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Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine

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Background and purpose: OnabotulinumtoxinA was effective and well tolerated for prophylaxis of headache in patients with chronic migraine (CM) in two randomized, double-blind, placebo-controlled, phase 3 trials. To further assess the safety and tolerability of onabotulinumtoxinA in CM prophylaxis in adults, the pooled safety data from four double-blind, placebo-controlled trials were analyzed.

Methods: The pooled analysis included two phase 2 and two phase 3 double-blind, placebo-controlled trials. The safety population was 2436 patients, 1997 of whom received ≥1 dose of onabotulinumtoxinA. The studies shared similar dosing intervals (approximately 12 weeks) with doses between 75 and 260 U. Safety assessments included adverse events (AEs), physical examination and clinical laboratory tests.

Results: OnabotulinumtoxinA was safe and well tolerated, with a low discontinuation rate (3.4%) due to AEs. The majority of patients in this pooled analysis received doses between 150 and 200 U, with an average of 163 U per treatment cycle. Of the 1997 patients who received any onabotulinumtoxinA injections, 1455 patients (72.9%) reported at least one AE. Neck pain (12.6%) was the most common onabotulinumtoxinA-associated AE, followed by muscle weakness (8.0%), musculoskeletal stiffness (6.1%) and eyelid ptosis (4.6%). Serious AEs were infrequent, occurring in 5.4% of patients who received any onabotulinumtoxinA treatment and 3.0% of patients receiving placebo. AEs were consistent with the known tolerability profile of onabotulinumtoxinA.

Conclusions: Multiple treatments with onabotulinumtoxinA at doses of 75–260 U administered every 12 weeks, and up to five treatment cycles, were well tolerated for the prophylaxis of headache in adults with CM.

Introduction

Currently, according to the third beta edition of the International Classification of Headache Disorders revised (ICHD-3 beta) criteria, chronic migraine (CM) is characterized by headache occurring on ≥15 days per month for at least 3 months, which has the features of migraine headache on at least 8 days per month [1]. CM is a complex and debilitating neurological disorder [2–4], with a prevalence of 1.4%–2.2% [5]. At present, prophylactic treatment options are limited; only onabotulinumtoxinA and topiramate have been evaluated in CM patients [6–10], and only onabotulinumtoxinA is specifically indicated for the prophylaxis of headache in patients with CM [11].

Results from two exploratory phase 2 studies in patients with chronic daily headache suggested the efficacy of onabotulinumtoxinA within the CM subgroup, which represented the predominant population enrolled in these studies [12,13]. In the phase 2 studies, onabotulinumtoxinA was shown to be safe and well tolerated in doses ranging from 75 to 260 U repeated at approximately 12-week intervals for up to three cycles [12,13]. More recently, two large-scale, placebo-controlled, multicenter trials (PREEMPT: Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) found onabotulinumtoxinA to be effective in the prophylaxis of CM. These studies demonstrated statistically significant and clinically meaningful improvements compared with placebo in headache

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day frequency and multiple other headache symptom measures. OnabotulinumtoxinA treatment also significantly reduced headache-related disability and improved functioning, vitality and overall health-related quality of life in patients treated with onabotulinumtoxinA compared with placebo. Furthermore, PREEMPT found that repeated treatment with 155–195 U of onabotulinumtoxinA every 12 weeks over 56 weeks (up to five treatment cycles) was safe and well tolerated [6–8,14].

The present analysis reports on the pooled safety data from the two exploratory phase 2 studies [12,13] and the two PREEMPT trials [6–8,14]. These trials enrolled similar patient populations and were subject to similar methodology and adverse event (AE) reporting requirements, allowing the pooling of data for analysis. Analyzing the pooled safety data from the four trials increases statistical power to detect trends in AE incidence that may not have been evident in the individual analyses, and as such sheds light on the safety and tolerability of up to five cycles of onabotulinumtoxinA in adult patients with CM.

Methods

Trial selection and subjects

Patients were men or women aged 18–65. Phase 2 participants experienced chronic daily headache, most commonly caused by CM, with headaches on >15 days during the 30-day baseline screening [12,13]. Patients in the PREEMPT studies had a history of migraine meeting ICHD-2 criteria [15,16], except for 'complicated migraine'. During the 28-day baseline, these patients were required to have had ≥15 headache days, of which ≥50% were migraine or probable migraine days, and ≥4 distinct headache episodes, each lasting ≥4 h. Excluded subjects had headache prophylactic medication use within 4 weeks prior to or during baseline, previous exposure to any botulinum toxin serotype or a positive urine pregnancy test [8].

