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Effectiveness of anti-CGRP monoclonal antibodies on central symptoms of migraine

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Abstract

Background: Clinical trials and observational studies with anti-calcitonin gene-related peptide antibodies poorly investigated their impact on migraine prodromal and accompanying symptoms. This information might help deciphering the biologics' pharmacodynamic and provide hints on migraine pathogenesis. Herein, we report the effects of erenumab, fremanezumab and galcanezumab on attack prodromal and accompanying symptoms and on neurological and psychiatric traits.

Methods: An explorative, prospective, questionnaire-based study was completed by a cohort (n = 80) of patients with chronic migraine patients presenting a sustained reduction of ≥50% of Migraine Disability Assessment Score and ≥30% of monthly migraine days three months after anti-calcitonin gene-related peptide antibodies treatment.

Results: The majority of patients experienced a complete prevention of migraine symptoms without evidence of initial onset followed by attack abortion. Few patients reported the recurrence of prodromal (from 10% to 12.5%) or accompanying (from 1.3% to 8.8%) symptoms without headache. All patients with migraine with aura reported a decrease of aura incidence. Sleep changes (51.2%), increase in appetite (20.0%) and weight (18.8%) as well as a reduction in stress (45.0%), anxiety (26.3%), and panic attacks (15%) were also reported.

Conclusion: Anti-calcitonin gene-related peptide antibodies seems to significantly impact brain functions of migraineurs, preventing not only migraine headache but also its anticipatory and accompanying symptoms.

Keywords

Erenumab, fremanezumab, galcanezumab, CGRP, migraine symptoms, chronic migraine

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Background

Migraine is the third most prevalent and the second most disabling disease worldwide, with chronic migraine (CM, ≥15 headache days per months with at least eight days with migraine features, for more than three months) affecting 1.4–2.2% of the general population (1). Even though cephalic pain is the most bothersome symptom during the migraine attack, the majority of patients report accompanying symptoms as nausea, vomiting, photo-, phono- and osmophobia. Prodromal disturbances including fatigue, difficulty concentrating, neck stiffness and yawning may also begin hours or days before the headache phase (2). Approximately 20–30% of patients may also experience aura. Because some of these symptoms could originate within the central nervous system (CNS), it has been proposed that migraine could be a primary neurological disorder leading to activation of the trigeminovascular system and cephalic pain (2).

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The monoclonal antibodies (mAbs) erenumab, eptinezumab, fremanezumab and galcanezumab that block the calcitonin gene-related peptide (CGRP) or its receptor (CGRP-r) are a new class of specific anti-migraine drugs approved for preventative treatment of episodic (EM) and chronic (CM) migraine (3). It is largely acknowledged that these biologics represent one of the most relevant therapeutic achievements for the treatment of migraine. How and where these biologics specifically operate to prevent migraine development needs to be fully deciphered. Because of their proteinaceous nature and the high molecular weight, it has been proposed that anti-CGRP mAbs exert their preventative effects by targeting the peripheral segment of the trigeminovascular system (4). According to preclinical studies, fremanezumab is able to counteract meningeal cross talk between C and Aδ fibers involved in trigeminal nociception (5), while it appears unable to cross the rat blood brain barrier (BBB) (6). Eptinezumab reduces cephalic allodynia in experimental migraine models when injected intraperitoneally but not intracerebroventricularly (7). A peripheral site of action is also suggested by the rapidity of the effects reported by some migraineurs undergoing the prophylactic treatment.

Accumulating clinical evidence (8–10) suggests that migraine prevention with biologics not only counteracts the pain component, but also prodromes and accompanying symptoms that originate in the brainstem, hypothalamus, thalamus and cortex. Given that these regions are beyond the BBB, how anti-CGRP mAbs acting at meningeal trigeminal afferents prevent development of migraine symptoms that stem in the CNS (and often precede activation of the nociceptive trigeminovascular fibers) remains unaddressed. To our knowledge, an observational study aimed at specifically investigating the impact of anti-CGRP mAbs on prevention of migraine symptoms of potential central origin has not been conducted.

Herein, we report an exploratory, prospective, questionnaire-based study evaluating the effectiveness of three anti-CGRP mAbs (erenumab, fremanezumab and galcanezumab) on migraine prodromal and accompanying symptoms in a population of chronic migraine patients. To better understand the possible CNS impact of these biologics, we also investigated whether the mAbs affected specific behaviors or coexisting neuropsychiatric disorders if present in migraineurs recruited in the study.

