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Anti-CGRP monoclonal antibodies and migraine with aura: a narrative review

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ABSTRACT

Background: Monoclonal antibodies against the calcitonin gene-related peptide (anti-CGRP mAbs) have been a game-changer in migraine treatment over the last decade. However, data regarding the reduction in the frequency of episodes of migraine with aura are limited, as no trials have been specifically designed to evaluate this outcome.

Methods: In this narrative review, we summarized clinical data from both randomized controlled trials (RCTs) and real-world studies (RWSs) on the efficacy and effectiveness of anti-CGRP mAbs in patients with migraine with aura and aura symptoms.

Results: Overall, anti-CGRP mAbs can reduce migraine frequency and burden regardless of the presence of aura, with efficacy and effectiveness in both patients with and without aura. A few studies suggested a potential influence on reducing aura occurrence. However, several limitations affect the available studies and prevent definitive conclusions regarding the effects of anti-CGRP mAbs on aura.

Conclusions: Further studies specifically aimed at assessing the impact of anti-CGRP therapies on the frequency, duration, and characteristics of aura are necessary. Such research could help elucidate the complex relationship between CGRP and aura.

Key words: migraine, aura, CGRP, cortical spreading depression.

Introduction

Migraine with aura (MwA), a subtype of migraine that accounts for about a third of migraine cases, is characterized by transient and fully reversible neurological symptoms occurring before, during, or in the absence of migraine pain (aura without migraine). (1,2) Visual aura is the most frequent form of aura. (3) Although less common, other forms of migraine aura include sensory (*e.g.*, paraesthesia) or motor (*e.g.*, weakness) symptoms, speech/language disturbances (*e.g.*, aphasia), or symptoms suggestive of brainstem involvement (brainstem aura). (2)

Cortical spreading depression (CSD) has long been proposed as the pathophysiological mechanism underpinning aura symptoms. It represents a wave of depolarization that occurs across the cortex and with a posterior-anterior propagation, leading to several changes on the cortical surface. These include neuronal depolarization with the release of neurotransmitters and inflammatory mediators, causing changes in the caliber of cerebral vessels. (4,5)

The first description of CSD and its association with migraine aura was provided in the animal model by Leão in 1944. (6) Subsequent studies in human regional cerebral blood flow (rCBF) in the 1970s linked the aura with an initial transient focal hyperaemia, (7) followed by delayed oligoemia that spreads anteriorly from the occipital regions within 15-45 minutes. (8,9) However, no electrophysiological confirmation of CSD as the mechanism underlying MwA has been collected in the last 50 years. Only recently, CSD has been recorded by intracranial electrodes in a patient experiencing a typical MwA episode during a presurgical electrophysiological monitoring for epilepsy, (10) representing the first human evidence supporting the existence of CSD in humans. (11)

Neuronal hyperexcitability of the migraine cortex is thought to be the neurophysiological counterpart of the CSD, (12) as suggested by genetic forms of MwA, including familial hemiplegic migraine (FHM), which are associated with mutations in ion channels. (13) However, the question of how CSD activates the trigeminal nerve remained unanswered. (12) A pivotal observation in a migraine model established a link between CSD and the activation of the trigeminovascular system. (14) Indeed, CSD can activate the release of ions, neurotransmitters, and metabolites into the extracellular and perivascular space, which may activate and sensitize the perivascular trigeminal fibers that, *via* trigeminal ganglia and trigeminal caudal nucleus, convey pain signals. (14) Recently, a preclinical study on a migraine model showed for the first time that the proteome of the cerebrospinal fluid (CSF) is altered after the CSD, (15) suggesting that cortical perturbations can impact peripheral structures. By changing CSF composition and enhancing CSF flow, CSD increases the CSF protein content, including calcitonin gene-related peptide (CGRP), and promotes extracellular solute elimination. CSF modified by CSD contacts the trigeminal ganglion, which, in part, is inside the blood-brain barrier (BBB), creating a non-synaptic communication pathway between the cortex and the trigeminal system. CGRP, once transported from the CSF into the extracellular space of the trigeminal ganglion, can then directly activate its receptors present in trigeminal ganglion neurons. (15)

