An Analysis of the Long-Term Safety Data of Repeat Administrations of Botulinum Neurotoxin Type A-ABO for the Treatment of Glabellar Lines

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BACKGROUND: A new formulation of botulinum neurotoxin type A (BoNTA-ABO; *Dysport* [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ) was recently approved by the US Food and Drug Administration for the treatment of moderate to severe glabellar lines.

OBJECTIVE: To assess the long-term safety of repeat administrations of BoNTA-ABO for the treatment of glabellar lines, including variable dosing. This report summarizes an interim analysis that does not address the efficacy profile.

METHODS: Over 24 months, 1415 subjects underwent open-label retreatment with BoNTA-ABO. Patients were retreated with 50 units or a variable dose of 50, 60, 70, or 80 units based on gender and muscle mass. Dose was divided among five points in the glabellar region. Retreatments were performed if at least 85 days had elapsed between treatments and the glabellar line severity score was reassessed as moderate or severe. Patients were followed up at seven, 14, and 30 days postinjection, then monthly. Endpoints were adverse events (AE).

RESULTS: Of 1415 patients, 932 (66%) experienced at least one AE. The rate of treatment-emergent AE (TEAE) was similar in both the fixed- and variable-dose groups. Most TEAE were rated mild (70%) or moderate (20%). The majority (87%; 3361/3861) of all TEAE instances were considered not related or unlikely to be related to study treatment. The overall incidence of TEAE and related events remained relatively constant or decreased over repeat cycles.

CONCLUSIONS: Multiple cycles with fixed or variable dosing of BoNTA-ABO are well tolerated. There was no evidence of cumulative safety issues because the incidence of AE remained relatively constant or decreased over repeated treatment cycles. *(Aesthet Surg J;29:S43–S49.)*

Frown lines or brow furrows (also known as glabellar facial lines) arise from the activity of the lateral penetrating corrugator and the vertical procerus muscles. The corrugator muscles are symmetric and are located on each side of the glabella. Each corrugator pulls the overlying skin, resulting in the formation of a line perpendicular to the underlying musculature. The procerus muscle pulls the skin down, resulting in a horizontal line in the skin perpendicular to the underlying musculature.[1]

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Clostridium botulinum toxin type A is an accepted treatment for glabellar lines of the face. A new formulation of a botulinum neurotoxin type A (BoNTA-ABO; *Dysport* [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ) has been recently approved by the US Food and Drug Administration for the treatment of glabellar lines. This formulation has been used successfully for many years in Europe and elsewhere. It was initially developed for the treatment of motor disorders and forms of muscle spasticity, and was later studied for applications within aesthetic medicine. It was introduced in the United Kingdom in 1991 and is marketed in more than 70 countries worldwide.[2] It is approved for the treatment of hyperkinetic lines in at least 20 countries and was approved in the United States for the temporary improvement of moderate to severe glabellar lines in patients younger than 65 years old as of April 2009. Compared with placebo, BoNTA-ABO has shown superior

Table 1. Trials from which subjects entered this extension study

Trial	Design (N)	BoNTA-ABO dosing	No. of possible BoNTA-ABO treatment cycles	Duration of follow-up
Brandt et al[3]	Randomized, placebo-controlled (N = 158)	Fixed (50 U)	1	180 days
Rubin et al[4]	Open label, then randomized, placebo-controlled (N = 311)	Fixed (50 U)	2-3 open label, then 1 randomized	23 months
Moy et al[6]	Open label (N = 1200)	Fixed (50 U)	Up to 5	13 months
Kane et al[8]	Randomized, placebo-controlled (N = 816)	Variable*	1	150 days (max)

BoNTA-ABO, abobotulinumtoxinA.
*50, 60, 70, or 80 units based on muscle mass and gender.

efficacy and similar safety in the treatment of moderate to severe glabellar lines.[3-5]

Repeat treatments with BoNTA-ABO are required to maintain efficacy, making it necessary to study and document long-term safety over multiple treatment cycles. For this reason, an open-label phase III study was performed and has documented the safety of up to five serial treatments with BoNTA-ABO over a period of 13 months.[6] This article reports findings from an extension study and further examines the long-term safety of serial treatment cycles, following patients who successfully completed one of four phase III trials and then underwent up to eight retreatments with BoNTA-ABO during a 24-month period.

