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Prospective evaluation of aura during anti-calcitonin gene-related peptide monoclonal antibody therapy after 52 weeks of treatment

Marina Romozzi,[1] Andrea Burgalassi,[2] Catello Vollono,[1,3] Maria Albanese,[4] Giulia Vigani,[2] Francesco De Cesaris,[5] Alberto Chiarugi,[2,5] Paolo Calabresi,[1,3] Luigi Francesco Iannone[2]

[1]Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome; [2]Section of Clinical Pharmacology and Oncology, Department of Health Sciences, University of Florence; [3]Unit of Neurophysiopathology, Department of Aging, Neurological, Orthopedic and Head and Neck Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome; [4]Department of Systems Medicine, Tor Vergata University, Rome; [5]Headache Center and Clinical Pharmacology Unit, Careggi University Hospital, Florence, Italy

ABSTRACT

Background: Clinical studies have shown the efficacy and safety of monoclonal antibodies (mAbs) against calcitonin gene-related peptide (anti-CGRP) in migraine patients with and without aura. Early evidence from *post hoc* and small subgroup analyses suggests that anti-CGRP mAbs reduce the frequency and intensity of aura. Herein, we prospectively assessed the changes in aura after 12 months of anti-CGRP mAb treatment and performed a literature review.

Methods: All outpatients treated with anti-CGRP mAbs for one year in two tertiary Headache Centers and who experienced ≥1 episode of aura/month were enrolled. The study reports data from one month before (baseline) and the last three months (months 10, 11, 12) of treatment.

Results: Data from 13 patients with a diagnosis of migraine with and without aura were collected. The mean duration from aura onset was 17.8±7.9 years. At baseline nine patients (69.2%) reported visual aura, and four (30.8%) visual and sensory aura. Mean duration of aura episodes was of 34.2±15.7 minutes. At baseline, the mean number of monthly migraine days (MMDs) was 22.3±7.5, and the mean number of MMDs preceded by aura was 9.15±9.0. At month 12 of treatment, there was a significant reduction of MMDs (6.2±9.0, p=0.002) and MMDs with aura (2.6±2.7, p=0.015). Three patients reported episodes of aura without subsequent headache, a phenomenon that was absent prior to treatment. We identified 14 studies that reported changes in aura during anti-CGRP mAbs treatment.

Conclusions: This prospective study shows that anti-CGRP mAbs reduce the number of migraine attacks with aura consistently with the reduction of MMDs. Randomized studies with anti-CGRP mAbs specifically assessing migraine aura are required.

Key words: migraine, calcitonin gene-related peptide, monoclonal antibodies, aura, cortical spreading depression.

Introduction

Migraine, a common neurovascular disorder that ranks as one of the most debilitating medical conditions, with a prevalence of approximately 12% in the general population (1), is characterized by recurrent, paroxysmal attacks of varying intensity and frequency (2). Close to one-third of individuals with migraine experience aura, a reversible neurological phenomenon that manifests with visual, sensory, speech, and motor focal neurologic symptoms (3), usually lasting 5-60 minutes, either preceding or accompanying headache pain (3). Although the underlying mechanism is poorly understood, migraine appears to be due to the activation and sensitization of the trigeminovascular system (TGVS), which eventually results in the release of the neurogenic inflammatory neuropeptide, calcitonin gene-related peptide (CGRP) (4, 5), and the ensuing arteriolar vasodilatation (6) and mechanical allodynia (7). Cortical spreading depression (CSD), a self-propagating wave of depolarization spreading across the cerebral cortex, has been proposed as the pathophysiological mechanism that underlies migraine aura (4). Although experimental evidence suggests that CSD can activate the TGVS in the meninges (8), the existence of a cause and effect relationship between aura and the subsequent headache remains a debated issue (9).

