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Preventive CGRP-targeted therapies for chronic migraine with and without medication-overuse headache

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Abstract

Background: Calcitonin gene-related peptide (CGRP) targeted therapies are an important breakthrough in migraine prevention. Randomized clinical trials, post-hoc analyses, and phase IV studies have demonstrated their efficacy and safety in chronic migraine patients, including those with concomitant medication-overuse and medication-overuse headache. Real world evidence studies support these findings and provide realistic endpoints for estimation of effect.

Methods and results: We have performed a narrative review including results from double-blind placebo-controlled randomized clinical trials and real-world evidence studies regarding efficacy of the CGRP(-receptor) monoclonal antibodies and CGRP-receptor antagonists (gepants) in patients with chronic migraine with concomitant medication overuse (headache). We have included patient profiles and main efficacy endpoints (monthly migraine days, monthly headache days, monthly acute medication days and percentage responder rates).

Conclusion: The results of this review show that CGRP monoclonal antibodies are effective in chronic migraine patients, also in those with medication overuse (headache). At the time of this review, atogepant clinical trials in chronic migraine have not been communicated. Direct comparative studies are needed for comparison with other treatment options.

Keywords

Chronic migraine, medication-overuse, medication-overuse headache, calcitonin gene-related peptide, monoclonal antibodies, gepants

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Introduction

Medication-overuse headache (MOH) is a disabling condition with high socio-economic burden that affects about 60 million people worldwide (1,2). The prevalence is estimated to be from 0.5% to 7.2% depending on the country and study (3,4). It more commonly affects women, with a prevalence ratio of 4:1, and it reaches peak prevalence between 50 and 60 years-old (5). Amongst risk factors for MOH are low socio-economic position, stress, obesity, physical inactivity, and daily smoking (6,7). It leads to greater disability and further reduced quality of life (QoL) in patients (8–10).

Clinically, MOH is a secondary headache attributed to the regular use of acute therapies in patients with a primary headache disorder. According to the International Classification of Headache Disorders (ICHD-3) (11), MOH is defined by headache occurring on 15 or more days/month in a patient with a pre-existing primary headache (the most common being underlying primary headache migraine or

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tension-type headache) and developing as a consequence of regular overuse of acute medication (on 10 or more or 15 or more days/month, depending on the medication) for more than three months (11). The term medication overuse (MO) often refers to the frequent intake of headache medication in a person with a primary headache disorder without causing an increase in headache frequency. Patients with a background of migraine and MOH transformed over months from an episodic migraine (EM) form to the chronic migraine (CM) form (12). Risks for chronification include frequent use of medication for acute therapy of migraine attacks as well as comorbid depression, anxiety and allodynia, which is as marker for central sensitization (13–15). However, it is still not clear whether frequent use of migraine acute medication leads to worsening of migraine or whether worsening of migraine leads to increased use of acute medication.

CM and MO(H) often go hand-in-hand and a therapeutic approach needs to take this into account to enable a patient to return to EM form with less frequent, long-lasting and severe migraine attacks. The treatment approach for CM with MOH may include: a) drug withdrawal, b) initiation of a preventive treatment, c) or a combination of both (15,16). Controversy exists regarding drug withdrawal and preventive treatment and the reversal of chronic headache after cessation of overused acute medication (9,17–19).

The development of calcitonin gene-related peptide (CGRP)-targeting drugs has ushered in a new era for migraine therapy. The first class of treatment approved was monoclonal antibodies targeting CGRP or the CGRP-receptor (CGRP-mAbs). These drugs became available in 2018 as treatment for migraine prevention. There are three mAbs against the CGRP ligand (fremanezumab, galcanezumab, eptinezumab) and one CGRP-receptor mAb (erenumab) approved for migraine prevention (20). CGRP-mAbs have proven efficacy for the preventive treatment of migraine with, so far, few side effects in clinical trials (21,22). Also, a new generation of CGRP receptor antagonists (gepants) such as atogepant (23–25) and rimegepant (26) have been shown to be effective for the preventive treatment of migraine, and were approved by the Food and Drug administration (FDA) and the European Medicines Agency (EMA), although not yet reimbursed in most countries.

