BOTULINUM TOXIN TYPE A VERSUS TOPICAL 20% ALUMINUM CHLORIDE FOR THE TREATMENT OF MODERATE TO SEVERE PRIMARY FOCAL AXILLARY HYPERHIDROSIS

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Abstract

Severe hyperhidrosis affects 2.8% of the population and can be emotionally devastating. First-line therapy employs topical agents such as aluminum chloride (AC), but efficacy and tolerability vary widely. Botulinum toxin type A (BTX-A) is FDA-approved for the treatment of primary focal axillary hyperhidrosis unresponsive to topical therapy. A single-center, randomized, parallel, open-label, 12-week study was performed to compare the efficacy and safety of BTX-A with 20% AC for the treatment of primary focal axillary hyperhidrosis. Twenty-five subjects were randomized to either BTX-A or AC treatment, and were evaluated for treatment response by an improvement of ≥2 grades on the Hyperhidrosis Disease Severity Scale (HDSS). At week 4, 92% of the subjects in the BTX-A group achieved treatment response compared with 33% of the subjects in the AC group. Overall, treatment with BTX-A was more effective and provided greater patient satisfaction than with AC. Treatment with AC was effective and tolerated in 29% of the subjects.

Introduction

Severe hyperhidrosis affects 2.8% of the population and can be socially unacceptable and emotionally devastating.[1] Approximately 1.4% of the US population has axillary hyperhidrosis, with one-third having severe axillary hyperhidrosis, ie, sweating that is barely tolerable and frequently interferes with daily activities, or is intolerable and always interferes with daily activities.[1] First-line medical therapy typically employs a topical agent such as aluminum chloride (AC). However, the effectiveness of topical AC is quite variable, long-term application is required, and local irritation can be a limiting factor for many patients. Iontophoresis, while an effective therapy for palmar and plantar hyperhidrosis, is not a practical treatment for axillary hyperhidrosis.

Botulinum toxin type A (BTX-A) is approved by the FDA for the treatment of severe axillary hyperhidrosis inadequately managed by topical agents.[2] It inhibits the release of acetylcholine at the presynaptic membrane on cholinergic neurons, and up to 94% of the patients respond successfully to treatment (ie, defined by at least a 50% reduction from baseline in axillary sweat production at 4 weeks posttreatment).[3] Botulinum toxin type A is reported to remain effective for 4 to 12 months and has an excellent tolerability profile.[2-4] The objective of this study was to compare the efficacy and tolerability of a single treatment session of BTX-A injections to daily topical applications of a prescription 20% AC antiperspirant in the treatment of moderate to severe primary axillary hyperhidrosis. No previous similar comparative study has been reported in the literature.

Methods and Materials

This was a single-center, randomized, parallel, open-label study conducted with patient recruitment beginning in March 2006 and ending in August 2006; the study concluded in November 2006. The goal for enrollment was a total of 50 patients with 25 patients in each group. The study duration was 12 weeks, beginning with the baseline/randomization visit at baseline and concluding with the last follow-up visit at week 12. At the baseline/randomization visit, patients were screened for inclusion and exclusion criteria. This study was approved by the Saint Louis University Institutional Review Board.

Inclusion Criteria

Inclusion criteria were outpatient subjects, male and female, at least 18 years of age with bilateral, primary axillary hyperhidrosis characterized by a score of 3 or 4 on the Hyperhidrosis Disease Severity Scale (HDSS). Female subjects of childbearing potential were required to have a negative urine pregnancy test result at baseline and practice a reliable method of contraception throughout the study.