Methods

All consecutive out-patients treated with an anti-CGRP mAbs at the Headache Center that achieved a $\geq$50% response in Migraine Disability Assessment (MIDAS) score and a monthly migraine days (MMDs) reduction $\geq$30% at three months of treatment, with a sustained response thereafter (if treated for more than three months) were enrolled in the study. The choice of a $\geq$50% response in MIDAS at three months of treatment was mandatory because it represents the cutoff necessary to keep the patient on anti-CGRP mAbs therapy according to the regulatory rules of the Italian Medicine Agency. The $\geq$30% MMDs reduction threshold has been adopted in accordance with the guidelines for controlled trials for prophylactic treatment of chronic migraine (11), and considered appropriate for pharmacological studies involving resistant CM patients (12).

All patients completed an ad hoc questionnaire (see supplemental material information) developed to assess prodromal and concurrent symptoms and specific behaviors related to migraine attacks.

Study participants were affected by CM according to ICHD-3 criteria (13), with or without medication overuse, and started a preventative therapy with erenumab (70 mg monthly, up to 140 mg), galcanezumab (240 mg first dose and then 120 mg monthly) or fremanezumab (225 mg monthly). All patients had previous treatment failures with at least three different classes of migraine-preventative medications (14).

Demographic, medical history, migraine characteristics (pain intensity, presence of aura, disease duration and chronicization onset), previous failures of $\geq$3 drug classes among beta-blockers, tricyclic antidepressants, antiseizure medications or onabotulinumtoxinA (failure with other preventative treatments were also recorded), current concomitant preventative and symptomatic treatments (class and number) were collected at baseline. All patients signed an informed consent. The primary aim of the study was to exploratively describe potential changes in migraine prodromal and accompanying symptoms in responders to anti-CGRP mAbs. A secondary aim was that of evaluating whether these mAbs altered specific behaviors or coexisting neuropsychiatric disorders.

Statistical analysis

Due to the exploratory and descriptive nature of the study, the sample size was not based on any statistical considerations. The analysis includes all the patients that completed the questionnaire (n = 80). Demographic and baseline characteristics were summarized descriptively, namely mean $\pm$ standard deviation (SD) or median interquartile range (IQR) for continuous variables and number (percentage) for categorical data. All the data were analyzed using SPSS software version 26.0 (IBM Corp. SPSS Statistics, Armonk, NY, USA).

Results

Clinical and demographic features

A total of 90 patients fulfilled the inclusion criteria but 80 patients (78.8% females, mean age 46.3 years) with CM (6.3% with aura [5/80]) completed the questionnaire and were included in the analysis (Figure 1). Demographic and baseline headache characteristics of patients included are reported in Table 1. At the time of the analysis, all patients completed at least three months of treatment with a mean (SD) treatment duration of 7.3 (3.8) months and showed a sustained response throughout treatment. Overall, 51.2% of patients (41/80) were treated with erenumab, 41.3% (33/80) with galcanezumab and 7.5% (6/80) with fremanezumab. The incidence of medication-overuse was 85.0%. A failure of $\geq$4 prior preventative treatment classes was reported by 78.9% (63/80) of patients and 13.8% (11/80) were on preventative concomitant medications (except for onabotulinumtoxinA) when they started anti-CGRP mAbs (Table 1). At baseline, the mean headache pain intensity in a 0–10 scale (numeric rating scale [NRS]) was 7.8 ± 1.1 points, the mean $\pm$ SD number of acute medications used was 28.4 ± 19.3 per month, and days with at least one symptomatic use were 20.0 ± 8.0. Patients presented mean MIDAS (97.6 ± 62.4) and Headache Impact Test 6 (HIT-6) (67.3 ± 5.3) scores at baseline.

Effects of anti-CGRP mAbs on migraine prodromal and accompanying symptoms

We first investigated how patients interpreted the mode of action of the antibodies in preventing their migraine (see supplementary information for questionnaire). We asked whether the patient had the impression that the antibody worked by interrupting attack upon initiation or simply preventing attack onset (Query 1). We found that only 12.5% of patients perceived that the mAbs counteracted progression of the attack once it is initiated. Conversely, more than half of patients (57.5%) reported that the biologics completely prevented onset of the attacks. This suggested that in these individuals migraine incidence was merely reduced, with the remaining attacks being unchanged in terms of prodromal and accompanying symptoms. Of note, a remaining 30% of patients chose both answers, therefore reporting a mixed effect (i.e., a net reduction of migraine incidence, with some of the remaining attacks aborting after onset of prodromal/accompanying symptoms) (Figure 2A).

