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Research Submission

Prophylactic Botulinum Type A Toxin Complex (Dysport®) for Migraine Without Aura

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Objective.—To evaluate the efficacy, safety, and optimum dose of a highly purified *Clostridium botulinum* type A toxin-hemagglutinin complex (Dysport) for migraine prophylaxis.

Background.—Botulinum toxin type-A has demonstrated good efficacy in several open-label studies of patients with migraine, involving either individualized or standardized protocols, although data from placebo-controlled trials have been conflicting.

Methods.—A 12-week, double-blind, randomized trial of Dysport (120 or 240 units) vs placebo was conducted in 6 centers in Thailand to evaluate the efficacy, safety, and optimum dose of botulinum toxin type-A (Dysport) for migraine prophylaxis. A total of 128 patients with migraine without aura were enrolled. The primary end point was the change in the mean number of migraine attacks per 4-week period from the pre-treatment period to 8-12 weeks post injection. Secondary efficacy measures included the change in the mean total intensity score from the pre-treatment period to 8-12 weeks, the investigator and patient global assessments of change at each visit compared with pre-treatment, and Migraine Disability Assessment and Short Form-36 scores.

Results.—Change in number of migraine attacks from pre-treatment to weeks 8-12 was not significantly different. There was a greater improvement in total intensity score at weeks 8-12 with Dysport-240 (not significant), and interim visit data showed that this was significant at weeks 0-4 ($P = .03$ Dysport-240 vs placebo). The mean duration of headache during weeks 0-4 was lower with Dysport-240 ($P = .04$ vs placebo). Improvements in patient and investigator global assessments of change between weeks 0-4 and 8-12 were significant for the Dysport-240 group (both $P < .05$ vs placebo).

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Conflict of Interest: SC, AA, NP, SN, PB, ST, PS, and SK have no conflicts of interest.

Conclusions.—Limitations in study design and assessment tools employed may have contributed to the inconclusive nature of the primary end point data. Dysport-240 showed significant benefit over placebo at some end points and further trials with more appropriate outcome measures are required to evaluate effectively this treatment.

Key words: botulinum toxin, migraine, prophylaxis, Dysport®

Abbreviations: BoNT-A botulinum toxin type A, IHS International Headache Society, ITT intention-to-treat, LD lethal dose, MIDAS Migraine Disability Assessment, SD standard deviation, SF-36 36-Item Short Form Health Survey

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Migraine is a common, primary, episodic headache disorder that is characterized by a combination of headache with one or more other neurological, gastrointestinal, and autonomic symptoms. The cause of migraine is unclear, although genetic defects are associated with certain forms.[1] Current knowledge about its pathophysiology indicates that migraine is a neurovascular disorder.[2,3]

Epidemiologic studies have documented a high prevalence of migraine worldwide and demonstrated both its high socioeconomic impact and the profound effect that the disorder can have on an individual's quality of life.[4] In the World Health Organization's study on the global burden of disease, migraine was ranked 20th among all diseases causing worldwide disability, and the 9th leading cause of disability in women.[5] In Western countries, migraine affects about 11% of adult populations, with a peak prevalence between the ages of 22 and 55 years – the period of highest productivity.[5] The highest prevalence of migraine is in North America, followed by Central and South America; Europe; Asia and Africa have the lowest prevalences.[5]

Although migraine is a highly prevalent and disabling condition, it is under-diagnosed and undertreated.[6-9] Recent advances have been made in the management of migraine, but pharmacologic treatment options are still far from optimum, leaving many patients without pain-free treatment or with unpleasant side effects.[10,11] Botulinum toxin type A (BoNT-A) is a potent neurotoxin that has been used to treat a variety of disorders associated with elevated muscle tension, including focal dystonias, spasticity, and achalasia.[12-14] The pain-relieving effects of BoNT-A were initially noted in studies of the treatment of cervical dystonia, and several studies subsequently showed that the toxin may be effective in the treatment of both tension-type headache and migraine.[15-17] Although an increase in muscle tenderness has been described in migraine,[18,19] muscle relaxation and pain relief may not always be associated. Therefore, the pain-relieving capacity of BoNT-A may not be correlated with direct neuromuscular effects.[20]

