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Botulinum toxin as an effective rescue treatment after failure of anti-CGRP monoclonal antibodies in chronic migraine patients

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ABSTRACT

anti-CGRP monoclonal antibodies (anti-CGRP mAbs) represent a highly effective prophylactic treatment for chronic migraineurs, but for some subjects they are ineffective. We aimed to determine if OnabotulinumtoxinA (BoNT/A) treatment may be helpful in these cases. We collected data from fourteen chronic migraineurs who attended our Headache Center and who did not benefit from anti-CGRP mAbs treatment. After anti-CGRP mAbs failure, these patients underwent at least one BoNT/A treatment according to the PREEMPT protocol. We then compared the variation in headache days (DOH), pain intensity (NRS), and symptomatic medication intake (ADI) before and after anti-CGRP mAbs therapy and before and after BoNT/A treatment: we confirmed that the interruption of anti-CGRP mAbs treatment had actually been due to a lack of benefit in terms of DOH (19.21 ± 7.58 days and 20.29 ± 8.32 days; $p = 0.74$), NRS (7.64 ± 0.75 vs 7.57 ± 1.01; $p = 0.85$) and ADI (42.86 ± 52.74 vs 45.64 ± 52.82; $p = 0.79$). All patients started BoNT/A therapy after discontinuing anti-CGRP mAbs. After a period without treatment, therapy with BoNT/A caused a significant reduction in DOH (23.86 ± 6.97 vs. 11.36 ± 10.10, $p = 0.010$), ADI (47.07 ± 51.19 vs. 20.50 ± 21.42, $p = 0.010$) and NRS (8.07 ± 1.00 vs. 6.64 ± 1.60, $p = 0.014$), improving clinical conditions in patients non-responders to anti-CGRP mAbs. It is not well established on which basis pharmacological resistance to anti-CGRP mAbs develops in such refractory patients. Still, these data may point towards a mechanism of pain relief that could not be solely related to CGRP pathways activity, thus being a good rescue therapy in resistant headache management, although further data are needed. Our preliminary results suggest that BoNT/A may be a promising salvage therapy option when anti-CGRP mAbs are ineffective, but evidence requires confirmation from basic research and in larger, uncontrolled, prospective studies in chronic migraineurs.

1. Introduction

According to the third edition of the International Classification of Headache Disorders ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition," 2018), Chronic Migraine (CM) is a condition of "headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache". Since its prevalence involves 2 % of the general population (Natoli et al., 2010), it is one of the most frequent chronic diseases (Su and Yu, 2018), with a great social and economic burden. Nowadays, we can dispose of several pharmacological therapies that either help migraineurs in controlling headache attacks or work as prophylactic treatments that impede them, thus ameliorating patients' quality of life.

One of the most effective treatments for CM, available for nearly fifteen years, is botulinum toxin, especially OnabotulinumtoxinA (BoNT/A). Due to its efficacy and the lack of serious adverse effects, it has become one of the leading therapies for chronic migraineurs, especially the most refractory ones to previous oral treatments. Some limited evidence also suggests an effective prophylactic role for the management of patients affected by hemiplegic migraine (Chen et al., 2018). According to the PREEMPT scheme (Dodick et al., 2010), BoNT/A is

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List of abbreviations

ADI	analgesic drugs intakes
anti-CGRP mAbs	anti-CGRP monoclonal antibodies
BoNT/A	OnabotulinumtoxinA
CM	chronic migraine
DOH	days of headache

administered subcutaneously in a set of predefined points on the scalp every three months. On a pharmacodynamic level, its mechanism of function is based on the blockade of nociceptive C-fibers peripheral terminals through the inhibition of both neuromodulatory peptides release (first of all, CGRP) and nociceptors (like TRPV1 or P2X3) delivery to the neuronal membrane (Becker, 2020; Burstein et al., 2020); its effects are also yielded by other neuromodulatory processes that take part in trigeminal ganglion, which have been only partially described (Becker, 2020).

