Neurological Sciences
https://doi.org/10.1007/s10072-020-05022-z

ORIGINAL ARTICLE

Early outcomes of migraine after erenumab discontinuation: data from a real-life setting

Eleonora De Matteis[1] · Giannapia Affaitati[2] · Ilaria Frattale[1] · Valeria Caponnetto[1] · Francesca Pistoia[1] · Maria Adele Giamberardino[2] · Simona Sacco[1] · Raffaele Ornello[1]

Received: 25 August 2020 / Accepted: 21 December 2020

Abstract

Background Monoclonal antibodies targeting the calcitonin gene-related peptide, including erenumab, are migraine-specific preventive treatments, whose long-term effectiveness has still to be evaluated in real-life settings. We assessed early outcomes of erenumab discontinuation after a 52-week treatment in patients with a continuous positive response to the drug.

Methods We evaluated the early outcomes after treatment completion in migraineurs from a real-life multicenter register. All patients received monthly erenumab for 52 weeks and attended a 8-week follow-up after treatment completion. Primary outcomes were responder rates and changes in monthly migraine days (MMDs), acute medications days (AMDs), and pain intensity on a Numerical Rating Scale (NRS score) during weeks 1–4 after erenumab treatment completion.

Results The 32 included patients reported a decrease in MMDs, AMDs, and NRS score during the last 4 weeks of treatment compared with baseline ($P<0.001$). During weeks 1–4 after treatment completion, all the outcome measures increased compared with the last 4 weeks of treatment ($P < 0.001$) despite staying lower than baseline (MMDs and AMDs $P < 0.001$, NRS score $P = 0.005$). Over the same time frame, 18 (56%) patients maintained a ≥ 50% reduction from baseline in MMDs. At week 4 after treatment completion, 10 (31%) patients restarted treatment due to disease rebound to baseline levels.

Conclusions More than half patients had an early disease worsening, while the remaining patients maintained their responder status during weeks 1–4 after treatment completion. Further studies might identify predictors of prolonged response to erenumab and define the optimal treatment duration according to patients' characteristics.

Keywords Migraine · Erenumab · Prevention · Calcitonin-gene-related peptide

Background

Migraine is a primary headache disorder affecting around 15% of adults worldwide [1–3]. Despite the high social and economic burden of the disease, its therapy has been empirical for decades [4]. Treatments targeting the calcitonin gene-related peptide (CGRP), one of the key mediators of migraine pain [5], have revolutionized the therapeutic scenario thanks to their specificity, efficacy, and excellent safety [6]. Anti-CGRP treatments include monoclonal antibodies (MoAbs) targeting the molecule or its receptor and non-peptide small molecules, i.e., gepants [7, 8]. Erenumab is the sole MoAb targeting the CGRP receptor, approved for the preventive treatment of both episodic and chronic migraine, and available in two monthly dosages of 70 mg and 140 mg [9]. Other MoAbs, such as galcanezumab, fremanezumab, and eptinezumab, have also been approved for both forms of disease and are available in different dosages. However, their mechanism of action is slightly different from erenumab as they target soluble CGRP instead of its receptor [10].

Preliminary evidence from 16 patients with chronic migraine enrolled in two randomized clinical trials (RCTs) suggests that the effect of erenumab and galcanezumab persists up to 3 months after the discontinuation of a prolonged treatment (12-month treatment with erenumab and 9-month treatment with galcanezumab) [11].

✉ Simona Sacco
simona.sacco@univaq.it

[1] Neuroscience Section, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Via Vetoio, 67100 L'Aquila, Italy

[2] Department of Medicine and Science of Aging, 'G. D'Annunzio' University, Chieti, Italy

Published online: 02 January 2021

In the present study, we aimed at assessing the early effect of erenumab discontinuation after a 52-week treatment on headache frequency, intensity, and acute medication consumption in patients with chronic or episodic migraine. We further aimed at comparing patients' baseline characteristics based on their responder status after erenumab discontinuation.

Methods

Study design and setting

The study was checked against relevant items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. Patients referring to two Centers (L'Aquila-Avezzano and Chieti) between December 2019 and October 2020 were included in a prospective real-life multicenter study [13].

