RESEARCH ARTICLE

Efficacy and Safety of IncobotulinumtoxinA (NT 201, Xeomin) in the Treatment of Blepharospasm—A Randomized Trial

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ABSTRACT: IncobotulinumtoxinA (NT 201, Xeomin) is a highly purified botulinum neurotoxin type A formulation, free from complexing proteins. A randomized, placebo-controlled, double-blind trial of efficacy and safety compared incobotulinumtoxinA (up to 50 U per eye) to placebo administered in a single treatment session to patients with blepharospasm. All patients had documented satisfactory response to 2 previous treatments with botulinum neurotoxin type A other than incobotulinumtoxinA and had Jankovic Rating Scale severity subscores $\geq$ 2. Patients (n = 109) were randomized in a 2:1 ratio to incobotulinumtoxinA or placebo and followed up to 20 weeks; 94% completed the study. A significant difference was observed in the primary efficacy variable (change in Jankovic Rating Scale severity subscore rated by an independent rater 6 weeks following treatment), favoring incobotulinumtoxinA by 1.0 point (95% CI [0.5–1.4]; $P < .001$). Functional impairment, as measured by the Blepharospasm Disability Index, improved by 0.5 points (95% CI [0.2–0.7]; $P = .002$) compared with placebo. There was a strong correlation between the 2 scale scores. In addition, all secondary outcome measures favored incobotulinumtoxinA. Patients rated the mean therapeutic effect of incobotulinumtoxinA significantly better than placebo ($P < .001$). Adverse events were reported in 70.3% of incobotulinumtoxinA patients and 58.8% of placebo patients. Eyelid ptosis (18.9% vs 5.9%), dry eye (18.9% vs 11.8%), and dry mouth (14.9% vs 2.9%) occurred most frequently. Tolerability was rated good/very good by 91.9% of incobotulinumtoxinA versus in 85.2% of placebo patients. In conclusion, incobotulinumtoxinA was well tolerated and was associated with statistically significant and clinically relevant reductions in blepharospasm severity and functional impairment. © 2011 *Movement* Disorder Society

Key Words: blepharospasm; botulinum toxin; dystonia; incobotulinumtoxinA

Idiopathic blepharospasm, also referred to as benign essential blepharospasm, is a focal dystonia involving the orbital and periorbital muscles and often resulting in functional disability because of involuntary eye closure, discomfort, and social impairment.[1] Prevalence rates are estimated at 16 to 133 per million[2,3] and the condition is 2 to 3 times more common in women than men.[3–7] In addition to physical and social disability,[8] blepharospasm adversely affects quality of life and may lead to anxiety and depression.[9]

Prior to the institution of botulinum toxin (BoNT) treatments, no generally accepted, effective therapy was available for blepharospasm.[10] Although BoNT has been described as safe and effective in most reports,[10–18] few efficacy data from properly controlled clinical trials exist, and, therefore, it has received only a level B ("may be offered" as a treatment option) recommendation after an evidence-based review.[10]

IncobotulinumtoxinA (adopted name of NT 201 [Xeomin, Merz Pharmaceuticals GmbH, Frankfurt, Germany] by the United States Adopted Names Council[19]) is a highly purified, freeze-dried BoNT type A

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(BoNT/A) formulation, free from complexing proteins.[20] The drug demonstrated efficacy and safety comparable to another BoNT/A formulation (onabotulinumtoxinA; Botox, Allergan Inc., Irvine, CA) in preclinical studies[21] and in phase 1,[22,23] phase 2,[21] and 2 noninferiority phase 3 clinical trials in cervical dystonia[24] and blepharospasm,[25] using a 1:1 dosing ratio with onabotulinumtoxinA.[21]

The present trial assessed the efficacy and safety of a single set of incobotulinumtoxinA injections compared with placebo in the treatment of blepharospasm.

Patients and Methods

This double-blind, parallel-group, placebo-controlled trial was conducted at 34 centers in the United States and Canada according to the Declaration of Helsinki and Good Clinical Practice from October 2006 to May 2008. The study protocol was approved by the responsible independent ethics committees, and all participating patients provided written informed consent prior to commencing the trial. The study has been registered at http://www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT00406367).