Exclusion Criteria

Exclusion criteria included pregnant or lactating females, or females of childbearing potential not practicing a reliable method of birth control; patients diagnosed with secondary hyperhidrosis (eg, hyperhidrosis secondary to underlying diseases); patients using or having used within 7 days of the baseline visit cholinomimetic agents, anticholinergic agents, prescription antiperspirants, any herbal medicine treatments or any other treatments for hyperhidrosis except over-the-counter (OTC) antiperspirants; patients who have used OTC antiperspirants or deodorants within 24 hours of the baseline visit; patients who have had a sympathectomy of any type or surgical debulking of the sweat glands; patients with neuromuscular disorders; current anticoagulant therapy; subjects planning inpatient surgery during the study period; and subjects with any uncontrolled systemic disease. Subjects were excluded if they had a history of a previous injection of botulinum toxin of any serotype for axillary hyperhidrosis within 12 months of the screening visit or a history of previous use of prescription-strength topical AC on the axilla

within 12 months of the screening visit. Subjects were excluded for the presence of an infection at the injection site or systemic infection, or for a history of an allergy or sensitivity to any component of the study medications.

Patients who met inclusion criteria and enrolled in the study were randomized to treatment with either BTX-A (Botox®, Allergan Inc, Irvine, CA) or 20% AC (Drysol®, Person & Covey Inc, Glendale, CA) after completing an informed consent form, medical history including current medications, physical examination, and urine pregnancy test, when appropriate. Participants completed 2 validated questionnaires, the HDSS and the hyperhidrosis impact questionnaire (HHIQ), which measure the severity and impact of axillary hyperhidrosis. Subjects randomized to the BTX-A group received 50 units of BTX-A injected in each axillae bilaterally at the level of the subcutaneous-dermal plane at the baseline visit. Subjects randomized to the AC group were instructed to apply a thin layer of AC without occlusion to clean, dry axilla nightly, unless limited by irritation, for which patients were instructed to use the AC every other night as tolerated.

Subjects received follow-up telephone visits at week 1 to assess for any adverse events related to either BTX-A or AC. Participants returned for an outpatient follow-up visit at weeks 4, 8, and 12 to assess for adverse events, changes in

Table 1. Baseline characteristics.

	Total (n=50)(%)	BTX-A (n=25)(%)	20% AC (n=25)(%)
Female	36 (72.0)	20 (80.0)	16 (64.0)
Male	14 (28.0)	5 (20.0)	9 (36.0)
Mean age (years)	29.9 ± 8.0	29.0 ± 8.8	30.9 ± 7.2
Race			
Caucasian	42 (84.0)	20 (80.0)	22 (88.0)
Black	7 (14.0)	4 (16.0)	3 (12.0)
Asian	1 (2.0)	1 (4.0)	0 (0.0)
Hyperhidrosis history			
Axillary	50 (100.0)	25 (100.0)	25 (100.0)
Palmar	17 (34.0)	10 (40.0)	7 (28.0)
Plantar	15 (30.0)	10 (40.0)	5 (20.0)
Facial	9 (18.0)	6 (24.0)	3 (12.0)
Truncal	13 (26.0)	7 (28.0)	6 (24.0)
Previous use of antiperspirants			
1: Never	1 (2.0)	0 (0.0)	1 (4.0)
2: Used, but not in the last 3 months	2 (4.0)	2 (8.0)	0 (0.0)
3: Used in the last 3 months	47 (94.0)	23 (92.0)	24 (96.0)
P value (Fisher)	0.4898		
Effectiveness of antiperspirants			
0: Not effective	28 (56.0)	11 (44.0)	17 (68.0)
1: Poor	19 (38.0)	12 (48.0)	7 (28.0)
2: Average	3 (6.0)	2 (8.0)	1 (4.0)
P value (Fisher)	0.0949		

concomitant medications, and to complete the HDSS, HHIQ, and the questions about irritation (QI), a third questionnaire. At week 4, participants who were randomized to the AC group who had not achieved an improvement in HDSS score of ≥2 points or who could not tolerate AC due to irritation (defined as redness, fissuring, stinging, pruritus, and/or pain) were offered injections of BTX-A. Subjects who received BTX-A at the week 4 visit were contacted 1 week later to assess for any adverse events, and otherwise followed the same study protocol as the other subjects.

