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OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline

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ABSTRACT

Acute headache medication overuse (MO) is common in patients with chronic migraine (CM). We evaluated safety and efficacy of onabotulinumtoxinA as preventive treatment of headache in CM patients with baseline MO (CM + MO) in a planned secondary analysis from two similarly designed, randomized, placebo-controlled, parallel, Phase III trials. Patients were randomized to treatment groups (155–195 U of onabotulinumtoxinA or placebo) using MO (patient-reported and diary-captured frequency of intake) as a stratifying variable. Of 1384 patients, 65.3% (n = 904) met MO criteria (onabotulinumtoxinA: n = 445, placebo: n = 459). For the CM + MO subgroup at Week 24, statistically significant between-treatment group mean changes from baseline favoring onabotulinumtoxinA versus placebo were observed for headache days (primary endpoint: −8.2 vs. −6.2; $p < 0.001$) and other secondary endpoints: frequencies of migraine days ($p < 0.001$), moderate/severe headache days ($p < 0.001$), cumulative headache hours on headache days ($p < 0.001$), headache episodes ($p = 0.028$), and migraine episodes ($p = 0.018$) and the percentage of patients with severe Headache Impact Test-6 category ($p < 0.001$). At Week 24, change from baseline in frequency of acute headache medication intakes (secondary endpoint) was not statistically significant ($p = 0.210$) between groups, except for triptan intakes ($p < 0.001$), where the onabotulinumtoxinA-treated group was favored. OnabotulinumtoxinA was effective and well tolerated as headache prophylaxis in CM + MO patients.

1. Introduction

Chronic migraine (CM) is a prevalent and highly disabling primary headache disorder [1,2] afflicting approximately 2.0% of the global population [3]. Patients suffering from CM (≥15 headache days per month for ≥3 months, of which ≥8 headache days per month are migraine and/or are treated and relieved by triptan/ergot) [4] report lower health-related quality of life (HRQoL), use a greater amount of direct and indirect medical/healthcare resources, and incur greater losses of productivity than patients suffering from episodic migraine (<15 headache days per month) [1,5,6]. Treatment of CM generally involves preventive medications, taken on a daily basis whether or not headache is present, and acute treatments, taken when attacks occur to relieve pain and restore function [7]. In addition, identifying and eliminating exacerbating factors, including the overuse of acute medications, is the conventional approach to treatment [7–9].

The frequent intake of analgesics and other acute headache medications may lead to the development of a secondary headache disorder classified as medication overuse headache (MOH), or, conversely, increasing headache frequency may lead to increased intake of acute headache medications. Improvement of headache symptoms upon withdrawal of drug therapy is the major criterion that distinguishes between these two possibilities [8]. Most CM patients seeking treatment in tertiary headache clinics overuse acute headache medications [10]. One study found that as many as 73% of CM patients overuse acute headache medications [7], including simple and combination analgesics, triptans, and opioids. The role of acute medication

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overuse in CM remains unclear: it may be unrelated to progression and consumption simply reflects a more aggressive disease biology, or it may contribute to the transformation from episodic to CM [7,11,12].

Although not always successful [13–15], and although there are no randomized, placebo-controlled trials demonstrating the effectiveness of drug withdrawal alone, termination of acute headache medication overuse is recommended. However, cessation of acute medications is often not a pragmatic treatment solution for many patients, and preventive medication in addition to rescue therapy is necessary to ensure compliance and successful outcomes. In the absence of evidence, textbooks and treatment guidelines have suggested that preventive migraine medications will have limited or no effectiveness in the presence of medication overuse [7,8,10,11,16]. Contrary to these assertions, data presented in this paper, as well as in one other report [17], suggest that certain headache prophylaxis treatments are effective in the preventive treatment of CM, even in the presence of acute medication overuse [18].

Until recently, no global regulatory body had approved any acute or preventive treatment specifically for the severely affected CM population. OnabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) is the first headache preventive treatment to receive such approval. Prior to this approval, there have been little controlled data on preventive treatments in CM [17,19,20] and very limited evidence-based data available to help physicians care for these patients [4]. A comprehensive Phase III program, the PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) clinical program (PREEMPT 1 and 2), demonstrated that onabotulinumtoxinA treatment is safe, tolerable, and efficacious as long-term (up to 56 weeks) headache prophylaxis in adults with CM [19,21]. These studies provide an excellent opportunity to test the hypothesis that headache preventive treatment in adults with CM may have benefits even in the face of acute headache medication overuse.

