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Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT

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ABSTRACT

Objective The approved use of onabotulinumtoxinA for prophylaxis of headaches in patients with chronic migraine (CM) involves treatment every 12 weeks. It is currently unknown whether patients who fail to respond to the first onabotulinumtoxinA treatment cycle will respond to subsequent treatment cycles. To help inform decisions about treating non-responders, we examined the probability of treatment cycle 1 non-responders responding in cycle 2, and cycle 1 and 2 non-responders responding in cycle 3.

Methods Pooled PREEMPT data (two studies: a 24-week, 2-cycle, double-blind, randomised (1:1), placebo-controlled, parallel-group phase, followed by a 32-week, 3-cycle, open-label phase) evaluated onabotulinumtoxinA (155–195 U) for prophylaxis of headaches in persons with CM (≥ 15 days/month with headache ≥ 4 h/day). End points of interest included the proportion of study patients who first achieved a $\geq 50\%$ reduction in headache days, moderate/severe headache days, total cumulative hours of headache on headache days, or a ≥ 5 -point improvement in Headache Impact Test (HIT)-6. For treatment cycle 1, all eligible participants were included. For subsequent cycles, responders in a previous cycle were no longer considered first responders.

Results Among onabotulinumtoxinA-treated patients ($n=688$) 49.3% had a $\geq 50\%$ reduction in headache-day frequency during treatment cycle 1, with 11.3% and 10.3% of patients first responding during cycles 2 and 3, respectively. 54.2%, 11.6% and 7.4% of patients first responded with a $\geq 50\%$ reduction in cumulative hours of headache, and 56.3%, 14.5% and 7.7% of patients first responded with a ≥ 5 -point improvement in total HIT-6 during treatment cycles 1, 2 and 3, respectively.

Conclusions A meaningful proportion of patients with CM treated with onabotulinumtoxinA who did not respond to the first treatment cycle responded in the second and third cycles of treatment.

Trial registration number NCT00156910, NCT00168428.

INTRODUCTION

Chronic migraine (CM) is a debilitating neurological disorder that affects approximately 2% of the general population.^{1–3} CM is currently defined as headache on 15 or more days per month, for more than 3 months, which has the features of migraine headache on at least 8 days/month.⁴ CM is associated with

significant disability and reduced health-related quality of life,^{2,5} but treatment options are currently limited.^{6,7} The only agent approved in patients with CM for use as headache prophylaxis is onabotulinumtoxinA. OnabotulinumtoxinA is typically given every 12 weeks following the standard treatment protocol and dose used in the Phase III studies and described on the approved labelling.

Migraine attacks may occur over a number of years, and the benefits of many preventive treatments develop slowly, over weeks to months.⁸ In patients who have not yet demonstrated a robust response, clinicians must decide whether to continue treatment or move on to another therapy. Since onabotulinumtoxinA is administered every 12 weeks, decisions about continuing therapy are made based on response in the past 4 weeks of a 12-week treatment cycle. The decision to offer a second treatment cycle in patients who do not respond to the first cycle should be based in part on research regarding the proportion of patients who do not respond to the first cycle but subsequently respond in treatment cycle 2. Similarly, the decision to offer a third cycle of treatment should be informed by data concerning the proportion of patients who do not respond in treatment cycles 1 and 2 who do respond in cycle 3.

The Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical programme is a combination of the two largest clinical trials of the CM population. These well-designed, placebo-controlled trials showed results that, among patients with CM, onabotulinumtoxinA was effective, safe and well tolerated in the treatment of headaches.^{9–11} Across the 56-week trial, patients treated with onabotulinumtoxinA were shown to have better outcomes compared with placebo-treated patients.⁹ However, it is unclear whether patients who fail to respond to the first onabotulinumtoxinA treatment cycle will respond to subsequent treatment cycles.

In this context, the definitions of response and responder rates are crucial.¹² In many headache studies, the proportion of patients who achieve a $\geq 50\%$ reduction in a headache outcome measure relative to baseline is often used. This $\geq 50\%$ responder rate has traditionally been considered clinically meaningful in episodic migraine (EM).^{13,14} A $\geq 30\%$ reduction from baseline in headache symptom measures has been suggested to be clinically meaningful in studies of CM because

of the greater severity and complexity of CM relative to EM.¹³ Farrar *et al*¹² identified a 30% change on the pain scale as a clinically meaningful change. In the present report, we evaluated $\geq 50\%$ and $\geq 30\%$ responder rates using a number of end point measures.

