Real-life assessment of erenumab in refractory chronic migraine with medication overuse headache

Real-life assessment of Erenumab in Refractory Chronic Migraine with Medication Overuse Headache

Keywords: anti-CGRP; calcitonin gene-related peptide; OnabotulinumtoxinA; migraine treatment, prophylaxis.

Abstract

Objective: To determine whether erenumab is effective and safe in refractory chronic migraine with medication overuse headache.

Methods: In this prospective, multicentric, real-life study, chronic migraine with medication overuse headache patients who received erenumab were recruited. Study inclusion was limited to patients who previously failed onabotulinumtoxinA in addition to at least three other pharmacological commonly used migraine preventive medication classes.

Results: Of 396 patients who received erenumab, 38% (n=149) met inclusion criteria. After three months, 51% (n=76) and 20% (n=30) patients achieved ≥ 50% and ≥ 75% reduction in monthly headache days, respectively. Monthly pain medications intake decreased from 46.1±35.3 to 16.8±13.9 ($p < 0.001$), whilst monthly headache days decreased from 25.4±5.4 to 14.1±8.6 ($p < 0.001$). Increasing efficacy of erenumab over the study period was observed. Allodynia was a negative predictive factor of erenumab response (odds ratio =0.47; p =0.03). Clinical conversion to episodic migraine with no medication overuse was observed in 64% (n=96) patients. No serious adverse events were observed.

Conclusions: Erenumab reduced significantly migraine frequency and pain medication intake in refractory chronic migraine with MOH patients.

Introduction

Chronic migraine (CM) patients represent 3-4% among migraineurs[1], and they are at higher risk of developing medication overuse headache (MOH)[2]. Both CM and MOH weigh significantly on disability and economic burden[3], thus requiring effective therapeutic treatments. Nonetheless, a subgroup of CM patients is refractory to recommended preventive treatments and has been historically neglected by research studies. Accordingly, despite different operational definitions of refractory/resistant migraine have been proposed[4-7], none has ever been included in the International Headache Classification so far[8].

Monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor have largely proven their efficacy in both episodic and chronic migraine patients[9-14], however, few studies have evaluated their benefit in difficult-to-treat migraineurs[15-19]. We aimed to investigate the effectiveness and safety of erenumab in patients suffering from CM with MOH, selected from four tertiary headache centers as the most refractory ones, who failed at least three migraine preventive classes in addition to onabotulinumtoxinA (BoNTA).

Methods

Standard protocol approvals, registrations, and patient consents

The study was approved by an independent ethics committee or local institutional review board at each participating site, and written informed consent was obtained from all enrolled patients. All clinical investigations were conducted according to the latest version of the Declarations of Helsinki.

Patients' eligibility criteria and Study design

This was an observational, multicentric, prospective, real-life, cohort study. We prospectively recruited patients from the four tertiary headache centers authorized to the prescription of onabotulinumtoxinA and monoclonal antibodies against GCRP or its receptor in Emilia-Romagna

Region (Bologna, Modena, Parma, and Ravenna), Italy. From May 2019 to May 2020, we included in the study consecutive patients who suffered from CM with MOH, defined by the International Classification of Headache Disorders-Third edition (ICHD-3)[8], who received erenumab and were followed up for at least three months. All recruited patients were aged 18–65 years and had migraine onset before 40 years of age. Furthermore, we included only the most resistant patients among CM and MOH sufferers, who have previously failed BoNTA in addition to at least three other migraine preventive medication classes, either because of lack of efficacy or intolerable side effects, amongst the following drug classes: (i) tricyclic antidepressants, (ii) calcium channel blockers, (iii) antiepileptic drugs and (iv) beta-blockers. We defined these patients as suffering from refractory chronic migraine. We excluded patients who did not fulfil the eligibility criteria, pregnant and breastfeeding women and individuals suffering from major cardiovascular/cerebrovascular conditions or headache disorders other than CM or MOH. Eligible patients were those who run a complete diary with monthly headache days (MHDs), monthly pain medication intake (MPMI), mean pain intensity (MPI) measured with the numeric rating scale and the 6-item Headache Impact Test (HIT-6)[20], before entering the study and during the 3-month follow-up. Patients who were already taking a migraine preventive medication prior to starting erenumab, were included in the study only if the medication dosage had been stable for at least three months and the dosage was not modified for the entire study period. At baseline, we collected demographic and anamnestic data, including headache characteristics. Patients were classified as triptan responders if they were headache free within two hours after treating with one triptan at least three attacks[21]. Patients were classified as BoNTA responders if they had ≥50% reduction in MHDs, otherwise they were classified as partial responders (30-50% reduction in MHDs) or non-responders (<30%)[22]. Patients were treated with a monthly subcutaneous injection of 70 mg of erenumab for the first two months, then they continued with erenumab 70 mg or escalated to erenumab 140 mg subcutaneous injection for the third month if they did not achieve a <30% reduction in MHDs[23].

