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To cite this article: Simona Sacco , Antonio Russo , Pierangelo Geppetti , Licia Grazzi , Andrea Negro , Cristina Tassorelli , Gioacchino Tedeschi & Paolo Martelletti (2020) What is changing in chronic migraine treatment? An algorithm for onabotulinumtoxinA treatment by the Italian chronic migraine group, Expert Review of Neurotherapeutics, 20:12, 1275-1286, DOI: [10.1080/14737175.2020.1825077](https://doi.org/10.1080/14737175.2020.1825077)

To link to this article: <https://doi.org/10.1080/14737175.2020.1825077>



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Published online: 30 Sep 2020.



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What is changing in chronic migraine treatment? An algorithm for onabotulinumtoxinA treatment by the Italian chronic migraine group

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ABSTRACT

Introduction: OnabotulinumtoxinA (OBT-A) and monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway are two of the few treatments that ameliorate chronic migraine (CM) in randomized controlled trials and real-life studies. Separate clinical practice guidelines have been developed for the management of CM with OBT-A or CGRP-targeting mAbs.

Areas covered: Considering the concomitant availability of OBT-A and CGRP-targeting mAbs as therapeutic treatment options, Italian migraine experts reviewed the evidence supporting the efficacy of OBT-A and CGRP-targeting mAbs in CM in order to rationalize the management of CM patients treated with OBT-A. Experts addressed everyday practice needs to shape the optimal pharmacological management by balancing adherence to regulatory indications, ethical considerations, and clinical expertise. Considering the remarkable challenge of improving the health and quality of life of patients with CM, even partial improvements may be clinically meaningful, particularly for those who are resistant or intolerant to oral migraine treatments.

Expert opinion: In this collaborative effort, we propose a treatment algorithm that integrates the relevant aspects of managing patients with CM to provide ready-to-use practical guidance regarding the appropriate use of OBT-A.

ARTICLE HISTORY

Received 6 August 2020
Accepted 15 September 2020

KEYWORDS

Chronic migraine;
onabotulinumtoxinA;
calcitonin gene-related
peptide; CGRP-targeting
monoclonal antibodies;
migraine prophylaxis;
treatment algorithm

1. Introduction

Migraine is the most common disabling brain disorder. Systematic analysis of the burden of neurological disorders by the GBD 2016 Neurology Collaborators for the Global Burden of Disease Study found that migraine is the second highest contributor to worldwide neurological disability-adjusted life-years (DALYs) [1]. Furthermore, among people aged 15 to 49 years, the age group most commonly affected by migraine, migraine is the leading cause of disability [2]. However, this condition is still underdiagnosed and undertreated, and there is poor global awareness of its burden [3,4].

Chronic migraine (CM), defined as the occurrence of at least 15 days with headache per month for at least 3 months, with headache having migraine characteristics for at least 8 days per month [5,6], affects 2–3% of the general population and is the most disabling form of migraine, representing a clinically distinct, more aggressive subtype of migraine [6,7,8]. Both the American Migraine Prevalence and Prevention (AMPP) and the Chronic Migraine Epidemiology and Outcomes (CaMEO) longitudinal cohort studies found significantly more severe headache-related disability in those with chronic versus episodic

migraine (EM) [9]. Compared to EM, CM has a higher impact on physical, social, and occupational functioning and is characterized by a poorer health-related quality of life (HRQoL) [10,11,12]. Patients with CM were reported to be twice as likely than those with EM to have psychiatric comorbidities, such as depression and anxiety [13,14]. Circulatory and endocrine conditions are also significantly more likely to be reported by those with CM [15].

CM patients are problematic and difficult to treat, and only partial benefit is obtained from oral preventive medications [3]. Managing CM is extremely challenging for several reasons. First, less than 50% of patients seek advice from a headache specialist, and a minority receive adequate acute and preventive treatment [4,16,17]. Only few drugs have a clearly established level of evidence of efficacy [16–18]; however, these medications are often poorly tolerated and their efficacy does not exceed, on average, 50% of cases [19].

To date, onabotulinumtoxinA (OBT-A) is one of the few treatments that proved effective in CM in randomized controlled trials (RCTs) [20,21] and in real-life studies [22–45]. OBT-A is specifically approved for CM prevention [46] and is

Article highlights

- Chronic migraine, a highly disabling neurological disease, is burdened by a high negative impact on the quality of life of patients and is a significant contributor to worldwide neurological disability.
- The condition remains underdiagnosed and undertreated.
- The availability of medications with proven efficacy is limited and the management of chronic migraine is challenging.
- OnabotulinumtoxinA (OBT-A) has been shown to be safe and effective for the prevention of chronic migraine in randomized controlled trials and in real-life studies and is a valid therapeutic option that should be proposed to patients as early as possible.
- OBT-A is also effective in patients with medication-overuse headache.
- Monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway have been developed and investigated for the prevention of episodic and chronic migraine. They ameliorate migraine in clinical trials.
- Although separate guidelines are available for the management of chronic migraine with OBT-A or with CGRP-targeting mAbs, guidance on the integration of these two different therapeutic strategies to optimize the management of chronic migraine is lacking.
- This proposed new algorithm aims to provide guidance for the management of OBT-A therapy taking into account that patients who start OBT-A have already failed or not tolerated at least two previous oral preventive medications.
- Decisions on further patient management after the initial administration of OBT-A should be reassessed every 3 months for the first year of treatment to establish efficacy. Subsequently, the timing to re-evaluate the patient will be guided by the response to treatment.
- Once criteria for the definition of responder patients are established, OBT-A dose and dosing interval, the continuation of OBT-A or switching to another therapy, or initiating complementary strategies with CGRP-targeting mAbs can be considered to optimize patient outcomes.