Tonabersat, a benzopyran derivative, is the only drug developed until now to counteract the migraine aura phenomenon directly. In preclinical studies on the rat brain, it inhibited experimentally induced CSD by acting as a gap junction modulator, independently of any vasoconstrictive action. (16) However, inconsistent results emerged for its efficacy in both the acute and preventive treatment of migraine. (17) A randomized, double-blind, placebo-controlled, proof-of-concept study failed to show efficacy of tonabersat as a migraine preventive, with no difference in the reduction of migraine days compared to placebo. (18) Another study reported that tonabersat effectively reduced the number of episodes of aura without influencing the number of migraine headache days. (19) Additionally, tonabersat was also evaluated for the acute treatment of migraine by one double-blind, randomized, placebo-controlled, parallel-group trial, which included one international cohort and a North American cohort. Interestingly, it showed a significant relief of headache pain at 2 hours compared to placebo only in the international cohort, while it failed to show any efficacy in the North American study. (20) To date, no other drugs acting directly against the pathophysiological mechanisms of aura have been developed. Notably, there is no conclusive evidence of a cause-and-effect relationship between aura and the painful phase of migraine attack. (18) Indeed, triptan assumption at the onset of aura did not provide a superior benefit on the subsequent headache. (21-23) Regarding preventive treatments, no trials have specifically compared drug effects in patients with MwA and migraine without aura (MwoA). It has been shown that some antiseizure medications, including lamotrigine or topiramate, suppress CSD in animal models, and a few open-label studies reported a slight reduction in aura frequency. (24) Then, treatment of migraine aura remains an unsolved challenge in the headache field. This is also due to the limited data in randomized controlled trials (RCTs) regarding patients with MwA and to the lack of RCTs specifically designed to address this unmet need. (24,25) Monoclonal antibodies against CGRP or its receptor (anti-CGRP mAbs) have recently emerged as new and efficacious migraine-specific treatments. Pharmacokinetic evidence in rodents indicates that their activity is mainly located at the peripheral level without a direct effect on CSD. (26) Clinical data from RCTs and real-world studies (RWSs) yielded conflicting conclusions regarding their efficacy on aura. (27-31)

In this narrative review, we will describe the role of CGRP in the CSD and summarize the current evidence on the efficacy and effectiveness of anti-CGRP mAbs in patients with MwA in reducing migraine frequency and aura manifestations.

Materials and Methods

A comprehensive literature search was performed in the EMBASE and MEDLINE databases through March 2025 with the following string: ("erenumab"/exp OR "erenumab" OR "galcanezumab"/exp OR "galcanezumab" OR "fremanezumab"/exp OR "fremanezumab" OR "eptinezumab"/exp OR "eptinezumab" OR "anti-CGRP monoclonal antibod*" OR "anti-calcitonin gene related peptide monoclonal antibod*" OR "CGRP antagonist*" OR "AMG 334" OR "LY2951742" OR "TEV-48125" OR "ALD403") AND ("migraine with aura"/exp OR "migraine with aura" OR "aura"/exp OR "migraine aura" OR "visual aura" OR "sensory aura" OR "motor aura" OR "brainstem aura" OR "hemiplegic migraine" OR "aura without migraine" OR "aura without headache") AND [humans]/lim AND [english]/lim AND [2017-2025]/py.

We included RCTs that: evaluated patients with MwA; assessed the effects of anti-CGRP mAbs on aura frequency, duration, or phenomenology; provided data on treatment effectiveness or tolerability in the MwA subpopulation; or prospectively assessed aura characteristics during anti-CGRP mAbs treatment. Observational studies, RWSs, and case series addressing these issues were also included. The characteristics and main findings of the studies included are summarized in **Table 1**.