The minimum dose for clinical effectiveness, duration of effect, and safety has been identified as 50 units per treatment cycle.[5,7] Three of the phase III trials from which patients could enter this extension study used this dose.[3,4,6] Another trial evaluated variable dosing based on muscle mass and gender.[8] Subjects entering from this trial initially were retreated with fixed dosing (50 units), similar to those entering from other studies. A protocol amendment dated October 20, 2007 allowed patients enrolled from the variable-dose study to be retreated with variable dosing. Patients who entered from the variable-dose study before this amendment were treated with fixed dosing. Following the amendment, any retreatments of patients from the variable-dose study were performed using variable dosing.

An earlier analysis of this extension study covered only data collected before this protocol amendment (through March 31, 2007) and therefore did not examine the long-term safety of variable dosing.[9] The current analysis was performed to evaluate this issue. Compared with the earlier publication, this article also includes an additional 20 months of data (through November 30, 2008) and nearly double the number of patients (1415 versus 768).

The effect of neutralizing antibodies was not an endpoint of this study and is addressed elsewhere in this supplement ("An Evaluation of Neutralizing Antibody Induction During Treatment of Glabellar Lines With a New US Formulation of Botulinum Neurotoxin Type A," page S66).

METHODS

Patients who satisfactorily completed participation in any one of four BoNTA-ABO phase III studies were eligible to enter this extension study if they met the other inclusion criteria (Table 1). Inclusion and exclusion criteria have been described previously.[9] Subjects with an ongoing treatment-related adverse event (TEAE) from a previous study or an ongoing non-TEAE that had not stabilized were excluded. Approximately 1500 patients were to be included by study completion. A total of 1415 patients had entered from 44 centers in the United States when enrollment was closed in May 2008. The study is ongoing and is scheduled to continue at least through the spring of 2010.

After enrollment in this extension study, subjects can receive up to eight treatments with BoNTA-ABO over approximately 24 months. No retreatments are performed unless at least 85 days have elapsed between treatments and patients reexhibit moderate or severe glabellar lines (glabellar line severity score [GLSS] of 2 or 3) at maximum frown based on both investigator's and patient's assessment. The GLSS is a validated scoring method in which 0 corresponds to no glabellar lines, 1 represents mild glabellar lines, 2 represents moderate glabellar lines, and 3 indicates severe glabellar lines.[10]

Each fixed-dose treatment consists of five injections of BoNTA-ABO totaling 50 units (which translates to 0.25 mL of product when reconstituted with physiologic saline to a concentration of 10 units BoNTA-ABO per 0.05 mL). Treatment is administered with a 30-gauge needle on day zero of each cycle.

Variable dosing also includes five injections, totaling 50, 60, or 70 units of BoNTA-ABO for female patients and 60, 70, or 80 units for male patients, based on muscle mass. Patients with the largest muscle mass receive the highest doses.[8] Muscle mass was assessed using a scale validated for inter- and intraevaluator consistency using weighted kappa coefficients.

Table 2. Baseline demographics and study of origin

Parameter	BoNTA-ABO, N = 1415 (%)
Age, y	
Mean ± SD	49.5 ± 9.7
≤50	789 (56%)
>50 but ≤65	527 (37%)
>65	99 (7%)
Sex	
Male	126 (9%)
Female	1289 (91%)
Race/ethnicity, n (%)	
White	1151 (81%)
Hispanic	124 (9%)
African	98 (7%)
Other	26 (2%)
Asian	11 (<1%)
Native American	5 (<1%)
Study of orgin	
Kane et al[8]	603 (43%)
Moy et al[6]	573 (40%)
Rubin et al[4]	149 (11%)
Brandt et al[3]	90 (6%)

BoNTA-ABO, abobotulinumtoxinA. SD, standard deviation

Table 3. AE resulting in patient discontinuation

AE	No. of patients
Death	
Complications of chronic alcoholism	1
Metastatic renal cancer	1
Exacerbated emphysema	1
Lung cancer	1
Multiple eye disorders	1
Myasthenia gravis affecting muscles near the eye	1
Pregnancy	1
Unrecorded adverse event	1*
Total	8

*No adverse event recorded at the time of data cutoff.
Note: A ninth patient discontinued from the study because of death from lung cancer, but no termination page was completed for this subject before data cutoff for this analysis. This patient is included as continuing in the study. Two other patients became pregnant but had not discontinued from the study at data cutoff. A third patient who became pregnant was discontinued as lost to follow-up.