Eligible patients were between 18 and 80 years old (inclusive) with bilateral blepharospasm and had a Jankovic Rating Scale (JRS)[26] severity subscore ≥ 2 and a documented stable therapeutic response to the last 2 consecutive injections with onabotulinumtoxinA (not exceeding 50 U per eye), administered at least 10 weeks prior to trial entry. Concomitant medication for focal dystonia (eg, anticholinergics or benzodiazepines) and tricyclic antidepressants and serotonin reuptake inhibitors were permitted, assuming doses had been stable for $\geq$12 weeks prior to trial entry. Nonsteroidal anti-inflammatory drugs were permitted for pain relief. Aminoglycoside antibiotics use was not permitted during the trial. Principle exclusion criteria were: apraxia of eyelid opening; neuroleptic-induced blepharospasm; hypersensitivity to botulinum toxins, human serum albumin, or sucrose; treatment with botulinum toxins for any indication other than blepharospasm within 16 weeks prior to the trial; and other exclusions that would potentially interfere with the action of BoNT/A or cause undesirable side effects. Focal dystonia in other body regions was not an exclusion, provided it did not interfere with the symptoms of blepharospasm and was not treated with BoNT during the trial or within 16 weeks prior to baseline. Female subjects of childbearing potential were excluded if they did not use adequate contraception or were pregnant or lactating.

Merz Pharmaceuticals GmbH (Frankfurt, Germany) was responsible for the funding, conduct, data collection, and statistical analysis of the study. Authors had full access to all study data.

Treatment

Following a 1-week screening period, patients were randomized by personnel not involved in other study procedures in an approximately 2:1 ratio to incobotulinumtoxinA or placebo treatment using RANCODE version 3.6 (IDV, Gauting, Germany) for blockwise randomization and distribution of trial medication to the centers, ensuring stratification by center. To allow for individualized patient dosing, the selection of doses, dilution, volume, and injection sites for treatment was based on the last 2 BoNT/A treatments ($\pm$10%) prior to the start of the study, up to a maximum of 50 U per eye. Investigators and patients were blinded to the treatment assignment: placebo and incobotulinumtoxinA vials had the same appearance, and neither the investigator nor other medical staff or any subject knew the identity of individual study medication. Study visits were performed 3 and 6 weeks after injection, and patients were asked about the need for a new injection every 2 weeks thereafter, up to 20 weeks postinjection. A new injection was permitted after 6 weeks. The need for a new injection (based on JRS severity subscore ≥ 2, rated by a blinded, independent rater) defined the final visit and marked the end of the double-blind treatment period for this study. If no new injection was needed, the final visit was performed in week 20 at the latest.

Treatment efficacy and safety were assessed 3 and 6 weeks postinjection and at the final visit, as well as during a telephone contact performed 28–35 days postinjection.

Efficacy Assessments

JRS (both subscores) and the BSDI[26] assessments were performed at each visit by the same blinded, independent rater, who was not involved in any other trial procedure. A second investigator was responsible for all other assessments and procedures during the course of the trial.

Jankovic Rating Scale

Severity and frequency of blepharospasm symptoms were measured using the JRS,[26] which ranges from 0 to 8 points (sum score) and includes 2 categories: severity (from 0 = none to 4 = severe) and frequency (from 0 = none to 4 = functionally "blind" due to persistent eye closure more than 50% of waking time). All raters attended a pretrial video training session designed to reduce interrater variability between the centers. In addition to raters' assessment, JRS scores were determined by daily patient self-assessments through the use of an interactive voice recognition system.

Blepharospasm Disability Index

Impairment in specific daily activities caused by blepharospasm was determined using the Blepharospasm Disability Index (BSDI).[26] The 6 activity items (''driving a vehicle,'' ''reading,'' ''watching TV,'' ''shopping,'' ''walking,'' and ''doing everyday activities'') were each rated on a 5-point scale ranging from 0 (no impairment) to 4 (no longer possible due to my illness). Apart from ''everyday activities,'' patients were permitted to rate any item as ''not applicable.'' The BSDI mean score is calculated by adding all applicable and answered items and dividing by the number of items answered. A change of 0.7 points is considered clinically meaningful in noninferiority trials.[26]

Patient Evaluation of Global Response

At the final visit, patients were asked to provide a global evaluation of their response to treatment using a descriptive, subjective response scale (PEGR) adapted from Wissel et al.[27] The scale ranges from −4 (very marked worsening) to +4 (complete abolishment of signs and symptoms).