Botulinum toxin type A has demonstrated good efficacy in several open-label studies of patients with migraine, involving either individualized or standardized protocols.[21-23] Data from placebo-controlled trials, however, have been conflicting.[24-32] These differences in outcomes may have been due to differences in study methodology, including the number of injections and total dose given at an individual visit, study duration and position of the injection sites (which muscles were injected, where they were injected, and whether this was individualized). In addition, the assessments and end points used were different and may not have been sufficiently sensitive or specific. It should also be noted that although BoNT-A preparations are formulated as mouse median lethal dose (LD_{50}) units, differences in assay methodology among different BoNT-A compounds mean that the units of measurement are not directly interchangeable. When comparing data among studies, a ratio of between 2 and 3 units of Dysport® (Ipsen Ltd, Slough, UK) to 1 unit of Botox® (Allergan Inc., Irvine, CA, USA) should be considered.[33-38]

This study was designed to evaluate whether BoNT-A was effective in the prophylaxis of migraine without aura. We conducted a 2-dose, double-blind, randomized, placebo-controlled trial in a large cohort of patients to evaluate the efficacy, safety, and optimum dose of a highly purified *Clostridium botulinum* type A toxin-hemagglutinin complex (Dysport) for migraine prophylaxis.

METHODS

Patients.—Men and women between the ages of 18 and 65 years attending the investigating centers were included in the study by investigators if they had experienced an average of 2-8 migraine attacks per month over the 3 months prior to a screening period and if 2-8 migraine attacks had occurred during the 4-week screening period. Medication for acute migraine was allowed during the study and prophylactic treatment was permitted if doses were stable. Patients who fulfilled the 2004 International Headache Society (IHS) diagnostic criteria for pure migraine with aura,[4] or who had a history of complicated migraine, such as migrainous infarction or hemiplegic migraine, were excluded from the study. Women who were pregnant, lactating, or not using adequate contraception were also excluded, as were patients who had a history of drug abuse, who had received treatment with BoNT-A within the past 6 months, who had previously experienced an adverse reaction to BoNT-A, who had a history of botulism or other neuromuscular disorders, or who were being treated with aminoglycoside antibiotics or other agents that could affect neuromuscular transmission. Patients were not allowed to have received unlicensed medication or investigational drugs within 6 months of the screening visit. Additionally, clinically significant medical conditions (including blood dyscrasia, thrombocytopenia, rheumatoid arthritis, congestive heart failure, coronary heart disease, dementia, psychosis, and major depression), or other conditions that could influence trial results, were criteria for exclusion. Liver transaminase levels had to be less than twice the upper normal values.

Study Design.—This was a 12-week, phase III, double-blind, randomized trial of 120 and 240 mouse LD_{50} units of Dysport (referred to as units of Dysport) vs placebo (normal saline solution) in patients with a diagnosis of migraine without aura according to IHS criteria. The study was carried out in 6 centers in Thailand. The study protocol was approved by the ethics committee of each participating center.

Patients underwent a 4-week screening period (pre-treatment period, weeks –4 to 0), to ensure they satisfied the inclusion and exclusion criteria. They then underwent randomization to one of 3 groups: 0.9% sodium chloride vehicle (placebo group), 120 units of Dysport (Dysport-120 group) or 240 units of Dysport (Dysport-240 group). Randomization was performed via a computer-generated schedule prepared before the start of the study. Allocated treatments were placed in sealed envelopes labeled with the randomization numbers; the envelopes were handed to the person responsible for preparing the injections and who was not otherwise involved in the study. The unallocated envelope with the smallest randomization number was used to assign treatment to each individual. All other personnel involved in the study were blinded to the assignment of treatments and the opened envelopes were not accessible to investigators. Dysport, supplied as a freeze-dried powder and reconstituted in saline solution, was used within 8 hours of preparation. To maintain study blinding, reconstitution was performed by a study nurse not involved with patient management. All patients received 2 subcutaneous injections into both the frontal and temporal regions of the face, and 2 intramuscular injections into the occipital region (Fig. 1). The volume for each injection was 0.1 mL, resulting in a total volume of 0.6 mL.

The trial was conducted in accordance with the Declaration of Helsinki. All study documents were approved by the independent ethics committee and informed consent was obtained from each patient before the start of the trial.