More recently introduced, monoclonal antibodies targeting CGRP, or its receptors CGRP-R (anti-CGRP mAbs) have proved to be drugs extremely effective in reducing disease burden, for both severe episodic migraine and CM (Han et al., 2019; Hong et al., 2017; Sevivas and Fresco, 2022), with minimal side effects. They work by impeding CGRP-mediated intracellular pathways involved in the so-called trigemino-vascular system, which are considered of paramount importance in migraine pathophysiology (Iyengar et al., 2019; Sevivas and Fresco, 2022; Tereshko et al., 2023).

A comparison between anti-CGRP mAbs and BoNT/A efficacy is difficult, due to the different technical approaches and statistical methods used in the literature (Frank et al., 2021). However, from the evidence of some pivotal studies, it seems plausible that, especially regarding side effects, anti-CGRP mAbs could be preferable to BoNT/A (Grazzi et al., 2024; Lu et al., 2021). Moreover, anti-CGRP mAbs has been shown to ameliorate migraine in patients who have undergone BoNT/A without any benefits (Alpuente et al., 2021).

Despite anti-CGRP mAbs effectiveness, some people with CM who have already undergone without success several oral prophylactic treatments have not enough benefit from therapy with monoclonal antibodies. The reasons of this condition of "resistant" or "refractory" migraine (Sacco et al., 2020) are not yet completely understood. It is not even straightforward how to manage headaches in these cases: it seems reasonable to switch monoclonal antibodies, particularly from one targeting CGRP-R to one targeting CGRP, so that CGRP could not mediate its pathological activity only via interaction with CGRP-R but also via different CGRP-targeted receptors (Fresán Restituto et al., 2023; López Moreno et al., 2022; Overeem et al., 2022; Tajti et al., 2015), but clear evidence on ample numbers of patients is still lacking.

In the present study, we describe a small case series of patients affected by CM and hemiplegic migraine who have been treated with BoNT/A after anti-CGRP mAbs treatment failure, in a sort of paradigm of rescue therapy opposite to that more widely described in the literature (Alpuente et al., 2021).

2. Materials and methods

First, we extracted from our records all the patients affected by CM according to ICHD-3 ("Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition," 2018), followed by our Headache Center, who had been treated with anti-CGRP mAbs, selecting among them those who had undergone at least three injections on March 1st, 2024, thus excluding all patients who had been treated for a too short period. As a second step, we proceeded to sort out which of them were no longer treated with such drugs and had switched to BoNT/A (Fig. 1).

We then proceeded to analyze the reasons why anti-CGRP mAbs have been discontinued by reviewing all medical reports of each patient. In particular, regarding the efficacy of anti-CGRP mAbs and since we dealt with an exploratory analysis, we chose arbitrarily to examine three variables: number of monthly days of headache (DOH), number of analgesic drugs intakes (ADI), and severity of headache (NRS), comparing the month just before anti-CGRP mAbs start and the last month while on treatment with anti-CGRP mAbs, just before treatment

