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Anti-CGRP monoclonal antibodies improve cognitive function in patients affected by chronic migraine complicated with medication overuse-headache

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ABSTRACT

Background: Migraine represents one of the most disabling neurological diseases in the world. This burden is primarily due to recurrent pain episodes, alongside cognitive function impairments that patients may experience. This paper aims to explore the effect of three anti-calcitonin Gene-Related Peptide (CGRP) monoclonal antibodies (mAbs) – erenumab, fremanezumab, and galcanezumab – on the cognitive performance of a sample of patients suffering from migraine using the Montreal Cognitive Assessment (MoCA) questionnaire.

Methods: A total of 215 patients suffering from migraine who visited the Modena Headache Center were enrolled. The MoCA questionnaire was filled in by the patients at the baseline and subsequent assessments were conducted at 6 and 12 months thereafter. Additionally, patients were requested to complete the 6-item *Headache Impact Test*, *Migraine Disability Assessment Score*, and *Hospital Anxiety and Depression Scale* every three months.

Results: The sample was composed of 82% of female participants and 87% of the enrolled patients were diagnosed with chronic migraine. Following one year of treatment, there was a significant enhancement observed in MoCA scores compared to baseline measurements. Moreover, higher consumption of analgesics, elevated body mass index (BMI), and prolonged chronic migraine history exhibited an inverse correlation with MoCA score improvements after 12 months.

Conclusions: Erenumab, fremanezumab, and galcanezumab have proven to be effective in relieving the cognitive impairment associated with migraine after 1 year of treatment. These findings underscore the reversibility of cognitive impairment among migraine sufferers, even among those suffering from chronic migraine, as delineated by the majority of the patients under study. This study revealed that prolonged chronic migraine history, higher baseline analgesic intake, and elevated BMI were all predictive of diminished cognitive enhancements following treatment.

Key words: Montreal Cognitive Assessment, calcitonin gene-related peptide, erenumab, fremanezumab, galcanezumab.

Introduction

Migraine is a primary headache disorder affecting about 14-15% of the general population (1-3). The progression of a migraine episode is now considered a *continuum* encompassing prodromal indications, the active phase (ictal), and post-episode symptoms, with multiple underlying pathophysiological mechanisms involved (4). Beyond the symptoms that characterize the different phases of migraine attacks, cognitive impairment is frequently reported by patients suffering from migraine (5). In particular, reversible cognitive impairment has been demonstrated during the prodromal phase (30%) and the ictal phase (38%), with patients suffering from low attention, and low information processing speed and displaying a deficit in executive functions and memory during a migraine attack (6).

While previous research primarily addresses the condition of episodic migraine sufferers (7, 8), it is noteworthy that individuals experiencing chronic migraine (CM) tend to endure more pronounced cognitive impairment, with the severity of impairment often correlating directly with the duration of CM episodes (9). Furthermore, CM patients are usually forced to regularly use painkillers to relieve the frequent pain, thus worsening CM itself and generating a secondary headache called medication overuse-headache (MOH) (1-10). Interestingly, the association of CM and MOH seems not to worsen the patients' cognitive impairment (11).

In this complex scenario, the monoclonal antibodies (mAbs) acting against the calcitonin gene-related peptide (CGRP) are drastically changing the treatment of migraine (12). To date, erenumab, galcanezumab, and fremanezumab have demonstrated good effectiveness even in treating CM complicated with MOH (13), however, the potential of anti-CGRP mAbs to improve cognitive function in patients suffering from migraine remains unexplored.

Thus, this study aims to investigate the effectiveness of anti-CGRP mAbs in restoring cognitive impairment among migraineurs, utilizing the Montreal Cognitive Assessment (MoCA) questionnaire, a valid tool for the early detection of mild cognitive impairment (14). Because of its sensitivity to impairments in execution, attention, and visuospatial functions (15), the MoCA questionnaire is particularly suitable as a neuropsychological assessment tool for patients suffering from migraine. However, no previous investigation has explored changes in MoCA scores among patients undergoing anti-CGRP mAb treatment for migraine prevention.

This study examines alterations in MoCA scores after 6 and 12 months of anti-CGRP mAb treatment compared to baseline, both in total scores and individual domains. Additionally, differ-

ences between various mAbs have been explored after one year of treatment. Furthermore, correlations between MoCA scores and baseline migraine features, such as chronicity, attack frequency, and absolute number of analgesic medications, have been investigated. Alongside MoCA scores, other scales have been collected to assess migraine impact on quality of life (*i.e.*, 6-item Headache Impact Test, Migraine Disability Assessment Score) and the presence of anxiety or depressive symptoms (Hospital Anxiety and Depression Scale). Associations between these scores and MoCA scores over one year were also investigated.