Assessments.—There were 5 assessment visits during the course of the study: one visit before treatment (week –4), one at the time of randomization and injection of either active treatment or placebo (day 0, baseline) and 3 during the double-blind follow-up at weeks 4, 8, and 12. Patients kept a headache diary for the entire 16 weeks, from pre-treatment (to allow the investigators to assess if they met the inclusion criteria) to week 12. Patients were asked to record each day a migraine attack occurred and its duration, measured as hours per day and documented in 1-hour units. Intensity of pain was measured in 1-hour units and scored on a 4-point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). The total intensity of pain was calculated as the sum of the scores over 28 days. At each visit, patients underwent

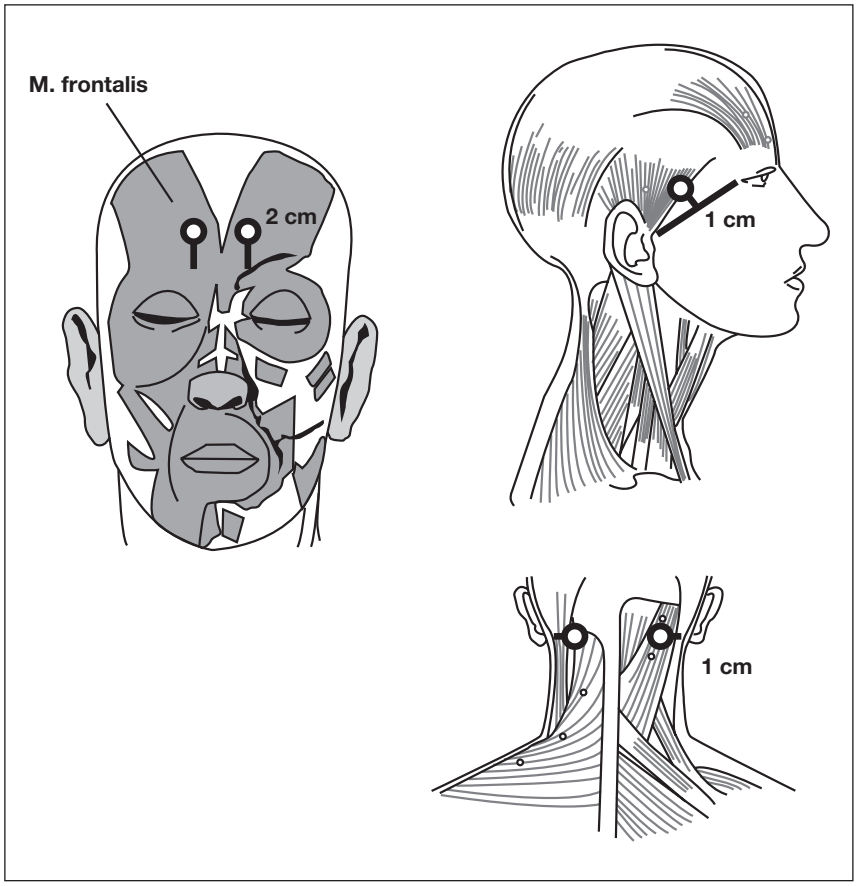

Fig 1.—Location of injection sites.

physical, neurologic, and laboratory examinations, and they were also asked to complete a questionnaire relating to their general health (36-Item Short Form Health Survey [SF-36][39] translated into Thai and validated).[40]

At day 0 and week 12, patients rated the disability caused by their migraines using the Migraine Disability Assessment (MIDAS) questionnaire (scale from 1 [no disability] to 4 [severe disability]). At the 3 post-treatment visits, both patients and investigators provided a global assessment of the change in treatment efficacy from baseline (scale from −3 [very much improved] to +3 [very much deteriorated]), and adverse events were recorded by the physician.

Efficacy and Safety End points.—The primary end point was the change in the mean number of migraine attacks from the pre-treatment period (the 28 days preceding baseline) to 8-12 weeks (the 28 days before the last visit). The number of migraine attacks was assessed using the IHS classification of headache disorders, which specifies that an individual attack lasts no longer than 72 hours.[4] Migraine attacks that lasted longer than 72 hours were recorded as more than one attack.

Secondary efficacy measures included the change in the mean total intensity score from the pre-treatment period to 8-12 weeks, the investigator and patient global assessments of change at each visit compared with pre-treatment, and MIDAS and SF-36 scores (at weeks 0, 4, 8, and 12 for SF-36, and weeks 0 and 12 for MIDAS).