Monoclonal antibodies (mAbs) against CGRP or its receptor (anti-CGRP mAbs) are a novel class of specific antimigraine drugs approved for migraine prophylaxis. Clinical trials and real-world studies have shown the efficacy and safety of anti-CGRP mAbs in patients with episodic migraine (EM) and chronic migraine (CM) (10-13). Evidence suggests that anti-CGRP mAbs attenuate the frequency and intensity of aura and reduce migraine attacks with or without aura equally (14-16). However, this conclusion mostly derives from post hoc subgroup analyses of clinical trials and retrospective case reports, or case series studies, whereas real-world studies that prospectively assess the number of attacks with aura in patients receiving long-term treatment with anti-CGRP mAbs have been limited to 3 or 6 months of follow up. Herein, we assessed the change of aura during anti-CGRP mAb treatment. Furthermore, we conducted a narrative review of the published literature on anti-CGRP mAbs treatment, with and without aura.

Results

Cohort characteristics. Overall, 315 patients were treated with anti-CGRP mAbs between December 2019 and July 2022, with the potential for a 12-month follow-up. Among the 27 (8.57%) patients who presented with aura at baseline, 6 patients were excluded due either to being lost to follow-up or not receiving treatment for 12 months. Eight additional patients were excluded due to incomplete data regarding aura in their headache diary (**Figure 1**). Of the remaining 13 patients, 9 were females (69.2%), 12 had CM (92.3%), and 12 experienced medication overuse (MO), (92.3%). Twelve patients received the diagnosis of migraine with aura and migraine without aura, while one patient had a diagnosis of migraine with aura and reported daily headaches (28/31 headache days per month) that were all pre-

ceded by aura. The mean age of the patients was 46.2±10.5 years, and the average duration of migraine was 32.0±17.2 years. **Table 1** provides further details on the demographic and clinical features, as well as concomitant and prior treatments at baseline per patient. Notably, all patients had tried at least three prior classes of ineffective preventive treatments (mean 4.3±0.9), and they exhibited a high burden of disease at baseline [monthly migraine days (MMDs) 22.3±7.5, analgesic medications per month (AMDs) 16.2±10.3, analgesic medications (AMNs) 19.9±15.9, and Migraine Disability Assessment (MIDAS) score 126.6±79.0)] (**Table 1**). Patients were treated with erenumab (4, 30.7%), galcanezumab (8, 61.5%), or fremanezumab (1, 7.6%).

Regarding aura characteristics, the mean duration from the onset of aura was 17.8±7.9 years, with an average duration of 34.2±15.7 minutes for aura episodes, regardless of type. Nine patients (69.2%) reported visual aura, while four patients (30.8%) experienced both visual and sensory aura. No other type of aura was reported. For detailed information on individual patients refer to **Table 1.**

Effectiveness of anti-calcitonin gene-related peptide monoclonal antibodies on aura. At baseline, the average number of MMDs was 22.3±7.5. Among these, an average of 9.15±9.0 were either preceded or accompanied by aura. Only one patient reported that aura preceded all his attacks. At month 12 (weeks 48-52) of treatment, the number of days with aura was reduced to 2.6±2.7 (-6.5±8.2; p=0.015), which is consistent with the stable reduction observed during the last three months of treatment (month 10 to 12) (**Figure 2**). At month 12, treatment with anti-CGRP mAbs reduced the number of MMDs (6.2±9.0, p=0.002) and other migraine-related variables (**Figure 2**), including Headache Impact Test (HIT-6) score, which dropped from 67.62±10.1 to 40.77±24.3 (p=0.005) from baseline to month-12 of treatment. A response rate ≥50% was achieved by 76.9% of patients at month 12 (**Table 1**). All patients, except one (patient number 7), reported a consistent reduction in aura episodes throughout the three months of observation during treatment. During treatment, three patients reported episodes of aura without subsequent headache, a phenomenon that was absent prior to anti-CGRP mAbs. Among these three patients, there was one case where only aura episodes without accompanying headache were reported in the absence of other types of migraine attacks.

