

A Prospective, Nonrandomized, Open-Label Study of the Efficacy and Safety of OnabotulinumtoxinA in Adolescents with Primary Axillary Hyperhidrosis

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Abstract

Objective: To evaluate the efficacy and safety of onabotulinumtoxinA in adolescents with primary axillary hyperhidrosis.

Methods: This 52-week, multicenter, nonrandomized, open-label study was conducted in 141 adolescents ages 12 to 17 years with severe primary axillary hyperhidrosis. Patients could receive up to six treatments with onabotulinumtoxinA (50 U per axilla), with re-treatment occurring no sooner than 8 weeks after the prior treatment cycle and no later than 44 weeks after the initial treatment cycle. The primary efficacy measure was treatment response, based on self-assessed hyperhidrosis severity following the first two treatments using the 4-point Hyperhidrosis Disease Severity Scale (HDSS). Other efficacy measures included spontaneous resting sweat production and health outcomes.

Results: Fifty-six (38.9%) participants underwent one treatment, 59 (41.0%) underwent two, 20 (13.9%) underwent three, 6 (4.2%) underwent four, and 3 (2.1%) underwent five. OnabotulinumtoxinA significantly improved HDSS scores and decreased sweat production compared with treatment cycle baselines. Seventy-nine patients (54.9%) responded to treatment based on HDSS criteria. From 56.6% to 72.3% of patients experienced a two-grade or more improvement at 4 and 8 weeks after each of the first two treatments. The majority (79.4%–93.2%) had a 75% or greater reduction in sweat production at

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week 4 (treatments 1–3). The median duration of effect for responders ranged from 134 to 152 days. Using quality of life measures, health outcomes improved markedly. Eight patients (5.6%) had mild or moderate treatment-related adverse events. No unexpected safety signals were observed in this study. Neutralizing antibodies to onabotulinumtoxinA did not develop.

Conclusion: OnabotulinumtoxinA injections provided beneficial effects in adolescents with primary axillary hyperhidrosis.

INTRODUCTION

Primary hyperhidrosis, thought to be related to primary overactivity of the central nervous system (1–6), can diminish an individual's psychosocial, professional, and physical well-being. Hyperhidrosis has a mean age of onset ranging from 14 to 25 years (1,3,7,8). Primary hyperhidrosis affects 1.6% of individuals ages 12 to 17 years; primary axillary hyperhidrosis (PAH) accounts for 75% of cases (1).

Hyperhidrosis may be caused by acetylcholine release from overactive sympathetic cholinergic nerves that innervate sweat glands. OnabotulinumtoxinA (Botox; Allergan, Irvine, CA) blocks acetylcholine release from these fibers, reducing excessive sweating (4,9,10). Intradermal injection of onabotulinumtoxinA is approved globally to treat severe axillary hyperhidrosis that cannot be managed using topical agents (11).

Numerous studies have shown that onabotulinumtoxinA is effective and safe in treating axillary hyperhidrosis in adults (9,10,12–20), but there are no data for children and limited data for adolescents (21). This study provided postmarketing data on the efficacy and safety of repeated onabotulinumtoxinA injections for treatment of hyperhidrosis in adolescents with PAH.

MATERIALS AND METHODS

Patients

Patients 12 to 17 years of age with PAH appearing 6 months or more before study enrollment and inadequately managed using topical agents were eligible if they rated themselves as having a score of 3 or 4 (considered severe) on the 4-point Hyperhidrosis Disease Severity Scale (HDSS; Table 1). Eligible patients demonstrated spontaneous resting axillary sweat production of 50 mg or more per axilla over a 5-minute period measured gravimetrically at room temperature. Inclusion and exclusion criteria are provided in Table 2.

Study Design

This 52-week, multicenter, open-label, nonrandomized, repeated-treatment study was conducted between August 2005 and June 2007 in accordance with Good Clinical Practice guidelines. The local ethics committee provided approval before study initiation. All patients, parents, and guardians provided written informed assent or consent.