Other data collected included the change in migraine duration from pre-treatment to the 28 days preceding weeks 4, 8, and 12, change in migraine intensity from pre-treatment to the 28 days preceding weeks 4 and 8, the number of hours per month with moderate-to-severe headache, and the improvement

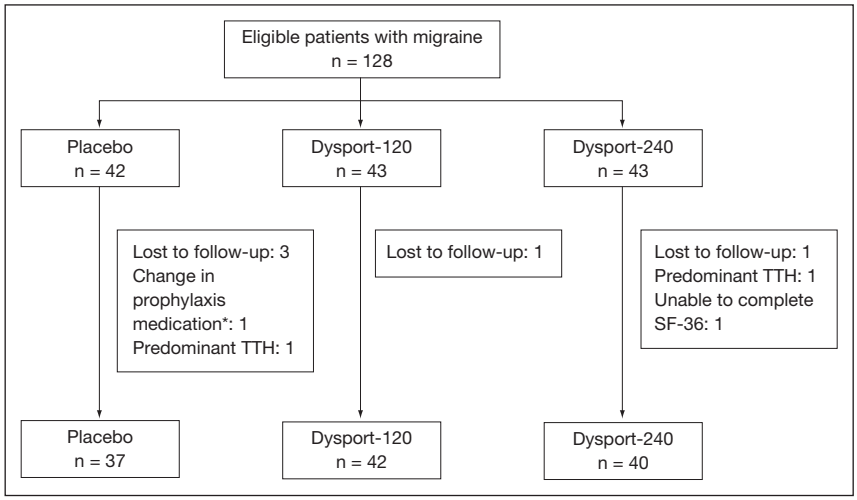

Fig 2.—Patient disposition through the study. SF-36 = 36-Item Short Form Health Survey; TTH = tension-type headache. *Change of prophylaxis medication after injection because of poor treatment efficacy.

(change in assessment score ≥1) in both investigator and patient global assessments of change.

Safety and tolerability were assessed based on the adverse events recorded on the case report forms.

Statistical Analyses.—At the start of the study, few data were available on the efficacy of BoNT-A in migraine. Hence, the sample size could not be calculated accurately and the study was intended as an exploratory analysis. The total number of patients planned, however, was large (n = 126).

SC and SK had full access to the study database, and the statistical software used for the analyses was Cytel Studio (StatXact Cytel, Cambridge, MA, USA). Analyses were performed among the 3 groups (placebo, Dysport-120, and Dysport-240) and also between pairs of groups (Dysport-120 vs placebo and Dysport-240 vs placebo). The primary statistical analyses of efficacy were based on the intention-to-treat (ITT) population, which included all patients who had received an injection of active treatment or placebo and who had had at least one post-baseline assessment. All analyses were on observed cases and there was no imputation for missing data. The safety population included all patients who had received an injection of active treatment or placebo and who had at least one recorded safety evaluation.

Descriptive data only are presented for the SF-36 and MIDAS data. For baseline binomial data and the rate of responders post-treatment (defined as an improvement in score from –3 to –1 in the investigator and patient global assessments of change), comparisons among the treatment groups were evaluated using the chi-square test: 2×3 for comparisons of the 3 groups and 2×2 for placebo comparisons. If the expected value of any placebo comparison was less than 5, the affected distribution was tested using the Fisher's exact test. All other analyses among the 3 groups were performed using the Kruskal-Wallis test; pairs of treatment groups were compared using the Wilcoxon rank sum test. As the sample size could not be calculated accurately and the study was intended as an exploratory analysis, no adjustment was made for multiplicity of testing and all statistical tests were performed at the 5% level of significance.

Summary statistics were calculated for the number of adverse events recorded on the case report forms.

RESULTS

Patients.—Patient recruitment began in January 2003 and was completed in March 2004; the last follow-up visit was 3 months later. Of 128 patients who underwent treatment randomization (placebo: n = 42, Dysport-120: n = 43, and Dysport-240: n = 43), one patient (in the placebo group) had no data post-treatment and was excluded; the ITT population therefore comprised 127 patients. A total of 119 patients completed the study (placebo: n = 37,

Table 1.—Patient Demographics and Baseline Migraine Characteristics (Intention-to-Treat Population)

		Units of Dysport®	
	Placebo (n = 41)	120 (n = 43)	240 (n = 43)
Mean (SD) age, years	38.7 (10.2)	38.9 (9.8)	38.1 (9.8)
Women, n (%)	39 (95.1)	40 (93.0)	41 (95.3)
Mean (SD) time since onset of migraine symptoms, years	8.1 (7.7)	7.7 (7.4)	8.8 (7.9)
Mean (SD) time since migraine diagnosis, years	4.7 (6.6)	4.3 (4.7)	5.4 (6.3)
Patients previously treated for migraine, n (%)	41 (100)	42 (97.7)	42 (97.7)
Patients with a family history of migraine, n (%)	9 (22.0)	16 (37.2)	14 (32.6)
Mean (SD) number of migraine attacks per month	5.1 (2.4)	4.9 (2.2)	5.3 (2.5)
Mean (SD) total intensity score	66.7 (233.1)	33.1 (42.9)	54.8 (103.6)
Mean (SD) hours per month with moderate-to-severe headache	27.8 (90.7)	15.5 (20.8)	25.1 (44.9)

SD = standard deviation.

