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Detoxification vs non-detoxification before starting an anti-CGRP monoclonal antibody in medication overuse headache

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Abstract

Background: Medication overuse headache significantly contributes to the chronification process and treatment refractoriness of migraine. Currently, abrupt discontinuation of the overused medication still represents the best management strategy for these patients, challenging public health system resources.

Methods: In this prospective study, chronic migraine and medication overuse headache sufferers with at least 28 days of analgesic consumption per month were included. Assessment of efficacy outcomes at three months were compared among patients who underwent in-hospital abrupt discontinuation of overused acute medication (YES-DETOX group) and patients who did not (NO-DETOX group) before starting an anti-CGRP monoclonal antibody.

Results: Of 401 patients who received either erenumab or galcanezumab, 28% (n = 111) satisfied inclusion criteria (YES-DETOX n = 28; NO-DETOX n = 83). After three months of treatment, 59% (n = 65; 47/83 YES-DETOX; 18/28 NO-DETOX) patients reverted from medication overuse headache and 51% (n = 57; 42/83 YES-DETOX; 15/28 NO-DEOTX) achieved ≥50% reduction in monthly headache days; yet no statistical differences were observed between the two groups (p = 0.4788 and p = 0.8393, respectively). Monthly consumption of pain medication was the only baseline prognostic factor in multivariate analysis in the overall cohort (p = 0.016).

Conclusion: Our results support the emerging evidence that anti-CGRP monoclonal antibodies may be effective in medication overuse headache patients irrespective of detoxification, yet further studies are needed to draw definitive conclusions.

Keywords

Refractory migraine, chronic migraine, erenumab, galcanezumab, drugs withdrawal, calcitonin gene-related peptide

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Introduction

Migraine is featured by recurrent attacks of unilateral, throbbing, moderate or severe pain associated with nausea and/or vomiting, photophobia and/or phonophobia. The recurrence of attacks for ≥15 days per month, for at least three months, defines chronic migraine (CM) (1). Oftentimes, CM sufferers are forced to regularly take painkillers to treat the recurrent migraine attacks, thus worsening their headache and generating the so-called medication overuse headache (MOH) (2). This condition is present in up to 70% of CM sufferers, significantly contributing to the

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related disability and economic burden (3,4). As a result, MOH represents one of the most prevalent disorders encountered in headache clinics worldwide. Nonetheless, strong evidence about its management is still lacking and, currently, the abrupt discontinuation of the overused painkiller(s), accompanied by the start of a pharmacological preventive therapy, is the most recommended strategy (4,5). While painkiller(s) withdrawal could be accomplished on an outpatient basis in most cases, an in-hospital setting may be required to achieve successful discontinuation in a subgroup of MOH patients (6), further weighing on individual and hospital costs. Additionally hampering this approach, the abrupt discontinuation of the overused painkiller(s) invariably results in disabling withdrawal symptoms for up to two weeks, including a transitory worsening of headache, the so-called "rebound headache" (6,7).

The advent of monoclonal antibodies (mAbs) against calcitonin gene-related peptide (CGRP) or its receptor has been revolutionizing both episodic and chronic migraine management, with potential huge impact also on MOH (8,9). Indeed, preliminary evidence suggest that this medication class may be effective in CM complicated by MOH, regardless of previous painkiller(s) withdrawal (8–11). Studies specifically aimed at evaluating such results have been warranted in order to inform both treatment and underlying pathophysiological mechanisms (10). To this end, our study investigates whether in-hospital detoxification is still necessary in CM and MOH sufferers before receiving anti-CGRP monoclonal antibodies.

Methods

Standard protocol approvals, registrations, and patient consent

The study was approved by an independent ethics committee or local institutional review board at each participating site (protocol numbers: 20073 for Bologna and 50/2020/OSS/AOUMO for Modena). Written informed consent was obtained from all enrolled patients, both for study participation and data publication. All procedures were conducted according to the latest version of the Declaration of Helsinki.

