Research Submission

Botulinum Toxin Type A for the Prophylaxis of Chronic Daily Headache: Subgroup Analysis of Patients Not Receiving Other Prophylactic Medications: A Randomized Double-Blind, Placebo-Controlled Study

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Objective.—To assess the efficacy and safety of botulinum toxin type A (BoNT-A; BOTOX®, Allergan, Inc., Irvine, CA) for the prophylaxis of headaches in patients with chronic daily headache (CDH) without the confounding factor of concurrent prophylactic medications.

Background.—Several open-label studies and an 11-month, randomized, double-blind, placebo-controlled study suggest that BoNT-A may be an effective therapy for the prophylaxis of headaches in patients with CDH.

Design and Methods.—This was a subgroup analysis of an 11-month, randomized double-blind, placebo-controlled study of BoNT-A for the treatment of adult patients with 16 or more headache days per 30-day periods conducted at 13 North American study centers. All patients had a history of migraine or probable migraine. This analysis involved data for patients who were not receiving concomitant prophylactic headache medication and who constituted 64% of the full study population. Following a 30-day screening period and a 30-day single-blind, placebo injection, eligible patients were injected with BoNT-A or placebo and assessed every 30 days for 9 months The following efficacy measures were analyzed per 30-day periods: change from baseline in number of headache-free days; change from baseline in headache frequency; proportion of patients with at least 30% or at least 50% decrease from baseline in headache frequency; and change from baseline in mean headache severity. Acute medication use was assessed, and adverse events were recorded at each study visit.

Results.—Of the 355 patients randomized in the study, 228 (64%) were not taking prophylactic medication and were included in this analysis (117 received BoNT-A, 111 received placebo injections). Mean age was 42.4 ± 10.90 years; the mean frequency of headaches per 30 days at baseline was 14.1 for the BoNT-A group and 12.9 for the placebo group ($P = .205$). After two injection sessions, the maximum change in the mean frequency of headaches per 30 days was −7.8 in the BoNT-A group compared with only −4.5 in the placebo group ($P = .032$), a statistically significant between-group difference of 3.3 headaches. The between-group difference favoring BoNT-A treatment continued to improve to 4.2 headaches after a third injection session ($P = .023$). In addition, BoNT-A treatment at least halved the frequency of baseline headaches in over 50% of patients after three injection sessions compared to baseline. Statistically significant differences between BoNT-A and placebo were evident for the change from baseline in headache frequency and headache severity for most time points from day 180 through day 270. Only 5 patients (4 patients receiving BoNT-A treatment; 1 patient receiving placebo) discontinued the study due to adverse events and most treatment-related events were transient and mild to moderate in severity.

Conclusions.—BoNT-A is an effective and well-tolerated prophylactic treatment in migraine patients with CDH who are not using other prophylactic medications.

Chronic daily headache (CDH) refers to a group of headache disorders that are defined in part by the presence of headache on more than 15 days per month for more than 3 months.[1] Approximately 4% (~12 million) of the population worldwide experience daily or near-daily headaches.[2-6] It has been estimated that approximately 70% to 80% of patients presenting to headache clinics in the United States are experiencing CDH, of whom the vast majority experience transformed migraine.[7] The disability and impact associated with this disorder is substantial and touches almost every aspect of the patient's life. These patients experience significantly diminished health-related quality of life and mental health, as well as impaired physical, social, and occupational functioning.[8-10] In addition, for a significant number of patients with CDH, the clinical course is often complicated and perpetuated by the overuse of acute headache medication.

The management of patients with CDH represents one of the major challenges for practicing clinicians. The use of prophylactic medications for CDH is supported mainly by open-label studies. A few controlled studies have been performed; however, these studies do not account for symptomatic medication overuse or concomitant prophylactic medication as major confounders, or do not provide specific diagnoses for patients with CDH.[11-15] Although there are well-designed placebo-controlled studies that demonstrate the effectiveness of several prophylactic medications in patient populations with less headache burden, tolerability continues to be an issue for many patients as reflected by the high discontinuation rates (13% to 21%) in these studies.[16-19] Tolerability issues may be one reason that prophylactic medications are vastly underutilized for those with migraine, even when the patients meet the frequency or disability criteria for the use of prophylactic medications.[20,21]

