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Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: Analysis of PREEMPT data

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Abstract

Background: The Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials demonstrated efficacy/tolerability of onabotulinumtoxinA for headache prevention in adults with chronic migraine. This post hoc analysis assessed time of onset of onabotulinumtoxinA after the first treatment in total and responder populations and consistency weekly through five treatment cycles.

Methods: In the 24-week, double-blind, placebo-controlled phase of PREEMPT, individuals were randomized 1:1 to onabotulinumtoxinA (155-195 U) or placebo every 12 weeks for two cycles. The primary pooled efficacy variable was change in headache days per 28 days at week 24. We assessed change in headache and migraine/probable migraine (hereafter migraine) days/week compared with baseline week 4.

Results: Baseline mean (SD) headache days/week (week 4 of baseline) for onabotulinumtoxinA ($n = 688$) and placebo ($n = 696$) were similar (4.8 [1.6] vs. 4.8 [1.6] days/week, respectively), as were migraine days/week (4.6 [1.7] vs. 4.6 [1.7] days/week). The effect of onabotulinumtoxinA on change in headache and migraine days/week was significantly greater than placebo at week 1, persisting from week 3 after the first treatment (−1.6 [2.2] vs. −1.1 [2.2] headache days/week [$p < 0.001$] and −1.6 [2.2] vs. −1.1 [2.2] migraine days/week [$p < 0.001$]). Headache and migraine days decreased in onabotulinumtoxinA responders beginning 1 week after treatment 1.

Conclusions: Treatment with onabotulinumtoxinA is associated with significant reductions in headache and migraine days/week at week 1, persisting after week 3, compared with placebo. Combined with earlier reports showing onabotulinumtoxinA treatment results in a persistent and progressive reduction in headache days over 56 weeks, it is suggested peak benefit may require multiple treatments.

Trial registration number: ClinicalTrials.gov: NCT00156910 and NCT00168428.

Keywords

Botulinum toxin type A, onset of action, patients with migraine, headache

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Introduction

Chronic migraine (CM) is a distinct neurologic disease affecting approximately 1–2% of the global population (1). Individuals with CM experience ≥ 8 migraine days per month and ≥ 15 headache days per month (2). It is differentiated from episodic migraine by its more debilitating disease profile, including but not limited to greater frequency of headache and migraine days (2) and greater prevalence of comorbid conditions such as chronic pain disorders, anxiety and depression (3). These disabling migraine attacks prevent individuals

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with CM from performing daily activities and significantly affect their quality of life if not adequately managed (4).

It is recommended that preventive medications be used alongside acute treatments and nonpharmacologic interventions for the management of headache in people with CM (5–7). Treatment guidelines mirror clinical practice and typically recommend onabotulinumtoxinA for adults with CM who have not responded to oral preventive treatments (5). However, adherence to traditional oral preventive treatments is typically poor (8), particularly among patients with CM (9). Individuals report a range of reasons for discontinuing preventive medications, including resolution of headaches (approximately 10%), lack of efficacy (approximately 40%), adverse effects (approximately 40%), and cost (approximately 5–10%) (9).

The Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials comprised two phase 3, 24-week (two treatment cycles), double-blind, parallel-group, randomized, placebo-controlled trials, each with 32-week (three treatment cycles) open-label, non-blinded onabotulinumtoxinA extension phases (10–12). In the double-blind phase, adults with CM were randomized to receive either onabotulinumtoxinA 155 to 195 U or placebo every 12 weeks, with the change in frequency of headache days (11) from baseline at week 24 as the primary or secondary efficacy outcome. The PREEMPT trials demonstrated the efficacy and safety of onabotulinumtoxinA over 56 weeks (13), supporting the approval of this treatment for the prevention of headache in adults with CM (14). Subsequently, the Chronic migraine OnabotulinuMtoxinA Prolonged Efficacy open Label (COMPEL) study has supported and extended the findings of the PREEMPT trials by assessing the efficacy and safety of onabotulinumtoxinA over nine treatment cycles (108 weeks) (15), demonstrating that onabotulinumtoxinA treatment is well tolerated and provides sustained headache day reduction with long-term use (16). Results from real-world studies also demonstrate that onabotulinumtoxinA is effective and well tolerated, with progressive improvements in headache prevention observed over 1 to 2 years of treatment (17).

Oral generic preventive medications for migraine often require a period of dose escalation and should be continued for a period of 2–3 months before treatment response is assessed (7). Recently, it has been reported that injectable monoclonal antibodies used for migraine have a more rapid onset of effect, with efficacy observed within a week of subcutaneous administration (18–20). The time to the first onset of the preventive benefits of onabotulinumtoxinA has not been explored. This analysis of PREEMPT data has been undertaken to identify the time to onset of action of onabotulinumtoxinA after the first treatment and the consistency of that action over five treatment cycles.

