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Efficacy and safety of anti-CGRP monoclonal antibodies for chronic migraine prophylaxis in patients treated with botulinum toxin A: A prospective monocentric study

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Abstract

Since the high burden of chronic migraine (CM), it is challenging to identify the best prevention treatment. Based on the preclinical evidence about the different therapeutic targets of onabotulinumtoxinA (BT-A), acting on C-fibers, and anti-CGRP monoclonal antibodies (mAbs), acting on Aδ-fibers, the rationale of using alternative or combining therapies has been hypothesized. Until now, the association of BT-A and mAbs has been poorly investigated. This study evaluated whether mAbs are effective and safe in CM patients previously treated with BT-A, either as an alternative or add-on treatment. We enrolled 47 patients: according to the response to BT-A treatment, patients were defined as non-responder (NR) and partial-responder (PR). NR were shifted to mAbs. PR were randomly divided into those who added mAbs therapy (PR-P) and those who shifted treatment (PR-S), interrupting BT-A. Clinical variables were collected at baseline, after three and six months. Study results evidenced the efficacy of mAbs in improving clinical outcomes in CM patients, with a better response in the PR group. No statistically significant differences in clinical changes were observed between PR-P and PR-S groups. No safety concerns were raised in combined treatments. Preventive prophylaxis with mAbs is effective, even in difficult to treat CM patients. Further studies, with larger samples, are needed to highlight a potential additive effect of combined therapies.

Keywords

chronic migraine, anti-CGRP monoclonal antibodies, botulinum toxin, migraine prevention

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Introduction

Migraine is one of the most common and disabling neurological diseases: data from the Global Burden of Neurological Diseases showed that migraine is the second leading cause of years lived with disability worldwide.[1]

Patients with chronic migraine (CM) experience headache for more than 15 days per month[2] and represents approximately 7.7% of all migraines.[3] Patients with a high frequency of migraine attacks experience a large functional impairment on their daily productivity, exerting poor performances and having a compromised quality of life.[4] Moreover, most CM patients overuse acute headache

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medications.[5] Since the high clinical, social and economic burden of CM, it is crucial to promptly identify the best prevention treatment, which should be effective, safe and well-tolerated. In fact, despite being frequently used in clinical practice, oral prophylactic treatments are often burdened by poor compliance due to both side effects and low efficacy.

CM often represents a challenge for neurologists: identifying the best preventive therapy is not always immediate and difficult-to-treat-patients may have failed several preventives before obtaining optimal control of their migraine attacks.

Indications for CM prevention are available for topiramate[6] and onabotulinumtoxinA (BT-A), which has been approved since 2010, given the proved efficacy and tolerability across multiple RCTs[7] and real-world[8] studies. BT-A has evidence of a high tolerability profile: a literature review of RCTs reports a low rate of adverse events and a low percentage of treatment discontinuation.[9–11]

Based on evidence supporting a key role of calcitonin gene-related peptide (CGRP) in migraine,[12] new promising preventive monoclonal antibodies (mAbs) targeting the CGRP receptor (erenumab) or the CGRP ligand (fremanezumab and glacanezumab) have been developed.

First proof of safety and efficacy of erenumab was published in 2016:[13,14] back then, erenumab was authorized for migraine treatment in Italy, but there are some limitations to prescription. A recent consensus of the European Headache Federation and national provisions (e.g., Italian Medicines Agency named AIFA) stated that BT-A and CGRP-mAbs should not be administered in combination, due to a possible superimposable mechanism of action and the high cost of both therapies.[15,16]

As a consequence, clinical trials and real-world prospective studies evaluating the combined effect and safety of BT-A and mAbs are still poor and, to date, just some retrospective studies are available.[17–20]

The rationale to combine both therapies is based on the evidence of the dual role of central and peripheral sensitization of nociceptive pathways in CM[21] and recent preclinical observations[18] demonstrate the different sites and mechanism of action of mAbs and BT-A: in fact, mAbs prevent the activation of Aδ-fibers, while BT-A has an inhibitory effect on C-fibers of nociceptive trigeminal neurons that innervate intracranial blood vessels and the dura mater.[19,22]

Against this background, this study aimed to prospectively evaluate whether mAbs therapy is effective and safe in patients partially or not responding to BT-A treatment and whether the synergic effect of these therapies in migraine patients would lead to better clinical outcomes, in terms of reduction of monthly headache and migraine days and migraine-related disability scales.

Methods

In this prospective, open-label study, we enrolled all migraine patients who attended the Neurophysiology Service and Headache Clinic at IRCCS San Raffaele Hospital (OSR) from February 2019 to January 2021 which met all inclusion/exclusion criteria.

All enrolled patients had a confirmed diagnosis of migraine, based on the ICHD-3 edition criteria.[2] All patients met the following inclusion criteria: age between 18–80 years, suffering from CM with or without medication overuse headache (MOH); previously failed or ongoing preventive treatment with BT-A, according to the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol,[7] administered in OSR outpatient Headache Clinic; clinical data and previous diaries stored in our digital database.