Narrative review. We identified 14 clinical studies that reported aura features or changes in aura during treatment with anti-CGRP mAbs (**Table 2**). Among these studies, 4 were case series and 2 were case reports, 3 were subgroup post hoc analyses of randomized controlled trials (RCTs), and 5 were observational real-world studies (two retrospective and three prospective) (14-26). None of these studies, except for the case series, reported changes in aura features as the primary outcome, which, however, were MMDs with aura or differences between patients with or without a history of aura. In addition, all these studies had a limited 3-month or 6-month follow-up period, with only 1 case report having a 12-month follow-up (18, 22).

In one *post hoc* analysis of a clinical trial, galcanezumab was found to reduce MMDs with aura compared to placebo. However, the study did not report specific aura features. Reduced MMDs with aura were reported in both galcanezumab groups (receiving 120 mg or 240 mg monthly) during months from 1 to 6 [least square mean -0.7 (-1.2 to -0.2)], but the difference from placebo was not statistically significant for the 240 mg dose group at month 4, the 120 mg dose group at month 5, or either dose group at month 6 (26).

The other two post hoc subgroup analyses evaluated the efficacy and safety of eptinezumab (PROMISE trials) or erenumab (four different RCTs) for migraine prevention in patients with migraine and self-reported aura (14, 25). Both analyses showed no differences in the efficacy and safety profiles between patients with or without a history of aura. A prospective observational study with erenumab reported, in a subgroup analysis, no difference in effectiveness or tolerability between patients with migraine with aura or without aura (24).

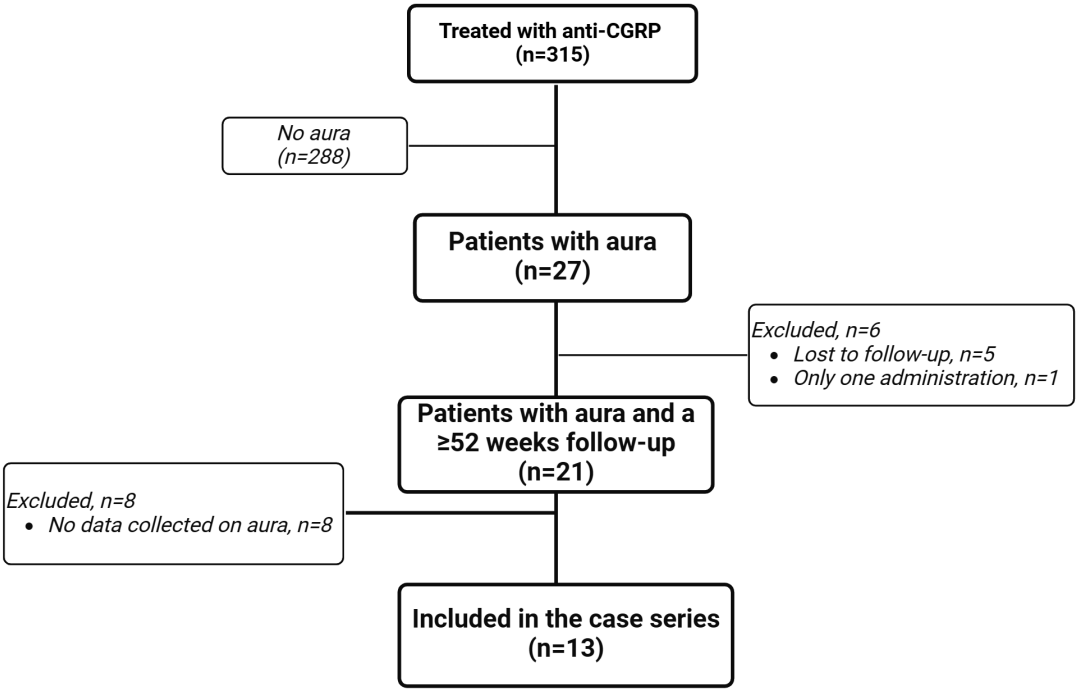
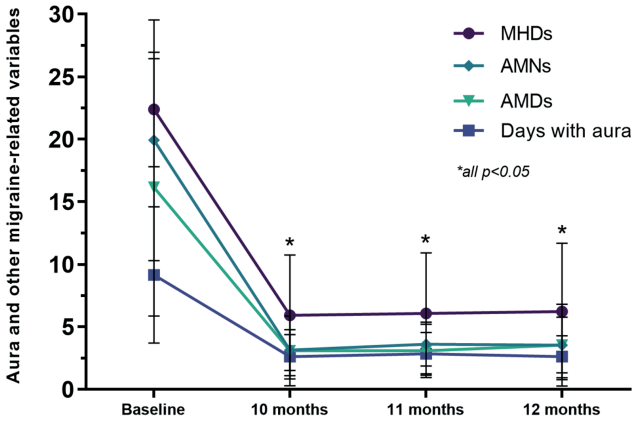