Methods

Study design and study participants

The PREEMPT trials are a pair of randomized, double-blind, placebo-controlled 24-week trials, each followed by a 32-week open-label phase. The study design has been previously described in detail (10,11), and will be briefly summarized here for context.

PREEMPT 1 was undertaken at 56 North American sites; adult patients with CM ($\geq$ 15 headache days of $\geq$ 4 hours during the 28-day baseline screening period, with $\geq$ 50% of the days being migraine/probable migraine days [hereafter referred to as migraine days]) were randomized in a 1:1 ratio to onabotulinumtoxinA or placebo, stratified by baseline medication overuse (10). OnabotulinumtoxinA 155 U or placebo was administered in 31 fixed-site, fixed-dose injections, with investigators having discretion to inject a further 40 U using a follow-the-pain strategy to a maximal dose of 195 U across 39 sites. Two cycles of treatment were administered during the double-blind phase of the trial. Patients were excluded if they used any preventive headache medication during the baseline screening period; patients with acute medication overuse were eligible for study enrollment unless they frequently used opioids as their acute headache medication. Patients recorded their headache symptoms and acute treatments via a daily telephone diary. Patients completing the double-blind phase were then eligible to continue in the 32-week open-label phase and received three cycles of onabotulinumtoxinA 155 to 195 U (13).

PREEMPT 2 had a similar study design and was undertaken at 66 global sites, and was also followed by a 32-week open-label phase (11). For both trials, Independent Ethics Committee or Institutional Review Board approval was obtained at each site prior to study initiation, and patients provided written informed consent.

Efficacy and safety measures

In PREEMPT 1, the primary endpoint was the mean change from the 28-day baseline period in frequency of headache attacks for the 28-day period ending at week 24 (10). Change in headache days at week 24 from baseline was the most important secondary efficacy measure (10). Subsequently, and partially in response to guidance issued by the International Headache Society (21), the primary endpoint for PREEMPT 2 was change in headache days from baseline (11). Thus, the mean

change from baseline in headache days and migraine days assessed over the 28-day period ending at week 24 were the key efficacy endpoints for this analysis. A headache day was defined as any calendar day (00:00 to 23:59) when the patient reported ≥ 4 continuous headache hours; to be classified as a migraine or probable migraine day, the patient had to report ≥ 4 continuous headache hours that met the International Classification of Headache Disorders II criteria (22) for migraine (1.1 *Migraine without aura*, 1.2 *Migraine with aura*, or 1.6 *Probable migraine*) (10). Safety and tolerability were also assessed in all randomized patients who received ≥ 1 dose of study treatment.

Onset of effect. To assess the timing of the onset of effect, this post hoc analysis of the PREEMPT data compared the frequency of headache days and migraine days over each 7-day period for the 4 weeks after each treatment with the frequency at baseline week 4 (the week immediately before the first treatment). Although all four baseline weeks are used to determine the pre-treatment baseline in most trials, given that the follow-up intervals were each 1 week long, the last week of the baseline pre-treatment run-in phase was selected as the reference. In addition, the timing of the onset of effect on headache days and migraine days was assessed in those individuals receiving onabotulinumtoxinA who had a $\geq 50\%$ reduction in headache days versus baseline at week 24 ($\geq 50\%$ headache day responders) to better understand the timing of effect in the responder population.

Statistical analysis

This was a pooled analysis of data from PREEMPT 1 and PREEMPT 2. Efficacy analyses included all randomized patients. In the primary analyses, missing counts of days for the 28-day periods were imputed using a modified last observation carried forward (mLOCF) methodology (10,11). For the analyses reported herein, data were based on 7-day diary data and only observed data were used. If patients had recorded ≥ 5 days and < 7 days of diary data, data were pro-rated to a 7-day count for use in the analyses.

Change from baseline was calculated using baseline week 4 values as the baseline period (i.e. the 7-day period immediately before the first treatment). Between-treatment comparisons were assessed using analysis of covariance (ANCOVA) with the baseline week 4 values used as the covariate for each post-treatment 7-day period. The main effects in the ANCOVA included treatment and medication overuse strata, and the type III sum of squares was used. p values ≤ 0.05 were considered statistically significant.