Using $\geq 50\%$ responder rates as our outcome of primary interest, we examined response rates to the first treatment cycle on measures of headache days, moderate to severe headache days, and hours of headache on headache days, as well as a change in the Headache Impact Test (HIT)-6 score of ≥ 5 points. For each end point, we examined the proportion of all onabotulinumtoxinA patients who first became responders in cycle 2, even though they did not achieve 'responder' status in the first treatment cycle. For those who did not respond in either treatment cycle 1 or 2, we examined rates of first responders in cycle 3 among all onabotulinumtoxinA patients. Finally, we repeated these analyses using a more liberal definition of response ($\geq 30\%$ improvement) to define response for each of the three key end points (headache days, moderate to severe headache days and hours of headache on headache days). We hope that these data will help clinicians make decisions about when to continue onabotulinumtoxinA treatment in the setting of lack of response to initial treatment.

METHODS

Study design

The PREEMPT study design and methodology have been described in full in the primary publications.^{9,10} There were two multicentre trials in the PREEMPT clinical programme: PREEMPT 1 (NCT00156910),¹⁵ in 56 North American sites, and PREEMPT 2 (NCT00168428),¹¹ in 66 North American and European sites. Each Phase III trial started with a 28-day baseline screening period, which was followed by a 24-week, double-blind, placebo-controlled phase (2 treatment cycles) and then a 32-week, open-label phase (3 treatment cycles; figure 1).¹⁰ Each day, patients recorded their headache symptoms and their intakes of acute headache medications, using an interactive voice response telephone diary. Study visits were every 4 weeks.¹⁰ Before the study was initiated, each investigator acquired approval from an Independent Ethics Committee or a local Institutional Review Board.¹⁰

For the double-blind, placebo-controlled phase, patients were randomised (1:1) to onabotulinumtoxinA (155–195 U) or placebo (0.9% saline without preservative).^{9,10} Overuse of acute headache medication during the 28-day baseline was used to stratify patients for further analysis. In the PREEMPT studies, the definition of

'medication overuse' was baseline intake of simple analgesics on ≥ 15 days, or other medication types or combinations of types for ≥ 10 days, with intake on ≥ 2 days/week from the category of overuse. Administration of the study medication was performed as 31 fixed-site, fixed-dose, intramuscular injections across seven pre-specified head and neck muscle areas every 12 weeks for 24 weeks (2 treatment cycles).¹⁰ Investigators had the option of administering an additional 40 U of onabotulinumtoxinA or placebo among three muscle groups (occipitalis, temporalis or trapezius; a total of 8 sites) using a follow-the-pain strategy as defined in the protocol.¹⁶ In each treatment cycle, the maximum total dose of onabotulinumtoxinA was 195 U in 39 injection sites.^{10,16} During the open-label phase, patients who had completed the double-blind, placebo-controlled phase were eligible for treatment with onabotulinumtoxinA at weeks 24, 36 and 48.⁹

These post hoc analyses focus on onabotulinumtoxinA because the goal was to determine whether patients become responders with additional onabotulinumtoxinA treatments. Response was defined as a $\geq 50\%$ improvement from the 4-week pretreatment baseline to any of the three 4-week periods during a treatment cycle. Key outcomes were a $\geq 50\%$ reduction in headache days, a $\geq 50\%$ reduction in moderate/severe headache days, a $\geq 50\%$ reduction in total cumulative hours of headache on headache days and a ≥ 5 -point improvement in HIT-6 scores.¹⁷ Additional outcomes were a $\geq 30\%$ reduction/improvement in the first three measures.

Study participants

Eligibility criteria have been described in more detail in the primary pooled studies.^{11,15} Patients had to be 18–65 years of age to enrol, and have had a history of migraine, excluding 'complicated migraine,' as defined in Section 1 of the International Classification of Headache Disorders (ICHD)-II.¹ During baseline, participants had to have headache occurring on at least 15 days over 4 weeks, with each day consisting of four or more hours of continuous headache, and at least 50% of headache days being migraine or probable migraine days (referred to as migraine days).¹⁰ They also had to experience at least four separate headache episodes, with each episode during this period lasting four or more hours. Patients were not allowed to use prophylactic medication for headaches in the 4 weeks before the 28-day baseline period or thereafter; however, patients were not excluded if they overused acute medications during baseline (with overuse defined as in the protocol). No patients could have previously received any serotype of botulinum toxin.