Results

Demographics. The study cohort comprised 215 patients, predominantly female (82%). Notably, the majority of participants suffered from CM with only 20 patients experiencing high-frequency episodic migraine. Collectively, the cohort exhibited considerable impairment, as evidenced by an average migraine duration of approximately 30 years and a mean number of failed preventive treatments exceeding 5. Additionally, all CM patients met the criteria for medication overuse headache (MOH), with an average duration exceeding nine and a half years. These demographic and clinical characteristics of the enrolled patients are summarized in **Table 1.**

Montreal Cognitive Assessment values at the different timepoints. The mean MoCA score significantly increased after 6 months of treatment compared to baseline (22.61±2.51 *vs* 25.79±1.60, p=0.001). Additionally, after 1 year of treatment, the MoCA score was significantly higher than baseline (22.61±2.51 *vs* 27.34±1.36, p=0.001). Moreover, at 12 months post-treatment, the MoCA score remained significantly higher than that recorded at 6 months (25.79±1.6 *vs* 27.34±1.36, p=0.001). Over time, significant improvement was observed in visuospatial function and attention domains (p <0.001). Specifically, scores in the visuospatial section of the MoCA questionnaire were notably higher than baseline (2.98±0.15 *vs* 4.15±0.85, p<0.001), though not significantly different from those at 6 months (3.72±0.92, p=0.122). No significant differences were found in other MoCA questionnaire scores across various time points. **Table 2** reports the MoCA questionnaire scores, whereas **Figure 1** provides an overview of the MoCA score variation.

Comparison of Montreal Cognitive Assessment between different antibodies after 1 year of treatment. The MoCA questionnaire scores were comparable among the different mAbs after 1 year of treatment. Specifically, erenumab yielded a MoCA score of 27.29±1.20, galcanezumab scored 27.35±1.11, and fremanezumab scored 27.37±1.79 (p=0.125). Similarly, at 6 months of treatment, MoCA scores did not significantly differ among the three mAbs: erenumab scored 26.12±1.30, galcanezumab scored 26.33±1.21, and fremanezumab scored 26.62±1.98 (p=0.11). Baseline MoCA values were also comparable across the different

Table 1. Demographic and clinical features of the study cohort.

Variable	Value
Number of patients	215
Age	47.12±10.36
Females	185/225 (82%)
BMI	24.51±3.06
Migraine duration	29.56±11.12
CM and MOH	195/215 (87%)
CM duration	15.49±10.43
MOH duration (months)	112.80±79.88
Familial history of migraine	170/215 (65%)
Aura	38/215 (22%)
MMDs	21.72±6.84
AC	43.69±39.88
NDM	23.42±6.12
NRS	9.27±0.57
HADSD	8.12±2.14
HADSA	7.79±3.21
MIDAS	69.04±40.12
Nr. of preventive treatments failed	5.33±2.75
Comorbidities	125/215 (56%)
mAbs in add-on	69/215 (31%)
Painkillers withdrawal	35/215 (17%)
Erenumab	121/215 (54%)
Galcanezumab	49/215 (26%)
Fremanezumab	45/215 (20%)

A comprehensive summary of demographic and clinical characteristics observed within the study cohort comprising 215 migraine patients. The variables include the number of patients, age, gender distribution, body mass index (BMI), migraine duration, the prevalence of chronic migraine (CM) and medication overuse headache (MOH), duration of CM and MOH, familial history of migraine, presence of aura, monthly migraine days (MMDs), number of analgesic medications (AC), non-dominant migraine days (NDM), numeric rating scale (NRS) score for pain intensity, Hospital Anxiety and Depression Scale (HADS) scores for depression (HADSD) and anxiety (HADSA), Migraine Disability Assessment Score (MIDAS), number of failed preventive treatments, presence of comorbidities, usage of mAbs as add-on therapy, painkiller withdrawal, and the utilization rates of specific anti-CGRP mAbs among the cohort.

Table 2. Changes in Montreal Cognitive Assessment total score and the various cognitive domains over time.

	Baseline	Month 6	Month 12	p
MoCA total score	22.88±2.61	25.86±1.61	27.37±1.45	<0.001*
Cognitive functions				
Visuospatial functions	2.98±0.79	3.72±0.93	4.15±0.85	<0.001*
Executive functions	2.98±0.15	2.97±0.16	2.97±0.18	0.98
Attention	0.98±0.15	0.976±0.14	0.98 ±0.17	0.99
Language	2.17±0.48	2.2±0.47	2.19±0.47	0.86
Memory	1.97±0.18	1.98±0.14	1.97±0.17	0.97
Orientation	5.88±0.33	5.88±0.33	5.88±0.33	0.99

