Botulinum Toxin Type A Is a Safe and Effective Treatment for Axillary Hyperhidrosis Over 16 Months

A Prospective Study

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Objective: To evaluate the safety and efficacy of botulinum toxin type A (BTX-A) (BOTOX) over 16 months in the treatment of bilateral primary axillary hyperhidrosis.

Design: A 16-month study with initial double-blind randomization to 50 U of BTX-A or placebo per axilla. After 4 months, participants could receive up to 3 further treatments with open-label BTX-A over 12 months.

Setting: Fourteen dermatology or neurology clinics in Germany, Belgium, and the United Kingdom.

Participants: Of 207 individuals aged between 17 and 74 years who had persistent bilateral primary axillary hyperhidrosis that interfered with daily activities, 174 (84%) completed the study. The baseline gravimetric assessment was a spontaneous sweat production of 50 mg or greater in each axilla prior to initial treatment.

Main Outcome Measures: At week 4 after each treatment, the response rate of subjects who had at least a 50% reduction from baseline in axillary sweating, as measured by gravimetric assessment, was evaluated. Adverse events were spontaneously reported throughout the study, together with quality-of-life parameters and assessment of neutralizing antibodies to BTX-A.

Results: Over the 16-month period, 356 BTX-A treatments were given to 207 subjects. After placebo treatment, the response rate at week 4 was 34.7%. After the first, second, and third treatment with BTX-A, response rates at week 4 were 96.1%, 91.1%, and 83.3%, respectively. For subjects receiving more than 1 treatment, the mean duration between BTX-A treatments was approximately 7 months; however, 28% of subjects completed the study after only 1 BTX-A treatment. Subjects' satisfaction after treatments was consistently high, their quality of life improved, and there was a reduction in the impact of the disease on their lives. The safety profile of BTX-A after repeated treatments was excellent and no confirmed positive results for neutralizing antibodies to BTX-A occurred.

Conclusion: Repeated intradermal injections of BTX-A over 16 months for treatment of primary axillary hyperhidrosis is safe and efficacious.

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PRIMARY FOCAL hyperhidrosis is a chronic idiopathic disorder of excessive sweating that most often affects the axillae, palms, soles, and forehead. This condition can cause significant problems in private and professional life, and has been shown to have an adverse impact on the daily activities of those affected by this disorder.[1]

The eccrine sweat gland is innervated by the sympathetic nervous system, but its principal periglandular neurotransmitter is acetylcholine. Botulinum toxin type A (BTX-A) inhibits the release of acetylcholine from the presynaptic membrane of cholinergic neurones and thus is a possible form of treatment for hyperhidrosis.[2] In a recent large, multicenter, randomized, controlled, double-blind study comparing the effects of a single treatment of BTX-A (BOTOX; Allergan Inc, Irvine, Calif) with those of placebo in primary axillary hyperhidrosis, 93.8% of subjects had a 50% reduction from baseline in axillary sweating at week 4 and were classified as responders.[3] The safety profile of BTX-A injections was similar to that of placebo. These results confirmed previous reports of the successful use of BTX-A for this condition.[4-11]

Hyperhidrosis is a chronic condition, and as such requires a safe and lasting treatment. At present, the only lasting treatments are surgical, and consist either of sympathectomy or the removal or reduction of the sweat glands by excision, curettage, or liposuction. However, these methods carry the general risks associated with surgery and can also lead to compensatory sweating.[12] Although BTX-A has been shown to be effective in treating hyperhidrosis with 1 treatment, few data are available on the efficacy

and safety of repeated treatments. In addition, there has been no formal assessment of antibody formation after treatment, which is a theoretical risk due to the protein content of BTX-A. Furthermore, systematic quality of life (QOL) information after repeated treatments was not previously known. All these points are covered in this study, whose objective was to evaluate the safety and efficacy of BTX-A over 16 months for the treatment of bilateral primary axillary hyperhidrosis.