Dysport-120: n = 42, and Dysport-240: n = 40; Fig. 2); 5 of the 128 patients randomly allocated to treatment were lost to follow-up, one patient changed prophylaxis medication after injection because of poor treatment efficacy, 2 patients were excluded because of a diagnosis of chronic tension-type headache, and one was unable to complete the SF-36 questionnaire.

Baseline characteristics were statistically similar among the groups (Table 1), with no differences considered clinically relevant by the investigators. The majority of patients were women (≥93%), with an average age of 38-39 years. The mean length of time that patients had experienced migraine was 8-9 years, although the mean time since diagnosis was 4-5 years. Most patients had previously received medication for migraine.

Treatment Efficacy – Frequency of Migraine Attacks.—During the pre-treatment period (weeks –4 to 0), the number of migraine attacks in each group in the ITT population was similar (approximately 5 attacks per month; Table 1). Between weeks 8-12, the mean (standard deviation [SD]) reduction from the 4-week pre-treatment period in the frequency of migraine attacks (primary end point) was 2.23 (2.62) for the placebo group, 1.95 (2.38) for the Dysport-120 group, and 1.83 (3.24) for the Dysport-240 group (Fig. 3). There was no significant difference among the 3 groups at week 12.

Exploratory analysis of migraine frequency at interim visits showed that at weeks 0-4 there was a significant difference compared with the pre-treatment period in favor of placebo over the Dysport-240 group in the mean (SD) reduction in migraine frequency (1.40 [2] vs 0.69 [2], respectively; $P = .04$), no differences were seen at weeks 4-8 or between the placebo and Dysport-120 group at any time point compared with the 4 weeks preceding baseline.

Treatment Efficacy – Severity of Migraine Attacks.—During the pre-treatment period, the mean total intensity scores for migraine pain were comparable across groups in the ITT population (Table 1).

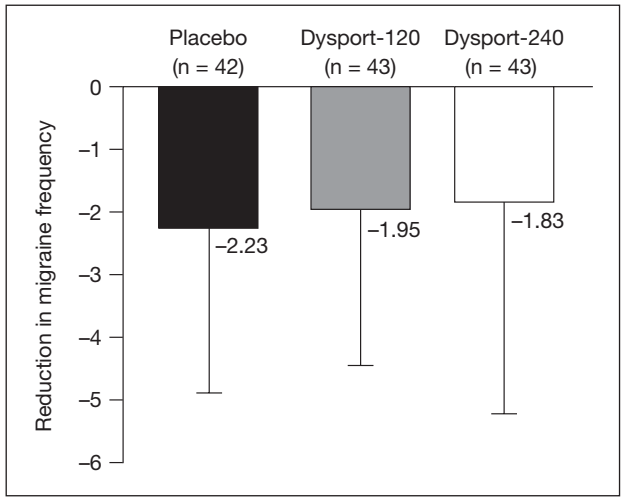

Fig 3.—Mean (standard deviation) reduction in migraine frequency from pre-treatment to weeks 8-12 (intention-to-treat population).

Table 2.—Mean (SD) Change From Baseline Over a 28-Day Period in Total Intensity Score and Duration of Moderate-to-Severe Headache, and Improvement in Investigator and Patient Global Assessment of Change Scores