Participants

Inclusion criteria

We included patients aged 18–65 years suffering from chronic or episodic migraine with or without aura, according to the International Classification of Headache Disorders (ICHD-3) [14], and reporting at least two prior preventive treatment failures [15]. Additional selection criteria were the completion of a 52-week treatment with erenumab 70 or 140 mg and ≥ 50% reduction from baseline in median monthly migraine days (MMDs) throughout the last 24 weeks of treatment. This criterion was established to mitigate fluctuations in patients' response unrelated to treatment discontinuation. Dose escalation from 70 to 140 mg of erenumab was allowed during the treatment period according to the physicians' judgment.

Exclusion criteria

Patients, who did not complete the 52-week treatment or did not attend all the follow-up visits, were excluded from the present analysis. Moreover, patients, whose response to drug fluctuated over the last 24 weeks of therapy, were also excluded.

Study procedures

The study comprised a 4-week baseline phase, a 52-week treatment phase, and an 8-week follow-up after treatment completion (i.e., 5–12 weeks from the last erenumab injection) (Fig. 1). All patients received monthly treatment with erenumab for 52 weeks and then discontinued the drug as suggested by the European guidelines [15]. Patients further attended visits at 4 and 8 weeks after erenumab treatment completion (i.e., at 8 and 12 weeks after the last erenumab injection).

Treatment restart was considered at week 4 after erenumab treatment completion based on patients' individual characteristics and needs. Due to the lack of guidelines on this issue, we generally restarted treatment in patients with a ≥ 70% increase MMDs compared with the last 4 weeks of erenumab treatment, and/or in those reporting an overall increased burden of disease affecting their quality of life. When restarted, erenumab was administered at the same dosage of the last 4 weeks of treatment. Besides, concurrent oral preventatives remained unchanged during the entire follow-up period.

Data collection and variables

We collected patients' age, sex, medication overuse, disease duration, and number of prior preventive treatment failures at baseline. Patients reported MMDs, monthly acute medications days (AMDs), and pain intensity measured on a 0–10 Numerical Rating Scale (NRS) scores in migraine-specific diaries for the entire study period (i.e., during baseline, during the last 4 weeks of treatment and up to week 8 after treatment completion). A "migraine day" was defined accordingly to the ICHD-3 criteria [14]. We further computed the responder rate as the reduction from baseline in median MMDs (i.e., a 30–50–75–100% response is a 30–50–75–100% reduction from baseline in MMDs). Data were entered in an electronic anonymized database for the analyses.

Study outcomes

Primary study outcomes were responder rates and changes in MMDs, AMDs, and NRS score during weeks 1–4 after erenumab treatment completion as compared with baseline and the last 4 weeks of erenumab treatment. Secondary study outcomes were responder rates and changes in MMDs, AMDs and NRS score in patients who did not restart erenumab treatment during weeks 5–8 after erenumab treatment completion compared with the last 4 weeks of treatment and with baseline. We further reported changes in the same outcome measures in patients restarting erenumab treatment.

Statistical analyses

We reported descriptive statistics about patients' demographic characteristics and outcome measures. Categorical data were reported as number and percentage, while continuous data were reported as median and interquartile range (IQR). We divided patients in two groups based on < 50% or ≥ 50% response during weeks 1–4 after treatment completion. We used the χ^2 test to compare categorical data and the Mann–Whitney U test to compare continuous data across these two

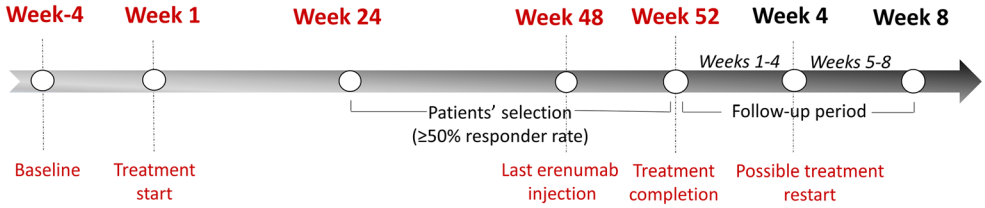

Fig. 1 Timeline of the study. According to inclusion criteria, patients, who completed a 52-week treatment and had ≥ 50% response throughout the last 24 weeks of treatment, were enrolled and attended an 8-week follow-up after treatment termination. Treatment restart was allowed at week 4 after treatment completion in case of ≥ 70% increase in monthly migraine days compared with the last 4 weeks of treatment and/or in case of patients' needs

groups throughout the assessment timepoints. We further used the Wilcoxon signed rank test to compare continuous data, namely MMDs, NRS score, and AMDs, across the study timepoints.