Global Assessment of Efficacy by the Investigator

Investigators performed a global assessment of efficacy at the end of the trial using a 4-point Likert scale ranging from 1 (very good) to 4 (poor).

Further Assessments of Treatment Effect

The time from injection to onset of treatment effect and time to waning of treatment effect were based on patients' subjective assessments. Patients who reported an onset of treatment effect were asked at each visit and telephone contact if they thought there had been a waning of treatment effect. The time interval between 2 treatments was defined as the time from injection to retreatment.

Safety Assessments

Safety was assessed throughout the study by adverse event monitoring and vital signs. Direct questioning was performed for adverse events, indicating potential systemic toxin spread. A physical and neurological examination and standard clinical and hematological laboratory testing were conducted at screening and trial termination visit. Pregnancy testing was performed at all visits. A standard two 6-lead ECG was performed at screening. Blood samples collected at screening, in week 6, and at trial termination were screened for botulinum toxin antibodies using a fluorescence immunoassay (FIA). Positive samples were subsequently tested using a mouse hemidiaphragm assay (HDA) for neutralizing antibodies.[28]

Investigators assessed the tolerability of the study medication at the final visit on a 4-point Likert scale ranging from 1 (very good) to 4 (poor).

Statistical Analysis

All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC). Efficacy was analyzed using the full analysis set (FAS) population, which included all randomized patients. Data of the per-protocol set (PPS) population, which included all FAS subjects without major protocol violations, were used for supportive analyses. Following regulatory advice, the primary efficacy variable was the change from baseline to week 6 in JRS severity subscore as assessed by the blinded, independent rater. Confirmatory analysis of the primary variable was performed using analysis of covariance comparison of least-squares means between the treatment groups, with the null hypothesis being equality of change in JRS severity subscore. Independent variables were treatment, baseline JRS severity subscore, sex, age, dose group, and pooled center. The last observation carried forward (LOCF) approach was used for missing data. To investigate the robustness of the results, analyses were performed using no imputation of missing data, imputation with group means, and data of the PPS population in week 6. Further sensitivity analyses were logistic regression models to compare responder rates (responders were defined as having an improvement in JRS severity $\geq$ 1 point [clinically meaningful]). Treatment differences were considered significant at $P < .05$.

Secondary efficacy variables included change from baseline to each subsequent visit in JRS severity subscores according to patient diary, change in BSDI from baseline to week 6, and PEGR evaluation at final visit. Baseline of JRS assessment by patient diary was the median of all diary data values collected before injection. For each further visit, a median value was calculated from the diary data of the last 7 days. Model building for all 3 secondary variables was performed as for the primary variable. LOCF was used for JRS assessments by patient diary and change in BSDI; missing data for PEGR were set to ''unchanged'' (= 0).

Further variables included changes from baseline in JRS frequency and sum scores and time to event variables (onset, waning, and duration of treatment effect), which were analyzed descriptively. Treatment comparison of investigators' global assessment of efficacy and tolerability used a descriptive Mann–Whitney test. Correlation analyses of JRS, BSDI, and PEGR scores were performed using Pearson's correlation coefficient.

As was defined in a previous noninferiority trial comparing incobotulinumtoxinA to onabotulinumtoxinA,[25] change from baseline in JRS severity