currently recommended for the treatment of patients who have not responded adequately or who are intolerant to a specified number (two, according to Italian regulations) of oral migraine treatments [47,48]. Recently, monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway have been developed and investigated for EM and CM prevention, showing that the blockade of both the peptide and its receptor are effective mechanisms to reduce the frequency of migraine attacks [18].

Separate guidelines are available for the management of CM with OBT-A or with CGRP-targeting mAbs [48–50]. As a group of Italian migraine experts, considering the concomitant availability of these two different therapeutic strategies, we felt it important to rationalize the management of CM patients treated with OBT-A. This paper reports the decisional

process and the treatment algorithm resulting from the discussion.

2. Methods

In September 2019, a panel of 7 Italian headache specialists (we, the authors) met in Rome to discuss the opportunity of reviewing the existing CM management algorithm for patients who start OBT-A according to the common practice of most of the more representative Italian Headache Centers. Such an opportunity was suggested by both the well-consolidated clinical experience with OBT-A and the advent of new treatments. To this purpose, we performed a complete review of the published RCTs and pooled analyses [20,21,51–56] and real-world evidence data about OBT-A in CM [22–45], and of the RCTs and a real-life study of the CGRP-targeting mAbs in CM patients [57–66], together with an analysis of the current guidelines and recommendations for CM management [48–50]. The overall data were reviewed and discussed, taking into account our personal clinical experience, with the aim of providing practical guidance for the optimal management of CM patients with OBT-A over a period of 3 years. A proposed algorithm was developed from the interactive discussion and is presented here.

3. Proposed new treatment algorithm for CM

OBT-A has been shown to be effective and safe in CM in RCTs (Table 1) [20,21] and in real-world studies (Table 2) [22–45]. A recent review focused on long-term treatment data and on the optimal timing of prophylaxis with OBT-A concluded that OBT-A represents a therapeutic option that should be proposed to patients as early as possible [47]. The effectiveness of OBT-A has also been demonstrated in both RCTs [20,21] and in real-life studies [26,28–30] in patients with medication-overuse headache (MOH), for whom our algorithm should also be considered. Four CGRP-targeting mAbs have recently been developed and evaluated in RCTs in patients with EM and CM [18], one targeting the CGRP receptor (erenumab) and three targeting CGRP itself (eptinezumab, fremanezumab, and galcanezumab). Placebo-controlled trials of CGRP-targeting mAbs in CM have been shown to reduce migraine frequency (Table 3) [57–61]. A recent guideline on CGRP-targeting mAbs concluded that there is medium to high-quality evidence to recommend erenumab, fremanezumab, and galcanezumab in patients with CM [49,50].

Table 1. Summary of pivotal randomized clinical trials with onabotulinumtoxinA in patients with chronic migraine.

Author	Year	Title	Patients (n)	Duration	Main efficacy results
Aurora [20]	2010	OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial	679	24 wks db treatment	Non-significant reduction in frequency of headache episodes Significant reduction in N. of headache/migraine days, cumulative hours of headache, frequency of moderate/severe headache days, burden of illness
Diener [21]	2010	OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial	1005	24 wks db treatment + 32 wks FU	Significant reduction in frequency of headache days

DB: double-blind; FU: follow-up; wks: weeks.

Table 2. Summary of real-world studies with onabotulinumtoxinA in patients with chronic migraine.