Query 2 was similar to Query 1 (see Discussion) and investigated the possibility that migraine attacks during treatment could be completely or at least in part pain free. We found that a negligible percentage (1.3%) of patients reported that attacks occur with the same frequency but are not accompanied by headache.

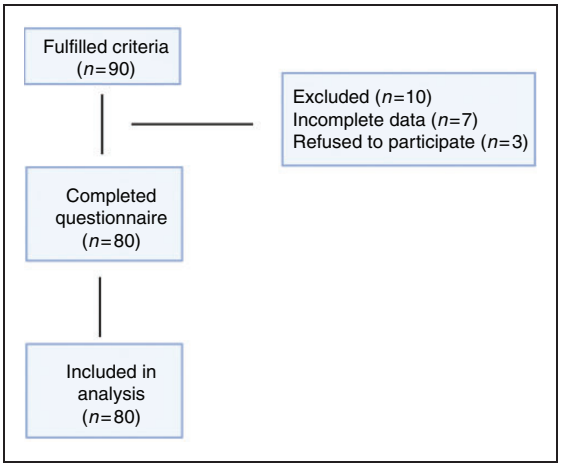

Figure 1. Flowchart of patients.

Table 1. Patient demographic and clinical features.

	Patients (n = 80)
Demographics	
Age [years], mean ± SD	46.3 ± 11.3
Sex female, n (%)	63 (78.8)
Migraine features	
Monthly migraine days, mean ± SD	23.1 ± 5.9
Aura, n (%)	5 (6.3)
Migraine duration [years], mean ± SD	30.1 ± 10.9
Chronicization duration [years], mean ± SD	15.1 ± 10.5
NRS score, mean ± SD	7.8 ± 1.1
Concomitant preventive treatment, mean (SD)	0.1 (0.4)
Prior preventive classes failures, mean ± SD	4.4 ± 0.9
Medication overuse, n (%)	68 (85.0)
Days with at least one analgesic use, mean ± SD	20.0 ± 8.0
Analgesic use, mean ± SD	28.4 ± 19.3
Migraine-related clinical burden	
Disability (MIDAS), mean ± SD	97.6 ± 62.4
Headache-related impact (HIT-6), mean ± SD	67.3 ± 5.3
Prior preventive class failures*	
4 classes	21 (26.3)
>4 classes	42 (52.6)
Drug Classes	
Beta-blockers	76 (95.0)
Tricyclic antidepressant	74 (92.5)
Calcium channel blockers	68 (85.0)
Antiepileptic drugs	75 (93.8)
SSRI/SNRI	13 (16.3)
OnabotulinumtoxinA	46 (57.5)

*All patients have at least three prior preventive class failures. HIT-6, Headache Impact Test 6; MIDAS, Migraine Disability Assessment; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitor. Percentages are expressed on column total.

