Topically Applied Botulinum Toxin Type A for the Treatment of Primary Axillary Hyperhidrosis: Results of a Randomized, Blinded, Vehicle-Controlled Study

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OBJECTIVE The objective was to demonstrate that botulinum toxin type A (BTX-A) can be delivered to targeted skin sites with topical application for the treatment of primary axillary hyperhidrosis.

METHODS This randomized, blinded, vehicle-controlled study enrolled 12 patients with primary axillary hyperhidrosis with greater than 50 mg of sweat produced per 5 minutes. BTX-A (200 U), combined with a proprietary transport peptide molecule to bind the toxin in a noncovalent manner, was topically applied to one axilla; vehicle without BTX-A was applied to the other axilla. Rates of sweat production were measured and imaged at baseline and 4 weeks after application.

RESULTS Two patients were excluded from analyses. At 4 weeks, 10 axillae treated topically with BTX-A demonstrated a 65.3 $\pm$ 21.5% mean reduction in sweating relative to the same-patient, vehicle-control axillae, which had a 25.3 $\pm$ 66.2% mean reduction. The 40% difference in mean sweat reduction between groups was statistically significant ($p < .05$). Quantitative image analysis of the results of the Minor's iodine starch test confirmed the reduction of sweat production in the BTX-A–treated versus the vehicle-treated axillae.

CONCLUSION Topically applied BTX-A appears to be safe and may prove to be effective for the treatment of axillary hyperhidrosis.

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Primary focal hyperhidrosis is a chronic disorder characterized by excessive sweating that occurs in the axillae in 51% of cases and less frequently in the palms, soles, or face.[1] In addition to causing social embarrassment, psychological distress, and difficulty with work, hyperhidrosis may result in skin maceration and secondary infections.[2] Most noninvasive treatments for hyperhidrosis provide temporary relief at best, with very little relief for severe cases. Sympathectomy or removal of the sweat glands, while effective, requires invasive surgery and may result in compensatory sweating.[3]

Injection of BOTOX (Allergan, Inc., Irvine, CA) botulinum toxin type A (BTX-A) is approved by the US Food and Drug Administration (FDA) for the treatment of severe primary axillary hyperhidrosis.[4] A 900-kDa protein complex, the neurotoxin prevents release of the neurotransmitter acetylcholine from the presynaptic membrane at the neuromuscular junction and in cholinergic autonomic neurons. To treat axillary hyperhidrosis, BTX-A is injected intradermally at numerous sites in the axillary skin; the toxin diffuses radially and thus disrupts eccrine gland secretion, often producing a significant reduction in sweat production for several months.[5] Despite its efficacy, however, clinical use of BTX-A may be limited due to multiple, repeated injections and the discomfort associated with intradermal injection as the primary route of BTX-A administration. Because it is projected that there are 4 million people in the United States with axillary hyperhidrosis,[1] there is a clear medical need for an effective, safe, noninvasive treatment for the disease.

The results of a 4-week, randomized, blinded, vehicle-controlled clinical study of a topical formulation of BTX-A with a proprietary, noncovalently

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bound, transport peptide backbone (Essentia Biosystems, Inc., now Revance Therapeutics, Inc., Mountain View, CA) for the treatment of bilateral primary axillary hyperhidrosis are presented.

Methods

Patient Recruitment

The study was a single-center, blinded, randomized, vehicle-controlled, within-patient comparison trial, approved by an independent ethics committee. Informed consent was obtained from all subjects and the study protocol conformed to the guidelines of the 1975 Declaration of Helsinki. Adult patients (>18 years of age) with a gravimetric measurement of sweat production of at least 50 mg over 5 minutes while at rest at room temperature could be enrolled. Key exclusion criteria included botulinum toxin injection within the 6 months prior to the day of screening, more than 25% asymmetrical sweating between the two axilla (by gravimetric assessment), and concurrent medication (or within 30 days prior to enrollment) with any anticholinergic, aminoglycoside, or calcium channel blocker medications. Patients with a medical history or physical examination suggestive of possible concurrent myasthenia gravis and hyperthyroidism were excluded. Forty patients with bilateral primary axillary hyperhidrosis were screened for inclusion, and 12 patients were enrolled in the study.