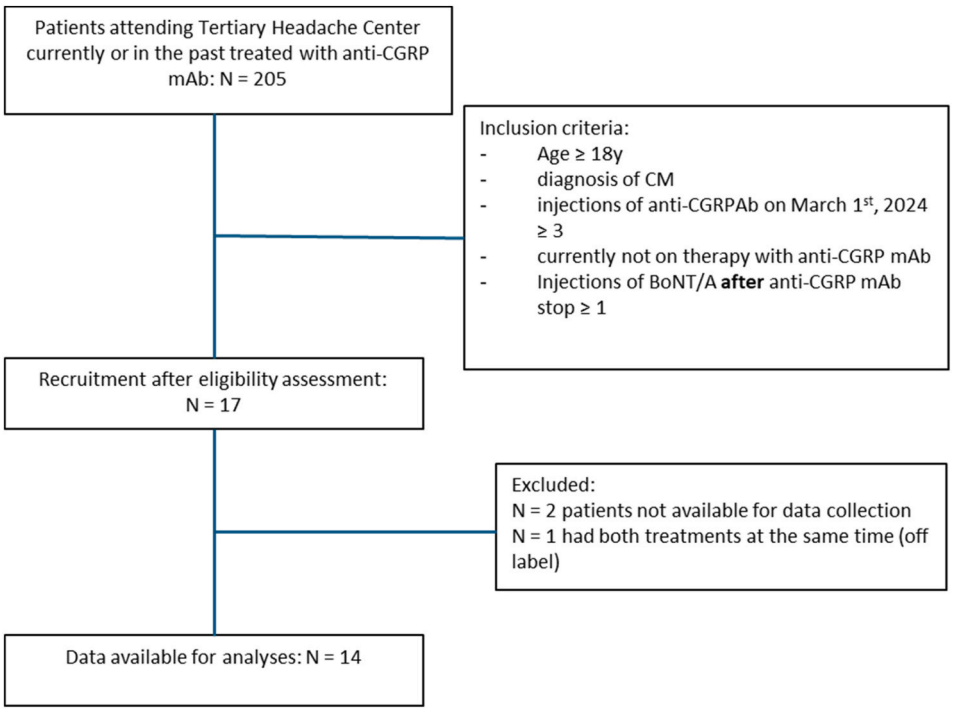

Fig. 1. Inclusion criteria and eligibility assessment.

discontinuation. ADI number was obtained by directly asking the patients how many painkillers had to be taken in a single day and in the time span of a month, either by counting or by approximating the exact number; when available, we detected this datum in updated medical documents. Likewise, DOH was obtained by directly asking the patient how many days in the considered month headache was present, whenever this information was not already described in our documents. NRS scale was used by instructing patients to describe the intensity of their pain, from 0 (= total absence of pain) to 10 (= the strongest imaginable pain).

We assumed that if interruption was actually due to failure, there had to be a non-significative difference between these two time periods. In everyday clinical practice and in several Works, a definition of failure is typically reached when a reduction less than 30–50 % of headache attacks is perceived by the patient, but we decided to establish a statistics-based definition of anti-CGRP mAbs failure in order to ease comparisons between different therapeutic regimens and to minimize eventual biases (however, it is noteworthy that none of our patients has reached a reduction of 30 % in at least 2 parameters when considering anti-CGRP mAbs effect). Finally, we evaluated BoNT/A efficacy by studying the same three variables, comparing their values in the month just before BoNT/A start and in the time window comprised between day 90 and 120 after the last BoNT/A injection (Fig. 2).

As already described, all the available data have been searched consulting the Regional Health System digital archives and headache diaries compiled by patients; data not available and possible doubts of interpretation have been solved by directly contacting the patients and asking them to answer our questions. We also collected other relevant information to better describe the patients' type of headache syndrome in terms of pain characteristics, number and type of previous prophylactic medications and analgesic drugs, and other previous headache treatments.

Following the inclusion criteria, we could identify 14 patients, all female, age range 28–63 years: 11 of them were affected by CM without aura, 1 by CM with aura, and 2 by hemiplegic migraine. Several of these patients were concomitantly affected by medication overuse headache, due to the high amount of painkillers intake per month. As previous prophylactic treatments, they had been administered a mean quantity of 3.1 drugs, amitriptyline being the most used one, followed by beta-blockers and topiramate (Table 1). Of note, 5 out of these 14 patients, after having failed at least one trial with oral medications, had also been treated in the past with BoNT/A before anti-CGRP mAbs commercialization, but with insufficient clinical benefit. Aiming to obtain better control of their headache symptoms, they were shifted to anti-CGRP mAbs when such therapy became available.

All patients had undergone at least three complete cycles of anti-CGRP mAbs: assuming one injection intake per month, the average duration of treatment was 10.07 months. Due to treatment failure, BoNT/A treatment was then subsequently started: the mean interval between anti-CGRP mAbs stop and BoNT/A start was 2.57 months (median 2 months). BoNT/A treatment was re-started even in those 5 patients who had been treated in the past with the same drug, with the aim of returning at least to their clinical conditions before anti-CGRP mAb administration. The mean number of treatments with BoNT/A was 4.86, and median number was 3 (for one patient, only one cycle of therapy was administered due to an allergic reaction). The mean interval between BoNT/A therapy start and clinical assessment was 14.64 months (median: 9 months); no patient has been evaluated before 3 months since start of BoNT/A therapy, given that full efficacy of treatment could require up to 12 weeks to manifest. As regards anti-CGRP mAbs, five patients were treated with erenumab, five patients with galcanezumab and two patients with fremanezumab; one patient had already switched from erenumab to fremanezumab and another one from fremanezumab to erenumab: for both patients, antibody switch had been made without any schedule interruption.

