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ORIGINAL ARTICLE

Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach

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Abstract

Background: In essential tremor and Parkinson disease (PD) tremor, administration of onabotulinumtoxinA via a fixed injection approach improves the tremor, but many patients (30%-70%) develop moderate to severe hand weakness, limiting the use of onabotulinumtoxinA in clinical practice.

Objective: To evaluate the safety and efficacy of incobotulinumtoxinA (IncoA) injection for the treatment of tremor in PD.

Patients and Methods: In this double-blind, placebo-controlled, crossover trial, 30 patients each received 7 to 12 (mean, 9) IncoA injections into hand and forearm muscles using a customized approach. The study was performed from June 1, 2012, through June 30, 2015, and participants were followed for 24 weeks. Treatment efficacy was evaluated by the tremor subsets of the Unified Parkinson's Disease Rating Scale and the Patient Global Impression of Change 4 and 8 weeks after each of the 2 sets of treatments. Hand strength was assessed using an ergometer.

Results: There was a statistically significant improvement in clinical rating scores of rest tremor and tremor severity 4 and 8 weeks after the IncoA injection and of action/postural tremor at 8 weeks. There was a significant improvement in patient perception of improvement at 4 and 8 weeks in the IncoA group. There was no statistically significant difference in grip strength at 4 weeks between the 2 groups.

Conclusion: Injection of IncoA via a customized approach improved PD tremor on a clinical scale and patient perception, with a low occurrence of significant hand weakness.

Trial Registration: clinicaltrials.gov Identifier: NCT02419313.

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Parkinson disease (PD) is a common neurodegenerative disorder with an estimated worldwide prevalence of 0.4% to 2% in the elderly population.[1] The spectrum of motor symptoms in PD can range from a purely akinetic-rigid subtype in which tremor is absent to a tremor-dominant subtype in which tremor is the earliest and most prominent feature. Striatal dopamine content seems to correlate with akinesia, rigidity, and disease severity; however, it does not correlate with the presence or severity of tremor, suggesting perhaps a different pathogenesis for PD tremor.[2] Usually, tremor is the presenting symptom of PD. Patients with PD typically have a resting tremor of 4 to 6 Hz, which gets better with volitional activity. The tremor in PD substantially impacts several domains of quality of life, from physical to psychosocial. One-third of patients with PD have clear tremor-related quality of life issues that interfere with activities such as writing, using a typewriter/computer, fixing small things, dressing, eating, and holding reading material, which adds psychosocial stress in more than 25% of patients with PD.[3] Unlike the other cardinal motor features of bradykinesia and rigidity, PD tremor may be refractory to pharmacologic treatment or may require the use of high doses of levodopa, which can cause debilitating motor fluctuations (on-off phenomenon/dyskinesia).[4,5] Anticholinergic medications (eg, trihexyphenidyl) can help some patients with refractory PD tremor, but their common adverse effects of cognitive dysfunction, blurring of vision, and urinary retention are poorly tolerated by elderly individuals.[6] Deep brain stimulation of either the

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subthalamic nuclei or global pallidum internus is effective against refractory PD tremor[7] but carries a 3% to 4% risk of comorbidity, including intracerebral hemorrhage and peripheral or intracerebral infection.[8,9] In addition, technical issues such as contact dysfunction, electrode displacement, and connecting wire fractures are among the deep brain stimulation–related complicating factors. Therefore, a need exists for a treatment modality for refractory PD tremor with a safe adverse effect profile, especially in elderly patients, who are sensitive to the systemic effects of medications and are not keen to have surgery.

For the past 25 years, botulinum neurotoxins (BoNTs) have been used extensively for the treatment of motor and movement disorders (blepharospasm, cervical dystonia, and spasticity), autonomic dysfunctions (sialorrhea and hyperhidrosis), and, more recently, migraine and neuropathic pain. A focal injection of BoNT is overall safe and has a low adverse effect profile.[10,11]

Four open-label studies have addressed the issue of BoNT treatment for PD tremor and reported some functional improvement.[12-15] This is the first blinded study assessing the efficacy and safety of a BoNT A, namely, incobotulinumtoxinA (IncoA), on the resting and action tremor of PD.

PATIENTS AND METHODS

Study Design and Intervention

This was a randomized, double-blind, placebo-controlled crossover study. All the study visits took place at the Yale Movement Disorder Center in New Haven, Connecticut. The crossover occurred at the end of week 12 after the first injection of IncoA or saline (Figures 1 and 2). The study protocol was approved by the Yale University institutional review board, and written informed consent was obtained from all the participants.