The aim of this review is to assess the benefit of CGRP-targeted therapies for patients with CM with and without MO(H).

Methods

This is a narrative review. We searched articles indexed in PubMed which assessed the efficacy of migraine CGRP-targeted therapies in patients with CM with and without MO and MOH (published to July 2022).

We sought randomized, double-blind, placebo-controlled studies of erenumab, fremanezumab, galcanezumab, eptinezumab, atogepant and rimegepant, as well as observational studies reporting real-world efficacy of the above-mentioned drugs for CM with and without MO and MOH. The selection process was performed in two phases: a first one of title and abstract reading and a second one after full article reading. Reviews, expert opinion articles and observational real-world studies with small samples (less than 20 patients) were excluded. Study selection was independently performed by two investigators (AA and MT-F). Disagreement was resolved by dialogue. We included double-blind randomized controlled trials, randomized crossover trials, open-label phase IV studies, and prospective observational studies. Case reports, meeting abstracts, editorials, commentaries, articles with a pediatric population (age <18 years), and articles with incomplete information were not eligible. There were no language or date restrictions. Reference lists of included articles were examined to identify studies that might have been missed by the initial database search. Additional papers were included if one of the three authors identified a paper fulfilling the criteria as described above which was missed.

Results

Evidence of CGRP-mAbs in CM

According to results of phase 3/3b clinical trials, eptinezumab (100/300 mg), fremanezumab (monthly 225 mg or quarterly 675 mg) and galcanezumab (120/240 mg) are effective, safe, and well tolerated for the preventive treatment of CM (27–31). The results from the phase 2 pivotal study of erenumab (70/140 mg) in CM patients have been included in this review (32). Studies included patients up to 75 years-old and all allowed concomitant use of other migraine oral prophylactics during the study except for the erenumab trial (32). Overall, the sample included in all studies had a female gender predominance and mean age between 39.6 and 44.8. In accordance with the CM diagnosis the mean headache frequency ranges were between 16.1 and 19.4 monthly migraine days (MMDs). Patients with MO(H) were not excluded (with the exception of the overuse of barbiturates or opioids) and 39% up to 65% patients included fulfilled criteria for MO(H) (31,32). The percentage of naïve patients for preventive therapies was not clearly reported in most studies. The two exceptions were that the erenumab study reported 34% of participants were preventive naïve (32) and 24% of patients treated

with galcanezumab had not been using preventive treatments for the past five years (31). Phase 3b studies with fremanezumab and galcanezumab included EM and CM patients with previous failure to 2–4 migraine oral prophylactics (27,31).

Main endpoints for CM clinical trials were reduction in MMDs, monthly headache days (MHDs) or ≥50% responder rate (50% RR) after 12 weeks of treatment. On average, the reduction in MMDs was between −4.6 and −8.2 for CGRP-mAbs and between −1.0 and −5.6 for placebo; reduction in MHDs between −4.6 and −8.8 for CGRP-mAbs and between −2.5 and −6.4 for placebo; and the proportion of subjects receiving CGRP-mAbs who achieved 50% RR varied among 38 and 61.4% of patients treated with CGRP-mAbs and between 18 and 39.3% for placebo. Between 7–31% of CM patients treated for three months and between 4.5 and 15% under placebo showed ≥75% RR (28–33) and a small percentage of patients in CGRP-mAb (0.7–4.3%) and placebo (0.4–0.5%) showed 100% response (31,33). Another interesting endpoint in CM trials is the percentage of patients treated that convert from CM to EM. Among 50.5 and 53.9% of CM patients treated with erenumab or fremanezumab converted to episodic form after three months of treatment (34,35).