	Intention-to-Treat Analysis			Per-Protocol Analysis		
	Placebo n = 41	Dysport-120 n = 43	Dysport-240 n = 43	Placebo n = 37	Dysport-120 n = 42	Dysport-240 n = 40
Total intensity score†						
Baseline-4 weeks	–10.50 (22.75)	–14.93 (35.90)	–14.55 (74.25)*	–11.92 (23.92)	–15.29 (36.26)	–15.65 (76.94)*
Baseline-8 weeks	–5.19 (39.34)	–10.65 (49.91)	–11.32 (85.54)	–5.89 (41.94)	–10.90 (50.49)	–12.18 (88.71)
Baseline-12 weeks	–9.71 (52.97)	–16.11 (32.49)	–22.25 (83.43)	–11.03 (56.40)	–16.50 (32.79)	–23.93 (86.34)
Hours per month with moderate-to-severe headache†						
Baseline-4 weeks	–4.45 (9.61)	–6.97 (17.06)	–6.93 (34.69)*	–5.05 (10.10)	–7.14 (17.24)	–7.45 (35.95)*
Baseline-8 weeks	–2.47 (16.30)	–4.74 (23.24)	–5.72 (40.22)	–2.81 (17.37)	–4.86 (23.51)	–6.15 (41.71)
Baseline-12 weeks	–4.61 (21.72)	–7.25 (15.48)	–10.23 (40.22)	–5.24 (23.11)	–7.43 (15.62)	–11.00 (40.75)
Improvement in global assessment of change score (change in score ≥1)						
Investigator score, n (%)						
Weeks 4-8	9 (22.0)	11 (25.6)	12 (27.9)	9 (24.3)	11 (26.2)	12 (30.0)
Weeks 4-12	10 (24.4)	18 (41.9)	17 (39.5)*	10 (27.0)	18 (42.9)	17 (42.5)*
Patient score, n (%)						
Weeks 4-8	9 (22.0)	14 (32.6)	11 (25.6)	9 (24.3)	14 (33.3)	11 (27.5)
Weeks 4-12	8 (19.5)	16 (37.2)	16 (37.2)*	8 (21.6)	16 (38.1)	16 (40.0)*

*$P < .05$ vs placebo.
†The additional analysis includes the one patient in the placebo group with no follow-up visits who was excluded from the primary analysis, so n = 42.

Kruskal-Wallis analysis of the medians indicated no significant difference between groups ($P = .55$). At weeks 8-12, improvement from the pre-treatment period in mean (SD) total intensity scores was greater in the Dysport-240 group (22.25 [83.43]) than in the Dysport-120 (16.11 [32.49]) and placebo (9.71 [52.97]) groups, although this did not reach statistical significance (Table 2). Exploratory analysis of interim visits showed that at weeks 0-4, the improvement in total intensity score over the pre-treatment period was significantly better in the Dysport-240 group than in patients who received placebo (14.5 [74] vs 10.0 [22], respectively; $P = .03$; Table 2). No significant differences between groups were noted at 4-8 weeks over the pre-treatment period.

During the pre-treatment period, the mean number of hours per month with a moderate-to-severe headache was not significantly different across the 3 groups (Table 1). Analysis of data from interim visits revealed that the mean (SD) reduction over 28 days in the number of hours with moderate to severe headache at 4 weeks was significantly greater in the Dysport-240 group (6.93 [34.69]) compared with the placebo group (4.45 [9.61]; $P = .04$; ITT population, Table 2, Fig. 4). Although the reduction was also greater in the active treatment groups at weeks 8 and 12, this did not reach statistical significance.

Treatment Efficacy – Global Assessment of Change.—There was no difference in either the investigator or the patient global assessment of change scores between each treatment group and placebo at each time point compared with baseline. No statistically significant difference between groups at any time was found in response rate, defined as an improvement in score from –3 to –1 on both the investigator and patient global assessments of change. However, additional analysis of between-visit differences showed that the improvement in investigator global assessment of change score (change in score ≥1) between weeks 4 and 12 demonstrated benefits for the Dysport-240 group vs placebo (39.5% vs 24.4%, respectively; $P < .05$; Table 2). The improvement in investigator global assessment of change score between weeks 4 and 12 for the Dysport-120