METHODS

STUDY SETTING

This study was carried out at 14 dermatology or neurology clinics in Germany, Belgium, and the United Kingdom in compliance with the ethical principles of the Declaration of Helsinki (October 1996); with the informed consent regulations of each participating country; and with the International Conference on Harmonization of Good Clinical Practice guidelines. All subjects who wished to participate in the study gave written informed consent prior to any study-related procedures.

PARTICIPANTS

Subjects could be included in the study if they were aged between 18 and 75 years and had idiopathic persistent bilateral primary axillary hyperhidrosis that interfered with their daily activities. Spontaneous sweat production in each axilla of at least 50 mg, measured over 5 minutes at room temperature and at rest, was required prior to initial treatment.[13] Women of childbearing potential had to have a negative urinary pregnancy test prior to each study treatment. Only subjects who continued beyond their initial double-blind treatment were included in this study report.

STUDY DRUG TREATMENT

Initially, subjects were randomly assigned to receive either 50 U of BTX-A per axilla (a total dose of 100 U) or placebo in a double-blind manner. The dilution used was 4 mL of unpreserved 0.9% sterile sodium chloride solution per 100-U vial. The hyperhidrotic area was identified using the Minor iodine-starch test, and BTX-A or placebo was administered by means of 10 to 15 intradermal injections distributed evenly within the hyperhidrotic area.[14] Subjects were followed up for 16 weeks (the method used during this phase is provided in detail with the publication of the study results[3]). After the 16-week follow-up visit, subjects could receive up to 3 additional open-label treatments with BTX-A. They were treated when they requested it, provided that sweat production in each axilla was at least 50% of the baseline value recorded at their entry into the study. Moreover, at least 16 weeks had to elapse between treatments and no treatments were permitted after week 48. Subjects were assessed at weeks 4 and 16 following each treatment. All subjects completing the study had an exit visit at week 68.

EFFICACY PARAMETERS

The primary efficacy parameter was the percentage of treatment responders. This was defined as subjects who showed a reduction in axillary sweating of at least 50% of their baseline value recorded immediately prior to the most recent treatment, measured by gravimetric assessment of spontaneous axillary sweat production over 5 minutes at room temperature and at rest. The primary end point was week 4 after treatment. Other efficacy assessments included the percentage change from baseline in sweat production; the mean raw gravimetric values at each assessment; the mean duration of effect (time between treatments); the change in the size of the sweat-producing area (measured by the Minor iodine-starch test); the subjects' global assessment of treatment satisfaction (based on a 9-point scale, from +4 for complete abolishment of signs and symptoms to –4 for a very marked worsening of signs and symptoms); and serum antibody testing for BTX-A–neutralizing antibodies using a standard mouse protection assay.

SAFETY PARAMETERS

Safety was assessed by the incidence and severity of spontaneously reported adverse events (AEs) and measurement of vital signs (blood pressure, heart rate, and body temperature).

QOL ASSESSMENTS

Quality-of-life assessments of the impact of hyperhidrosis on various aspects of the patient's life (eg, daily activities, work/productivity, and satisfaction with treatment) were carried out using the Short Form-12 (SF-12) questionnaire[15] and the Hyperhidrosis Impact Questionnaire,[16] an instrument developed by the University of Würzburg and Allergan, Inc. This report addresses satisfaction with BTX-A treatment compared with previous treatments; satisfaction with ability to perform work activities; limitations while in public places; limitations while meeting people for the first time; and number of times per day a change of clothes is needed.

STATISTICAL ANALYSIS

A target number of subjects of 200 was considered sufficient to provide data on longer-term safety (over 16 months). All efficacy and QOL data were summarized by treatment cycle using descriptive statistics and frequency tables. All analyses were intent to treat, ie, outcomes were analyzed for all subjects who were randomized to treatment. For the gravimetric assessment, missing values were replaced using the last-observation-carried-forward method. Measurements taken immediately prior to each treatment were considered the baseline data for that cycle and bilateral values were averaged for each subject at each time point. For the primary parameter of treatment responder rates, the 95% confidence interval was calculated. Within-group changes from baseline were tested at the .05 level against the null hypothesis that there was no change from baseline. The duration of effect was assessed by calculating the mean time between 2 consecutive treatments.