Exclusion criteria were: hypersensitivity to active substance or excipients of erenumab, hypersensitivity to latex, pregnancy and breastfeeding and major cardiac-cerebral vascular diseases.

All subjects participating in the study provided a written Informed Consent Form approved by the local Independent Ethics Committee.

Study design: all patients had to be previously treated with at least three injection cycles with BT-A, before considering starting erenumab. Patients with an unsatisfying response to at least 3 cycles of BT-A treatment were defined as non-responders (NR) or partial responders (PR), according to the entity of monthly headache days (MHD) reduction. In particular, NR had a reduction of MHD < 30% respect to baseline, while PR had a reduction of MHD < 50% but >30% respect to baseline.[23]

The unsatisfactory response was due to a still high migraine burden, despite the partial reduction in terms of headache days, considering the headache-related disability and the symptomatic drug intake.

All patients (NR and PR) received erenumab at baseline. All NR patients interrupted BT-A treatment at least three months before starting erenumab. PR were randomized into two groups: the Plus group (PR-P) added erenumab to the ongoing BT-A treatment, the Shift group (PR-S) interrupted BT-A treatment at least three months before starting erenumab.

Clinicians performed randomization consecutively; every PR patient meeting criteria was assigned to the two groups starting from PR-P and then PR-S, alternatively.

All patients were evaluated at baseline (T0), after three (T3) and six (T6) months of treatment with erenumab. Monthly subcutaneous injections of erenumab 70 mg were administered every 28 days for the first three months. If patients had a partial response to erenumab at T3, defined as a percentage reduction of MHD between 30–50% *vs* baseline, the erenumab dosage was increased to 140 mg; on the other hand, if patients had a reduction of MHD ≥ 50% *vs* baseline, considered as full responders, the dosage did not change.

By the time of the enrollment phase of the study, erenumab was approved by European Medicines Agency (EMA) and Italian Medicines Agency (AIFA), but the current Italian guidelines on the use of anti-CGRP mAbs in migraine

prevention had not been released yet. The current restriction on the concomitant use of anti-CGRP mAbs and BT-A treatment had not been released at that time.

Data Collection: All patients underwent a neurological examination and the following demographic and clinical features of migraine were collected: medical history, age of migraine onset, characteristics and severity of pain according to the Numerical Rating Scale (NRS),[24] frequency of MHD, frequency of monthly migraine days (MMD), number of pills and days of abortive treatments currently used to stop migraine attacks per month. Patients' disability was quantified using the Migraine Disability Assessment Test (MIDAS)[25] and the Headache Impact Test (HIT-6)[26] scales. Allodynia Symptom Checklist (ASC-12)[27] and the presence of adverse events (AEs) at each timepoint were also collected. All above mentioned clinical data were collected at baseline and at each follow-up visit and registered in a digital database.

The primary objective of the study was to evaluate the reduction of MHD after three (T3) and six (T6) months of treatment compared to baseline (T0), obtained from a 30-day headache diary before the first visit.

Secondary objectives were: reduction of at least 50% of MHD after six months (T6) of treatment compared to baseline; reduction between 30 and 50% of MHD at T3 or T6 compared to baseline;[23] reduction of acute drug intake in terms of pills and days; and improvement of disability and severity scales (MIDAS, HIT-6 and NRS, ASC-12) at T3 or T6 respect to baseline; reduction of 50% of MIDAS after three and six months of treatment respect to baseline.[28]

Statistical analysis

Sample size

Sample size was calculated to reach the primary endpoint of the study, which meant the reduction of MHD at T3 and T6 compared to baseline. A sample size of 18 achieves 91% power to detect a difference of −5.0 between the null hypothesis mean of 0.0 and the alternative hypothesis mean of 5.0 with an estimated standard deviation of 6.0 and with a significance level (alpha) of 0.05 using a two-sided one-sample t-test. Considering that at the time of the start of the study, the population under investigation was quite different respect to the one enrolled in the published trials available on erenumab efficacy in chronic migraine (i.e., patients had already received BT-A treatment), we decided to double the sample size to increase the possibility to have the power to reach the primary endpoint, so the sample size became 36. Moreover, considering the possibility of a 25% of drop out, to be sure to reach the target number for statistical evaluation, we needed 9 more patients for a total of 45 patients.

Statistical analysis

For all measures considered, data demonstrated a skewed distribution with a significant deviation from normal distribution (Kolmogorov-Smirnov test; $p < 0.05$).

Independent t test and the Mann-Whitney test, with Bonferroni correction, were used to assess statistically significant differences in demographic and clinical characteristics between the average values of the variables under examination in each group and between groups at time T0, T3 and T6.

Within-group and between-group differences in treatment efficacy over time were assessed using Wilcoxon and mixed-effect ANOVA tests, with post-hoc and Tukey's method comparison, respectively (version 26.0; SPSS software, IBM).

Results

Demographic and clinical features

The main demographic and clinical characteristics of enrolled patients at baseline (i.e., before starting mAb) are summarized in Table 1.

NR group, PR-S group and PR-P group were composed of 16 (69% female), 15 (93% female) and 16 (100% female) patients, respectively. Median age was 49 years (IQ range: 45–52) in NR, 52 years (46–56) in PR-S and 53 years (46–58) in PR-P group.