Results

Patient disposition and demographics

A total of 679 patients were randomized to onabotulinumtoxinA (n = 341) or placebo (n = 338) in PREEMPT 1 (10) and 705 (onabotulinumtoxinA, n = 347; placebo, n = 358) in PREEMPT 2 (11), for a total of 1384 patients (onabotulinumtoxinA, n = 688; placebo, n = 696) (12,13). Compliance with reporting daily diary data was high at baseline (> 99%) and across the 24-week period (> 93%) for both treatment groups in PREEMPT 1 (10) and PREEMPT 2 (11), and consequently in the pooled population (12). As reported previously, the baseline demographics of treatment groups were similar (Table 1), except that the onabotulinumtoxinA group in the pooled population had significantly fewer headache attacks and migraine attacks than did the placebo group (12,13). However, there were no significant differences between the treatment groups for the variables of interest in the current analysis (i.e. headache days and migraine days). Furthermore, across the pooled population, the mean (SD) headache days (19.9 [3.7] days/28-day period) were similar to the mean (SD) migraine days (19.1 [4.0] days/28-day period), suggesting that most headache days qualified as migraine days.

Efficacy results

The previously reported pooled analysis from the PREEMPT studies demonstrated significant reductions in headache days per 28-day period at the primary study endpoint of 24 weeks, but also at other time points as early as 4 weeks (12). Time points earlier than 4 weeks have not previously been explored.

Reduction in headache days. In pooled PREEMPT data, the mean (SD) headache days at baseline week 4 (the week immediately pre-treatment) were 4.8 (1.6) days/week for both the onabotulinumtoxinA and the placebo populations. At week 1 after the first treatment, onabotulinumtoxinA was associated with a statistically greater mean (SD) reduction than placebo in headache days per week compared with the week before the first treatment (−0.9 [2.2] days/week versus –0.7 [2.1] days/week for onabotulinumtoxinA and placebo, respectively; $p = 0.046$), and persisting from week 3 after the first treatment. At week 3, the mean (SD) number of headache days decreased by −1.6 (2.2) days/week among onabotulinumtoxinA recipients versus −1.1 (2.2) days/week for placebo ($p < 0.001$; Figure 1(a)); at week 4 the reduction was −1.6 (2.2) days/week for those receiving onabotulinumtoxinA versus −1.2 (2.2) days per week for those on placebo ($p < 0.001$).

Table 1. Baseline patient demographics and headache characteristics.

	Pooled population	
	OnabotulinumtoxinA (n = 688)	Placebo (n = 696)
Mean age, years	41.1	41.5
Female, %	87.6	85.2
White, %	89.7	90.5
Medication overuse during 28-day baseline period, %	64.8	66.1
Mean (SD) headache metrics for 28-day baseline period		
Headache days	19.9 (3.7)	19.8 (3.7)
Migraine days	19.1 (4.0)	18.9 (4.1)
Mean (SD) headache metrics for 7-day period immediately before the first treatment		
Headache days	4.8 (1.6)	4.8 (1.6)
Migraine days	4.6 (1.7)	4.6 (1.7)

Migraine: migraine/probable migraine days.