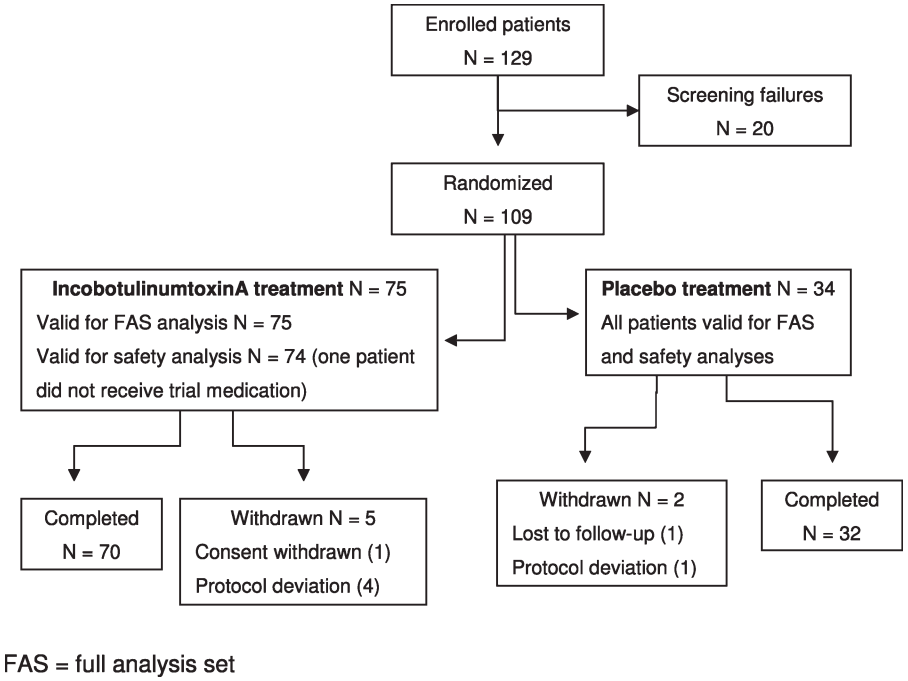


FIG. 1. CONSORT flow chart; FAS, full analysis set.

subscore was defined as being clinically relevant if there were at least a 0.8-point difference for incobotulinumtoxinA compared with placebo treatment.[25] This applied to 2 times the noninferiority region of this subscale. Assuming a common standard deviation of 1.0, a 2-group t test with a 2-sided significance level of $\alpha = 0.05$ had 90% power to detect such a difference if data of 52 patients in the incobotulinumtoxinA group and 26 patients in the placebo group were available for analysis. It was determined that 75 patients (incobotulinumtoxinA group) and 37 patients (placebo group) were required for randomization.

All patients who received the trial medication were included in the descriptive safety analysis. Adverse effects (AEs) were encoded using MedDRA version 9.1.

Results

Of the 109 randomized patients, 75 patients received incobotulinumtoxinA, and 34 patients received placebo treatment (Fig. 1). The majority of patients (94%) completed the trial; no patient discontinued prematurely because of adverse events or insufficient efficacy. All 109 randomized patients were included in the FAS analysis, and 102 patients were valid for PPS analysis. Baseline demographics and disease characteristics were comparable between the treatment groups (FAS population; Table 1). The majority of the patients (65.1%) were women, consistent with other studies showing female preponderance among blepharospasm patients.[3]

All patients had previously received onabotulinumtoxinA for the treatment of blepharospasm except for 1 patient in the incobotulinumtoxinA group, who had not been diagnosed with blepharospasm and was previously treated for presumed hemifacial spasm. The median time since the most recent BoNT/A treatment was similar for incobotulinumtoxinA (13.6 weeks) and placebo (12.0 weeks) patients. The median trial medication dose administered was 65 U (range, 20–100 U; mean, 66.9 U; median, 32.3 U for the right eye and 32.5 U for the left eye) in the incobotulinumtoxinA group. Both treatment groups received a similar number of injections before trial entry: 18.5 (18.9) for the incobotulinumtoxinA group and 22.3 (21.1) for the placebo group.

Efficacy

Six weeks after treatment, mean symptom severity as assessed by an independent rater using the JRS severity subscore (primary efficacy variable) was reduced for incobotulinumtoxinA patients by −0.83 points and increased in the placebo group by 0.21 points, resulting in a significant difference in favor of incobotulinumtoxinA of 1.0 (95% CI [0.5–1.4]; $P < .001$; Fig. 2). Stratification by sex and JRS severity showed more marked reductions for female incobotulinumtoxinA patients (−1.02 points, compared with −0.46 for men) and increasing JRS severity baseline scores (−0.15, −0.86, and −1.17 with a baseline score of 2, 3, and 4, respectively). Responder rates in week 6 were also significantly higher for incobotulinumtoxinA (54.7%) compared with placebo (14.7%), with an odds ratio of 11.29 (95% CI [3.23–39.42]; $P < .001$).