Author	Year	Title	Patients (n)	FU duration	Main efficacy results
Khalil [22]	2014	Prospective analysis of the use of OnabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U. K.	254	1 IS + 30 days FU	Significant reduction in the N. of headache/migraine days; increase in the N. of headache-free days; improvement of QoL
Boudreau [23]	2015	Prophylactic onabotulinumtoxinA in patients with chronic migraine and comorbid depression: An open-label, multicenter, pilot study of efficacy, safety and effect on headache-related disability, depression, and anxiety	32	24 weeks (2 IS)	At 24 weeks, significant improvements in N. of headache-free days, HIT scores, BDI-II and Generalized Anxiety Disorder scores
Cernuda-Morollon [24]	2015	Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: What happens after one year?	132	≥1 year	81.8% responders during first year; reduction in consumption of acute medications (53%; 62.5% in triptan overusers) and in emergency visits (61%)
Grazzi [25]	2015	Onabotulinum toxin A (Botox) for chronic migraine treatment: an Italian experience	75	6–12 months	Significant reduction in monthly headache days, medications intake, MIDAS and HIT-6 scores
Guerzoni [26]	2015	Increased efficacy of regularly repeated cycles with OnabotulinumtoxinA in MOH patients beyond the first year of treatment	57	18 months	Progressive reduction in headache frequency, pain intensity, headache disability score; overall marked improvement in HRQoL; significant reduction in anxiety and depressive symptoms (ZUNG-A and ZUNG-D scores)
Pedraza [27]	2015	OnabotulinumtoxinA treatment for chronic migraine: experience in 52 patients treated with the PREEMPT paradigm	52	6 months (1–2 IS)	76.9% of responder. Significant reduction in headache/migraine days, medication intake days and triptan intake days
Negro [28]	2015	OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study	143	2 years	Progressive significant reduction in N. of headache/migraine days, acute pain medication intake days and HIT-6 score
Negro [29]	2016	A 2 years open-label prospective study of OnabotulinumtoxinA 195 U in medication overuse headache: a real-world experience	132	2 years	Significant reduction in N. of headache/migraine days, acute pain medication intake days and HIT-6 score.
Aicua-Rapun [30]	2016	Real-life data in 115 chronic migraine patients treated with Onabotulinumtoxin A during more than one year	115	≥1 year	195 U OBT-A superior to 155 U in all efficacy measures. Discontinuation of MO (61.9%); discontinuation of concurrent preventatives (48.6%); discontinuation of OBT-A for lack of efficacy (15.7%)
Butera [31]	2016	Refractory chronic migraine: is drug withdrawal necessary before starting a therapy with onabotulinum toxin type A?	44	36 weeks	Significant improvements in N. of headache/migraine days and episodes, total cumulative headache hours, MIDAS and HIT-6 scores
Demiryurek [32]	2016	Effects of onabotulinumtoxinA treatment on efficacy, depression, anxiety, and disability in Turkish patients with chronic migraine	60	3 months (1 IS)	Significant decrease in the N. of days/severity of headaches, MIDAS disability scores Beck Depression and Beck Anxiety Inventory scores
Kollewe [33]	2016	Long-term treatment of chronic migraine with OnabotulinumtoxinA: efficacy, quality of life and tolerability in a real-life setting	27	1 year (5 IS)	96% reported benefit; significant reduction in headache/migraine days, medication days; improvements in HRQoL, migraine-specific QoL, HIT-6, BDI, GCI
Russo [34]	2016	The use of onabotulinum toxin A (Botox) in the treatment of chronic migraine at the Parma Headache Center: a prospective observational study	52	Up to 9 months	Significant reduction in headache and medication intake days
Grazzi [35]	2017	Onabotulinumtoxin A for chronic migraine with medication overuse: clinical results of a long-term treatment	>1 year	>1 year	Long-term clinical benefit

(Continued)

Table 2. (Continued).

Author	Year	Title	Patients (n)	FU duration	Main efficacy results
Matharu [36]	2017	Utilization and safety of onabotulinumtoxinA for the prophylactic treatment of chronic migraine from an observational study in Europe	1160	1 year	Confirmation of feasibility and safety of the PREEMPT protocol in real life
Andreou [37]	2018	Prospective real-world analysis of OnabotulinumtoxinA in chronic migraine post-National Institute for Health and Care Excellence UK technology appraisal	200	Up to 3 years	63.5% of 30+ responders 58% of responders reclassified as EM
Yalınay Dikmen [38]	2018	A single-center retrospective study of onabotulinumtoxinA for treatment of 245 chronic migraine patients: survey results of a real-world experience	149	Up to 1 year	82.8% of patients reporting that OBT-A was effective in controlling their headaches; mean score of perceived effectiveness (0–10) 6.94
Stark [39]	2019	Real-world effectiveness of onabotulinumtoxinA treatment for the prevention of headaches in adults with chronic migraine in Australia: a retrospective study	211	6 months (2 IS)	74% responders Significant reductions in headache days, medication intake days, HIT-6 scores
Ahmed [40]	2019	An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study	633	2 years	Significant reduction in headache-days: improvements in all MSQ domains and in EQ-5D total and health state scores
Rothrock [41]	2019	FORWARD Study: Evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine	282	36 weeks	Significantly more 50+ responders with OBT-A compared to topiramate
Blumenfeld [42]	2018	Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study	716	108 weeks	Significant reduction in headache days and significant improvements in HIT-6 scores
Young [43]	2019	Effects of onabotulinumtoxinA treatment in chronic migraine patients with and without daily headache at baseline: results from the COMPEL Study	Sub-analysis of COMPEL N = 138 vs 503	108 weeks	Reductions from baseline in headache-day frequency and improvements in disability and QoL for up to 108 weeks in CM patients with daily headache
Young [44]	2019	Effects of onabotulinumtoxinA treatment in patients with and without allodynia: results of the COMPEL study	Sub-analysis of COMPEL N = 289 vs 426	108 weeks	Reductions from baseline in multiple efficacy outcomes for up to 108 weeks whether or not allodynia was present
Ornello [45]	2020	Sustained response to onabotulinumtoxin A in patients with chronic migraine: real-life data	115	15 months	Two thirds of patients who gain $\geq 50\%$ response to OBT-A within the 3 rd cycle of treatment maintained this response over time.

FU: follow-up; IS: injection series; HIT: headache impact test; BDI: Beck Depression Inventory; MIDAS: migraine disability assessment scale; HRQoL: Health-related quality of life; OBT-A: onabotulinumtoxinA; MOH: medication overuse headache; GCI: global clinical impression; EM: episodic migraine; MSQ: migraine-specific quality of life; EQ-5D: EuroQoL-5D.