Apart from robust evidence coming from CGRP-mAbs, it is also interesting to review the increasing number of publications showing real world evidence (RWE) of CGRP-mAbs. The majority of reports come from European countries that, following local financial conditions policies only include resistant high frequency episodic migraine (HFEM) or CM patients. Of special interest for this review are a series of multicentric Italian studies that assess the effectiveness of erenumab, galcanezumab and fremanezumab in a real-life EM and CM population (36–38). 55.5% of CM patients treated with erenumab 70 mg achieved ≥50% reduction at month 3 (36). The ≥50% RR for fremanezumab 225 mg monthly or 675 mg quarterly CM patients was 58.3% (38) and 66.7% for galcanezumab 120 mg (39). Previously mentioned studies reported up to 33.5% patients achieving ≥75% response in CM patients, as well up to 5.9% and 2.3% of EM or CM participants with a 100% responder rate, that is at least one month of no headache (36–38).

Evidence of CGRP-mAbs in CM with MO and MOH

The efficacy of CGRP-mAbs in CM patients with MO and MOH has been evaluated mainly in *post-hoc* analyses, except for the preplanned exploratory analysis of a pivotal study that evaluated efficacy and safety of erenumab in patients with CM (32) (see Table 1, Figure 1). Furthermore, eptinezumab was the only CGRP-mAb that assessed MOH prospectively, whereas erenumab, galcanezumab and fremanezumab assessed it retrospectively. In all of them, existing MO(H) was not treated.

Regarding erenumab, the aforementioned subanalysis showed no differences in treatment effect between the CM with MO group and CM without MO group. Of 667 patients randomized, 41% (n = 274) met MO criteria. In both groups erenumab 70 and 140 mg resulted in a significant response with a larger reduction in MMDs and acute migraine-specific medication treatment days (MSMD) than the placebo group at month 3. A larger percentage of patients achieving a ≥50% RR compared with placebo was also observed. Furthermore, a substantial proportion of patients who overused acute medications at baseline transitioned to non-overuse status, regardless of the type of medication for acute therapy of migraine attacks. More than half of the erenumab-treated patients who overused simple analgesics or triptans at baseline switched to non-overuse status after one month. Improvements in patient-reported outcomes (PROs) showed consistent benefit of erenumab in CM with MO subgroup across multiple measures of impact, disability, and QoL (39).

Erenumab reduced monthly acute medication days (MMeD), in particular migraine specific medication (MSM) in a post-hoc analysis based on data from the double-blind treatment phase (DBTP) of the two pivotal studies (EM and CM trials) (40). This analysis included patients with and without MO. The respective change in monthly MSM days over months 4-5-6 compared with the pre-double blind period was 0.5, 2.1 and 2.8 for placebo, erenumab 70 mg and 140 mg (for the EM study) whereas the respective change in monthly MSM days was 2.1, 4.5, and 5.4 respectively for the CM study. These reductions were sustained in the extension periods (week 52). Erenumab was also associated with a higher proportion of MSM users achieving ≥50%, ≥75 and 100% reduction from baseline in monthly MSM days versus placebo in both EM and CM. Corresponding numerical reductions were also observed for non-MSM days (paracetamol/acetaminophen, combination analgesics, and NSAIDs). This information is important in order to prevent the excessive use of acute medication. Furthermore, another post-hoc analysis of the erenumab pivotal clinical trial showed that more than half of patients treated with erenumab convert from CM to EM and from acute migraine medication overuse to non-overuse status (41).

Post-hoc analyses of fremanezumab phase 3 clinical trial (HALO) assessing its efficacy in CM patients also showed positive results independently of the presence of MO. In this study, of 1130 patients enrolled, 587

Table 1. Post-hoc analyses of CGRP-mAbs clinical trials assessing their efficacy in patients with migraine and medication overuse.