Most patients who enrolled from the variable-dose study were initially treated with a fixed dose and later with a variable dose after a protocol amendment permitted it. Patients receiving both types of doses are counted in both groups. Patients treated with a variable dose based on muscle mass can receive a different variable dose at each cycle, depending upon the administering physician's calculation before each treatment. Patients can therefore be counted in multiple variable-dose groups.

Subjects remain at the study center for 30 minutes after each treatment for the measurement of vital signs and assessment for adverse events (AE). They are contacted by telephone seven days posttreatment to check for AE and concomitant medications. Follow-up clinic visits occur on days 14, 30, and monthly until retreatment, study completion, or early termination. The final study visit should occur at month 24 of the study or 30 days after the patient's final study treatment, whichever is later. Patients will be followed for another year thereafter. Initial endpoints were instances of AE and changes in vital sign measurements. AE are categorized by severity (mild, moderate, or severe) and investigator-assessed relationship to study medication (probable, possible, unlikely, or not related). No statistical testing of AE incidence has been performed. Ptosis events are recorded based on either the patient's report or the physician's observation. This interim analysis does not report on vital sign measurements. An earlier interim analysis of data from this study reported no clinically significant changes in vital signs.[9] Therefore, vital signs were no longer measured after January 1, 2008.

Serum samples were collected to screen for anti-*Clostridium* toxin antibodies at baseline, before retreatment, and at study completion or earlier discontinuation. This collection continued until January 1, 2008, when a protocol amendment removed the requirement to collect blood samples.

RESULTS

Table 2 lists the demographic and baseline characteristics of the subjects who had received at least one treatment at the time of this interim analysis (N = 1415). The majority of subjects (1289/1415; 91%) were female. Most subjects (93%) were 65 years of age or younger; the median age was 49 years. The largest group of subjects entered from the variable dosing study (603; 43%).

Disposition of Patients

As of data cutoff, 85% (1209/1415) of subjects enrolled and who had received at least one treatment remained in the study. Of those continuing in the study, 546 (39% of total) had completed two years of treatment. Another 30 (2%) had fully completed the study through the third-year follow-up period. For the 176 (12%) who discontinued before completion, the most common reasons for withdrawal included patient decision (109 patients; 8%) or loss to follow-up (48 patients; 3%). Ten subjects were removed because of noncompliance with study requirements, eight subjects withdrew because of an AE, and one was removed because of investigator decision. After this patient was diagnosed with chronic lymphocytic leukemia, an AE deemed severe and not related to study treatment, an investigator thought that removal from the study was in the patient's best interest. Table 3 lists the instances of AE that resulted in patient discontinuation.

Treatment Exposure

A total of 6760 BoNTA-ABO treatments were administered during the period covered by this analysis. Maximum exposure to fixed-dose therapy was eight treat-

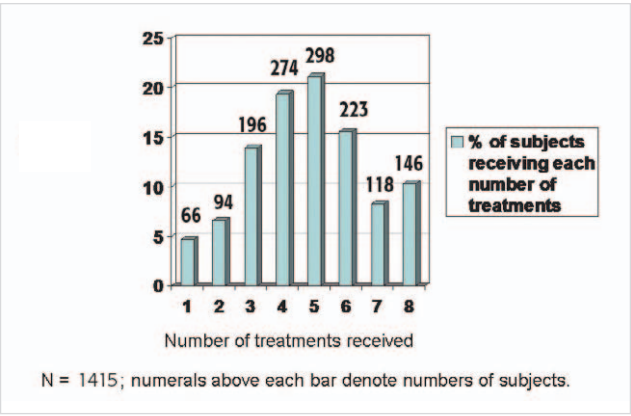

Figure 1. Extent of treatment exposure percentage of subjects receiving each number of treatments.