Patient eligibility criteria

Patients from the tertiary headache centers of Bologna and Modena in the Emilia-Romagna region (Italy) were prospectively recruited. All consecutive patients referred to the headache centers between April 2019 and November 2020 who met the inclusion criteria were enrolled and followed up for at least three months. Inclusion criteria were: (i) diagnosis of CM and MOH according to the International Classification of Headache Disorders-Third edition (ICHD-3) (1), (ii) $\geq$28 days of analgesic consumption per month and $\geq$28 monthly headache days (MHD) in the three-month period preceding the baseline (far higher as compared to those required to satisfy ICHD-3 diagnostic criteria of MOH), (iii) initiation of an anti-CGRP mAb treatment after the baseline visit, (iv) age 18-65 years, (vi) migraine onset before 40 years of age and (vii) a 100% adherence in filling in the headache diary. Patients who were already taking a migraine preventive medication prior to starting erenumab or galcanezumab were included in the study only if the medication dosage had been stable for at least three months and the dosage was not modified for the entire study period. Pregnant and breastfeeding women were excluded, as well as subjects suffering from major cardiovascular/cerebrovascular conditions or headache disorders other than CM and MOH, including post-concussion headache or migraine worsening following concussion.

Study design

This was a multicenter, prospective, real-life, cohort study. All participants received an anti-CGRP mAb, according to the EHF guidelines (10). Detoxification (YES-DETOX group) was carried out as in-hospital abrupt withdrawal from acute pain medication for five to seven days combined with supportive symptomatic therapy (i.e., levosulpiride or metoclopramide in case of nausea, paracetamol or steroids in case of headache and benzodiazepines to prevent the rebound headache-depending on the type of previously overused medication) (12,13). All other patients who did not undergo in-hospital detoxification for personal reasons or limitations related to the shortage of hospital beds forced by the COVID-19 pandemic were advised to stop the overused painkiller, as recommended by the EAN guidelines (NO-DETOX group) (4). The first dose of the anti-CGRP mAb was administered during the last day of detoxification, with either erenumab 70 mg or galcanezumab 240 mg. Anti-CGRP mAbs preventive treatment was then self-administered every four weeks at a dosage of 70 or 140 mg for erenumab and every 30 days at the dosage of 120 mg for galcanezumab, according to local indications for drug reimbursement. Patients who did not achieve a reduction in MHDs $\geq$30% after two erenumab injections, were escalated to 140 mg subcutaneous injection from the third month. A follow-up visit was scheduled three months after treatment initiation. At the baseline, demographic and clinical data, including age, sex,

body mass index (BMI), presence of menopause, comorbidities, age at migraine onset and migraine chronification, duration of medication overuse and pharmacologic history were collected. Both at the baseline and during the follow-up visit, specifics about the previous three months' headache history were gathered through the consultation of patients' headache diaries: monthly headache days (MHD), monthly pain medication intake (MPMI) and mean pain intensity (MPI) via subjective numeric rating scale (NRS). Additionally, the headache-related disability was evaluated throughout the 6-item Head Impact Test (HIT-6) and the Migraine Disability Assessment Score (MIDAS), at both visits.

Endpoints and assessments

The primary endpoint of the study was to compare MOH responders' rate, defined as patients who did not satisfy MOH ICHD-3 diagnostic criteria at the three-month evaluation between the YES-DETOX and NO-DETOX groups. The second endpoints were: (i) to assess MHDs, MPMI, MPI, HIT-6 and MIDAS reduction, as well as $\geq$50% reduction in MHDs, in the general study population and in the two treatment groups; (ii) to evaluate the potential baseline predictive factors of MOH relapse/refractoriness; and (iii) to evaluate safety.

Statistical analysis

The statistical analysis was performed with IBM SPSS Statistics Version 26. Continuous variables were checked for normality using the Shapiro-Wilk test and expressed as mean $\pm$ standard deviation (SD). Continuous variables that followed a Gaussian distribution were compared using the one-way analysis of variance followed by the Tuckey-Kramer post-hoc comparison test. The Bonferroni's correction was applied in case of multiple comparisons. Continuous variables not normally distributed were compared with the Wilcoxon rank-signed test. Categorical variables were expressed as subject-counts and percentages or odds and relative 95% confidential intervals, as appropriate; they were compared with the chi-squared test for the homogeneity of odds. Baseline characteristics were compared between patients who were MOH responders and those who were not after three months of treatment. Specifically, a multiple logistic analysis with backward elimination was performed to evaluate the potential predictors of treatment failure. Multicollinearity between these potential predictors was assessed using the phi correlation coefficient. The Pearson's chi-squared goodness of fit test was then performed to assess the overall goodness of fit of the whole model. P-values reported are two-tailed and considered significant if lower than 0.05.