	ERENUMAB (70/140)		GALCANEZUMAB (120/240)		FREMANEZUMAB (q/m)		EPTINEZUMAB (100/300)
	MO	No-MO	MO	No-MO	MO	No-MO	MOH†
MO (%)	41%	–	64%	–	51.9%	–	40.2%†
↓MMDs (d/m)	−6.6/−6.6	−6.7/−6.7	−4.8/−4.5	−4.9/−4.8	−4.8/−5.2	−4.8/−4.7	−8.4/−8.6
	Pbo −3.5	Pbo −4.7	Pbo −2.3	Pbo −3.5	Pbo −2.8	Pbo −3.4	Pbo −5.4
50% RR (%)	36%/35%	42%/46%	27.1%/27.4%	27.2%/26.1%	34.8%/39.4%	40.8%/42.4%	60.4%/61.9%
	Pbo 18%	Pbo 27%	Pbo 13.8%	Pbo 17.4%	Pbo 13.8%	Pbo 22.4%	Pbo 34.5%
75% RR (%)	–	–	–	–	–	–	27.3%/29.9%
							Pbo 21%
↓MMeD (d/m)	–	–	−5.3/−4.7	−3.5/−3.1	−4.9/−5.5	−2.1/−2.8	from 20.6 to 10.6 (↓49%)
							from 20.7 to 10.5 (↓49%)
			Pbo −2.5	Pbo −1.5	Pbo −3.1	Pbo −0.5	Pbo from 19.8 to 14.0 (↓29%)
↓SM use (d/m)	−5.4/−4.9	−2.1/−3.6	–	–	–	–	−6.9/−6.7
	Pbo −2.1	Pbo −1.2					Pbo −4.5
↓non-SM use (d/m)	–	–	–	–	–	–	−4.9/−3.4
↓headache days of at LMS (d/m)	–	–	–	–	−4.7/−5.2	−3.7/−3.7	–
					Pbo −2.5	Pbo −2.3	
Patients who reverted to no-MO (H) (%)	*f*65%/54%	–	*51.7%/47.6%	–	55.2%/60.6%	–	50.5%/49.5%
							‡29.0%
	Pbo 33%		Pbo 40.2%		Pbo 46.3%		Pbo 27.1%
							‡6.3%
↓MO (%)	–	–	47.9%/47.7%	–		–	–
			Pbo 29.6%				
HIT6	−5.2/−5.4	−6.0/−5.8	–	–	− 6.0/− 6.9	− 7.07−6.8	–
	Pbo −2.9	Pbo −3.4			Pbo −4.5	Pbo −4.5	
MIDAS	−22.0/−16.1	−18.4/−23.5	–	–	–	–	–
	Pbo −3.6	Pbo −11.2					
MSQ	RFR: 17.1/17.4	RFR: 18.4/20.6			RFR: 19.6/21.4	RFR: 21.9/21.6	
	RFP: 11.6/10.5	RFP: 14.2/16.7			RFP: 17.5/18.4	RFP: 16.4/14.2	
	EF: 17.1/15.9	EF: 19.4/21.2			EF: 20.2/22.0	EF: 22.4/19.7	
	Pbo RFR: 11.7	Pbo RFR: 12.0			Pbo RFR: 14.7	Pbo RFR: 14.5	
	RFP: 7.7	RFP: 10.0			RFP: 14.2	RFP: 10.2	
	EF: 8.2	EF: 11.3			EF: 17.3	EF: 16.7	
PHQ-9	–	–	–	–	− 2.8/− 2.3	− 2.6/−2.3	–
					Pbo −2.4	Pbo −1.6	

CM, chronic migraine; EM, episodic migraine; PBO, placebo; MO, medication overuse; MMDs, monthly migraine days; RR, response rate; d/m, days/month; MMeD, monthly medication days; SM, specific medication; non-SM, nonspecific medication; LMS, least moderate severity; HIT-6, Headache Impact Test; MIDAS, Migraine Disability Assessment; MSQ, Migraine Specific Quality of Life Questionnaire; PHQ-9, Patient Health Questionnaire; q/m, quarterly/monthly.

Study periods: Erenumab week-12, Fremanezumab week-12, REGAIN week-12; Eptinezumab week-12 for MMDs and 50% RR, week-24 for % reversion, reduction in MMeD.

* % of patients who reverted to no-MO regarding triptans, at week-12.