Trial design

The PREEMPT 1 and 2 multicenter trials included a 24-week, randomized, double-blind, placebo-controlled (DBPC), parallel-group phase, followed by a 32-week, open-label extension (Fig. 1). After the 4-week baseline, patients were randomized (1:1) to onabotulinumtoxinA (155–195 U) or placebo at day 0 and week 12 (DB phase). Treatments were administered intramuscularly (IM) as 31 fixed-site, fixed-dose (FSFD) injections across seven specific head/neck muscle areas [17]. At the investigator's discretion, an additional 40 U of onabotulinumtoxinA or placebo could be administered unilaterally or bilaterally, using a 'follow-the-pain' injection paradigm that varied across treatment visits. The maximum dose was 195 U across 39 sites per treatment cycle (Table S1) [8]. Patients who completed the DB phase entered the open-label phase, where they received 155–195 U of onabotulinumtoxinA at 12-week intervals, according to the paradigm described above (weeks 24, 36 and 48).

The phase 2 trials were multicenter, randomized, DBPC, parallel-group studies of three injection cycles given at 90-day intervals (Fig. 1). After the 30-day baseline, patients were injected with placebo and followed for a 30-day placebo run-in period. They were then randomized and stratified according to their placebo-response status. In the first phase 2 trial [12], 105–260 U of onabotulinumtoxinA or placebo was administered IM over six to seven muscle areas. In each treatment cycle, patients received the minimum required dose of 105 U administered as FSFD injections across six muscle groups. Additional 'follow-the-pain' doses were injected at the investigator's discretion, based on the location and severity of pain. In the second phase 2 trial [13], patients received 20 bilateral FSFD IM injections of 75, 150

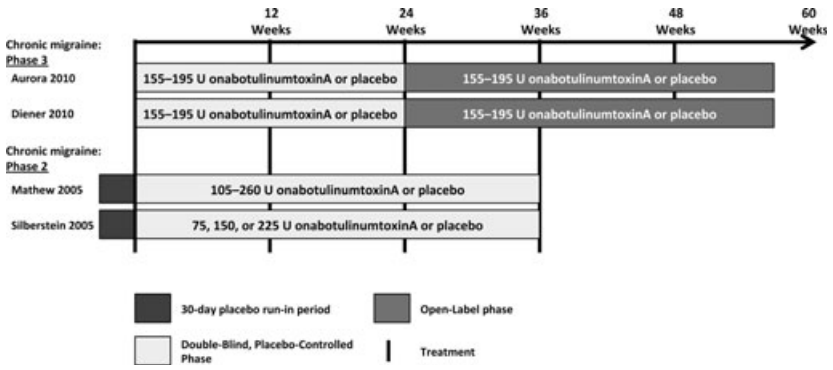

Figure 1 Schematic of trial designs.

or 225 U of onabotulinumtoxinA or placebo across seven specific muscle areas in all treatment cycles (Table S1).

Safety assessments included spontaneously reported AEs, clinical laboratory tests, vital signs, physical examinations and urine pregnancy tests. All AEs were monitored and recorded throughout the study. Serum samples for toxin-neutralizing antibody titer analysis were collected at exit from both phase 2 studies and analyzed using the mouse protection bioassay.

All four studies were conducted in compliance with the ethical principles that originated in the Declaration of Helsinki regarding biomedical research on human subjects and informed consent regulations. Each investigator obtained approval from an independent ethics committee or a local institutional review board prior to study initiation.

Data analysis

Patient demographics, medical history, onabotulinumtoxinA doses and AEs were pooled and summarized with descriptive statistics. AEs were summarized for each organ system class and preferred term using MedDRA version 11 [18]. All patients were counted only once for each AE when multiple occurrences of the same AE were reported, except that in the by-treatment-cycle analysis each new onset of an AE was counted in the cycle in which it started. An ongoing AE was not counted in subsequent cycles unless it worsened. Serious AEs were any that resulted in death, a life-threatening event, hospitalization (initial or prolonged), disability, a congenital anomaly or a medical event that could require medical or surgical intervention to prevent the above outcomes.