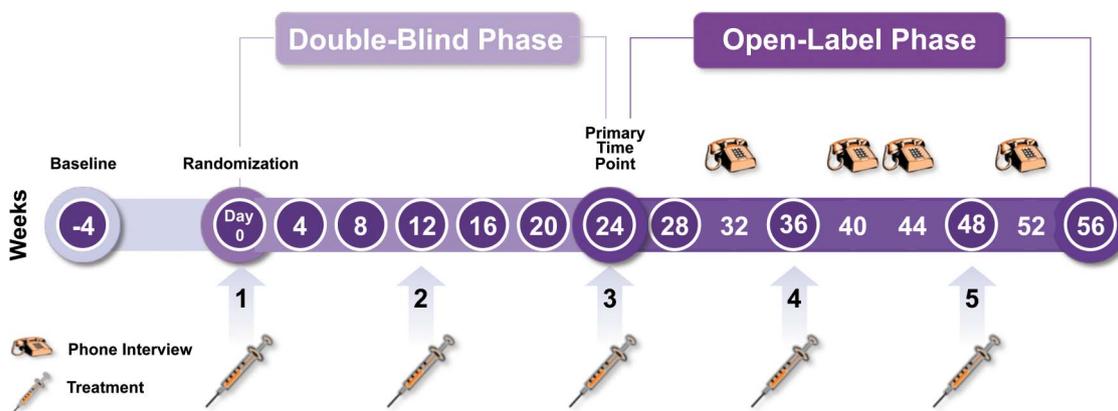


Figure 1 Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) study design. Reprinted from ref. 10.

Statistical analyses

Previous publications have discussed the statistical methodology used for pooling the PREEMPT data for an integrated analysis of efficacy and safety.^{9–10} All efficacy analyses used the intent-to-treat population including all randomised patients (analysed as randomised rather than as treated). The two studies were run almost simultaneously under essentially identical data-collection protocols. In this post hoc analysis, first-time responders for a given treatment cycle were defined as patients who had never responded to any previous treatment cycle. Notably, the denominators were not decreased for patients who had previously responded; thus, the responder rates are additive across treatment cycles. A prespecified modified last-observation-carried-forward methodology (mLOCF) was used to impute missing data.

The impact of headache on psychological distress, functioning and vitality was measured using change from baseline in the HIT-6 score, and responders were defined as patients with a change from baseline in the individual HIT-6 score of ≥ 5 points, which is considered a clinically meaningful improvement for an individual patient.¹⁸ As described above, the additive first-time responder proportions for a given treatment cycle were based on the count of responders who had not responded to any previous treatment cycle; the denominators were not decreased for previous responders. From the additive first-responder proportions, the conditional first-responder proportions are simply the ratio of the first-responder proportion to the quantity one minus the cumulative first-responder proportions across previous treatment cycles.

Safety

Safety and tolerability analyses were previously performed on all patients who received at least one dose of study medication.^{9–11 15} Additional safety and tolerability findings were not a part of this post hoc analysis.

RESULTS

Demographic and baseline headache characteristics

A total of 1384 adults were randomised to onabotulinumtoxinA (n=688) or placebo (n=696). Baseline patient demographics and headache characteristics were similar between the onabotulinumtoxinA and placebo groups (table 1).^{9–10} Among outcome measures examined herein at baseline, significant imbalances were observed for total cumulative hours of headache on headache days (table 1), which, as published previously, is consistent with baseline demographics of the PREEMPT intent-to-treat population.^{9–10} The most frequently ($\geq 20\%$) used prestudy headache prophylactic medications included anticonvulsants (primarily topiramate), followed by antidepressants (primarily amitriptyline), non-selective monoamine reuptake inhibitors, β -blockers (primarily propranolol) and fatty acid derivatives.

