Confinia Cephalalgica 2024; 34:15767

Back to the future: a case series on revisiting onabotulinumtoxinA for chronic migraine management after anti-CGRP therapies failure

Davide Mascarella,[1,2] Benedetto Carandente,[1] Valentina Favoni,[2] Elisa Maria Bruno,[2] Pietro Cortelli,[1,2] Giulia Pierangeli,[1,2] Sabina Cevoli[2]

[1]DIBINEM – Alma Mater Studiorum Bologna; [2]IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy

ABSTRACT

Background: Chronic migraine (CM) management is still a challenge. Notwithstanding the success of anti-calcitonin gene-related peptide antibodies (anti-CGRP mAbs), not all patients respond to these treatments. Here, we revisit the efficacy of onabotulinumtoxinA (BTA) in patients who did not respond to anti-CGRP mAbs.

Methods: This case series included 36 CM patients who demonstrated an insufficient response (<10% reduction in monthly headache days [MHD]) to anti-CGRP mAbs and who received a subsequent BTA treatment between December 2022 and February 2024. All patients had a minimum follow-up duration of six months with anti-CGRP mAb and BTA treatments.

Results: The cohort comprised 12 patients (92% females, mean age of 49 years) affected by CM. Treatment with anti-CGRP mAbs produced in 7 (58.3%) patients an initial 20% reduction in MHD which, after a few months, was less than 10%; in 5 patients (41.6%) the response was >10% from the beginning of the treatment. A reduction in MHD of >50% was reported in 6 patients (50%) treated with BTA, and in 6 patients (50%) there was a less pronounced reduction (30-50%).

Conclusions: This case series is the first report of patients who showed a meaningful response to BTA after an unsuccessful trial with anti-CGRP mAbs, suggesting a CGRP-independent action of BTA. However, due to the small sample size, further research is needed to support the proposal of a positive response to BTA in CM patients resistant to anti-CGRP mAbs and the consequent mechanistic implications.

Key words: migraine, chronic migraine, onabotulinumtoxinA, botulinum toxin A, anti-CGRP.

Introduction

The discovery of the calcitonin gene-related peptide **(**CGRP) and its crucial role in migraine pathophysiology marked a milestone in migraine research, thus leading to the development of novel and specific therapies for both prophylaxis and acute attack treatment, such as gepants (non-peptidic CGRP-receptor antagonists that can be used for either the acute or the preventive treatment of migraine) and, most importantly, monoclonal antibodies targeting CGRP (*i.e.* galcanezumab, fremanezumab, eptinezumab) or CGRP receptor (*i.e.* erenumab) (anti-CGRP mAbs) dedicated to migraine prophylaxis. (1) The introduction of therapies that directly target the CGRP has deeply changed the management of CM, achieving unprecedented levels of efficacy and safety. (2-10) Reimbursement policies for anti-CGRP antibodies, although differing internationally, have generally permitted the utilization of these pharmaceuticals exclusively after unsuccessful attempts with the so-called first-line preventive therapies. Among them, onabotulinumtoxinA (BTA) is a first choice treatment option for CM management. The mechanism of action of BTA consists in the proteolytic cleavage of synaptosomal-associated protein-25 kDa (SNAP-25), one of the Soluble N-ethylmaleimide-Sensitive Factor Attachment Proteins (SNAP) Receptor (SNARE) proteins, crucial for the vesicular fusion to the plasma membrane at the synaptic level. It has been suggested that BTA anti-migraine activity is due to the possibility that its proteolytic activity is directed not only to acetylcholine-containing vesicles but also to vesicles containing CGRP, resulting in inhibition of the neuropeptide release. (11)

Interestingly, anti-CGRP mAbs have been prescribed to patients classified as «resistant or refractory», who frequently experience an unsuccessful outcome with BTA therapy. (12) Emerging evidence indicates that CM patients unsuccessfully treated with BTA treatment reported a better clinical response to subsequent therapy with anti-CGRP mAbs, with a more prominent amelioration in patients who received more than three previous BTA cycles. (13) Despite years of successful clinical experience with anti-CGRP mAbs, a small proportion of migraine patients shows an unsatisfactory or absent clinical response to this treatment. The failure of anti-CGRP mAbs, which are often considered «last chance», is remarkably frustrating to patients and their doctors, encouraging the search for additional therapeutic options.