Results

Patient demographics, baseline headache characteristics and exposure

Baseline characteristics are consistent with published reports on CM patients: predominantly middle age (mean 42 years), Caucasian (91%) females (85%) who have had frequent migraine for approximately 20 years (Table 1) [2]. Of 2436 patients in the phase 2 and PREEMPT studies, 1997 received at least one onabotulinumtoxinA treatment, providing 16 926 patient-months of exposure; 1448 patients received three treatment cycles or fewer and 513 completed five treatment cycles of onabotulinumtoxinA. Most patients (77.6%) received an initial dose of 150–200 U; per-cycle mean and median onabotulinumtoxinA doses were 163 and 158.3 U, respectively.

Table 1 Baseline demographics

Demographic characteristic	OnabotulinumtoxinA (N = 1384)	Placebo (N = 1052)
Age (years), mean ± SD	42.1 ± 10.34	42.3 ± 10.89
Female, *n* (%)	1196 (86.4)	878 (83.5)
Caucasian, *n* (%)	1262 (91.2)	952 (90.5)
Body mass index (kg/m^2), mean ± SD	26.60 ± 6.145	26.94 ± 6.362
Time since onset of frequent migraine (years),[a] mean ± SD	20.1 ± 12.55	19.8 ± 12.89
Age of onset of frequent migraine (years),[b] mean ± SD	21.0 ± 11.09	21.6 ± 11.79
Baseline use of acute headache medication – yes, *n* (%)	1332 (96.2)	1008 (95.8)
Baseline overuse of acute headache medication – yes,[c] *n* (%)	897 (64.8)	693 (65.9)
Prior headache prophylactic medication use – yes, *n* (%)	745 (53.8)	609 (57.9)

SD, standard deviation.
[a]Time since onset was calculated from date of onset to day of patient's first injection (day 0).
[b]Age of onset was calculated from birth date to date of onset.
[c]To qualify for acute headache medication overuse, a patient had to take this type of medication at least twice per week in any week with at least 5 diary days and for at least 10–15 days during the baseline period (varying with medication category).

Safety

Adverse events

The majority (72.9%) of patients with onabotulinumtoxinA exposure reported at least one AE. The frequency of AEs was higher with onabotulinumtoxinA than with placebo (71.4% vs. 56.8%) during the DB phase (Table 2). The most frequently reported AEs were musculoskeletal in origin (Fig. S1).

During the DB phase, neck pain was the most frequently reported AE in the onabotulinumtoxinA group (13.8% vs. 2.4% with placebo) (Table 2). Other AEs that were reported by ≥5% of patients and occurred more frequently with onabotulinumtoxinA treatment than with placebo were muscular weakness, headache, facial paresis and musculoskeletal stiffness (Table 2). Most muscular weakness was local to onabotulinumtoxinA injection sites or adjacent muscles in the head, neck or shoulder/upper arm regions. The incidences of infections such as sinusitis were similar between the onabotulinumtoxinA and placebo groups (Table 2). The overall and individual incidence rates of AEs that were considered treatment related by the investigator are displayed in Table S2. The onset,

Table 2 Adverse events reported in ≥2% of patients

Adverse event (preferred term)	DBPC exposure		
	OnabotulinumtoxinA (N = 1384)	Placebo (N = 1052)	Any onabotulinumtoxinA exposure[a] (N = 1997)
Overall, n (%)	988 (71.4)	598 (56.8)	1455 (72.9)
Neck pain	191 (13.8)	25 (2.4)	252 (12.6)
Muscular weakness	127 (9.2)	3 (0.3)	160 (8.0)
Headache	111 (8.0)	58 (5.5)	142 (7.1)
Facial paresis	109 (7.9)	1 (0.1)	122 (6.1)
Musculoskeletal stiffness	99 (7.2)	14 (1.3)	122 (6.1)
Upper respiratory tract infection	84 (6.1)	66 (6.3)	127 (6.4)
Sinusitis	76 (5.5)	47 (4.5)	134 (6.7)
Injection site pain	68 (4.9)	28 (2.7)	89 (4.5)
Musculoskeletal pain	65 (4.7)	16 (1.5)	89 (4.5)
Nasopharyngitis	65 (4.7)	49 (4.7)	118 (5.9)
Eyelid ptosis	63 (4.6)	5 (0.5)	91 (4.6)
Nausea	51 (3.7)	29 (2.8)	73 (3.7)
Migraine	53 (3.8)	25 (2.4)	88 (4.4)
Bronchitis	45 (3.3)	22 (2.1)	65 (3.3)
Muscle tightness	43 (3.1)	3 (0.3)	71 (3.6)
Myalgia	39 (2.8)	9 (0.9)	58 (2.9)
Hypoaesthesia facial	38 (2.7)	4 (0.4)	41 (2.1)
Influenza	35 (2.5)	31 (2.9)	59 (3.0)
Dizziness	33 (2.4)	17 (1.6)	53 (2.7)
Depression	27 (2.0)	22 (2.1)	43 (2.2)