Results

Patient disposition and baseline characteristics

Among 401 patients who received erenumab or galcanezumab during the study period, 111 patients (27%) satisfied inclusion criteria (43 out of 194 from Bologna and 68 out of 207 from Modena). Eight (7%) patients received galcanezumab, while 103 patients received erenumab. Baseline epidemiological and anamnestic characteristics of the study groups are summarized in Table 1. Twenty-eight patients (25%) underwent in-patient withdrawal (YES-DETOX), whilst the other 83 (75%) did not (NO-DETOX). Detoxified patients were homogeneously distributed during the whole study period. No significant differences were seen between the two groups regarding demographic and baseline headache features. A long mean history of CM (15.95 ± 11.57 years) and MOH (13.89 ± 9.39 years) was reported, as well as a high number of preventive migraine treatments failures (7.32 ± 2.83), including onabotulinumtoxinA in most of the patients (92%). Underlying overused acute medications were heterogeneous (triptans = 77%; non-steroidal anti-inflammatory drugs = 46%; combinations of analgesics = 21% and tramadol = 2%) and some patients overused more than one class concomitantly. Erenumab was titrated up to 140 mg in 39 cases, equally distributed between the YES-DETOX (31/83; 37%) and NO-DETOX (8/28; 29%) groups (OR = 0.67; $0.26 \div 1.72$, P = 0.4023).

Efficacy outcomes

After three months of treatment 65/111 (59%) patients were MOH responders (47/83 [57%] NO-DETOX vs 18/28 [64%] YES-DETOX; OR = 0.73, $0.3 \div 1.77$, p = 0.4788). The MHDs significantly reduced from 29.93 ± 0.35 to 18.63 ± 9.32 ($P < 0.0001$) at the third month of treatment. Moreover, the MPMI and the MPI significantly decreased from 62.58 ± 48.38 to 27.90 ± 34.64 and 8.57 ± 1.38 to 6.53 ± 1.6, respectively ($p < 0.0001$). Also, the HIT-6 score significantly improved at the third month compared to the baseline (65.99 ± 9.21 vs 58.57 ± 7.65; $p < 0.0001$) and 57/111 (51%) patients achieved $\geq$50% reduction in MHDs, equally distributed between patients who underwent in-patient withdrawal and the ones who did not (OR = 1.07, $0.57 \div 2.01$; p = 0.8393). The MIDAS score significantly decreased from 78.67 ± 45.76 to 32.24 ± 25.83 at the third month of treatment

Table 1. Demographic and baseline characteristics between YES-DETOX and NO-DETOX groups.

	Total patients (n = 111)	YES-DETOX (n = 28)	NO-DETOX (n = 83)	P-value (Bonferroni-adjusted)
Epidemiological characteristics				
Age (years) ± SD	52.5 ± 8.67	54.04 ± 6.51	51.98 ± 9.26	0.2013
Female sex	97 (87%)	13 [3.09 ÷ 54.77]	5.92 [3.21 ÷ 10.91]	0.3156
Body Mass Index	23.92 ± 3.78	23.02 ± 2.7	24.2 ± 4.03	0.0925
Number of female patients in menopause	51/97 (52.58%)	2.6 [0.93 ÷ 7.29]	1.65 [0.98 ÷ 2.77]	0.442
Age of menopause	49.45 ± 3.82	51.11 ± 3.41	48.97 ± 3.84	0.14
Migraine assessment				
Migraine history (years) ± SD	36.38 ± 10.82	37.75 ± 10.97	35.92 ± 10.8	0.4405
Chronic migraine history (years) ± SD	15.95 ± 11.57	19.54 ± 12.74	14.73 ± 10.98	0.0574
Medication overuse history (months) ± SD	13.89 ± 9.40	16.57 ± 9.59	12.99 ± 9.21	0.0808
Number of patients concomitantly taking another preventive treatment	62 (55.86%)	2.11 [0.96 ÷ 4.67]	1.08 [0.7 ÷ 1.65]	0.1409
Mean number of preventive treatments failed ± SD	7.32 ± 2.83	8 ± 3.28	7.1 ± 2.65	0.1451
Number of patients who failed BT-A in the past	102 (91.89%)	4.6 [1.75 ÷ 12.1]	19.75 [7.23 ÷ 53.93]	0.0296
MHD	29.93 ± 0.35	29.95 ± 0.27	29.86 ± 0.52	0.217
MPMI	62.58 ± 48.38	78.86 ± 70.18	57.08 ± 37.39	0.039
MPI	8.57 ± 1.379	8.46 ± 1.31	8.6 ± 0.41	0.649
HIT-6	65.99 ± 9.21	68.11 ± 3.68	65.3 ± 10.32	0.17
MIDAS	78.67 ± 45.76	90.41 ± 56.37	74.59 ± 41.36	0.222
Comorbidities				
Psychiatric	30 (27.03%)	0.47 [0.21 ÷ 1.05]	0.34 [0.21 ÷ 0.56]	0.4828
Cardiovascular	31 (27.93%)	0.47 [0.21 ÷ 1.05]	0.36 [0.22 ÷ 0.59]	0.5671
Gastrointestinal	23 (20.72%)	0.22 [0.08 ÷ 0.57]	0.28 [0.16 ÷ 0.47]	0.6669
Endocrinological	13 (11.71%)	0.12 [0.04 ÷ 0.4]	0.14 [0.07 ÷ 0.27]	0.8501
Gynecological	11 (9.91%)	0.12 [0.04 ÷ 0.4]	0.11 [0.05 ÷ 0.22]	0.8697
Respiratory	3 (2.70%)	0.08 [0.02 ÷ 0.32]	0.04 [0.01 ÷ 0.09]	0.0953