The groups had a median of 5 (NR group) and 4 (PR-S and PR-P group) past preventives used, including beta-blockers, antiepileptics, tricyclic antidepressants and calcium-antagonists. Median disease duration was between 32 and 38 years.

No statistically significant differences in demographic and clinical characteristics between the three groups at baseline were found, except for sex between NR and PR-P groups and the number of previous BT-A treatment cycles (Table 1).

All the other collected clinical parameters were similar in the three groups, except for MHD and MMD, which were higher in NR patients (median MHD = 30, IQR: 25–30; median MMD = 25, IQR: 15–30) respect to PR-S (median MHD = 17, IQR: 15–24, $p = 0.007$; median MMD = 16, IQR: 15–20; $p = 0.046$) and PR-P patients (median MHD = 18, IQR: 11–30, $p = 0.058$; median MMD = 14, IQR: 10–16; $p = 0.008$) at baseline (see Tables 3, 4 and 5).

In the Table 2 we reported the median and the interquartile range (25th – 75th percentiles) of the clinical variables studied of all enrolled patients at baseline, after 3 and 6 months of treatment with erenumab.

Tables 3, 4 and 5 show median values of clinical data collected at baseline, T3 and T6 in the three study groups. The majority of patients had MOH, in particular 93% of NR, 100% of PR-S and 81% of PR-P patients. All NR patients had CM at baseline, while 80% and 69% of patients in the PR-S and PR-P groups were chronic, respectively (see Tables 3, 4 and 5).

Within-group treatment response to erenumab: All enrolled patients

All clinical variables under examination significantly decreased during the treatment in all patients after three

Table 1. Main demographic and clinical characteristics of enrolled patients at baseline (T0), before erenumab. Statistical differences between paired groups at baseline.

	NR	PR-S	PR-P	NR *vs* PR-S* *p* value	NR *vs* PR-P* *p* value	PR-S *vs* PR-P* *p* value
Median age [IQR] (years)	49 [45–52]	52 [46–56]	53 [46–58]	0.651	0.482	0.842
Women - Men	11 (69%) – 5 (31%)	14 (93%) – 1 (7%)	16 (100%) – 0 (0%)	0.065	**0.021**	0.302
Median disease duration [IQR] (years)	32 [25–30]	37 [30–41]	38 [30–45]	0.324	0.592	0.102
Median of preventive treatments used [IQR]	5 [4–7]	4 [4–5]	4 [3–5]	0.264	0.101	0.658
Median of number of BT-A treatment [IQR]	5 [4–6]	8 [6–13]	16 [14–19]	**0.019**	**<0.001**	**0.003**
Monthly headache days (MHD)	30 [25–30]	17 [15–24]	18 [11–30]	**0.007**	0.058	0.952
Monthly migraine days (MMD)	25 [15–30]	16 [15–20]	14 [10–16]	**0.046**	**0.008**	0.146
Monthly tablets of acute treatments	31 [16–62]	21 [17–30]	26 [15–33]	0.276	0.336	0.766
Monthly days of acute treatments	25 [15–30]	17 [15–23]	15 [10–23]	0.176	**0.042**	0.311
MIDAS score	95 [15–115]	34 [20–63]	56 [24–71]	0.429	0.534	0.429
HIT-6 score	67 [66–71]	68 [65–70]	64 [63–65]	0.751	**0.004**	**0.004**
NRS score	8 [7–9]	9 [8–10]	8 [8–9]	0.149	0.250	0.386
ASC-12 score	4 [2–9]	6 [1–10]	5 [2–8]	0.984	0.939	0.968

Measures are reported as medians and interquartile ranges (25th – 75th percentiles). Sex is reported as frequency.
* Independent *t* test or Mann-Whitney test with a $p < 0.05$ were considered significant.

Table 2. Clinical variables under observation of all enrolled patients at baseline (T0), after 3 (T3) and 6 (T6) months of erenumab. Significance of changes of variables during the treatment with erenuamb in the entire population of study.

	T0	T3	T6	T0 *vs* T3 *p* value*	T0 *vs* T6 *p* value*
Monthly headache days (MHD)	23 [15–30]	13 [7–25]	12 [8–25]	<0.001	<0.001
Monthly migraine days (MMD)	9 [12–25]	11 [7–19]	10 [8–16]	<0.001	<0.001
Monthly tablets of acute treatments	25 [16–35]	15 [10–24]	12 [8–23]	<0.001	<0.001
Monthly days of acute treatments	17 [1 –26]	12 [7–21]	11 [8–19]	<0.001	<0.001
MIDAS score	51 [20–100]	21 [8–55]	24 [9–45]	0.006	<0.001
HIT-6 score	66 [63–69]	62 [55–66]	61 [56–64]	<0.001	<0.001
NRS score	8 [8–10]	7 [6–8]	7 [6–8]	<0.001	<0.001
ASC-12 score	4 [2–9]	2 [0–9]	3 [0–6]	0.031	0.006

Measures are reported as medians and interquartile ranges (25th – 75th percentiles).
Abbreviations: ASC-12: Allodynia Symptom Checklist; HIT-6: Headache Impact Test; IQR = interquartile range; MIDAS: Migraine Disability Assessment Test; NRS: Numeric Rating Scale (NRS).
*Within-group differences in treatment efficacy over time were assessed using Wilcoxon test.

and six months of therapy with mAb. These results show a rapid but sustained effect of erenumab in our cohort of patients, evidencing the efficacy of this therapy.