Studies focusing exclusively on MwoA or failing to report specific outcomes related to aura were excluded, as well as editorials, meta-analyses, or study protocols.

The role of CGRP in aura and cortical spreading depression and the potential of anti-CGRP therapies. Aura can be followed or not by headache, thus suggesting independent mechanisms for the auratic and painful phase. Even if the role of CGRP in migraine headache is well established, the connection between CGRP and the aura is still unsolved. The initial hyperemia seen in CSD has been shown to be mediated in part by the release of CGRP from ipsilateral trigeminal nerve fibers (32,33) and activation of trigeminal sensory and parasympathetic nerve fibers. (34) Preclinical studies in mouse models have shown that CGRP is released during CSD and can facilitate its propagation through the activation of CGRP receptors expressed on neurons and glia. (35) Administration of exogenous CGRP has been shown to lower the threshold for CSD initiation, while CGRP antagonists reduce both the amplitude and the propagation speed of the depolarization wave. (35) Another study showed that CSD upregulated CGRP-positive cells in the rat trigeminal ganglion. (36) Furthermore, an antibody directed against the CGRP receptor reduced the susceptibility to CSD both *in vitro* and *in vivo*. (37)

Close *et al.* (38) suggested a bidirectional communication model of CGRP at the intersection of vascular-neural communication. First, CSD promotes CGRP release from trigeminal afferents in the meninges. Second, CGRP dilates meningeal arteriolar in the pia and brain parenchyma. Third, vasodilation and the ensuing increase in blood flow in parenchymal vessels sustain increased neural activity and CGRP release, in a feedforward neural-vascular-neural circuitry. Of note, this model did not explain how CGRP may contribute to CSD. More recently, Gimeno-Ferrer *et al.* (39) explored additional effects of CGRP on rat cortex *in vivo*: topical CGRP induced periods of epileptiform discharges and plasma extravasation, which were associated with reduced ramification of microglial cells. The local application of a CGRP receptor antagonist, olcegepant, prevented these effects. These findings propose that CGRP induces pathophysiological changes in the cortex, consisting of neuronal hyperexcitability and neuroinflammation, with a relevant impact on brain functions during migraine episodes.

However, to date, the role of CGRP as a trigger of CSD remains uncertain. Initial pharmacological provocation studies reported few cases of aura after CGRP infusion. In 2008, Hansen *et al.* administered intravenous (i.v.) CGRP in 9 patients with FHM, with a *CACNA1A* gene and in 10 healthy controls. Twenty-two percent of the patients and 10% of the healthy controls had a migraine attack, but none of them presented the usual aura, failing to show a role of this molecule in the pathophysiology of aura in FHM. (40) Notably, when the experiment was performed in MwA patients, 86% of patients who received i.v. CGRP experienced headache and 28% reported aura symptoms like those of their spontaneous attacks. (41) In a recent open-label, non-randomized, single-arm study, 13 out of 34 (38%) participants with MwA developed a usual aura after CGRP infusion. (42)

Dux *et al.* found that fremanezumab decreases CGRP levels in rat dura mater and trigeminal ganglion and CGRP release evoked by noxious stimulation. (43) Another *in vitro* study showed that galcanezumab induces multiple functional changes in the trigeminovascular complex of rats. While reducing the release of CGRP from trigeminal afferents, it increases that of substance P, suggesting a shift in the balance of neuropeptides after treatment. (44) Furthermore, galcanezumab reduced the histamine release induced by CGRP

Table 1. Characteristics and main findings of the included studies.