Adolescents with PAH completed baseline assessments at screening 7 to 10 days before onabotulinumtoxinA administration. The hyperhidrotic area of each axilla was identified using Minor's iodine starch test, then onabotulinumtoxinA was injected intradermally (50 U per axilla in a 2-mL volume using 10–15 injections per axilla; total dose, 100 U). Follow-up evaluations occurred by telephone 1 week after treatment, at office visits scheduled 4 and 8 weeks after each treatment, and monthly by telephone.

Patients with HDSS scores of 3 or greater during monthly evaluations returned to the office within 14 days but no sooner than 8 weeks from the prior treatment injection and no later than 44 weeks from the initial injection. Patients were re-treated with onabotulinumtoxinA if they had 50 mg or more of spontaneous resting axillary sweat production in each axilla. Patients could receive up to six onabotulinumtoxinA treatments.

The primary efficacy endpoint, according to the statistical analysis plan, was the percentage of treatment responders, based on HDSS scores for the first two treatment cycles. Patients completed the HDSS at

TABLE 1. *The Hyperhidrosis Disease Severity Scale*

Score	Description—My underarm sweating is:
1	Never noticeable and never interferes with my daily activities
2	Tolerable but sometimes interferes with my daily activities
3	Barely tolerable and frequently interferes with my daily activities
4	Intolerable and always interferes with my daily activities

TABLE 2. Inclusion and Exclusion Criteria

Inclusion criteria
Boy or girl* 12 to 17 yrs of age with primary axillary hyperhidrosis with an onset ≥ 6 mos before study enrollment that was inadequately managed using topical agents
Score of 3 or 4 (considered severe) on the 4-point Hyperhidrosis Disease Severity Scale†
Spontaneous resting axillary sweat production of ≥ 50 mg per axilla over a 5-minute period measured gravimetrically at room temperature
Body mass index above the fifth percentile according to age
Body weight ≥ 17 kg
Clinically acceptable laboratory test results or results within reference ranges
Ability to provide written informed consent
Exclusion criteria
Previous exposure to any serotype of botulinum toxin
Any medical condition that might place the participant at risk of exposure to onabotulinumtoxinA
Secondary hyperhidrosis
Use of cholinomimetics, anticholinergic agents, prescription antiperspirants and deodorants, any herbal medicine treatments, and other treatments for hyperhidrosis except over-the-counter antiperspirants or deodorants within 7 days before the first dose of the study drug or during the study
Use of over-the-counter antiperspirants or deodorants within 24 hours before any office visit
Infection or skin disorder at the injection site
Previous surgical treatment for axillary hyperhidrosis
Laser hair removal in the axillary region within 12 wks of study entry or during the study
Known uncontrolled systemic disease (e.g., hyperthyroidism)

*For girls of childbearing potential, a negative urine pregnancy test on day 0 was required.

†Patients chose one of four descriptions that best reflected how they felt about their underarm sweating and its effect on daily activities.

each visit, during monthly telephone interviews, and before each treatment. Patients were considered responders if they reported a 2-point or greater improvement 4 weeks after each of the first two treatment cycles or a 2-point or greater improvement 4 weeks after the first treatment cycle and completed the study through week 44 without qualifying for re-treatment. Patients with baseline HDSS scores of 4 who achieved a 2-point or greater improvement after the first treatment needed only a 1-point improvement after the second treatment cycle if re-treated, with an HDSS score of 3. Patients who met the HDSS criteria but used a prohibited medication for PAH during the first two treatment cycles were considered nonresponders.

The secondary efficacy measure, gravimetric measurement of spontaneous resting axillary sweat production (mg) over a 5-minute period, was performed before the starch test at each injection visit and 4 weeks after injections.

At each office visit, patients completed the Children's Hyperhidrosis Impact Questionnaire (CHHIQ) regarding specific daily activity limitations and functional impairments associated with hyperhidrosis and

the Children's Dermatology Life Quality Index (CDLQI) regarding the degree of impairment to dermatology-specific quality of life (QOL) based on six domains: symptoms and feelings, leisure activities, school or holidays, personal relationships, sleep, and treatment (22,23).

Adverse events (AEs) were coded using the *Medical Dictionary for Regulatory Activities* version 10.0. Laboratory testing and physical examinations were performed at screening and final study visits. Vital signs were measured at each office visit. Serum samples were collected at screening, each re-treatment visit, and the final visit to test for neutralizing antibodies to onabotulinumtoxinA.