Within-group treatment response to erenumab: NR Group

After 3 months with erenumab 70 mg, NR patients reported a reduction of clinical outcome measures, in terms of MHD and MMD and migraine related disability scales. In particular, a mean of −3 days of MHD ($p = 0.102$) and −4 days of MMD ($p = 0.043$) was observed, which increased to −5 ($p = 0.029$) and −7 ($p = 0.003$) at T6 (Table 3 and Table 6). Furthermore, a statistically significant reduction of −1 point of the mean of pain intensity on NRS was observed ($p = 0.048$) (Table 3).

At T6 a significant reduction of HIT-6 score ($p = 0.001$), number of pills ($p = 0.005$) and days of acute medication intake ($p = 0.002$) was also observed (Table 3).

We also observed an evolution of the disease during erenumab treatment: four patients (25%) with CM at baseline became episodic after three months of treatment and 6 (38%) at T6 (Table 3). Furthermore, a progressive reduction of patients who had MOH was observed: from 15 cases at baseline to 11 (69%) at T3 and 8 (53%) patients at T6, with a global reduction of 47% of cases (Table 3).

Table 3. Clinical features under examination in NR group at baseline (T0) and after three (T3) and six (T6) months of treatment with erenumab.

	NR				
	T0	T3	T6	T0 *vs* T3 *p* value**	T0 *vs* T6 *p* value**
Monthly headache days (MHD)	30 [25–30]	27 [17–30]	24 [11–30]	0.102	**0.029**
Monthly migraine days (MMD)	25 [15–30]	19 [10–26]	13 [10–21]	0.043	**0.003**
Monthly tablets of acute treatments	31 [16–62]	21 [11–39]	16 [10–35]	0.266	**0.005**
Monthly days of acute treatments	25 [15–30]	19 [9–28]	16 [10–22]	0.062	**0.002**
MIDAS score	95 [15–115]	46 [11–160]	38 [18–101]	0.683	0.127
HIT-6 score	67 [66–71]	65 [57–68]	61 [55–65]	0.077	**0.001**
NRS score	8 [7–9]	7 [6–8]	7 [6–8]	**0.048**	0.082
ASC-12 score	4 [2–9]	2 [1–7]	2 [0–6]	0.457	0.059
Episodic/Chronic migraine	0 (0%) – 16 (100%)	4 (25%) – 12 (75%)	6 (38%) – 10 (62%)	0.050*	0.012*
Medication overuse (MOH) yes/no	15 (93%) – 1 (7%)	11 (69%) – 5 (31%)	8 (50%) – 8 (50%)	0.688*	0.375*

Measures are reported as medians and interquartile ranges (25th – 75th percentiles). Type of migraine and medication overuse headache are reported as frequencies. Abbreviations: ASC-12: Allodynia Symptom Checklist; HIT-6: Headache Impact Test; IQR = interquartile range; MIDAS: Migraine Disability Assessment Test; NRS: Numeric Rating Scale (NRS).

*Independent *t* test or Mann-Whitney test with a $p < 0.05$ was considered significant.

**Within-group differences in treatment efficacy over time were assessed using Wilcoxon test.

Table 4. Clinical features under examination in PR-S group at baseline (T0) and after three (T3) and six (T6) months of treatment with erenumab.

	PR-S				
	T0	T3	T6	T0 *vs* T3 *p* value**	T0 *vs* T6 *p* value**
Monthly headache days (MHD)	17 [15–24]	12 [6–16]	11 [7–14]	**0.001**	**0.001**
Monthly migraine days (MMD)	16 [15–20]	9 [6–13]	11 [7–14]	**0.001**	**0.002**
Monthly tablets of acute treatments	21 [17–30]	12 [5–16]	11 [7–16]	**0.002**	**0.001**
Monthly days of acute treatments	17 [15–23]	9 [5–15]	10 [7–14]	**0.001**	**0.001**
MIDAS score	34 [20–63]	15 [9–22]	11 [9–23]	**0.001**	**0.001**
HIT-6 score	68 [65–70]	60 [54–63]	62 [59–64]	**0.014**	**0.046**
NRS score	9 [8–10]	7 [6–8]	7 [6–8]	**0.001**	**0.003**
ASC-12 score	6 [1–10]	2 [1–10]	3 [0–5]	0.201	**0.024**
Episodic/Chronic migraine	3 (20%) – 12 (80%)	11 (69%) – 4 (31%)	12 (75%) – 3 (25%)	0.363*	0.484*
Medication overuse (MOH) yes/no	15 (100%) – 0 (0%)	4 (27%) – 11 (73%)	3 (20%) – 12 (80%)	0.123*	0.554*

Measures are reported as medians and interquartile ranges (25th – 75th percentiles). Type of migraine and medication overuse headache are reported as frequencies. Abbreviations: ASC-12: Allodynia Symptom Checklist; HIT-6: Headache Impact Test; IQR = interquartile range; MIDAS: Migraine Disability Assessment Test; NRS: Numeric Rating Scale (NRS).