Study Design

All patients underwent a prescreening evaluation consisting of clinical assessment, objective quantification of sweat production via gravimetric measurement, Minor's iodine starch test,[6] and photography. Participants were requested to shave both axillae 2 days prior to clinical assessments and not to use any antiperspirants during the course of the study. Each patient served as his or her own control with random and blinded assignment of each axilla to a treatment group. BTX-A (200 U) was first combined with a proprietary transport peptide molecule to bind the toxin in a noncovalent manner. BTX-A in this formulation was topically applied to one axilla; an identical formulation (vehicle) without BTX-A was applied as to the other axilla. There was no visual difference between the two formulations.

Drug Application

BTX-A (200 U; BOTOX, Allergan, Inc.) was dissolved in 1.5 mL of 0.9% sterile, preservative-free saline and mixed by inversion with transport peptide. The solution was mixed uniformly in the same volume of Cetaphil cream (Galderma, Fort Worth, TX) using a metal spatula. The mixture was then massaged (while wearing nitrile gloves) into the skin of the hyperhidrotic area, defined as 1 cm beyond the hair-bearing skin, for 1 minute. The treatment formulations remained on the skin for 60 minutes, with the patient's arms in a resting position along the side of the body. The vehicle contained 1.5 mL of 0.9% sterile preservative-free saline with transport peptide and was mixed and applied in an identical manner.

Efficacy Measures

The primary efficacy measure in this study was the sweat production. Sweat production was measured gravimetrically before treatment and at every subsequent visit. Measurements were made after the patient had rested for 15 minute at a room temperature of 70 to 75°F. Briefly, 90-mm filter paper (Whatman, Middlesex, UK) was weighed on a high-precision laboratory scale (Sartorius AG, Goettingen, Germany; accuracy, $\pm$ 0.1 mg), placed in the precleaned and dried axillae for 5 minutes, and then weighed again. The sweat production was then calculated in milligrams per 5 minutes. Minor's iodine starch test was also performed at each clinical visit.

Statistical Analysis

Statistical analyses were performed with Analyze-it software (Analyze-it Software Ltd., Leeds, England). A total of 12 patients were enrolled, including 2 patients who had not met the exclusion criteria of >25% asymmetry at baseline ($p < .05$ by Wilcoxon

ranked sums); thus results for the remaining 10 patients are presented. The relative reduction in sweating was computed as the percentage difference between the pretreatment (baseline) and posttreatment (Week 4) rates of sweat production. The mean values for the 10 patients were then evaluated statistically as ratios either to baseline or to control; p values were calculated using the Wilcoxon signed rank sum test.

Results

Participants

A total of 12 patients with bilateral primary axillary hyperhidrosis were randomized to receive 200 U of BTX-A combined with a proprietary transport peptide molecule applied topically to one axilla; an identical formulation (vehicle) without BTX-A was applied as to the other axilla. There were 6 men and 6 women enrolled, with a mean age of 35 years. At baseline, the mean sweat production for the axillae to be treated with BTX-A was 89.8 mg per 5 minutes, and for the axillae to be treated with vehicle it was 96.8 mg. All patients completed the treatment (baseline) and posttreatment (Week 4) visits. The data of 2 patients were excluded from analyses due to >25% asymmetry of axillary sweating at baseline.

Efficacy

Topically applied BTX-A quantitatively reduced sweating compared with vehicle. The change in sweat production was measured gravimetrically. Sweat production at 4 weeks was compared to baseline for the same axilla (Figure 1). The ratio of mean sweat production ($\pm$ SE) of the BTX-A–treated axillae relative to baseline was 0.35 ± 0.22, whereas that of the vehicle-treated axillae relative to baseline was 0.75 ± 0.66. By this analysis, topical BTX-A reduced mean sweat production by $65.3 \pm 21.5\%$, whereas mean sweat production for the control axillae decreased by $25.3 \pm 66.2\%$. The decrease in sweat production by the BTX-A–treated axillae compared to the placebo–control axillae was statistically significant ($p < .05$).