Endpoints and assessments

The primary endpoint was to assess the ≥50% reduction in MHDs at three months (≥50% responder rate). The secondary endpoints were: to assess the ≥75% reduction in MHDs at three months (≥75% responder rate); the reduction of monthly pain medication intake and MHDs at each month; the evaluation of the MPI and the headache-related disability measured with the HIT-6 questionnaire. Additionally, we evaluated the percentage of patients who clinically converted from CM with MOH to EM every month, according to ICHD-3. Finally, we evaluated treatment safety, tolerability and adherence.

Statistics

The statistical analysis was performed with IBM SPSS Statistics Version 26. The distribution of continuous variables was verified with the Kolmorogov-Smirnov normality test. The continuous normally distributed variables were expressed as mean ± standard deviation (SD) and compared using the paired t-test; while the continuous not normally distributed variables were expressed as median and interquartile range (IQR) and compared with the Wilcoxon signed-rank test. Fisher's exact test was used for the categorical variables reported as counts and percentages. Logistic regression models were used to determine baseline epidemiological and anamnestic factors associated with erenumab response. The variables significantly associated with the responder status were then tested as independent variables in a multiple logistic regression model in order to test potentially independent association with responder status and to check for collinearity. Pearson's chi-squared goodness of fit test was performed to assess the overall goodness of fit of the model. The odds ratios (ORs) and the 95% confidence intervals (CI) of the risk factors were reported. All calculated p-values were two-tailed. Statistical significance was set at $p<0.05$.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Patient disposition and baseline characteristics

During the study period, 149 patients satisfied inclusion criteria among 396 migraineurs who received erenumab. Patients were selected from the tertiary headache centers of Bologna (73 out of 167 patients), Modena (56 out of 137 patients), Parma (14 out of 53 patients) and Ravenna (six out of 37 patients). Baseline epidemiological and anamnestic characteristics are summarized in **Table 1**. Most of the patients were females and medical history of depressive disorders were common (23%). More than half of the patients were responsive to triptans. Eighty-nine patients (59%) were taking at least one further migraine preventive drug treatment concomitantly with erenumab. Almost all patients failed BoNTA due to lack of efficacy (61% zero effect; 36% poor effect), while only four patients reported clinical benefits but discontinued BoNTA treatment due to tolerability issues. Previous failed migraine preventive medication classes are illustrated in **Figure 1**. Seventy-nine patients (53%) escalated dosage of erenumab to 140 mg at the third dose because they displayed a <30% reduction in MHDs (BoNTA non-responders). Only two patients discontinued study treatment after two doses due to personal choice related to lack of efficacy of erenumab 70 mg. No patients were lost to follow-up.

Efficacy outcomes

After three months 76/149 (51%) patients achieved the primary outcome as ≥ 50% responders, including 30 (20%) patients who obtained a reduction of MHDs ≥ 75%. Rates of responders increased over time as shown in **Figure 2 and Figure 3**. Similarly, we observed a statistically significant increasing benefit over time in secondary therapeutic outcomes (**Figure 4**). Mean number of MHDs decreased from 25.4 ± 5.4 to 14.1 ± 8.6 ($p<0.001$), while the mean number of monthly pain medications intake decreased from 46.1 ± 35.3 to 16.8 ± 13.9 ($p<0.001$). Moreover,

disability evaluated with HIT-6 decreased from 66.2 ± 6.3 to 56.7 ± 9.2 ($p<0.001$). Finally, MPI decreased from 7.9 ± 1.7 to 5.9 ± 1.6 ($p<0.001$) at last follow-up.