Statistical Analysis

The primary goal of this study was to determine the incidence of treatment response as measured by a change of ≥2 points in the HDSS score in patients treated with BTX-A compared to those treated with 20% AC from baseline to week 4. Participants who achieved a minimum 2-point reduction in HDSS score from baseline were designated as "responders," and patients achieving a 1-point reduction or less were considered "non-responders." Secondary outcomes included changes in HDSS scores and responses to the HHIQ and QI at weeks 4, 8, and 12, the frequency of subjects discontinuing AC and crossing over to receive BTX-A at week 4, and the durability of treatment response from weeks 4 to 12. Adverse events and safety outcomes were also compared between the treatment groups.

The sample size was determined by assuming the following: a 90% responder rate in the BTX-A group, a 45% difference in the percentage of responder subjects by week 4, and an approximate 15% drop-out rate. This study was designed to detect an α=0.05 with 90% power based on an enrollment of 50 subjects in the study. All pair-wise statistical tests were 2-sided and interpreted at a 5% significance level. Efficacy and safety analyses were conducted on an intent-to-treat basis, and all patients who received study medication were included in the analysis. Demographic and baseline characteristics were evaluated for comparability between treatment groups. A chi-square test was used to assess differences between treatment groups and a *t* test was used for continuous variables. The Wilcoxon Rank-Sum test was used if the necessary assumptions for parametric tests were not satisfied. No interim analyses were conducted.

Figure 1. The incidence of treatment success (an improvement in HDSS score of ≥2 points) with a single BTX-A treatment compared with daily applications of AC at week 4.

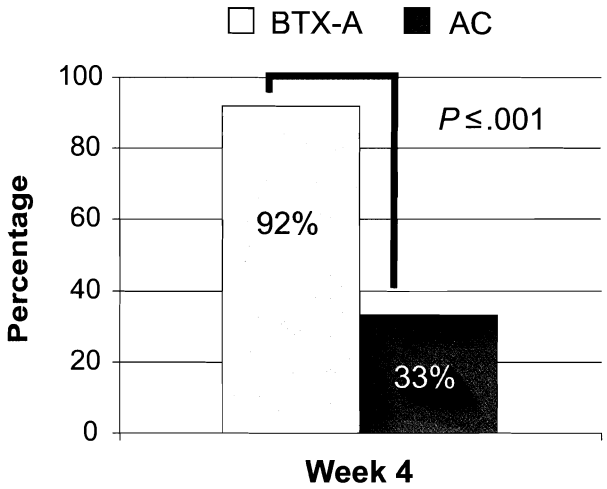
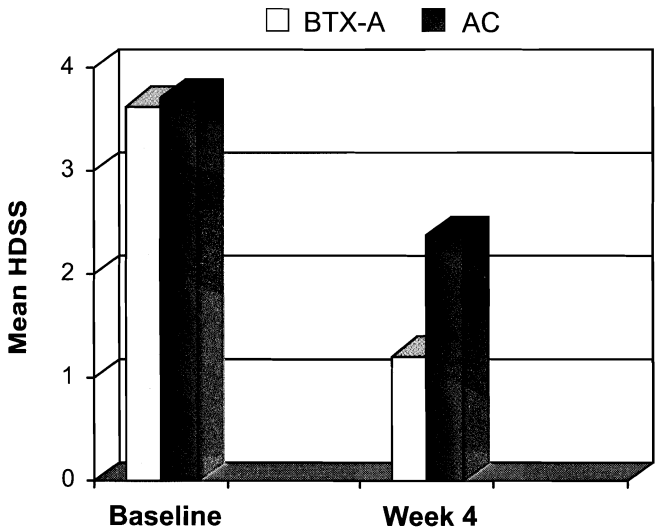


Figure 2. The mean HDSS score after a single BTX-A treatment compared with daily applications of 20% AC at week 4 (P <.0001).