Table 3. Summary of randomized clinical trials with CGRP-targeting monoclonal antibodies in patients with chronic migraine.

Author	Year	Title	Patients (n)	FU duration	Main efficacy results
Tepper [57]	2017	Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomized, double-blind, placebo-controlled phase 2 trial	667 3 arms: erenumab 70 mg, erenumab 140 mg, placebo	12 weeks	Significant reduction in MHDs with both erenumab doses vs placebo Subgroup analysis confirmed efficacy in patients resistant to previous treatments (≥ 2) and with MO [64]
Silberstein [58]	2017	Fremanezumab for the preventive treatment of chronic migraine	875 3 arms: F 675 mg quarterly; F monthly, 675 mg at baseline then 225 mg; placebo	12 weeks	Both fremanezumab regimens significantly reduced average number of MHDs
Ferrari [59]	2019	Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomized, double-blind, placebo-controlled, phase 3b trial	509 with CM 3 arms: F quarterly, F monthly, placebo	12 weeks	Both fremanezumab regimens significantly reduced average MHDs
Detke [60]	2018	Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study	1113 3 arms: G 240 mg loading dose + 120 mg monthly; G 240 mg monthly; placebo	3 months + 9 months OLE	Both galcanezumab regimens induced greater overall mean reduction in the number of MHDs
Dodick [61]	2019	Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial	616 4 arms: eptinezumab 300, 100, 30, 10 mg or placebo	12 weeks	$\geq 75\%$ migraine responder rates at week 12 were weakly significantly higher than placebo only for the highest dose eptinezumab group ($p = 0.033$); more $\geq 50\%$ responders in the 3 highest dose groups

CGRP: calcitonin gene-related peptide; CM: chronic migraine; F: fremanezumab; FU: follow-up; G: galcanezumab; MHDs: migraine headache days; MO: medication overuse; OLE: open-label extension.

The new algorithm presented in Figures 1 and 2 is aimed at providing guidance for the management of OBT-A therapy in CM patients, taking into account that in several countries OBT-A is not approved as a 1st-line treatment, meaning that patients can be started on OBT-A only after having failed or not tolerated a specified number of previous oral medications. The decision on further patient management after the initial administration of OBT-A should be reassessed every 3 months during the first year of treatment to establish efficacy (Figure 1). After the first year of treatment, timing to reevaluate the patient is dependent on the clinical response (Figure 2), which should be evaluated using headache diaries or other outcome indicators (Table 4(A,B)) [14,22,47,48,52,53,54,55,68,69,70,72–77]. As additional efficacy/benefit indicators, we identified the following: headache intensity, intake of acute medications, headache-related disability, QoL, and patient-reported impression of effectiveness. The assessment of all levels of response should refer to the changes from baseline and should be performed using validated tools, e.g. a categorical, 4-level rating scale or 11-point numerical rating scale to rate the intensity of headache [78], MIDAS or HIT-6 score for disability [79,80], MSQ for QoL [81], PGCI for patient's impression of efficacy [82].

For the proposed treatment algorithm, patients are classified as:

- 75+ responders when they experience a $\geq 75\%$ reduction in headache days from baseline or a $\geq 75\%$ improvement in one of the efficacy/benefit indicators listed above. These subjects are defined as *excellent responders*.
- 50+ responders, when they experience a reduction in headache days from baseline ranging from $\geq 50\%$ to

$<75\%$ and/or experience an improvement ranging from $\geq 50\%$ to $<75\%$ in one of the efficacy/benefit indicators listed above. These subjects are defined as *good responders*.

- 30+ responders, when they experience a reduction in headache days from baseline ranging from $\geq 30\%$ to $<50\%$ and this is associated to a clinically meaningful improvement in at least one of the efficacy/benefit indicators indicated above. These subjects are defined *low responders*.
- Non-responders when they experience $<30\%$ reduction in headache days from baseline and no improvement in the other outcome indicators.

3.1. Excellent responders

After the first injection of OBT-A 155 U, the dose can be kept steady or escalated to 195 UI to consolidate the clinical response (Figure 1). We suggest administering 155–195 U injection every 3 months for 1 year. During the second year, if the excellent response persists, we suggest increasing the inter-injection interval to 4 months (Figure 2). After the second year, discontinuation may be considered for patients showing stable clinical improvement also with the increased (4-month) inter-injection period (Figure 2).

3.2. Good responders

After the first injection of OBT-A 155 U, we suggest increasing the dose to 195 U at the second cycle to try to improve the

**Proposal of a treatment algorithm for chronic migraine (according to ICHD-III)
according to the physicians' judgement**