† diagnosis of MOH determined by the study investigator at screening.

‡ percentage of patients with sustained resolution of both CM and MOH diagnoses over the entire 24 weeks of treatment (eptinezumab and placebo).

f % of patients related to triptans.

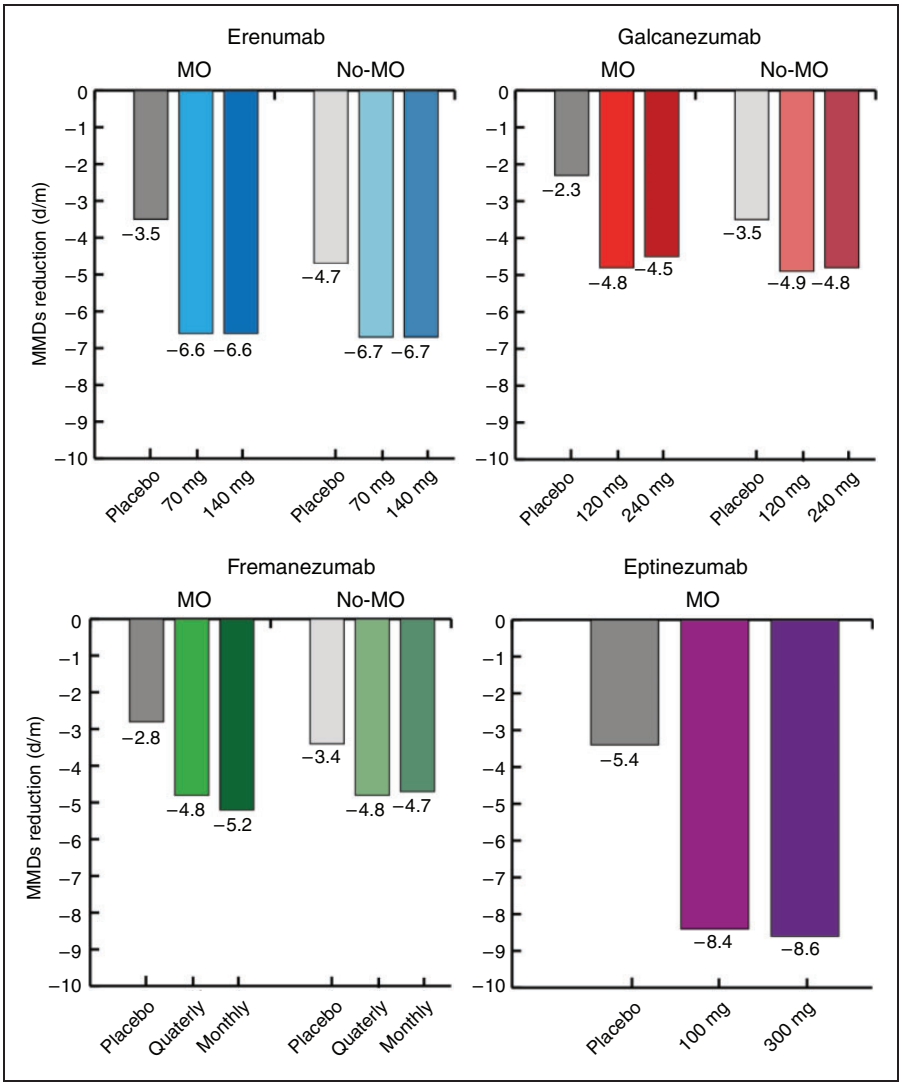

Figure 1. Reduction in monthly migraine days in patients with MO(H) and no-MO(H) for the four monoclonal antibodies.