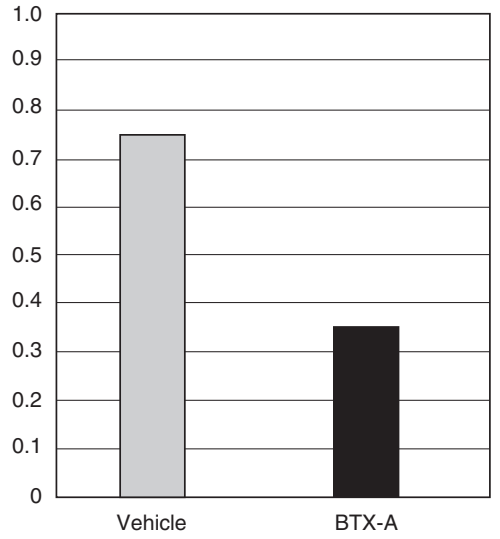

Figure 1. Axillary sweat production 4 weeks after treatment with 200 U topically applied BTX-A or vehicle. Ratios are expressed as gravimetrically measured mean sweat production ($\pm$ SE) at Week 4 relative to baseline (before treatment). Topical delivery of BTX-A yielded a statistically significant reduction of $65.3 \pm 21.5\%$ compared to the vehicle-treated reduction of $25.3 \pm 66.2\%$ ($n = 10$, $p < .05$).

In an additional analysis, the ratio of mean sweat production for the treated axillae relative to the vehicle-treated axillae was calculated at baseline and 4 weeks after treatment (Figure 2). The BTX-A/vehicle ratio changed from 1.3 at baseline to 0.8 at 4 weeks after treatment. Thus, after 4 weeks, topical BTX-A resulted in a statistically significant mean reduction in gravimetrically measured sweat production relative to the vehicle-treated axillae ($p < .05$). The results of the Minor's iodine starch test demonstrated sweat reduction patterns consistent with the gravimetry results (representative results, Figure 3).

Safety

Very few local adverse events were reported, and none of them was considered to be related to the BTX-A treatment. No systemic adverse events were reported. All local adverse events ($n = 4$) reported through Week 4 occurred in the vehicle-treated axillae and included mild folliculitis or razor bumps, tenderness, erythema, and eczema (2 cm inferior to the axilla on the lateral trunk).

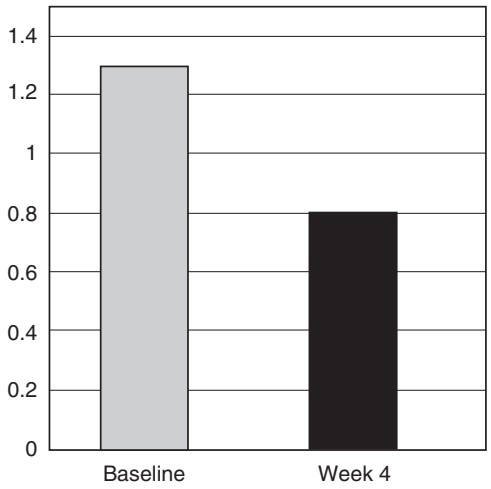

Figure 2. Ratio of mean sweat production in BTX-A–treated and vehicle-treated axillae. The ratio (± SE) changed from 1.3 ± 0.12 at baseline to 0.8 ± 0.11 at 4 weeks after treatment ($n = 10$; $p < .05$).

Discussion

BTX-A (BOTOX) injection is FDA approved for the treatment of severe primary axillary hyperhidrosis. The treatment is effective in the vast majority (81%–91%) of affected patients, with a duration of approximately 6 to 7 months. The treatment requires multiple injections in each axilla, however, which many patients find objectionable, especially because primary axillary hyperhidrosis is a chronic condition that requires repeated treatments with BTX-A.

To address the need for painless BTX-A delivery, this clinical trial was designed to investigate a topical formulation of BTX-A with a novel, proprietary transport peptide to deliver BTX-A through the skin. Owing to the molecule's large size, BTX-A has long been considered highly resistant to transdermal delivery, thus necessitating injection. The study objectives were to demonstrate that BTX-A is delivered to targeted skin sites and to evaluate the safety and effectiveness of this painless, topical application of BTX-A for the treatment of primary axillary hyperhidrosis. In this formulation, the neurotoxin is noncovalently coupled with a proprietary transport peptide that has also been demonstrated to successfully transport insulin and other macromolecules across intact skin (Revance Therapeutics, Inc., personal communication).