As a first step, we described anti-CGRP mAbs efficacy in terms of DOH, NRS and ADI, in order to confirm the therapy failure as the cause of anti-CGRP mAbs treatment interruption. After checking the global lack of efficacy for anti-CGRP mAbs treatment in our population, we analyzed the differences before and after BoNT/A treatment evaluating the same variables. We also analyzed separately the 5 patients who had been previously treated with BoNT/A, comparing the month before anti-CGRP mAbs start (when effect of first cycle was still ongoing) and the last month of therapy with toxin after anti-CGRP mAbs, to evaluate the effect of the new cycle of BoNT/A. We performed our statistical analysis using Wilcoxon signed-rank test to compare quantitative data related to periods of time before and after treatments. We also provided Hodges-Lehmann median differences and estimated paired effect sized with rank-biserial r for detection of differences before and after each treatment.

3. Results

All 14 subjects found with our workflow could be included in our

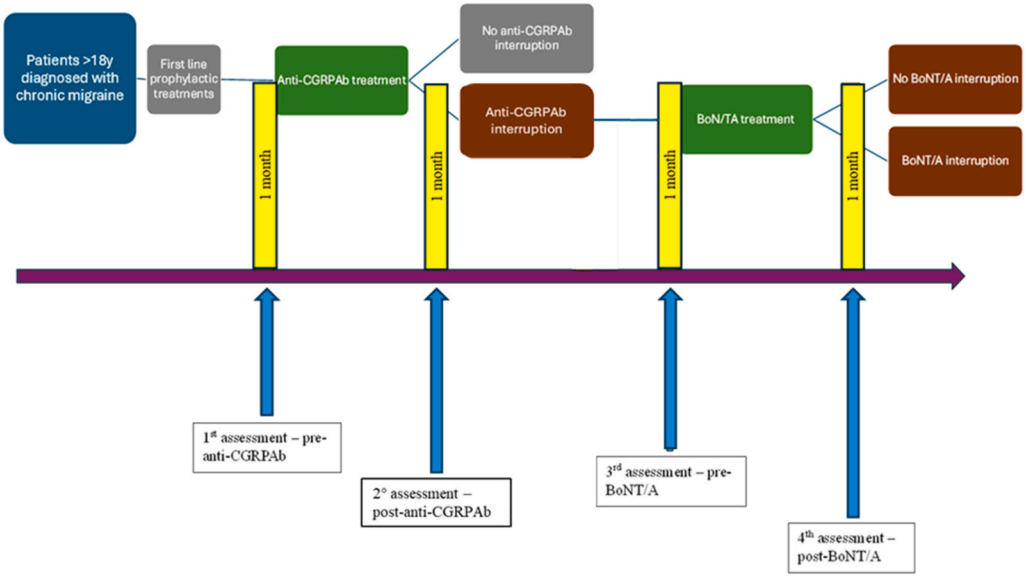

Fig. 2. Workflow.

Table 1
CM = chronic migraine. NA: not available.

PATIENT	AGE (years)	BMI (Kg/m^2)	DIAGNOSIS	AGE AT ONSET	PREVIOUS PROPHYLACTIC TREATMENTS
A	25	18.61	CM without aura	5	Flunarizine, Amitriptyline
B	28	17.97	CM without aura	14	Venlafaxine, Amitriptyline
C	56	NA	CM without aura	9	Bisoprolol, Topiramate, Amitriptyline
D	54	25.10	CM without aura	37	Bisoprolol, Topiramate, Amitriptyline, Ketogenic Diet
E	55	26.77	CM without aura	14	Flunarizine, Topiramate, Amitriptyline
F	44	27.50	Hemiplegic migraine	29	Propranolol, Bisoprolol, Topiramate, Lamotrigine, Amitriptyline, Ketogenic Diet, Zonisamide, BoNT/A
G	70	17.71	CM without aura	10	Ketogenic Diet, Topiramate, Valproate, Propranolol, Flunarizine, BoNT/A
H	50	22.50	CM with aura	14	Amitriptyline, Lamotrigine, BoNT/A
I	52	NA	CM without aura	35	Amitriptyline, Topiramate, Lamotrigine, Dihydroergotamine, BoNT/A
J	63	22.30	CM without aura	26	Radiofrequency ablation, Local nerve blocks, Duloxetine, Topiramate, Propranolol, BoNT/A
K	42	22.68	Hemiplegic migraine	30	Bisoprolol, Topiramate, Amitriptyline, Propranolol
L	45	NA	CM without aura	22	Amitriptyline, Venlafaxine
M	63	22.04	CM without aura	30	Lamotrigine, Local nerve block, Amitriptyline, Propranolol, Flunarizine, Topiramate
N	57	30.86	CM without aura	25	Amitriptyline, Topiramate