MoCA, Montreal Cognitive Assessment.
This table illustrates the trajectory of cognitive performances among migraine patients receiving anti-CGRP mAb treatment (erenumab, galcanezumab, and fremanezumab) over 12 months. The mean scores of the MoCA questionnaire and its subdomains at baseline, and 6- and 12-months post-treatment are reported, along with corresponding p-values. The MoCA total score and various cognitive functions, including visuospatial functions, executive functions, attention, language, memory, and orientation, are presented.
*Statistical analysis highlights the significance of changes over time in MoCA total score and individual cognitive domains.

mAbs, with patients receiving fremanezumab scoring an average of 22.39±1.70, erenumab patients scoring 22.23±1.60, and galcanezumab patients scoring 22.55±1.40. These findings are summarized in **Table 3** and graphically represented in **Figure 2**.

Comparison of Montreal Cognitive Assessment between chronic migraine sufferers and episodic migraine sufferers. No significant differences emerged between the MoCA scores when comparing high-frequency episodic migraineurs and chronic migraineurs. At baseline, episodic migraine sufferers showed higher MoCA scores compared to CM sufferers, although not significantly different (23.93±2.70 *vs* 23.65±1.6, p=0.11). Similarly, after 6 months of treatment, episodic migraine sufferers displayed a higher MoCA score than the CM sufferers, but differences were not significant (26.14±2.40 *vs* 25.95±1.50, p=0.12). After 1 year of treatment, the two groups displayed similar values of the MoCA score, as well (28.03±2.51 *vs* 27.89±1.5, p=0.51).

Montreal Cognitive Assessment relationship with the baseline values. The value of the MoCA score after 12 months was significantly associated with the BMI, AC, and the duration of chronic migraine at the baseline. In particular, patients with a higher BMI, a higher AC, and a longer history of CM had lower values of the MoCA score after 12 months of treatment. No other significant associations were found. In the univariate analysis, only the AC remained significantly associated. These results are summarized in **Table 4.**

Discussion

The present study provides the first evidence that anti-CGRP mAbs are effective in relieving cognitive function in migraineurs. Cognitive assessment in migraine patients undergoing preventive treatments has been explored using various methodologies, as recently demonstrated (16). Cognitive improvements have been evaluated even in CM patients receiving preventive treatments, such as onabotulinumtoxinA, which exert their action exclusively outside the blood-brain barrier, indicating that CM-related cognitive impairment may predominantly stem from pain-related mechanisms, akin to those observed in fibromyalgia (17).

Furthermore, a recent voxel-based morphometric investigation

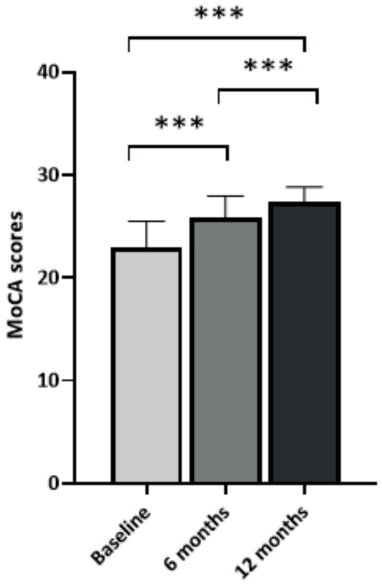

Figure 1. Montreal Cognitive Assessment (MoCA) questionnaire scores at the baseline and after 6 and 12 months of treatment with anti-CGRP monoclonal antibodies (mAbs). MoCA questionnaire scores were recorded at the baseline (light grey bar) and after 6 (grey bar) and 12 (black bar) months of treatment with anti-CGRP mAbs. Data are represented as means ± standard deviation and were analyzed with one-way ANOVA followed by Tukey-Kramer's *post-hoc*. ***p<0.001.

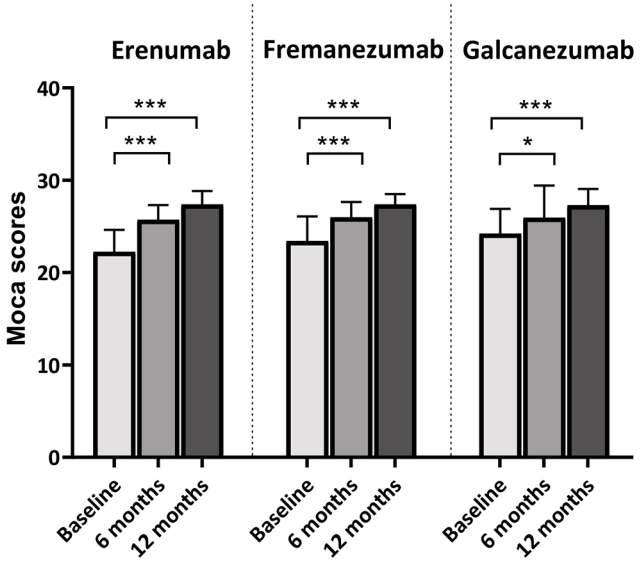

Figure 2. Montreal Cognitive Assessment (MoCA) questionnaire scores at baseline, and 6, and 12 months post-treatment with different anti-CGRP monoclonal antibodies. MoCA questionnaire scores were recorded at the baseline and after 6 and 12 months of treatment with erenumab, galcanezumab and fremanezumab. Data are represented as means ± standard deviation. Significant differences are reported in Table 3. Data were analyzed with one-way ANOVA followed by Tukey-Kramer's *post-hoc*. ***p<0.001, *p<0.05.