Recent guidelines published by the International Headache Society (IHS) clinical trials subcommittee recognize the high prevalence of medication overuse in CM patients and recommend stratification of these patients in clinical trials [22]. To ensure that the study population reflected the population of patients seen in clinical practice, the PREEMPT clinical program included and stratified CM patients with and without evidence of acute headache medication overuse during the 28-day baseline [19], which is in accordance with the IHS guidelines [22]. Patients with CM enrolled into either PREEMPT study were stratified using a predefined algorithm, based on their frequency of acute headache medication intakes during the 28-day baseline screening period, as "medication overuse-yes" (CM + MO) or "medication overuse-no" (CM − MO) [23,24] and not based on a diagnosis of MOH, which is a secondary headache disorder. The PREEMPT 1 and 2 pooled efficacy, safety, and tolerability results for the CM + MO patient subgroup are the focus of this report.

2. Methods

2.1. Study design

The details of the PREEMPT study design have been previously described elsewhere [19]. The PREEMPT 1 and 2 clinical trials consisted of a 28-day screening period (baseline), a 24-week double-blind (DB) phase with 2 injection cycles, and a 32-week open-label phase with 3 injection cycles. Study visits occurred at every 4 weeks. During baseline, and throughout the trials, patients used an interactive voice response system daily telephone diary to record their headache symptoms and acute headache medication intakes.

Both studies were conducted in accordance with the Declaration of Helsinki ethical principles, Good Clinical Practices, and principles of informed consent. Each investigator obtained approval from an Independent Ethics Committee or a local Institutional Review Board prior to study initiation. Written informed consent was obtained from each randomized patient [23,24].

2.2. Study participants

Inclusion and exclusion criteria for the PREEMPT 24-week DB phase have been previously described elsewhere [19,23,24]. Men or women aged 18 to 65 years with a history of migraine as defined in the second edition of the International Classification of Headache Disorders (ICHD-II) Section 1, Migraine [1], with the exception of "complicated migraine," were included. Eligible patients were recruited from 6 countries (United States, Canada, Germany, United Kingdom, Switzerland, and Croatia) and were required to have headache occurring on ≥15 days in 4 weeks, with each day consisting of ≥4 h of continuous headache, and ≥50% of baseline headache days being migraine or probable migraine days (referred to as migraine days) and ≥4 distinct headache episodes lasting ≥4 h each month. Patients diagnosed with another primary or secondary headache disorder (i.e., MOH) were not enrolled. Due to the high prevalence of acute headache medication overuse in patients with CM, these patients were enrolled into the PREEMPT program and were stratified. The investigators for these studies were headache experts and, per protocol, they were instructed to recruit patients who had a primary migraine headache diagnosis and to exclude patients with secondary headache disorders. Patients were excluded if they had used any headache prophylactic medication within 4 weeks prior to start of baseline, or had previous exposure to any botulinum toxin serotype. Patients were also excluded if they were not in the baseline phase for at least 28 days or they did not record a minimum of 20 days' worth of diary data during the baseline.

2.3. Acute headache medication overuse

Investigators were trained to carefully evaluate potential trial participants, and although opioid intake was not a specific protocol exclusion criterion, patients who were frequently using opioids were an example of participants who should be carefully screened in view of the year-long trial duration. Once enrolled, patients could take acute headache medications as prescribed. Per protocol, investigators did not provide any further instructions or counsel to patients with regard to changing their usual type and pattern of acute headache medication intake.

To be categorized as CM with acute headache medication overuse (CM + MO) during the 28-day baseline, the following criteria had to be met: (1) patients reported the intake of simple analgesics (e.g., acetaminophen) on ≥15 days or (2) patients reported the intake of other medication types or combination of types for ≥10 days, and (3) intakes, overall and in the case of each of the subtypes, had to occur on ≥2 days/week in each week that had at least 5 diary days. Counts were standardized to 28-day equivalents (by prorating) if only 20–27 days of diary data were reported. Also, unless there were diary data for ≥5 days for a given week, intakes on fewer than 2 days/week were insufficient to exclude that patient from the CM + MO subgroup (e.g., a patient reporting medication intake every day for 3 weeks and not reporting any diary data for the remaining week would still be considered to be CM + MO).

2.4. Randomization, stratification, and study treatment

Patients' baseline acute headache medication overuse status was determined using data from the 28-day baseline diaries. Randomization was stratified based on patients' acute headache medication overuse status at the end of the 28-day baseline period, with treatments balanced in blocks of 4 within each acute headache medication overuse stratum for each investigator site.