Although current literature reports several examples of response to anti-CGRP mAbs following an unsuccessful BTA treatment, to the best of our knowledge, there are no cases of response to BTA after failure with anti-CGRP mAbs. As anti-CGRP mAbs can be used for both episodic and CM, whereas BTA is approved only for CM, it is possible that a small subgroup of CM who had received anti-CGRP mAbs have not received a previous BTA trial. Here, we report a series of patients who exhibited no adequate response to anti-CGRP mAb but achieved a sufficient response to BTA, highlighting the nuanced landscape of migraine management and the ongoing evolution of therapeutic strategies that may find a new place in therapy for BTA.

Methods

This case series includes patients who, following unsuccessful treatment with anti-CGRP antibodies, received treatment with BTA between December 2022 and February 2024 at the Headache Centre, IRCCS Institute of Neurological Sciences of Bologna, with the following three inclusion criteria: (i) a diagnosis

of CM according to ICHD-3 criteria; (ii) unsuccessful outcomes from at least four prophylactic therapies, with at least one being an anti-CGRP mAbs; (iii) meaningful clinical benefits from BTA treatment. All patients had a follow-up duration of at least 6 months for anti-CGRP mAbs and for BTA therapy. Data collected from outpatient medical records and headache diaries included demographic details, past medical history, clinical migraine history including age at onset, baseline features, pharmacological history including previous anti-migraine prophylaxis, and usage of acute migraine medications. The primary outcome measure was monthly headache days (MHD), and the secondary outcome measure was attack intensity. We also collected data regarding responses to both BTA and anti-CGRP mAbs, evaluating the patients' subjective overall impression regarding the treatments through the Patients Global Impression of Change (PGIC) questionnaire.

Statistical analysis was conducted utilizing descriptive statistics to summarize the data. For continuous variables, such as MHD and age at onset, both the mean and median were calculated to provide central tendency measures. Insufficient response to anti-CGRP mAb or BTA treatment was defined as initial improvement followed by loss of response, defined as at least a 20% reduction in MHD during the first three months of therapy, followed by a 0%-10% response in the subsequent months of treatment. Absent response from the beginning of treatment, defined as a 0-10% reduction in MHD from the start of the treatment. Successful response to BTA has been subdivided as 'moderate' or 'excellent' if, after six months, the reduction in MHD was >30<50% or >50%, respectively.

Results

Thirty-six patients received BTA treatment after an unsuccessful trial with anti-CGRP mAbs at our Headache Center (89% female), 12 of which reported a successful response to BTA (33.3%). Of these, 12 CM patients enrolled in the present study, 11 were female (91,6%), with a mean age of 49 ± 14.3 years. Demographics, baseline features, and comorbidities are summarized in **Table 1**. Ten patients (83%) had an additional diagnosis of medication overuse headache (MOH) and two (24%) reported visual aura. The mean age of migraine onset was 14.8 ± 6.6 years. The mean treatment duration with anti-CGRP mAbs and BTA was 6.0 ± 3.74 and 14.33 ± 9.34 months, respectively. Migraine characteristics and details regarding treatment with anti-CGRP mAbs and BTA for each patient are summarized in **Table 2** and **Table 3**, respectively.