DBPC, double-blind, placebo-controlled.
[a]The number of patients who received any onabotulinumtoxinA injections during the study, including original placebo patients who received onabotulinumtoxinA in the open-label phase.

duration and severity of the AEs reported by ≥5% of patients were analyzed and are presented in Table 3. Most of these were mild (15.9%) to moderate (35.6%) in severity. Sixty-seven patients (3.4%) with any onabotulinumtoxinA exposure discontinued the studies due to an AE.

Deaths and serious adverse events

One death was reported in the placebo group in one of the phase 2 studies. This event was considered to be due to 'cardiac irregularity' and was determined to be unrelated to the study treatment. Serious AEs were reported for 4.7% of onabotulinumtoxinA patients and 3.0% of placebo patients during the DB phase. The most frequently reported serious AE was migraine, followed by pneumonia, uterine leiomyoma and headache (Table 4). Amongst the 1997 patients with any onabotulinumtoxinA exposure, serious AEs were reported in 5.4% (n = 107) of patients. The most frequently reported serious AEs were the same as for the DBPC phase (Table 4).

Adverse events by treatment cycle

To assess AE incidence for each onabotulinumtoxinA cycle and the effect of multiple treatments over time, PREEMPT patients who completed all five treatment cycles (n = 513) were analyzed. Due to a lack of available data in five treatment cycles following a standardized protocol over a limited dose range, the phase 2 studies were excluded from this analysis. The overall incidence of AEs decreased from 48.3% in the first cycle to 19.1% in the fifth cycle. The majority of the individual AEs (≥2%) decreased in subsequent treatment cycles, as displayed in Fig. 2. When taking the entire PREEMPT population into account (n = 1384), the decreased incidence of AEs was not due to discontinuations, as the discontinuation rates per treatment cycle were similar (cycle 1, 5.4%; cycle 2, 5.3%; cycle 3, 5.7%; cycle 4, 6.3%; cycle 5, 4.7%).

Adverse events by dose

When compared by dose ranges, overall AEs were similar in the <150 U group (83.1%) and the >200 U group (80.2%) but lower in the 150–200 U group (66.6%) (Table 5). Neck pain was the most frequently occurring AE, with an incidence of 18.5%, 11.1% and 20.2%, respectively, in the three dose groups (from low to high) (Table 5). The same incidence pattern was observed for the other frequently reported AEs,

Table 3 Onset, duration and severity of adverse events reported by ≥5% of patients in the DBPC phase