* Independent *t* test or Mann-Whitney test with a $p < 0.05$ was considered significant.

**Within-group differences in treatment efficacy over time were assessed using Wilcoxon test.

Erenumab dosage was increased to 140 mg in 14 (88%) patients after the first three months due to a partial response to treatment.

A reduction of MHD days of 30–50% compared to baseline was obtained in 2 patients (13%) at T3 and 1 (6%) at T6, considered as partial responders to treatment (Table 7).

A reduction greater than 50% of MHD compared to baseline was registered in 2 (13%) patients at T3 and 2 (13%) at T6.

Considering the response to treatment based on more than 50% reduction of MIDAS score, we obtained a good response in 6 (38%) patients between baseline and T3, and 8 (50%) patients at T6 (Table 8).

Within-group treatment response to erenumab: PR-S Group

PR-S patients were treated with erenumab 70 mg for the first three months; then 4 patients continued with the same dosage, while 11 (73%) patients increased erenumab to 140 mg.

At T3 and T6, a significant reduction of MHD ($p = 0.001$ for both), MMD (T3: $p = 0.001$, T6: $p = 0.002$), pills (T3: $p = 0.002$, T6: $p = 0.001$) and days of abortive treatment intake ($p = 0.001$ for both), MIDAS ($p = 0.001$), HIT-6 (T3: $p = 0.014$, T6: $p = 0.046$) and pain severity on NRS scale (T3: $p = 0.001$, T6: $p = 0.003$) was obtained

Table 5. Clinical features under examination in PR-P group at baseline (T0) and after three (T3) and six (T6) months of treatment with erenumab.

	PR-P				
	T0	T3	T6	T0 *vs* T3 *p* value**	T0 *vs* T6 *p* value**
Monthly headache days (MHD)	18 [11–30]	12 [7–22]	9 [6–20]	**0.002**	**0.001**
Monthly migraine days (MMD)	14 [10–16]	10 [7–13]	9 [6–10]	**0.008**	**0.004**
Monthly tablets of acute treatments	26 [15–33]	16 [11–23]	11 [7–23]	**0.004**	**0.002**
Monthly days of acute treatments	15 [10–23]	12 [7–17]	10 [5–18]	**0.043**	**0.003**
MIDAS score	56 [24–71]	22 [5–58]	22 [9–41]	0.088	**0.052**
HIT-6 score	64 [63–65]	62 [54–64]	61 [58–64]	**0.046**	0.118
NRS score	8 [8–9]	6 [5–8]	7 [6–8]	**0.004**	**0.009**
ASC-12 score	5 [2–8]	2 [0–4]	3 [1–8]	0.107	0.345
Episodic/Chronic migraine	5 (31%) – 11 (69%)	10 (63%) – 6 (37%)	10 (63%) – 6 (37%)	0.093*	0.093*
Medication overuse (MOH) yes/no	13 (81%) – 3 (19%)	5 (31%) – 11 (69%)	6 (38%) – 10 (62%)	0.213*	0.522*

Measures are reported as medians and interquartile ranges (25th – 75th percentiles). Type of migraine and medication overuse headache are reported as frequencies. Abbreviations: ASC-12: Allodynia Symptom Checklist; HIT-6: Headache Impact Test; IQR = interquartile range; MIDAS: Migraine Disability Assessment Test; NRS: Numeric Rating Scale (NRS).

* Independent *t* test or Mann-Whitney test with a $p < 0.05$ was considered significant.

**Within-group differences in treatment efficacy over time were assessed using Wilcoxon test.

(Table 5). Moreover, at T6, a significant reduction of ASC-12 score was observed ($p = 0.024$) (Table 4).

CM patients at baseline who became episodic during monthly erenumab injections were 11 (69%) at T3 and 12 (75%) at T6.

Considering MOH data, we observed a significant reduction of patients who reported having a pharmacologic abuse of acute abortive treatment, in particular: 15 patients at baseline, 4 at M3 and 3 at M6, with a global percentage reduction of 80% (Table 4).

In the PR-S group, we observed a reduction of MHD days of 30–50% compared to baseline in 5 (33%) patients at T3 and 4 (27%) patients of T6 (Table 7). Full responders were 5 (33%) patients at T3 and 6 (27%) at T6 (Table 7), with a mean day reduction of −7 at T3 and −8 days at T6 (Table 7).

Patients who reduced MIDAS score more than 50% compared to baseline were 10 (67%) at T3 and 11 (73%) at T6 (Table 8).

Within-group treatment response to erenumab: PR-P Group

PR-P group was constituted by patients with a partial response to BT-A treatment who continued to use BT-A in association with erenumab over six months. Three patients continued with erenumab 70 mg up to T6, while at T3, 13 (81%) out of 16 patients received erenumab 140 mg, in association with BT-A.