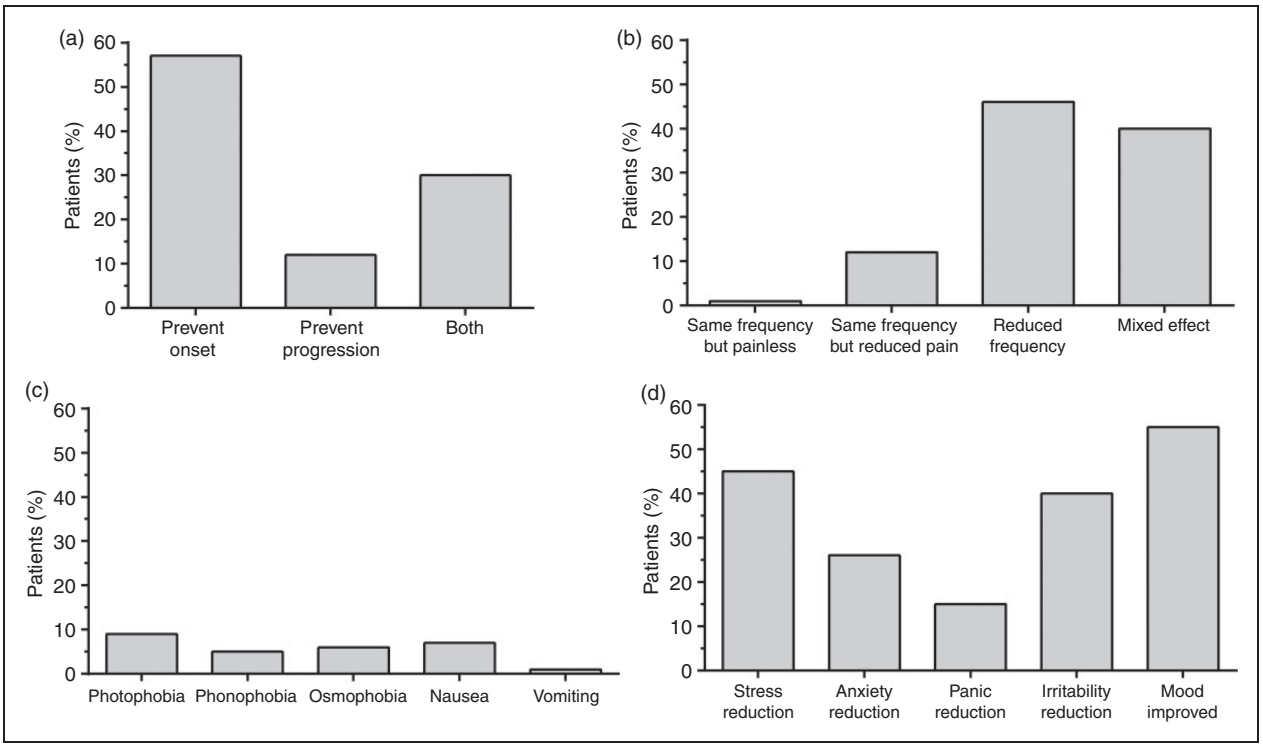

Figure 2. Effects of anti-CGRP mAbs on central migraine symptoms.
Patients' interpretation of the mode of action of anti-CGRP mAbs (a), and their impact on attack pain and/or frequency (b). In (c) the percentage of patients reporting the occurrence of isolated migraine accompanying symptoms without evidence of attack progression is shown and the percentage of patient reporting improvement of migraine-associated neuropsychiatric traits is shown in (d).

Similarly, a low proportion of patients (12.5%) stated that migraine attack incidence was unaltered but pain partially prevented. Of note, most patients (46.3%) reported that migraine episodes during therapy were simply reduced in number without evidence of partial onset. A significant proportion of patients (40.0%) reported a mixed effect, experiencing a decrease in number of attacks, as well as a reduction of pain intensity of the remaining migraine episodes (Figure 2B).

We also specifically interrogated patients with ad hoc questions about the possibility that migraine prodromal and/or accompanying symptoms were still occurring in the absence of concomitant or subsequent headache (Query 3). According to the patients' reports, only a minority of them experienced photophobia (8.8%), phonophobia (5.0%), osmophobia (6.3%), nausea (7.5%) or vomiting (1.3%) not followed by the headache phase (Figure 2C). As far as the prodromal symptoms are concerned, we found that patients scarcely reported their occurrence. Specifically, prodromal mood changes and yawns occurred without migraine headache in 10% and 12.5% of patients, respectively, whereas occurrence of salivation, food craving and diarrhea resulted not evaluable.

Finally, we investigated whether patients on anti-CGRP mAbs experienced a reduction of aura, a classic migraine-related CNS-disorder (Query 4). Remarkably, even though few patients in our cohort reported the occurrence of aura (6.3%, referred as exclusively visual), all of them (100%) affirmed that this symptom was reduced. When asked whether the reduction of aura was related to a decrease in severity and/or incidence, all the patients indicated an exclusive reduction of incidence.

