

Botulinum Toxin Type A in the Treatment of Bilateral Primary Axillary Hyperhidrosis: Efficacy and Duration With Repeated Treatments

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BACKGROUND. Botulinum toxin type A (BTX-A) has been shown to be effective for the temporary reduction of local hyperhidrosis.

OBJECTIVE. To investigate the duration of efficacy of BTX-A with repeat treatments for axillary hyperhidrosis.

METHODS. Patients who completed a prior randomized, controlled, parallel-group study comparing BTX-A with vehicle for bilateral primary axillary hyperhidrosis were eligible for this 18-month, open-label, noncomparative, follow-up study. Patients had to request further treatment, fulfill the preceding study inclusion/exclusion criteria, and have spontaneous sweat production that was more than 50% of the baseline value of the previous study. Patients received up to four treatments of intradermal BTX-A (2 mL, 50 U). All of the 12 patients who

were enrolled completed the study. Two of the 12 patients (17%) were previously treated with placebo.

RESULTS. In the 18 months of study and follow-up, five patients (42%) required a total of two active injections. Three patients (25%) required a total of three active injections, and four patients (33%) required a total of four active injections. The response rate was 83% (10 of 12) at 4 weeks after the first treatment. The mean percentage change from baseline in overall sweat production was approximately 80% at Week 4. The mean time between the first and second treatment in this study was just over 29 weeks, with a range of 17.8 to 57.5 weeks.

CONCLUSION. BTX-A is an effective repeat treatment for axillary hyperhidrosis giving variable but clinically helpful remission. No clinically relevant changes in vital signs or safety parameters were noted.

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PRIMARY HYPERHIDROSIS is a chronic, idiopathic disorder of excessive sweating that may effect any body part, including the axillae (axillary hyperhidrosis). The condition may cause significant social problems in both a private and a professional life. Profuse sweating can also lead to painful skin maceration, which can result in a secondary infection.

Current treatments, which include topical applications of acids, aldehydes and metal salts, iontophoresis, and systematic therapies, are often ineffective or produce improvements of short duration. Surgical treatments, such as sympathectomy and removal of the sweat glands by liposuction or curettage, may provide relief for longer periods of time, but these methods carry significant risks.¹

Recently, botulinum toxin type A (BTX-A) has demonstrated a sustained relief of symptoms with a good safety profile in open-label studies of the

treatment of axillary hyperhidrosis.²⁻⁷ A previous randomized, double-blind, placebo-controlled trial demonstrated a 93.8% response rate after a single treatment with BTX-A and a safety profile that was comparable to the placebo injections.⁸ Another study showed an efficacy of BTX-A against placebo, but the patients had only one treatment session and short-term follow-up.⁹

This study was designed to evaluate the long-term safety and efficacy of repeated dosing with BTX-A treatment for axillary hyperhidrosis.

Methods

The patients had all been enrolled at one center of a multicenter BTX axillary hyperhidrosis previously reported (Naumann and Lowe).

Study Design

This was a single-center, open-label, noncomparative, follow-up study.

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Patients

These were the key inclusion criteria: adult patients with primary axillary hyperhidrosis who had completed a previously randomized, placebo-controlled study, with sweat production measured by gravimetric assessment of more than 50% of baseline pretreatment in a previous study in both axillae and at least 16 weeks since last treatment.

These were the key exclusion criteria: any medical condition (e.g., myasthenia gravis, amyotrophic lateral sclerosis) or agent (e.g., aminoglycoside antibiotics) that interferes with neuroglandular transmission, infections or skin problems at the anticipated treatment site, any other concurrent treatment for hyperhidrosis, or any other investigational drug within the past 30 days.

Study Medication

Each vial of BTX-A (Botox; Allergan, Inc., Irvine, CA) contained 100 U of BTX-A and was reconstituted with 4.0 mL of 0.9% sterile saline without preservatives.

Protocol

The enrollment visit of this study was the exit visit of the preceding study (Naumann and Lowe, 2001). Patients wanting but not qualifying for treatment returned monthly until gravimetric requirements were met. Those who did not request immediate treatment were contacted monthly by telephone. Patients shaved both axillae 2 days before and withheld antiperspirant/deodorants for 24 hours before each study visit. Each axilla was treated with 50 U of BTX-A divided into 10 to 15 intradermal injections in an even distribution within the hyperhidrotic area (previously defined by Minor's iodine-starch test) for up to three treatments, as determined by gravimetric sweat measurement. Primary assessments of efficacy and safety were made at Weeks 4 and 16, with telephone visits at Week 8 and 12 for treatment satisfaction, and with adverse events.

Outcome Measures

Gravimetric measurements of sweat production

One preweighed Whatman 80-mm filter paper was placed on a plastic bag and was securely taped to the axilla; the arm was lowered until abducted to the body. After 15 minutes, the filter paper was removed and reweighed. The test was repeated for the other axilla.

Safety evaluations

The safety evaluations included the following: serum antibody tests, vital signs, pregnancy tests, and adverse events monitoring.

Iodine starch test

After the gravimetric test, an iodine solution (2 g of iodine in 10 mL of castor oil and 90 mL of alcohol) was painted over the axilla (Figures 1 and 2). Potato starch powder was applied after the iodine mixture dried. The presence of sweating was indicated by the dark blue color. Borders of the hyperhidrotic area were marked. Photographs were taken with a 3-cm ruler next to the axilla, and image-analysis software calculated the area in mm^2 .

Results

Patient Disposition

Twelve patients enrolled in the study: Seven (58%) were female, and five were male (42%); all 12 patients



Figure 1. Minor's iodine starch reaction in a patient before BTX-A injection to the axilla.