(51.9%) met MO criteria. In both groups fremanezumab reduced MHDs of at least moderate severity, MMDs, MMeD, and ≥50% RR. In the CM with MO subgroup, fremanezumab led to a greater proportion of patients who reverted to no-MO compared to placebo (58% and 46% respectively). Interestingly, those who reverted to no-MO showed greater reduction in MMeD. Regarding PROs and psychiatric comorbidities, fremanezumab impacted positively on disability, QoL, and depression in both groups, with significant differences from placebo observed for the Headache Impact Test-6 questionnaire (HIT-6) and the Migraine-Specific Quality-of-Life questionnaire domain scores (42). Interestingly, fremanezumab was shown to be effective in preventing and reversing the development of MO in a preclinical animal model (43). These findings suggest acute medications may promote MOH through CGRP-dependent mechanisms and therefore CGRP-mAbs may be efficacious for the treatment of MOH.

Post-hoc analyses evaluated galcanezumab treatment efficacy among patients with CM with MO and MOH versus CM without MO and MOH at baseline compared with placebo. Among randomized patients (n = 708), 64% of CM patients in REGAIN had MO. Both galcanezumab doses (120 mg and 240 mg) showed significant reduction in MMDs, MHDs, MMeD and monthly medication overuse rate in CM with MO and without MO at baseline, with the exception of galcanezumab 240 mg in the no-MO group. Furthermore, this analysis also showed that onset of efficacy occurred during month 1 in CM patients treated with both galcanezumab doses in MO and no-MO groups at baseline (44). The EVOLVE studies, which were pivotal galcanezumab EM studies, are not evaluated in this review.

Galcanezumab also resulted in a significantly greater proportion of patients achieving a ≥50% reduction in MHDs regardless of the presence of MO at baseline (31). Triptan overuse was also reduced with galcanezumab in the pivotal trial. Roughly 77–89% of patients treated with galcanezumab with triptan-MO at baseline reverted to triptan non-MO at any time during the six months of the study compared to 44–53% of placebo patients. No differences in common treatment-emergent adverse events in patients with CM, with or without MO and MOH were observed (45).

Post-hoc analyses of the eptinezumab phase 3 clinical trial (46,47) in CM patients also showed its efficacy compared with placebo in CM patients with MOH. It is the only CGRP-mAbs demonstrating sustained response over the entire study period in MOH patients, since erenumab and fremanezumab post-hoc analyses included patients with MO, and galcanezumab included patients with MO and MOH, but the ICHD-3 diagnostic criteria were not formally applied for MOH. Efficacy results were similar for both subgroups (MOH population of the study and no-MOH) for both the 100 and 300-mg doses. It is worth mentioning that inclusion of patients with dual diagnosis was specified in the protocol due to the potential early onset of eptinezumab. They hypothesized that eptinezumab would be an effective preventive treatment for patients with MOH due to its administration through intravenous infusion. Of 1121 patients included, 431 (40.2%) met MOH criteria. Both doses of eptinezumab (100 and 300 mg) demonstrated greater efficacy than placebo over 24 weeks of treatment in patients with MOH. Eptinezumab also showed onset of efficacy in weeks 1 through 4 reducing MMDs, and this efficacy was sustained over weeks 13 through 24. Eptinezumab also resulted in a greater proportion of patients achieving ≥50% RR in MMDs compared with placebo, at each time point during the study. Furthermore, approximately one third of eptinezumab-treated patients experienced ≥75% RR as early as weeks 1 through 4 (vs 16% of placebo-treated patients) which improved to >40% during weeks 13 through 24 (vs 18% of placebo patients). The therapeutic benefit with eptinezumab was observed as early as day 1 after dosing, with an approximately >50% reduction in the percentage of patients with a migraine on the day after dosing as compared to baseline. Regarding change in CM and MOH status across the six months of the study, 51.1% and 54.4% of those receiving eptinezumab 100 and 300 mg, respectively, had been below the diagnostic thresholds for CM for the complete six-month treatment period, compared with 32.4% of the patients receiving placebo. There were minor differences in tolerability outcomes observed between the eptinezumab dose groups. Tolerability and safety were also similar in the MOH subgroup and were similar to placebo (46). The other post-hoc study showed reductions in MMeD and sustained changes in the diagnostic status of CM and MOH. In particular, roughly 29% of patients treated with eptinezumab did not meet the diagnostic thresholds for either CM or MOH for the entire treatment period (47).