statistical analysis. To assess anti-CGRP mAbs effects, we performed a Wilcoxon signed-rank test considering the population of patients before and after treatment, and, as expected, there were no apparent differences between the period before anti-CGRP mAbs therapy start and after its discontinuation in terms of DOH (19.210 ± 7.580 days and 20.290 ± 8.320 days; $p = 0.740$). Similarly, no improvements were found for NRS (7.640 ± 0.750 vs. 7.570 ± 1.010; $p = 0.850$) or for ADI (42.860 ± 52.740 intakes vs. 45.640 ± 52.820; $p = 0.790$). Due to the lack of statistically significant differences in patients' diaries for DOH, NRS and ADI comparing observation periods before and after start of anti-CGRP mAbs treatment, patients can be defined as non-responders to anti-CGRP mAbs therapy on the basis of our operational definition (see previous paragraph). This was also confirmed by reviewing the medical records of our out-patient clinic, reporting that for all patients discontinuation of therapy had been chosen due to inefficacy. The limited numerosity of our samples has prevented us from further exploring links between the particular type of monoclonal antibody used and clinical effects. Using the same tests, we compared the period just before and after BoNT/A start and we observed a statistically significant reduction of headache burden in terms of DOH (23.860 ± 6.970 vs 11.360 ± 10.100 days per month, $p = 0.010$), ADI (47.070 ± 51.190 vs 20.500 ± 21.420, $p = 0.010$), and NRS (8.070 ± 1.000 vs 6.640 ± 1.600, $p = 0.014$) (Tables 2 and 3; Fig. 3).

Considering just the patients who had been treated in the past with BoNT/A, we sought if there were any changes when considering our variables in the period before anti-CGRP mAb start (when effect of first trial of BoNT/A was still lasting) and after the subsequent trial with BoNT/A. With the limit of scarce numerosity, through Wilcoxon signed-rank test we could identify a non-significant difference in terms of DOH just above significance level ($p = 0.063$) and ADI ($p = 0.063$); a difference was even more uncertain when considering NRS ($p = 0.144$). Yet the rank biserial correlation showed a large effect size at least for DOH and ADI (r_s: 1.00), indicating potentially meaningful changes.

4. Discussion

Both BoNT/A and anti-CGRP mAbs have proved to be effective in managing CM, but how to choose between them and how to individualize therapy for each patient remains a matter of debate in everyday clinical practice. According to the work by Lu and Colleagues, the efficacy and safety of anti-CGRP mAbs and BoNT/A are pretty comparable, with the former having a slightly better usage profile (Lu et al., 2021). However, even fewer evidence is available about anti-CGRP mAbs failure and related rescue therapies, since biological mechanisms of resistance to such treatments remain to be fully described. The lack of therapeutic effectiveness of anti-CGRP mAbs treatment in these patients may characterize them as a subset of migraineurs in which pathophysiological mechanisms of headache do not rely exclusively on CGRP-mediated pathways, which monoclonal antibodies can halt. It is reasonable that BoNT/A can inhibit other molecular pathways by interrupting the upstream release of several peripheral and, probably, central neurotransmitters and neuromodulators, not limiting its action on CGRP release and signaling. Indeed, migraine pain origin could be regarded as a complex phenomenon, where CGRP signaling is just one of the implied actors: more and more molecules are being proved to play a role in this process, like the pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), with intriguing therapeutic applications (Pellesi et al., 2024a). As a concrete, related example, post-traumatic headache, a particular and severe consequence of traumatic brain injury, proved to respond significantly better to botulinum toxin than to fremanezumab, even though current evidence are too limited to establish clear therapeutic guidelines (Pellesi et al., 2024b). As a conclusion, accumulating evidence in literature is unveiling data about CGRP-independent pathogenetic mechanisms of migraine, many of them possibly responsible for unresponsiveness in this context (Al-Hassany et al., 2023; Ernstsen et al., 2022).