Botulinum toxin type A (BoNT-A; BOTOX®, Allergan, Inc., Irvine, CA) is a focally administered neurotoxin that inhibits the release of acetylcholine at the neuromuscular junction.[22] It is used therapeutically in disorders characterized by muscle hyperactivity, including dystonia and movement disorders, spasticity, cerebral palsy, and gastrointestinal and urological disorders.[23] Preclinical *in vitro* and *in vivo* evidence demonstrates that BoNT-A also inhibits the release of nociceptive mediators such as glutamate, substance P, and calcitonin gene-related peptide (CGRP) from nociceptive fibers, suggesting that BoNT-A may have direct antinociceptive action distinct from its neuromuscular activity.[24-26] Presumably, through a peripheral mechanism, BoNT-A has also been shown to inhibit central sensitization of central trigeminovascular neurons,[27] which is felt to be integral to the development, progression, and maintenance of the headache associated with migraine.[28] Central sensitization is also considered to be a potential mechanism underlying the development of chronic daily headache in patients with migraine.[1] In addition, several clinical trials suggest that BoNT-A may be an effective and safe prophylactic headache medication in the treatment of migraine.[29,30] The results of three large-scale, uncontrolled, retrospective studies involving 1011 patients with a variety of episodic and chronic headache disorders provide further support for a role for BoNT-A in the prophylaxis of headaches.[31-33]

The therapeutic value of BoNT-A in the prophylaxis of headaches has been further investigated in an exploratory phase 2, randomized, double-blind, placebo-controlled study in 355 patients with CDH. The results of this study, reported elsewhere in this issue,[34] demonstrated that BoNT-A, at 105 U to 260 U, was safe and well tolerated. Furthermore, BoNT-A produced beneficial effects relative to placebo on most efficacy parameters assessed, and statistically significant differences relative to placebo were observed for some parameters. Despite the observation of consistent numerical advantages for BoNT-A over placebo in this study, the prospectively defined primary efficacy end point was not met; however, the secondary and

other prospectively defined efficacy end points were achieved. This suggested that further analysis of the efficacy data was warranted to determine whether consistent statistically significant advantages were present in specific patient subgroups.

In this exploratory phase 2 study, approximately one-third of patients were receiving one or more other headache prophylactic therapies. Yet, these patients still qualified for the study by having 16 or more headache days during the 30-day baseline period. The discontinuation of concurrent prophylactic therapy was not required by the study protocol. While some patients with CDH may supplement their current headache treatment regimens with additional prophylactic therapies, others may stop other prophylactic medication when initiating a new therapy. Discontinuation of prophylactic headache medication has been specified in study protocols for several of the contemporary prophylactic medication trials for migraine.[14,16-19] Patients taking a prophylactic treatment in this study still reported 16 or more headache-days, which may be an indication of a refractory subpopulation. In order to determine the impact of BoNT-A alone, the data were analyzed for the subgroup of patients in this study who were not receiving prophylactic therapy. This corresponds to almost two-thirds of the study population, divided approximately equally between BoNT-A and placebo treatment. The results of this subgroup analysis are presented here.

METHODS

Study Design.—Full details of the study design, population characteristics, treatment paradigm, and schedule, as well as efficacy and safety assessments, are described in the accompanying article.[34] This study was conducted in compliance with the ethical principles in the Declaration of Helsinki regarding biomedical research on human subjects and with standard informed consent regulations. Prior to study initiation, the investigators obtained Institutional Review Board's approval.

This placebo-controlled study consisted of a 30-day baseline period during which headache frequency was monitored; a 30-day single-blind placebo-run-in period during which response to placebo was determined; and a 9-month double-blind treatment period during which patients received three treatment cycles (BoNT-A or placebo) separated by 90 days. Throughout the study, specific characteristics of the patient's headache episodes were captured daily using an electronic telephone diary (ClinPhone, Nottingham, UK).

Efficacy Measures.—Data regarding the occurrence of headaches and their intensity were obtained from the electronic telephone diaries and analyzed for the following: (i) mean change from baseline in the number of headache-free days per 30-day periods; (ii) mean change from baseline in number (ie, frequency) of headaches per 30-day periods; (iii) percentage of patients achieving a decrease from baseline in the frequency of headaches per 30-day periods of $\geq 30\%$ (30% response rate) or $\geq 50\%$ (50% response rate); (iv) mean change from baseline in headache severity (recorded in telephone diaries on scale from 0 to 3 corresponding from none to severe [0 = none, 1 = mild, 2 = moderate, 3 = severe]) per 30-day periods.