Data from clinical trials confirm that CGRP-mAbs are effective preventive treatments in CM patients including those with MO and MOH. Pending the results of the ongoing clinical trials that aim to assess efficacy of CGRP-mAbs specifically on MOH patients, the data from RWE studies are crucial to shed light to this clinical question.

In this regard, the efficacy of erenumab in patients with CM with MOH has been specifically evaluated in four studies (48–51). The 50% RR after three months of treatment ranges from 44.4 to 65.0% (48–50) and increases to 76.9% after six months of treatment (50). Twenty percent of CM with MOH participants treated with erenumab reported ≥75% reduction in monthly headache frequency (48). These studies have also shown reduction in headache frequency (6.75 to 11.3 MHDs), total medication for acute therapy of migraine attacks consumption (including triptans and anti-inflammatory drugs), pain intensity or migraine-related disability measured by Migraine Disability Assessment questionnaire (MIDAS) and HIT-6 scores (50–52). The maintenance of response to CGRP-mAbs has been reported in a small cohort of CM with MOH patients, where 85% showed a constant ≥50% reduction of MMDs and ≥50% reduction in medication for acute therapy of migraine attacks during the 15-month follow-up period (51).

As MOH is a common comorbidity of treatment-resistant migraine (52), the majority of RWE studies include high percentages of CM with MOH patients. Those studies have reported reduction in MOH rates (52,53). Up to 71.6% of patients treated with erenumab (54–57) and 82% of patients treated with galcanezumab (37,58) converted from MOH to no-MOH. One unanswered question is whether a diagnosis of MOH alters anti-CGRP-mAb overall response rates. Some studies have reported association of lower response rates with higher MOH duration and medication for acute therapy of migraine attacks intake (54,59). This association was not found by other authors (36, 60–62) and some studies found even higher treatment response rates in the group of patients with MOH and triptan consumption (37,58).

Based on the high rates of efficacy of anti-CGRP mAbs in CM with MOH patients reported in clinical trials as well as in real-world studies, the value or need of drug withdrawal process in patients with CM with MOH has been called into question. Pensato et al. (63)

included a group of CM patients with MOH (more than 28 days/month of headache frequency and medication consumption) and compared the efficacy of erenumab or galcanezumab combined or not with in-hospital abrupt drug withdrawal from acute pain medication. Although all patients were advised to stop painkillers and the group assignation was not obligatory, the authors did not find significant differences between headache and medication for acute therapy of migraine attacks reduction or responder rates between the group of patients that underwent in-hospital detoxification or not, suggesting that abrupt drug withdrawal did not add further benefits to the effectiveness of anti-CGRP mAbs in CM patients with MOH.

Efficacy of gepants in chronic migraine with and without medication overuse headache. Atogepant is the only CGRP receptor antagonist approved exclusively for prophylaxis of EM (23–25). The study population in clinical trials phase 2 and 3 were patients with EM without MOH. Atogepant has completed a randomized clinical trial in CM prevention (ClinicalTrials.gov ID: NCT03855137). Unfortunately, at the moment this review was performed, no results were communicated. Thus, there are no available data about its efficacy on patients with CM with and without MOH so far.

However, since gepants can be used both for the acute and preventive treatment of migraine, it is worth mentioning the relationship between them and MOH. Based on preclinical data, latent sensitization or cutaneous allodynia is not induced by gepants, suggesting an absence of the risk of MOH for this class of drugs (64,65). Ditans (the novel class of anti-migraine medication targeting the 5-HT1F receptor) seem to induce cutaneous allodynia (66). The preclinical data are in agreement with preliminary clinical results, which show no evidence of MOH development after exposure to gepants (67).