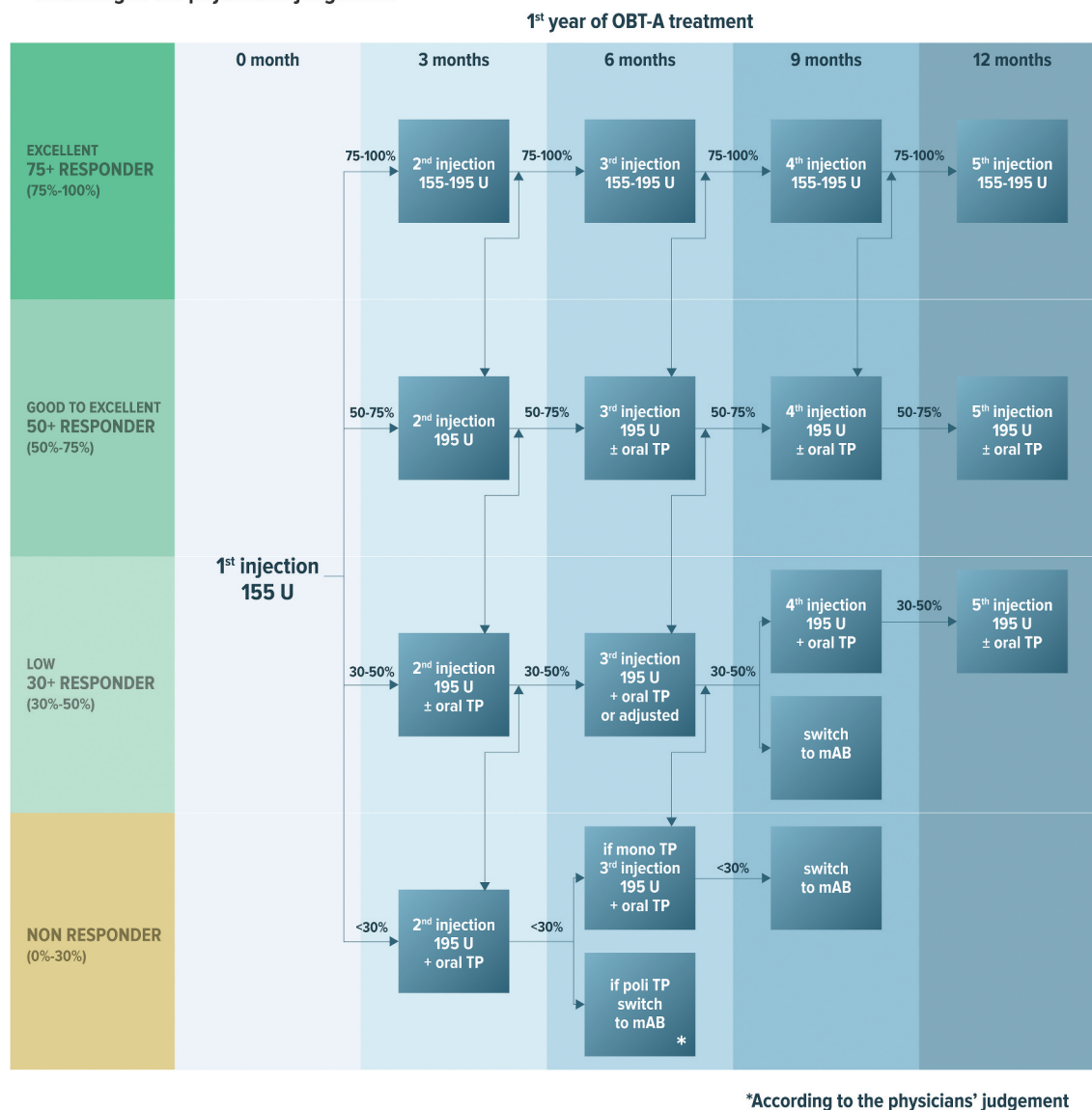


Figure 1. Proposed treatment algorithm for the preventive treatment of chronic migraine according to the clinical response. TP: Therapy; mAB: monoclonal antibodies; 75+ responder: $\geq 75\%$ reduction in headache days and/or equivalent improvement in one of the efficacy/benefit indicators (see text); 50+ responder: $\geq 50\%$ and $< 75\%$ reduction in headache days and/or equivalent improvement in one of the efficacy/benefit indicators; 30+ responder: $\geq 30\%$ and $< 50\%$ reduction in headache days and/or equivalent improvement in one of the efficacy/benefit indicators; Nonresponder: $< 30\%$ reduction in headache days and no improvements in any of the efficacy/benefit indicators. All patients should be assessed for response to treatment (changes from baseline) using a headache diary and validated tools for the detection of the other efficacy/benefit indicators.

clinical response (Figure 1). Thereafter, patients who further improve will follow the algorithm for excellent responders; for those who remain good-responders, we suggest considering the addition of a second drug starting from the third injection cycle onward in order to further improve clinical outcomes. In more detail, if the number of monthly headache days is consistently < 8 with OBT-A 195 U, OBT-A can be continued as monotherapy; if the monthly headache days are ≥ 8 , we suggest the addition of a second preventative therapy (Figure 1). The second preventative should be selected considering the clinical and pharmacological history and comorbidities of the patient. The second preventative drug can theoretically be represented by a CGRP-targeting mAB, though evidence in

favor of the association is currently lacking and local regulations may not allow the combination.

In patients who have benefited from this treatment approach, OBT-A should be administered every 3 months also during the second year of treatment (Figure 2). During the third year of treatment, the inter-injection interval of OBT-A 195 U administrations can be tentatively increased to 4 months.