Figure 1. Flowchart of patients.

Regarding aura features, other real-world studies described a reduced incidence of aura regardless of the anti-CGRP mAb used or the type of migraine (CM or EM) (16, 19). To note, a recent study showed that after galcanezumab treatment for three months, the incidence of visual and sensory aura followed by headache was reduced regardless of responder status (namely in responders, non-responders, and super-responders) (15). However, another study showed that four patients reported a worsening of aura during treatment (21).

Recently, a case series described the effectiveness of galcanezumab in patients with sporadic and familial hemiplegic migraine, with improvement in weakness symptoms (20). However, two patients reported increased weakness during treatment (20). Finally, two case series and one case report described the complete disappearance of aura or a reduction in aura duration and intensity, or migraine frequency, with aura occurring no more than once a month in patients treated with anti-CGRP mAbs (18, 22, 27). In the most recent case series, treatment with anti-CGRP mAbs did not affect the frequency of migraine with aura. However, it reduced both the intensity and duration of headache phases of migraine aura. Additionally, some patients experienced aura attacks without accompanying headaches throughout the treatment period (28).

On the other hand, a case report describing a patient with no previous history of aura reported a new onset of visual aura after initiating galcanezumab treatment, which ceased after switching to fremanezumab (23).



AMDs, days with at least one analgesic; AMNs, absolute number of analgesics; MHDs, monthly headache days.
MHDs p=0.002; AMDs p=0.001; AMNs p≤0.006; days with aura p≤0.018.

Figure 2. Number of monthly headache days, number of analgesics per month and days with at least one analgesic use per month, and days with aura in the last three month of treatment.

Table 1. Patients demographic and clinical features at baseline and after 12 months (weeks 48-52) of treatment.