Discussion

Results from clinical trials and real world evidence studies on CGRP-targeted therapies, mainly monoclonal antibodies, demonstrated their efficacy as preventive treatments in CM patients with and without MO and MOH. The difference in monthly migraine days compared with placebo seems to be relatively low, but as most of CM patients often failed on earlier preventive therapies and MO(H) has huge impact on daily quality of life, the CGRP-targeted therapies open new possibilities for treatment. Furthermore, CGRP-targeted therapies seem to be effective in reverting the MO(H) status. In addition, adverse events are not different in these subgroups suggesting good tolerability and safety in this population, as assessed specifically in the case of eptinezumab. This information should result in a worldwide discussion as to what will be the most patient centered approach to treat patients with MOH in the future.

CM is the primary headache disorder that underlies most cases of MOH, and MO is one of the most important risk factors for chronification. Debate persists regarding whether frequent use of acute migraine medication is cause or effect of non-controlled migraine. Patients increase the amount of their medication usage in an effort to gain or maintain control of their headache disorder (18). Results of this review show that CM patients with MOH who respond to preventive treatment and reverted to EM stopped overusing medication accordingly.

The need for drug withdrawal of the overused medication before starting a preventive treatment has been a matter of debate. It is generally accepted that there is a therapeutic gain from drug withdrawal because of the drug withdrawal itself or because preventive treatments are more effective in absence of MO (68). In the case of topiramate, studies have demonstrated its efficacy and safety as preventive treatment of CM in patient populations both with and without MO (69). Behavioral interventions (70,71), complete or gradual drug withdrawal (72–74), or starting preventive treatment with or without drug withdrawal are also still debated. In a head-to-head comparison of three differing treatment modalities, secondary endpoints indicated that drug withdrawal combined with prophylactic treatment may be more effective than either treatment alone, but the primary outcome (reduction in monthly headache days) was not reached (75). Evidence from other studies also suggested that adding preventive medication may be helpful (76,77). In contrast, in a large investigator-initiated randomized double-blind clinical trial (CHARM) assessing the benefit of onabotulinumtoxinA (BTX-A) for drug withdrawal in patients with CM and MOH, BTX-A did not afford any additional benefit over drug withdrawal alone (78). A concealed sub-trial within this CHARM study assessing the effect of maximal versus minimal behavioral intervention by a headache nurse during drug withdrawal therapy showed a modest benefit of behavioral intervention (71).

Indeed, it seems that the MO group, in particular patients overusing specific medications (triptans), showed greater efficacy results than the no-MO group. Previous studies indicated that migraine patients overusing triptans have shorter duration and severity of drug withdrawal headache after triptans cessation (79). One possible explanation would be that triptan-overuse could be understood as a marker of underlying migraine pathophysiology. The definition of a migraine day within these studies and by ICHD3 criteria is not only

based on migraine characteristics, but criteria for a migraine day can also be met based on the intake of a triptan alone. Not taking a triptan for a headache can mean that the day is not characterized as a migraine day, while taking an NSAID for a significant headache does not meet criteria for a migraine day. There may be inadequate sensitivity and lack of specificity in the current set of criteria for a migraine day, which must be considered when evaluated the study data.

Post-hoc analyses have limitations including the possibility of multiple comparison bias (type I error). A potential limitation for subgroup analysis is that a given study was not designed or powered to show statistical significance in subgroups. Another limitation to the studies reviewed is that they either excluded patients taking opioids and barbiturates or limited usage to four days or less per month for the screening and treatment period.

The new generation of migraine-specific preventive treatments, specifically monoclonal antibodies, which have a large data base, are effective preventive therapies for CM with or without medication overuse and including those with the dual diagnosis of CM and MOH. Future randomized clinical trials should evaluate whether adding behavioral therapies or prescribed withdrawal protocols add additional benefit to the use of the monoclonal antibodies alone in the treatment of CM with MOH patients.

Clinical implications

- Monoclonal antibodies targeting CGRP are effective in the treatment of CM.
- The effect of CGRP-mAbs in CM is also seen in those with MO(H).
- We still need data on gepants for CM prevention with MO(H).
- The results of ongoing randomized control trials in CM with MOH patients will provide more exact information of the effect of CGRP therapies in this subgroup of patients, and the effect of combining behavioral therapies with CGRP-mAbs.

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