Adverse event	DBPC exposure: OnabotulinumtoxinA (*N* = 1384)	DBPC exposure: Placebo (*N* = 1052)
Neck pain	*N* = 191 (13.8%)	*N* = 25 (2.4%)
Onset (days since most recent injection)	6.9	25.5
Duration (days)	24.3	14.4
Severity, *n* (%)		
Mild	42 (22.0)	2 (8)
Moderate	116 (60.7)	19 (76)
Severe	36 (18.8)	4 (16)
Muscular weakness	*N* = 127 (9.2%)	*N* = 3 (0.3%)
Onset (days since most recent injection)	4.9	33
Duration (days)	30.2	8
Severity, *n* (%)		
Mild	47 (37)	1 (33.3)
Moderate	70 (55.1)	2 (66.7)
Severe	13 (10.2)	0 (0)
Headache	*N* = 111 (8.0%)	*N* = 58 (5.5%)
Onset (days since most recent injection)	23.9	18.2
Duration (days)	26.5	22.3
Severity, *n* (%)		
Mild	22 (19.8)	9 (15.5)
Moderate	51 (45.9)	26 (44.8)
Severe	37 (33.3)	23 (39.7)
Facial paresis	*N* = 109 (7.9%)	*N* = 1 (0.1%)
Onset (days since most recent injection)	5.5	0
Duration (days)	55.6	15
Severity, *n* (%)		
Mild	64 (58.7)	1 (100)
Moderate	36 (33.0)	0 (0)
Severe	7 (6.4)	0 (0)
Musculoskeletal stiffness	*N* = 99 (7.2%)	*N* = 14 (1.3%)
Onset (days since most recent injection)	6.1	33.9
Duration (days)	20.8	17.2
Severity, *n* (%)		
Mild	37 (37.4)	5 (35.7)
Moderate	60 (60.6)	8 (57.1)
Severe	8 (8.1)	1 (7.1)
Upper respiratory tract infection	*N* = 84 (6.1%)	*N* = 66 (6.3%)
Onset (days since most recent injection)	52.8	49.6
Duration (days)	13.1	15.6
Severity, *n* (%)		
Mild	41 (48.8)	25 (37.9)
Moderate	40 (47.6)	33 (50.0)
Severe	5 (6.0)	10 (15.2)
Sinusitis	*N* = 76 (5.5%)	*N* = 47 (4.5%)
Onset (days since most recent injection)	47	40.2
Duration (days)	16.6	18.2
Severity, *n* (%)		
Mild	26 (34.2)	14 (29.8)
Moderate	43 (56.6)	27 (57.4)
Severe	9 (11.8)	7 (14.9)

DBPC, double-blind, placebo-controlled.

i.e. muscular weakness, musculoskeletal stiffness and headache.

Laboratory evaluations, vital signs and physical examinations

There were no clinically meaningful mean changes or shifts in laboratory parameters, vital signs (including systolic or diastolic blood pressure, pulse rate and temperature) or physical examinations. For laboratory parameters with both lower and upper limit potential abnormalities, both decreases and increases were observed in the mean parameter values, indicating incidental fluctuations.

Hypersensitivity, immunogenicity and possible distant muscle weakness

The overall incidence of AEs potentially associated with hypersensitivity (e.g. urticaria, seasonal allergy and eyelid edema) in patients with any onabotulinumtoxinA exposure was low (2.5%) and similar to that reported by patients during the DB phase (2.2% onabotulinumtoxinA and 2.0% placebo). None of these AEs was considered treatment related.

Immunogenicity and antibody formation after onabotulinumtoxinA treatments were evaluated for toxin-neutralizing antibodies from serum samples collected in phase 2 studies. There were no positive toxin-neutralizing antibodies, and one patient had inconclusive results. Assessment of immunogenicity was not conducted in the PREEMPT clinical program because there were sufficient data from the phase 2 studies that demonstrated no heightened risk for immunogenicity in the CM population [8]. Possible distant muscle weakness AEs were assessed by an in-depth medical evaluation of each case performed according to a standard approach [19] using 40 MedDRA terms potentially reflective of distant

Table 4 Serious adverse events reported by more than two patients

Serious adverse event (preferred term)	DBPC exposure		Any onabotulinumtoxinA exposure (N = 1997)
	OnabotulinumtoxinA (N = 1384)	Placebo (N = 1052)	
Overall, *n* (%)	65 (4.7)	32 (3.0)	107 (5.4)
Migraine	5 (0.4)	1 (0.1)	9 (0.5)
Pneumonia	3 (0.2)	2 (0.2)	5 (0.3)
Uterine leiomyoma	3 (0.2)	1 (0.1)	6 (0.3)
Headache	3 (0.2)	0 (0.0)	3 (0.2)
Appendicitis	2 (0.1)	1 (0.1)	2 (0.1)
Cholelithiasis	2 (0.1)	1 (0.1)	2 (0.1)
Breast cancer	2 (0.1)	0 (0.0)	3 (0.2)
Major depression	2 (0.1)	0 (0.0)	2 (0.1)
Endometriosis	1 (0.1)	3 (0.3)	1 (0.1)
Intervertebral disc protrusion	1 (0.1)	2 (0.2)	2 (0.1)
Basal cell carcinoma	1 (0.1)	1 (0.1)	2 (0.1)
Abdominal pain upper	1 (0.1)	0 (0.0)	2 (0.1)
Calculus ureteric	1 (0.1)	0 (0.0)	2 (0.1)
Cholecystitis	1 (0.1)	0 (0.0)	2 (0.1)
Depression	1 (0.1)	0 (0.0)	2 (0.1)
Nephrolithiasis	1 (0.1)	0 (0.0)	2 (0.1)
Small intestinal obstruction	0 (0.0)	1 (0.1)	2 (0.1)

DBPC, double-blind, placebo-controlled.

