

P30

Efficacy and Safety of Repeated Botulinum Toxin Type A Treatment for Primary Axillary Hyperhidrosis: 12-Month Interim Analysis of a Multicenter, Open-Label Trial

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INTRODUCTION

Primary axillary hyperhidrosis is a pathologic condition that is characterized by underarm sweating in excess of that required to respond to environmental conditions and of at least 6 months' duration without apparent cause.¹ A recent survey of US households found that as many as 0.5% of the population (~1.3 million persons) have axillary hyperhidrosis that is barely tolerable or intolerable and frequently or always interferes with daily activities.² Patients with focal hyperhidrosis report significant work limitations, emotional impairment, and considerable difficulties in interpersonal situations.^{3,5} These patients also spend a substantial amount of time and effort managing their symptoms.^{3,5} Therapy with topical agents, such as aluminum chloride, often has a short-lived effect and is often discontinued because of skin irritation.^{1,6} Surgery may improve symptoms, but its success is limited by high rates of recurrence (as high as 65%)⁷ and compensatory sweating (68% to 88%).^{8,9} Surgery may also expose patients to potentially serious complications.^{7,8,10} In July 2004 the FDA approved botulinum toxin type A (BoNTA) for the treatment of primary axillary hyperhidrosis that cannot be managed with topical agents such as prescription antiperspirants. As shown in clinical trials, BoNTA treatment results in significant, meaningful, rapid, and durable reductions in disease severity and functional impairment, as well as improvements in health-related quality of life, in patients with primary axillary hyperhidrosis.^{3,5,11} In this open-label study we evaluated the efficacy and safety of repeated treatments with BoNTA over 3 years in patients with primary axillary hyperhidrosis that interferes with daily activities. Here we report the results of the first year of the open-label study, combined with data from an earlier 1-year double-blind study.

METHODS

Study design

- Patients who completed a 1-year randomized double-blind placebo-controlled study (RCT)⁴ were eligible for this 3-year open-label extension trial
 - In the RCT, patients had received 1 of 3 treatments (placebo, 50 U or 75 U BoNTA/axilla)

- In the open-label extension study, patients received 50 U BoNTA/axilla and were assessed during a telephone visit 7 days postinjection, at office visits 4 and 8 weeks postinjection, and during monthly telephone visits thereafter until they were eligible for reinjection or exited the study
- One year of data from the RCT and 1 year of data from the open-label extension study available at the time of analysis were combined for all patients who were enrolled in the open-label extension study
- Retreatment criteria
 - Patients were eligible for reinjection 8 weeks after each treatment session if symptoms persisted or recurred
 - A score of 3 or 4 on the Hyperhidrosis Disease Severity Scale (HDSS), indicating that their underarm sweating was barely tolerable or intolerable and frequently or always interfered with their daily activities
 - A gravimetric measurement of at least 50 mg of spontaneous sweat in each axilla over 5 minutes at rest

Inclusion criteria

- Completion of the RCT
- Inclusion criteria for the RCT were
 - 18 to 75 years old, with persistent bilateral primary axillary hyperhidrosis
 - Score of 3 or 4 on the HDSS (axillary sweating is barely tolerable or intolerable and frequently or always interferes with daily activities) (Table 1)
 - Baseline gravimetric measurement of at least 50 mg of spontaneous resting sweat production in each axilla measured over 5 minutes at room temperature

Exclusion criteria

- Concurrent use of agents that might interfere with neuromuscular function
- Concurrent use, or use within 7 days before the first treatment, of any treatment for hyperhidrosis other than over-the-counter antiperspirants or deodorants
- Allergy or sensitivity to any component of the study medication
- Previous treatment for hyperhidrosis with botulinum toxin of any serotype

Table 1. Hyperhidrosis Disease Severity Scale

Question: How would you rate the severity of your hyperhidrosis?	Score
My underarm sweating is never noticeable and never interferes with my daily activities	1
My underarm sweating is tolerable but sometimes interferes with my daily activities	2
My underarm sweating is barely tolerable and frequently interferes with my daily activities	3
My underarm sweating is intolerable and always interferes with my daily activities	4