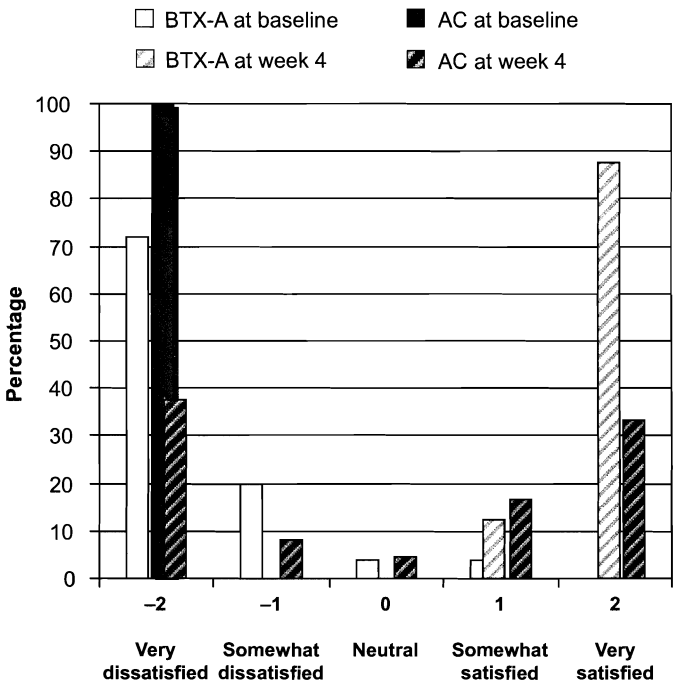


Results

Demographics

Fifty subjects were enrolled and 45 subjects completed the study, with 22 subjects from the BTX-A group and 23 subjects

Figure 3. Patient satisfaction after a single BTX-A treatment compared with daily applications of 20% AC at week 4.



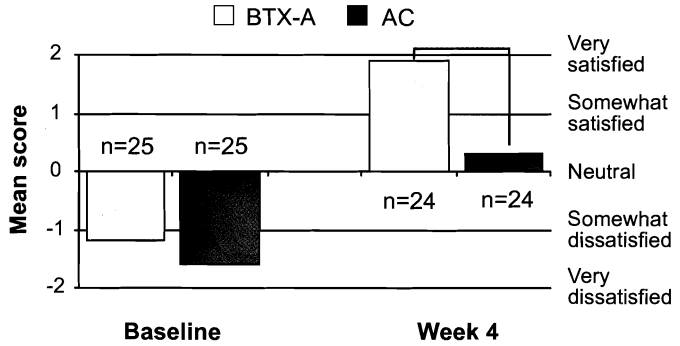
from the AC group. Of the 5 participants who did not complete the study, 3 (from the BTX-A group) were lost to follow-up by week 8. Of the 2 who discontinued the study from the AC group, 1 subject was lost to follow-up and the other discontinued the study due to an exacerbation of a previously existing medical condition. There were no significant differences in the demographics and baseline characteristics of the enrolled subjects (Table 1). The mean age of subjects was 29.9 ± 8.0 years, and 84% were Caucasian, 14% were Black, and 2% were Asian. Subjects were predominantly female (72%). Although not statistically significant, over 30% of the subjects reported palmar and plantar hyperhidrosis in addition to axillary hyperhidrosis, and 26% reported truncal hyperhidrosis. Also, 18% of subjects reported facial hyperhidrosis.

Previous Treatments

Over 90% of the subjects in the study had used OTC antiperspirants (8.0% had used "high strength" antiperspirants). These participants described them as "poor" or "ineffective." A total of 18% of the subjects had taken oral medications for hyperhidrosis either in the preceding 3 months or previously, however, 80% of these subjects rated the effectiveness of medications to be "poor" or "not effective." Very few subjects (2%) had used iontophoresis for axillary hyperhidrosis, and described its effectiveness as "poor."

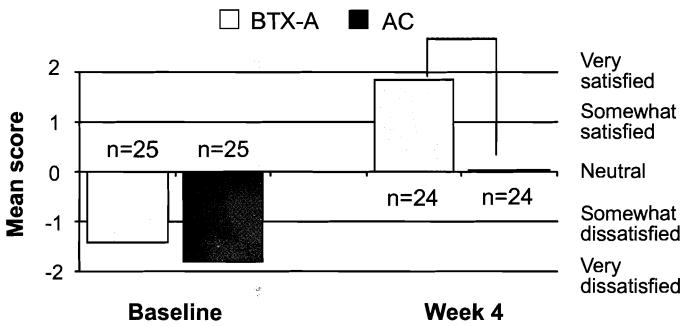
Figure 4. Overview of the impact on daily life due to the treatment of hyperhidrosis with BTX-A compared with 20% AC.

a. Satisfaction with ability to perform current work activities with respect to hyperhidrosis.