For the QOL questions relating to the impact of hyperhidrosis on limitations in meeting people for the first time and being in public places, a scoring system from 0 (no limitations) to 4 (extremely limited) was used. For assessment of patient satisfaction the proportion of subjects responding that they were "very or somewhat satisfied" or "much more or somewhat more satisfied" was calculated for each parameter. Means (SDs) were calculated using the total number of subjects who answered a particular question as the denominator.

The safety analyses included all subjects who received at least 1 treatment with BTX-A or placebo. All AEs were tabulated and summarized by relationship to study treatment and severity (mild, moderate, and severe). For the analysis of AEs by treatment cycle, events were counted in the treatment cycle in which they first began. For blood pressure, heart rate, and body temperature, mean baseline values and mean changes from baseline (measurement prior to each treatment) were calculated for each treatment cycle.

RESULTS

STUDY POPULATION

A total of 207 subjects were enrolled in 14 dermatology or neurology centers in Europe: 6 in Germany, 6 in the United

Kingdom, and 2 in Belgium. A total of 356 BTX-A treatments were given during the 16-month study period. Of the 207 study subjects, 38.6% (80) had 1 treatment, 44.9% (93) had 2 treatments, 14.5% (30) had 3 treatments, and 1.9% (4) received only placebo during the study period. None had the maximum of 4 treatments allowed. Eighty-four percent of the subjects (174/207) completed the 16-month study. Only 33 subjects discontinued: 1 because of an AE not related to treatment, 1 because of pregnancy, 1 because of protocol violation, 1 because of a lack of efficacy, and 17 because of other reasons (eg, failure to return for a scheduled visit, not meeting the treatment criteria although additional treatment was wanted, and personal reasons); 12 were lost to follow-up.

The overall mean age of the population was 31 years. There were similar numbers of men and women enrolled (46.4% [96/207] and 53.6% [111/207], respectively), and the population was primarily white (98.1%, 203/207).

EFFICACY RESULTS

The response rates following each treatment with BTX-A were consistently high and were substantially better than the response rates following treatment with placebo (**Figure 1**). Although only descriptive statistics were performed, there appears to be no major diminution of effect with repeated treatment cycles. Response rates were 96.1%, 91.1%, and 83.3% at week 4 after the first, second, and third treatments, respectively, compared with 34.7% after treatment with placebo. A similar pattern was seen for the mean percent change from baseline in sweat production and the mean raw values at each visit, with BTX-A causing a greater reduction in these values than placebo (**Table 1**). The size of the hyperhidrotic area, as measured by the Minor iodine-starch test, also markedly decreased following each treatment with BTX-A (Table 1).

A prolonged duration of effect was seen following each BTX-A treatment, with an overall mean duration of 30.6 weeks between any 2 consecutive treatments (range, 15.4-51.3 weeks). However, this calculation only applies to subjects who received at least 2 BTX-A treatments, and 28% of subjects who completed the 16-month study period did not receive additional treatments. In a substantial proportion of subjects the effect duration may thus be considerably longer.

Subjects rated their satisfaction with BTX-A treatment very high. Mean scores at week 4 were +3.5, +3.4, and +3.3 after the first, second, and third treatments, respectively. This indicates marked improvements in the subjects' assessment of their signs and symptoms. In comparison with placebo, assessments of treatment satisfaction showed little change from baseline (a mean rating of +1.4 at week 4).