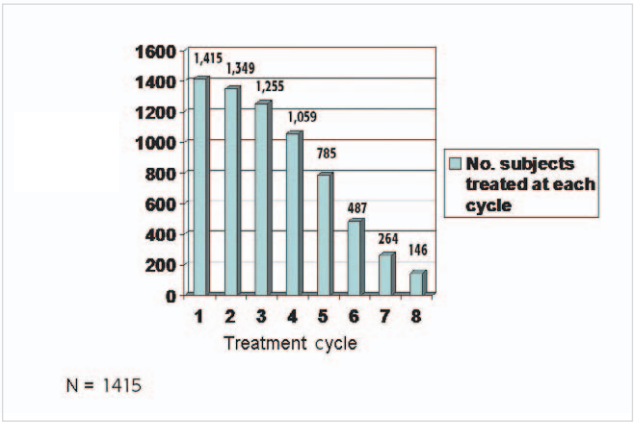

Figure 2. Number of patients treated at each cycle.

ments over roughly 24 months (Figure 1). No more than six cycles of variable-dose therapy were administered because the protocol amendment allowing this option was made about 13 months before data cutoff. Patients received, on average, 4.8 or 4.9 treatments (female and male patients, respectively). Two female patients incorrectly received 80 units of BoNTA-ABO. Figure 2 lists the number of patients treated at each cycle.

Treatment-Emergent Adverse Events

Of the 1415 patients, 932 (66%) experienced 3887 instances of AE. All but 26 AE were TEAE (3861/3887). Table 4 lists the incidence of patients experiencing any TEAE overall by both gender and dosing group. The proportion of patients reporting any TEAE and the rate of TEAE per patient were judged similar between the fixed-dose group and each variable-dose group. Table 5 lists the incidence of patients experiencing any TEAE by study of origin and by gender and dosing group. The incidence of all TEAE remained relatively constant or decreased over repeat cycles of BoNTA-ABO therapy (Table 6).

Investigators assessed the majority of TEAE to be mild (2707/3861; 70%) or moderate (758/3861; 20%) in severity; 5% (200/3861) of TEAE were judged to be severe (Table 7). The remaining 5% were medical procedures recorded as AE in accord with the study design; therefore, no severity rating is associated with these events. The most frequently reported TEAE were nasopharyngitis (12.1% of patients who received a fixed dose and 3.0% of those who received a variable dose based on muscle mass), headache (5.8% of the fixed-dose group, 4.2% of the variable-dose group), upper respiratory tract infection (5.7% of the fixed-dose group, 2.8% of the variable-dose group), and sinusitis (6% of the fixed-dose group, 1.2% of the variable-dose group). As noted, the same subjects could have received both fixed- and variable-dose treatment, and more than one variable dose of BoNTA-ABO; those subjects are therefore counted in both groups. The safety profiles for male and female patients were similar. No trends in type or frequency of TEAE were observed at any dose.

Table 4. Incidence of any TEAE in any treatment cycle by gender and dosing group

Dosing group	Percent (n) experiencing any TEAE	TEAE per patient
Female patients		
Fixed	60% (755/1266)	2.45
Variable		0.78
50 U	44% (71/163)	
60 U	32% (114/356)	
70 U	45% (53/117)	
Male patients		
Fixed	51% (63/124)	1.71
Variable		0.65*
60 U	25% (3/12)	
70 U	29% (10/35)	
80 U	28% (9/32)	

TEAE, treatment-emergent adverse events.
*Variable dosing group as a whole.
Note: The sum of all subjects in the fixed- and variable-dose groups exceeds the total number of subjects in the study because most patients enrolling from the variable-dose study initially were treated with a fixed dose. Patients receiving both types of doses are counted in both dosing groups.

Serious AE (SAE) occurred among 7% (95) of patients. Of the 145 SAE, all but one was deemed unlikely to be related or unrelated to study treatment. The sole exception was a patient who was hospitalized to rule out stroke when presenting with eyelid ptosis without disclosing participation in this clinical trial. This event was considered mild and probably related to study treatment.