Safety Measures.—At each visit following treatment at day 0, adverse events were recorded and documented. The relationship between an adverse event and study treatment was assessed by the investigator as none, possible, probable, or definite.

Health Outcome Measures.—Health outcomes measures that were collected in the study included MIDAS, SF-36, Headache Pain Specific Quality of Life measure, and the Headache Impact Questionnaire. However, for this analysis of the subgroup of patients not taking concurrent headache prophylaxis medications, only the MIDAS and SF-36 were analyzed.

Statistical Analyses.—This article presents an analysis of data for the subgroup of patients who received no prophylactic therapy during the study. In the planned analysis of the data for the total study population (reported in accompanying manuscript),[34] efficacy data were analyzed for placebo responders and placebo nonresponders separately. In the subgroup analysis presented in this article, data for placebo responders and placebo nonresponders were pooled, since trends for both strata were generally equivalent.

The Wilcoxon rank-sum test was used to assess the statistical significance of differences between treatment groups in baseline characteristics (age, years since onset, age at onset), and per 30-day periods the change from baseline in number of

Table 1.—Baseline Characteristics of CDH Patient Population With and Without Concomitant Prophylactic Medication*

Baseline Characteristics	No-Prophylactic Medication			Receiving Prophylactic Medication
	BoNT-A (n = 117)	Placebo (n = 111)	Total (n = 228)	Total (n = 127)
Age [mean years (SD)]	42.2 (10.35)	42.5 (11.49)	42.4 (10.90)	45.6 (9.60)
Sex (%)				
Male	9.4	19.8	14.5	17.3
Female	90.6	80.2	85.5	82.7
Race (%)				
Caucasian	87.2	83.8	85.5	92.1
Non-Caucasian	12.8	16.2	14.5	7.9
Years since onset, mean years (SD)	15.3 (13.17)	14.3 (12.77)	14.8 (12.96)	14.0 (11.48)
Age at onset, mean years (SD)	26.2 (12.24)	27.6 (13.11)	26.9 (12.67)	31.1 (13.10)
Baseline MIDAS, mean score (SD)	54.0 (44.38)	55.7 (60.03)	54.8 (52.47)	62.6 (59.10)
Baseline Beck Depression Inventory, mean score (SD)	6.9 (6.55)	7.3 (7.04)	7.1 (6.78)	9.0 (6.83)
Acute headache pain medication overuse, %	53.8	39.6	46.9	48.0
Headache type, %				
Transformed migraine	40.2	32.4	36.4	49.6
CTTH	6	9	7.5	7.1
Incidence of patients with migraine or probable migraine, %	100	100	100	100
Frequency of headaches per 30-day periods at baseline	14.1	12.9	13.5	12.5
Number of headache days per 30-day periods at baseline	23.4	23.5	23.4	23.3

*Acute headache pain medication overuse ($\geq$15 days and $\geq$2 days/week per 30-day periods).
SD, standard deviation; MIDAS, migraine disability assessment; CTTH, chronic tension-type headache.

headache-free days, frequency of headaches, and usual headache severity were analyzed. Pearson's χ^2 test or Fisher's exact test was used for comparison of baseline characteristics (sex and race), adverse events, 30% response rate, and 50% response rate.

RESULTS

Demographics and Baseline Characteristics.—Of the 355 patients who were enrolled in the study, 228 (64%) were not taking prophylactic headache medication and were the focus of this analysis. Of these, 117 received BoNT-A and 111 received placebo. The baseline characteristics of the no-prophylactic-medication patients and those receiving prophylaxis are given in Table 1.

For the no-prophylactic-medication subgroup, there were no statistically significant baseline differences between the two treatment groups, except for gender (BoNT-A: 90.6% female; placebo: 80.2% fe-

male; $P = .025$). Comparison of this subgroup with the patient population receiving prophylaxis showed that the no-prophylactic-medication subgroup was younger (mean age: 42.4 vs 45.6 years; $P = .010$), had a younger age at onset (mean age: 26.9 vs 31.1 years; $P = .005$), and a lower Beck Depression Inventory (mean score: 7.1 vs 9.0; $P = .004$) at baseline.