In 7 (58.3%) patients, an initial 20% reduction in MHD after some months was less than 10%, and in 5 patients (41.6%) the response was >10% from the beginning of the treatment. The response to BTA was >50% in 6 patients (50%), whereas the additional 6 patients showed a reduction in MHD between 30% and 50%. Four (33%) of the 12 patients had been treated with BTA before the anti-CGRP mAb trial. In each case, the second therapeutic attempt with BTA was undertaken more than 2 months after anti-CGRP mAb withdrawal. The comprehensive report of MHD for each patient, covering the three months prior to therapy and the six months of follow-up for both anti-CGRP mAbs and BTA, is shown in **Figure 1**. Patients completed a recalled PGIC, which indicated that 2 (16.6%) out of 12 patients reported a slight amelioration with anti-CGRP mAbs, while 11 (91.6%) reported improvement with BTA. The detailed PGIC results are presented in **Table 4**.

Discussion

To the best of our knowledge, this case series is the first report of a patient series with CM mostly associated with MOH which, after an unsuccessful trial with anti-CGRP mAbs, exhibits a satisfactory response to preventive treatment with BTA. The attempt to treat patients with BTA after an unsuccessful trial with anti-CGRP mAbs is rather unusual and is based on the limited therapy options for CM. (13) A possible explanation for the benefit obtained with BTA is that this cohort of patients experiences a spontaneous amelioration, considering the fluctuating nature of migraine course. (14) This hypothesis is strengthened by the observation that 4 patients had received a previous unsuccessful BTA treatment. Nevertheless, the failure of the last treatment option, anti-CGRP mAbs, raised the critical question of what to do next for these patients, thus justifying an additional attempt with BTA.

Several studies have investigated potential predictive factors for response to anti-CGRP mAb therapies. (15-18) It is well-established that chronic daily headaches, obesity, and psychiatric comorbidity are factors associated with a lower likelihood of response. Conversely, the presence of unilateral cranial autonomic symptoms, strictly unilateral pain, and, albeit less conclusively, allodynia, are factors associated with a higher likelihood of clinical response to anti-CGRP mAbs.(15,19,20) Nonetheless,

Table 1. Demographics, baseline features and comorbidities.

	Age	Sex	BMI	Allodynia	Autonomic Cranial Symptoms during attacks	Significant comorbidities
Patient 1	29	Male	31,9	None	None	Obstructive Sleep Apnea Syndrome, obesity
Patient 2	56	Female	28,1	None	None	Previous breast cancer, mood disorder
Patient 3	33	Female	30,1	Both inter and intra-ictal	None	PCOS, MTHFR and Factor II heterozygosis, obesity
Patient 4	24	Female	22,0	None	None	Irregular menstrual cycle, mood disorder
Patient 5	66	Female	24,6	None	None	Dyslipidemia
Patient 6	54	Female	18,7	Both inter and intra-ictal	None	B12 deficiency, previous thyroidectomy
Patient 7	41	Female	23,2	None	None	Hashimoto's thyroiditis
Patient 8	49	Female	24,5	None	None	Hypothyroidism, PFO, fibromyalgia, spondyloarthrosis
Patient 9	54	Female	16,8	None	None	Hepatic steathosis, hypercholesterolemia, osteoporosis
Patient 10	68	Female	23,0	None	None	None
Patient 11	53	Female	25,4	Both inter and intra-ictal	None	Mood disorder
Patient 12	62	Female	27,4	None	None	Asthma, hypothyroidism, fibromyalgia, mood disorder

PCOS, Polycystic Ovary Syndrome.

negative predictive factors often underlie a more severe and challenging phenotype in a broader sense, not specifically related to anti-CGRP mAb therapy. Our patient group comprises a more complex subset of migraine patients, distinguished by a reduction in negative predictive factors and an increase in positive predictive factors, such as unilateral autonomic signs. However, we acknowledge that the limited number of patients presented is insufficient to draw conclusions in this regard. However, it is crucial to maintain a commitment to in-depth phenotyping of treatment-resistant patients in order to optimize future therapeutic choices.