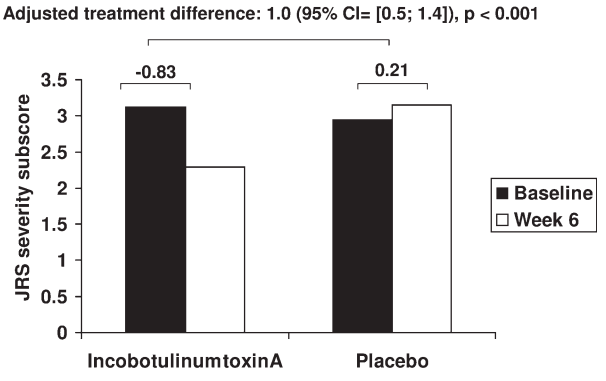
TABLE 1. Baseline demographics and clinical characteristics of the full analysis set

	IncobotulinumtoxinA (n = 75)	Placebo (n = 34)
Demographics		
Mean age, y (SD)	61.5 (11.0)	62.6 (8.7)
Male/female, %	35/65	35/65
Mean body mass index, lb/inch^2 (SD)	28.6 (5.5)	28.1 (6.1)
Disease characteristics		
Mean JRS sum score (SD)[a]	5.87 (1.49)	5.76 (1.42)
Mean JRS severity subscore (SD)[a]	3.12 (0.73)	2.94 (0.81)
Mean JRS frequency subscore (SD)[a]	2.75 (0.9)	2.82 (0.76)
Mean BSDI score (SD)	1.60 (0.79)	1.37 (0.84)
Weeks since first diagnosis of blepharospasm, mean (median, range)	233.2 (169.2; 2.4–1121.2)	278 (184, 38.4–1088.4)
Estimated duration of blepharospasm (weeks), mean (median, range)	387.6 (336.0; 24.0–1296.9)	495.6 (336.0, 48.0–1872.0)
Previous eyelid surgery, n (%)	10 (13.3)	6 (17.6)
Preexisting ocular disease, n (%)	22 (29.3)	8 (23.5)
Dystonia in other muscles (if incidence $\geq$ 4%)		
None, n (%)	51 (68.0)	19 (55.9)
Facial, n (%)	18 (24.0)	7 (20.6)
Cervical, n (%)	6 (8.0)	4 (11.8)
Perioral, n (%)	5 (6.7)	3 (8.8)
Mandibular, n (%)	3 (4.0)	4 (11.8)

BSDI, Blepharospasm Disability Index; JRS, Jankovic Rating Scale.
[a]Scored by blinded, independent rater.

In addition, significant improvements compared with placebo were demonstrated for JRS frequency subscore and sum score, as assessed by an independent rater and by patient diary (Table 2). Independent rater assessment and patient diary data correlated positively at all visits with the JRS sum score and both subscores. The correlation was high and was stronger for active treatment and before the final visit.

There was a significant treatment difference in favor of incobotulinumtoxinA for the mean change from baseline in BSDI in week 6 ($P = .002$; Table 2). Again, the mean score change was more marked for women in the incobotulinumtoxinA group (−0.52 compared with −0.16 for men). BSDI scores correlated significantly with all independent-rater JRS scores at all visits ($P < .05$), except for the final visit JRS severity subscore for the placebo group.



JRS = Jankovic Rating Scale; LOCF = last observation carried forward

FIG. 2. Mean JRS severity subscore at baseline and 6 weeks following treatment (full analysis set; LOCF).

Fifty-one patients (68%) in the incobotulinumtoxinA group and 6 patients (17.6%) in the placebo group reported improvement of their symptoms at the final visit using the PEGR scale. The majority of placebo patients evaluated their symptoms as unchanged (35.3%) or worsened (38.2%). The mean therapeutic effect was rated as 1.3 (slight to moderate improvement) for incobotulinumtoxinA compared with −0.6 (unchanged to slightly worsened) for the placebo group, with a statistically significant treatment difference ($P < .001$; Table 2).

Investigators rated therapeutic efficacy as good or very good for 65.3% of incobotulinumtoxinA patients and 23.5% of placebo patients. Efficacy was considered poor for 24% of incobotulinumtoxinA patients and 67.6% of placebo patients. A statistical comparison showed a significantly better therapeutic efficacy for incobotulinumtoxinA treatment ($P < .001$).

