- Adverse events, regardless of their relation to the treatment, occurred in 141 (76%) of the 186 patients treated with BoNTA
  - The most frequently reported adverse events were infection (body as whole, 18%), respiratory infection (17%), injection site pain (11%), accidental injury (10%), and rhinitis (10%)
- The incident of adverse events was lower in patients who had been treated with placebo in the RCT than in those who had been treated with BoNTA (47% vs 83%)

SUMMARY

- Treatment with intradermal BoNTA eliminated or substantially reduced the impairment that is associated with primary axillary hyperhidrosis in at least 80% of patients at week 4 after each of 5 treatments over a period of 4 years, as measured by the HDSS
- BoNTA also produced consistent reductions in sweat production, with a ≥75% reduction in sweat production in ≥78% of patients at week 4 after each of 5 treatments
- The median duration of effect suggests that primary axillary hyperhidrosis can be managed with only 1 or 2 treatments a year
- Long-term treatment with BoNTA was safe, with no serious treatment-related adverse events reported. The most frequent adverse events were infection, injection-site pain, accidental injury, and respiratory and nasal infections
- The formation of antibodies was observed in 3 patients but was not associated with a change in clinical responsiveness. Two of the patients tested negative for antibody formation after their final treatment

CONCLUSIONS

Repeated BoNTA treatment is safe, well tolerated, and effective for up to 4 years in patients with severe primary axillary hyperhidrosis. Impairment of daily activities by hyperhidrosis, as measured by the HDSS, was eliminated or substantially reduced in ≥80% of patients after each of 5 BoNTA treatments. The effect of BoNTA was durable, indicating that relatively few treatments are required to sustain improvements in hyperhidrosis over a 4-year period.

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Notes

The 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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4-Year Longitudinal Data on the Efficacy and Safety of Repeated Botulinum Toxin Type A Therapy for Primary Axillary Hyperhidrosis

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INTRODUCTION

Primary axillary hyperhidrosis is characterized by underarm sweating in excess of physiological needs and of at least 6 months' duration without apparent cause.[1] It is a chronic medical condition that can cause significant occupational, physical, and emotional impairment.[2–5] In a recent study of the clinical characteristics of hyperhidrosis, Hamm and colleagues reported that more than 50% of patients reported moderate to extreme impairment in personal relationships and in social situations.[5] In addition, 63% of patients reported occupational impairment, indicating that hyperhidrosis has a significant impact on the quality of life of those afflicted.

The US Food and Drug Administration (FDA) has approved botulinum toxin type A (BoNTA) for patients with hyperhidrosis that cannot be managed with topical agents such as prescription antiperspirants. Clinical trials in patients with primary axillary hyperhidrosis have shown that BoNTA produces rapid and durable reductions in sweat production and associated functional impairment, with benefits that include improvements in dermatology-specific quality of life.[2–4,6]

Little is known, however, about the long-term efficacy and safety of BoNTA, which often requires repeated treatments in a normal course. The durability of effect with repeated therapy with BoNTA over 1.3 to 2.5 years has been reported in 3 studies, but none of them used standard criteria for determining a patient's need for retreatment—the protocols either required a second treatment or permitted retreatment at the patient's request.[6–8]

Here we report the combined results of a 1-year randomized placebo-controlled trial (RCT) and a subsequent 3-year open-label extension study in patients with severe primary axillary hyperhidrosis. This study evaluated the long-term safety and efficacy of BoNTA treatment, with the need for retreatment and the degree of response assessed by using both patient-reported measures of the severity of their hyperhidrosis and gravimetric measures of sweat production.

METHODS

Study design

- Patients who had completed the 1-year double-blind RCT[2] were eligible for this 4-year open-label extension trial (OLET)
  - Patients in the RCT were treated with placebo, BoNTA 50 U/axilla, or BoNTA 75 U/axilla
  - Patients who met the criteria for retreatment in the OLET were treated with BoNTA 50 U/axilla
  - Assessments were made at 1 week after treatment (by phone) and at 4 and 8 weeks after treatment (in person). Phone calls were made monthly thereafter until the patient either was eligible for retreatment or exited the study
- Retreatment criteria
  - Patients were eligible for retreatment 8 weeks after each treatment session if the following 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 ≥50 mg of spontaneous resting sweat production in each axilla measured over 5 minutes at room temperature