Of the 207 subjects treated over the 16-month study period, only 1 possible seroconversion from negative to positive for neutralizing antibodies to BTX-A occurred. This subject had a negative antibody test result at enrollment and a positive result at the end of the 16 months after 1 treatment. However, this subject was still classified as a responder on completion of the study and did not receive additional treatments. However, subsequent test results during follow-up after completion of the study were negative for BTX-A antibodies after completion of the study. Furthermore, this subject was retreated with BTX-A after the end of the study and still showed a marked response to

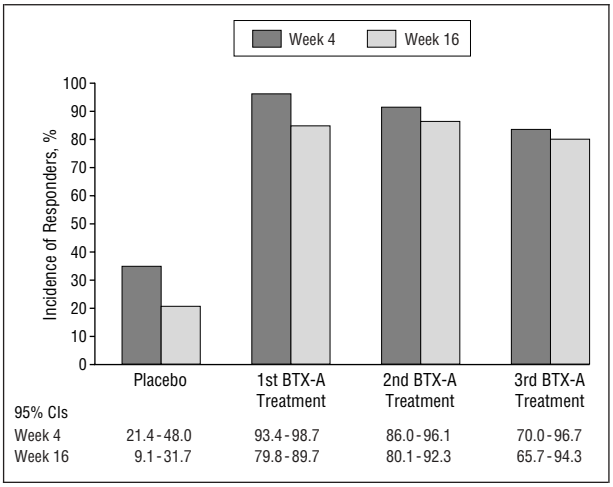

Figure 1. Incidence of treatment responders (ie, subjects who experienced at least a 50% reduction in axillary sweating from baseline). CI indicates confidence interval; BTX-A, botulinum toxin type A.

treatment, with a reported complete disappearance of axillary sweating 7 days after injection.

SAFETY RESULTS

The safety profile of BTX-A was excellent, with no increase in the number of AEs with additional treatment cycles. Of the 49.3% of subjects (102/207) who reported at least 1 AE, 13.5% (28/207) reported events that were considered treatment related (**Table 2**). The most common AE was infection (predominantly common cold), followed by flu syndrome, and a perceived increase in nonaxillary sweating (which occurred at several sites including the forehead, hands, face, feet, back, chest, trunk, and groin). The latter was the most common treatment-related AE, with an incidence of 4.3% (9/207), although no clear pattern to this sweating was seen.[3] A total of 11 subjects reported serious AEs during the study, and there was 1 death due to myocardial ischemia complicated by purulent bronchitis. None of the serious AEs were considered to be related to the study drug. One subject became pregnant during the study approximately 4 months after receiving BTX-A treatment, and the pregnancy continued to term without complications with the delivery of a healthy boy. No changes of clinical relevance were seen in any of the vital signs recorded.

QUALITY OF LIFE

The results of the QOL assessments are shown in **Table 3** and **Figure 2**. Following each BTX-A treatment the robust positive effects on QOL parameters were maintained, with a sustained reduction in the adverse impact of hyperhidrosis and a high level of satisfaction.

COMMENT

Many studies have shown that BTX-A is a highly effective treatment option for axillary hyperhidrosis, but sufficient long-term treatment data are lacking for this chronic condition. This is the first large-scale study systematically collecting data on the effects of longer-term, repeated treatment of hyperhidrosis with BTX-A. Of the

Table 1. Efficacy Results After Placebo Treatment and After 1, 2, and 3 BTX-A Treatments*