Publication year and authors	Study design	Total sample size (n)	pts with MwA (n)	Anti-CGRP mAbs	Treatment duration (months)	Effects on patients with MwA or on aura
2021, Straube *et al.*[29]	Retrospective study	542	N/A	Erenumab	3	35.2% of pts reduced frequency of aura episodes
2021, Scheffler *et al.*[56]	Case series	32	17	Fremanezumab Galcanezumab Erenumab	3	No effects on aura frequency
2021, Schoenen *et al.*[31]	Prospective study	156	37	Erenumab 140 mg	3	No effects on aura frequency
2022, Iannone *et al.*[47]	Prospective study	203	14	Erenumab Galcanezumab Fremanezumab	1-6	No associations between aura and response rate at different time points (1, 3, and 6 months)
2022, Albanese *et al.*[53]	Case series	2	2	Galcanezumab Erenumab	2	Complete disappearance of aura after 3 months of treatment with galcanezumab in first patient; shorter duration of aura episodes (15-20 min *vs.* previously 30+ min) in the second patient treated with erenumab
2022, Mahovic *et al.*[52]	Prospective, observational study	54	17	Erenumab 70 mg	6	No significant difference in the reduction of headache frequency and pain intensity between MwA and MwoA
2022, Iannone *et al.*[51]	Prospective study	80	5	Erenumab Galcanezumab Fremanezumab	7.3±3.8	All patients with MwA reported a reduction in aura incidence during treatment
2022, Ashina *et al.*[30]	Post-hoc analysis	2443	1140	Erenumab	3	No significant reduction in monthly aura days with comparable efficacy between MwoA and MwA
2022, Ashina *et al.*[45]	Post-hoc analysis	1741	877	Eptinezumab	3	Similar efficacy and tolerability between MwoA and MwA
2023, Alpuente *et al.*[58]	Prospective study	158	72	Erenumab Galcanezumab Fremanezumab	6	In the RR50 group, the reduction in the number of aura episodes was greater than the reduction inMHDs after six months
2023, Ashina *et al.*[28]	Observational, open-label, cohort study	46	30.4%(14)	Galcanezumab	3	Headache occurrence after visual and sensory aura was significantly reduced in responders (RR>50%), non-responders (RR<50%) and super responders (RR>70%)
2023, Igarashi *et al.*[50]	Post-hoc analysis	459	N/A	Galcanezumab	6	Significantly greater reductions of migraine days with aura compared to placebo
2023, Braca *et al.*[54]	Case series	12	12	Erenumab Galcanezumab Fremanezumab	12	Significant reduction of MMD and aura frequency
2024, Cresta *et al.*[55]	Case series	12	12	Erenumab Fremanezumab Galcanezumab	12	No significant difference in the frequency of aura attacks. Some pts reported increased episodes of aura attacks without headache
2024, Romozzi *et al.*[27]	Case series	13	13	Erenumab Galcanezumab Fremanezumab	3	Significant reduction of aura episodes and MMD. 3 pts reported a new onset of aura without migraine

MwA, migraine with aura; pts, patients; MHDs, monthly headache days; MMD, monthly migraine days; MOH, medication overuse headache; MwoA, migraine without aura; RR50, response rate ≥50%; RR75, response rate ≥75%.

from dural mast cells, indicating an inhibitory effect on mast cell activation that might be relevant to migraine pain. These changes may contribute to reducing nociceptive signalling and pain sensitivity, and to the overall therapeutic effect of anti-CGRP therapies. (44) Notably, experiments in rats indicate that, due to their dimension and peptidic nature, the passage of anti-CGRP mAbs across the BBB is negligible and pharmacodynamically irrelevant, as only 0.1-0.3% of the plasma concentration of galcanezumab was detected in the CNS. (45,46) Therefore, the anti-migraine effects of anti-CGRP mAbs are likely exerted through peripheral mechanisms on the trigeminovascular system. However, despite the predominantly peripheral antimigraine action, some studies suggest that some effects on premonitory and accompanying symptoms, suggesting a possible central site of action of anti-CGRP drugs. (28,47)