Statistical Analyses

Approximately 130 patients were planned for enrollment to ensure a sample size of 100. Analyses were conducted in all patients who received one or more onabotulinumtoxinA treatments. For each treatment cycle, baseline was defined as the most recent evaluation before injection.

The percentage of responders and two-sided 95% confidence intervals (CIs) were determined using normal approximation 4 and 8 weeks after treatment for the primary efficacy analysis. The percentage change from cycle baseline in spontaneous resting axillary sweat production was summarized 4 and 8 weeks after treatment for each treatment cycle using descriptive statistics; within-group comparisons were performed using the Wilcoxon signed-rank test. The percentage of patients achieving a two-grade improvement from cycle baseline in HDSS or a reduction from cycle baseline of 50% or more, 75%, and 90% in axillary sweating 4 and 8 weeks after treatment for each cycle and two-sided 95% CIs were determined using normal approximation.

The duration of treatment effect, defined as the number of days from onabotulinumtoxinA injection until the first recording of an HDSS score of 3 or greater, was analyzed separately for the first two treatment cycles using the Kaplan–Meier method, with the 95% CI of the median based on Greenwood's formula for the standard error.

CHHIQ responses were summarized according to frequency distribution and dichotomized at weeks 4 and 8 after treatment for each treatment cycle; within-group comparisons were performed using the Mc Nemar test. Responses to the 10 CDLQI questions were scored from 0 to 3 and analyzed under the six domains and according to total score. Changes in domain and total scores from baseline to weeks 4 and 8 for each

cycle were analyzed using the Wilcoxon signed-rank test.

AEs were summarized using descriptive statistics according to treatment cycle and for the entire study period. Other safety parameters were analyzed using descriptive statistics or frequency distributions as appropriate.

RESULTS

In total, 144 patients received one or more treatments (Fig. 1). Most patients were female (86.1%) and white (82.6%) and had a mean age of 15.4 years (Table 3). All patients had experienced excessive sweating in the axillae, and many reported sweating in other body areas. The mean age at onset of axillary hyperhidrosis was 11.8 years. One hundred thirteen (78.5%) patients reported an equal bilateral distribution of their axillary hyperhidrosis.

Efficacy of OnabotulinumtoxinA

In the primary efficacy analysis, 79 patients (54.9%, 95% CI 46.7%, 63.0%) were classified as responders for the first two treatment cycles. HDSS scores showed statistically significant improvement from

cycle baseline in the first three treatment cycles, as early as 1 week and at 4 and 8 weeks (Table 4). Significant HDSS score improvements from cycle baseline were observed at 12 weeks and at later time points for the first three treatment cycles, up to 52 weeks (data not shown). Before the first treatment, patients were approximately equally divided between HDSS scores of 3 and 4 (Fig. 2). Four weeks after the first treatment, 92.9% of patients had a score of 1 or 2; similarly, 4 weeks after the second treatment, 93.1% had a score of 1 or 2.

Of patients who had never used a prohibited medication for axillary hyperhidrosis, 72.3% (95% CI 65.0%, 79.7%) experienced a 2-point or greater improvement from cycle baseline in HDSS scores at 4 weeks after the first treatment and 63.4% (95% CI 55.3%, 71.6%) at 8 weeks, while 69.9% (95% CI 59.3%, 80.4%) experienced a 2-point or greater improvement from cycle baseline in HDSS scores at 4 weeks after the second treatment and 56.6% (95% CI 45.4%, 67.7%) at 8 weeks. The number of patients in the third through fifth treatment cycles was insufficient to provide reliable estimates.