The reason for the difference in the response between anti-CGRP mAbs and BTA remains poorly understood. Although CM is the sole approved indication for BTA, (21) no specific clinical characteristic appears to predict the response to BTA in the present limited case series. Regarding the sites of action of BTA and anti-CGRP mAbs, the size and pharmacokinetic features of the two classes of drugs suggest a peripheral site, outside the blood-brain barrier, including the peripheral trigeminal nerve endings or the trigeminal ganglion. Anti-CGRP drugs have been proposed to inhibit the excitatory action of CGRP on Ad-fibers but not C-fibers and *vice versa* for BTA. (22,23) Recent evidence

Table 2. Headache features.

	Migraine diagnosis (ICHD-3)	Medication overuse	Age at migraine onset (years)	Age at migraine chronification (years)	Number of previous preventive treatments*	Anti-CGRP mAb	Time interval between onset and anti-CGRP therapy (years)	Time interval between onset and BTA therapy (years)
Patient 1	CM wo Aura	Yes	17	26	3	Galcanezumab	12	12
Patient 2	CM wo Aura	No	11	N/A	4	Galcanezumab	54	50
Patient 3	CM wo Aura	Yes	10	29	5	Eptinezumab	22	22
Patient 4	CM wo Aura	Yes	16	21	5	Galcanezumab	22	23
Patient 5	CM w Aura	Yes	10	18	5	Galcanezumab	62	64
Patient 6	CM wo Aura	Yes	30	N/A	3	Galcanezumab	54	53
Patient 7	CM wo Aura	Before BTA, not before anti-CGRP	12	30	5	Galcanezumab	38	40
Patient 8	CM wo Aura	Yes	10	44	6	Galcanezumab	48	49
Patient 9	CM wo Aura	No	8	12	5	Galcanezumab	52	49
Patient 10	CM wo Aura	Yes	25	40	5	Fremanezumab	42	43
Patient 11	CM wo Aura	Yes	15	43	5	Galcanezumab	37	38
Patient 12	CM wo Aura	Before BTA, not before anti-CGRP	10	59	5	Fremanezumab	51	49

CM w/o Aura, Chronic Migraine without Aura; CM w Aura, Chronic Migraine with Aura; BTA, onabotulinumtoxinA; CGRP, Calcitonin Gene-Related Peptide; mAb, monoclonal antibodies; *Other than anti-CGRP mAbs or BTA.

Table 3. Pharmacological treatment features.

	Mean MHD three months before anti-CGRP treatment	Mean MHD three months before BTA treatment	Response to anti-CGRP	Response to BTA treatment	Latency between anti-CGRP therapy and BTA therapy (months)	BTA treatment before and after anti-CGRP failure	Persistence of clinical benefit through BTA treatment after CGRP failure
Patient 1	18	30	Transient	Moderate (30-50%)	2	No	N/A
Patient 2	15	30	Transient	Excellent (>50%)	3	Yes	Yes
Patient 3	>15	>15	Absent	Excellent (>50%)	3	No	N/A
Patient 4	14	28	Transient	Moderate (30-50%)	6	No	N/A
Patient 5	25	20	Transient	Moderate (30-50%)	3	No	N/A
Patient 6	>15	>15	Transient	Moderate (30-50%)	3	Yes	Yes
Patient 7	17	>15	Transient	Moderate (30-50%)	3	No	N/A
Patient 8	15	N/A	Transient	Moderate (30-50%)	5	No	N/A
Patient 9	10	15	Absent	Excellent (>50%)	8	Yes	Yes
Patient 10	30	30	Absent	Excellent (>50%)	3	No	N/A
Patient 11	20	17	Transient	Excellent (>50%)	5	No	N/A
Patient 12	10	30	Absent	Excellent (>50%)	2	Yes	Yes

MHD, Mean Headache Days; BTA, onabotulinumtoxinA; CGRP, calcitonin gene-related peptide; mAb, monoclonal antibodies.

did not show the expression of the two components of the CGRP receptor in mouse trigeminal nerve fibers; however, they are expressed in the surrounding Schwann cells, where CGRP exerts its pro-migraine activity. (24) As both anti-CGRP mAbs and BTA are characterized by long half-life and duration of action, it seems unlikely that the different responses to the two treatments might be due to the different durations of action of the two types of treatment.