	Single patient data													Overall data	
	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean (±SD)	n (%)
Age (years)	38	45	41	53	43	57	40	42	47	53	69	48	25	46.2 (10.6)	
Sex	F	M	F	F	M	M	F	F	F	F	M	F	F		
Migraine duration (years)	26	31	31	48	19	44	33	35	7	31	NA	40	2	28.9 (13.8)	
Chronicization duration (years)	2	20	21	42	0	37	20	22	7	12	NA	23	1	17.3 (13.5)	
Years from first aura onset (years)	24	31	29	38	26	42	19	21	7	35	56	40	1	28.4 (14.7)	
Type of aura at baseline	V	V	V	V	V	V	V+S	V	V+S	V	V+S	V+S	V		
Comorbidities	N	N	N	N	Y[a]	Y[b]	Y[c]	Y[c]	N	N	N	N	N		4 (30.7)
Number of previous preventive treatments	4	3	5	3	3	5	5	5	6	4	4	5	5	4.4 (1.0)	
Concomitant treatments	N	N	N	N	N	Y	N	N	Y	N	N	Y	N		3 (23.1)
Anti-CGRP mAb	E	G	G	E	G	G	E	G	G	G	Fr	E	G		
Baseline															
Monthly migraine days	20	30	15	15	12	30	18	15	30	16	30	30	30	22.4 (7.6)	
Days with aura	2	2	8	2	1	8	10	10	10	1	30	10	25	9.1 (9.0)	
Mean aura duration (minutes)	40	20	5	30	30	60	30	30	40	20	30	50	60	34.2 (15.8)	
Days with at least one analgesic use	9	30	13	13	12	0	18	14	30	16	25	30	0	16.2 (10.3)	
Analgesics number	9	30	13	13	12	0	43	14	30	16	25	54	0	19.9 (15.9)	
MIDAS score	150	37	21	38	40	210	180	83	140	212	135	270	130	126.6 (79.0)	
HIT-6 score	66	55	70	40	65	76	72	66	72	76	76	72	73	67.6 (10.2)	
12-months follow-up															
Monthly migraine days	4	18	5	1	2	0	0	14	0	3	2	2	30	6.2 (9.0)	
Days with aura	0	0	4	0	0	4	9	6	3	0	4	2	2	2.6 (2.8)	
Days with at least one analgesic use	4	7	3	1	1	0	0	10	0	3	2	2	8	3.1 (3.3)	
Analgesics number	5	7	3	2	1	0	0	10	0	3	2	2	11	3.5 (3.7)	
MIDAS score	8	15	2	2	8	0	0	0	0	18	3	15	13	6.5 (6.7)	
HIT-6 score	50	70	52	50	48	0	0	66	0	48	54	50	42	40.8 (24.4)	

SD, standard deviation; F, female; M, male; NA, not available; N, no; Y, yes; E, erenumab; Fr, fremanezumab; G, galcanezumab; CGRP, calcitonin gene related peptide; mAb, monoclonal antibody; HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment.
[a]Tumour; [b]psychiatric comorbidities; [c]cardiovascular comorbidities.

Table 2. Clinical studies on anti-CGRP monoclonal antibody evaluating aura features or efficacy/safety in patients with migraine with aura.

First author (year)	Study design	Study description	Type of anti-CGRP mAb	N. of patients with MwA (n)	ICHD-3 diagnosis of MwA patients (n)	Treatment duration	Results
Evaluation of aura features							
Kearney (2020)	Case report	*De novo* visual aura during treatment	Galcanezumab	1	CM without aura	6 months	Emerging of aura starting treatment with galcanezumab that ceased switching to fremanezumab
Straube (2021)	Retrospective study	Treatment response on 542 patients (EM and CM) treated with erenumab	Erenumab	N/A	N/A	3 months	35.2% of patients reported a reduction of accompanying aura
Matteo (2021)	Case report	Efficacy of erenumab in a patient with MwA	Erenumab	1	CM	12 months	Migraine and aura frequency dropped to a maximum one attack per month
Scheffler (2021)	Retrospective study	Treatment response in patients with migraine and daily headache	Erenumab, galcanezumab, fremanezumab	20	CM	3 months	Self-reported reduction of aura in 4 patients, 4 worsened and 13 unchanged
Albanese (2022)	Case series	Effectiveness of anti-CGRP mAbs in patients with MwA	Galcanezumab (1), erenumab (1)	2	EM (1), MOH (1)	12 months	Complete disappearance of aura or reduced aura duration and intensity
Iannone (2022)	Prospective study	Effect of anti-CGRP mAbs on attack prodromal and accompanying symptoms in 80 patients with CM ± MOH	Erenumab, galcanezumab, fremanezumab	5	CM ± MOH (5)	3 months	All patients with MwA reported a decrease in aura incidence
Ashina S. (2023)	Observational, open-label, cohort study	Effect of galcanezumab on migraine premonitory symptoms, triggers and aura episodes in 46 patients (EM and CM)	Galcanezumab	14	EM, CM	3 months	The incidence of visual and sensory aura followed by headache was reduced in responders, non-responders, and super-responders
Igarashi (2023)	*Post hoc* analysis	*Post hoc* analysis of a RCT on the efficacy of galcanezumab in EM patients	Galcanezumab	N/A	EM	6 months	Significantly greater reductions of migraine days with aura compared to placebo
Danno (2023)	Case series	Treatment response in patients with HM	Galcanezumab	6	HM (sporadic and familial)	3 months	In 2 patients weakness improved, in 2 disappeared and in 2 increased
Braca (2023)	Case series	Effectiveness of anti-CGRP mAbs in patients with MwA	Erenumab (7), galcanezumab (3), fremanezumab (2)	14	EM (3), CM (11)	12 months	Significant reduction of migraine days with aura frequency
Cresta (2024)	Case series	Effectiveness of anti-CGRP mAbs in patients with MwA	Erenumab (3), galcanezumab (5), fremanezumab (6)	12	EM (4), CM (8)	12 months	No impact on frequency of migraine days with aura; increase number of aura attacks without headache