Table 5 Number (%) of patients with adverse events reported by ≥5% of patients in any dose group in the DBPC phase

Preferred term	OnabotulinumtoxinA dose group			Placebo (N = 1052)
	<150 U (N = 189)	150–200 U (N = 937)	>200 U (N = 258)	
Overall, *n* (%)	157 (83.1)	624 (66.6)	207 (80.2)	598 (56.8)
Neck pain	35 (18.5)	104 (11.1)	52 (20.2)	25 (2.4)
Muscular weakness	24 (12.7)	62 (6.6)	41 (15.9)	3 (0.3)
Upper respiratory tract infection	23 (12.2)	45 (4.8)	16 (6.2)	66 (6.3)
Headache	21 (11.1)	59 (6.3)	31 (12.0)	58 (5.5)
Musculoskeletal stiffness	20 (10.6)	46 (4.9)	33 (12.8)	14 (1.3)
Sinusitis	15 (7.9)	48 (5.1)	13 (5.0)	47 (4.5)
Facial paresis	15 (7.9)	47 (5.0)	47 (18.2)	1 (0.1)
Nausea	13 (6.9)	28 (3.0)	10 (3.9)	29 (2.8)
Musculoskeletal pain	11 (5.8)	39 (4.2)	15 (5.8)	16 (1.5)
Nasopharyngitis	11 (5.8)	38 (4.1)	16 (6.2)	49 (4.7)
Bronchitis	11 (5.8)	24 (2.6)	10 (3.9)	22 (2.1)
Injection site pain	10 (5.3)	38 (4.1)	20 (7.8)	28 (2.7)
Arthralgia	10 (5.3)	14 (1.5)	6 (2.3)	13 (1.2)
Eyelid ptosis	7 (3.7)	40 (4.3)	16 (6.2)	5 (0.5)
Muscle tightness	7 (3.7)	19 (2.0)	17 (6.6)	3 (0.3)
Hypoesthesia facial	7 (3.7)	12 (1.3)	19 (7.4)	4 (0.4)

DBPC, double-blind, placebo-controlled.

spread. It was determined that none of these AEs was due to distant spread of toxin.

Discussion

This pooled analysis supports onabotulinumtoxinA safety and tolerability for headache prophylaxis in adult patients with CM. Multiple onabotulinumtoxinA treatments were safe and well tolerated, with low AE-related discontinuation rates. In the DBPC phase, the overall AE rate for onabotulinumtoxinA-treated patients was lower in the PREEMPT population (62.4%) [8] compared with the pooled CM safety population (71.4%). Individual AE rates for onabotulinumtoxinA-treated patients, such as neck pain (9% vs. 14%), muscle weakness (4% vs. 9%), headache (5% vs. 8%) and facial paresis (2% vs. 8%), were also lower in the PREEMPT clinical program [11] compared with the pooled CM safety population, respectively. This reduction in AE incidence probably reflects the optimized dosing regimen, injection paradigm, experience of the injectors in the trial, and modified injection sites used in PREEMPT [8,12,13,17].

Focally administered onabotulinumtoxinA inhibits the release of acetylcholine at the neuromuscular junction and has been used therapeutically in disorders characterized by muscle hyperactivity [20,21]. Muscular weakness, eyelid ptosis and facial