BTA has been proposed to act at the «intracranial» level through mechanisms of central transcytosis, (25) and it is possible that its therapeutic activity is linked to the inhibition of the release of pro-migraine mediators other than CGRP**.** Thus, patients resistant to anti-CGRP mAbs may respond to drugs, like BTA, with a broader mechanism of action that may reduce the release of other neuropeptides implicated in migraine mechanism, including the pituitary adenylyl cyclase polypeptide (PACAP). (26) As previously stated, the major limitations of this study are the limited number of cases, the retrospective nature of the study design, and the unavailability in our database of records of the patients who, after anti-CGRP mAbs, received BTA without any amelioration. Considering recent evidence of late responders and very-late responders, (27) an additional limitation of the study is the short duration of follow-up in some patients during anti-CGRP mAb therapy. However, even late and very-late responders were reported to show an initial 20% reduction in MHDs during the first three months of therapy, (27) a result that was not observed in our case series. A prospective study design with a larger sample size is needed to identify potential clinical and biological predictors not only of the response to BTA but also of the lack of response to anti-CGRP therapies.

Table 4. Patients Global Impression of Change (PGIC).

	PGIC for anti-CGRP mAb therapy	PGIC for BTA therapy
Patient 1	No Change (or condition has worsened)	Moderately better, and a slight but noticeable change
Patient 2	Almost the same, hardly any change at all	Moderately better, and a slight but noticeable change
Patient 3	Almost the same, hardly any change at all	Better, and a definite improvement that has made a real and worthwhile difference
Patient 4	A little better, but no noticeable change	Moderately better, and a slight but noticeable change
Patient 5	Almost the same, hardly any change at all	Moderately better, and a slight but noticeable change
Patient 6	No Change (or condition has worsened)	Better, and a definite improvement that has made a real and worthwhile difference
Patient 7	Almost the same, hardly any change at all	Almost the same, hardly any change at all
Patient 8	A little better, but no noticeable change	Moderately better, and a slight but noticeable change
Patient 9	No Change (or condition has worsened)	Better, and a definite improvement that has made a real and worthwhile difference
Patient 10	Almost the same, hardly any change at all	Somewhat better, but the change has not made any real difference
Patient 11	A little better, but no noticeable change	Moderately better, and a slight but noticeable change
Patient 12	No Change (or condition has worsened)	Better, and a definite improvement that has made a real and worthwhile difference

PGIC, Patient Global Impression of Change; BTA, onabotulinumtoxinA; CGRP, calcitonin gene-related peptide; mAb, monoclonal antibodies.