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Table 2. Continued from previous page.

First author (year)	Study design	Study description	Type of anti-CGRP	N. of patients with MwA mAb (n)	ICHD-3 diagnosis of MwA patients (n)	Treatment duration	Results
Ashina M. (2022)	*Post-hoc* analysis	*Post hoc* analysis of 4 RCTs to assess efficacy and safety profiles of erenumab in patients with MwA	Erenumab	1140	EM (866), CM (274)	3 months	Erenumab reduced migraine frequency and migraine-specific medication days in patients with migraine with and without a history of aura
Mahović (2022)	Prospective study	Efficacy and safety of anti-CGRP mAbs in CM patients treated with erenumab	Erenumab	17	CM	6 months	No difference in effectiveness between patients suffering from MwA and patients suffering from migraine without aura
Ashina M. (2022)	*Post-hoc* analysis	*Post hoc* analysis from the PROMISE trials to assess the efficacy and safety of eptinezumab for the preventive treatment of migraine in patients who self-reported a history of aura	Eptinezumab	877	EM (507), CM (231), MOH (139)	3 months	Eptinezumab demonstrated efficacy and tolerability in patients with migraine and self-reported history of aura. Safety profile was similar regardless of aura history

CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; HM, hemiplegic migraine; ICHD-3, The International Classification of Headache Disorders, 3rd edition; mAb, monoclonal antibody; MOH, medication overuse headache; MwA, migraine with aura; N, number; N/A, not available; RCT, randomized controlled trials.

Discussion

The present data strengthen previous findings reviewed in this paper and obtained from post hoc analyses of RTCs and real-world studies that anti-CGRP mAbs reduce MMDs both with and without aura and describe modifications in the aura symptoms after long (12 months) periods of treatment. These findings imply a role of CGRP in aura, although the underlying mechanism is unclear. Changes induced by CSD, including blood flow modifications, have been proposed to contribute to the genesis of aura and migraine headache (29). Preclinical and clinical evidence indicate that CSD may activate both peripheral and central components of TGVS (reviewed in (30, 31)). In particular, CSD has been found to release CGRP from trigeminal fibers in the dura where it triggers neurogenic inflammation, or within cerebral blood vessels thus affecting vascular tone (30). In agreement with this data, in rat cortical brain slices, endogenous CGRP was released in a calcium-dependent manner by CSD (32), and sensory denervation in the meningeal tissue eliminated the CSD-dependent neurogenic inflammatory response (32). On the other hand, there is the possibility that CGRP influences CSD, as intracerebral ventricular perfusion of an anti-CGRP antibody in rats reduced susceptibility to CSD (33).

However, other studies challenged the hypothesis that CSD is associated with CGRP. Induction of CSD did not increase CGRP levels in a cat model (34). In a study on 14 patients with migraine with aura, CGRP infusion did not trigger aura in patients who experienced headache pain after the infusion (35). In a more recent study on 139 patients with migraine, including 34 with aura, participants with migraine with aura had lower odds of developing CGRP-induced migraine attacks (36).