In YES-DETOX and NO-DETOX groups, continuous variables are reported as mean ± standard deviation (SD), whereas categorical variables are expressed as odds and relative 95% confidence intervals.
HIT-6: 6-item headache impact test; MHD: monthly headache days; MIDAS: migraine disability assessment score; MPI: mean pain intensity; MPMI: monthly pain medication intake.

($p < 0.0001$). At every time point there were no significant differences between the MHDs, the MPMI, the MPI and the HIT-6 score between YES-DETOX and NO-DETOX groups. These data are graphically summarized in Figure 1 and summarized in Supplementary Table 1. The odds of being a MOH responder was not significantly different between YES-DETOX and NO-DETOX groups (OR = 0.89; 0.36 ÷ 2.17, p = 0.7897), as well as the odds of achieving a ≥50% reduction in MHDs (OR = 1.07; 0.57 ÷ 2.01, p = 0.8393). MPMI was the only baseline characteristic associated with MOH refractoriness following anti-CGRP mAbs treatment on the multivariate analysis (Table 2). No significant differences were found in treatment response between patients who received galcanezumab and those who received erenumab.

Safety and tolerability

No serious adverse event was reported during the study period. Minor adverse events were reported by 33/111 (30%) patients, mostly gastrointestinal, including constipation, abdominal pain and nausea. All adverse events were equally distributed between the YES-DETOX and NO-DETOX groups (OR = 0.43; 0.14 ÷ 1.27, p = 01136). All adverse events are summarized in Table 3.

Discussion

The present study explored the potential additional benefit of in-hospital painkiller withdrawal to anti-CGRP mAbs therapy effectiveness in CM complicated by MOH. Notably, in our cohort, hospital admission for abrupt acute medication withdrawal did not