Effects of anti-CGRP mAbs on neuropsychiatric traits, weight, and appetite

We found that stress was reduced in 45.0% of patients, whereas 40.0% stated that this parameter was unchanged and the remaining ones that it was not evaluable. As for anxiety, 26.3% of patients reported a reduction, 43.7% reported no difference compared to baseline and the remaining ones were unable to evaluate. Irritability and mood improvements were reported by 40.0% and 55.0% of patients, respectively (41.8% and 31.2% stated that the single parameter was unaffected) (Figure 2D). Of note, 71.3% patients attributed their neuropsychiatric improvements to the biologic therapy and not to the occurrence of accidental events (Query 7). In the overall population, none

experienced a worsening in stress, anxiety, irritability, and mood.

Sleep changes in quality/duration occurred in the 51.2% of patients, with 38.8% and 5.0% of them reporting sleep improvement or worsening, respectively. Further, 18.8% of patients experienced weight increase, 20.0% an increase in appetite, and 3.8% appetite loss. None of them reported disgust for specific aliments before treatment, thereby precluding the possibility of analyzing the biologics' effects on food aversion.

Discussion

We report here the findings of an explorative, questionnaire-based, prospective cohort study aimed at evaluating the effects of anti-CGRP mAbs on potential CNS-mediated migraine symptoms. The understanding of whether and how prodromal and accompanying migraine symptoms are affected by these mAbs can be useful to gather specific information on their mode of action. If the biologics exclusively counteract the nociceptive component, then patients might experience the CNS-related migraine symptoms almost unaffected even though the attack does not reach the headache phase. Of note, although based on patients' subjective interpretation, only a minority of patients reported that the mAbs abort attack progression after onset. Conversely, most of them experienced a complete prevention of the onset, including prodromal and accompanying symptomatology. For patients that chose both options (i.e., net reduction of attack incidence with some remaining aborted attacks), it might be ascribed to the fact that the antibodies are occasionally unable to fully prevent the events leading to migraine onset. Query 2, that is similar to Query 1, confirms these findings. The similitude was planned to obtain answer consistency and understand the reliability of patients' interpretation. Specifically, only a very small fraction (1.3%) of the patient population reported that the biologics lead to an unaltered incidence of attacks that then do not reach the pain phase (no progression). Similarly, a limited percentage (12.5%) of patients experienced unvaried onsets followed by reduced pain (partial progression). Most of the patients stated that migraine attacks were simply reduced in terms of number (complete prevention of migraine symptoms). Further corroborating the patients' indication of complete prevention of attack onset, we found that the large majority of migraineurs (more than 90%) did not experience the recurrence of isolated migraine accompanying symptoms as possible index of central migraine onset not followed by pain (Query 3).

These findings taken together indicate that in the vast majority of migraineurs anti-CGPR mAbs prevent not only the pain component but also the migraine-associated CNS dysfunctions. Of note, our findings are in keeping with post hoc analyses of efficacy studies showing that fremanezumab (8) and eptinezumab (10) reduce migraine accompanying symptoms. Additional post hoc analyses of three clinical studies demonstrate that galcanezumab efficiently reduces bothersome migraine symptoms (9). Findings of a very recent contribution reporting a post hoc analysis shows the ability of erenumab to prevent migraine attacks rather than reducing their length (15).

Accordingly, we found that anti-CGRP mAbs reduced incidence of migraine aura in all patients. Given that aura is the clinical correlate of cortical spreading depression (CSD) mostly occurring before migraine pain, its reduction by anti-CGRP mAbs could indicate the ability of these biologics to change the neurochemical milieu within the migraineur's brain. This interpretation is in keeping with a recent case report describing an immediate, complete and persistent response of aura to erenumab in a migraine patient otherwise resistant to classic preventatives (16). These findings therefore suggest that considering CGRP exclusively involved in the pain phase of migraine with aura is reductive. This interpretation is in keeping with the ability of CGRP to promote CSD in brain slices (17), as well as trigger aura when infused in migraineurs (18). Our data, along with evidence that fremanezumab is unable to prevent experimentally-induced CSD in vivo (19), suggest that the antibody could act upstream from CSD in preventing aura in migraineurs.

We also investigated whether migraineurs on anti-CGRP biologics experienced changes of their neuropsychiatric traits. Of note, numerous patients (50 out of 80, 62.5%) reported improvements of at least one among stress, anxiety, irritability, panic, mood and sleep. It makes sense that migraine reduction per se (i.e., alleviation of the migraine burden) might be responsible for the neuropsychiatric improvements. Given that preclinical evidence indicates CGRP is a key player in appetite suppression and food aversion (20), we also investigated whether the anti-CGRP mAbs affected appetite, body weight and food consumption. We found that 20% of patients experienced increased appetite and 18.8% of them reported a body weight increase. Changes in food consumption might be an indirect effect of migraine improvement. Unfortunately, lack of preexisting food aversion in our patients hampered the possibility of studying the antibodies' impact on this symptom.