Table 3. Montreal Cognitive Assessment total score for each monoclonal antibodies at the different time points.

	Baseline	Month 6	Month 12
Erenumab (121)	22.25±2.37	25.72±1.6	27.38±1.45
Galcanezumab (49)	23.42±2.67	25.82±1.66	27.33±1.72
Fremanezumab (45)	24.22±2.68	26.3±1.56	27.37±1.14
p	0.099	0.344	0.125

The mean Montreal Cognitive Assessment questionnaire scores recorded at baseline and 6- and 12-month post-treatment with anti-CGRP monoclonal antibodies (mAb; erenumab, galcanezumab, and fremanezumab) are reported. The number of patients receiving each treatment is indicated in parentheses. Additionally, p-values indicate that there were no significant differences among the mAbs.

revealed grey matter alterations in multiple brain regions associated with both cognition and pain modulation in CM patients (18), thereby substantiating the clinically observed cognitive deficits. Interestingly, the efficacy of peripherally acting drugs in ameliorating cognitive impairment in migraine suggests that the observed modifications in pain modulation areas may be, at least partially, driven by peripheral mechanisms (19). Furthermore, Russo *et al.* (2020) found out that the cutaneous allodynia is correlated with brain-network disarrangement; hence, cognitive impairment observed in CM may be justified by the same mechanisms of central sensitization and network de-arrangement that are associated with pain chronicization (20).

Hence, the anti-CGRP mAbs-mediated reduction of the peripheral sensitization is replied in a reduction of the central sensitization and, conversely, in a restored functional connectivity of the cognitive network (21), thus justifying the ameliorations observed in the cognitive performance.

Having shown that a peripheral-acting drug may also impact central function is strongly suggested by the effectiveness of anti-CGRP mAbs on prodromal symptoms in migraine, as well as psychiatric features (21). This underscores the involvement of CGRP in both peripheral and central sensitization processes, as delineated in a comprehensive review by Iyengar *et al.* (2017) (22). Notably, visuospatial function exhibited a significant enhancement throughout treatment.

Regarding visuo-spatial function, some studies found an impairment in the visuo-spatial memory, especially during migraine attacks, whilst others did not (5). The brain of CM sufferers is featured by a high grade of segregation between different neural networks, thus suggesting an abnormal brain pattern connectivity between sensory and cognitive brain networks. This may explain the abnormalities in cognitive functions observed in clinical settings (23). Visual network seems to be de-arranged both in episodic migraine (24), as well as CM (25).

Table 4. Association between Montreal Cognitive Assessment score at 12 months post-treatment and the explored variables at the baseline.

	MoCA after 12 months	p
Age	-0.08 [-1.27÷1.12]	0.89
BMI	-0.63 [-0.99÷-0.21]	0.001*
Migraine duration	-0.94 [-2.67÷0.37]	0.22
CM	0.18 [-0.58÷0.85]	0.21
CM duration	-2.02 [-0.86÷3.37]	0.001*
MOH duration (months)	-4.78 [-15.4÷5.77]	0.22
MMDs	0.2 [-0.54÷0.93]	0.61
AC	-3.81 [-0.16÷-7.72]	0.04*
NDM	0.19 [-0.58÷0.94]	0.63
NRS	0.02 [-0.05÷0.1]	0.21
HADSD	0.16 [-0.20÷0.57]	0.12
HADSA	0.12 [-0.27÷0.5]	0.35
MIDAS	0.14 [-5.08÷5.35]	0.96
A number of preventive treatments failed	0.11 [-0.21÷0.43]	0.49

MoCA, Montreal Cognitive Assessment; BMI, body mass index; CM, chronic migraine; MOH, medication overuse headache; MMDs, monthly migraine days; AC, analgesic medications; NDM, non-dominant migraine days; NRS, numeric rating scale; HADSD, Hospital Anxiety and Depression Scale scores for depression; HADS, Hospital Anxiety and Depression Scale scores for anxiety; MIDAS, Migraine Disability Assessment Score.
Associations between different baseline characteristics and cognitive outcomes following 12 months of anti-CGRP mAb treatment among migraine patients are reported.
*The value of the MoCA score after 12 months was significantly associated with the BMI, AC, and CM duration at the baseline.