Baseline headache characteristics were analyzed using logistic regression models in order to identify prognostic factors of erenumab response (**Table 1**). The univariate analysis revealed an association with a longer history of MOH, a more frequent presence of allodynia and being BoNTA non-responders. According to multivariate analysis, only the presence of allodynia remained a significant negative predictor of treatment response (OR= 0.47; CI 0.24-0.94; p=0.034) **(Table 1)**. The Pearson chi-squared goodness of fit test indicated that the model fitted reasonably well (χ^2=116.25, P=0.127).

Considering international headache diagnostic criteria, 96/149 (64%) of patients were clinically converted to EM with no medication overuse at three months. Status change increased over time during the study period as shown in **Figure 3.**

Safety and tolerability

During the three months of follow-up, no serious adverse event was observed. Minor adverse events were reported by 47 (32%) patients, among which the most commons were: constipation, stomach ache/nausea, flu-like symptoms, injection-site reaction and pruritus. **Table 2** summarized all adverse events.

Discussion

The results of our study confirm the effectiveness and safety of erenumab, even in very difficult-to-treat migraine patients who suffer from refractory chronic migraine with MOH. Notably, we observed a clinically significant response to erenumab since the very first month of treatment and an increase of such response during follow-up. Since a placebo response usually decreases with a longer treatment duration, increasing effectiveness is likely related to erenumab itself, either secondary to a longer drug exposure duration or a higher dosage. Similarly, another study showed a persistent trend of increasing benefit even after six months of treatment[15].

The percentage of patients achieving ≥50% responder status in our cohort (51%) is comparable to that reported in erenumab randomized controlled trials (RCTs), ranging from 30% to 50%[11,24,25]. However, RCTs were limited to chronic migraine patients who experienced less than 2-4 preventive treatment failures[11,24,25], excluding more therapy resistant/refractory patients. Accordingly, resistant and refractory migraine are disabling conditions which have been historically neglected by both clinical studies and diagnostic criteria; hence the two terms have been long used interchangeably. Few real-life retrospective[18,26] and prospective[15,16,27,28] studies have investigated specifically erenumab efficacy in resistant migraine so far, however, no one selected such a difficult-to-treat migraine population in terms of therapy refractoriness, headache frequency and analgesic consumption compared to ours. Notably, all these studies, as ours, showed a consistent efficacy of erenumab in resistant migraine patients, regardless of different inclusion criteria. Raffaeli et al.[26] retrospectively analyzed the effect of erenumab in patients who had six previous therapeutic failures including BoNTA and, at three months of follow-up, one third of the patients achieved a ≥50% responder rate. Two further recent studies[15,28] prospectively analyzed resistant chronic migraine patients, irrespective of BoNTA use and medication overuse. Lambru et al.[15] prospectively evaluated migraine patients who failed at least three preventive pharmacological treatments and observed a ≥50% responder rate of 35% at three months of follow-up, while Russo et al.[28] showed a 53% responder rate in 70 patients with previous treatment failure of at least four migraine medication classes or BoNTA. Our group previously showed a 38% responder rate in a preliminary analysis of a monocentric prospective study evaluating CM patients with MOH who failed at least ten preventive pharmacological and non-pharmacological migraine treatments[27].

Noteworthy, in our and previous studies, anti-CGRP mAbs have consistently showed efficacy also in BoNTA non-responders, regardless of a shared trigeminal targeted mechanism. The underpinning biologics still remain to be fully unveiled, yet preclinical evidence showed partially complementary and synergistic action of these therapies, potentially explaining the observed different treatment responses[29]. Indeed, BoNTA acts peripherally inhibiting the release of pain-modulating substances,

including CGRP, from extracranial and meningeal C-fibres. Conversely, anti-CGRP mAbs act more systemically, yet selectively, on CGRP ligand and receptor interaction, predominantly within meningeal vessel walls and meningeal Aδ-fibres[29].

Status change from chronic to episodic migraine with resolution of MOH was observed in 64% of our cohort. Even though in a smaller sample size cohort and with less drug refractoriness compared to our study, similar results have been already observed in both real-life studies[16,18] and a RCT subgroup analysis[30], where MOH resolution after treatment ranged from 47% to 73%, irrespective of whether detoxification treatment strategies were adopted or not. Notably, nowadays there is no evidence regarding a potential additional benefit of detoxification in migraine patients with MOH starting an anti-CGRP treatment[31]. Looking at baseline predictive factors of erenumab response (**Table 1**), we found that a longer MOH duration, a zero response to BoNTA as well as a higher recurrence of allodynia during migraine attacks were associated, yet only allodynia was persistently a negative predictive factor in multivariate analysis. Cutaneous allodynia is associated with higher serum CGRP levels and anti-CGRP monoclonal antibodies have shown therapeutic benefit also in these patients[32]. However, it is considered a symptom of central sensitization in CM[33] that leads to neuroplastic changes over time and usually reflects a more severe disease status[34], potentially resulting in higher resistance to treatment[35], as in our patients.