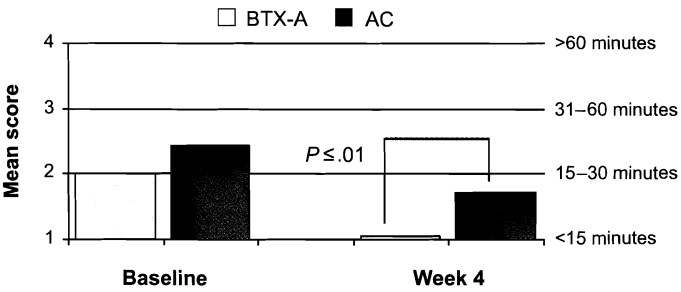
Mean satisfaction scores significantly different between groups at baseline ($P \leq .001$).

b. Satisfaction with ability to perform current nonwork activities with respect to hyperhidrosis.

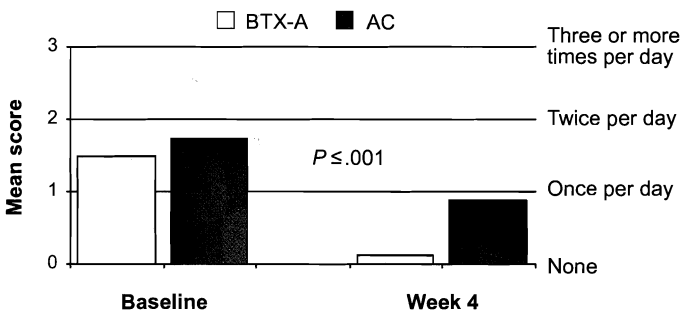


Mean satisfaction scores significantly different between groups at baseline ($P \leq .001$).

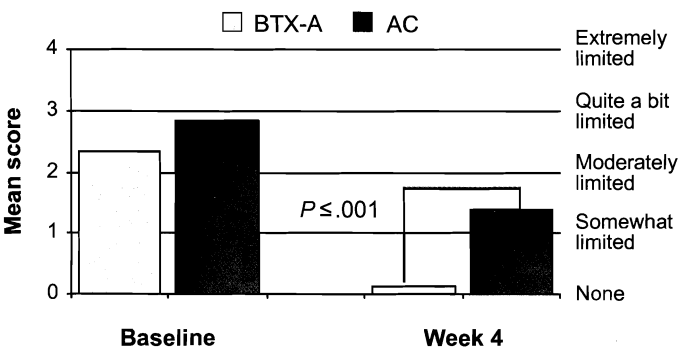
c. Amount of time spent daily treating hyperhidrosis.



d. Frequency of changing clothes due to hyperhidrosis.



e. Degree of limitation experienced due to hyperhidrosis in public places.



f. Degree of emotional injury/damage due to hyperhidrosis.

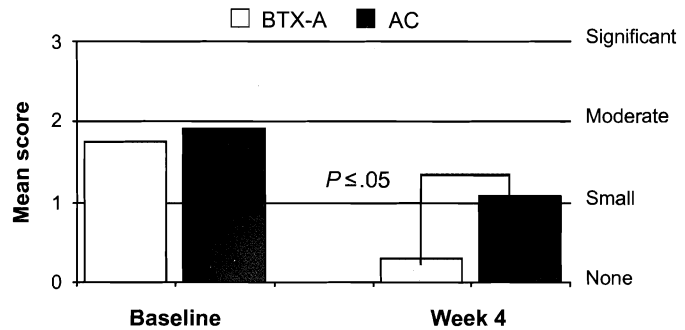


Figure 5a. Response of subjects in the BTX-A and AC groups regarding questions about irritation at week 4.