Results

Demographic and baseline patients' characteristics

Out of 57 patients who completed a 52-week treatment with erenumab, 32 (56.1%) were > 50% responders throughout the last 24 weeks of treatment and were included in the present analysis. Overall, patients were mostly female (27; 84%) with a median age of 50 years (IQR 41–53) and a median migraine duration of 28 years (IQR 30–37). Specifically, 8 (25%) suffered from episodic migraine and 24 (75%) from chronic migraine; 17 patients (53%) reported medication overuse (Table 1).

Primary outcomes

During weeks 1–4 after erenumab treatment completion, 18 (56%) patients were ≥ 50% responders; in detail, 11 (34%) were 50–75% and 7 (22%) 75–100% responders. Conversely, 14 (44%) patients reported < 50% response; specifically, 8 (25%) were < 30% and 6 (19%) 30–50% responders. There was no statistical difference between ≥ 50 and < 50% responders in terms of baseline characteristics and severity of disease (Table 1).

During the last 4 weeks of erenumab treatment, median MMDs, AMDs and NRS scores significantly decreased compared with baseline. During weeks 1–4 after treatment completion, all the outcome measures remarkably increased compared with the last 4 weeks of treatment although staying lower than baseline (Fig. 2 and Table 2).

Secondary outcomes

During weeks 1–4 after treatment completion, ≥ 50% responders registered a significant increase in MMDs, AMDs and NRS score compared with the last 4 weeks of treatment up to median values, which were still lower than baseline (Fig. 3; Table 2). Conversely, over the same time frame, < 50% responders reported a significant increase in MMDs, AMDs, and NRS score compared with the last 4 weeks of treatment up to values similar to baseline (Fig. 3; Table 2).

During weeks 5–8 after treatment completion, 22 (68.7%) patients did not restart erenumab treatment due to sustained benefits, whereas 10 (31.2%) restarted the treatment. Specifically, 14 (63.6%) of the 22 patients who did not restart treatment were ≥ 50% responders; 9 (40.9%) were 50–75% and 5 (22.7%) > 75% responders. During weeks 1–4 after treatment completion, the 22 patients not restarting treatment reported a significant increase in MMDs, AMDs, and NRS scores compared with the last 4 weeks of treatment up to values still lower than baseline. Similar results were reported during weeks 5–8 after treatment completion (Table 1—Supplementary).

Contrariwise, during weeks 5–8 after treatment completion, 8 (80%) of the 10 patients who restarted erenumab were ≥ 50% responders: 4 (40%) were 50–75% and 4 (40%) were > 75% responders. During weeks 1–4 after treatment completion, the 10 patients restarting treatment reported median MMDs, AMDs, and NRS score remarkably higher than the last 4 weeks of treatment and similar to baseline. However, during weeks 5–8 after treatment completion, MMDs and AMDs were similar to the last 4 weeks of treatment and remarkably lower than baseline; NRS score was the sole measure remaining comparable to baseline (Table 1—Supplementary).

At week 8 after treatment completion, 15 more patients restart erenumab, thus leading to a total of 25 (78.1%) patients restarting the treatment.

Discussion

Overall, our preliminary data showed that early outcomes of erenumab discontinuation vary across patients. Indeed, more than half of our cohort reported ≥ 50% response during weeks 1–4 after erenumab treatment completion. Some of those patients continued reporting low headache frequency, acute medication consumption, and headache intensity compared

Table 1 Baseline characteristics of the whole study cohort and of patients who had a < 50% or ≥ 50% response to erenumab during weeks 1–4 after treatment completion