During the follow-up period, we did not observe any serious adverse event. In our study, constipation was observed far more frequently (19%) compared to RCTs (1,3-4,0%), consistently with previous real-life studies (13,5-23,9%) [15,16,26,28,36]. Nonetheless, we did not observe any adverse event-related discontinuation in our study. This result confirms the high tolerability and adherence to erenumab, which is remarkable since patients who suffer from CM are notoriously more prone to discontinue treatment over time[37]. Notably, despite CGRP involvement in the gastro-intestinal tract regulation[38], an open-label extension study proved long-term tolerability of erenumab without an increased constipation risk over time[39].

Our study has several limitations. First, we did not compare baseline treatment response to each dose of erenumab (70 mg vs 140 mg). Therefore, increasing effectiveness over time may have been related to a higher dosage rather than a longer treatment duration since more than half of our cohort escalated to erenumab 140 mg at the third dose. Second, our study lacks a controlled group, preventing to detect a potential placebo effect. Third, we were not able to address whether a higher treatment effectiveness and resolution of MOH could be achieved based on detoxification strategies prior to erenumab treatment. Ultimately, the study follow-up was limited to three months.
Further research will be needed to evaluate whether resistant migraine patients should initiate treatment with erenumab 140 mg and whether detoxification prior anti-CGRP treatment may result in additional benefit in MOH patients. Moreover, future studies will need to consider a longer follow-up aiming to evaluate long-term effectiveness, safety and adherence to treatment in difficult-to-treat migraineurs and uniformly use the appropriate nomenclature for such patients.

Conclusions

Our study confirms the effectiveness, safety and tolerability of erenumab in a large, multicentric population of highly resistant chronic migraine with MOH. Clinical responses to erenumab in such populations suggest that temporary-related definitions such as *refractory migraine* should not weigh on the already substantial burden that migraine patients bear. On the other hand, it warrants clinical and pre-clinical research on migraine pathophysiology, especially its chronification and refractoriness to treatments, as well as on the pharmacodynamics of monoclonal antibodies. Such knowledge would allow a more personal management of migraine and would finally avoid the long search for effective preventive treatments.

Acknowledgments: We would like to thank Cecilia Baroncini who edited the English text.

References

1. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia 2010;30:599-609.
2. Munksgaard SB, Jensen RH. Medication overuse headache. Headache 2014;54:1251-7.
3. Lanteri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. Cephalalgia 2011;31:837-50.
4. D'Amico D, Leone M, Grazzi L, Bussone G. When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? Neurol Sci 2008;29 Suppl 1:S55-8.
5. Schulman EA, Brahin EJ. Refractory headache: historical perspective, need, and purposes for an operational definition. Headache 2008;48:770-7.
6. Schulman EA, Lake AE, 3rd, Goadsby PJ, et al. Defining refractory migraine and refractory chronic migraine: proposed criteria from the Refractory Headache Special Interest Section of the American Headache Society. Headache 2008;48:778-82.
7. Sacco S, Braschinsky M, Ducros A, et al. European headache federation consensus on the definition of resistant and refractory migraine : Developed with the endorsement of the European Migraine & Headache Alliance (EMHA). J Headache Pain 2020;21:76.
8. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
9. Urits I, Jones MR, Gress K, et al. CGRP Antagonists for the Treatment of Chronic Migraines: a Comprehensive Review. Curr Pain Headache Rep 2019;23:29.
10. Tepper S, Ashina M, Reuter U, 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;16:425-34.
11. Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med 2017;377:2123-32.
12. Barbanti P, Aurilia C, Egeo G, 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 2020.
13. Tepper SJ. CGRP and headache: a brief review. Neurol Sci 2019;40:99-105.
14. Matteo E, Favoni V, Pascazio A, et al. Erenumab in 159 high frequency and chronic migraine patients: real-life results from the Bologna Headache Center. Neurol Sci 2020.
15. Lambru G, Hill B, Murphy M, Tylova I, Andreou AP. A prospective real-world analysis of erenumab in refractory chronic migraine. J Headache Pain 2020;21:61.