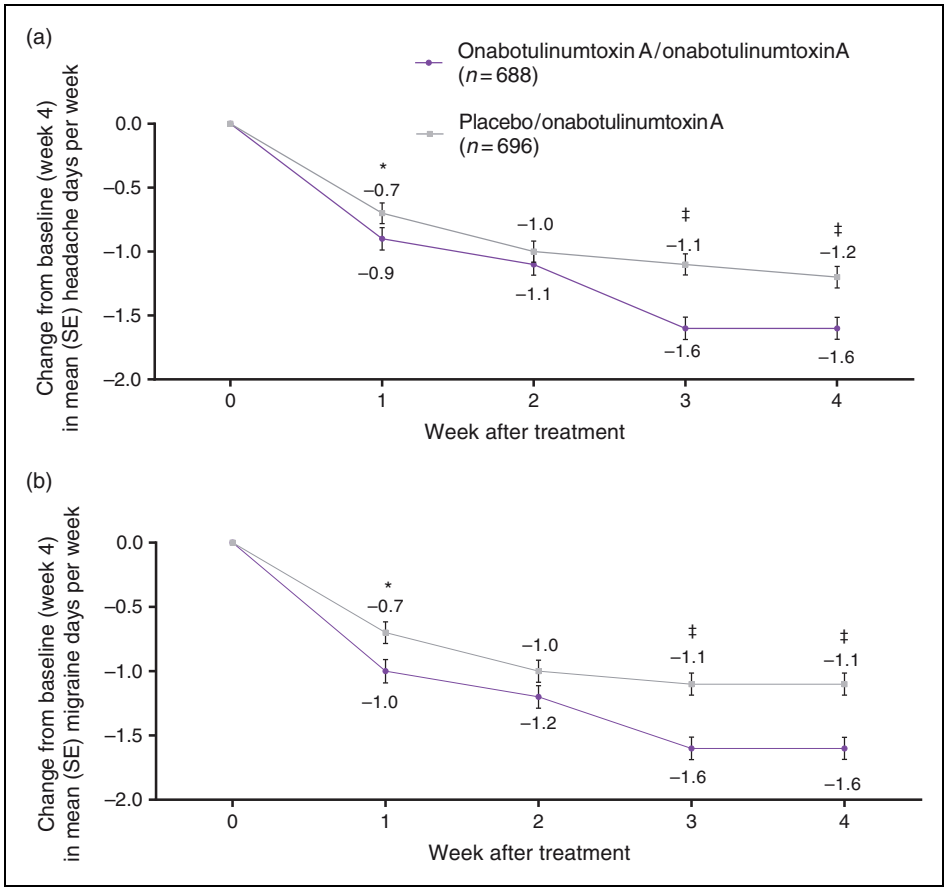

Figure 1. Change in mean (SE) weekly (a) headache days and (b) migraine days in the pooled population for the first 4 weeks after the initial treatment with onabotulinumtoxinA 155 to 195 U or placebo.
Week −1: baseline week 4.
*$p < 0.05$ for between treatment group comparisons with week −1.
†$p < 0.01$ for between treatment group comparisons with week −1.
‡$p < 0.001$ for between treatment group comparisons with week −1.

The frequency of headache days continued to decrease after week 3 after the first treatment and persisted over five treatment cycles, as seen in pooled data of all treatment cycles. Pooled data demonstrated that onabotulinumtoxinA was associated with a significantly greater change in mean (SD) headache day frequency compared with the week before the first treatment (baseline week 4) than did placebo (−1.9 [2.3] vs. −1.5 [2.3] days/week; $p < 0.001$) at week 1 after the second treatment and that this effect was sustained from week 3 (Figure 2(a)).

Reduction in migraine days. In the pooled PREEMPT data, the mean (SD) migraine days at baseline week 4 were 4.6 (1.7) days/week for both the onabotulinumtoxinA and the placebo populations. OnabotulinumtoxinA was associated with a statistically greater reduction than placebo in mean (SD) migraine days per week compared with baseline week 4, which was first observed at week 1 after the first treatment (−1.0 [2.4] vs. −0.7 [2.2] days/week; $p = 0.031$), persisting from week 3 after the first treatment. At week 3, onabotulinumtoxinA reduced the mean (SD) number of migraine days by −1.6 (2.3) days/week versus −1.1 (2.2) days/week for placebo ($p < 0.001$; Figure 1(b)); at week 4 the reduction was −1.6 (2.2) days/week for those receiving onabotulinumtoxinA and −1.1 (2.2) for those receiving placebo ($p < 0.001$).

The frequency of migraine days continued to decrease after week 3 of the first treatment cycle and