Improvement in multiple headache symptom measures

Overall, a high proportion of onabotulinumtoxinA-treated patients had a $\geq 50\%$ improvement from baseline in one or more of the responder criteria variables in the first treatment cycle, and additional patients became $\geq 50\%$ responders with subsequent onabotulinumtoxinA treatment cycles (table 2). Forty-nine per cent of onabotulinumtoxinA patients showed a $\geq 50\%$ improvement in headache days after the first treatment cycle. An additional 11% of the entire baseline cohort who did not respond at that level after the first treatment cycle responded after the second treatment cycle, and another 10% first

Table 1 Pooled patient baseline demographics and characteristics¹⁰

	OnabotulinumtoxinA (n=688)	Placebo (n=696)	p Value
Mean age, years	41.1	41.5	0.579
Female, %	87.6	85.2	0.185
Caucasian, %	89.7	90.5	0.602
Mean headache days	19.9	19.8	0.498
Mean moderate/severe headache days	18.1	18.0	0.705
Mean total cumulative hours of headache occurring on headache days	295.93	281.22	0.021
Mean total HIT-6 score*	65.5	65.4	0.638
Patients with severe (≥ 60) HIT-6 score, %*	93.5	92.7	0.565
Patients overusing acute headache medications, %†	64.8	66.1	0.450

*HIT-6 scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; 60–78, severe impact.

†Patients must have taken acute headache medication at least twice per week in any week with ≥ 5 diary days and on ≥ 10 –15 days (depending on the medication category) during the baseline period.
HIT, Headache Impact Test.

responded at that level after the third treatment cycle (table 2). Similarly, more than half of the patients (53%) had a $\geq 50\%$ response in moderate/severe headache days after the first treatment cycle, another 13% responded after the second treatment cycle, and 9% first responded after the third treatment cycle. Also, more than half of the patients (54%) were responders for total cumulative hours of headache on headache days after the first treatment cycle; another 12% of patients responded after the second treatment cycle, and an additional 7% responded after the third treatment cycle. The results for $\geq 50\%$ responders to the first and second treatment cycles for all headache measures are shown in figure 2. Additionally, a high proportion of patients had a $\geq 30\%$ improvement from baseline in one or more of the responder criteria variables in the first treatment, and additional patients who had not responded in the first treatment cycle became responders during the second or third treatment cycle. Results for $\geq 30\%$ responders are shown in table 3.

≥ 5 -Point improvement in HIT-6 scores

More than half of the patients (56%) in the onabotulinumtoxinA group demonstrated a clinically meaningful¹⁸ ≥ 5 -point improvement from baseline in the total HIT-6 score in the first treatment cycle (table 4). Additional patients who failed to demonstrate a ≥ 5 -point improvement from baseline in the total HIT-6 score in the first treatment cycle first did so in the second (15% of onabotulinumtoxinA-treated patients) or third (8%) cycle (table 4).

DISCUSSION AND CONCLUSIONS

Previous analysis of the PREEMPT clinical programme demonstrated that patients who improve with onabotulinumtoxinA treatment continue to improve over time; at week 56, patients treated earlier with onabotulinumtoxinA had better outcomes.¹⁹ These findings demonstrate the benefit over time of repeated treatment with onabotulinumtoxinA. We performed this post hoc analysis to determine the probability of response to the second treatment cycle, given a lack of response to the first cycle, and to determine the probability of response to the third

Table 2 Per cent of first-time responders* with a $\geq 50\%$ improvement from baseline in treatment cycles 1–3 for multiple headache outcome measures

$\geq 50\%$ First-time responders, variable	OnabotulinumtoxinA (n=688)		
	Treatment cycle 1	Treatment cycle 2	Treatment cycle 3
Frequency of headache days, n (%)	339 (49.3)	78 (11.3)	71 (10.3)
95% CI	45.5% to 53.0%	9.0% to 13.7%	8.1% to 12.6%
Frequency of moderate/severe headache days, n (%)	365 (53.1)	90 (13.1)	59 (8.6)
95% CI	49.3% to 56.8%	10.6% to 15.6%	6.5% to 10.7%
Total cumulative hours of headache on headache days, n (%)	373 (54.2)	80 (11.6)	51 (7.4)
95% CI	50.5% to 57.9%	9.2% to 14.0%	5.5% to 9.4%

*First-time responders for a given time point are patients who never responded at any previous time points.

treatment cycle, given a lack of response to the first two cycles. We believe these data may be helpful for physicians who want to optimise onabotulinumtoxinA treatment plans for patients with CM who have not responded to initial treatment cycles.