16. Ornello R, Casalena A, Frattale I, et al. Real-life data on the efficacy and safety of erenumab in the Abruzzo region, central Italy. J Headache Pain 2020;21:32.
17. Curone M, Tullo V, Bussone G. Effectiveness of erenumab in chronic migraine patients with associated medication overuse headache: a prospective observational study. Neurol Sci 2020;41:509-10.
18. Scheffler A, Messel O, Wurthmann S, et al. Erenumab in highly therapy-refractory migraine patients: First German real-world evidence. J Headache Pain 2020;21:84.
19. Cainazzo MM, Baraldi C, Ferrari A, Lo Castro F, Pani L, Guerzoni S. Erenumab for the preventive treatment of chronic migraine complicated with medication overuse headache: an observational, retrospective, 12-month real-life study. Neurol Sci 2021.
20. Shin HE, Park JW, Kim YI, Lee KS. Headache Impact Test-6 (HIT-6) scores for migraine patients: Their relation to disability as measured from a headache diary. J Clin Neurol 2008;4:158-63.
21. Sarchielli P, Pini LA, Zanchin G, et al. Clinical-biochemical correlates of migraine attacks in rizatriptan responders and non-responders. Cephalalgia 2006;26:257-65.
22. Bendtsen L, Sacco S, Ashina M, et al. Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. J Headache Pain 2018;19:91.
23. Ornello R, Tiseo C, Frattale I, et al. The appropriate dosing of erenumab for migraine prevention after multiple preventive treatment failures: a critical appraisal. J Headache Pain 2019;20:99.
24. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38:1026-37.
25. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet 2018;392:2280-7.
26. Raffaelli B, Kalantzis R, Mecklenburg J, et al. Erenumab in Chronic Migraine Patients Who Previously Failed Five First-Line Oral Prophylactics and OnabotulinumtoxinA: A Dual-Center Retrospective Observational Study. Front Neurol 2020;11:417.
27. Pensato U, Favoni V, Pascazio A, et al. Erenumab efficacy in highly resistant chronic migraine: a real-life study. Neurol Sci 2020.

28. Russo A, Silvestro M, Scotto di Clemente F, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. J Headache Pain 2020;21:69.
29. Pellesi L, Do TP, Ashina H, Ashina M, Burstein R. Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale? Headache 2020;60:1056-65.
30. Tepper SJ, Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. Neurology 2019;92:e2309-e20.
31. Sacco S, Bendtsen L, Ashina M, et al. 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 2019;20:6.
32. Lipton RB, Burstein R, Buse DC, et al. Efficacy of erenumab in chronic migraine patients with and without ictal allodynia. Cephalalgia 2021:3331024211010305.
33. Ashkenazi A, Sholtzow M, Shaw JW, Burstein R, Young WB. Identifying cutaneous allodynia in chronic migraine using a practical clinical method. Cephalalgia 2007;27:111-7.
34. Seo JG, Park SP. Clinical significance of sensory hypersensitivities in migraine patients: does allodynia have a priority on it? Neurol Sci 2019;40:393-8.
35. Lovati C, Giani L, Mele F, et al. Brain plasticity and migraine transformation: fMRI evidences. Expert Rev Neurother 2016;16:1413-25.
36. Barbanti P, Aurilia C, Egeo G, Fofi L. Erenumab: from scientific evidence to clinical practice-the first Italian real-life data. Neurol Sci 2019;40:177-9.
37. Schwedt TJ. Preventive Therapy of Migraine. Continuum (Minneap Minn) 2018;24:1052-65.
38. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients - a review of pros and cons. J Headache Pain 2017;18:96.
39. Ashina M, Goadsby PJ, Reuter U, et al. Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine. Cephalalgia 2019;39:1455-64.