	Baseline characteristics ($n = 32$)	< 50% responders at weeks 1–4 after treatment completion ($n = 14$)	≥ 50% responders at weeks 1–4 after treatment completion ($n = 18$)	*P* value
Female sex, *n* (%)	27 (84.4)	11 (78)	16 (89)	0.425
Form of disease				0.681
Episodic migraine, *n* (%)	8 (25)	3 (21)	5 (28)	-
Chronic migraine, *n* (%)	24 (75)	11 (79)	13 (72)	-
Age, median (IQR)	50 (41–53)	49 (38–59.5)	49 (38–51)	0.077
Medication overuse, *n* (%)	17 (53.1)	8 (57)	9 (50)	0.688
Disease duration (years), median (IQR)	28 (20–37)	27 (19.7–43.5)	28 (19–35)	0.110
No. of prior preventive failure, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.064
Erenumab 140 mg dose at week 52, *n* (%)	10 (31.3)	3 (21)	7 (39)	0.290
MMDs, median (IQR)	23 (14.2–29.5)	25.5 (14.7–30)	20.5 (12.7–27.2)	0.377
AMDs, median (IQR)	17 (11–26.5)	15.5 (6–25.5)	19 (11.7–27.7)	0.377
NRS, median (IQR)	8 (6.2–9)	8 (6–9)	8 (7–9.5)	0.667

AMDs days of acute medication, *IQR* interquartile range, *MMDs* monthly migraine days, *n* number, *No.* number, *NRS score* Numerical Rating Scale

with pre-treatment levels even during weeks 5–8 after erenumab treatment completion. However, the remaining patients had < 50% responder rate during weeks 1–4 after treatment completion and a subsequent increase in the burden of migraine, which made necessary a new course of treatment in some cases. Pharmacokinetics of the drug might justify a prolonged response in some patients. Indeed, erenumab has a half-life of 28 days [9]; its plasma concentration progressively reduces to 50% after one month and 25% after 2 months. A residual action of the drug after discontinuation might explain the persistent benefit in some patients.

The European guidelines on the use of MoAbs suggest a 12-month (i.e., 52-week) treatment duration. This recommendation is based on expert consensus and on data from RCTs. However, it is still unclear whether long treatment courses might lead to a persistent downregulation of the CGRP pathway and exert a "disease-modifying" action on migraine. The progression of disease from an episodic into a more severe chronic form is the result of structural and functional brain

Table 2 Outcome measures of the whole study cohort and of patients who had a < 50% or ≥ 50% response to erenumab during weeks 1–4 after treatment completion

	Baseline	Last 4 weeks of treatment	*P* value*	Weeks 1–4 after treatment completion	*P* value*	*P* value**
MMDs						
≥ 50% response ($n = 18$)	20.5 (IQR 12.7–27.2)	3.5 (IQR 2–5.5)	*P < 0.001*	5 (IQR 3.7–8.5)	*P < 0.001*	*P = 0.018*
< 50% response ($n = 14$)	25.5 (IQR 14.7–30)	4 (IQR 1–5.5)	*P = 0.001*	15 (IQR 12.5–30)	P = 0.074	*P = 0.001*
Overall ($n = 32$)	23 (IQR 14.2–29.5)	4 (IQR 2–5)	*P < 0.001*	8 (IQR 5–15)	*P < 0.001*	*P < 0.001*
AMDs						
≥ 50% response ($n = 18$)	19 (IQR 11.7–27.7)	3 (IQR 2–5.5)	*P < 0.001*	5 (IQR 3.7–9.5)	*P < 0.001*	*P = 0.004*
< 50% response ($n = 14$)	15.5 (IQR 6–25.5)	3.5 (IQR 1–5.5)	*P = 0.003*	15 (IQR 8–30)	P = 0.328	*P = 0.001*
Overall ($n = 32$)	17 (IQR 11–26.5)	3 (IQR 1.2–5)	*P < 0.001*	8 (IQR 5–15)	*P < 0.001*	*P < 0.001*
NRS score						
≥ 50% response ($n = 18$)	8 (IQR 7–9.5)	5.5 (IQR 4.7–7)	*P < 0.001*	8 (IQR 5–8.2)	*P = 0.013*	*P = 0.002*
< 50% response ($n = 14$)	8 (IQR 6–9)	7 (IQR 3.7–7)	*P = 0.003*	7.5 (IQR 5.7–8.2)	P = 0.191	*P = 0.011*
Overall ($n = 32$)	8 (IQR 6.2–9)	6 (IQR 4.2–7)	*P < 0.001*	8 (IQR 5–8)	*P = 0.005*	*P < 0.001*