Responses to Treatment	Sweat Production				Area of Sweating					Subject Satisfaction Score	
	n	% Change From Baseline	*P* Value	Raw Values, mg	n	Change From Baseline, cm^2	*P* Value	n	Raw Values, cm^2	n	Score
After 1 placebo treatment											
Baseline	49	. . .	. . .	268.0 ± 244.9	. . .	. . .	. . .	43	6.5 ± 7.5	. . .	. . .
Week 4	49	−19.1 ± 54.0	.01	173.0 ± 157.3	43	−1.1 ± 9.0	.28	46	5.7 ± 8.7	9	1.4 ± 1.5
Week 16	49	3.2 ± 112.7	.08	210.0 ± 202.4	39	−3.9 ± 5.8	<.001	44	3.2 ± 6.6	43	0.4 ± 1.1
After 1st BTX-A treatment											
Baseline	203	. . .	. . .	235.8 ± 193.7	. . .	. . .	. . .	186	5.7 ± 7.4	. . .	. . .
Week 4	203	−84.6 ± 18.2	<.001	27.4 ± 35.2	183	−5.7 ± 7.4	<.001	200	0.1 ± 0.5	72	3.5 ± 0.9
Week 16	203	−69.7 ± 37.5	<.001	59.3 ± 73.0	160	−5.8 ± 7.4	<.001	174	0.3 ± 1.4	178	2.8 ± 1.3
After 2nd BTX-A treatment											
Baseline	123	. . .	. . .	193.5 ± 137.6	. . .	. . .	. . .	113	2.1 ± 3.7	. . .	. . .
Week 4	123	−80.8 ± 25.3	<.001	30.6 ± 48.6	93	−2.2 ± 3.8	<.001	103	0.0 ± 0.1	112	3.4 ± 0.8
Week 16	123	−66.7 ± 80.8	<.001	43.6 ± 60.0	79	−1.5 ± 4.1	<.001	85	0.4 ± 1.9	103	2.9 ± 1.1
After 3rd BTX-A treatment											
Baseline	30	. . .	. . .	185.5 ± 131.4	. . .	. . .	. . .	27	2.5 ± 4.4	. . .	. . .
Week 4	30	−78.2 ± 30.5	<.001	37.5 ± 56.7	20	−1.7 ± 4.0	<.001	22	0.0 ± 0.1	27	3.3 ± 1.0
Week 16	30	−53.3 ± 99.0	<.001	62.3 ± 100.9	8	−2.0 ± 4.0	.047	9	0.1 ± 0.2	20	1.9 ± 2.3

Abbreviation: BTX-A, botulinum toxin type A.
*Data are given as mean ± SD unless otherwise specified.

Table 2. Most Frequently Occurring AEs and Treatment-Related AEs by Cycle*

Body System and Preferred Term	Total (n = 207)	Placebo Treatment (n = 49)	1st BTX-A Treatment (n = 203)	2nd BTX-A Treatment (n = 123)	3rd BTX-A Treatment (n = 30)
Overall No. of AEs	102 (49.3)	17 (34.7)	78 (38.4)	29 (23.6)	8 (26.7)
Common cold	27 (13.0)	6 (12.2)	13 (6.4)	7 (5.7)	1 (3.3)
Influenza	14 (6.8)	1 (2.0)	11 (5.4)	3 (2.4)	1 (3.3)
Sweating	12 (5.8)	1 (2.0)	9 (4.4)	2 (1.6)	0
Pharyngitis	11 (5.3)	4 (8.2)	6 (3.0)	1 (0.8)	1 (3.3)
Sinusitis	10 (4.8)	1 (2.0)	7 (3.4)	2 (1.6)	0
Increased coughing	9 (4.3)	0	6 (3.0)	3 (2.4)	0
Overall No. of treatment-related AEs	28 (13.5)	2 (4.1)	20 (9.9)	6 (4.9)	1 (3.3)
Sweating	9 (4.3)	0	7 (3.4)	2 (1.6)	0
Pain in injection site	4 (1.9)	0	3 (1.5)	1 (0.8)	0
Pain†	4 (1.9)	0	4 (2.0)	0	0
Vasodilation (hot flushes)	3 (1.4)	0	3 (1.5)	0	0
Stinging in injection site	2 (1.0)	1 (2.0)	1 (0.5)	0	0
Muscular weakness	2 (1.0)	0	1 (0.5)	1 (0.8)	0

Abbreviations: AEs, adverse events; BTX-A, botulinum toxin type A.
*Data are given as number (percentage) of patients. The AEs were not included in the analysis by cycle if the starting date was missing. The AEs can be included in more than 1 cycle.
†Pain under clothing straps, mild ache in left shoulder, soreness in axillae, and pain in axillae in stressing situations.