Sweat production also improved significantly (Table 5). Mean sweat production (109.7 mg at

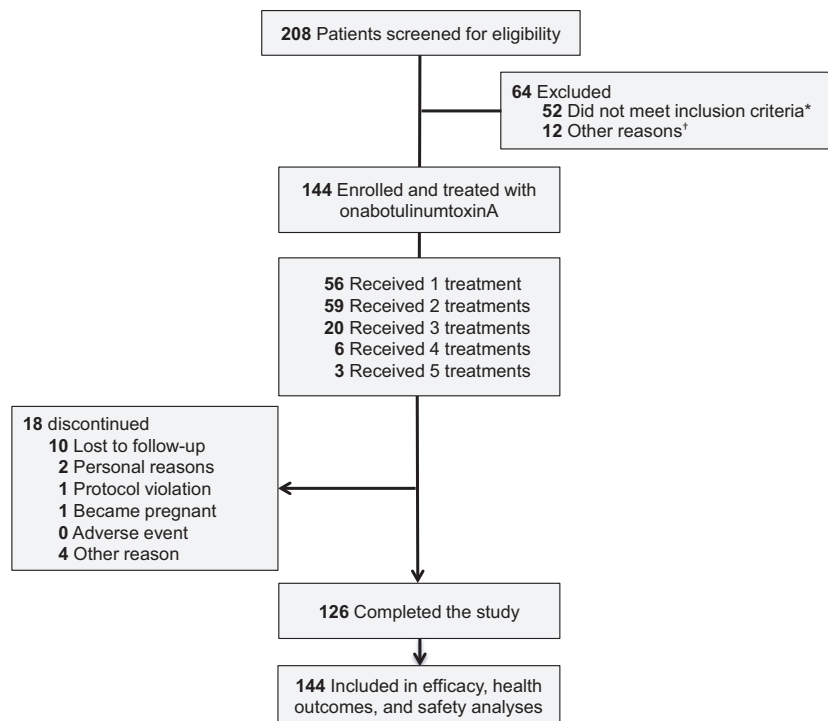


Figure 1. Flow diagram of patient disposition. *Fifty patients had less than 50 mg spontaneous resting axillary sweat production; 1 patient had a Hyperhidrosis Disease Severity Scale score less than 3; 1 patient was unable to follow study instructions. †Six patients withdrew consent; 3 were unable to return for visit; 2 changed their minds; study closed for 1 patient.

TABLE 3. Demographic and Baseline Characteristics (N = 144)

Parameter	Value
Age, mean ± SD (range)	15.4 ± 1.3 (12–17)
Sex, n (%)	
Male	20 (13.9)
Female	124 (86.1)
Race/ethnicity, n (%)	
White	119 (82.6)
Black	9 (6.3)
Hispanic	9 (6.3)
Asian	2 (1.4)
Other*	5 (3.5)
Hyperhidrosis history	
Body area with excessive sweating, n (%)	
Axillae	144 (100.0)
Palms	65 (45.1)
Soles	49 (34.0)
Face	19 (13.2)
Other†	12 (8.3)
Age at onset, yrs, mean ± SD	
Axillae	11.8 ± 2.4
Palms	11.3 ± 3.4
Soles	10.8 ± 3.0
Face	10.9 ± 3.3
Other†	11.7 ± 2.4

*Asian/white, biracial white/Asian, white/Hispanic, mixed race (white and black), Pakistani.

†Chest, back, lower back, knees, under knees, scalp, breasts, and under breasts.

SD, standard deviation.

baseline) declined an average of 83.9% (20.1 mg) 4 weeks after onabotulinumtoxinA treatment and 78.1% (30.9 mg) 8 weeks after treatment (p < 0.001 for both). More than 50% of patients experienced reduced sweat production of 90% or more at week 4 for each of the first three cycles (Fig. 3).

The median duration of effect after onabotulinumtoxinA treatment was 131 days (95% CI 118, 157 days) for cycle 1 and 135 days (95% CI 121, 152 days) for cycle 2. In the subgroup of initial responders (patients responding with a 2-grade or greater improvement from baseline to week 4 in cycle 1), the median duration of effect was 152 days (95% CI 128, 182 days) for cycle 1 and 134 days (95% CI 119, 152 days) for cycle 2.