The injection pattern (dose and muscle selection) was customized to each patient rather than following a fixed approach. The injections were performed by movement disorders neurologists (D.M., D.R., B.J.). Patient hand tremor was clinically evaluated, and the muscles causing the prominent tremor involving the various joints, such as fingers (proximal and distal interphalangeal joint, metacarpophalangeal joint), wrist (radial or ulnar flexion and extension), or elbow (flexion, extension, supination, or pronation), were identified. The tremor activity in these muscles was confirmed by rhythmic burst potentials on electromyography (EMG). The dose of botulinum toxin was quantified based on the tremor activity on EMG and the size of the muscle. The goal was to avoid unnecessary injections into muscles with no tremor activity and to distribute the botulinum toxin in small doses to the active muscles to avoid hand weakness. The number of injections in each patient ranged from 7 to 12, with an average of 9 injections per patient. The total dose of IncoA varied from 85 to 110 U per patient (mean, 100 U per patient). In the placebo group, the same techniques were used to identify the active muscles. The muscles injected and the doses used are summarized in Table 1. IncobotulinumtoxinA was prepared for injection by adding 1 mL of preservative-free saline into 100-U vials. Injections were performed using a sterile 27-gauge needle under EMG guidance.

Outcome Measures

Demographic data were collected at the beginning of the study (Table 2). Clinical assessments were performed at the beginning of the study and at 4 and 8 weeks. Tremor severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), which includes rest tremor score (UPDRS section 20; range, 0-4), action/postural tremor score (UPDRS section 21; range, 0-4), and symptomatic complaint of tremor score (UPDRS section 16; range, 0-4).[16] Tremor severity was assessed by the National Institutes of Health Collaborative Genetic Criteria (NIHCGC) tremor severity score (range, 0-4).[17] The overall effect on patient quality of life was assessed by the Parkinson's Disease Quality of Life Questionnaire (PDQL; range, 37-185).[18] Patient self-estimated clinical improvement was based on the Patient Global Impression of Change (PGIC; range, 0-7). Grip strength was examined using an ergometer at baseline and 4 weeks after the injection. All the clinical assessments were made by a rater masked to the treatment assignment. Study patients were advised to call immediately if any adverse effects occurred, and potential

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adverse reactions were assessed regularly by asking the patient at each visit and during the telephone conversation.

The primary end point was the change in severity of rest tremor. Changes after IncoA injection were determined by calculating the difference in the UPDRS section 20 score between before and after the IncoA injection at 4 and 8 weeks. Changes after placebo injection were determined by calculating the difference in the UPDRS section 20 scores between before and after the placebo injection at 4 and 8 weeks. We then analyzed the within-patient difference between the change scores observed across the 2 periods (1 with placebo, the other with IncoA). Secondary outcomes were changes in symptomatic tremor control (UPDRS section 16), action or postural tremor (UPDRS section 21), tremor severity (NIHCGC), quality of life (PDQL), patient perception of change (PGIC), and weakness of grip strength.

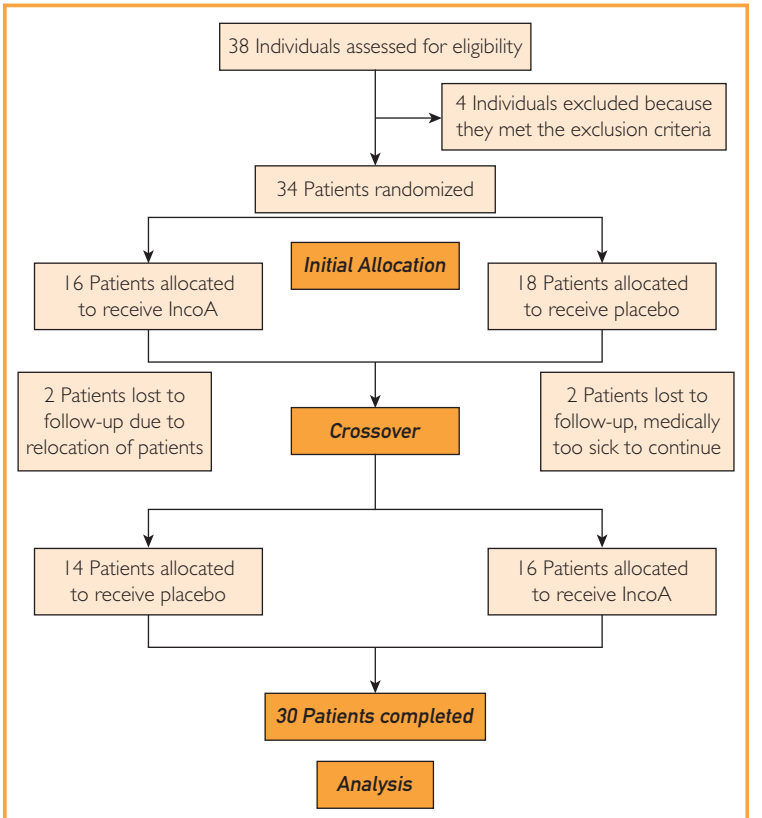

FIGURE 1. Consort flow diagram of the study participants. IncoA = incobotulinumtoxinA.

Study Population

All the study participants had a clinical diagnosis of PD with moderate to severe tremor refractory to standard medical treatments. The tremor limited their functionality or caused major discomfort. A patient's existing medications and nonpharmacologic treatments for PD were not changed during the study.