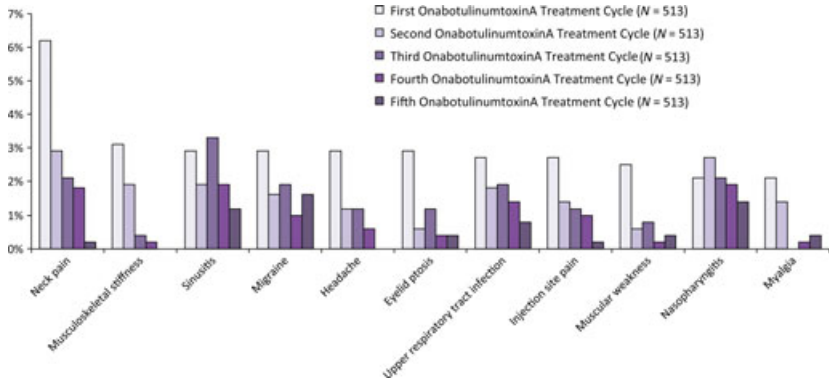

Figure 2 Adverse events reported by ≥2% of patients who completed five cycles of onabotulinumtoxinA treatment per treatment cycle, including subjects who received onabotulinumtoxinA at all five injection cycles and completed the study.

paresis are thus expected side effects of onabotulinumtoxinA due to its action on muscle activity and were amongst the most frequently reported AEs. Most of the muscular weakness was local to the head, neck or shoulder/upper arm regions, which involved either the injected muscles or adjacent muscles. Weakness of nearby muscles may also occur due to local diffusion; however, distant effects were not reported.

Headache and migraine were frequently (≥2%) reported AEs; they occurred more often with onabotulinumtoxinA (8.0% and 3.8%, respectively) than with placebo (5.5% and 2.4%, respectively), although the distribution of headache severity was similar between the two groups (Table 3). Additionally, for the subset of patients that completed all five treatment cycles of the PREEMPT clinical program, the incidence of migraine and headache decreased after the first treatment cycle (Fig. 2). Patients treated with onabotulinumtoxinA did not have a worsening of headache or migraine, and the onabotulinumtoxinA-treated patients in the PREEMPT clinical program [8] experienced significant improvements in multiple headache symptom measures compared with those treated with placebo.

The chronic nature of CM requires repeated treatments, and thus the long-term safety of onabotulinumtoxinA treatment is an important consideration. For other conditions, treatment also requires long-term, repeated, multi-muscle injection of onabotulinumtoxinA in the head/neck areas. A 10-year multicenter study of onabotulinumtoxinA treatment for primary hemifacial spasm showed that the rate of local AEs (including upper lid ptosis, facial weakness and diplopia) diminished significantly in the tenth year of treatment compared with the first year, whilst efficacy was maintained [22]. In a long-term cervical dystonia study [23], 326 patients were treated with up to 15 onabotulinumtoxinA treatments (median 9), and mean dose per session ranged from 148 to 213 U over a mean of 2.5 years (range 3.2 months to 4.2 years). The incidence of muscular weakness and dysphagia, the two most commonly reported AEs, decreased with repeat injection sessions. Our analysis shows that no new safety findings emerged in patients receiving onabotulinumtoxinA long-term treatment over 56 weeks compared with the first treatment cycle, suggesting that there is no cumulative toxicity with long-term onabotulinumtoxinA use.

Although not specifically indicated for CM, other currently prescribed treatments can have significant treatment-limiting, systemic AEs. Antiepileptics are associated with systemic AEs including gastrointestinal problems, somnolence, difficulty with concentration/attention, nervousness, alopecia, tremor, liver toxicity and paresthesia. Beta-blockers are associated with depression, fatigue, dizziness, sexual dysfunction and sleep disturbances [24].

In the only other large DBPC study in CM (n = 328), which compared topiramate with placebo for CM [9], AEs were reported by the majority of patients in both treatment groups (82.5% topiramate vs. 70.2% placebo). The most common AEs associated with topiramate were paresthesia (28.8% vs. 7.5% placebo), upper respiratory tract infection (13.8% vs. 12.5% placebo) and fatigue (11.9% vs. 9.9% placebo). Additional AEs occurring in >5% of the topiramate-treated patients were hypoesthesia, dry mouth, difficulty with concentration or memory, taste perversion, nausea and somnolence [9]. In a small pilot study of CM prophylaxis (n = 60) comparing onabotulinumtoxinA (two IM injections of 100–200 U every 12 weeks) and topiramate (100–200 mg/day), efficacy results were comparable. However, fewer treatment-related AEs were reported with onabotulinumtoxinA (69.2%) than with topiramate (86.2%). A greater percentage of topiramate-treated than onabotulinumtoxinA-treated patients (24.1% vs. 7.7%, respectively) discontinued the study due to treatment-related AEs [25].