TABLE 4. Baseline and Change from Baseline in Hyperhidrosis Disease Severity Scale (HDSS) Scores After First Three Treatment Cycles

Treatment cycle	Baseline* HDSS score, n, mean ± SD	Change in HDSS score, n, mean ± SD, p-Value†			
		Wk 1	Wk 4	Wk 8	Wk 12
1	144, 3.5 ± 0.50	143, -1.9 ± 0.92, <0.001	141, -2.0 ± 0.87, <0.001	134, -1.8 ± 0.97, <0.001	113, -1.6 ± 0.93, <0.001
2	88, 3.2 ± 0.42	79, -1.8 ± 0.63, <0.001	73, -1.7 ± 0.73, <0.001	76, -1.6 ± 0.72, <0.001	60, -1.3 ± 0.80, <0.001
3	29, 3.2 ± 0.38	29, -1.6 ± 0.69, <0.001	24, -1.6 ± 0.78, <0.001	24, -1.0 ± 1.00, <0.001	18, -0.9 ± 0.76, <0.001

*Most recent evaluation before injection.

†p-Value for within-group comparison based on Wilcoxon signed-rank test.

SD, standard deviation.

Health Outcomes

OnabotulinumtoxinA treatment significantly improved health outcomes on the CHHIQ (Table 6) and CDLQI. When patients responded to the CHHIQ at weeks 4 and 8 of the first two cycles, onabotulinumtoxinA treatment significantly decreased the percentage of patients feeling not satisfied or neutral about performing school and nonschool activities (p < 0.001 for all) and feeling at least moderately limited by hyperhidrosis in these activities (all p < 0.001, except p = 0.003 for “when shaking hands” at week 4 of cycle 2). After onabotulinumtoxinA treatment, a significantly smaller proportion of patients than at baseline spent 15 minutes or longer treating their hyperhidrosis (p < 0.001), changing clothes at least twice daily (p < 0.001), and showering at least twice daily (p < 0.005). Finally, 73 patients (50.7%) reported feeling moderately to extremely damaged or injured emotionally because of hyperhidrosis before onabotulinumtoxinA treatment, versus 13.6% and 11.2% of those assessed at weeks 4 and 8 after treatment, respectively, for the first cycle (p < 0.001 for both). In the second treatment cycle, 35.1% had these feelings at cycle baseline, versus 15.3% and 15.8% at weeks 4 and 8, respectively (both p < 0.001).

OnabotulinumtoxinA treatment significantly improved all six CDLQI domains and total scores at weeks 4 and 8 from baseline in the first and second cycles (p < 0.001 for all, except for the sleep domain at weeks 4 and 8 of cycle 2; data not shown). Significant improvements in total score and in symptoms and feelings, leisure activities, and school or holiday domains were observed up to week 8 of the third cycle (p < 0.05).

Safety

Overall, 92 patients (63.9%) reported AEs, most commonly upper respiratory tract infection (21.5%), nasopharyngitis (4.9%), and tonsillitis (3.5%). Most were mild or moderate in severity. Three patients (2.1%) reported serious AEs (pneumonia, abdominal

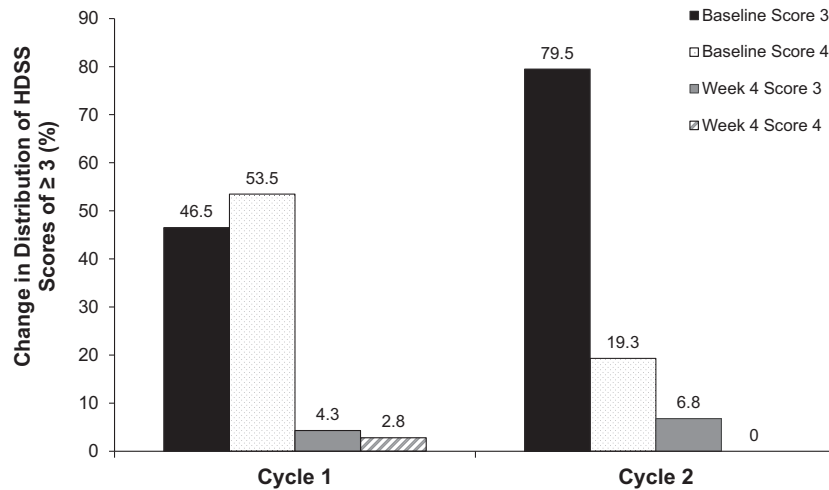


Figure 2. Change in the distribution of Hyperhidrosis Disease Severity Scale (HDSS) scores of at least 3 from treatment cycles 1 and 2, baseline to 4 weeks after treatment.