3.3. Low responders

In patients qualifying in this group after the first injection of OBT-A 155 U, we suggest increasing the dose to 195 U during the second injection and considering to add an oral

Approach after the first year of treatment

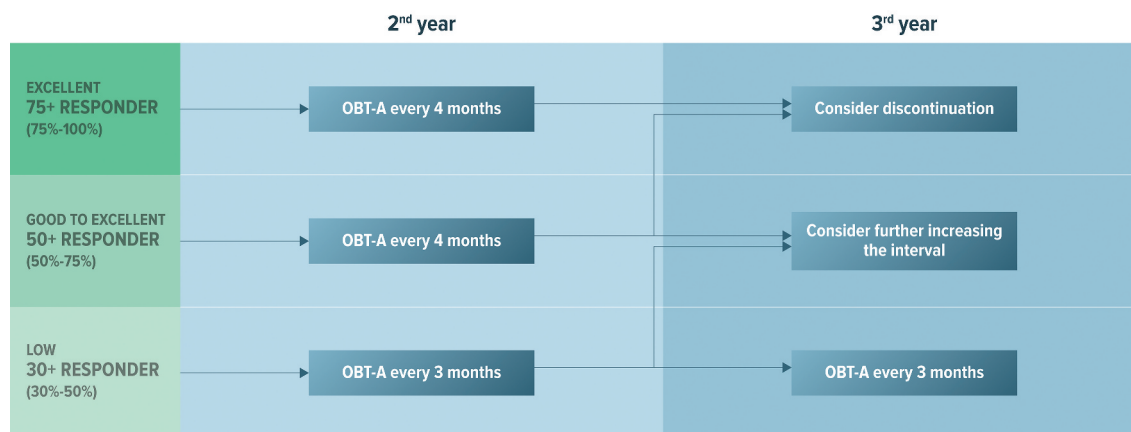


Figure 2. Proposed treatment algorithm for the use of onabotulinumtoxinA for preventive treatment of chronic migraine after the first year according to the clinical response.

Table 4. Criteria of response to treatments in chronic migraine from the literature.

A. Definitions of response to CM treatment	Reference
≥50% reduction in migraine days or ≥30% reduction of migraine days or of headache days with moderate-severe headache	Silberstein [71]
≥30% reduction in headache days per month after two treatment cycles	NICE [67]
50% reduction in headache/migraine days or an increment in headache-free days twice that of the baseline in a 30-day period	Khalil [22]
< 30% reduction in migraine days, provided it is accompanied by improvement ≥ in another efficacy variable among: a) patient satisfaction with treatment; b) QoL; c) intensity of headache pain; d) use of medication for symptom relief; and e) duration of headache attacks	Tassorelli [47]
2-day reduction in headache days as minimal clinically meaningful change	Aurora [52]
Clinically meaningful change defined as having positive and meaningful impact on patient's life	Dodick [14]
B. Other indicators	Reference
Reduction in migraine/headache days	Dodick [72]
Reduction in headache pain intensity or duration	Bendtsen [48]
Reduction in medication intake	Silberstein [73]
Improvement in HRQoL	Lipton [53]
Migraine disability assessment scale (MIDAS)	Stewart [74]
Headache Impact test-6 (HIT-6)	Haywood [75]
Patient's satisfaction with treatment	Ford [76]

CM: chronic migraine; HR-QoL: health-related quality of life; QoL: quality of life.

preventive (Figure 1) or modifying the dosage of the oral therapy in the first course. For patients who achieve a good response with this approach, we suggest following the algorithm for good responders. For those who continue to be low responders, there are two possible options: 1) to continue with OBT-A plus oral preventative or 2) to switch to an approved CGRP-targeting mAb.

In patients who show partial improvement with the former approach, we suggest maintaining the combined OBT-A+ oral prevention approach for at least 1 year if patients are good or near-good responders (Figure 1). During the second year of treatment, we suggest trying to taper off the oral drug, while continuing OBT-A. During the third year of treatment, only in cases of good-to-excellent response, it will be possible to increase the inter-injection interval of OBT-A 195 U to 4 months (Figure 2). Conversely, if there is a fluctuation between good and low response, we suggest continuing OBT-A at 3-month intervals.

For patients who remain low responders after 2 cycles of OBT-A in association with an oral treatment, we suggest stopping OBT-A and switching to a CGRP-targeting mAb (Figure 1).

3.4. Non-responders

For non-responders after one injection of OBT-A 155 U, we suggest increasing the OBT-A dose to 195 U at the second injection and adding an oral preventative (Figure 1). In patients who are still non-responders after 2 cycles of OBT-A with the combination of oral treatment for at least 3 months, we suggest switching to a CGRP-targeting mAb. If there is some improvement at 6 months, but the response is still low, we suggest following the algorithm for low responders, and thus to go ahead with a further OBT-A injection, then consider maintaining or withholding treatment, taking into consideration the clinical response at 9 months.

4. Discussion

The primary objective of treating CM is to reduce the frequency and duration of headache attacks and migraine-related disability, to decrease the burden of the disease and its impact on patients' lives [83,84]. OBT-A is the first treatment specifically approved for the prevention of CM in the European Union and guidelines recommended

preventive medication for CM [48,67,68]. However, further significant progress is currently being made in the preventive treatment of migraine, prompting clinicians to rethink the treatment algorithm for CM in the light of the new preventive therapies.