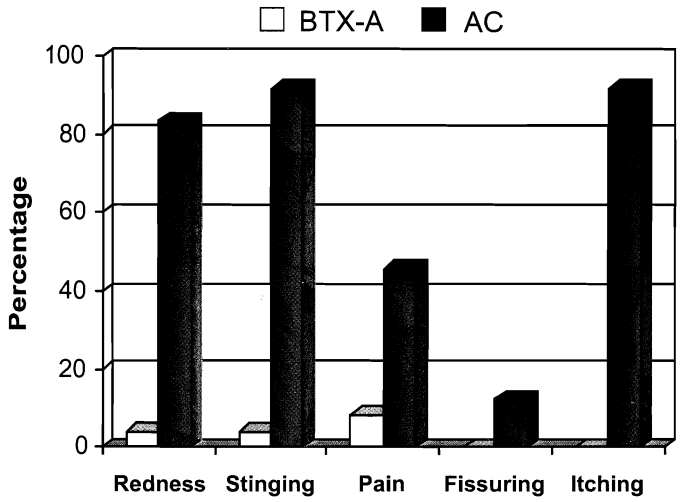


Figure 5b. Response of subjects in the BTX-A, AC, and BTX-A crossover groups regarding questions about irritation at week 12.

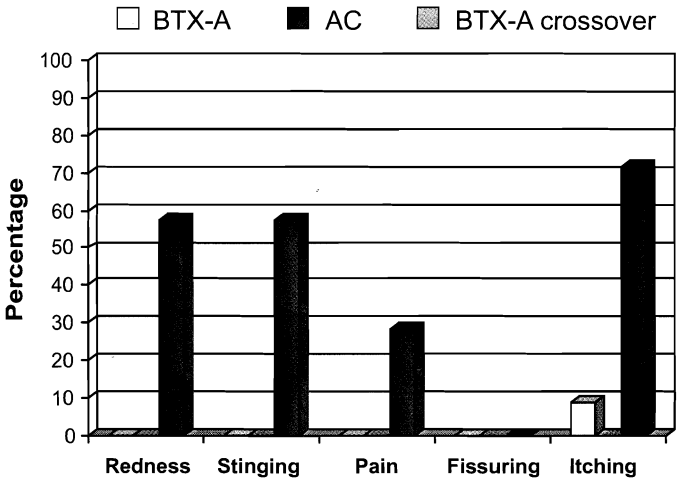
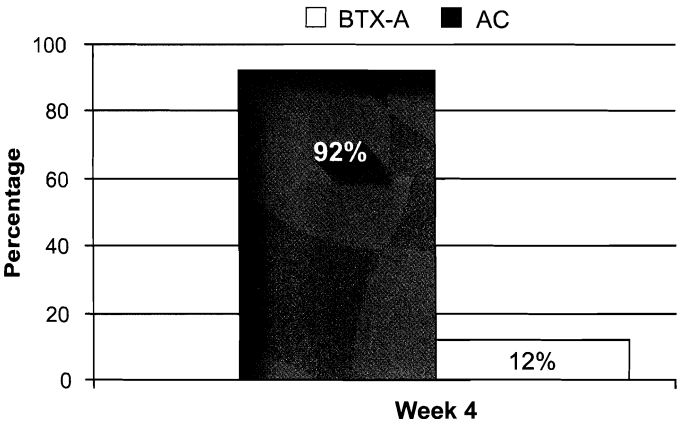


Figure 6. Incidence of adverse events in the BTX-A group compared with the AC group at week 4.



BTX-A Injections

Twenty-five subjects (100%) randomized to the BTX-A group received BTX-A injections. The BTX-A was reconstituted with 4 cc of normal saline without preservative and 50 units were injected into each axilla at the dermal-subcutaneous fat junction. The mean number of injections was 11.8 ± 1.6 per axilla. In the subjects who received BTX-A at week 4, the mean number of injections was 12.5 ± 1.3.

Primary Endpoints

There was no significant difference in HDSS score between treatment groups at baseline. At week 4, 24 subjects remained in each treatment group. A total of 91.7% of subjects in the BTX-A group were considered to be responders as defined by an improvement in HDSS score of ≥2 points compared with 33.3% of subjects in the AC group (Figure 1). The subjects in the BTX-A group had a mean change in their HDSS score of -2.42 ± 0.65 versus -1.33 ± 1.13 in the AC group ($P<.0001$) (Figure 2). At week 4, the mean HDSS score for the BTX-A group was 1.21 ± 0.41 compared with 2.38 ± 1.06 in the AC group ($P<.0001$).