AMDs days of acute medication, *IQR* interquartile range, *MMDs* monthly migraine days, *n* number, *NRS score* Numerical Rating Scale

**P* value compared with baseline; ***P* value compared with the last 4 weeks of treatment, *P values* in italics are statistical significant

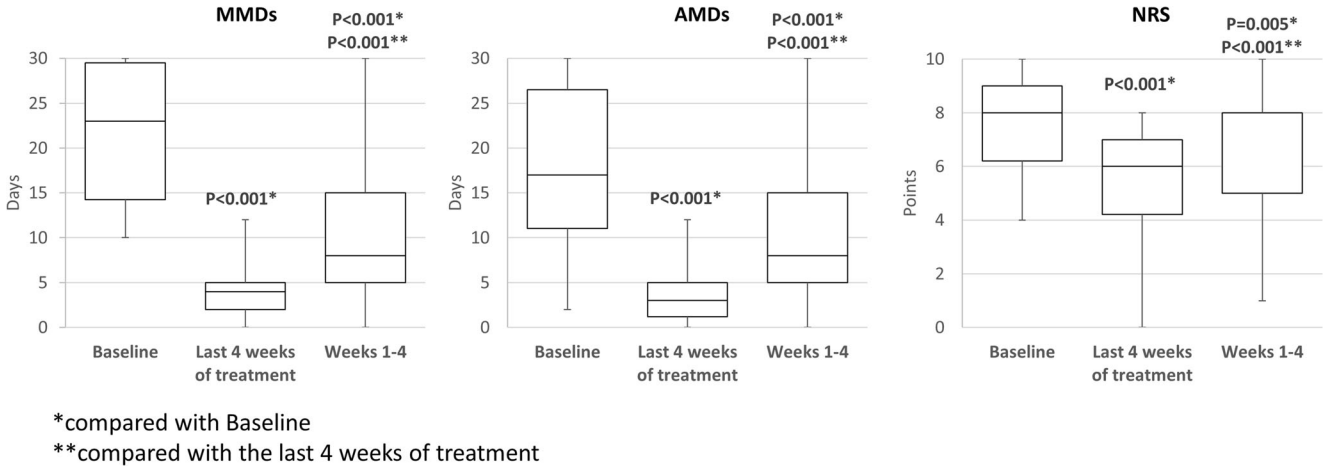

Fig. 2 Box plots representing monthly migraine days, monthly days of acute medication consumption, and headache intensity at baseline, during the last 4 weeks of treatment and during weeks 1–4 form treatment completion. Data refer to the 32 patients, who received a 52-week treatment, attended an 8-week follow-up after treatment completion and reported a ≥ 50% response throughout the last 24 weeks of treatment

changes leading to pain sensitization [16]. Reverting these changes is the ultimate goal of preventive treatments [5], which, in our opinion, might require a longer treatment duration.

This is the first study evaluating the effects of erenumab discontinuation in a real-life setting. The sole published study assessing the therapeutic effect of MoAbs after treatment completion was a retrospective pooled analysis of patients suffering from chronic migraine, who completed the open-label extension study phase of the REGAIN trial on galcanezumab and NCT02174861 trial on erenumab [11]. Patients included in that analysis had been treated for 9 months with galcanezumab and 12 months with erenumab and had attended a 12- week follow-up after treatment discontinuation. In that work, MMDs, as well as the other outcomes, did not significantly increase 1–4 weeks after treatment