The first issue under discussion is the definition of responders, given that, as previously pointed out, several different definitions are available in the literature, and there is not a generally accepted one. This appears also to be confirmed in clinical practice. The previously mentioned 2017 Italian survey [84] revealed that nearly 60% of participants, i.e., representing 46 third-level headache centers experienced in the use of OBT-A in CM according to the PREEMPT protocol, defined response to treatment with OBT-A as a $\geq 50\%$ reduction from baseline in the number of headache days (50+ responders), while one-quarter of them defined it as a $\geq 30\%$ reduction (30+ responders). The remaining 15% also considered as response a reduction in headache days lower than 30% (<30-responders) if it was associated with the improvement of at least another efficacy variable, such as patient satisfaction with treatment, intensity of headache, use of medications for symptom relief, and duration of headache attacks [84]. The patients' perspective also emerged from the survey. In the opinion of their physicians, patients placed more value on an improvement in their QoL rather than in a simple reduction in headache days. While not hard clinical outcomes, the relevance of such patient-reported outcomes should not be underestimated, especially since they are important for patient and may also reflect isolated improvement in pain.

Another question still being debated is whether it is appropriate to administer further courses of treatment in case of low or non-response to the first course of OBT-A. Analyzing the pooled data of the PREEMPT program, approximately 10% of non-responders to the first OBT-A cycle responded to each of the two subsequent cycles [74]. Real-life studies have also shown progressive improvements with continuous OBT-A treatment [26,29]. As a general rule, the expert group agreed on the administration of at least one additional course of OBT-A at an increased dosage (195 U) in all patients who receive a first administration of a 155-U dose. It is further recognized that patient-reported outcomes such as MIDAS and HIT-6, as well as general quality of life indicators, are heterogeneous measures that are quantitatively different. It is also possible that the different scales do not give equal weight to headache intensity and frequency. Despite this possible shortcoming, different outcome measurements nonetheless provide valuable information on the efficacy of different treatments and help to categorize responses to various therapies. While it is possible that a decrease in headache intensity alone might be a good outcome measure for efficacy, this has been poorly tested to date.

Regarding the optimal treatment duration in responders, some evidence from real-world studies suggests that discontinuing treatment in responding patients may lead to worsening of the disease [24,26]. The Italian survey found that the most frequent duration of OBT-A therapy in clinical practice is 1 year, with a tendency to enlarge the interval between cycles when prolonging treatment beyond 1 year [84]. When considering that CM is an aggressive type of migraine that tends

to be treatment-resistant and to relapse over time, it is reasonable and ethical to consider prolonging OBT-A treatment into the second year in excellent responders, and into the third year in less brilliant responders, while putting in place corrective measures, such as distancing of cycles in patients showing a satisfactory improvement, or adding additional drugs in those with limited improvement.

5. Conclusions

Oral migraine preventive medications are the first-line treatment for patients with frequent debilitating migraines, but most evidence on the efficacy of these medications in CM is extrapolated from studies in patients with high-frequency EM [85,86]. Of note, in patients with CM, poor adherence to therapy is mostly due to insufficient effectiveness [87,88]. However, combining treatments for migraine prevention when a patient has an inadequate response to a single therapy, although supported by limited evidence, is a common practice in the clinical setting [45]. We considered that approved oral medications could be a potentially useful add-on therapy in CM patients partially responding to OBT-A, if not tried before and not contraindicated. Erenumab, fremanezumab, and galcanezumab ameliorate CM, reducing the number of headache/migraine days and the days of intake of acute medications, and improving disability, with a favorable safety profile [57–60,62,63].

Until now, clinical data on the association of CGRP-targeting mAbs and OBT-A are lacking. Initial real-life data suggest that patients who are OBT-A non-responders may benefit from the combined therapy with CGRP-targeting mAbs [64]. However, there is still a proportion of patients who are non-responders to CGRP-targeting mAbs or OBT-A alone. Patients with refractory migraine are a noticeably difficult-to-treat subgroup [89]. In those patients, further studies are needed to understand the possible benefits of combining the two treatments. Even in the current absence of clinical evidence, we think that the combination of OBT-A with monoclonal antibodies targeting CGRP may provide clinical benefit to a subset of treatment-refractory CM patients and may be ethically indicated when all other options have proved ineffective. The association of OBT-A with anti-CGRP treatments should be assessed, in our opinion, on solid efficacy outcomes, such as decrease in headache days and use of acute medications. Assessing the combined efficacy of two potent anti-migraine injectables is problematic if it is based solely upon patient-reported outcomes. Demonstrating this will require well-designed observational studies based on solid outcome assessments, given that OBT-A and anti-CGRP are both very effective treatments.

6. Expert opinion

The treatment of CM is a dynamic and rapidly evolving area of research, and significant advances have been made in the preventive treatment of CM. Clinicians managing patients with migraine now have multiple choices ranging from oral medications to OBT-A and CGRP-targeting mAbs. Strong evidence supports the efficacy of OBT-A and CGRP-targeting mAbs, while the

level of evidence in favor of oral treatments is limited. The benefit of OBT-A in CM has been established in real-life studies, as well as RCTs, but it is important to establish the optimal treatment duration and to determine whether patients are responding to OBT-A, as different durations of treatment or higher doses may be required to allow the full benefits of treatment to emerge, and there may be issues of worsening rebound following treatment interruption. To optimize patient outcomes, it is crucial that treatment is continued at an appropriate dosage for an adequate period of time, and it is also important to know when to continue or discontinue treatment when a patient appears as not responding, or whether there is value in adding another therapy to OBT-A.