A total of 172 (75.4%) subjects completed the study; 74.4% (87/117) in the BoNT-A group and 76.6% (85/111) in the placebo group. Only 5 (2.2%) patients (BoNT-A: 4 patients; placebo: 1 patient) in the no-prophylactic-medication subgroup withdrew from the study due to adverse events. The main reasons for adverse event-related withdrawal in the BoNT-A group were muscle weakness (1.7% [2/117]) and neck pain (1.7% [2/117]).

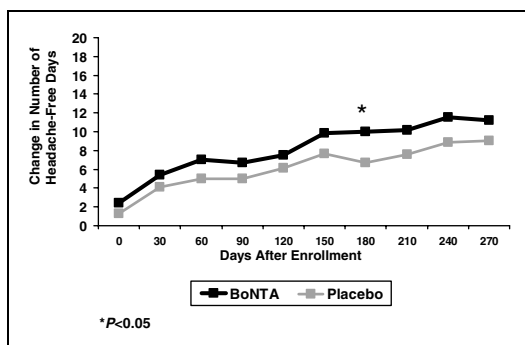**BoNT-A Treatment.—**The mean (median) total BoNT-A dose used for the three treatments (day 0,

Fig 1.—BoNT-A in CDH with no-prophylactic therapy: Mean change from baseline in number of headache-free days per 30-day periods. The baseline period (day −60 to day −30) precedes the 30-day placebo run-in period (day −30 to day 0). Mean frequency of headache-free days at baseline: BoNT-A (6.6), placebo (6.5).
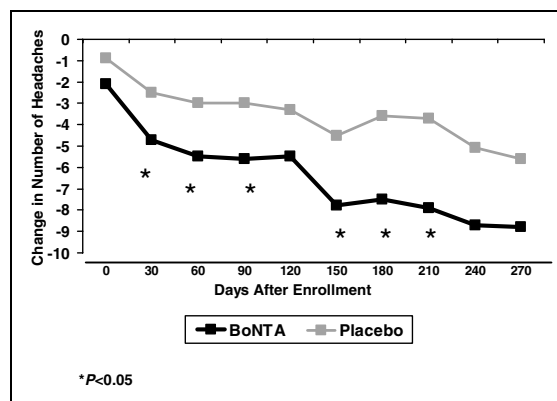

Fig 2.—BoNT-A in CDH with no-prophylactic therapy: Mean change from baseline in the frequency of headaches per 30-day periods. The baseline period (day −60 to day −30) precedes the 30-day placebo run-in period (day −30 to day 0). Mean frequency of headaches at baseline: BoNT-A (14.1), placebo (12.9).

day 90, and day 180) was 190.8 (195.0), 191.8 (200.0), and 190.6 (200.0), respectively.

Efficacy.—*Headache-Free Days.*—At baseline the number of headache-free days was similar for both treatment groups (BoNT-A: 6.6 days; placebo: 6.5 days; $P = .866$). Beginning with the first month of treatment, the mean change from baseline in the number of headache-free days improved over the course of the study in both treatment groups but the increase was greater in the BoNT-A group than the placebo group, with a statistically significant difference observed at day 180 (increase in headache-free days: BoNT-A: 10.0 days; placebo: 6.7; $P = .038$) (Figure 1).

Frequency of Headaches.— The baseline mean frequency of headaches was similar for the two treatment groups (BoNT-A: 14.1 headaches; placebo: 12.9 headaches; $P = .205$). Patients reported that headaches often lasted longer than 24 hours; consequently, the mean number of headache days was greater than the mean number of headaches during the 30-day baseline period.

Beginning within the first month of treatment, and throughout the treatment phase of the 9-month study, there was a decrease in the mean change from baseline for the frequency of headaches in both treatment groups. At all time points, the mean decrease from baseline was greater in the BoNT-A group. The between-group difference was statistically significant at the first month ($P = .004$), and at most time points thereafter (Figure 2), Always favoring BoNT-A, the

between-group difference in the mean change from baseline frequency of headaches ranged from 2.2 to 4.2 headaches per 30-day periods.