Overall, the present study seems to suggest that anti-CGRP mAbs do not simply target the peripheral

nociceptive trigeminovascular system but also alter the neuropathophysiological events that prompt and accompany the migraine attack. In principle, the impact of anti-CGRP mAbs on potential central migraine symptoms may be related to their peripheral actions. Indeed, the persistent block of the pronociceptive effects of CGRP within the meningeal trigeminal afferents by mAbs can well counteract the trigeminovascular sensitization and the constant excitatory input to the CNS migraine matrix of CM patients. This, in turn, might counteract hyperactivity of the putative migraine generator, leading to diminished incidence of attacks including prodromal and accompanying symptoms. On the other hand, data might also be interpreted considering that mAbs counteract these symptoms via direct inhibition of CGRP neurotransmission within the brain. However, this possibility is rejected because it is assumed that mAbs do not cross the BBB.

Some preclinical and clinical evidence seems in contrast with this assumption. Indeed, even if immunohistochemistry cannot reveal entrance of fluorescently-labeled fremanezumab in the rodent brain (6), radiolabeled galcanezumab accumulates within the brain parenchyma (21). Further, clinical evidence that subcutaneously-injected anti-amyloid mAbs such as aducanumab (22), lecanemab (23), donanemab (24) and ganterenumab (25) cross the BBB and strongly reduce the brain amyloid load in patients demonstrates that peripherally-administered mAbs can exert a pharmacodynamic effects within the brain. Rather, the questions should be whether anti-CGPR biologics reach a functionally-active brain concentration, and how intersynaptic CGRP sequestration might prevent migraine onset. Theoretical calculations reveal that the concentration reached by mAbs within the brain may exceed that necessary to sequester extra synaptic CGRP (26). How brain CGRP might contribute to migraine generation is still unknown. It is worth noting that brain CGRP behaves as a glutamatergic co-transmitter and sustains a basal "volume neurotransmission" rather than a fast synaptic-restricted signaling (27), a feature that would facilitate antibody-dependent neuropeptide scavenging. Further, CGRP sustains nociceptive signaling within the cat trigeminal nucleus (28), and plays a key role in signaling of the glutamatergic parabrachial-to-amygdala pathway (20) which mediates trigeminal nociception (29). In keeping with these central pronociceptive properties, intrathecally-administered CGRP antiserum prompts analgesia in rats (30). Together, these neurochemical features suggest a role of the neuropeptide in sustaining dysfunctional neuronal excitation within the CNS, an event likely occurring in the migraineur's brain (31,32). Hints that anti-CGRP biologics affect CNS functions also stem from studies showing that erenumab counteracts migraine aura (16) and reduces trigeminal nociception-dependent activation of several migraineurs' brain regions (33,34). The ability of fremanezumab to sustain the brain descending pain inhibitory control pathway of mice (35) further suggest that these biologics can affect the migraine matrix.

Limitations of this exploratory study are the use of a not-validated questionnaire and a relatively small sample size. However, symptomatology of patients was carefully examined, and answers were consistent with their clinical charts. Answers consistency among the different interrelated questions further suggests reliability of findings and a reduced risk of recall bias.

Conclusion

The present study furthers our understanding of the impact that anti-CGRP mAbs can exert on migraine generation. Data prompt additional preclinical and clinical studies that might help elucidating the pharmacokinetics, as well as the site and mode of action of anti-CGRP biologics.

Clinical implications

- Clinical trials and observational studies with anti-CGRP antibodies poorly investigated their impact on migraine prodromal and accompanying symptoms.
- Anti-CGPR mAbs seem to prevent not only the pain component but also the migraine-associated CNS dysfunctions.
- The impact of anti-CGRP antibodies on central migraine symptoms may be related to their peripheral and/or direct actions on CNS.

Data availability

The data collected and analyzed for the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study was approved as part of the Registro Italiano Cefalee (RICe) study by the local Ethics committee (Studio RICe, 14591_oss).

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Supplemental material

Supplemental material for this article is available online.

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