TABLE 5. Baseline and Percentage Change from Baseline in Sweat Production Measured Gravimetrically According to Treatment Cycle

Treatment cycle	Baseline sweat production (mg), <i>n</i> , mean ± SD	Percentage change, <i>n</i> , mean ± SD	
		Wk 4	Wk 8
1	144, 109.7 ± 98.1	141, 83.9 ± 20.0*	134, 78.1 ± 30.9*
2	88, 87.9 ± 43.3	73, 86.9 ± 21.4*	76, 81.5 ± 24.8*
3	29, 101.4 ± 60.9	23, 84.7 ± 19.9*	24, 44.3 ± 49.7*
4	9, 121.1 ± 89.7	8, 79.3 ± 19.8†	7, 70.9 ± 15.7‡
5	3, 104.3 ± 80.3	3, 68.9 ± 44.3	3, 47.2 ± 43.6

* $p < 0.001$, † $p = 0.008$, ‡ $p < 0.016$ versus cycle baseline.

pain, and extremity pain), and three (2.1%) experienced severe AEs (pneumonia, abdominal pain, and irritable bowel syndrome); none were considered related to treatment or led to discontinuation. Eight patients (5.6%) had 10 treatment-related AEs, including hyperhidrosis (back and palms) and injection-site pain (each $n = 2$; 1.4%) and lymphadenopathy, nausea, injection-site irritation, self-reported compensatory sweating (palms), dizziness, and pruritus (each $n = 1$; 0.7%). No patients experienced a distant spread of toxin effect associated with onabotulinumtoxinA.

No clinically significant changes in laboratory test results, vital signs, or physical examination occurred. One patient became pregnant during the study and had an uncomplicated delivery of a healthy girl.

No patient developed neutralizing antibodies to onabotulinumtoxinA during the study. Neutralizing antibodies were detected in one patient at screening but were absent at all subsequent visits and study exit. This patient was not a treatment responder based on HDSS criteria.

DISCUSSION

This study demonstrated that the efficacy and safety of onabotulinumtoxinA in treating PAH reported in previous registration clinical trials in adults can be extended to adolescents. OnabotulinumtoxinA treatment markedly reduced hyperhidrosis severity based on patient HDSS evaluations and objective measurement of spontaneous resting sweat production. The treatment effect on HDSS was evident by day 7 and sweat production decreased by week 4. The percentage of responders in this adolescent cohort based on HDSS improvements over the first two treatment cycles was 54.9%, nearly identical to the 54.8% seen in a study of adults with PAH treated using onabotulinumtoxinA 50 U per axilla (24). The median duration of effect in the first treatment cycle was approximately 4.5 months, suggesting that adolescents may need onabotulinumtoxinA treatments two to three times annually to control PAH.

The median duration of effect seemed to decrease with more treatments, although patients who had a short treatment duration were likely to have received more treatments, whereas those with longer treatment durations may have received only one or a few treatments. Thus, although all patients were included in calculating the median duration of the first treatment cycle, only those with shorter treatment durations (and more treatments) were included in the calculation of later treatment cycle durations. Although later treatments are associated with shorter treatment duration, this does not imply that the duration of effect