At T3, a significant reduction of MHD ($p = 0.002$), MMD ($p = 0.008$), pills ($p = 0.004$) and days of abortive treatment intake ($p = 0.043$), HIT-6 ($p = 0.046$) and pain severity on NRS scale ($p = 0.004$) was observed (Table 5). After six months of treatment, MHD ($p = 0.001$), MMD ($p = 0.004$), pills ($p = 0.002$) and days of abortive treatment intake ($p = 0.003$) and NRS scale ($p = 0.009$) were significantly reduced (Table 5).

Cases of CM converted to episodic migraine were 10 both at T3 and T6 (63%). Regarding MOH data, 13 (81%) patients had abuse intake at baseline, 5 (31%) at T3 and 6 (38%) at T6. A global reduction of 54% of cases of medication overuse was observed (Table 5).

In the PR-P group, we obtained 3 (19%) at T3 and 3 (19%) at T6 partial responders, considering a reduction of MHD days between 30 and 50% compared to baseline i.e., before starting erenumab (Table 7). Full responders, who reduced more than 50% of MHD compared to baseline, were 4 (25%) at T3 and 6 (38%) at T6, with a mean day reduction of −6 at T3 and −7 days at T6 (Table 6).

In this group, patients who reported a reduction of MIDAS score $\geq 50\%$ compared to baseline were 7 (44%) at T3 and 8 (50%) at T6 (Table 8).

Between-group differences in treatment response to erenumab

Evaluating changes of clinical features under examination among the three groups of patients over time, we observed a statistically significant difference in changes of MHD, MMD, number of pills of acute medication intake and MIDAS score, both between T0 vs T3 and T0 vs T6 (Table 6). Post-hoc comparisons showed that differences in changes were only observed between NR group and both PR-S and PR-P groups, indicating a better response for PR patients. No statistically significant differences were observed between PR-S and PR-P groups (Table 6).

Safety of treatment with erenumab

The presence of AEs, including constipation and injection-site reactions, was investigated. No patient complained AEs

Table 6. Changes of clinical features under examination in the three groups of patients over time.

	NR		PR-S		PR-P		T0 *vs* T3*				T0 *vs* T6*			
	Mean reduction ± SD T0 *vs* T3	Mean reduction ± SD T0 *vs* T6	Mean reduction ± SD T0 *vs* T3	Mean reduction ± SD T0 *vs* T6	Mean reduction ± SD T0 *vs* T3	Mean reduction ± SD T0 *vs* T6	*p* value	NR *vs* PR-S	NR *vs* PR-P	PR-S *vs* PR-P	*p* value	NR *vs* PR-S	NR *vs* PR-P	PR-S *vs* PR-P
Monthly headache days (MHD)	−3 ± 7.24	−5 ± 7.92	−7 ± 7.09	−8 ± 7.35	−6 ± 6.18	−7 ± 6.77	**0.004**	**0.006**	**0.024**	1	**0.004**	**0.006**	**0.022**	0.860
Monthly migraine days (MMD)	−4 ± 7.05	−7 ± 7.11	−7 ± 5.12	−7 ± 5.44	−5 ± 6.31	−5 ± 6.06	**0.001**	**0.006**	**0.002**	0.952	**0.004**	**0.023**	**0.005**	0.873
Monthly tablets of acute treatments	−5 ± 17.95	−14 ± 18.06	−11 ± 10.42	−11 ± 10.05	−10 ± 10.91	−13 ± 11.69	**0.027**	**0.030**	**0.096**	0.849	**0.049**	0.056	0.134	0.896
Monthly days of acute treatments	−4 ± 7.88	−7 ± 7.05	−8 ± 7.50	−8 ± 6.97	−4 ± 6.46	−5 ± 5.65	0.071				0.108			
MIDAS score	−4 ± 90.88	−41 ± 94.48	−27 ± 24.44	−30 ± 29.10	−9 ± 48.61	−13 ± 51.33	**0.018**	**0.016**	**0.117**	0.654	**0.030**	**0.024**	0.241	0.505
HIT-6 score	-4 ± 7.6	-8 ± 7.26	-8 ± 11.00	-6 ± 11.72	-4 ± 6.54	-3 ± 8.80	0.232				0.248			
NRS score	-1 ± 1.02	-1 ± 1.97	-2 ± 1.42	-2 ± 2.41	-2 ± 2.56	-2 ± 2.34	0.711				0.829			
ASC-12 score	-1 ± 4.57	-2 ± 4.9	-1 ± 2.50	-3 ± 4.02	-3 ± 6.11	-2 ± 5.95	0.826				0.833			

* Mixed-effect ANOVA tests with $p < 0.05$ was considered significant. If significant, post-hoc and Tukey's method comparison was performed.

Table 7. Number of partial responders (PR) (reduction of MHD of 30–50%) and full responders (R) (reduction of MHD ≥ 50%) based on differences of MHD in each group, at two timepoints (T3 and T6).