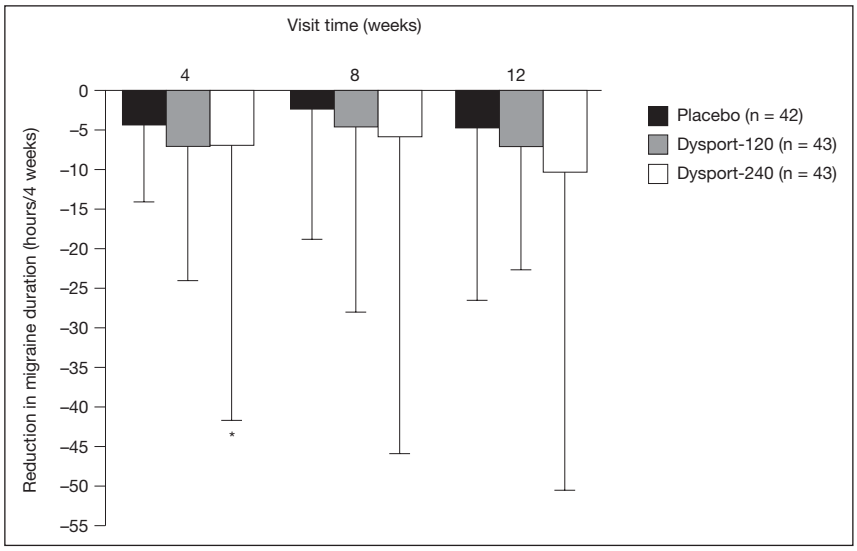

Fig 4.—Mean (standard deviation) reduction in the duration of migraine attacks in the previous 4 weeks from pre-treatment to each treatment visit. *$P < .05$ vs placebo.

group and placebo did not reach statistical significance (41.9% vs 24.4%, respectively). Similar results were obtained for the improvement in patient global assessment of change score between weeks 4 and 12 (Dysport-240 vs placebo: 37.2% vs 19.5%, $P < .05$). Neither the investigator nor the patient global assessment of change scores between weeks 4 and 8 were significantly different for any group.

For both the SF-36 and MIDAS questionnaires, there were no significant differences among the 3 groups on any domain at any of the time points at which they were assessed.

Safety Analyses.—Injections were generally well tolerated, and adverse events were those known to be associated with the use of BoNT-A. A total of 32 adverse events were reported across all 3 treatment groups (10, 15, and 7 events in the placebo, Dysport-120, and Dysport-240 groups, respectively) (Table 3). These adverse events were reported in 5/42 (11.9%) patients in the placebo group, 8/43 (18.6%) in the Dysport-120 group, and 7/43 (16.3%) in the Dysport-240 group. Most adverse events were reported in no more than one patient per treatment group; the 3 that were reported in more than one patient per treatment group all occurred in the Dysport-120 group (muscle tightness, dizziness, and neck pain). Adverse events were considered by the investigator to be probably related to treatment in 4/10 (40.00%) events in the placebo group, 2/15 (13.33%) events in the Dysport-120 group, and 3/7 (42.86%) events in the Dysport-240 group.

The majority of adverse events (22/32 [68.8%]) were mild or moderate and no serious adverse events occurred during the 12 weeks of follow-up.

DISCUSSION

This randomized, placebo-controlled study design was one of the first to investigate the prophylactic effect of Dysport in patients with migraine without aura and was conducted in over 120 patients. At the initiation of this study, there was limited information available on the effects of BoNT-A in migraine prophylaxis, and this exploratory study was conducted according to the best knowledge available at the time.

The treatment groups were statistically matched at baseline. Although there was some apparent discrepancy between groups in terms of total intensity score and the number of hours per month with moderate-to-severe headache, the investigators did not consider these differences clinically relevant.

The difference in treatment efficacy between the 2 doses of Dysport and placebo were not statistically significant with respect to the primary end point

Table 3.—All Adverse Events Reported by Patients

	Placebo (n = 42)	Dysport-120 (n = 43)	Dysport-240 (n = 43)
Eye disorders			
Eyelid edema	1 (2.4)	1 (2.3)	0
Eyelid ptosis	0	0	2 (4.7)
Gastrointestinal disorders			
Nausea	0	1 (2.3)	0
Vomiting	0	0	1 (2.3)
General disorders and administration site conditions			
Injection site pain	1 (2.4)	0	0
Edema	0	0	1 (2.3)
Pyrexia	1 (2.4)	0	0
Tenderness	0	0	1 (2.3)
Musculoskeletal and connective tissue disorders			
Muscle tightness	0	2 (4.7)	0
Musculoskeletal stiffness	0	1 (2.3)	0
Neck pain	1 (2.4)	2 (4.7)	0
Trismus	1 (2.4)	0	0
Nervous system disorders			
Dizziness	0	2 (4.7)	1 (2.3)
Dyskinesia	0	1 (2.3)	0
Headache	1 (2.4)	0	0
Hypoesthesia	0	1 (2.3)	0
Mastication disorder	0	0	1 (2.3)
Radicular pain	0	1 (2.3)	0
Sedation	2 (4.8)	1 (2.3)	0
Somnolence	0	1 (2.3)	0
Tension headache	0	1 (2.3)	0
Reproductive system and breast disorders			
Menorrhagia	1 (2.4)	0	0
Skin and subcutaneous tissue disorders			
Herpes zoster	1 (2.4)	0	0

All values are number of events, n (%).