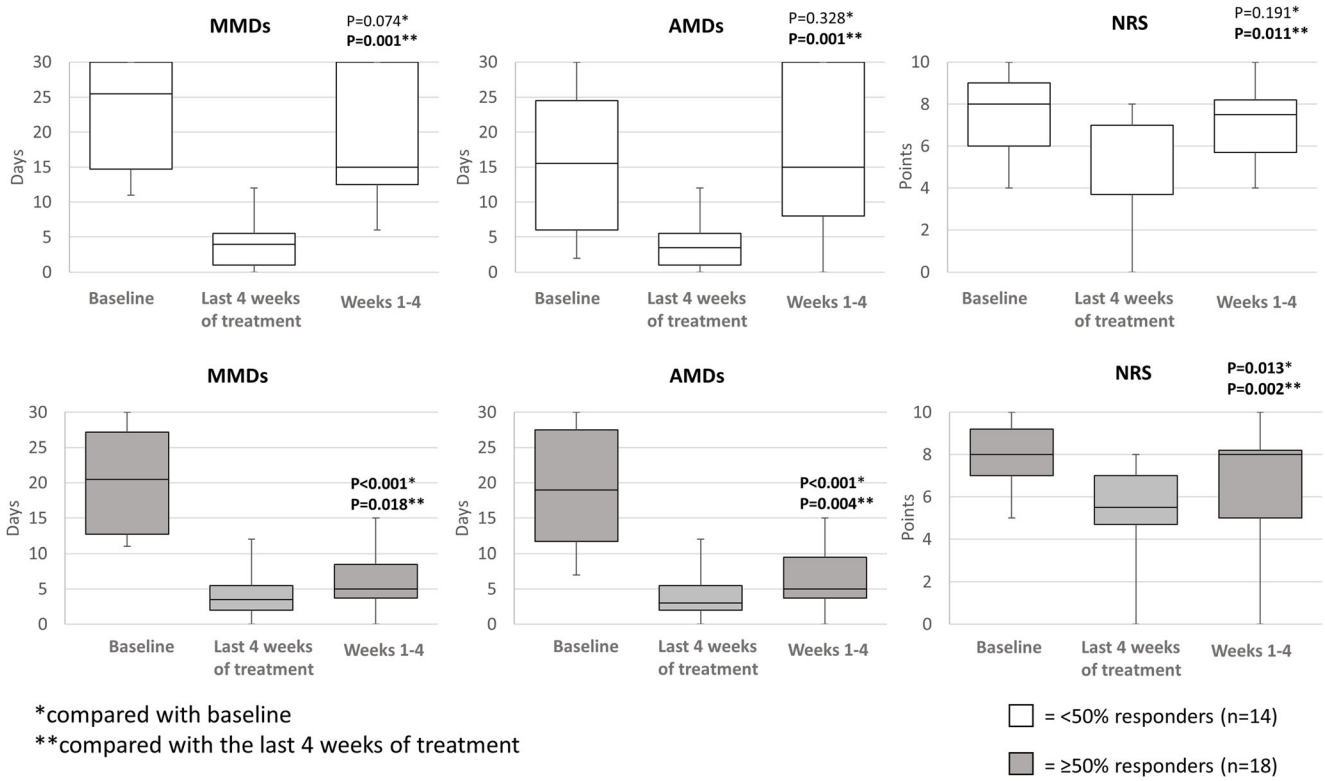

Fig. 3 Box plots representing monthly migraine days, monthly days of acute medication consumption, and headache intensity at baseline, during the last 4 weeks of treatment and during weeks 1–4 after treatment completion. Data refer to the 14 patients with < 50% response (white) and to the 18 with ≥ 50% response (grey) during weeks 1–4 after treatment completion

discontinuation compared with the last 4 weeks of treatment. We achieved similar results in our cohort of patients suffering from a more severe form of disease, as indicated by a higher number of MMDs (23 median days vs 18.38 mean days) and AMDs (18 median days vs 12.75 mean days) at baseline.

A limitation of the present study is the small cohort of 32 patients, which did not allow us to identify predictors of sustained response, such as baseline disease severity. Besides, we did not evaluate long-term effects of treatment discontinuation due to the short 8-week follow-up. Nevertheless, a group of migraineurs suffered from disease rebound just a few weeks after treatment discontinuation and benefitted from prompt erenumab restart. The Italian Health System reimburses a 12-month treatment with anti-CGRP MoAbs followed by a minimum 3-month washout. Therefore, the immediate consequences of drug discontinuation would be useful to redefine optimal treatment duration according to patients' characteristics. As a final consideration, patients' negative expectation following treatment completion could have led to a subjective feeling of disease rebound known as nocebo effect and partially affected our results. Future randomized controlled studies might evaluate the real impact of the nocebo effect in disease worsening after treatment discontinuation.

Conclusions

According to our real-life study, erenumab discontinuation after a 52-week treatment is followed by a sustained short-term response in many patients; however, some of them presented a rebound of the attacks. Further studies with longer follow-up will provide insights on the optimal duration of treatment and identify predictors of sustained response.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-020-05022-z.

Acknowledgments The authors wish to thank all the study patients for their kind cooperation.