207 subjects who were recruited, 174 completed the 16-month study and thus provided substantial longer-term safety and efficacy data. The results of this study demonstrated that repeated treatment with BTX-A over 16 months is safe; that BTX-A maintains its efficacy over repeated treatment cycles; and that it has a positive impact on patients' QOL. However, these results are applicable only to the formulation used (BOTOX), and not necessarily to other formulations or serotypes.

Since hyperhidrosis is a chronic condition, and the known pharmacologic properties of BTX-A indicate that the treatment effect will not be permanent, it is likely that subjects will request repeated treatments. With 96.1%, 91.1%, and 83.3% of our subjects experiencing a 50% or greater reduction in sweating after the first, second, and third treatments, we demonstrated that BTX-A reduces the amount of sweating over repeated treatments. This robust response reflects the results of previously published studies, where similar levels of response were seen following a single administration of BTX-A.[3-11,17] It also confirms the data of a recent report, where intradermal injections of BTX-A repeated over 3 years in a limited number of subjects with axillary and palmar hyperhidrosis were as effective as the first treatments.[18] However, in our study, not all subjects required additional treatment and even fewer needed more than 2 treatments; hence, the data for the second and third treatments include those whose duration of response was

Table 3. Quality-of-Life Outcomes After Repeated Treatments

	Placebo Treatment		1st BTX-A Treatment		2nd BTX-A Treatment		3rd BTX-A Treatment	
	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %
Limitation score on being in public places*†								
Baseline	48	2.4 (1.2)	195	2.1 (1.3)	119	0.8 (0.9)	30	0.9 (0.9)
Week 4	48	1.9 (1.2)	197	0.2 (0.6)	113	0.2 (0.6)	26	0.2 (0.4)
Week 16	44	1.8 (1.4)	178	0.4 (0.6)	102	0.4 (0.7)	18	0.7 (1.0)
Limitation score on meeting people for the first time*†								
Baseline	48	2.7 (1.2)	195	2.5 (1.3)	119	1.2 (1.0)	29	1.1 (1.0)
Week 4	48	2.0 (1.3)	196	0.3 (0.7)	113	0.4 (0.7)	25	0.5 (0.8)
Week 16	44	1.8 (1.4)	178	0.6 (0.8)	101	0.5 (0.8)	18	1.1 (1.2)
Subjects changing clothes more than twice a day‡								
Baseline	46	78	190	76	114	36	29	38
Week 4	47	68	194	7	113	5	27	11
Week 16	42	64	175	14	102	16	17	18
Proportion of subjects very or somewhat satisfied with their ability to perform daily tasks with current level of hyperhidrosis‡								
Baseline	40	18	168	18	114	75	30	60
Week 4	9	44	70	94	109	95	27	85
Week 16	40	18	170	92	101	89	18	78

Abbreviation: BTX-A, botulinum toxin type A.
*Scoring system: 0 = not limited; 1 = somewhat limited; 2 = moderately limited; 3 = quite a bit limited; 4 = extremely limited.
†Data are given as mean (SD).
‡Data are given as percentage.

somewhat shorter. Although they had a good response, they may be considered a less responsive cohort. It is anticipated that treatment optimization may enhance their response in the clinical setting. There was no indication that response increased with repeated treatment.

The decrease in sweat production after each treatment indicates that disuse atrophy of the sweat glands is not occurring. This is in agreement with previous quantitative histological studies, which have shown that even after sympathectomy or in severe autonomic neuropathy with anhidrosis, there is no evidence of sweat gland atrophy.[19] Thus, denervation of sweat glands, either chemically (by botulinum toxin) or by degeneration of sudomotor fibers, has no obvious influence on sweat gland morphology.