Response Rates.—Response rates were determined for patients achieving a decrease from baseline of $\geq 30\%$ (30% RR) and $\geq 50\%$ (50% RR) in the frequency of headaches per 30-day periods. Overall, a high percentage of the overall study population had at least a 30% RR. However, the 30% RR was greater for BoNT-A compared with placebo, and the difference was statistically significant at most time points up to day 240 (Figure 3A). The maximum 30% RR of 78% was observed in the BoNT-A group at day 150, compared with 57% of placebo patients having a 30% RR at this time point ($P = .040$). Similar differences between BoNT-A and placebo were observed for 50% RR, with differences between groups reaching significance at day 150 and day 210 time points (Figure 3B). At least 50% of the BoNT-A group were 50% responders from day 150 onward.

The relative differences between the percentages of BoNT-A- and placebo-treated patients achieving a decrease from baseline of $\geq 30\%$ or $\geq 50\%$ in headache frequency diminished over the last three time points (Figure 3A and 3B). It is unclear why this occurred; however, the percentage of patients in the placebo group achieving a reduction $\geq 30\%$ or 50% is more variable across the duration of the study than the
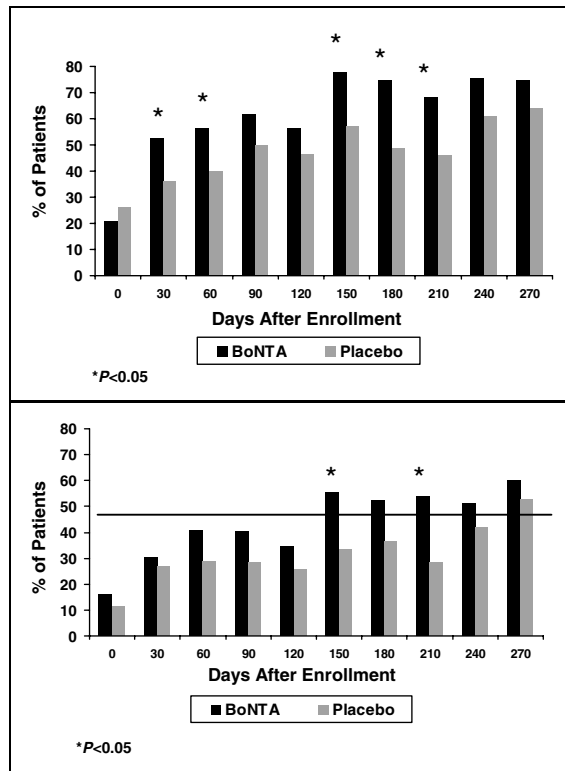
Fig 3.—BoNT-A in CDH with no-prophylactic therapy: Percentage of patients achieving a decrease in mean headache frequency from baseline of (A) ≥30% or (B) ≥50% in a 30-day period. The baseline period (day −60 to day −30) precedes the 30-day placebo run-in period (day −30 to day 0).

Fig 4.—BoNT-A in CDH with no-prophylactic therapy: Mean change from baseline in usual headache severity per 30-day periods. The baseline period (day −60 to day −30) precedes the 30-day placebo run-in period (day −30 to day 0). Mean headache severity rating at baseline: BoNT-A (.9), placebo (.8).

BoNT-A treatment group. Furthermore, this observation was not mirrored by other efficacy variables.

Headache Severity. — At baseline, mean usual headache severity was similar for the two treatment groups (BoNT-A: .9; placebo: .8) [0 (no pain) to 3 (severe pain) scale]. Mean usual headache severity decreased over the course of the study in both groups but plateaued at approximately −.4 in the placebo group from day 60 onward. In contrast, mean usual headache severity in the BoNT-A group continued to decrease to a −.7 at day 240 (Figure 4). The decrease in mean usual headache severity from baseline was greater in the BoNT-A group throughout the study and the difference between groups was statistically significant from day 180 to day 270.

Health Outcomes Measures. — At day 90, mean improvements favored BoNT-A on the SF-36 for role physical-functioning (BoNT-A: 15.6 vs placebo: 4.3), and bodily pain (BoNT-A: 9.1 vs placebo: 3.8). How-
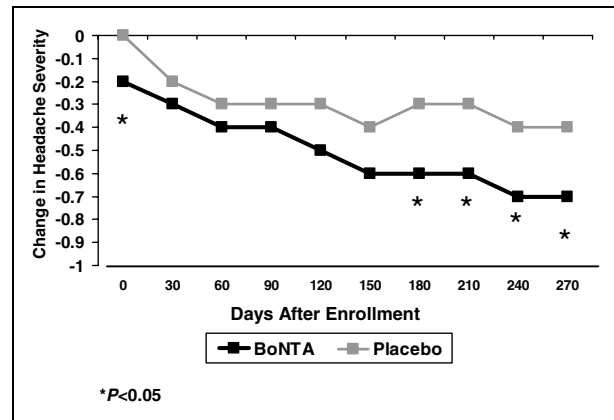
ever, these results were not statistically significant. There were no other observable differences in the other domains of the SF-36. The mean change in the number of headache days affected was consistently lower, but not statistically significant, favoring BoNT-A-treated patients at days 90, 180, and 270. Furthermore, there were no differences between BoNT-A and placebo in any of the mean changes from baseline on the five MIDAS questions and usual severity of headaches.