In patients suffering from migraine with aura, the heath stimulation of the trigeminal nerve enhances an abnormal response from the visual network (24). This may suggest, besides the deep involvement of the visual area in the pathophysiology of migraine, even an adaptive pattern of visual connectivity in migraineurs, which ineffectiveness may be responsible for the visuospatial memory alteration observed.

Messina *et al.* (2021) have recently demonstrated an adaptive functional plasticity mechanism potentially aiding migraine patients in mitigating compromised visuospatial abilities and maintaining satisfactory performance during visuospatial tasks (26). Notably, regions implicated in the modulation of pain in migraine, such as the orbitofrontal cortex, appear to also play a facilitative role in augmenting the visual cortex (26). Indeed, an increase in pain levels would likely compromise the ability of certain brain regions to compensate for impaired visual cortex function. Conversely, alleviation of pain could engender a beneficial effect on the functioning of these networks, as confirmed by the improvement in visuospatial function compared to other domains assessed by the MoCA questionnaire. Similarly, the enhancement in attention observed in these patients should be elucidated.

Attention deficits are frequently encountered in individuals affected by migraine (27), stemming from the same network disarray mentioned earlier, which contributes to the disruption of visual efficiency in migraine sufferers (26). Hence, the reduction of pain may lead to amelioration in attentional capacities, as the underlying neural network dynamics become less perturbed.

These insights underscore the intricate interplay between pain perception, cognitive function, and neural network organization in migraine pathology, warranting further exploration to optimize therapeutic strategies targeting these interconnected domains. Hence, the restoration of the brain network arrangement may induce the restoration of a normal attention status in patients suffering from migraine (28).

No differences were found regarding the MoCA score between the different antibodies. This may be – at least in part – explained considering that the anti-CGRP mAbs act peripherally, outside the BBB, with a peripheral rather than central mechanism, independently from the block of the CGRP receptor or the CGRP itself (21). Overall, it is intriguing that the treatment with mAb, different mechanisms of action on the CGRP signaling, exhibit analogous effects. This suggests the presence of alternative mechanisms or converging pathways contributing to the observed outcomes. Further investigation into the precise molecular interactions underlying these phenomena could provide valuable insights into the complexities of neurobiological signaling and therapeutic interventions targeting migraine pathology.

No association between the MoCA score and age was found. It has to be highlighted that the analyzed sample had an average age of 47.12±10.36, thus justifying the insignificant association between the MoCA score after 1 year and the age of the patients at the baseline.

No differences emerged between episodic patients suffering from migraine and migraine sufferers affected by CM and MOH, but MoCA scores at every time-point were higher for the episodic migraineurs, even if not statistically significant. The statistical non-significance may be due to the lower number of episodic patients suffering from migraine in the sample compared with CM sufferers.

Furthermore, no differences were explorable between patients with and without MOH among CM, because all CM in the sample were also MOH-sufferers. In this study, the MoCA score was negatively associated with the BMI, the AC, and with the duration of CM. The BMI has been found negatively associated with cognitive performance (29).

Higher BMI has been also correlated with a lower effectiveness of anti-CGRP mAbs (30). Patients with a higher BMI display a

higher percentage of body fat, thus causing systemic sub-clinical inflammation (31), which has been correlated both with migraine (32) and with poorer cognitive function (33). Indeed, the peripheral sterile neurogenic inflammation at the meningeal level is also a key factor in migraine pathogenesis (34) and an important role of circulating cytokines has emerged (35). Furthermore, higher CGRP levels have been found in obese individuals (36). Hence, in patients with a higher BMI, a higher trigeminal sensitization and higher CGRP levels may impair the effectiveness of anti-CGRP mAbs, even on cognitive symptoms.

Additionally, an association between the overuse of painkillers and poorer cognitive performances emerged (37). Despite this, the overuse of non-steroidal anti-inflammatory drugs seems to not influence cognitive performance (38).

On the other hand, the low permeability of the BBB towards triptans should rule out these drugs in determining cognitive impairment. In this study, the number of AC seemed to be associated with the MoCA score after 1 year, but the duration of MOH was not. It may sound strange that the AC is associated with cognitive performance in this sample, whilst migraine frequency was not, as assessed in other studies (39, 40). This may be because many patients were CM sufferers with a nearly daily headache at the baseline, with the biggest differences being in their AC. Since that, it could be even possible that a higher AC at the baseline reflects better than the MMDs real severity of the CM. Hence, the AC is better correlated with cognitive performance.