Combined data from the PREEMPT studies provide the largest CM clinical trials data set collected to date for examining issues of onset of treatment effects. The analysis in this paper is consistent with earlier findings showing onabotulinumtoxinA to be an effective prophylactic treatment for CM; onabotulinumtoxinA is shown to demonstrate clinically meaningful improvements during the first treatment cycle in multiple headache symptom measures, as defined by a $\geq 50\%$ improvement in a headache measure.^{13 14} Forty-nine per cent of patients demonstrated a $\geq 50\%$ improvement for frequency of headache days, and 54% of patients demonstrated a $\geq 50\%$ improvement in cumulative headache hours on headache days. Of the patients who did not gain a benefit of a $\geq 50\%$ response after the first treatment cycle, 11% and 12% of all onabotulinumtoxinA patients achieved a $\geq 50\%$ improvement after the second treatment cycle, and 10% and 7% reached a $\geq 50\%$ improvement after the third treatment cycle in headache-day frequency and cumulative headache hours on headache days, respectively. The additive first-responder proportions (table 1) imply conditional

first-responder percentages of 22% and 26% of previous non-responders, respectively, for the second and third treatment cycles. Similarly, for a responder threshold of 30% improvement in headache-day frequency (table 3), the additive first-responder proportions imply conditional first-responder percentages of 33% and 28% of previous non-responders, respectively, for the second and third cycles.

In addition, 56% of patients responded with an improvement in headache impact (≥ 5 -point improvement from baseline in the total HIT-6 score) during the first treatment cycle. Another 15% responded to this measure of disability during the second treatment cycle, and an additional 8% responded during the third treatment cycle (figure 2 and table 4). Correspondingly, the conditional first-responder percentages were 33% and 26% of previous non-responders, respectively, for the second and third treatment cycles.

These analyses suggest that patients with CM who do not have the desired treatment response after the first cycle of onabotulinumtoxinA treatment may indeed experience clinical improvement after one or two additional treatments, as indicated by a robust clinical improvement (a $\geq 50\%$ improvement from baseline), as well as significantly reduced headache-related disability and improved functioning and overall quality of life.¹⁹ Although many patients will respond after the first treatment, for those who do not respond initially, it is important to continue therapy for an additional 1–2 cycles before categorising patients as non-responders.

The PREEMPT clinical trials were well designed, and a large number of patients completed the study. The large sample size leads to relatively precise estimates of first-responder rates. We are using the active treatment arm of the clinical trial to mimic a clinical experience. The study supports the inference that

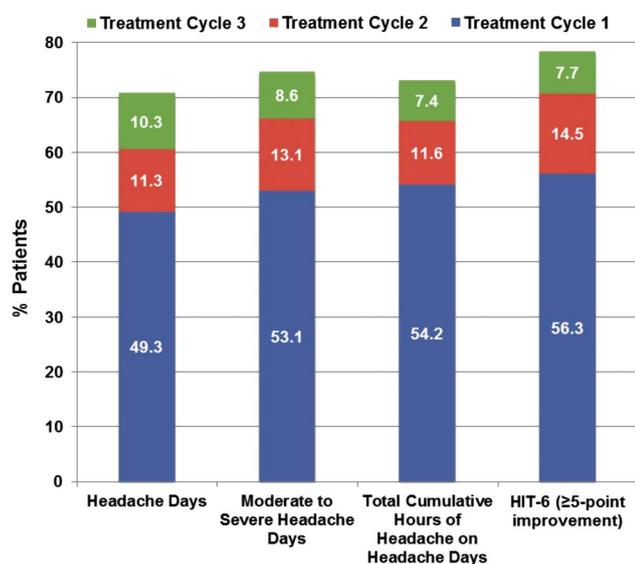


Figure 2 Per cent of first-time responders* with a $\geq 50\%$ improvement from baseline in treatment cycles 1, 2 and 3 for multiple headache outcome measures (HIT, Headache Impact Test). *First-time responders for a given time point are patients who never responded at any previous time points.