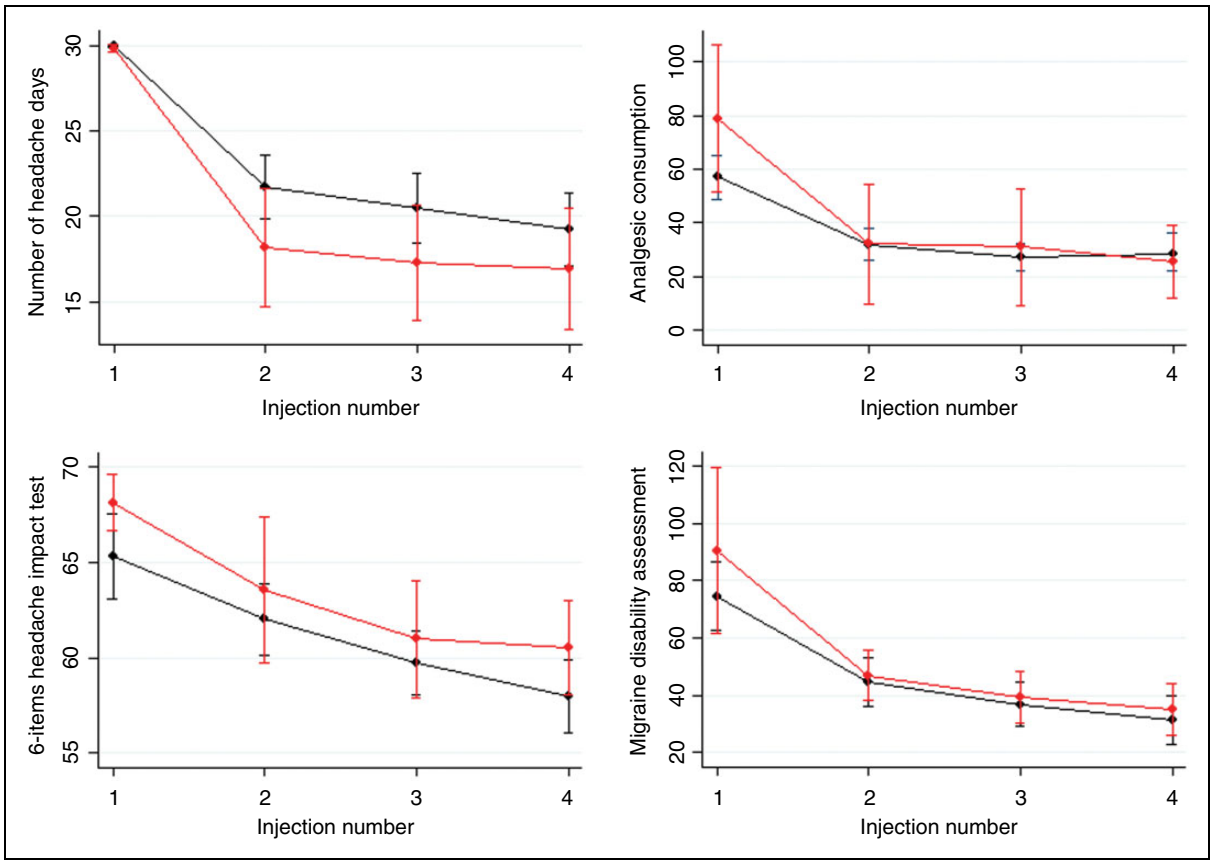

Figure 1: Efficacy (MHD; MPMI) and disability (HIT-6; MIDAS) outcome measures at every injection.
YES-DETOX group is shown in black lines, whereas NO-DETOX group is shown in red lines. MHD, monthly headache days; MPMI, monthly pain medication intake; HIT-6, 6 items headache impact test; MIDAS, migraine disability assessment score.

influence the effectiveness of anti-CGRP mAbs. Indeed, at every injection, subjects who underwent in-hospital abrupt discontinuation of overused acute medication and those who did not displayed similar values of the explored parameters, with no significant differences (Figure 1 and Supplementary Table 1).

Nowadays, the identification of the optimal treatment strategy for MOH is still a matter of debate. Indeed, the 2020 European guidelines outline the means available to the neurologist, yet some questions remain open (2). A recent randomized clinical trial, the DEFINE-3, has been conducted to fill this gap, directly comparing three different MOH treatment strategies: withdrawal plus preventive, preventive alone and withdrawal alone (5). The authors concluded that withdrawal plus preventive therapy is the best strategy to reduce MHD and monthly medication intake, as well as to achieve conversion to episodic migraine (3). However, the DEFINE-3 study did not include anti-CGRP mAbs. Investigations on this topic were also warranted in the EAN guidelines on MOH therapy (10). Some evidence on the efficacy of the anti-CGRP mAbs as preventive agents in patients affected by CM with MOH comes from post-hoc analysis of the RCTs that has led to the approval of erenumab (8), fremanezumab (9) and galcanezumab (14). However, the additional benefit of in-hospital abrupt overused drug(s) discontinuation preceding the start of anti-CGRP mAbs was never investigated (11); hence, our study is the first to specifically address this issue. MOH is a very disabling condition which impacts significantly on both disability and the economic burden of patients. In particular, medical costs and indirect costs, such as loss of productivity and work absenteeism were estimated at the annual cost of €3561 per patient in the Eurolight study (15), whereas a cumulative annual cost of €13.5 billion was estimated in Italy (16). This gigantic economic cost is boosted by MOH therapy failures, relapses and the impracticability of in-hospital detoxification for most of the patients. An effective preventive treatment, irrespective of the detoxification strategy, as shown by anti-CGRP mAbs in our preliminary results, would significantly impact on MOH management and costs which are currently challenging most of the public health systems worldwide. Biologic underpinnings which may explain a different action

Table 2. Comparison of baseline factors related with MOH refractoriness after three months of treatment.