Despite the MOH duration was not associated with poorer cognitive performance after one year of treatment, the duration of CM was. Several neuroimaging studies have demonstrated that migraine attacks induce a thalamocortical network dearrangement that may cause the ictal cognitive decline during migraine attacks and that these alterations last in time, even in inter-ictal phases (41). CM is associated with an altered functional connectivity between cortical and somatosensory areas, which may contribute to cognitive decline (42). Additionally, some studies have also raised some doubts about a faster cognitive decline in migraineurs, but long-term studies excluded this hypothesis (43). However, CM is associated with more complaints and more psychological comorbidities than episodic migraine. Indeed, anxiety and depression are common among CM sufferers, especially if CM is long (44, 45), thus contributing to cognitive impairment, even if subclinical (45). In the present sample, a small number of patients suffered from depressive and/or anxiety symptoms, and no correlation was found between HADS score and MoCA after 1 year.

Our study has some limitations. While the MoCA is a widely used screening tool for assessing cognitive function, its applicability to migraine patients, especially those with CM, may be limited. Chronic migraine itself can significantly impact cognitive function due to factors such as frequent headache episodes, pain intensity, sleep disturbances, and medication usage. Consequently, relying solely on MoCA results to infer cognitive impairment in this population may not accurately capture the full extent of cognitive difficulties experienced by individuals with CM. Moreover, the MoCA's lack of specific validation for migraine patients raises concerns about its sensitivity and specificity in detecting subtle cognitive changes related to migraine pathology. Migraine-related cognitive impairment can manifest in various domains, including attention, memory, executive function, and processing speed, which may not be adequately assessed by the MoCA alone. Additionally, the presence of comorbidities commonly associated with CM, such as mood disorders and sleep disturbances, further complicates the interpretation of MoCA scores in this population. Therefore, while the MoCA provides valuable insights into cognitive function, its utilization as the sole measure of cognitive impairment in CM patients warrants cautious interpretation. Supplementing MoCA assessments with comprehensive neuropsychological evaluations tailored to the specific cognitive challenges faced by migraine patients would provide a more accurate assessment of cognitive function in this population.

Thus, future research efforts will focus on developing and validating assessment tools specifically designed to evaluate cognitive function in migraine patients, including those with CM, to improve the accuracy and reliability of cognitive assessments in clinical practice and research settings.

Additionally, the study's one year may not fully capture the long-term effects of anti-CGRP mAbs on cognitive performance. Among the four mAbs approved for the preventive treatment of migraine, erenumab, galcanezumab, and fremanezumab have demonstrated good effectiveness even in treating CM complicated with MOH. Moreover, although not yet reported in real-world evidence studies, also eptinezumab demonstrated efficacy in the same population, paving the way for future studies aimed at investigating the effects of eptinezumab on cognitive impairment among patients suffering from migraine. However, the results of the current study indicate an overall improvement in patients' cognitive functions after an effective prophylactic treatment for migraine. Furthermore, patients affected by EM were fewer than patients with CM, so that, the conclusions about the slight and not significant differences of the MoCA score in the 2 groups were affected by the different sizes of the groups.

Indeed, while the primary focus of the study was assessing the cognitive effects of anti-CGRP mAbs in patients suffering from migraine, exploring potential correlations between cognitive enhancement and treatment response is a valuable avenue for investigation that cannot be overlooked. Understanding whether improvements in cognitive function coincide with or contribute to treatment response can provide crucial insights into the mechanisms underlying the therapeutic effects of anti-CGRP mAbs in migraine management. Investigating the relationship between cognitive enhancement and treatment response could involve analyzing longitudinal data to determine whether changes in cognitive function precede or follow improvements in headache frequency, severity, and disability. Additionally, examining the association between changes in cognitive performance and other clinical outcomes, such as quality of life, mood symptoms, and medication usage, can provide further context for understanding the broader impact of treatment on migraine patients' well-being. Furthermore, exploring potential predictors or moderators of treatment response, such as baseline cognitive function, disease severity, medication adherence, and demographic factors, can help identify subgroups of patients who may benefit most from anti-CGRP mAb treatment in terms of both migraine symptom management and cognitive outcomes. Integrating these analyses into the study framework can enrich our understanding of the interplay between cognitive function and migraine pathology, as well as the mechanisms through which anti-CGRP mAbs exert their therapeutic effects. Ultimately, such insights have the potential to inform personalized treatment approaches and optimize clinical outcomes for migraine patients. Therefore, while evaluating treatment effectiveness may not be the primary aim of the study, exploring the correlation between cognitive enhancement and treatment response remains a valuable and pertinent aspect of the research.