Table 3 Per cent of first-time responders* with a $\geq 30\%$ improvement from baseline in treatment cycles 1–3 for multiple headache symptom measures

$\geq 30\%$ First-time responders, variable	OnabotulinumtoxinA (n=688)		
	Treatment cycle 1	Treatment cycle 2	Treatment cycle 3
Frequency of headache days, n (%)	491 (71.4)	65 (9.4)	37 (5.4)
Frequency of moderate/severe headache days, n (%)	519 (75.4)	61 (8.9)	30 (4.4)
Total cumulative hours of headache on headache days, n (%)	506 (73.5)	51 (7.4)	42 (6.1)

*First-time responders for a given time point are patients who never responded at any previous time points.

Table 4 Per cent of first-time responders* with a ≥ 5 -point improvement in the total HIT-6 score

Per cent of patients with a ≥ 5 -point improvement from baseline in the total HIT-6 score	OnabotulinumtoxinA (n=688)		
	Treatment cycle 1	Treatment cycle 2	Treatment cycle 3
	387 (56.3)	100 (14.5)	53 (7.7)

*First-time responders for a given time point are patients who never responded at any previous time points.
HIT, Headache Impact Test.

incremental responses will occur with additional cycles of onabotulinumtoxinA treatment, but it does not rigorously support the notion that the response is due solely to onabotulinumtoxinA, and extending the responder analysis to the placebo group would not achieve that goal. A study designed to test the benefits of a subsequent treatment cycle of onabotulinumtoxinA in non-responders to the first cycle would randomise non-responders to active drug versus placebo in a double-blind fashion. The group of patients who do not respond to placebo for the first cycle are not comparable to the group who did not respond to onabotulinumtoxinA, and therefore, response rates to placebo in placebo nonresponders is not the relevant comparison.

The recommendation to administer 2–3 treatment cycles of onabotulinumtoxinA in order to determine clinical response is in agreement with the migraine treatment guidelines, which state that clinical benefit from preventive medications may take time to occur, and an adequate trial of preventive treatment is recommended before deeming it ineffective.^{20–23} Based on the current notion of the pathophysiology of CM, the mechanism of action of onabotulinumtoxinA supports the clinical results presented. Migraine is a complex neurobiological system disorder comprising sensory pathways, emotional networks, autonomic systems and cortical functions.²⁰ Some aspects of CM and some associated symptoms reflect abnormal excitability in central and peripheral neurons, in particular those of the trigeminal neural and vascular structures; additionally, the clinical presentation involves peripheral and central sensitisation. The neurobiological substrate of this system disorder involves proinflammatory mediators and/or upregulation of sensory receptors or ion channels found on nociceptive nerve endings.^{20–21} Furthermore, akin to other pain disorders, the dynamic process of time-dependent neuroplasticity with increased synaptic strength ('gain') and enlargement of receptive fields plays a key role and would need to be reversed with treatment.^{22–24}

OnabotulinumtoxinA blocks the release of neuropeptides, neurotransmitters and the surface expression of pain receptors and ion channels on nerve membranes and, consequently, facilitates the gradual reversal of peripheral sensitisation, which then indirectly reduces central sensitisation associated with chronic pain.^{20–21} Contributors to time-dependence and treatment-dependence include the following: (1) receptor downregulation takes time; it is not a rapid process. Although individual neurons may respond promptly, as a population of neurons, the effect is more gradual. (2) Not all involved peripheral nerves (c-fibre afferents) are affected to the same degree with each administration: some nerves are maximally or submaximally impacted and some are not within the zone of injection. (3) Central sensitisation requires time to recalibrate towards a normal state, and simply removing the peripheral stimulus may not result in prompt resolution of the central signature. Indeed,

once initiated, central sensitisation may persist after the peripheral stimulus is removed.²⁰

The resolution of central and peripheral sensitisation is time-dependent, and involves the reversal of a potentiated state.^{20–21} Repeat dosing may be required to ensure sufficient time for decreased peripheral inputs to enable resolution of individual cellular and related biological system changes associated with sensitisation.

We suggest that clinicians who treat patients with CM discuss these expectations of efficacy when starting onabotulinumtoxinA treatment and recommend that their patients maintain a diary to track their response to treatment. As with many prophylactic agents, sustained exposure to the drug for several months (eg, 6 months) is often required to fully evaluate response to the treatment. Owing to the unique delivery and mechanism of action of onabotulinumtoxinA, this may be achieved with up to three repeated treatments, as demonstrated in this study. At least two or three treatments with onabotulinumtoxinA are recommended to determine responsiveness.

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