Acute Medication Use. — During the 30-day baseline period of the study, BoNT-A-treated patients used acute headache pain medication 15.5 days, compared to 13.5 days for the placebo group ($P = .069$). At day 180, the mean change from baseline in the number of days using acute pain medication was significantly reduced by −7.8 days for patients in the BoNT-A treatment group and −4.1 days in the placebo group ($P = .015$). In addition, there were statistically significant differences between BoNT-A and placebo groups in days using acute headache pain medication at day 90, day 210, and day 240. No significant differences were observed at baseline between the BoNT-A-treated patients and the placebo group in the number of uses of acute headache pain medication (BoNT-A: 25.1 vs placebo: 21.0; $P = .058$). Following BoNT-A treatment, acute headache medication use was significantly reduced at day 90 (BoNT-A, −10.3 vs

Table 2.—CDH With No-Prophylactic Therapy*

	BOTOX (n = 117)	Placebo (n = 111)	*P* Values**
Patients reporting ≥1 adverse event (%)	76.1 (89)	63.1 (70)	.033[†]
Muscular weakness (%)	24.8 (29)	0 (0)	<.001[†]
Infection (general) (%)	12 (14)	13.5 (15)	.726
Neck pain (%)	12 (14)	0 (0)	<.001[†]
Headache (%)	10.3 (12)	9 (10)	.750
Infection (respiratory) (%)	9.4 (11)	10.8 (12)	.724
Blepharoptosis (%)	8.5 (10)	.9 (1)	.007[†]
Neck rigidity (%)	6 (7)	2.7 (3)	.334***
Shoulder pain (%)	6 (7)	.9 (1)	.066***
Hypesthesia (%)	6 (7)	.9 (1)	.066***
Accidental injury (%)	5.1 (6)	4.5 (5)	.826***
Pain (%)	5.1 (6)	2.7 (3)	.500***
Hypertonia (%)	5.1 (6)	1.8 (2)	.282***
Skin tightness (%)	5.1 (6)	0 (0)	.030[†],***

*Incidence (n) (≥ 5%) of adverse events according to treatment group.
**Pearson's χ^2 test was performed to evaluate the equality of proportions between treatment groups. If 25% or more of the cells had expected counts of less than 5, Fisher's exact test was used.
***P values from Fisher's exact test.
[†]Statistically significant between-group difference.

placebo, −6.2; *P* = .047) and day 210 (BoNT-A, −14.6 vs placebo, −7.4; *P* = .018), as compared to placebo treatment.

Safety and Tolerability.—During the course of the study, the incidence of adverse events was higher in the BoNT-A group (BoNT-A: 76.1%; placebo: 63.1%; *P* = .033). The incidence of muscular weakness, neck pain, blepharoptosis, and skin tightness was significantly greater in the BoNT-A treatment population, as compared to placebo (Table 2); however, for most adverse events, the incidence did not differ significantly between treatment groups. Most adverse events were transient and mild to moderate in severity.

COMMENTS

This report presents the results of a subgroup analysis of a large, placebo-controlled study involving 355 patients with CDH and a history of migraine or probable migraine, who received treatment with BoNT-A or placebo for up to 9 months. Efficacy and safety data were analyzed for 228 patients who were not receiving concomitant headache prophylactic medications at baseline or during the study. The treatment group did not differ significantly from the placebo group with

regard to most baseline demographic characteristics. During the 30-day baseline period, patients experienced approximately 13 headaches lasting approximately 23 days.