The majority of all TEAE (3361/3861; 87%) and of severe TEAE (199/200; 99%) were considered not related or unlikely to be related to the study treatment. Only one SAE, a headache, was classified as possibly related to BoNTA-ABO treatment. No severe TEAE occurred in 1% or more of patients in any group broken down by dose and gender (eg, female patients, fixed-dose group).

Ocular Reactions

This category includes at least 18 types of reactions around the eyes (eg, eyelid ptosis, eyelid edema, dry eye, blepharospasm, ocular hyperemia, blurred vision,

Table 5. Incidence of any TEAE in any treatment cycle by study of orgin, gender, and dosing group

Origin study*	Dosing group	Percent (n) experiencing any TEAE	TEAE per patient
Female patients			
Brandt et al[3]	Fixed	75% (60/80)	5.98
Moy et al[6]	Fixed	71% (380/537)	3.38
Rubin et al[4]	Fixed	68% (88/130)	2.44
Kane et al[8]	Fixed	44% (227/519)	0.95
Kane et al	Variable		0.78†
	50 U	44% (71/163)	
	60 U	32% (114/356)	
	70 U	45% (53/117)	
Male patients			
Brandt et al[3]	Fixed	70% (7/10)	3.70
Moy et al[6]	Fixed	64% (23/36)	2.53
Rubin et al[4]	Fixed	58% (11/19)	1.58
Kane et al[8]	Fixed	37% (22/59)	0.92
Kane et al	Variable		0.65†
	60 U	25% (3/12)	
	70 U	29% (10/35)	
	80 U	28% (9/32)	

TEAE, treatment-emergent adverse event.
*Data in this table were not included in the publications of the studies of origin, but relate to patients entering the extension study described here.
†Variable dosing group as a whole.

Table 6. Incidence of any TEAE by cycle, gender, and dosing group

			Amount of variable dose			
Cycle	Gender	Fixed dose (50 U)	50 U	60 U	70 U	80 U
1	Female	36% (450/1266)	50% (2/4)	57% (4/7)	42% (5/12)	–
	Male	25% (31/124)	–	*	*	50% (1/2)
2	Female	32% (334/1049)	41% (20/49)	30% (29/98)	26% (9/34)	–
	Male	23% (24/103)	–	0% (0/1)	29 (2/7)	33% (2/6)
3	Female	34% (233/695)	35% (37/107)	24% (60/264)	30% (24/80)	–
	Male	24% (14/58)	–	29% (2/7)	29% (6/21)	13% (3/23)
4	Female	31% (201/639)	16% (10/64)	15% (30/205)	33% (18/54)	–
	Male	33% (17/51)	–	13% (1/8)	12% (2/17)	25% (5/20)
5	Female	28% (151/546)	28% (10/36)	14% (13/93)	17% (5/30)	–
	Male	25% (12/48)	–	13% (1/8)	0% (0/10)	14% (2/14)
6	Female	26% (104/397)	0% (0/7)	26% (6/23)	8% (1/13)	–
	Male	22% (8/36)	–	1/1 (100)	0%†	0%†
7	Female	16% (38/239)				
	Male	24% (6/25)				
8	Female	32% (4/130)				
	Male	19% (3/16)				

*No male patients treated at these cycles.
†A total of 10 male patients were treated with 70 or 80 units at cycle 6.
The numbers of patients in each dosing group appear in parentheses.
Note: Variable dosing has not yet been administered beyond cycle 6. No male patients received the 50-unit variable dose; no female patients received the 80-unit variable dose. The sum of all subjects in the fixed-dose and variable-dose groups exceeds the total number of subjects in the study because most patients enrolling from the variable-dose study were initially treated with a fixed dose. Patients receiving both types of doses are counted in both dosing groups. In addition, patients receiving a variable dose based on muscle mass could receive a different variable dose at each treatment cycle depending upon the administering physician's assessment of patients' corrugator and procerus muscle mass. Patients could therefore be counted in multiple variable-dose groups.