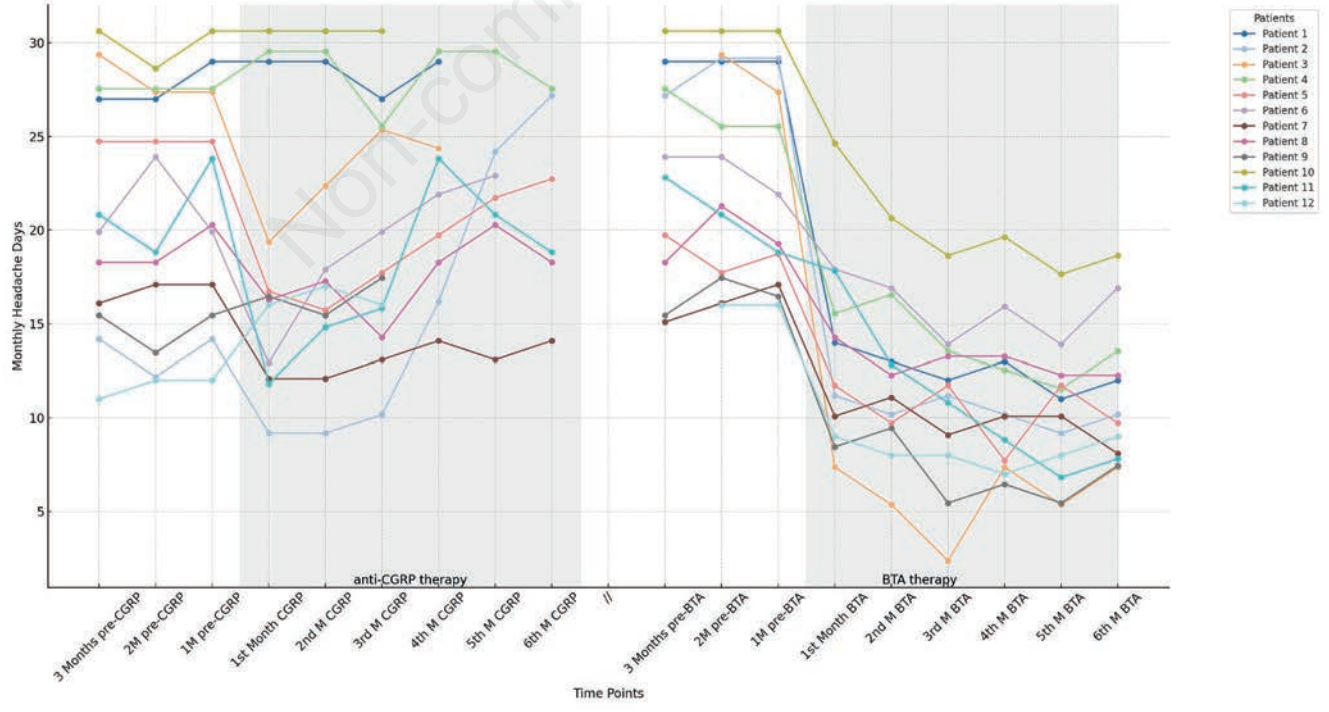

Figure 1. Comprehensive report of MHD for each patient, covering the three months prior to therapy and six months of follow-up for both anti-CGRP mAbs and BTA.

Conclusions

In this case series, we present for the first time a subgroup of CM patients responsive to prophylactic BTA therapy despite therapeutic failure with anti-CGRP mAbs. This finding underscores the complexity of migraine pathophysiology and suggests a distinct clinical profile that might uniquely benefit from BTA therapy. While these results are intriguing, they primarily serve to delineate avenues for future, more extensive prospective studies, which could support the refinement of treatment approaches, thus improving patient outcomes.

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Correspondence: Sabina Cevoli, IRCCS ISNB, Ospedale Bellaria, Via Altura, 3 – Bologna 40139.
E-mail: sabina.cevoli@isnb.it

Authors' contributions: DM study conception, data gathering, manuscript drafting and data analysis, interpretation; BC data gathering, manuscript drafting, data analysis, interpretation; VF study conception, manuscript editing, and supervision; EMB data gathering and data analysis; GP study conception, manuscript editing, and supervision; PC manuscript editing and interpretation supervision; SC study conception, manuscript editing and supervision.

Funding: no funding to declare.

Ethics approval and consent to participate: this case series is part of a study protocol approved by the local Ethics Committee (protocol number 20073). All patients signed informed consent for data gathering and publication.

Competing interests: the authors declare no competing interests regarding this case series.

Availability of data and materials: complete pseudonymized dataset is available upon reasonable request from the corresponding author.

Received: 23 April 2024. Accepted: 6 November 2024.

Confinia Cephalalgica 2024; 2:15767. doi:10.4081/cc.2024.15767