Side-effect profiles may vary amongst different botulinum neurotoxin preparations [26]. Safety information in the present analysis is specific to the formulation of onabotulinumtoxinA manufactured by

Allergan Inc. and cannot be generalized to other botulinum neurotoxin preparations or serotypes.

Conclusions

This pooled analysis of four DBPC trials confirms the favorable safety and tolerability profile of repeated treatment with onabotulinumtoxinA (five cycles over 56 weeks; 75–260 U) for the prophylaxis of headache in adults with CM.

Clinical experience and optimal muscle targeting is important in improving the safety and tolerability profile in onabotulinumtoxinA treatment [26]. Our analysis shows that the dosing and injection paradigm used in the PREEMPT clinical program (155–195 U), which resulted in fewer individual AEs in addition to demonstrating robust long-term (up to 56 weeks) efficacy [6–8,14], is preferred for this CM patient population.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Adverse events reported in ≥2% of patients clustered by system organ class.
Table S1. Summary of studies.
Table S2. Treatment-related adverse events reported in ≥2% of patients.

References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; **33:** 629–808.
2. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* 2008; **71:** 559–566.
3. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry* 2010; **81:** 428–432.
4. Dodick DW. Clinical practice. Chronic daily headache. *N Engl J Med* 2006; **354:** 158–165.
5. Natoli J, Manack A, Dean B, *et al*. Global prevalence of chronic migraine: a systematic review. *Cephalalgia* 2010; **30:** 599–609.
6. Aurora SK, Dodick DW, Turkel CC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010; **30:** 793–803.
7. Diener HC, Dodick DW, Aurora SK, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010; **30:** 804–814.
8. Dodick DW, Turkel CC, DeGryse R, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010; **50:** 921–936.
9. Silberstein SD, Lipton RB, Dodick DW, *et al*. Efficacy and safety of topiramate for the treatment of chronic

migraine: a randomized, double-blind, placebo-controlled trial. *Headache* 2007; **47:** 170–180.
10. Diener HC, Bussone G, Van Oene JC, *et al*. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; **27:** 814–823.
11. Allergan Inc. *BOTOX (onabotulinumtoxinA) Full Prescribing Information*. Irvine, CA: Allergan Inc., 2013.
12. Mathew NT, Frishberg BM, Gawel M, *et al*. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache* 2005; **45:** 293–307.
13. Silberstein SD, Stark SR, Lucas SM, *et al*. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc* 2005; **80:** 1126–1137.
14. Aurora SK, Winner P, Freeman MC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache* 2011; **51:** 1358–1373.
15. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia* 2004; **24**(Suppl. 1)**:** 9–160.
16. Olesen J, Bousser MG, Diener HC, *et al*. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006; **26:** 742–746.
17. Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Onabotulinumtoxin-A for chronic migraine: PREEMPT trials establish a safe and effective dose and injection paradigm. Presented at the 2nd European Headache and Migraine Trust International Congress – EHMTIC, #78: 2010.
18. International Federation of Pharmaceutical Manufacturers and Associations. *Introductory Guide, Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1*. Reston, VA: MedDRA Maintenance and Support Services Organization, 2008.
19. Brin MF, Boodhoo TI, Pogoda JM, *et al*. Safety and tolerability of onabotulinumtoxinA in the treatment of facial lines: a meta-analysis of individual patient data from global clinical registration studies in 1678 participants. *J Am Acad Dermatol* 2009; **61:** 961–970.
20. Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta-analysis. *Curr Med Res Opin* 2004; **20:** 981–990.
21. Dolly O. Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. *Headache* 2003; **43**(Suppl. 1)**:** S16–S24.
22. Defazio G, Abbruzzese G, Girlanda P, *et al*. Botulinum toxin A treatment for primary hemifacial spasm: a 10-year multicenter study. *Arch Neurol* 2002; **59:** 418–420.
23. Brin MF, Comella CL, Jankovic J, Lai F, Naumann M. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord* 2008; **23:** 1353–1360.
24. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. *Neurol Sci* 2008; **29** (Suppl. 1)**:** S110–S122.
25. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxinA (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. *Headache* 2009; **49:** 1466–1478.
26. Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of botulinum toxin type A following long-term use. *Eur J Neurol* 2006; **13**(Suppl. 4)**:** 35–40.