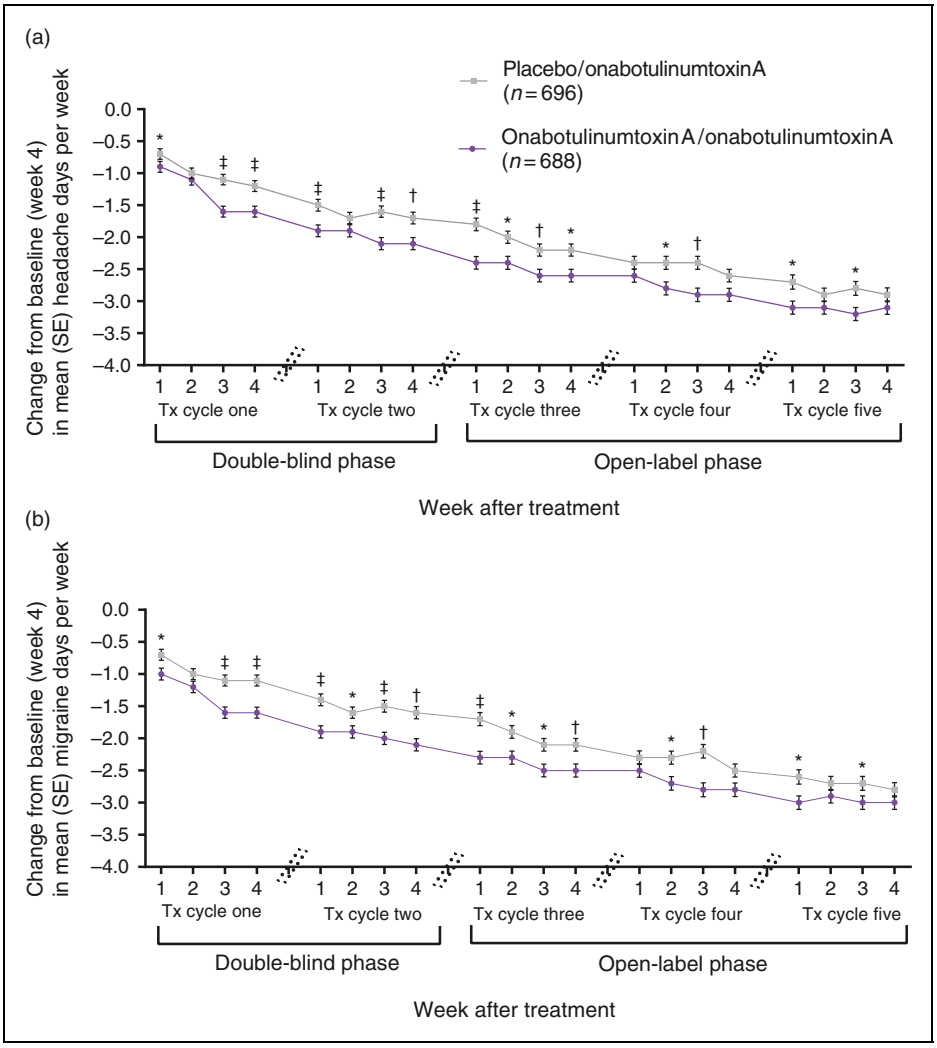

Figure 2. Change in mean (SE) weekly (a) headache days and (b) migraine days for the pooled population for the first 4 weeks after all five treatments with onabotulinumtoxinA 155 to 195 U or placebo/onabotulinumtoxinA.
*$p < 0.05$ for between treatment group comparisons with week −1.
†$p < 0.01$ for between treatment group comparisons with week −1.
‡$p < 0.001$ for between treatment group comparisons with week −1.

persisted over five treatment cycles. Pooled data demonstrated that onabotulinumtoxinA was associated with a significantly greater change than did placebo in migraine day frequency compared with baseline week 4 (−1.9 [2.4] vs. −1.4 [2.3] days/week; $p < 0.001$) at week 1 post-treatment 2; the difference in favor of onabotulinumtoxinA persisted throughout the five treatment cycles (Figure 2(b)).

Effect in ≥ 50% responders

Reduction in headache days. In the subgroup of 308 patients (44.8%) who were ≥ 50% headache day responders to onabotulinumtoxinA at week 24 based on mLOCF methodology, the mean (SD) headache days at baseline week 4 were 4.6 (1.5) days/week. Among 50% responders, onabotulinumtoxinA was associated with a mean (SD) reduction in headache days per week compared with baseline week 4 (the week before the first treatment) of −1.8 (2.0) days/week during week 1 versus −0.9 (2.2) days/week during week 1 for all onabotulinumtoxinA patients. The mean (SD) number of headache days per week decreased for each subsequent week in ≥ 50% headache day responders by −2.2 (2.2) days/week versus −1.1 (2.2) days/week (overall) during week 2, −2.6 (2.0) days/week versus −1.6 (2.2) days/week (overall) during week 3 and −2.7 (2.0) days/week versus −1.6 (2.2) days/week (overall) during week 4 (Table 2). Differences were more pronounced between ≥ 50% headache day responders and those who were non-responders at week 24, because the overall group included the responders.

Similar patterns of an increasing reduction in headache days were observed in ≥ 50% headache day responders after treatment 2 (−3.2 days/week during week 1 to −3.5 days/week during week 4) to treatment 4 (−3.9 days/week during week 1 to −4.2 days/week during week 4); however, by treatment 5 the increased reduction in headache days over the first four weeks after treatment was relatively constant (−4.4 days/week during week 1 and −4.3 days/week during week 4). For comparison, the non-responders at week 24 reported less reduction in headache days after treatment 2 (−1.5 to −1.7 days during weeks 1 to 4), after treatment 4 (−2.1 to −2.5 days during weeks 1 to 4), and after treatment 5 (−2.6 to −2.9 during weeks 1 to 4).

Placebo responders, by definition, started the open label component of the study with a greater reduction in headache days per week than placebo non-responders (Figure 3(a)). OnabotulinumtoxinA treatment initiated in these patients from cycle 3 onwards was associated with a similar further reduction in headache days per week from baseline (week −1) at weeks 1 to 4 after treatment cycles 3, 4 and 5 in both placebo responders and placebo non-responders.