CGRP efficacy in migraine with aura. *Randomized controlled trials and* post-hoc *analyses.* Pivotal RCTs that led to the regulatory approval of four anti-CGRP mAbs enrolled mixed populations of patients with MwA and MwoA and were not specifically designed to evaluate the efficacy between these migraine subtypes. Only *post-hoc* analyses have examined outcomes in MwA patients, providing valuable insights despite their inherent methodological limitations. In fact, these studies relied on patient self-reporting of aura symptoms at the screening phase instead of a formal criterion as defined by the International Classification of Headache Disorders (ICHD). (48) This potential bias may account for the unexpectedly high rate of aura reported in some trials, leading to over-representation of aura in clinical trial populations. (28,30,49)

A comprehensive *post-hoc* analysis of four RCTs with erenumab, encompassing 2,682 patients, of whom 1,140 (46.7%) reported a history of MwA, revealed reductions in migraine frequency and acute medication use in patients with MwA comparable to those observed in MwoA patients. Despite these positive effects, the analysis found no significant difference in monthly aura days (MAD) between placebo and treatment groups, suggesting that while erenumab can effectively reduce migraine frequency, it did not seem to have a specific effect on aura occurrence. (30) However, the *post-hoc* analysis of pooled data from the two trials with eptinezumab, PROMISE-1 and PROMISE-2, which investigated patients with episodic (EM) and chronic migraine (CM), respectively, reported different results. A reduction of monthly migraine days (MMD) was reported over weeks 1-12 of treatment *vs.* baseline for both EM and CM patients, regardless of self-reported history of aura. The authors examined changes in the proportion of migraine attacks with aura in 877 patients (50.4%) with self-reported aura. At baseline, approximately one-third of migraine attacks included aura (33.6-36.0%). Over weeks 1-12, this percentage decreased by 5.0 percentage points with eptinezumab 100 mg and by 4.7 percentage points with eptinezumab 300 mg, compared to 3.1 percentage points with placebo. Although modest, this difference suggests a potential specific effect on reducing aura occurrence, with an effect on migraine reduction also in patients with a history of aura. (49) Similar results emerged from a secondary analysis of a Japanese phase-2 RCT with galcanezumab, in which both 120 mg and 240 mg doses significantly reduced the number of MAD compared to placebo. This effect was statistically significant for the overall 6-month period, though no significant differences were found at every monthly time point. Therefore, it remains unclear whether this represents a specific effect or simply reflects the overall reduction in migraine days. (50)

Overall, findings across these *post-hoc* analyses consistently support the robust efficacy of these agents in reducing overall migraine frequency in patients with a diagnosis of MwA, with effect sizes comparable to those observed in patients without aura, suggesting that aura status does not significantly predict treatment response to anti-CGRP mAbs. However, evidence regarding specific effects on the aura itself remains limited and somewhat inconsistent.

Real-world studies. An increasing number of RWS have provided additional insights into the therapeutic profile of anti-CGRP therapies, even in difficult-to-treat patients. In two studies, respectively involving 54 and 203 patients with CM and at least three previous therapeutic failures, anti-CGRP mAbs significantly reduced headache frequency and migraine-related disability. (51) Notably, both studies found no significant difference in treatment effectiveness between patients with MwA and MwoA. (51,52)

Although the presence of aura does not seem to negatively affect treatment response, the impact of anti-CGRP drugs on aura symptoms remains only partially elucidated with inconsistent findings. A multicentric, real-world study on a German cohort of 542 participants retrospectively evaluated the effectiveness of a three-month treatment with erenumab and reported that 35.2% of them observed a decreased number of accompanying aura episodes. (29) Additionally, this finding was supported by two smaller studies in which patients experienced either a complete resolution of aura episodes or a marked reduction in their intensity and frequency following treatment with anti-CGRP mAbs. (53,54)