At week 4, 17 (71%) subjects in the AC group did not tolerate AC and/or did not achieve an improvement of ≥2 points in their HDSS score, and opted to crossover to treatment with BTX-A. Of the 7 subjects responding to and tolerating AC therapy at week 4, there was no significant difference in HDSS scores when compared with the BTX-A responders.

Secondary Endpoints

Week 8 HDSS Scores and Treatment Responses

At week 8, 22 (88%) subjects remained in the BTX-A group and 90.9% were treatment responders. The subjects in this group had a mean change in HDSS score of -2.32 ± 0.78 from baseline ($P<.001$). At week 8, 6 (24%) were evaluable subjects in the AC group, and 83% continued to be responders to AC. These subjects had a mean change in HDSS of -2.83 ± 0.41. Of the 17 subjects who crossed over to BTX-A injections at week 4 from the AC group, 16 (94.1%) subjects were treatment responders and had a mean change in HDSS score of -2.53 ± 0.62 from baseline to week 8, which was significant ($P<.0001$).

Week 12 HDSS Scores and Treatment Responses

At week 12, 77.3% of subjects in the BTX-A group continued to be treatment responders and experienced a mean change in HDSS score from baseline of -2.23 ± 0.92. Between weeks 8 and 12, there were 7 evaluable subjects in the AC group, and 100% were treatment responders with a mean change in HDSS score of -2.86 ± 0.38 from baseline to week 12. The difference in treatment response between the BTX-A and AC groups was not significant. The mean HDSS score at the end of the study for the AC group was 1.14 ± 0.38, which was not significantly different from the BTX-A treatment group. At week 12, 1 subject from the crossover group was lost to follow-up, but of the 16 remaining subjects, 93.8% sustained a significant mean change in HDSS score from baseline to week 12 of -2.56 ± 0.63 ($P<.0001$) and re-

mained treatment responders at study end after BTX-A injections at week 4.

Satisfaction With Treatment

At baseline, 72% of subjects in the BTX-A group were "very dissatisfied," 20% were "somewhat dissatisfied," and 4% were "somewhat satisfied" with the current treatment. At study enrollment, all subjects in the AC group responded that they were "very dissatisfied" with current treatment compared with 72% of the subjects in the BTX-A group (P=.0088). At week 4, 21 (87.5%) subjects in the BTX-A group described themselves as "very satisfied" with current treatment, compared with 8 (33.3%) in the AC group (P<.0003), while 11 (45.8%) subjects rated their satisfaction as either somewhat or very dissatisfied.

At week 12, 81.1% of subjects in the BTX-A group replied that they were "very satisfied with treatment" whereas 13.6% were "somewhat satisfied," and 4.5% were "very dissatisfied" (Figure 3). Of the 7 subjects who remained in the AC group through week 12, 100% of subjects were "very satisfied" at week 4, 83.3% were "very satisfied" at week 8, and 85.7% remained "very satisfied" at week 12 compared with baseline (P=.0156), which did not differ significantly from the BTX-A group.

Of the 17 patients in the AC group who crossed over to treatment with BTX-A injections at week 4, 64.7% reported being either "somewhat dissatisfied" or "very dissatisfied" with the AC at week 4 (P=.0078). At week 8, 100% of the 17 patients described being "very satisfied" with BTX-A treatment, and at week 12, 93.8% of subjects were "very satisfied" with current treatment compared with baseline (P<.0001).

In the other categories evaluated by the HHIQ regarding the impact on daily life that treatment with BTX-A compared with AC had, subjects in the BTX-A group noted significant improvement compared with the AC group in all categories at week 4 (Figure 4).