Despite these limitations, this study provides a comprehensive approach to evaluating the cognitive effects of three anti-CGRP mAbs over one year of treatment. Moreover, the inclusion of multiple assessments at baseline, 6-month, and 12-month intervals allowed for longitudinal analysis of cognitive changes over time. Furthermore, the study's robust sample size of 215 patients predominantly diagnosed with chronic migraine, enhances the generalizability of the findings to similar populations. The use of additional measures such as HIT-6, MIDAS, and HADS provides a comprehensive evaluation of migraine severity, disability, and psychological comorbidities, which could potentially confound the observed cognitive changes.

Moreover, the identification of predictors such as prolonged

chronic migraine history, higher baseline analgesic intake, and elevated BMI for diminished cognitive enhancements following treatment adds valuable insights into individual factors that may influence treatment outcomes. Overall, these strengths contribute to a robust assessment of the cognitive benefits of anti-CGRP mAbs in patients suffering from migraine, highlighting their potential efficacy in ameliorating cognitive impairment associated with migraine pathology.

Conclusions

The present study suggests that erenumab, fremanezumab, and galcanezumab could be effective in relieving the cognitive impairment associated with migraine after 1 year of treatment. This data could confirm that the cognitive impairment experienced by patients suffering from migraine is reversible, even if patients are CM sufferers. A longer history of CM, a higher consumption of analgesics at the baseline, and a higher BMI were all associated with a lower amelioration. Further large-scale studies are warranted to unveil the association between migraine and the trend of cognitive function, as well as to explore more fairly the difference between EM and CM in terms of cognitive impairment. Finally, more studies exploring a linkage between anti-CGRP mAbs and the improvement in cognitive functions are needed.

Materials and Methods

Study design and approval. This is a retrospective observational study for which both episodic and CM sufferers receiving one of the 3 anti-CGRP mAbs currently available in the Headache Center of the University of Modena and Reggio Emilia were consecutively enrolled during one of their visits. Only patients who filled the MoCA score, at least, at the baseline and after 1 year of treatment were included. Patients were enrolled between the 31st of August 2019 to the 31st of December 2022 at the headache center of the University of Modena and Reggio Emilia. This study was approved by the Area Vasta Emilia Nord ethics committee (protocol number: 625/2020/OSS/AOUMO and 50/2020/OSS/AOUMO) and all participants signed a written informed consent to participate in the study, which was conducted in accordance with the latest version of the declaration of Helsinki.

Procedures. Patients (N=215) suffering from migraine (87% suffering from CM) received erenumab, galcanezumab, or fremanezumab as a preventive treatment. 65% of the enrolled patients had a familial history of migraine, and 22% reported aura episodes. Treatments were administered subsequent to the control visit in compliance with directives mandated by our regulatory authority. Erenumab (administered to 54% of the enrolled patients) was always started at 70 mg monthly and eventually titrated up to 140 mg monthly from the 4th injection onward, in case the patient displayed a <30% response in the previous injections (46). Fremanezumab was administered to 20% of the enrolled patients, who received the dosage of 225 mg monthly, whilst galcanezumab (administered to 26% of the enrolled patients) was started with a loading dose of 240 mg and then administered at the dose of 120 mg from the 2nd injection onwards (47) (**Figure 3**). Visits were scheduled every 3 months, and the following variables were collected: monthly migraine days (MMDs), the number of painkillers taken per month (NPM), the number of days per month in which the patient took, at least, one painkiller, the Hospital Anxiety and Depression Scale (HDAS) score (48). Additionally, patients were asked to fill out the 6-item Headache Impact Test (HIT-6) (49) as well as the Migraine Disability Assessment Questionnaire (MIDAS) score (50, 51). At the baseline and after 6 and 12 months of treatment, patients completed the Montreal Cognitive Assessment (MoCA) questionnaire (14).

Montreal Cognitive Assessment questionnaire. The MoCA questionnaire (**Supplementary material**) is a 10-minute-long question-