An association of anti-CGRP mAbs and BoNT/A, targeting multiple molecular pathways involved in migraine pathogenesis, could represent an effective treatment option for the most severe cases, supported by initial evidence in favor of a combined treatment, but that could face significant difficulties in several countries related to costs and reimbursement issues (Guerzoni et al., 2022, 2022, 2022; Salim et al., 2024).

A subgroup of our patients had been treated in the past with BoNT/A without enough benefit; unfortunately, we do not possess clinical data before start of their first BoNT/A trial. Anti-CGRP mAb therapy failed in improving their condition, consequently they were newly treated with toxin with the aim of reobtaining at least their baseline clinical conditions. Interestingly, we noted a non-significant trend towards a better response during the second trial with BoNT/A: this deserves more attention, and it still cannot be entirely explained on the basis of our knowledge. When trying to study this phenomenon, we speculated that a beneficial long-lasting effect may derive from changes in receptors

Table 2
Raw data collected by patients. ADI = number of analgesic drugs intakes per month; Anti-CGRP mAbs = monoclonal antibodies anti-CGRP; BoNT/A = OnabotulinumtoxinA; DOH = days of headache per month (0–30); NRS = numeric pain rating scale (0–10).

SUBJECT	MONOCLONAL ANTIBODY	Anti-CGRP mAbs						BoNT/A					
		Before treatment			After treatment			Before treatment			After treatment		
		DOH	NRS	ADI	DOH	NRS	ADI	DOH	NRS	ADI	DOH	NRS	ADI
A	Galcanezumab	12	7	15	14	9	19	14	9	19	30	9	20
B	Fremanezumab	30	8	45	30	8	22	30	7	22	10	6	3
C	Erenumab	20	7	20	16	7	19	27	7	19	6	7	6
D	Galcanezumab	18	8	18	19	8	20	20	8	20	4	5	5
E	Galcanezumab	30	8	120	29	6	120	30	10	105	4	5	6
F	Erenumab	10	8	25	10	8	25	25	9	25	4	9	5
G	Erenumab > Fremanezumab	20	9	30	20	9	30	30	8	30	7	5	15
H	Erenumab	9	8	20	3	6	15	16	8	15	4	6	6
I	Erenumab	15	7	20	20	7	20	15	9	20	6	7	14
J	Fremanezumab	30	7	200	30	7	200	30	7	200	15	4	15
K	Erenumab	14	7	12	14	7	72	12	7	72	12	7	72
L	Galcanezumab	25	9	30	25	9	30	30	9	60	30	9	60
M	Fremanezumab > Erenumab	24	7	30	24	7	30	25	7	35	26	7	35
N	Galcanezumab	12	7	15	30	8	17	30	8	17	1	7	25

Table 3
Sample's mean values with standard error, inter-quartile and Hodges-Lehmann differences with 95 % confidence intervals of DOH, NRS and ADI with both treatments, comparing before and after therapy. No apparent differences between the period before anti-CGRP mAbs therapy start and after its discontinuation were evident, regarding days of headache (p = 0.740), pain intensity (p = 0.850), and symptomatic drugs intakes (p = 0.790). As regards BoNT/A, we documented a significative reduction of all parameters (*)(DOH: p = 0.010, ADI: p = 0.010, NRS: p = 0.014). ADI = number of analgesic drugs intakes per month; Anti-CGRP mAbs = monoclonal antibodies anti-CGRP; BoNT/A = OnabotulinumtoxinA; DOH = days of headache per month (0–30); NRS = numeric pain rating scale (0–10).