For patients treated with incobotulinumtoxinA, median (range) time to onset of treatment effect was 4 days (0–30 days), time to waning of treatment effect after injection was 6.0 weeks (1– 15 weeks), and duration of effect was 10.6 weeks (6.1–19.1 weeks); median interval between injections was 11.3 weeks.

Safety

Treatment-emergent adverse events were reported for 52 patients (70.3%) in the incobotulinumtoxinA group and 20 patients (58.8%) in the placebo group; for the majority, final outcome was reported as recovered/resolved. Table 3 summarizes all adverse effects occurring in at least 2% of patients. Most AEs were of mild intensity (63.5% for the incobotulinumtoxinA

TABLE 2. Secondary and further selected efficacy outcome parameters (full analysis set)

Variable	Treatment group	n	Mean (SD)	LS mean difference (95% CI)	*P* value (ANCOVA)
Change in JRS frequency subscore in week 6 (IR)	IncobotulinumtoxinA	75	−0.59 (1.03)	0.6 (0.2, 1.0)	.006
	Placebo	34	−0.03 (0.9)		
Change in JRS sum score in week 6 (IR)	IncobotulinumtoxinA	75	−1.41 (1.98)	1.5 (0.8, 2.3)	<.001
	Placebo	34	0.18 (1.68)		
Change in JRS severity subscore in week 6 (diary)	IncobotulinumtoxinA	67	−0.75 (1.24)	0.8 (0.4, 1.3)	.001
	Placebo	32	0.16 (1.07)		
Change in JRS frequency subscore in week 6 (diary)	IncobotulinumtoxinA	67	−0.53 (1.13)	0.6 (0.1, 1.0)	.009
	Placebo	32	0.16 (1.05)		
Change in JRS sum score in week 6 (diary)	IncobotulinumtoxinA	67	−1.29 (2.19)	1.5 (0.6, 2.3)	.002
	Placebo	32	0.31 (2.0)		
Change in BSDI in week 6	IncobotulinumtoxinA	75	−0.4 (0.69)	0.5 (0.2, 0.7)	.002
	Placebo	34	0.11 (0.67)		
PEGR at final visit	IncobotulinumtoxinA	75	1.3 (2.1)	1.9 (1.1, 2.8)	<.001
	Placebo	34	−0.6 (2.2)		

ANCOVA, analysis of covariance; BSDI, Blepharospasm Disability Index; CI, confidence interval; IR, independent rater; JRS, Jankovic Rating Scale; LS, least squares; PEGR, Patient Evaluation of Global Response.
Negative mean values denote improvement, except for PEGR assessment

group, 44.1% for the placebo group); 4 incobotulinumtoxinA patients reported 4 occurrences of severe AEs (dry eye, dysphagia, epiglottitis, and muscular weakness). Only 1 patient had a treatment-emergent serious AE (dyspnea; placebo treatment), which was unrelated to study medication and resolved prior to trial completion. In contrast with the placebo group, in the incobotulinumtoxinA group, several cases of diarrhea (6 patients) and visual disturbance (6 patients) were reported; however, most were unrelated to the study medication (except for visual disturbance in 2 patients). No patients prematurely discontinued because of AEs. Drug-related AEs were more frequent in the incobotulinumtoxinA group (45.9%) than in the placebo group (20.6%); the most common were eyelid ptosis (17.6% for the incobotulinumtoxinA group vs 2.9% for the placebo group) and dry eye (14.9% vs 8.8%).

There were no notable differences between treatment groups regarding laboratory parameters, vital signs, or physical and neurological examinations.

Treatment tolerability was rated "good" or "very good" for most patients (91.9% of incobotulinumtoxinA patients vs 85.2% of placebo patients).

No patients had neutralizing antibodies at screening and at the final visit as measured by HDA.