Conversely, findings from a single-center prospective investigation encompassing 156 patients with EM or CM showed that erenumab administration yielded no significant impact on visual aura manifestations. Indeed, despite a significant reduction in monthly headache days (MHD), the frequency of MAD remained unchanged after three months of treatment in the 37 participants with MwA. (31) Similar results were observed in other case series that found no significant difference in the mean number of migraines with aura episodes during anti-CGRP mAbs therapy. (55,56) Curiously, three patients without a previous history of aura reported sporadic episodes of visual aura after initiating erenumab therapy. Similarly, one patient described a worsening of his aura in one of the first post-market analyses that evaluated the real-world performance of erenumab. (57)

More recently, a comprehensive prospective evaluation of 13 patients with MwA followed for 12 months during anti-CGRP mAbs treatment reported a significant decrease in MAD, consistent with the overall reduction in MMD. Interestingly, three patients reported a novel phenomenon of aura episodes without subsequent headache, which was absent prior to treatment. (27) Along the same lines, in a prospective real-life observational study, recruiting 158 patients treated with erenumab mAbs, 72 of whom were affected by MwA, the number of MAD was superior to that of MHD over the six months of observation in patients who had a response rate ³50%. (58) Finally, an observational, open-label cohort study with 46 patients affected by high-frequency EM or CM treated with galcanezumab found that the frequency of visual and sensory aura that was followed by headache was reduced in responders (reduction of MMDs ³50%), non-responders (reduction of MMDs <50%), and super-responders (reduction of MMDs ³70%), but not in super non-responders (reduction of MMDs <30%). (28)

Discussion

Data obtained from *post-hoc* analysis of pivotal RCTs showed a similar treatment efficacy between patients with MwA or MwoA. (30,49) Additionally, a pooled analysis from PROMISE1 and PROMISE 2 for eptinezumab and a secondary analysis from Japanese studies for galcanezumab showed a slight reduction in the proportion of migraine attacks accompanied by aura, (49,50) supporting that blockade of the CGRP pathway at the peripheral level can directly or indirectly mitigate the mechanisms underlying the aura, including cortical excitability and CSD. Data from real-world and observational cohorts provided contrasting results, with several centers reporting a marked reduction of aura in up to one third of responders, (29,53,54) while others observed no changes (31,55) or even *de novo* aura in rare cases. (57)

Taken together, these results suggest that anti-CGRP mAbs reduce migraine frequency and burden regardless of the presence of aura, with efficacy and effectiveness on both patients with MwA or MwoA. Additionally, a few studies suggested a possible influence on reducing aura occurrence, indicating a potential role of anti-CGRP mAbs on the aura phenomenon. Considering the negligible penetrance of anti-CGRP mAbs across the BBB and that fremanezumab was unable to reduce CSD occurrence in an animal model with a compromised BBB, (59) it seems implausible that anti-CGRP mAbs reduce aura through direct central mechanisms. In contrast, it is tempting to speculate that this effect may be mediated by an indirect reduction of trigeminovascular firing, which in turn may modulate the excitability of the cortex and the threshold for CSD initiation. Another intriguing hypothesis could be that, given their high receptor affinity, even minimal intracerebral concentrations of anti-CGRP mAbs may influence the sensitized CGRP-CSD axis, reducing CSD threshold.

However, several limitations preclude the formulation of definitive conclusions on the effects of anti-CGRP mAbs on aura. These limitations included the lack of aura-related endpoints in RCTs and the short duration of the blind phase, which may be inadequate to capture the modulation effect on cortical excitability. Further and dedicated studies are needed to elucidate whether anti-CGRP mAbs can directly influence MwA and reduce the occurrence of aura symptoms. This knowledge can help reveal the intricate relationship between CGRP and aura.

Conclusions

The current literature endorses anti CGRP mAbs as effective and well tolerated preventives across the migraine spectrum, irrespective of aura status. In contrast, the evidence regarding the effectiveness of anti-CGRP mAbs in MwA remains heterogeneous. The pathophysiological implications of these findings merit further exploration through prospective studies specifically designed to evaluate effects on aura frequency, duration, and characteristics.

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