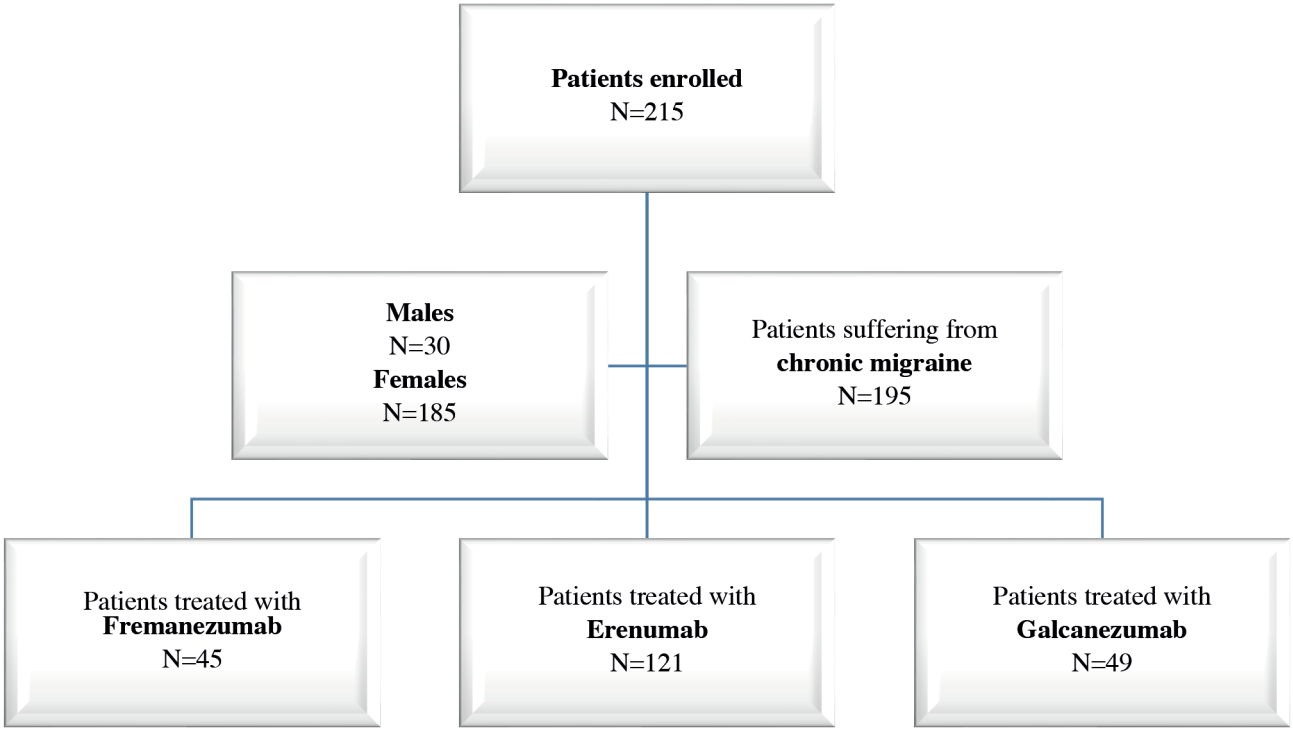

Figure 3. Flowchart of the patients enrolled and their treatments.

naire exploring different cognitive domains (memory, executive functioning, attention, language, visuospatial abilities, and orientation), for which a score above 26 is considered normal, with a maximum score of 30 (14). It explores different domains of cognitive function through different tasks, such as: connecting sequentially dots, alternating numbers, and letters, drawing a cube, and making a copy of a clock for visual abilities. Furthermore, patients are asked to name 3 animals to explore their capability of naming things. Attention is explored by repeating a series of numbers backwards and verbalism is explored by repeating 2 phrases. The ability of abstraction is explored by asking the patient what 2 different things have in common and orientation is explored by asking the patient the data and where is he/she. In this study, the MoCA score was filled every 6 months to avoid patients' memory altering their answers. People who were already taking a preventive treatment before starting the study were allowed to participate if the dose of the preventative taken had been stable for, at least, 6 months. Nevertheless, patients taking antidepressants or anticonvulsants as migraine preventive treatment were excluded, due to the high impact of these medications on cognitive function, as well as patients older than 65 years of age (4).

Statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD) and checked for normal distribution using the Shapiro-Wilk test. Categorical variables were expressed as subject counts and percentages. Normally distributed continuous variables were compared with the One-way analysis of variance (ANOVA) followed by the Tukey-Kramer *post hoc* comparison test, whilst continuous variables that were not normally distributed were compared with the Kruskal-Wallis rank sum test. Bonferroni's correction was applied for multiple comparisons. A linear regression model was performed to explore the correlation between the MoCA value after 1 year of treatment and the continuous variables at the baseline. p-values lower than 0.05 were considered significant. Statistical calculations were made with STATA Ic15 software and graphs were generated using Prims v.10 for Microsoft.

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Online supplementary material:

The Montreal Cognitive Assessment questionnaire (in Italian).

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Contributions: SG, conceptualization; data curation; investigation; methodology; project administration; resources; supervision; validation; visualization; writing - review & editing. CB, data curation; investigation; validation; visualization; writing – original draft. FLC and DB, data curation; investigation; validation; visualization; and writing - review & editing. FT, resources; supervision; writing - review & editing. VR, data curation; visualization; writing – original draft. LP, conceptualization; project administration; resources; supervision; writing - review & editing. All the authors participated in designing the study, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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Ethics approval and consent to participate: this study was approved by the Area Vasta Emilia Nord ethics committee (protocol number: 625/2020/OSS/AOUMO and 50/2020/OSS/AOUMO) and all participants signed a written informed consent to participate in the study, which was conducted in accordance with the latest version of the declaration of Helsinki.

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