Measures**Efficacy**• **HDSS**

The primary efficacy measurement was the HDSS (Table 1), a validated single-item 4-point scale in which the patient rates the degree of interference of his or her hyperhidrosis symptoms with his or her daily activities.² A higher score indicates greater interference

• **Gravimetric measurement of sweat production**

Gravimetric measurement of spontaneous resting axillary sweat production was performed at room temperature over a period of 5 minutes and was quantified as the mean sweat production of both axillae

• **Duration of response**

The duration of response was calculated as the number of days after each BoNTA treatment to the first reporting of a score of 3 or 4 on the HDSS (or discontinuation from the study)

• **Toxin-neutralizing antibodies**

The presence of toxin-neutralizing antibodies in the serum was detected by using the mouse protection assay

- Patients were primarily of white ethnicity (84%), with approximately equal percentages of men (52%) and women (48%), and with a mean age of 33 years (range 18–65) (Table 2)

Table 2. Demographics

Characteristic	Enrolled population (N = 193)
Age, y, mean (range)	33 (18–65)
Sex, %	
Male	52
Female	48
Ethnicity, %	
White	84
Hispanic	9
Black	5
Other	2
Treatment in 1-year RCT, %	
Placebo	22
BoNTA 50 or 75 U/axilla	78

Efficacy**HDSS**

- Four and 8 weeks after treatment session 1, 83% (141/171) and 78% (131/169) of patients, respectively, reported at least a 2-grade improvement from baseline on the HDSS (Figure 1)
 - For comparison, 28% (11/40) and 25% (9/36) of patients in this study had this level of improvement at weeks 4 and 8, after the first placebo session in the RCT
- BoNTA showed continued effectiveness with repeated treatment
 - 81% (83/103) and 78% (40/51) of patients reported at least a 2-grade improvement from baseline in HDSS score 4 weeks after treatment sessions 2 and 3, respectively

RESULTS**Demographics**

- A total of 193 (77%) patients who completed the 1-year RCT enrolled in the open-label study; 78% (150/193) had previously been randomized to treatment with BoNTA, the remaining 43 patients had previously received placebo
 - Among those 193 patients, during the combined 2 years of follow-up, 185 patients (96%) had received at least 1 BoNTA treatment; 3 (2%) had completed or discontinued the open-label study without having received any BoNTA treatment; and 5 (3%) were still enrolled but had not received any BoNTA treatment
 - Of the patients who had received BoNTA treatment, during the 2 years of follow-up 34% (62/185) received 1 treatment; 30% (55/185) received 2 treatments; 21% (39/185) received 3 treatments; 10% (18/185) received 4 treatments; and 5% (11/185) received 5, 6, or 7 treatments