	Timepoint (T3)				Timepoint (T6)			
Group	PR (30–50%)	R > 50%	Total PR + R (>30%)	*p* value*	PR (30–50%)	R > 50%	Total PR + R (>30%)	*p* value*
NR	2	2	4 (25%)	1	1	2	3 (19%)	0.376
PR-S	5	5	10 (67%)	0.068	4	6	10 (67%)	0.007
PR-P	3	4	7 (44%)	0.059	3	6	9 (56%)	0.116

*Chi-square performed between total PR + R patients, considered as those who reduced MHD more than 30% respect to baseline, at T3 and T6, for each group.

Table 8. Number of responders based on reduction greater than 50% of points of MIDAS in each group, at two timepoints (T3 and T6)

Group	Timepoint (T3) N. Responder >50%	Timepoint (T6) N. Responder >50%
NR	6 (38%)	8 (50%)
PR-S	10 (67%)	11 (73%)
PR-P	7 (44%)	8 (50%)

during six months of treatment. For patient who received BT-A in association with erenumab, no additional AEs were reported.

Discussion

CM is a complex disorder with a multifactorial etiology. Its pathophysiology involves many neuroanatomic pathways, vasoactive neuropeptides and different receptors,[29] so it is highly improbable that a single prophylactic treatment will result in optimal management of CM patients.

Headache guidelines recommend several pharmacological therapies, including oral medications, BT-A and the newly approved monoclonal antibodies targeting the CGRP or its receptor.[30] In clinical practice, a significant proportion of patients do not benefit from monotherapy, so clinicians often have to modify the prophylaxis approach by increasing the dose, switching medication, or adding a second medication.[31] Thus, the combination of more than one preventive drug is potentially attractive in such a demanding and refractory condition.

The recent development and release to the market of mAbs targeting the CGRP pathway has stimulated discussion on whether they should be added to current migraine preventive drugs. Considering that the majority of headache experts prescribe BT-A for managing CM patients, this question is of great interest. In fact, BT-A has represented, until the availability of mAbs, one of the few effective authorized therapies in CM.

It is well established that the trigeminovascular system plays a fundamental role in migraine pathogenesis and CGRP together with other neuropeptides are strongly involved in inducing the migraine attack. CGRP is highly expressed both in the trigeminal ganglion neurons and in the C-fibers of trigeminal sensory afferents. With the release of CGRP from C-fibers, afferent and efferent nociceptive transmission are modulated, through the binding with its receptors located in Aδ-fibers of trigeminal sensory afferents, trigeminal ganglion neurons, and satellite glial cells.

The key role of CGRP in the migraine attack is well established, having an effect on both central and peripheral sensitization phenomena. In fact, it contributes to vasodilation, local release of inflammatory mediators in meningeal vessels, and induces central sensitization acting on trigeminal ganglion neurons. Moreover, its presence in brain areas involved in migraine pathophysiology, such as the trigeminal nucleus caudalis, locus coeruleus, thalamus, hypothalamus, hippocampus, amygdala, and cortex supports the involvement of CGRP in many migraine-related symptoms.[18]

Evidence of the BT-A action on CGRP system has been given: BT-A inhibits the acetylcholine-dependent release of pain-mediating peptide, such as CGRP, in meningeal and extracranial C-fibers, probably inducing the block of peripheral sensitization; moreover, it can be hypothesized that the reversal of peripheral sensitization could reverse even the central sensitization, besides the hypothesized direct central effect of BT-A.[32]

As well as BT-A, mAbs, stated their large size, most likely inhibit CGRP signaling pathway outside the blood-brain barrier, binding the CGRP or its receptor and blocking the activation of Aδ-fibers.

Looking at the above described mechanism of action of BT-A and mAbs, it seems reasonable to combine these two therapies for migraine prevention; in fact, BT-A blocks CGRP-release from meningeal and extracranial C-fibers, whereas mAbs neutralize the CGRP before it binds CGRP receptors or the receptors itself on the Aδ-fibers, so these two molecules can work synergistically and induce a better clinical response in CM patients.[18]

In the last few years some evidence emerged from literature data on safety and efficacy of combining mAbs to BT-A. Clinical retrospective trials support the additive benefit of combining BT-A and CGRP mAbs in patients with CM, with no adjunctive safety concern.[17,20,33]

In a recent review published by Choen,[33] 66 CM patients were retrospectively investigated to assess whether the addition of erenumab to BT-A treatment had provided a synergic

effect on ameliorating clinical outcomes. Authors described an additional reduction of headache days with a total decrease of 16.6 monthly headaches days ($p < 0.001$) from baseline when BT-A was combined to erenumab for at least two cycles. A comparison of groups distinguished for preventive treatment was not performed.

Blumenfeld et al.[17] retrospectively evaluated efficacy, safety and tolerability of treatment with mAbs in add-on to BT-A in CM patients: administration of both therapies was well tolerated and 45% of patients showed an improvement in migraine-related disability score, with a reduction of more than 5 points in approximately six months. In the study, administration of therapies was not consistent and some variation in the timing of injections was very likely; moreover the findings may have been vitiated by all limits of a retrospective study. Similar results are reported by Mechtler et al. in a recent study, where clinical records of 148 patients treated with CGRP antibodies in addition to BT-A were reviewed.[20]

The aim of our pilot, prospective, study was to evaluate the efficacy and safety of mAbs blocking CGRP-receptor (erenumab) in patients with CM, treated with BT-A, with no (NR-group) or partial response (PR-group) to this prophylactic treatment. It was decided that NR patients would have been shifted to erenumab, instead half of PR patients would have been shifted (PR-S) and half added erenumab (PR-P), in a random way.