Table 1: Demographic and baseline disease characteristics

	Total patients	≥ 50% Responders		Univariate		Multivariate	
	(N=149)	Yes (N=76)	No (N=73)	OR (95% CI)	P value	OR (95% CI)	P value
Epidemiological characteristics							
Female (%)	116 (78%)	56 (74%)	60 (82%)	0.66 (0.3-1.45)	0.3010		
Age, years (mean -SD)	51.6 ± 9.2	51.9 ± 9.8	51.3 ± 8.8	0.88 (0.68-1.09)	0.7166		
Psychiatric comorbidity							
History of depressive disorders (%)	34 (23%)	14 (18%)	20 (27%)	0.79 (0.27-1.31)	0.1933		
Migraine assessment							
Migraine duration, years	35.6 ± 11.5	36.3 ± 11.6	35.0 ± 11.6	1.01 (0.98-1.04)	0.58		
Chronic Migraine duration, years	15.4 ± 10.0	15.0 ± 9.0	16.0 ± 11.2	0.99 (0.96-1.03)	0.57		
MOH duration, months	89.1 ± 109.2	70.1 ± 106.8	108.2 ± 115.0	**1.00 (0.99-1.00)**	**0.025**	0.99 (0.99-1.00)	0.037
No. of previous pharmacological treatments failed	7.2 ± 2.4	7.1 ± 2.5	7.2 ± 2.4	0.96 (0.84-1.10)	0.53		
No. of previous non-pharmacological treatments failed	2.0 ± 2.2	1.8 ± 2.2	2.2 ± 2.1	0.91 (0.78-1.06)	0.21		
Monthly headache days	25.4 ± 5.3	25.3 ± 5.3	25.8 ± 5.3	0.98 (0.92-1.04)	0.45		
Monthly pain medication intake	46.1 ± 35.3	44.3 ± 38.1	49.7 ± 33.1	1.00 (0.99-1.00)	0.31		
Allodynia	87 (58%)	38 (52%)	49 (70%)	**0.50 (0.25-0.95)**	**0.035**	**0.47 (0.24-0.94)**	**0.034**
Triptans responders	92/149 (62%)	46/76 (60%)	46/73 (63%)	0.90 (0.46-1.74)	0.75		
HIT-6 score	66.2 ± 6.3	66.1 ± 5.4	66.3 ± 7.1	0.99 (0.94-1.05)	0.76		
Headache intensity (NRS)	7.9 ± 1.7	8.2 ± 1.6	7.7 ± 1.7	1.19 (0.98-1.47)	0.10		
Concurrent headache preventive treatment	89 (59%)	45 (59%)	44 (60%)	0.85 (0.44-1.65)	0.63		
BoNTA non-responders	91 (61%)	40 (53%)	51 (70%)	**0.48 (0.24-0.94)**	0.03	0.54 (0.27-1.07)	0.080

Baseline epidemiologic and anamnestic characteristics of the overall study cohort and further subdivided by responders and non-responders. Logistic regression analysis of baseline epidemiological and anamnestic characteristic as predictive factors of responder status is shown.

Abbreviations: MOH; Medication overuse Headache; HIT-6: headache impact test-6; NRS: numeric rating scale; BoNTA: OnabotulinumtoxinA

Table 2: List of side effects reported during study period.

Event	Number of patients (%)
Constipation	29 (19%)
Stomach ache/nausea	5 (3%)
Flu-like symptoms	4 (3%)
Injection-site reaction	3 (2%)
Pruritus	3 (2%)
Dysgeusia	1 (1%)
Skin rash	1 (1%)
Hair loss	1 (1%)
Chest constriction	1 (1%)
Low libido	1 (1%)
Total	**47 (32%)**

Figure 1: Previous migraine pharmacological treatments failed

Figure 2: Reduction from baseline in MHDs over time

Subdivision of responder rate per month based on percentage of MHDs reduction compared to baseline. Abbreviations: MHDs: monthly headache days.

Figure 3: Proportion of patients achieving ≥50% responder status and changing status to episodic migraine with no medication overuse.

The number and percentage of patients achieving ≥50% responder status, defined as reduction ≥50% of monthly headache days compared to baseline, are shown on the left. The number and percentage of patients who changed status to episodic migraine with no medication overuse, defined according to ICHD-3, are shown on the right. Abbreviations: EM: episodic migraine.

Figure 4: Reduction from baseline in MHDs, MPMI and HIT-6 over time.

Evaluation of monthly headache days, monthly pain medication intake and HIT-6 subdivided per month after erenumab treatment. Abbreviations: MHDs: monthly headache days. MPMI: monthly pain medications intake. HIT-6: Headache Impact Test.