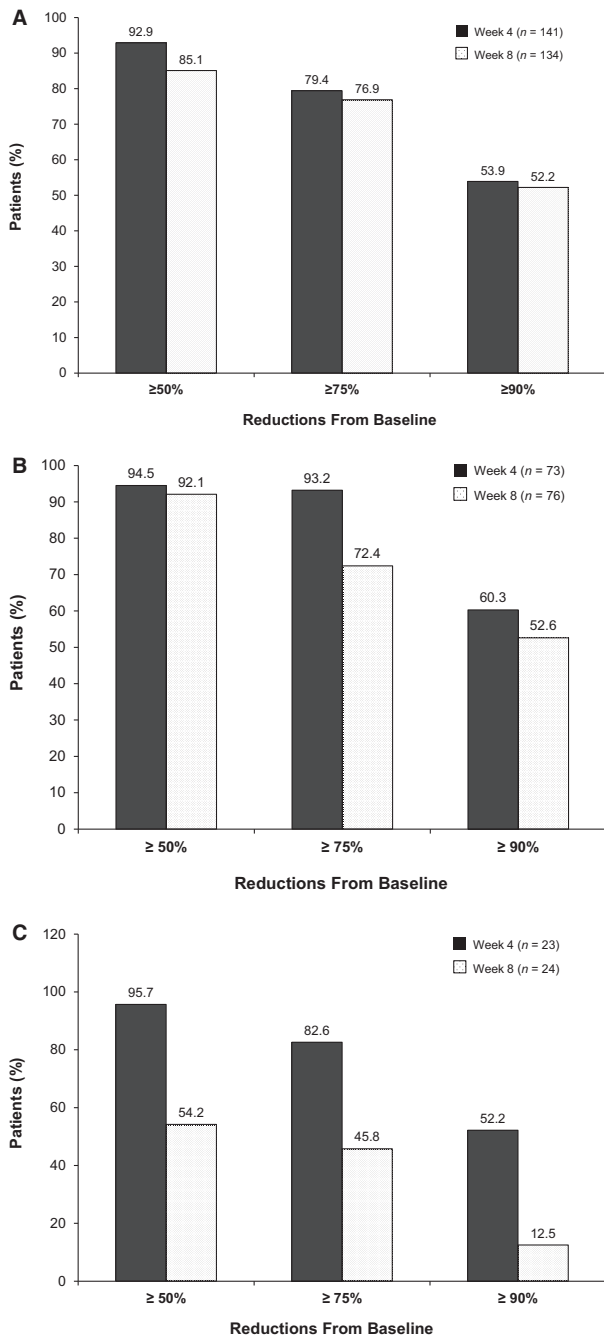


Figure 3. Percentage of patients achieving at least 50%, 75%, and 90% reductions in sweat production from baseline at weeks 4 and 8 of the (A) first, (B) second, and (C) third treatment cycles.

for individuals will decrease with subsequent injections over time. Furthermore, the duration of effect includes not only the interval between treatment sessions (treated patients returning for re-treatment), but also the interval between treatments and study discontinuation or completion.

Patients may still have been demonstrating a response to treatment beyond the date of discontinuation or exit, so the duration of effect would have been underestimated for these later treatment sessions. The median duration of effect better illustrates consistency of response, as shown by the analysis of a subpopulation of patients who responded initially (median duration of effect 152 days for cycle 1, 134 days for cycle 2).

In this study population, excessive axillary sweating appeared at a mean age of 11.8 years, confirming the early age of PAH onset. The study confirmed that PAH has a substantial negative effect on daily activities and health-related QOL based on the CHHIQ and CDLQI. By reducing hyperhidrosis severity and sweat production, onabotulinumtoxinA treatment also consistently and markedly improved daily activities impaired by hyperhidrosis and health-related QOL.

Long-term onabotulinumtoxinA treatment was well tolerated. Few treatment-related AEs, all mild or moderate, were observed. No unexpected safety signals were noted in this study; the AE profile was similar to that reported for adults with PAH and was consistent with the established onabotulinumtoxinA safety profile (24). No patient developed neutralizing antibodies to onabotulinumtoxinA.

This study addressed the need to evaluate long-term treatment with onabotulinumtoxinA in adolescents with PAH. The follow-up period was the same as in a previous study in adults but lacked a placebo control (24). Nevertheless, patient-reported disease severity scores and health outcome measures were congruent with the objective measurement of spontaneous resting sweat production, suggesting that the effects are unlikely to have been the result of a placebo effect.

Several study limitations deserve mention. This was an open-label study with no placebo or active comparator. Nevertheless, the efficacy and safety findings mirror those of the placebo-controlled trial of onabotulinumtoxinA in adults (24). Although this study used only one dose, 50 U per axilla is the recommended dose in adults (12). Moreover, the sweat production inclusion criterion for this study (resting axillary sweat production of 50 mg or more per axilla over a 5-minute period) was the same as that used in the adult studies that resulted in the approval of onabotulinumtoxinA for the treatment of axillary hyperhidrosis at a 50-U dose per axilla.