During the study, headache symptoms improved (according to all efficacy parameters assessed) and acute headache medication use decreased in both treatment groups, as would be expected given the well-recognized placebo effect observed in clinical trials with prophylactic migraine therapies.[35] However, for all efficacy parameters there was a greater effect for BoNT-A compared with placebo, and at many time points statistically significant differences favoring BoNT-A treatment were observed. This was particularly the case for the frequency of headaches per 30-day periods and the percentage of patients achieving a 30% decrease in the frequency of headaches per 30-day periods (ie, 30% response rate). For the population evaluated, this meant approximately four less headaches per 30 days. BoNT-A treatment also showed greater improvement in the number of headache-free days. There was a between-group difference of three headache-free days achieved at day 180, which was statistically significant. Mean usual headache severity also improved, and significantly

favored BoNT-A treatment from day 180 to the end of the study at day 270.

BoNT-A treatment resulted in statistically significant reductions in headache frequency, which were evident within the first month after the initiation of treatment and persisted for 2 to 3 months (ie, day 60 to 90). Additional BoNT-A treatments resulted in improved response, and by 6 months (ie, day 180) most efficacy variables evaluated significantly favored BoNT-A over placebo. A 6-month therapeutic window is consistent with the observations from other trials of repeated BoNT-A treatment for chronic headache disorders.[32,33]

Although comparisons between studies are complicated by differences in study design, sample size, patient populations (eg, severity of the disorder as reflected in baseline headache frequency and/or days of headache), and the choice of efficacy measures and assessment time points, the results of this study, when assessed in the context of the published studies of other prophylactic headache medications, support that BoNT-A may be similarly effective in the treatment of severe headache.[11-19] After two injection sessions, BoNT-A treatment decreased the frequency of headaches in over 50% of patients by at least half, and approximately tripled the mean number of headache-free days per month (from 6 to 16 days). This decrease in the frequency and severity of headaches were also accompanied by a statistically significant decrease in acute medication use (data will be reported in a follow-up publication). It is unlikely that acute medication use contributed to headache improvement in patients of this study as there was a high percentage of patients using such treatments at baseline, and there were no significant differences in the number of acute medication uses or the number of days acute medications used between treatment groups during baseline. Furthermore, patients were not allowed to start new acute treatments during the study. So, although symptomatic treatment of headache pain may have prophylactic effects,[36] any such effect resulting from acute medication use would have already been present at the time of enrollment into the study. Furthermore, during the course of the study the use of acute medications decreased.

The MIDAS and SF-36 were the only health outcome measures included in the analysis for this study. There were no statistically significant differences found between BoNT-A and placebo, but trends in favor of BoNT-A were found. Unfortunately, the sample sizes in this subanalysis were insufficient at most time points to critically appraise BoNT-A's affect over placebo. The studies were not designed or powered to show differences on these health outcome measures for this subpopulation.

In this study, only 2.2% (5/228) of patients withdrew early because of adverse events.[34] The most frequently reported treatment-related adverse events leading to study discontinuation for BoNT-A in this study were muscular weakness and neck pain; however, this occurred in less than 2% of patients. Other treatment-related adverse events that led to study withdrawal were shoulder pain, neck rigidity, headache, and injection site pain and hemorrhage. The favorable safety profile of BoNT-A is also supported by a wealth of data in other indications.[37] The withdrawal rates from this study specifically due to adverse events were low compared to other medications used as prophylactic migraine treatment (in some cases up to 25% of patients) according to the regulatory labeling information for these medications.[38,39]

Thus, the efficacy and safety profile of BoNT-A demonstrated in this analysis suggest that BoNT-A is an effective, well-tolerated prophylactic treatment in patients with CDH who are not using other prophylactic headache treatments. Furthermore, the results also suggest that assessment of the frequency of headaches is a sensitive measure of efficacy in this patient population and that future studies to confirm these findings are needed.

Patients in this trial, on average, experienced headaches for approximately 14 years and over 35% were taking prophylactic medications, indicating that patients with CDH tend to be a more challenging and refractory population who are, in our clinical experience, less responsive to therapy than those with episodic migraine. The efficacy of BoNT-A was demonstrated in the broader population of patients experiencing CDH.[34] The results of this study support the conclusion that BoNT-A is effective and well

tolerated as a stand-alone prophylaxis agent for headache in patients with CDH who have a history of migraine or probable migraine headache. Efficacy of BoNT-A in combination with other prophylactic agents was inconclusive in this study, and further research may be warranted.

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