(change in mean number of migraine attacks over the previous 28 days from baseline to week 12). This may have been due to the low power of the study, with a small number of patients in each of the 3 arms. The multidisciplinary approach using 3-way comparisons of Dysport-120, Dysport-240, and placebo showed some borderline significance in the secondary end points in both the ITT and per-protocol populations: at week 4 only, a significant improvement was demonstrated in favor of 240 units of Dysport over placebo in the mean reduction in duration of migraine attacks and in the mean change in total intensity score over the previous 28 days compared with the pre-treatment period, and although both doses of Dysport gave numerically lower values than placebo at the other 2 time points, statistical significance did not persist throughout the 12 weeks of the trial. It should be noted that neither of these end points reached statistical significance at a more conservative level of $P < .025$ that may be considered for secondary analyses. Secondary analyses also revealed that there were significant improvements with 240 units of Dysport over placebo in both the investigator ($P = .01$) and patient ($P = .03$) global assessment of change scores between weeks 4 and 12, indicating that both physicians and patients considered Dysport treatment to be beneficial.

This study demonstrated some benefit with 240 units of Dysport. Therefore, we suggest that a total dose of 240 units of Dysport injected into 6 pericranial sites may be an appropriate dose for the treatment of migraine. Adverse events were few and were those commonly associated with BoNT-A treatment.

The lack of a sensitive assessment for measuring the frequency of migraine attacks may have been a key reason for the inconclusive evidence of the effect of BoNT-A in patients with migraine. Importantly, we recorded the duration of attack as the number of hours of migraine per 28 days, measured in 1-hour units, which is a more accurate representation of the duration of attack than is the number of attacks. The reduction in duration of attacks may therefore have had a fragmentary effect on the headache period – patients appeared to have had the same number of attacks but of shorter duration. For example, a patient experiencing a single migraine attack lasting 24 hours has a lower attack frequency than another patient who may have 2 attacks each lasting one hour in the same time period. In such circumstances, although the frequency of attacks is greater, the duration of migraine would be much shorter, and thus we believe that number of hours with attacks per month may be a more appropriate end point. Measurement of attack frequency therefore may not be the most appropriate primary assessment. We suggest that future trials should also consider duration and severity as potential primary end points. We also question whether the MIDAS and SF-36 questionnaires are sufficiently sensitive tools for the assessment of patients with migraine in clinical trials of BoNT-A. Indeed, the correlation of MIDAS scores and headache diary mea-

sures has been shown to be low.[41] Like many other migraine trials of BoNT-A, our study did not assess any additional migraine symptoms, such as vertigo and dizziness, and in future it may be appropriate to include the reduction in these disabling symptoms as secondary outcomes.

Large improvements from baseline on a number of end points were noted in the placebo group and, at week 4, reduction in migraine frequency over the previous 28 days was significant for placebo compared with 240 units of Dysport. The injection itself, however, may have caused an effect and, as such, may not have been a true placebo. The confounding effect of needle insertion has been noted in studies of acupuncture in migraine and tension-type headache, in which sham acupuncture using non-acupuncture points was found to be as effective as acupuncture, and both interventions were significantly better than no treatment.[42,43] Patients with headache disorders may also have high expectations of their treatment, which the authors of both these studies noted may have been a relevant factor in their findings. It is also possible that injection alone may stimulate physiological effects, with pain diminished through the mechanism of the reward pathway.

The low side effect profile of BoNT-A coupled with the potential to reduce polypharmacy in chronic migraine sufferers suggests that BoNT-A could be a cost-effective option for the management of chronic migraine. Studies on the effects of BoNT-A treatment on functional ability and quality of life in patients with migraine may also help to elucidate further the benefits of this treatment on a potentially disabling condition.

In conclusion, this exploratory study suggests that Dysport may be beneficial in the treatment of migraine, particularly at a dose of 240 units. In this study of chronic migraine sufferers, the injections were well tolerated and adverse events were as expected with BoNT-A treatment. Although we found no effect on the primary efficacy end point, the frequency of migraine attacks, we found that the number of hours with migraine and the total intensity score at 4 weeks were both significantly improved in the Dysport-240 group compared with placebo. In the context of these findings, we suggest that further studies will be useful to validate the most appropriate outcome measures for future therapeutic trials. Larger studies will also enable subgroup analyses, which will help to determine if some patients gain more benefit than others.

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