Dosing and results reported in this study are specific to onabotulinumtoxinA. This formulation is

TABLE 6. Effect of Hyperhidrosis on Daily Activities as Assessed According to the Children's Hyperhidrosis Impact Questionnaire

Daily activity	Treatment cycle 1			Treatment cycle 2		
	Baseline	Wk 4	Wk 8	Baseline	Wk 4	Wk 8
Patients not satisfied or neutral with ability to perform activities, (%)n/N						
School activities	109/126 (86.5)	16/130 (12.3)*	12/125 (9.6)*	32/74 (43.2)	4/70 (5.7)*	3/71 (4.2)*
Nonschool activities	120/135 (88.9)	14/141 (9.9)*	16/132 (12.1)*	26/74 (35.1)	3/72 (4.2)*	5/74 (6.8)*
Patients at least moderately limited by hyperhidrosis in activities						
At school	106/142 (74.6)	18/136 (13.2)*	12/131 (9.2)*	36/76 (47.4)	4/70 (5.7)*	6/73 (8.2)*
Being in public places	116/144 (80.6)	21/140 (15.0)*	17/134 (12.7)*	44/77 (57.1)	5/71 (7.0)*	7/76 (9.2)*
When meeting people	104/144 (72.2)	29/140 (20.7)*	27/134 (20.1)*	43/75 (57.3)	12/72 (16.7)*	14/76 (18.4)*
On family occasions	94/144 (65.3)	17/140 (12.1)*	13/134 (9.7)*	36/77 (46.8)	6/72 (8.3)*	6/76 (7.9)*
When shaking hands	72/144 (50.0)	33/140 (23.6)*	35/133 (26.3)*	34/77 (44.2)	19/72 (26.4)†	16/76 (21.1)*
Developing relationships	79/144 (54.9)	20/139 (14.4)*	18/134 (13.4)*	32/77 (41.6)	7/72 (9.7)*	7/76 (9.2)*
In sports	83/144 (57.6)	16/139 (11.5)*	20/134 (14.9)*	32/77 (41.6)	4/72 (5.6)*	10/76 (13.2)*
Spent ≥15 min on treatment of hyperhidrosis	69/144 (47.9)	19/140 (13.6)*	19/132 (14.4)*	26/77 (33.8)	5/72 (6.9)*	9/76 (11.8)*
Changed clothes ≥2 times	108/144 (75.0)	12/140 (8.6)*	19/134 (14.2)*	33/77 (42.9)	4/72 (5.6)*	10/76 (13.2)*
Took ≥2 showers or baths	58/144 (40.3)	11/140 (7.9)*	17/134 (12.7)*	20/77 (26.0)	6/72 (8.3)†	6/76 (7.9)‡

All values presented as n/N (%).

*p < 0.001, †p = 0.003, ‡p = 0.004 versus cycle baseline based on McNemar test for within-group comparison.

not interchangeable with other botulinum toxin products, and units cannot be converted using a dose ratio. Therefore the results of this study cannot be extrapolated to other botulinum toxin formulations.

In conclusion, this study demonstrated that long-term onabotulinumtoxinA treatment is effective in reducing the severity of PAH and is well tolerated in adolescents. Patients reported marked improvement in health-related QOL and reduced social, physical, and emotional impairment. Based on the duration of effect, adolescents with PAH may need only two to three onabotulinumtoxinA treatments per year.

CONFLICT OF INTEREST

Dr. Glaser serves as a remunerated consultant and investigator for Allergan, Dermira, and Miramar Labs; has received research grants and honoraria from these companies; and is an investigator for Ulthera. Drs. Pariser and Landells serve as remunerated consultants and investigators and have received research grants and honoraria from Allergan. Dr. Hebert serves as a remunerated consultant and investigator and has received honoraria from Allergan. Dr. Hebert's affiliation, the University of Texas Medical School, has received research grants from Allergan. Ms. Weng and Dr. Brin are employees of Allergan. Dr. Beddingfield and Ms. Somogyi were employees of Allergan at the time of this study.

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