	MOH non-responders	MOH responders	P-value	Odds Ratio	P-value (Bonferroni's adjusted)
Number	46/111 (41.44%)	65/111 (58.56%)	–	–	–
Age	51.2 ± 9.34	53.42 ± 8.11	0.1850	–	–
Females	41/46 (89.13%)	56/65 (86.15%)	0.6432	–	–
Menopause	20/41 (48.78%)	31/56 (55.36%)	0.7540	–	–
Age of menopause	50 ± 3.44	49.12 ± 4.06	0.4873	–	–
Migraine duration	36.35 ± 10.48	36.4 ± 11.14	0.9802	–	–
CM duration	14.33 ± 9.92	17.09 ± 12.57	0.2165	–	–
Medication overuse duration	11.71 ± 8.18	15.44 ± 9.94	**0.0389**	1 [0.99÷1]	0.428
Number of preventive treatments Failed	6.57 ± 2.81	7.86 ± 2.74	**0.0168**	0.86 [0.73÷1.02]	0.088
Failed BT-A	42/46 (91.3%)	60/65 (92.31%)	0.8494	–	–
Depression	10/46 (21.74%)	13/65 (20%)	0.8246	–	–
Anxiety	1/46 (2.17%)	6/65 (9.23%)	0.1336	–	–
Fibromyalgia	1/46 (2.17%)	1/65 (1.54%)	0.9875	–	–
Other comorbidities	28/46 (60.87%)	31/65 (47.69%)	0.1725	–	–
Anti-CGRP mAbs as add-on	27/46 (58.7%)	35/65 (53.85 %)	0.6138	–	–
Detoxification	10/46 (21.74%)	18/65 (27.69%)	0.9268	–	–
MPMI	46.91 ± 32.1	73.66 ± 54.76	**0.0037**	0.98 [0.97÷0.99]	**0.016**
MPI (NRS)	8.59 ± 1.15	8.55 ± 1.53	0.9015	–	–
HIT-6	65.91 ± 5.83	66.05 ± 11.07	0.9405	–	–
MIDAS	67 ± 44.37	87.26 ± 45.42	0.0752	–	–

BT-A, onabotulinumtoxin-A; CM, chronic migraine; HIT, head impact test; mAbs, monoclonal antibodies; MIDAS, migraine disability assessment score; MHD, monthly headache days; MOH, medication overuse headache; MPI, mean pain intensity; MPMI, monthly pain medication intake; NRS, numeric rating scale.

Table 3: Adverse events reported during the study period.

Type of adverse event	Number of patients (%)
Constipation	27 (29.73%)
Abdominal pain	3 (2.7%)
Asthenia	3 (2.7%)
Vertigo	2 (1.8%)
Flu-like symptoms	2 (1.8%)
Nausea	2 (1.8%)
Low-back pain	2 (1.8%)
Muscular pain	2 (1.8%)
Laringodinia	1 (0.9%)
Dysgeusia	1 (0.9%)
Total	33 (29.73%)

profile of anti-CGRP mAbs on MOH compared to the other preventive migraine medications still need to be fully elucidated (11). Hints may come from the acute anti-CGRP therapies, namely gepants, which have shown both preclinical and clinical evidence of a reduced potential MOH risk profile. Persistent exposure to acute medications, such as NSAID, triptans and ditans, leads to neuroplastic changes in trigeminal sensory afferents (sensitization), via different mechanisms, including increased expression of CGRP in trigeminal terminals and increased basal trigeminal nociception activity (17). Perhaps surprisingly, overused gepants explored in preclinical models did not result in these biological alterations and did not lead to MOH neuroplastic changes (17). This is also supported by preliminary clinical data that did not reveal MOH in gepants consumers so far (18). Whereas monoclonal antibodies against CGRP or its receptors are used only for preventive treatment, their pharmacological profile overlaps with gepants, with differences limited to pharmacokinetic properties, such as half-lives and routes of elimination. Thus, their biological action may reduce the necessity of acute medications and prevent peripheral and central sensitization, which is a leading factor for both chronification process and medication overuse headache development.

The results of our study also confirm the effectiveness of these anti-CGRP mAbs even in a severely impaired population. Accordingly, a significant benefit was achieved in multiple efficacy and disability measures including MHDs, MPIM, MPI, HIT-6 and MIDAS. These results are in line with previous studies evaluating the efficacy of anti-CGRP mAbs in

difficult-to-treat migraineurs, such as those suffering from MOH and refractory CM (8,9,14,19–24), yet nearly daily (≥28 days per month) painkiller consumers were never selected before.