Table 7. Percentage of patients experiencing mild, moderate, or severe TEAE by dose group and gender

	Fixed dose 50 U	Variable dose		
Female patients	**n = 1266**	**n = 163, 50 U**	**n = 356, 60 U**	**n = 177, 70 U**
Mild	36%	26%	22%	23%
Moderate	17%	13%	9%	5%
Severe	7%	4%	1%	1%
Severe TEAE per patient	0.12	0.08	0.04	0.02
Male patients	**n = 124**	**n = 12, 60 U**	**n = 35, 70 U**	**n = 32, 80 U**
Mild	31%	25%	17%	16%
Moderate	14%	0%	9%	13%
Severe	6%	0%	3%	0%
Severe TEAE per patient	0.12	0.00	0.06	0.02

TEAE, treatment-emergent adverse event.
The sum of all subjects in the fixed-dose and variable-dose groups exceeds the total number of subjects in the study because most patients enrolling from the variable-dose study were initially treated with a fixed dose. Patients receiving both types of doses are counted in both dosing groups. In addition, patients receiving a variable dose based on muscle mass could receive a different variable dose at each treatment cycle depending upon the administering physician's assessment of patients' corrugator and procerus muscle mass. Patients could therefore be counted in multiple variable-dose groups.

and eye irritation). The overall incidence of TEAE around the eyes was low (7% to 9% of patients in the male and female fixed-dose groups, respectively, and 0% to 6% or 3% to 5% in the male and female variable-dose groups, respectively). It should be noted that smaller numbers of patients were treated in the variable-dose groups (n = 715) compared with the fixed-dose groups (n = 1390). Statistical comparisons of these data were not performed. It was concluded that the incidence of TEAE around the eyes did not appear related to BoNTA-ABO dose. Regardless of dosing, the incidence of periocular complaints and reactions tended to decrease with each subsequent treatment cycle (Figure 3).

Ocular reactions accounted for 5.8% of all TEAE in the fixed-dose group (193/3314) and for 6.9% of all TEAE in the variable-dose group (38/547). Eyelid ptosis accounted for 1% (35/3314) of all TEAE in the fixed-dose group and 2% (11/547) of TEAE in the variable-dose group. A total of 42 patients (3%) experienced 46 eyelid ptosis events. Roughly 13% resolved within one week, 43% resolved within three weeks, 61% resolved within 30 days, and 78% resolved within 60 days (Figure 4).

Almost all eyelid ptosis events (44; 96%) were considered possibly or probably related to study treatment. Most (40/46; 87%) were rated as mild, six (13%) were rated as moderate, and none was rated as severe. The incidence of eyelid ptosis events per patient ranged from 0.01 to 0.03 events per patient depending on dosing group and gender, suggesting that the incidence of eyelid ptosis was not related to dosing group or gender. No patient withdrew from the study because of eyelid ptosis. One instance of eyelid ptosis recurrence in the same eye was recorded over the course of subsequent injections in the study. The next most commonly reported eye events were dry eye and eyelid edema, each occurring in 1% of patients.

DISCUSSION

This study represents the first examination of long-term safety with variable dosing of BoNTA-ABO. It includes data from 549 patients treated with variable dosing over roughly 13 months. The rate of TEAE per patient and the proportion of patients reporting any TEAE were comparable in both the variable- and fixed-dose groups. This suggests that the safety profile of repeat administration of variable doses based on muscle mass is similar to that of repeat treatment with the lesser or fixed 50-unit dose.

In addition, this analysis includes substantially more treatment exposure than the earlier interim report, with nearly double the number of patients (1415 patients versus 768 patients).[9] It identifies no significant changes in the safety profile or trends in safety with repeated treatment over time. As was the case in the earlier publication, there is no suggestion of cumulative safety issues, because the incidence of TEAE remained relatively constant or decreased with successive treatment cycles. When complete, this study will provide data for 2.5 to 3.5 years of follow-up using BoNTA-ABO. This is unique; no other trial of botulinum toxins has yet studied the safety and efficacy of repeat administration and variable dosing based on muscle mass in a long-term clinical trial.