Reduction in migraine days. In the subgroup of patients who were ≥ 50% headache day responders to onabotulinumtoxinA at week 24, the mean (SD) migraine days at baseline week 4 were 4.4 (1.6) days/week. Among 50% responders, onabotulinumtoxinA was associated with a mean (SD) reduction in migraine days per week compared with baseline week 4 (the week before the first treatment) of −1.4 (2.3) days/week during week 1 versus −1.0 (2.4) days/week during

Table 2. Effect of onabotulinumtoxinA on headache days and migraine days per week in patients who were ≥ 50% headache day responders and non-responders at week 24 and the overall onabotulinumtoxinA population.

Week after treatment one	≥ 50% headache day responders at week 24 (n = 308)	Headache day non-responders at week 24 (n = 380)	Overall onabotulinumtoxin A population (n = 688)
Change in headache days/week, mean (SD)*			
1	−1.8 (2.0)	−0.8 (2.2)	−0.9 (2.2)
2	−2.2 (2.2)	−0.9 (2.1)	−1.1 (2.2)
3	−2.6 (2.0)	−1.4 (2.1)	−1.6 (2.2)
4	−2.7 (2.0)	−1.3 (2.2)	−1.6 (2.2)
Change in migraine days/week, mean (SD)†			
1	−1.4 (2.3)	−0.6 (2.3)	−1.0 (2.4)
2	−1.7 (2.2)	−0.7 (2.1)	−1.2 (2.3)
3	−2.2 (2.2)	−1.1 (2.2)	−1.6 (2.3)
4	−2.2 (2.1)	−1.0 (2.2)	−1.6 (2.2)

Migraine: migraine/probable migraine days.
*Compared with headache days at baseline week 4.
†Compared with migraine days at baseline week 4.