In our cohort, multivariate analysis revealed a higher number of acute medication intakes as the only positive predictive factor of MOH refractoriness. Underpinnings of this result remain largely unknown. However, analgesics and triptans exposure results in up-regulation of CGRP in the trigeminal root ganglion and blood (11); hence, patients with elevated MPMI may have a higher enhancement of the CGRP system, potentially reflecting a higher propensity to respond to anti-CGRP therapies. Notably, neither the higher number of treatment failures nor MOH duration were associated with anti-CGRP treatment responses, further confirming the effectiveness of this medication class in difficult-to-treat migraine patients.

During the follow-up period no serious adverse event was observed, while a relatively high rate of mild adverse events, mostly constipation, was observed. Real-life studies investigating anti-CGRP monoclonal antibodies in refractory migraine patients revealed higher frequency of constipation (13.5-23.9%) compared to randomized clinical trial (19,20,22,24,25), yet this adverse event was even more common in our study (29%). While underlying mechanisms remain to be fully elucidated, a relationship between migraine treatment refractoriness and constipation frequency might exist.

Some potential limitations of the current study require an in-depth discussion. Whereas all included patients satisfied current diagnostic criteria for MOH, worsening of headache directly related to medication overuse can be assessed only evaluating amelioration following a detoxification protocol, in the absence of pharmacological treatment modification. However, considering the unfeasibility of such approach to diagnose and manage this condition, current diagnostic criteria are based only on the number of monthly analgesics intakes (1), resolving clinical practice issues, yet hampering interpretations of the results of the largest number of studies. Therefore, to overcome such limitations, we included only MOH patients who used to consume far more analgesics than required by ICHD-3 diagnostic criteria. On the other hand, the selection of severe and refractory MOH patients may have limited the potential effectiveness of detoxification in our sample. Hence, further studies are needed to evaluate whether detoxification in conjunction with anti-CGRP mAbs treatment may have an additional beneficial role in less severe MOH migraineurs. Another limitation of our study is the relatively small sample, related to the strict inclusion criteria applied, and the unparallel distribution of the two groups. Indeed, even though most of the included patients were scheduled for in-hospital detoxification, this was feasible only for a subgroup of them, explaining the uneven distribution of the two groups. Nonetheless, the minimum number of patients was calculated as appropriate for statistical power. No blind randomization was applied in our study, hence a selection bias may have occurred in selecting patients for in-hospital detoxification for either medical or patient's related factors. Indeed, in the NO-DETOX group there may have been patients less inclined toward treatment, especially in an in-hospital setting, which might reflect poor clinical responses to previous pharmacological, or medical at large, treatment or there may have been patients who had a heavier work-load, which is a well-known factor contributing to migraine worsening. Conversely, from the medical perspective, more severe patients might have been prioritized for in-hospital detoxification, even though these same patients might have been delayed from in-hospital detoxification in resource limited settings, as occurred during the COVID-19 pandemic, considering their higher likelihood of treatment failure. Notably, comparison of baseline characteristics of the two groups did not reveal significant differences, even though the YES-DETOX group had a higher baseline MPMI, potentially reflecting a higher clinical complexity. Future studies, especially a large multicentre randomized control study, are warranted to confirm and support our findings and to identify potential subgroups of patients who may still benefit from an in-hospital detoxification strategy. Additionally, considering the high frequency of MOH relapse within one year since treatment and/or detoxification (26), studies with longer follow-up are also warranted.

Conclusion

Medication overuse headache significantly contributes to the chronification process and treatment refractoriness of migraine. Historically, abrupt discontinuation of the overused medication in an in-patient setting, accompanied by the start of a pharmacological preventive therapy, has represented the best management strategy for MOH patients, challenging public health system resources. Our results support the emerging evidence that anti-CGRP drugs may be effective in these patients irrespective of the detoxification program. Further studies are needed to definitively confirm these results, potentially leading to a paradigm shift in the management of MOH.

Clinical Implications:

- Medication overuse headache significantly contributes to the treatment refractoriness of migraine, hence, abrupt discontinuation of the overused medication was recommended as the best management strategy.
- In our cohort, hospital admission for abrupt acute medication withdrawal did not influence the highly effectiveness of anti-CGRP monoclonal antibodies.
- Our results reinforce the emerging evidence that anti-CGRP monoclonal antibodies may be effective irrespective of the detoxification program.