Questions About Irritation

Subjects in both groups completed a questionnaire about irritation associated with each treatment. The questionnaire asked subjects to rate symptoms of redness, stinging, itching, fissuring, pain, or other symptoms that developed in the interval between study visits as absent, mild, moderate, or severe. Overall, the BTX-A group sustained very few side effects of irritation, but the AC group reported significant complaints of irritation across all of the categories except fissuring at week 4 (Figure 5a). The difference was significant between the treatment groups regarding all symptoms of irritation except fissuring at week 4.

At week 12, significant differences between the 22 subjects in the BTX-A group and the remaining 7 subjects in the AC group persisted; however 85% of subjects in the AC group described the symptoms as mild or absent (Figure 5b). However, 2 of the 7 subjects in the AC group complained of pain, with 1 subject rating it as mild and the other describing it as severe. This disparity in complaints of pain was significant between the two groups (P=.0126). At both weeks 8 and 12, the subjects who crossed over from the AC group at week 4 to receive BTX-A injections had no complaints of redness, stinging, itching, fissuring, or pain.

Adverse Events

Sixty adverse events in 37 subjects were reported (Figure 6). Of these, 31 events were related to study treatments, with the majority (68.3%) of adverse events occurring in the AC group (P<.0001). A total of 92% of subjects in the AC group compared with 12% of subjects in the BTX-A group reported adverse events that were deemed to be related to study treatment. These adverse events were related to skin irritation experienced in the AC group, with burning, itching, and redness of the bilateral axillae in the areas of application. In the BTX-A group, adverse events reported included mild redness and tenderness at injection sites that resolved in 2 to 3 days without sequelae in 3 subjects. One subject in the BTX-A group complained of a flu-like illness lasting 3 days after injection that resolved without sequelae, and may have possibly been due to the injection. There were no serious adverse events reported during the study in either group.

Discussion

The results of this single-center, randomized, parallel, open-label study demonstrate that BTX-A is superior to AC in the treatment of patients with moderate to severe axillary hyperhidrosis. A greater number of subjects treated with BTX-A injections achieved treatment response at week 4 compared with subjects treated with AC. The majority of subjects in the AC group did not achieve treatment response or could not tolerate AC at week 4, but those who crossed over to treatment with BTX-A injections at week 4 achieved treatment response at week 8, which was maintained through the end of the study (week 12). Subject satisfaction with treatment was greater in the BTX-A group at week 4 compared with the subjects in the AC group, and remained significantly higher through week 12. In other secondary endpoints regarding activities of daily life assayed by the HHIQ, subjects treated with BTX-A reported significant improvements in all areas compared with subjects in the AC group at week 4.

Subjects who crossed over to receive BTX-A injections at week 4 were significantly more satisfied with this treatment compared with the treatment with AC. However, those subjects who responded to treatment with AC at week 4 and stayed in the AC group through the end of the study had greater satisfaction than the subjects in the BTX-A group, although this difference was not statistically significant, and the numbers in the AC group at the end of the study were small compared with the BTX-A group.

Adverse events occurred more frequently in the AC group compared with the BTX-A group, but were predictably related to irritation caused by the high percentage of AC in the treatment. It was notable that even those subjects who remained in the AC group through the end of the study had complaints of irritation at some point in the study.

To date, this is the first study directly comparing the efficacy and tolerability of BTX-A compared with 20% AC for the treatment of moderate to severe axillary hyperhidrosis. The study demonstrates the superiority of BTX-A compared with 20% AC in achieving treatment response as well as significantly improving patient satisfaction with treatment and numerous indices of disease impairment as measured by the HHIQ. Both products can provide efficacy, however, 20% AC is well tolerated and effective in the minority of patients. For patients with moderate to severe axillary hyperhidrosis who do not respond to or who cannot tolerate high strength AC, BTX-A is an effective and well-tolerated therapy, which can meaningfully ameliorate the impact of hyperhidrosis on their quality of life.

Disclosure

Allergan provided financial support through an unrestricted educational grant. The sponsor had no role in the analysis or interpretation of the results of this research. No limitations on publication were imposed, and review before final publication was not required. The authors made final decisions on all aspects of the manuscript. Dr. Glaser is a consultant for Allergan.

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