The results of our study show the efficacy of erenumab in reducing MHD, both in all enrolled patients and in each study groups (NR, PR-S and PR-P) after 3 and 6 months of treatment. Even secondary outcome measures such as MMD, acute medication intake and quality of life and impact scales improved. No safety concerns raised when treatments were combined.

The study sought to identify significant inter-group differences regarding all collected clinical outcome measures. At baseline, the three groups were similar across all clinical variables examined, except for MHD and MMD, with the NR group having the highest frequencies. During the treatment period, a statistically significant difference was observed in almost all clinical variables (MHD, MMD, monthly tablets of acute treatments, and MIDAS) between the NR group and the PR groups (both PR-S and PR-P) at T3 and T6, in term of a better outcome for PR groups. However, no statistically significant differences in clinical scales improvement were found between the PR-S and PR-P subgroups, indicating that in this case series, addiction or shifting to mAbs resulted in similar outcomes.

Our findings suggest that a previous partial response to BT-A treatment is highly associated with a better outcome to mAbs prophylaxis in CM patients, but even NR patients to BT-A treatment can benefit from mAbs administration, obtaining a slightly but meaningful improvement of clinical outcomes. Therefore, mAbs can be considered as a valid alternative for difficult-to-treat CM patients when BT-A seems to be ineffective. It is important to highlight that NR group was composed of patients with no or very low modification after at least 3 BT-A treatments, which had already failed a mean of 4 oral preventive treatments and that can defined as "super-NR". So, even a slight modification of migraine in this subgroup must be considered as a great result.

Despite the intrinsic potential of our study, linked to its prospective nature and the randomization of PR group of patients, this study has some limitations: the sample size is small and consequentially the number of patients in each group is probably too low to detect some clinically significant differences, mostly between subgroup of PR. A larger sample size would be needed to highlight a potential additive effect of mAbs treatment.

Moreover, the similar clinical outcome of PR-S and PR-P groups could be related to a carry-over effect of BT-A, which probably lasts for more than the canonical three months: in fact, it is well known that three months is the duration of the pharmacological effect of BT-A, thus we have chosen this interval to switch patients from a BT-A treatment to mAbs. However, it can be speculated that in long-term BT-A treatment the above-described interval could not be enough to completely erase the clinical modification obtained with BT-A treatment. In fact, it can be hypothesized that central desensitization mechanisms are at play: in addition to the supposed direct central effects of BT-A, the reversal of peripheral sensitization may extend to central system, sustaining the effect of BT-A treatment even following its cessation.

Lastly, another critical point of our study is linked to the duration of the whole BT-A treatment. The median number of BT-A cycles was extremely variable between groups, ranging between 4 and 19 cycles. Thus, due to our small sample size, we were not able to stratify patients based on BT-A treatment duration to evaluate whether the higher number of cycles of BT-A could relate to a better response to mAbs.

Conclusion

In conclusion, our report evidenced the efficacy of mAb treatment as adjunctive or alternative drug to BT-A treatment in CM patients, which have no or partial response to BT-A. No safety concerns were evidenced.

The proven efficacy in NR patients sustains the indication in using anti-CGRP mAbs in very resistant CM patients. As expected, the clinical outcome is better in PR patients, but further studies must be designed to state if the combined treatment is more effective than changing therapy in patients with a partial effectiveness of BT-A treatment; in fact, a larger cohort number and a longer observation period could make possible all clinical stratifications needed for better understanding the unmet needs.

Clinical implications

- A partial response to prior BT-A therapy is associated with better outcomes during mAbs therapy

- Even Non-responders (NR) (difficult-to-treat/super NR) can benefit from mAbs treatment.
- The similar outcome within the PR group (Shift and Plus groups) may be due to a sustained effect of BT-A, lasting beyond three months (pharmacological effect).
- The combination therapy is safe.

Authors' contributors

B.C. and C.I. share the first authorship because of a similar contribution to the study and the draft of the manuscript.
B.C.: Conceived and designed the analysis, collected the data, wrote the main manuscript text
C.I.: Collected the data, performed the analysis, wrote the main manuscript text
M.R.: Conceived and designed the analysis, contributed to revision the manuscript
Z.L.: Contributed to collect data
S.R.: Contributed to collect data
C.B.: Contributed to collect data and to revision main manuscript
F.M.: Contributed to revision the manuscript
D.C.U.: Contributed to revision the manuscript
All Authors discussed the results, commented, revised and approved the final version of the manuscript.

Availability of data and materials

Data is owned by the Authors and is available on request.

Declaration of conflicting interests

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Ethical approval

All subjects participating in the study provided a written Informed Consent Form (ICF) approved by local Independent Ethics Committee to collect and publish data.

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