In rats, a selective CGRP receptor antagonist (MK-8825) inhibited pain behavior but not changes in cerebral hemodynamic responses induced by CSD (37). Furthermore, CSD induced pial and dural arterial dilation in rats, but fremanezumab did not affect cerebral blood flow elicited by CSD (38). In the presence of a compromised blood-brain barrier, fremanezumab slowed down propagation velocity and shortened the cortical recovery period or neuronal silencing induced by CSD, but did not prevent initiation or propagation of pinprick-induced CSD waves in rats (38). A recent case report with functional magnetic resonance imaging of trigeminal nociception, suggests that the aura is just an epiphenomenon that is unrelated and does not initiate headache attacks (9).

Due to their dimension and peptidic nature, anti-CGRP mAbs poorly penetrate the blood-brain barrier (39). In rats, between 0.1-0.3% of the plasma concentration of galcanezumab was detected in the central nervous system (40). Thus, assuming that aura originates in the brain tissue, a direct action of anti-CGRP mAbs at this level remains to be demonstrated. However, in a functional magnetic resonance imaging study of migraine patients treated with erenumab, a reduction in hypothalamus activation was reported only in responders, suggesting that the small amount of CGRP mAbs that crosses the blood-brain barrier may exert a direct action at this level (41). The alternative possibility is that inhibition of CGRP or CGRP receptor in the periphery indirectly influences brain functioning, including CSD. However, the proposal that CSD triggers attacks of migraine pain is challenged by the observation that tonabersat, which successfully inhibited CSD responses in rodents (42, 43), reduced the number of auras but not of migraine attacks in

patients (17). Thus, the link between CSD, migraine aura, and the ensuing headache remains undetermined. Independently from the role of CSD as the main trigger of the migraine attack, CSD remains the major culprit of the migraine aura (17).

The present findings suggest that the hypothesis that CGRP is exclusively involved in the pain phase of migraine with aura may be reductive. Anti-CGRP drugs reduced the number of MMDs with aura in a manner comparable to the reduction of MMDs without aura and days with the use of migraine-specific analgesics. Only one real-world study reported a reduction of the number of auras in patients who did not show a significant reduction in MMDs (non-responders) after anti-CGRP mAbs (44). On the other hand, in a few patients a worsening of the intensity or frequency of auras was reported, and in one patient galcanezumab treatment caused a de novo onset of aura that surprisingly disappeared after switching to fremanezumab (23). Additional difficult-to-explain findings were also reported in our cohort. In fact, three patients reported episodes of aura without subsequent headache, which were not present prior to anti-CGRP treatment, consistent with the observations in the case series by Cresta *et al.* (28). These findings also suggest the necessity to monitor whether these phenomena occur in patients with migraine with aura who are treated with anti-CGRP mAbs or if it is only coincidental.

The study has several strengths and limitations. This is a multicentric study with data collected prospectively, carefully collecting acute medication use and including disability questionnaires. There are also some limitations to acknowledge. First, the sample size is relatively small, although higher than most real-world studies published so far on the topic. Second, the exclusion of a proportion of patients with migraine with aura due to insufficient data may have resulted in a selection bias.

Conclusions

The present prospective study, accurately reporting not only the number of migraine days with aura, but also auras without headache, their duration, and type of aura, presents a better quality of results obtained in migraine patients treated with anti-CGRP mAbs compared to previous literature. However, although increasing evidence supports the view that inhibition of the CGRP signaling pathway ameliorates the frequency and severity of aura, further studies are needed to establish a cause-and-effect relationship between CGRP and migraine aura. In clinical practice, aura and autonomic symptoms are often overlooked, with more emphasis placed on pain and other troublesome symptoms. However, migraine aura, due to the intrinsic alarming effect in the clinical management of the disease, requires more attention and specifically dedicated studies, particularly in view of the potential beneficial effects of treatment with anti-CGRP mAbs.