		MEAN ± SE (before treatment)	MEAN ± SE (after treatment)	HL estimate	95 % CI lower	95 % CI upper	Rank-biserial *r*
Anti-CGRP mAb	DOH	19.21 ± 7.58	20.29 ± 8.32	0.0	−1.0	2.5	0.18
	NRS	7.64 ± 0.75	7.57 ± 1.01	0.0	−0.5	0.01	−0.20
	ADI	42.86 ± 52.74	45.64 ± 52.82	0.0	−1.5	2.0	0.14
BoNT/A	DOH	**23.86 ± 6.97***	**8.07 ± 1.00***	−13.5	−20.5	−6.0	−0.83
	NRS	**8.07 ± 1.00***	**6.64 ± 1.60***	−1.5	−2.5	0.0	−1.00
	ADI	**47.07 ± 51.19***	**20.50 ± 21.42***	−10.0	−49.5	−3.5	−0.88

expression on synaptic walls as an effect of drugs modulating CGRP-related pathways (Labastida-Ramírez et al., 2023), with an impact on central processing of pain, as already described with functional MRI studies in human patients who responded positively to erenumab (Ziegeler et al., 2020). Consistently, fremanezumab demonstrates a long-lasting effect by disrupting the cross-signaling between trigeminal neurons paralleling a slower synthesis and redistribution of CGRP receptors, thereby dampening neuronal excitability (Vogler et al., 2023), whereas CGRP itself appears to enhance glutamate release at presynaptic sites in these pain-related circuitries (Liu et al., 2020). Therefore, we think that the use of anti-CGRP agents might contribute to a reduced pre-synaptic baseline activity involved in pain processing, and, in our hypothesis, successive treatments with BoNT/A could possibly further impede synaptic trafficking, acting in a summatory mode. In other words, antiCGRP mAb might induce some changes on synaptic proteins pattern that may facilitate successive BoNT/A effects. Of course, this is only speculative and needs further investigation to be ascertained.

Our study has several limits. First, our case series has a limited size, thus preventing us from conducting a deeper statistical analysis; at the same time, heterogeneity in diagnoses and in previous prophylactic treatments has probably influenced our results, since people refractory to a higher burden of drugs in the past may represent distinct subgroups of migraineurs, and scarce numerosity of our sample have impeded further analysis. A higher number of patients with different diagnoses may allow us to understand different responses to first- and second-line prophylactic treatments, and the diagnosis-specific effect of BoNT/A in case of anti-CGRP mAbs failure. Secondly, we only detected female patients, therefore caution is needed in extending our results to male population. Moreover, we relied on subjective variables like NRS for pain evaluation, and we had to rely on patients' information about number of medication intake and number of days of headaches per month. We did not evaluate antibodies targeting anti-CGRP mAbs, thus being unable to identify non-responders to anti-CGRP mAbs for this reason. Unfortunately, such a test is currently unavailable in most public Italian Headache Centers. Finally, our sample size was insufficient to stratify our population for the different specific monoclonal antibodies; the relative prevalence of erenumab over the other two drugs is related to the much longer availability of the former in Italy.

5. Conclusions

The number of patients experiencing anti-CGRP mAbs failure is likely to grow due to the progressive diffusion of such treatment, thus valid alternatives for these people are urgently needed. Other efforts are warranted to establish the most useful rescue therapy in these cases, hopefully confirming BoNT/A as a valid rescue therapy for chronic migraineurs. Alongside clinical improvement, we expect the studies on rescue therapies will contribute to better understand the pathophysiological mechanisms underlying CM.