Inclusion criteria

- Completion of the RCT
  - Inclusion criteria for the RCT were[2]
    - 18 to 75 years old, with persistent bilateral primary axillary hyperhidrosis
    - Score of 3 or 4 on the HDSS
    - Baseline gravimetric measurement of ≥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 any 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 BoNTA
- Previous treatment for hyperhidrosis with any serotype of botulinum toxin, not including treatment in the RCT

Measures

Efficacy

- HDSS—a self-reported measure on a validated single-item 4-point scale of the degree of hyperhidrosis-related interference with daily activities, in which a higher score indicates greater interference[9] (Table 1)
- Gravimetric measurement of spontaneous resting axillary sweat production—performed at room temperature over a period of 5 minutes
- Duration of response—calculated as the number of days after each BoNTA treatment to the first report of a score of 3 or 4 on the HDSS or discontinuation from the study
- Toxin-neutralizing antibodies—detected in the serum by a mouse protection assay

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

Safety

- Safety was assessed by evaluating the frequency and severity of adverse events

Statistical analysis

- All efficacy and safety data were analyzed in the enrolled population, defined as all patients who were enrolled in the RCT and the OLET
- Adverse events were analyzed in the enrolled or treated population, defined as patients who received at least one BoNTA treatment across the RCT and the OLET
- All efficacy measures were analyzed by visit in each treatment session, with baseline referring to session baseline (ie, the most recent evaluation before the treatment)
- All analyses were of the observed data, with no imputation for missing data
- Data on demographic and baseline characteristics, efficacy, and safety were summarized by descriptive statistics
- Duration of effect was analyzed by using the Kaplan-Meier method
- Within-group differences in change from baseline HDSS scores and percent change from baseline gravimetric measurements of axillary sweat production were analyzed by using the Wilcoxon signed-rank test

RESULTS

Demographics and populations

- 193 patients who completed the RCT enrolled in the OLET
  - 186 (96%) of these 193 patients received ≥1 BoNTA treatments in the OLET
    - 150 (81%) of these 186 patients had been treated with BoNTA and 36 (19%) had been treated with placebo in the RCT
  - The remaining 7 patients completed or discontinued the OLET without having been treated with BoNTA
- Number of treatments with BoNTA in the 186 patients treated in the OLET:
  - 1: 46 patients (25%)
  - 2: 36 patients (19%)
  - 3: 37 patients (20%)
  - 4: 24 patients (13%)
  - 5: 13 patients (7%)
  - ≥6: 30 patients (16%)
- The majority of patients, 71% (137/193), completed the study. Only 1 patient discontinued because of an adverse event, which was determined to be unrelated to the treatment
- Patients who were treated with BoNTA in the OLET were primarily Caucasian (83%), with equal proportions of men (51%) and women (49%) and a mean age of 33 years (range, 18–65) (Table 2)

Table 2. Demographics of the 186 Patients Treated With BoNTA

Characteristic	Treated Population (n = 186)
Age, y, mean (range)	33 (18–65)
Sex, %	
Male	51
Female	49
Ethnicity, %	
Caucasian	83
Non-Caucasian	17
Treatment in previous study, %	
Placebo	19
BoNTA 50 or 75 U/axilla	81

Efficacy

The results with the first 5 treatments with BoNTA are presented, since few patients (16%; 30/186) received more than 5 treatments

HDSS

- After treatment session 1, 82% (141/172) and 77% (131/170) of patients reported a ≥2-point improvement in their HDSS score at 4 and 8 weeks (Figure 1A)
  - The mean reduction in HDSS scores was 2.1 points at week 4 and 2.0 points at week 8 (Figure 1B)
- BoNTA showed continued effectiveness with repeated treatment
  - After treatment sessions 2–5, 82% (98/119), 85% (76/89), 80% (45/56), and 84% (32/38) of patients reported a ≥2-point improvement in their HDSS score at 4 weeks. There was a ≥2-point improvement at 8 weeks in 50%–74% of patients (Figure 1A)
  - The mean reductions in HDSS scores were 1.9, 1.9, 1.8, and 1.9 points at 4 weeks after treatment sessions 2–5 (Figure 1B); the mean reductions at 8 weeks were 1.8, 1.8, 1.4, and 1.4 points
- Within-group comparisons showed that the reductions in HDSS scores after treatment sessions 1–5 were significant ($P < 0.001$)