Materials and Methods

Design. This is a case series of patients from two outpatient headache clinics (*Careggi University Hospital in Florence* and *Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome*). The inclusion period ranged from December 2019 to February 2023. Data were collected following the usual clinical practice. All patients signed informed consent and started treatment with anti-CGRP mAbs (anti-ligand or receptor). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and is part of the *Registro Italiano Cefalee* study, which was approved by the local Ethics committee (CEAVC Studio RICe, 14591_oss and subsequent amendments 2022-609).

Patient selection and variables collected. Study participants were patients older than 18 years with EM or CM according to The International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria (3), with or without MO, who started a preventive therapy with anti-CGRP mAbs (erenumab 70-140 mg monthly; galcanezumab 240 mg first dose and 120 mg monthly; or fremanezumab 225 mg monthly). Before the first anti-CGRP mAb, all patients reported failure for lack of efficacy (no meaningful improvement in the frequency of headaches after the administration of drugs for ≥3 months at appropriate dose) with at least three preventive treatments, including otulinumtoxinA for CM.

According to a previous proposal (17), the present case series included patients who experienced at least one episode of aura per month in the previous three months, as reported in their medical history and during the baseline period (one month prior to treatment initiation). Data were collected during the baseline period (month-0) and the last three months of treatment (month-10, month-11 and month-12). Aura was defined according to the following features: visual aura was determined when participants described experiencing zigzag lines, scintillation, scintillating scotoma, hemianopsia, fortification spectra, flickering lights, flashes of bright light, and blind spots, as well as C-shaped zigzag lines; sensory aura was determined when participants described experiencing tingling, numbness, or paresthesia in their fingers, hands, face, or legs; speech aura was determined when participants described having trouble with word-finding or speech production.

Throughout the treatment duration, patients were required to complete a paper headache diary on a monthly basis. This diary recorded the number of MMDs and the use of acute medication, including the absolute number of AMNs and the number of days with at least one AMDs. A headache day was defined as any day a patient recorded experiencing any type of headache. MO is codified according to ICHD-3 criteria, regardless of the diagnosis of MOH.

Response rate was assessed based on reduction in MMDs, ≥50%. Additionally, patients completed the HIT-6 questionnaire on a monthly basis and the MIDAS questionnaire on a quarterly basis. Adverse events were reported for all patients. We collected demographic information, including age, gender, and relevant medical history. Migraine characteristics, such as disease duration and chronic migraine onset, were also recorded. Additionally, we gathered data on previous treatment failures with various drug classes, including beta-blockers, tricyclic antidepressants, antiseizure medications, and onabotulinumtoxinA. Information on current concomitant preventive and acute symptomatic treatments was also documented.

Statistical analysis. Demographic and baseline characteristics were summarized descriptively, namely mean ± standard deviation or median interquartile range for continuous variables and number (percentage), for categorical data. Normality assumption was assessed using the Shapiro-Wilk test. Considering the non-normally distributed data for headache days and HIT-6 score, a Wilcoxon signed-rank test was calculated. For other variables, a dependent t-test was used. No missing data were present. A p-value <0.05 was considered significant for all variables. All data were analyzed using SPSS software version 26.0 (IBM Corp. SPSS Statistics, Armonk, NY, USA), and graphs were designed using GraphPad Prism version 9.00 (La Jolla, CA, USA).

Narrative review. We conducted a narrative review to examine the changes in aura experienced by patients receiving anti-CGRP mAbs, as well as the effectiveness and tolerability of these treatments, specifically in patients with aura. Our review included studies that evaluated patients with migraine with aura, as well as studies that prospectively assessed aura during treatment with anti-CGRP mAbs.

A comprehensive search was conducted in the Embase and

MEDLINE databases using the following keywords: "erenumab", "galcanezumab", "fremanezumab", "eptinezumab", "anti-CGRP", and combinations with "aura", "migraine with aura", and "aura without migraine". The search was conducted to identify relevant studies published up to March 2024.

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Correspondence: Marina Romozzi, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Roma (RM), Italy.
E-mail: marinaromozzi@gmail.com

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