CRediT authorship contribution statement

Giovanni Ermanis: Writing – original draft, Investigation, Formal analysis, Data curation. **Yan Tereshko:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Enrico Belgrado:** Supervision, Data curation. **Christian Lettieri:** Supervision, Formal analysis, Conceptualization. **Gian Luigi Gigli:** Writing – review & editing. **Mariarosaria Valente:** Writing – review & editing,

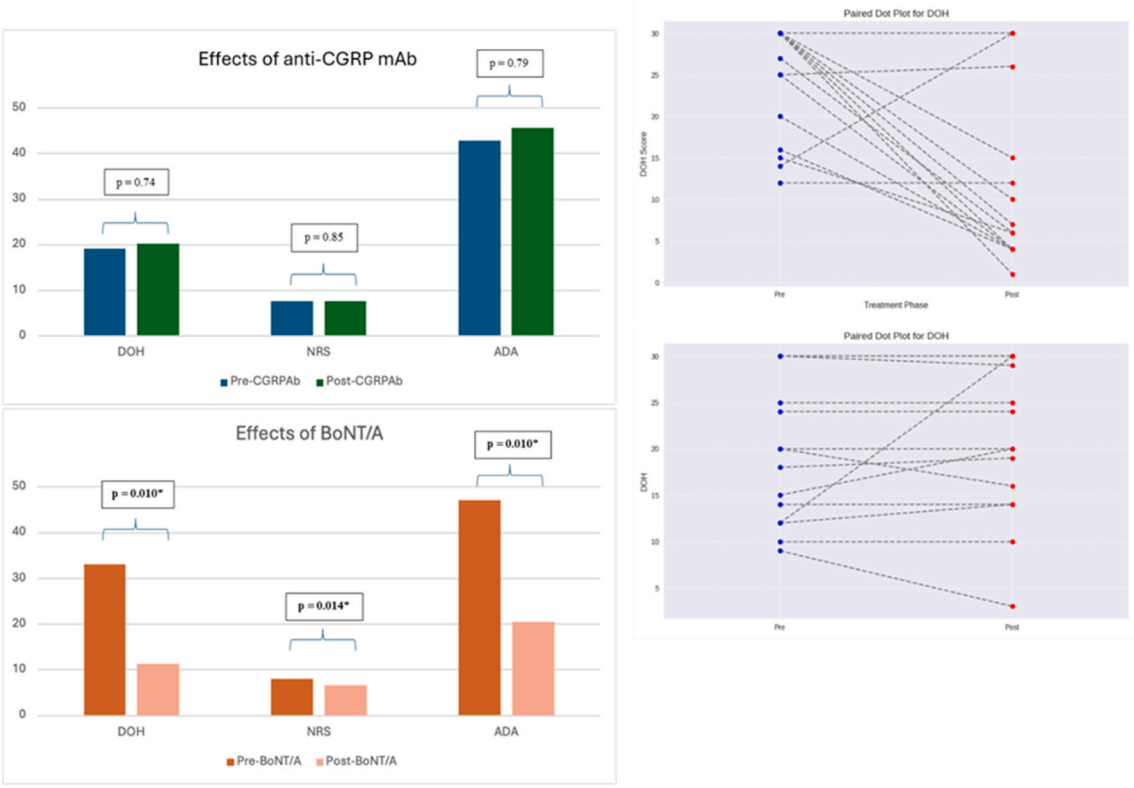

Fig. 3. Effects of anti-CGRP mAb and BoNT/A on variables on study. Left panels, effects on all variables on study related to anti-CGRP mAb (top graph) and BoNT/A (bottom graph); significative effects on all variables were obtained with BoNT/A therapy. Right panels, dot-plot representing DOH before (blue dots) and after (red dots) therapy with BoNT/A (top graph) and anti-CGRP mAb (bottom graph). ADI = number of analgesic drugs intake per month; Anti-CGRP mAbs = monoclonal antibodies anti-CGRP; BoNT/A = OnabotulinumtoxinA; DOH = days of headache per month (0–30); NRS = numeric pain rating scale (0–10). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Visualization.

Funding sources and conflict of interest

No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Ethical compliance statement

All the procedures needed for this work have been done in accordance with the declaration of Helsinki and with every ethical standard of relevant national and international committees on human experimentation. All patients gave a formal written consent for BoNT/A treatment and for their clinical anonymised/pseudonymised data to be used for research purposes. Friuli Venezia Giulia's ethics committee (CEUR) waived the need for this study's approval due to the fact that the responsibility of case reports and case series is entirely in the hands of authors and, at the same time, they describe something that has already been carried out (statement of December 3rd, 2021). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Financial disclosures for the previous 12 months

The authors declare that there are no additional disclosures to report.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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