Figure 2. Minor's iodine starch reaction in a patient 4 weeks after BTX-A injection to the axilla.

completed the study. Two (17%) of the subjects, both female, received placebo in the previous double-blind study, and both required further treatment. In the 18 months of follow-up, five patients (42%) required a total of two BTX injections. Three patients (25%) required a total of three BTX injections, and four patients (33%) required a total of four BTX injections.

Data Summaries for 12 Patients

The change in sweat production, as measured by gravimetric assessment from baseline value, has been summarized for the Week 4. The baseline visit for patients receiving active BTX-A treatment during the double-blind phase of the study is defined as the day that active treatment was administered. For patients that previously received vehicle in the double-blind phase of the study, the baseline visit is defined as the day of the first active BTX-A injection in the open-labeled phase.

The sweat production, as measured by gravimetric assessment, was summarized for both the right and left

axillae and the overall areas. The percentage change at Week 4 compared with baseline was produced for all patients.

Patients were classified as a treatment success if they had a reduction in sweat production as measured by gravimetric assessment of 50% or more at Week 4. A patient was defined as being an overall success if they had achieved success for both the right and the left areas.

Patients were classified as treatment failure if they did not achieved a 50% reduction from baseline at Week 4. Patients were classified as overall failure if either the left or right area failed (Table 1).

Table 1. Patient Baseline Suppression of Gravimetric Sweat Production (Before Treatment With BTX-A)

Percentage Change From Baseline	Left	Right	Overall
Mean	-121.8	-171.9	-293.7
Median	-55.2	-122.4	-189.9
SD	173.5	156.5	305.8
Minimum	-651.1	-478.2	-1129.3
Maximum	-9.7	-9.3	-19
N	12	12	12

Table 2. Overall Success Based on 50% or More Reduced Sweat

Treatment Success	Left	Right	Overall
Success	10 (83%)	11 (92%)	10 (83%)
Failure	2 (17%)	1 (8%)	2 (17%)

Table 3. Second Injection of BTX-A; Time To Relapse (Days)

Time to Second Injection (Days)	
Mean	205.7 days
SD	74.4 days
Minimum	129.0 days
Maximum	402.0 days
N	12

Table 4. Third Injection of BTX-A; Time to Relapse

Time to Third Injection (Days)	
Mean	158.7 days
SD	40.2 days
Minimum	111.0 days
Maximum	217.0 days
N	6

Table 5. Fourth Injection of BTX-A; Time to Relapse

	<i>Time to Fourth Injection (Days)</i>
Mean	141.3 days
SD	28.5 days
Minimum	106.0 days
Maximum	175.0 days
N	4 days

The duration of effective treatment can be estimated from the number of days to active BTX-A injection in the open-label study (injection 2), between injections 2 and 3 and between injections 3 and 4. Summaries of the duration of effect between injections 2 and 3 and injections 3 and 4 have been included for consistency of presentation of results with previous studies (see Tables 2-5).

Hence, the summaries of duration between the latter injections are representative of the patient population that required further injections, whereas the summary for time to injection 1 represents the duration of effective treatment for the entire patient population.

The time between injections 2 and 3 (days) was an overall mean of 158.7 days. The time between injections 3 and 4 (days) was an overall mean of 141.3 days.

Discussion

This study shows that long-term efficacy of BTX in suppression of axillary hyperhidrosis is sufficient to consider BTX as an important choice of therapy. Of the 20 patients studied, 5 (40%) required only one BTX injection in the 18 months of follow-up. There were no significant side effects noted other than occasional, transient minimal bruising. Discomfort was minimal, using a slow intradermal injection with 30-gauge needle introduced at a 30° angle from the skin surface to the depth of the needle bevel, this raising the optimal intradermal bleb.

A 50% sweat reduction was selected as study success; however, most of the responding patients achieved greater amounts of reduction. The patients could be retreated if they had less than a 50% reduction. This was a research decision to select 50% reduction; in some patients, it represented a significant clinically relevant suppression. Others would have requested earlier retreatment if they were not in the study.

It was noted that the patient's length of duration remained approximately similar after each BTX injection. In other words, the duration of benefits observed was similar between before and first, first and second, and second and third BTX-A injections. The duration after first injection may therefore act as a broad guideline to advise patients on their expected

frequency of injection. It may help to advise them as to the practicality of them having further BTX-A therapy. The mean duration of effect was approximately 6 months, with no development of disease resistance or serum BTX antibody production in this group of patients. A previous report showed a treatment benefit, but patients were only followed over a 3-month period.

Another study of a larger group of patients has configured a major impact of decreased quality of life in similar patient with severe axillary hyperhidrosis. The quality of life was very significantly improved after BTX-A.¹⁰

It is possible that different responses and duration of benefit would be observed with different doses and/or dilution of BTX-A; these studies are needed. The reason for the prolonged benefit in some compared with other patients is not known at this stage but may involve feedback inhibition of Cholinergic eccrine gland stimulation by unknown mechanisms.

Conclusion

Consistent responder rates, with reduced sweat production, were observed after multiple treatments with BTX-A. The mean duration of effect, as measured by the time between consecutive BTX-A treatments, was approximately 6 months. A longer duration of effect was seen in a substantial proportion of patients, with 5 of 12 patients (42%) requiring only one additional active treatment in 18 months of follow-up.

Long-term treatment with repeated intradermal dosing of BTX-A is safe and effective for the treatment of primary bilateral axillary hyperhidrosis.

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