This clinical study demonstrates that topical BTX-A with a transport peptide reduced the mean gravi-

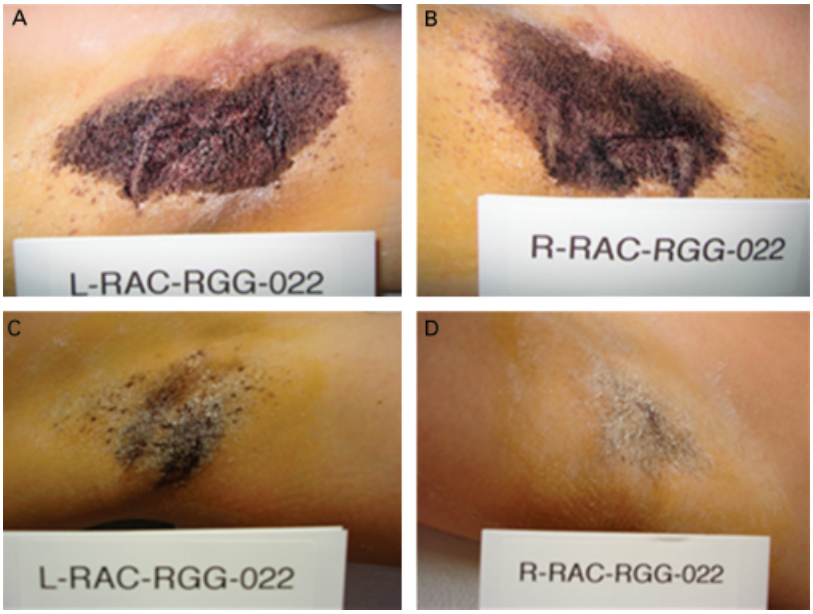

Figure 3. Minor's iodine starch test on control (A, C) and topically BTX-A–treated (B, D) axillae from a single patient at baseline (top row) and Week 4 (bottom row).

metrically measured sweat production by 65%, compared to a 25% reduction in vehicle-treated axillae by 4 weeks. Despite the small number of patients in this study, the decrease in sweat production mediated by BTX-A was statistically significant ($p < .05$). These data are supported by imaging results from Minor's iodine starch test.

Interestingly, sweat production also diminished in the vehicle-treated axillae. This effect is certainly not related to local application of a vehicle, but is consistent with an effect noted in a prior study of another injected botulinum toxin versus placebo.[7] In that study, patients were treated with BTX-A in one axilla and placebo in the other. At 2 weeks, there was a significant difference in the mean rate of sweat production in both axillae, although the difference was greater for the axillae treated with BTX-A. The authors suggested that the axilla injected with placebo benefitted from the contralateral injection due to systemic spread of BTX-A. This hypothesis may be substantiated by the observation of subclinical changes in the activity of distant muscles following intramuscular administration of BTX-A. In another study, however, when BTX-A was injected into just one axilla, the contralateral axilla did not show any improvement in gravimetric measurements of sweat.[8] Subjective reports of change in sweating in axillary or nonaxillary areas have been noted after medical and surgical interventions; this could represent heightened awareness of sweat production. A plausible alternative explanation is that a central upregulation of the autonomic nervous system may occur.[2] It is similarly plausible that down-regulation of the autonomic nervous system occurs and may explain decreased sweating in areas distant to those treated, as in this study in the contralateral axillae. The precise mechanism for this effect deserves greater study.

The topical application of BTX-A resulted in no systemic and very few local adverse events, suggesting that topically applied BTX-A is safe. Although decreasing motor function of adjacent muscles continues to be a concern with BTX-A injections, no such effects were observed in this study. There are no data on duration of effect, a point that remains an area for potential future study.

Results from this clinical study represent the first statistically significant, quantitative reduction of sweat production by topically applied BTX-A in the treatment of primary axillary hyperhidrosis. Although this study addressed axillary hyperhidrosis, an effective topical BTX-A formulation may also prove useful in treating hyperhidrosis of the palms, soles, face, or other body surface areas.

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