Authors' contributions RO and SS conceived the study and its design. EDM and RO performed the analysis and the interpretation of data. The first draft of the manuscript was written by EDM. Data were collected by IF, VC and GA. RO, SS, MAG, and FP revised the manuscript. All authors read and approved the final manuscript.

Data availability Source data of the study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest GA has received funds for congress participation from Innovet Italia Srl, Epitech Group, and Lusofarmaco; MAG received funds for congress participation from IBSA; SS has received speaking honoraria from and has served on Advisory Boards of Abbott, Allergan, Eli-Lilly, Medscape, Novartis, Teva; RO has received sponsorship to attend meetings from Novartis and Teva; EDM, IF, VC, and FP report no conflict of interest.

Ethics approval and consent to participate The study was approved by the Internal Review Board of the University of L'Aquila (Italy), and patients gave written informed consent according to the Declaration of Helsinki.

Consent to publish Not applicable.

Code availability The study was approved by the Internal review Board of the University of L'Aquila with the number 44/2019.

References

1. (2019) Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 18(5):459–480. https://doi.org/10.1016/s1474-4422(18)30499-x
2. Stovner LJ, Andree C (2010) Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain 11(4):289–299. https://doi.org/10.1007/s10194-010-0217-0
3. Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB (2010) Migraine prevalence by age and sex in the United States: a lifespan study. Cephalalgia 30(9):1065–1072. https://doi.org/10.1177/0333102409355601
4. Martelletti P (2015) The therapeutic armamentarium in migraine is quite elderly. Expert Opin Drug Metab Toxicol 11(2):175–177. https://doi.org/10.1517/17425255.2015.982089
5. Martelletti P, Edvinsson L, Ashina M (2019) Shaping the future of migraine targeting calcitonin-gene-related-peptide with the disease-modifying migraine drugs (DMMDs). J Headache Pain 20(1):60. https://doi.org/10.1186/s10194-019-1009-9
6. Favoni V, Giani L, Al-Hassany L, Asioli GM, Butera C, de Boer I, Guglielmetti M, Koniari C, Mavridis T, Vaikjarv M, Verhagen I, Verzina A, Zick B, Martelletti P, Sacco S (2019) CGRP and migraine from a cardiovascular point of view: what do we expect from blocking CGRP? J Headache Pain 20(1):27. https://doi.org/10.1186/s10194-019-0979-y
7. Edvinsson L, Haanes KA, Warfvinge K, Krause DN (2018) CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol 14(6):338–350. https://doi.org/10.1038/s41582-018-0003-1
8. De Matteis E, Guglielmetti M, Ornello R, Spuntarelli V, Martelletti P, Sacco S (2020) Targeting CGRP for migraine treatment: mechanisms, antibodies, small molecules, perspectives. Expert Rev Neurother 20:627–641. https://doi.org/10.1080/14737175.2020.1772758
9. Agency EM (2019) Aimovig, INN-erenumab
10. Raffaelli B, Neeb L, Reuter U (2019) Monoclonal antibodies for the prevention of migraine. Expert Opin Biol Ther 19:1307–1317
11. Raffaelli B, Mussetto V, Israel H, Neeb L, Reuter U (2019) Erenumab and galcanezumab in chronic migraine prevention: effects after treatment termination. J Headache Pain 20(1):66. https://doi.org/10.1186/s10194-019-1018-8
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2014) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 12(12):1495–1499. https://doi.org/10.1016/j.ijsu.2014.07.013

13. Ornello R, Casalena A, Frattale I, Gabriele A, Affaitati G, Giamberardino MA, Asseta M, Maddestra M, Marzoli F, Viola S, Cerone D, Marini C, Pistoia F, Sacco S (2020) Real-life data on the efficacy and safety of erenumab in the Abruzzo region, central Italy. J Headache Pain 21:32
14. (2018) Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 38(1):1–211. https://doi.org/10.1177/0333102417738202
15. Sacco S, Bendtsen L, Ashina M, Reuter U, Terwindt G, Mitsikostas DD, Martelletti P (2019) Correction to: European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain 20(1):58. https://doi.org/10.1186/s10194-019-0972-5
16. May A, Schulte LH (2016) Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol 12(8):455–464. https://doi.org/10.1038/nrneurol.2016.93