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Supplemental material

Supplemental material for this article is available online.

References

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
2. Diener HC, Holle D, Solbach K, et al. Medication-overuse headache: risk factors, pathophysiology and management. *Nat Rev Neurol* 2016; 12: 575–83.
3. Colas R, Munoz P, Temprano R, et al. Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. *Neurology* 2004; 62: 1338–1342.
4. Diener HC, Antonaci F, Braschinsky M, et al. European Academy of Neurology guideline on the management of medication-overuse headache. *Eur J Neurol* 2020; 27: 1102–1116.
5. Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 Treatment Strategies for Medication Overuse Headache: A Randomized Clinical Trial. *JAMA Neurol* 2020; 77: 1069–1078.
6. Diener HC, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. *Lancet Neurol* 2019; 18: 891–902.
7. Chen PK, Wang SJ. Medication overuse and medication overuse headache: Risk factors, comorbidities, associated burdens and nonpharmacologic and pharmacologic treatment approaches. *Curr Pain Headache Rep* 2019; 23: 60.
8. Tepper SJ, Diener HC, Ashina M, et al. Erenumab in chronic migraine with medication overuse: Subgroup analysis of a randomized trial. *Neurology* 2019; 92: e2309–e20.
9. Silberstein SD, Cohen JM, Seminerio MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain* 2020; 21: 114.
10. Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain* 2019; 20: 6.
11. Sun-Edelstein C, Rapoport AM, Rattanawong W, et al. The evolution of medication overuse headache: history, pathophysiology and clinical update. *CNS Drugs* 2021; 35: 545–565.
12. Cevoli S, Giannini G, Favoni V, et al. Treatment of withdrawal headache in patients with medication overuse headache: a pilot study. *J Headache Pain* 2017; 18: 56.
13. Paolucci M, Altamura C, Brunelli N, et al. Methylprednisolone plus diazepam i.v. as bridge therapy for medication overuse headache. *Neurol Sci* 2017; 38: 2025–2029.
14. Dodick DW, Doty EG, Aurora SK, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. *Cephalalgia* 2021; 41: 340–352.

15. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. *Eur J Neurol* 2012; 19: 703–11.
16. Raggi A, Leonardi M, Sansone E, et al. The cost and the value of treatment of medication overuse headache in Italy: a longitudinal study based on patient-derived data. *Eur J Neurol* 2020; 27: 62–e1.
17. Saengjaroentham C, Strother LC, Dripps I, et al. Differential medication overuse risk of novel anti-migraine therapeutics. *Brain* 2020; 143: 2681–2688.
18. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. *Lancet Neurol* 2020; 19: 727–737.
19. Lambru G, Hill B, Murphy M, et al. A prospective real-world analysis of erenumab in refractory chronic migraine. *J Headache Pain* 2020; 21: 61.
20. Raffaelli B, Kalantzis R, Mecklenburg J, et al. Erenumab in chronic migraine patients who previously failed five first-line oral prophylactics and onabotulinumtoxina: A dual-center retrospective observational study. *Front Neurol* 2020; 11: 417.
21. Pensato U, Favoni V, Pascazio A, et al. Erenumab efficacy in highly resistant chronic migraine: a real-life study. *Neurol Sci* 2020; 41: 457–459.
22. Russo A, Silvestro M, Scotto di Clemente F, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. *J Headache Pain* 2020; 21: 69.
23. Cainazzo MM, Baraldi C, Ferrari A, et al. Erenumab for the preventive treatment of chronic migraine complicated with medication overuse headache: an observational, retrospective, 12-month real-life study. *Neurol Sci* 2021; 42: 4193–4202.
24. Pensato U, Baraldi C, Favoni V, et al. Real-life assessment of erenumab in refractory chronic migraine with medication overuse headache. *Neurol Sci* Epub ahead of print 5 July 2021. DOI: 10.1007/s10072-021-05426-5.
25. Ornello R, Tiseo C, Frattale I, et al. The appropriate dosing of erenumab for migraine prevention after multiple preventive treatment failures: a critical appraisal. *J Headache Pain* 2019; 20: 99.
26. Chiang CC, Schwedt TJ, Wang SJ, et al. Treatment of medication-overuse headache: A systematic review. *Cephalalgia* 2016; 36: 371–386.