Our data show that the number of ptosis events tended to decrease with each treatment cycle. We speculate that this decrease may have occurred because, over time, patients learned what to expect with each treatment and could distinguish true ptosis from the feeling that typically follows a series of injections into the glabellar area. It also is possible that physicians' technique improved with experience. The latter factor also may explain our

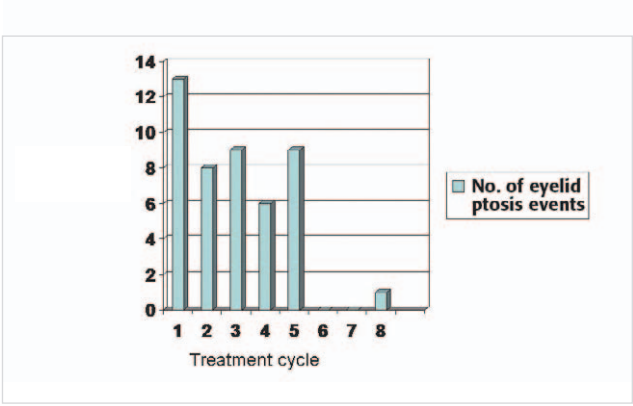

Figure 3. Eyelid ptosis events by treatment cycle.

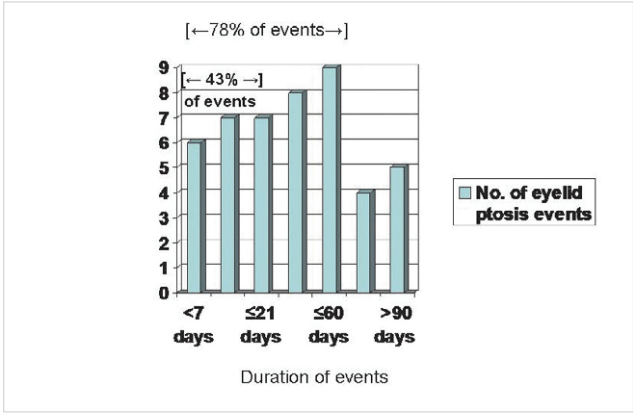

Figure 4. Duration of eyelid ptosis events.

observation that incidence of TEAE per patient was lower in the more recently conducted trials than in those conducted earlier (Table 5). Indeed, TEAE incidence rates fell with each subsequent trial.

To our knowledge, long-term safety data covering a comparable length of follow-up in a similar number of patients have not been reported for Botox Cosmetic (onabotulinumtoxinA [BoNTA-ONA]; Allergan, Irvine, CA) used in the treatment of glabellar lines. A similar incidence of ptosis (3%) was reported with Botox Cosmetic in clinical trials during which a substantially smaller number of patients received the product (405 versus 1415 in our BoNTA-ABO study).[11] As in our study, the incidence of ptosis fell with subsequent treatment cycles (up to three cycles).[12] A review reported that headache occurred in 13% of patients treated with BoNTA-ONA in two large placebo-controlled trials (n = 537). The incidence of headache declined with subsequent treatment cycles.[12] Our analysis reports headache in 5.8% of patients treated with fixed doses of BoNTA-ABO and in 4.2% of those treated with variable dosing.

CONCLUSIONS

The data in this study, taken from multiple cycles with fixed or variable dosing of BoNTA-ABO, show that BoNTA-ABO is well tolerated for the treatment of glabellar lines. The incidence of AE remained relatively constant, even decreasing over repeated treatment cycles, so there was no evidence of cumulative safety issues. ◗

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DISCLOSURES

The authors were compensated for their contributions in preparing this manuscript and as investigators for the study. Dr. Cohen is a consultant and clinical trial participant for Medicis. Dr. Schlessinger is a researcher, advisor, and stockholder in Medicis. Dr. Cox has received research grants from Allergan and is on the advisory board of and serves as consultant and principal investigator for Allergan. Dr. Cox is on the advisory board of and serves as consultant for Coapt System, and is on the advisory board of and serves as a consultant and principal investigator for Medicis, as well as has received research grants from Medicis. Ms. Lin is an employee of Medicis.

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