TABLE 3. Adverse events with an incidence > 2% in any treatment group regardless of relationship to trial medication (safety population)

MedDRA preferred term	IncobotulinumtoxinA (n = 74)	Placebo (n = 34)
Eyelid ptosis	14 (18.9)	2 (5.9)
Dry eye	14 (18.9)	4 (11.8)
Dry mouth	11 (14.9)	1 (2.9)
Diarrhea	6 (8.1)	0
Headache	7 (9.5)	1 (2.9)
Visual disturbance	6 (8.1)	0
Vision blurred	4 (5.4)	2 (5.9)
Dyspnea	4 (5.4)	1 (2.9)
Respiratory tract infection	5 (6.8)	1 (2.9)
Nasopharyngitis	4 (5.4)	2 (5.9)
Dysphagia	3 (4.1)	2 (5.9)
Asthenia	3 (4.1)	0
Injection site pain	3 (4.1)	0
Lacrimation increased	2 (2.7)	1 (2.9)
Injection site hematoma	2 (2.7)	1 (2.9)
Upper respiratory tract infection	1 (1.4)	3 (8.8)
Muscular weakness	1 (1.4)	1 (2.9)

Data are number of patients (%).

Discussion

In this randomized, double-blind, controlled study, a single set of incobotulinumtoxinA injections (mean total dose, 66.9 U) proved significantly more efficacious than placebo in the treatment of blepharospasm. Six weeks after injection, the treatment difference in mean JRS severity subscore was considered clinically relevant in favor of incobotulinumtoxinA when rated by an independent rater. This was also supported by the patients' diary JRS severity self-assessments and by a markedly higher proportion of incobotulinumtoxinA responders with improved symptom severity, highly significant improvements in functional impairment compared with placebo, and the fact that no premature study withdrawals occurred because of insufficient treatment efficacy. Our results are consistent with the findings of a previous incobotulinumtoxinA noninferiority trial comparing incobotulinumtoxinA and onabotulinumtoxinA.[25] Collectively, both trials clearly demonstrate the benefits of incobotulinumtoxinA for the treatment of blepharospasm.

It should be noted that because of the relatively low incidence of the disease,[2,3] the target population for this study was in patients already receiving treatment for blepharospasm. The use of incobotulinumtoxinA in other indications shows efficacy in both treatment-naive and pretreated patients, and so the authors consider the data from the current study to be appropriate in extending to the general population of patients with blepharospasm.

In addition to the JRS, we used the recently developed disease-specific patient assessment scale, the BSDI, to evaluate the effect of incobotulinumtoxinA treatment on patients' functional impairment and potential improvements in their quality of life. High internal consistency and acceptable retest reliability on a single item level have been demonstrated for this scale.[26] In the present trial, a highly significant treatment difference in favor of incobotulinumtoxinA was observed, indicating meaningful improvement in activities of daily living and quality of life.[9]

There have been, to our knowledge, only 2 large-scale randomized trials investigating BoNT/A for treatment of blepharospasm published in peer-reviewed journals.[25,29] Roggenkämper et al compared incobotulinumtoxinA and onabotulinumtoxinA in a single injection in a noninferiority trial[25] and found equal efficacy for both drugs 21 days following injection with mean adjusted changes in the JRS sum score of −2.9 for incobotulinumtoxinA and −2.67 for onabotulinumtoxinA when used at equivalent doses. Together with the results of the present study, these data provide evidence of the high efficacy of incobotulinumtoxinA treatment for blepharospasm and support the moderate to marked improvements observed in open-label treatment.[30]

A placebo-controlled trial by Truong et al[29] compared 3 fixed abobotulinumtoxinA (Dysport, Ipsen Ltd., Slough, UK) doses to placebo and found reduced functional impairment and reduced frequency and intensity of facial spasms with BoNT/A treatment. However, it is difficult to compare the findings from this study with our results because of differences in patient populations and in efficacy outcome measures.

IncobotulinumtoxinA was safe and well tolerated, with a safety profile largely consistent with previously published results for BoNT/A treatment of blepharospasm.[25,29] Adverse events were not cited as a reason for premature study withdrawal, and the investigator's rating of tolerability of incobotulinumtoxinA was similar to placebo in doses up to 50 U per eye.

IncobotulinumtoxinA is free from complexing proteins and thus might be associated with a relatively low risk of immunogenicity.[31,32] This may be of therapeutic advantage for the long-term treatment of chronic conditions such as blepharospasm. Botulinum toxin–neutralizing antibodies were not detected following a single incobotulinumtoxinA injection in this trial, but long-term studies are required to investigate the immunoresponse following repeated long-term incobotulinumtoxinA treatments.

In conclusion, incobotulinumtoxinA led to statistically significant, clinically relevant reductions in disease severity and functional impairment and was well tolerated in patients with blepharospasm. ■

Appendix

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