Besides scientific evidence, the choice of drugs in everyday practice needs to be shaped by adherence to regulatory indications, ethical considerations, and the expertise of clinicians. The availability of an individualized treatment algorithm that acknowledges all of these aspects and incorporates them into a ready-to-use, practical guidance for physicians who undertake the difficult challenge of improving the health and the life of CM patients is extremely useful, as it is our belief that even partial improvements in these patients are extremely important and clinically meaningful.

The treatment algorithm presented here is the result of the collaborative efforts of an expert panel of Italian headache specialists with extensive expertise in the management of patients with migraine. The algorithm also has relevance for patients with medication-overuse headache. It represents an evidence- and experience-based synthesis of clinical information that provides a practical tool for clinicians to guide and individualize their approach to the management of this difficult-to-treat patient group. Many of our suggestions, including the classification of responders, some of the suggested outcomes to evaluate, and the possibility of prolonging the time intervals between the doses of OBT-A are based upon common clinical practice and not entirely evidence-based. Nevertheless, our suggestions might serve as a basis for commonly accepted guidelines, subject to field testing and further improvement.

Although the algorithm enhances the decision-making process for determining OBT-A dosage and injection interval based on clearly defined responder profiles and provides options for the addition of other therapies, including CGRP-targeting mAbs, the management of CM remains challenging. However, our understanding of the pathophysiology of migraine is rapidly advancing, and ongoing research will provide new insights into the genetic causes, anatomical and physiological aspects, and disease mechanisms of CM. Identification of additional therapeutic targets and a better understanding of how the different pharmacological interventions can be best combined will possibly allow more efficacious and individualized treatments for this disabling condition.

Acknowledgments

Medical writing support was provided by Renata Perego on behalf of Health Publishing & Services srl. The authors thank Ray Hill, an

independent medical writer, who provided English-language editing and journal styling prior to submission on behalf of Health Publishing & Services Srl.

Reviewer disclosures

A peer reviewer on this manuscript has received grants for research (no personal compensation) from: Alder, Allergan, Amgen, Dr. Reddy's, ElectroCore, Eli Lilly, eNeura, Neuroief, Novartis, Satsuma, Scion Neurostim, Teva and Zosano. They have also acted as a consultant and/or on advisory boards (honoraria) for: Acorda, Aeon, Alexsa, Align Strategies, Allergan, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, Charleston Labs, CRG, Currax, Decision Resources, DeepBench, Eli Lilly, eNeura, Equinox, ExpertConnect, GLG, GSK, Guidepoint Global, Healthcare Consultancy Group, Health Science Communications, Impel, Lundbeck, M3 Global Research, Magellan Rx Management, Marcia Berenson Connected Research and Consulting, Medicxi, Navigant Consulting, Neuroief, Nordic BioTech, Novartis, Pulmatrix, Reckner Healthcare, Relevale, Revance, SAI MedPartners, Satsuma, Scion Neurostim, Slingshot Insights, Sorrento, Spherix Global Insights, Sudler and Hennessey, Synapse Medical Communications, Teva, Theranica, Thought Leader Select, Trinity Partners, XOC, Zosano. They receive a salary from Dartmouth-Hitchcock Medical Center and the American Headache Society. This reviewer also holds stock options in Nocira and Percept and has received CME honoraria from: American Academy of Neurology, American Headache Society, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital, Ontario, Canada, Headache Cooperative of New England, Henry Ford Hospital, Detroit, Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians' Education Resource, Rockpointe, ScientiaCME and WebMD/Medscape. Another reviewer on this manuscript has consulted for Allergan/Abbvie, Aeon, Supernus and Revance all of whom manufacture/sell neurotoxins. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Funding

Technical editing and publication fees were funded by Allergan plc, Dublin, Ireland, at the request of the investigator.

Declaration of interest

S Sacco has received fees as speaker or for participation to advisory boards from Abbott, Allergan, Eli-Lilly, Medscape, Novartis, Teva. C Tassorelli has participated in advisory boards or lectured at symposia sponsored by Allergan, Eli Lilly, Novartis and Teva; she has lectured at symposia sponsored by Allergan, Eli Lilly, Novartis and Teva; she is principal investigator or collaborator in clinical trials sponsored by Alder, Eli-Lilly, Novartis and Teva. She has received research grants from the European Commission, the Italian Ministry of Health and the Italian Ministry of University. P Geppetti has received personal fees and non-financial support from Allergan, Electrocore, Eli Lilly, IBSA, Novartis, Pfizer, Sanofi, TEVA; non-financial support from Amgen, Chiesi; Scientific Advisory Board, Endosome Therapeutics; FloNext srl, shareholder; Associate Editor Physiological Reviews, Pain, Pain Therapeutics; The Journal of Headache and Pain. A Negro has participated in advisory boards or lectured at symposia sponsored by Allergan, Eli Lilly, Novartis and Teva; he is collaborator in clinical trials sponsored by Allergan, Novartis and Teva; he is in the Editorial Board of Neurology and Therapy and The Journal of Headache and Pain. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

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