of the 22 patients for whom the first treatment was suspended due to partial response: in 63.6% of the patients, treatment was still effective and was continued, and in 36.4%, treatment was suspended again due to partial response. Adverse effects led to discontinuation of the second monoclonal antibody in 12.5% of the patients in whom the first treatment was suspended for the same reason. Furthermore, treatment was suspended or modified in 8% of our sample (n = 15) due to intolerance (mainly vertigo and/or constipation, or skin rashes after infection).

Therefore, and considering the limitations of our study, we may conclude that switching to a second CGRP-mAb is effective in a significant percentage of patients (64%), representing a therapeutic alternative after failure of the first-line treatment due to partial response or adverse effects. The change in therapeutic target (galcanezumab and fremanezumab target the ligand and erenumab targets the receptor) may explain the effectiveness of this approach in 63.3% of the patients.

Furthermore, switching molecule due to adverse effects does not lead to discontinuation of the second-line treatment for the same reason (rate of failure due to adverse effects: 12.5% vs 8%).

Further studies are needed to analyse the effectiveness and safety of treatment in patients showing no response to the first CGRP-mAb, or switching to a molecule with the same target.

| Table 1  | Characteristics of patients who completed 3 months of treatment with a second monoclonal antibody. |
|----------|---------------------------------------------------------------------------------------------------|
| Sex: M, W | Age (years): M = man; W = woman. Diagnosis: CM: chronic migraine; SSD: somatic symptom disorder. |
| First mAb: Galcanezumab | Second mAb: Erenumab, Fremanezumab. Reason for discontinuation: PR: partial response; AE: adverse effects. |
| Sex | Age | Diagnosis | First mAb | Reason for discontinuation | Second mAb | Continuation after 3 months of treatment (YES/NO) | Reason for discontinuation |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | W | 47 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 2 | M | 52 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 3 | W | 32 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 4 | W | 44 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 5 | W | 57 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 6 | W | 65 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 7 | M | 71 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 8 | W | 70 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 9 | W | 40 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 10 | W | 52 | CM | Galcanezumab | PR | Erenumab | YES | - |
| 11 | W | 44 | CM | Galcanezumab | PR | Erenumab | NO | PR |
| 12 | W | 62 | CM | Galcanezumab | PR | Erenumab | NO | PR |
| 13 | W | 45 | CM | Galcanezumab | PR | Erenumab | NO | PR |
| 14 | M | 82 | CM | Galcanezumab | PR | Erenumab | NO | PR |
| 15 | W | 61 | CM | Galcanezumab | PR | Erenumab | NO | PR |
| 16 | M | 70 | SSD | Galcanezumab | PR | Erenumab | NO | PR |
| 17 | W | 54 | CM | Galcanezumab | PR | Erenumab | NO | PR |
| 18 | W | 51 | CM | Galcanezumab | PR + AE (vertigo) | Erenumab | YES | - |
| 19 | W | 63 | CM | Galcanezumab | PR + AE (dizziness) | Erenumab | YES | - |
| 20 | M | 45 | EM | Galcanezumab | PR + AE (post-treatment seizure) | Erenumab | YES | - |
| 21 | W | 49 | CM | Galcanezumab | PR + AE (vertigo) | Erenumab | NO | PR |
| 22 | W | 76 | CM | Galcanezumab | AE (vertigo) | Erenumab | YES | - |
| 23 | W | 57 | CM | Galcanezumab | AE (pruritis, arterial hypotension) | Erenumab | YES | - |
| 24 | W | 45 | CM | Galcanezumab | AE (constipation and vertigo) | Erenumab | YES | - |
| 25 | W | 44 | CM | Galcanezumab | AE (constipation and vertigo) | Fremanezumab | NO | AE (vertigo) |
| 26 | W | 58 | CM | Fremanezumab | PR | Erenumab | YES | - |
| 27 | W | 58 | CM | Fremanezumab | CT | Galcanezumab | YES | - |
| 28 | W | 53 | EM | Fremanezumab | CT | Galcanezumab | NO | AE (skin rash) |

AE: adverse effects; CM: chronic migraine; CT: clinical trial; EM: episodic migraine; M = man; PR: partial response; SSD: somatic symptom disorder; W = woman.
same action mechanism; there is also a need for similar studies with longer study periods and larger patient samples.

**Ethical considerations**

We declare that we followed our centre’s protocols on the publication of patient data.

**Conflicts of interest**

María Martín Bujanda has received lecture honoraria from Lilly and Allergan. Esther Lacalle Fabo has received honoraria from GSK for moderating a training session on severe asthma. The lead author has no conflicts of interest to declare.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.11.009.