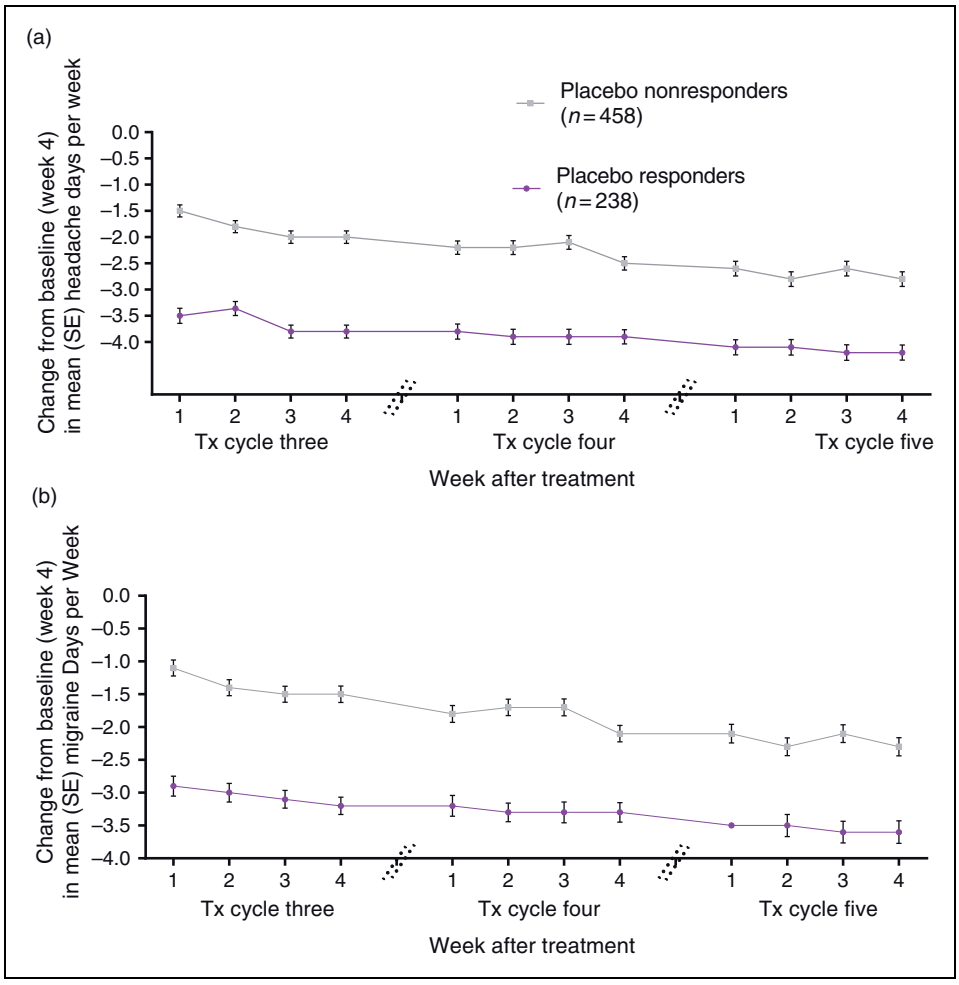

Figure 3. Change in mean (SE) weekly (a) headache days and (b) migraine days for the placebo responders and non-responders for the first 4 weeks after each of the three treatments with onabotulinumtoxinA 155 to 195 U in the open-label phase of the trial.

week 1 for all onabotulinumtoxinA recipients. The mean (SD) number of migraine days per week decreased for each subsequent week in $\geq 50\%$ headache day responders by −1.7 (2.2) days/week versus −1.2 (2.3) days/week (overall) during week 2, −2.2 (2.2) days/week versus −1.6 (2.3) days/week (overall) during week 3 and −2.2 (2.2) days/week versus −1.6 (2.2) days/week (overall) during week 4 (Table 2). Differences were more pronounced between $\geq 50\%$ headache day responders and those who were non-responders at week 24, because the overall group included the responders.

Similar patterns of an increasing reduction in migraine days were observed in $\geq 50\%$ headache day responders after treatment 2 (−2.7 days/week during week 1 to −2.9 days/week during week 4) to treatment 4 (−3.4 days/week during week 1 to −3.6 days/week during week 4); however, by treatment 5 the increased reduction in migraine days over the first four weeks after treatment was relatively constant (−3.9 days/week during the first week and −3.8 days/week during the fourth week). For comparison, the non-responders at week 24 reported less reduction in migraine days after treatment 2 (−1.1 to −1.3 days during weeks 1 to 4), after treatment 4 (−1.7 to −2.0 days during weeks 1 to 4), and after treatment 5 (−2.1 to −2.4 during weeks 1 to 4).

Treatment with onabotulinumtoxinA was associated with a similar further reduction from baseline (week −1) in migraine days/week from cycle 3 in placebo responders and placebo non-responders (Figure 3(b)).

Discussion

This onset of effect analysis of the change in headache days per week and migraine days per week during the first 4 weeks after treatment compared with the week immediately before the first treatment found that the effect of onabotulinumtoxinA was significantly superior to placebo as early as week 1, and that the difference

was sustained starting at week 3 after the first treatment. In those who were $\geq 50\%$ headache day responders at week 24, a reduction in headache and migraine days was observed to have an approximately twofold greater magnitude of reduction from the first week post-injection, compared with the headache day non-responders, which may be an important consideration for healthcare professionals when communicating the potential treatment benefit of onabotulinumtoxinA for CM to their patients. There appeared to be no difference in the response to onabotulinumtoxinA in placebo responders and placebo non-responders.

Although the efficacy of onabotulinumtoxinA has been typically assessed over 4-week intervals (12,15,23,24), our findings are consistent with clinical experience that many patients report a reduction in headache and migraine days as well as reductions in headache and migraine severity earlier than week 4 after the first treatment. The design of preventive trials in migraine, in particular the recommended 3-month treatment period, has largely been informed by the time of onset of traditional oral medications (21) that typically require gradual dose escalation and, thus, are associated with a delayed onset of action (7). In contrast, our findings demonstrate that onabotulinumtoxinA produces statistically significant benefit at 1 week post treatment. While the early between-group difference was modest (0.2–0.3 migraine days per week), by weeks 3 and 4 the difference of 0.5 migraine days per week (0.4–0.5 headache days per week), when considered cumulatively, met the clinically meaningful threshold of a reduction of one headache day per month (25). Further, the absolute magnitude of response in the treatment group is the most important to determine clinical relevance since, in clinical practice, the integration of and response to a therapy is not attenuated by placebo. A reduction of approximately one headache day per week versus baseline in the first week after treatment is likely to be clinically meaningful to patients. The failure to detect a significant difference in week 2 could be related to the natural fluctuation in headache frequency in the CM population (26).