Additional treatment in this study was permitted every 16 weeks based on subject request, and although a return to 50% of the baseline value was required, complete return to the baseline value was not mandatory. This is thought to give a reasonable reflection of clinical practice, where patient request is likely to be the primary factor in the decision to retreat. However, although subsequent treatment was allowed after 16 weeks, the average time between treatments was 7 months; and in 28% of subjects who completed the study, no additional treatment was needed following their first BTX-A treatment. This indicates a much longer duration of effect in a substantial number of subjects. Although a longer duration of effect has been suggested in a recent publication[20] after treatment with a much higher dose of BTX-A (200 U of BTX-A per axilla, for a total dose of 400 U), these data were generated from particularly low subject numbers, with no quantitative inclusion criteria, no objective measures of treatment success, and no objective criteria for receiving additional treatments. Comparison of these data with those of our present study is therefore not appropriate, and we consider that they do not provide a foundation for recommending treatment at this dose.

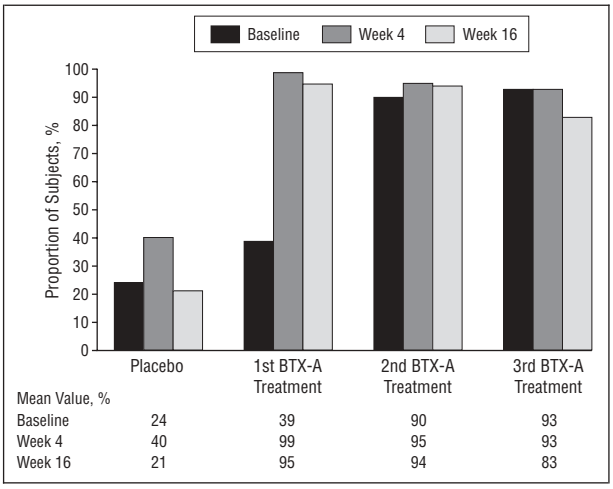

Figure 2. Quality of life: satisfaction with current treatment compared with prior treatments (percentage of patients much more or somewhat more satisfied). BTX-A indicates botulinum toxin type A.

The formation of neutralizing antibodies with repeated BTX-A treatments was not apparent in this study. Only 1 seroconversion from negative to positive was recorded; however, this subject remained a responder to treatment, and follow-up after completion of the study showed a negative result for BTX-A–neutralizing antibodies. Furthermore, the subject responded to subsequent treatment. This result is consistent with the low protein load of this specific BTX-A formulation, which is believed to result in a low risk of neutralizing-antibody formation.[21] The

Hyperhidrosis Clinical Investigators Group

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long duration between additional treatments also further diminishes any potential risk of antibody formation.

Results from the 356 BTX-A treatments received in this study show that the safety profile was excellent, with no increase in the occurrence of AEs over repeated treatment cycles. These results provide reassurance that BTX-A treatment is safe in this chronic condition and can be administered repeatedly upon request without additional risk.

The only AE of note was the occurrence of a treatment-related subjective increase in nonaxillary sweating in 4.3% of subjects. This low incidence of perceived increase in sweating with BTX-A, compared with its problematic occurrence following other long-term treatments, has been discussed elsewhere.[3] However, this study demonstrated that this AE did not affect either the subjects' decision to continue with subsequent treatments or their satisfaction with treatment, as none withdrew from the study because of increased nonaxillary sweating.

The excellent safety and efficacy results were reflected in the improved QOL and a decrease in the adverse impact of the condition. The positive effects of a single treatment of BTX-A have recently been reported.[1] With multiple treatments, a considerable carryover effect was observed whereby the benefits of treatment continued regardless of whether the patient had returned to excessive sweating. The BTX-A was seen to have a dramatic effect on the subjects' perception of how their condition impacted their lives and even resulted in behavioral changes.