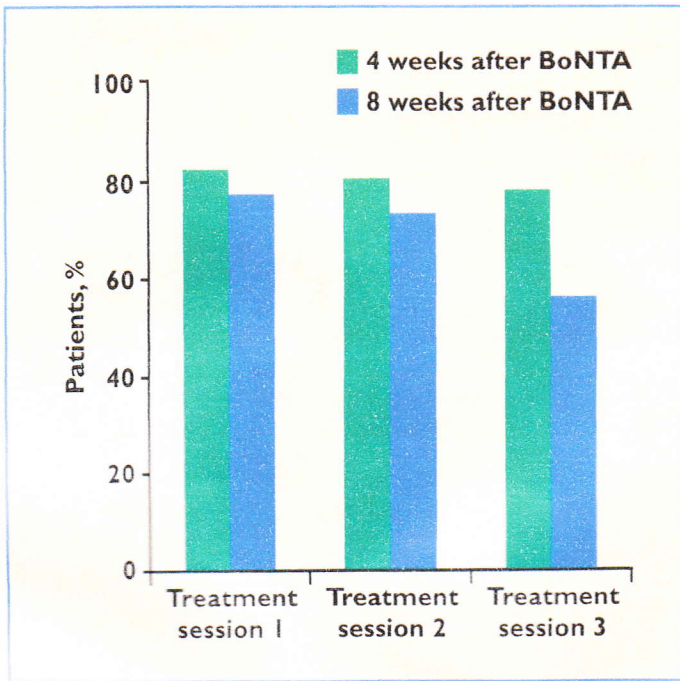


Figure 1. Patients with at least a 2-grade improvement from baseline in HDSS score at 4 and 8 weeks after BoNTA treatment for each treatment session.

- The benefit was similar in patients who had been treated with placebo and those who had been treated with BoNTA in the RCT
 - 82% (117/143) and 86% (24/28) of patients previously treated in the RCT with BoNTA and placebo, respectively, reported at least a 2-grade improvement from baseline in HDSS score 4 weeks after treatment in the open-label extension study
 - Similarly, 80% (79/99) and 100% (4/4) of patients previously treated in the RCT with BoNTA and placebo, respectively, reported at least a 2-grade improvement from baseline in HDSS score 4 weeks after treatment session 2 in the open-label extension study

Gravimetric sweat production

- Four and 8 weeks after the first treatment session, 82% (138/168) and 70% (19/27) of patients, respectively, had a $\geq 75\%$ reduction from baseline in sweat production, measured gravimetrically (Figure 2)
 - For comparison, 23% (9/39) of patients in this study had this level of sweat reduction 4 weeks after the first placebo session in the RCT
- The mean percent reduction from baseline in sweating, as assessed by gravimetric measurement, was 86% and 80% at week 4 and week 8, respectively
- BoNTA showed continued effectiveness with repeated treatment
 - 79% (76/96) and 79% (38/48) of patients had a $\geq 75\%$ reduction from baseline in sweat production at 4 weeks after treatment sessions 2 and 3, respectively

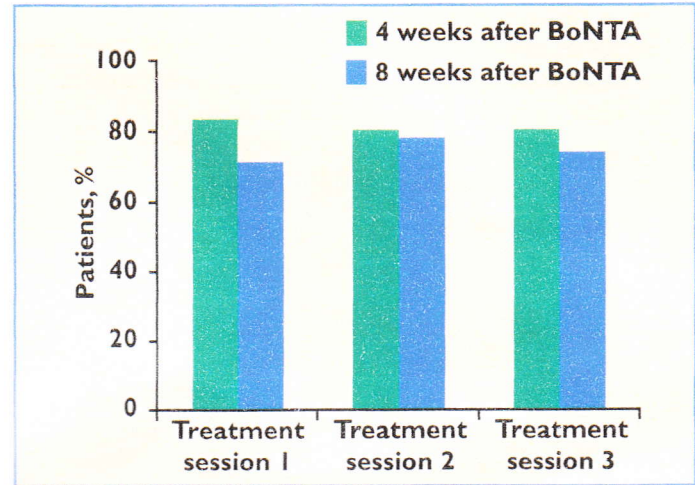


Figure 2. Patients with at least a 75% reduction from baseline in gravimetric sweat production at 4 and 8 weeks after BoNTA treatment for each treatment session.

Duration of effect

- The treatment effect was durable
- In patients with at least a 2-grade decrease in HDSS score from baseline to week 4 after treatment session 1, the median duration of effect was 226 days (Figure 3)
- The efficacy of BoNTA was durable with repeated treatment
 - The median durations of effect were 225 and 179 days, respectively, in patients with at least a 2-grade decrease in HDSS score from baseline to week 4 after treatment sessions 2 and 3
 - The magnitude of effect duration may be underestimated in this study since length of effect duration was defined as the last day of the follow-up period for patients who continued to respond at the end of the follow-up period
- Among those 185 patients receiving at least one BoNTA treatment, 94% (174/185) of patients required ≤ 4 BoNTA treatments over the 2-year period