Although a rapid onset of effect is important, it is equally important that the effect persists and is consistent. In addition to demonstrating the early onset of effect of onabotulinumtoxinA treatment, our results also complement growing clinical evidence indicating that multiple treatment cycles may be necessary to achieve a consistent benefit and optimal results (27–30). As observed in the pooled data over five treatment cycles, onabotulinumtoxinA patients achieved a more consistent pattern in the reduction of headache day frequency and migraine days by the third treatment cycle, eliminating most of the variability observed in week 1 and 2 of the first two treatment cycles, whereas placebo patients who have been switched to onabotulinumtoxinA at the third treatment mimic the variance observed in onabotulinumtoxinA patients in the first two cycles. Of further note is the cumulative response to multiple cycles of treatment, once again highlighting the value of patient adherence to the long-term outcome of preventive treatment. The earlier pooled analysis over the entire 56-week PREEMPT trial period found that onabotulinumtoxinA was associated with a mean reduction in headache days from baseline of -8.4 days/28-day period at week 24, increasing to -11.7 days/28-day period at week 56 (13). Further, the proportion of individuals in the PREEMPT trials first experiencing a $\geq 50\%$ headache day response continued to increase over the first three treatment cycles (first treatment cycle, 49.3%; second treatment cycle, 11.3%; third treatment cycle, 10.3%), highlighting the need to persist with onabotulinumtoxinA treatment for three cycles to determine responsiveness (31).

An early reduction in the frequency of headache days and/or migraine days may contribute to improved adherence for preventive treatment. Despite preventive treatment being key to achieving optimal outcomes for individuals with CM (32), claims database studies demonstrate poor adherence, with over two-thirds of patients non-adherent to current oral preventive treatments (e.g. topiramate, beta-blockers) after 6 months (8). Improvement in adherence to preventive medications, as a result of increased efficacy and tolerability, along with education, avoidance of migraine triggers, and lifestyle modification, is key to improving outcomes for individuals with migraine, and may also result in a reduction in the use of healthcare resources (8). A well–tolerated and effective preventive medication with a simple regimen and an early onset of action may improve adherence and consequently patient outcomes. With its physician administration cycle of every 12 weeks and well-tolerated safety profile, onabotulinumtoxinA offers a treatment option that has been demonstrated to have better adherence to commonly prescribed traditional oral preventives and to be a successful treatment for individuals who have poor compliance or adherence to traditional oral preventives or do not tolerate them (33).

Study limitations

In this analysis of the PREEMPT study data, we compared post-treatment 7-day periods with the week immediately before the first treatment. We could have alternatively presented an average of the baseline period as the reference point, or the first week of the baseline period. Regardless of the approach, the differences in baseline data between the onabotulinumtoxinA

and placebo groups were minimal. For example, for headache days per week, using baseline week 4, onabotulinumtoxinA and placebo groups both had a mean of 4.8 days/week; averaging across the four baseline weeks, both treatment groups had a headache frequency of 4.9 days/week; and for week 1, both treatment groups had a headache frequency of 5.2 days/week. Arguably, using baseline week 4 was the most conservative approach because the headache days and migraine days were lower than for the alternative approaches.

As a post hoc analysis, the endpoints of headache and migraine day reduction per week for weeks 1 to 4 post treatment were not pre-specified. Therefore, the results of our analyses must be interpreted with caution. Nonetheless, the headache and migraine day reductions observed after the first treatment cycle in pooled data from the double-blind phase of the PREEMPT trials align with clinical experience, suggesting our findings are robust and clinically relevant. Furthermore, the consistency of headache and migraine reduction over the entire 56-week study period also supports the robustness of the data.

Conclusions

OnabotulinumtoxinA treatment significantly reduced headache days per week and migraine days per week as early as week 1, persisting after week 3 after the first treatment compared with placebo. Headache days and migraine days were further reduced after the second and subsequent treatments. The greater magnitude of reductions in $\geq 50\%$ headache day responders was observed from week 1 after the first treatment. Despite the early onset of effect of onabotulinumtoxinA, data from the PREEMPT and other clinical studies in combination with clinical experience strongly suggest that it may take at least two to three treatments to determine responsiveness and peak benefit may require multiple treatments.

Clinical implications

- OnabotulinumtoxinA is associated with an early and sustained onset of action of starting from 3 weeks after the first treatment.
- Headache day responders had a greater reduction in headache and migraine days as early as week 1 after the first treatment than observed among all onabotulinumtoxinA recipients as a whole.
- For preventive treatment, it is equally important that the beneficial effect persists and is consistent.
- It may take at least two to three treatments to determine responsiveness to onabotulinumtoxinA and peak benefit may require multiple treatments.

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Declaration of conflicting interests

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Dr Dodick reports the following conflicts:

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- Miller Medical
- PeerView,
- WebMD/Medscape
- Chameleon
- Academy for Continued Healthcare Learning
- Universal meeting management
- Haymarket
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