In conclusion, these results represent the first robust longer-term study on the effects of repeated treatment with BTX-A in a substantial number of subjects. Treatment with 50 U of BTX-A is useful and safe over 16 months for subjects with idiopathic axillary hyperhidrosis, and it contributes significantly to improving their quality of life.

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REFERENCES

1. Naumann MK, Hamm H, Lowe NJ. Effect of botulinum toxin type A on quality-of-life measures in patients with excessive axillary sweating: a randomized controlled trial. *Br J Dermatol*. 2002;147:1218-1226.
2. Scott AB. Clostridial toxins as therapeutic agents. In Simpson LL, ed. *Botulinum Neurotoxin and Tetanus Toxin*. San Diego, Calif: Academic Press; 1989:399-412.
3. Naumann M, Lowe NJ. Botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double-blind, placebo-controlled trial. *BMJ*. 2001;323:596-599.
4. Bushara KO, Park DM, Jones JC, Schutta HS. Botulinum toxin: a possible new treatment for axillary hyperhidrosis. *Clin Exp Dermatol*. 1996;21:276-278.
5. Bushara KO. Botulinum toxin for axillary and palmar hyperhidrosis. *J Neurol Sci*. 1997;150(suppl):S71.
6. Glogau RG. Botulinum A neurotoxin for axillary hyperhidrosis: no sweat Botox. *Dermatol Surg*. 1998;24:817-819.
7. Odderson IR. Hyperhidrosis treated by botulinum A exotoxin. *Dermatol Surg*. 1998;24:1237-1241.
8. Naumann M, Hofmann U, Bergmann I, Hamm H, Toyka KV, Reiners K. Focal hyperhidrosis: effective treatment with intracutaneous botulinium toxin. *Arch Dermatol*. 1998;134:301-304.
9. Naver H, Aquilonius SM. The treatment of focal hyperhidrosis with botulinum toxin. *Eur J Neurol*. 1997;4(suppl 2):S75-S79.
10. Naver H, Swartling C, Aquilonius SM. Treatment of focal hyperhidrosis with botulinum toxin type A: brief overview of methodology and 2 year's experience. *Eur J Neurol*. 1999;6(suppl 4):S117-S120.
11. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin for axillary hyperhidrosis (excessive sweating). *N Engl J Med*. 2001;344:488-493.
12. Greenhalgh RM, Rosengarten DS, Martin P. Role of sympathectomy for hyperhidrosis. *BMJ*. 1971;1:332-334.
13. Hund M, Kinkelin I, Naumann M, Hamm H. Definition of axillary hyperhidrosis by gravimetric assessment. *Arch Dermatol*. 2002;138:539-541.
14. Minor V. Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung. *Dtsch Z Nervenheilkd*. 1927;101:301-306.
15. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996; 34:220-233.
16. Teale C, Hann H, Naumann M, Roberts G, Kowalski JW. Development, validity, and reliability of the hyperhidrosis impacts questionnaire (HHIQ) [abstract]. *Qual Life Res*. 2002;11:7.
17. Schnider P, Binder M, Kittler H, et al. A randomized, double-blind, placebo-controlled study trial of botulinum toxin type A for severe axillary hyperhidrosis. *Br J Dermatol*. 1999;140:677-680.
18. Schnider P, Moraru E, Kittler H, et al. Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol*. 2001;145: 289-293.
19. Itoh Y, Yagishita S, Nakajima S, et al. Congenital insensivity to pain with anhidrosis: morphological and morphometrical studies on the skin and peripheral nerves. *Neuropediatrics*. 1986;17:103-110.
20. Wollina U, Karafilov T, Xonrad H. High-dose botulinum toxin type A therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval. *J Am Acad Dermatol*. 2002;46:536-540.
21. Aoki KR. Pharmacology and immunology of botulinum toxin serotypes. *J Neurol*. 2001;248(suppl 11):3-10.