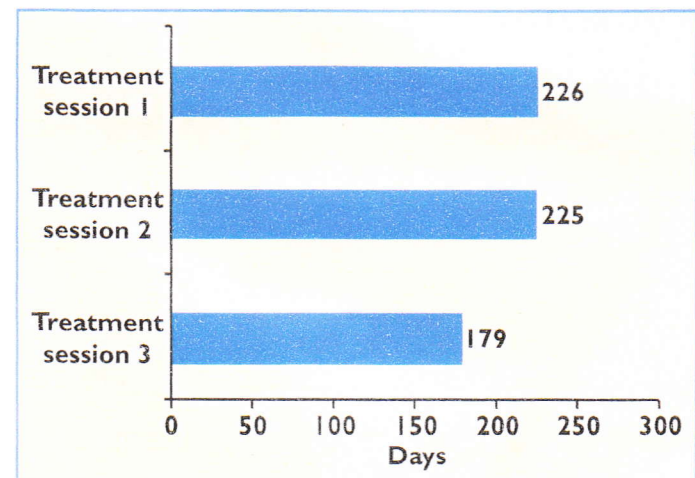


Figure 3. Median duration of treatment effect in patients with at least a 2-grade improvement from baseline in HDSS score at week 4 for each treatment session.

Toxin-neutralizing antibodies

- No toxin-neutralizing antibodies to BoNTA were detected at any time during the RCT. Two patients who received BoNTA treatment in both the RCT and the open-label extension study had positive antibody findings during the open-label extension study
 - Antibody formation was not associated with a decreased clinical response to BoNTA

Adverse events

- No serious treatment-related adverse events were reported
- No patients discontinued the extension study prematurely because of adverse events
- Across all BoNTA treatment sessions, 68% (125/185) of the patients enrolled in the open-label extension study who had received at least 1 BoNTA treatment in the 2-year follow-up period experienced adverse events
 - The most frequently reported adverse event was injection-site pain (11%, 21/185). Unrelated to treatment, respiratory system infection and overall bodily infection occurred in 14% (26/185) and 12% (23/185) of patients, respectively
 - The majority of adverse effects were mild in severity
- The incidence of adverse events overall and of individual events generally decreased over subsequent BoNTA treatments. No clinically relevant adverse events had a late onset

SUMMARY

- In patients with primary axillary hyperhidrosis, BoNTA treatment and retreatment result in meaningful improvements in symptoms as well as meaningful improvements in daily activity impairment, as measured by the HDSS
 - Impairment in activities of daily living, as measured by the HDSS, was eliminated or substantially reduced in 78%–83% of patients
- BoNTA produced consistent reductions in sweat production ($\geq 75\%$) with repeated treatment
 - Results obtained with gravimetric measurement support those obtained with patient-reported measures of treatment efficacy
- BoNTA produced a durable effect, with a median duration of approximately 226 days with treatment sessions 1 and 2 in patients reporting at least a 2-grade decrease from baseline in HDSS score at week 4
 - These results suggest that at least half of patients who respond to treatment may not have to return for a second BoNTA treatment until 7 to 8 months after their first treatment
- BoNTA treatment for up to 2 years was safe and well tolerated

CONCLUSIONS

Intradermal BoNTA is safe and effective for repeated treatment of primary axillary hyperhidrosis. Impairment of daily activities, as measured by the HDSS, was eliminated or substantially reduced in more than 75% of patients after each of 3 BoNTA treatments given during a period of 2 years.

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Disclosures

Dr. Glaser is an investigator for and consultant to Allergan, Inc. Dr. Coleman is an investigator for Allergan, Inc. Mr. Daggett, Dr. Weng, and Dr. Brin are employees of Allergan, Inc.

Notes

Dosing and results reported in this study are specific to the formulation of botulinum toxin type A manufactured by Allergan, Inc. (Irvine, Calif.). The Allergan, Inc., formulation is not interchangeable with other botulinum toxin products and cannot be converted by using a dose ratio.

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