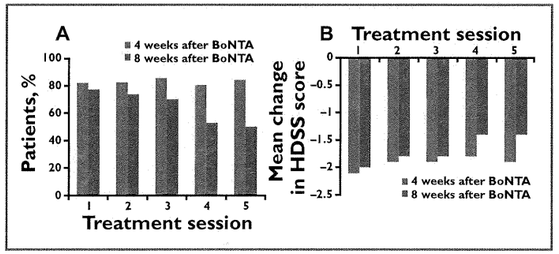

Figure 1. Improvements in primary axillary hyperhidrosis, as measured by the HDSS at 4 and 8 weeks after treatment with BoNTA in sessions 1–5. (A) Patients with a ≥2-point reduction from baseline in HDSS score. (B) Mean change in HDSS score.

Gravimetric sweat production

- After treatment session 1, there was a ≥75% reduction in sweat production in 83% (140/169) and 71% (20/28) of patients at 4 and 8 weeks (Figure 2A)
  - The mean percent reduction in sweat production was 86% and 81% at weeks 4 and 8, respectively, after treatment session 1 (Figure 2B)
- BoNTA showed continued effectiveness with repeated treatment
  - Sweat production was reduced by ≥75% in 80% (89/112), 85% (71/84), 86% (47/55), and 78% (29/37) of patients at 4 weeks after treatment sessions 2–5. There was a ≥75% reduction at 8 weeks in 52%–84% of patients (Figure 2A)
  - The mean percent reduction in sweat production was 81%, 86%, 83%, and 81% at week 4 after treatment sessions 2–5. At week 8 the reductions ranged from 38% to 85% (Figure 2B)
- Within-group comparisons showed that the reductions in sweating at weeks 4 and 8 after treatment sessions 1–5 were significant ($P \leq 0.002$)

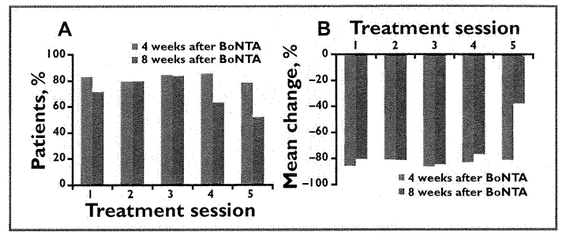

Figure 2. Improvements in primary axillary hyperhidrosis, as measured by gravimetric sweat production at 4 and 8 weeks after treatment with BoNTA in sessions 1–5. (A) Patients with a ≥75% reduction from baseline in sweat production. (B) Mean percent change in sweat production.

Duration of effect

- BoNTA treatment had a durable effect
- After treatment session 1 the median time to an HDSS score of 3 or 4 or discontinuation from the study (duration of effect) in patients with a ≥2-point improvement in their HDSS score from baseline to week 4 was 232 days (Figure 3)
- After treatment sessions 2–5 the median durations of effect in patients with a ≥2-point improvement in their HDSS score from baseline to week 4 were 238, 223, 183, and 175 days (Figure 3)
  - The duration of effect was ≥307 days in at least 25% of patients after treatment sessions 1–4

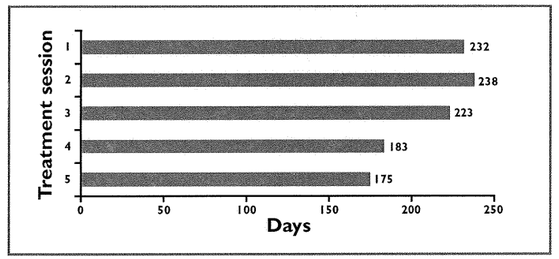

Figure 3. Median duration of treatment effect, by treatment session, in patients with a ≥2-point improvement in their HDSS score from baseline to week 4.

Toxin-neutralizing antibodies

- Antibodies were detected in the serum of 3 patients
  - 2 of these patients continued to respond to BoNTA treatment and tested negative after their final treatment, and thus, in these patients, a positive antibody test did not appear to affect efficacy
  - The third patient did not meet the criteria for retreatment; there are insufficient data to determine whether there was a clinical effect of the antibody formation

Safety

Adverse events

- No serious treatment-related adverse events were reported over 4 years
- No patients discontinued because of treatment-related adverse events