Children (aged <18 years) and individuals with sensitivity or allergy to BoNTs; the presence of neuromuscular junction disorders; a history of BoNT injections in the past 4 months, anesthetic medications within 2 weeks, and corticosteroid injections within 4 weeks; pregnancy/breastfeeding; preexisting significant acute medical conditions (ie, cardiovascular, neoplastic, infectious, or autoimmune disorders), and swallowing or breathing difficulties were excluded from the study. Participants were not to participate in another investigational study during the course of this study.

Randomization and Blinding

A computer-generated randomization software program was used for patient assignment using no specific treatment sequence. A nurse not involved in the patient interview or rating was aware of the sequence and dispensed IncoA or placebo accordingly. She concealed the data in a password-protected computer. All the study patients, caregivers, and investigators (injector or rater) were blinded. The IncoA was supplied by Merz Pharmaceuticals. Placebo was normal saline administered in identical volumes.

Statistical Analyses

The primary objective of this double-blind, placebo-controlled crossover trial was change in the rest tremor score (UPDRS section 20; range, 0-4) at 4 and 8 weeks. Thirty patients with a clinical diagnosis of PD with moderate to severe tremor refractory to standard medical treatments were randomized to receive IncoA during the first phase of the study (12 weeks) and placebo (saline) during the second phase of the study (12 weeks) or placebo during the first phase of the study and IncoA during the second phase of the study (Figure 1). For each patient, the change in rest tremor score from the time of the injections to 4 weeks after the injections was

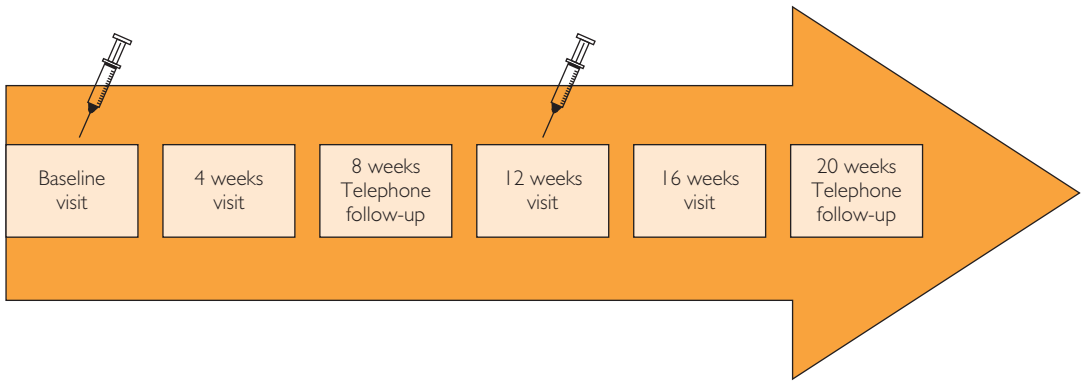

FIGURE 2. Study design.

calculated and recorded. The same calculation was recorded from the time of the injections to 8 weeks after the injections.

The null hypothesis that there is no difference in change scores for the rest tremor score from the time of the injections to 4 weeks after the injections between IncoA and placebo (between-group comparison) was tested by the Wilcoxon signed rank test. The Mann-Whitney *U* test was used to evaluate the carryover effect for all analyzed variables. All the statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp), and $P<.05$ was used to denote statistical significance.

TABLE 1. Summary of the Muscles Injected and Their Doses

Muscle	Patients (No. [%]) (N=30)	IncobotulinumtoxinA (U)
Lumbricals	29 (97)	2.5-20
Flexor carpi radialis	27 (90)	10-15
Flexor digitorum superficialis	26 (87)	10-20
Flexor carpi ulnaris	25 (83)	10-20
Pronator	25 (83)	10
Biceps	25 (83)	10-20
Triceps	23 (77)	10-15
Extensor carpi radialis	19 (63)	5-10
Extensor digitorum	18 (60)	5-10
Flexor pollicis brevis	11 (37)	5-10
Extensor carpi ulnaris	10 (33)	5-10
Flexor digitorum profundus	7 (23)	10
Abductor pollicis brevis	6 (20)	5-10
Brachioradialis	5 (17)	10
Supinator	3 (10)	10
Opponens pollicis	1 (3)	5

Sample size was calculated based on preliminary observations of 80% efficacy in the experimental group vs 25% anticipated as the placebo effect (Power beta 1%-80% and significance level alpha of 5% [sealed envelope sample size calculator]).

RESULTS

Of 38 patients screened for the study, 4 were excluded from the screening, and 34 patients were enrolled in the study (Figure 1). Of the 30 patients who completed the study, 7 were women. Baseline characteristics are summarized separately for each sequence group in Table 2. There was no statistically significant difference in demographic characteristics between the IncoA-first and placebo-first groups (Table 2).

The change in UPDRS rest tremor after IncoA injection was significant at 4 and 8 weeks ($P<.001$) (Table 3) compared with the placebo group. Evaluating the effect of IncoA on action/postural tremor, there was a change in clinical rating that was significant at 8 weeks ($P=.01$). Tremor affecting activities of daily living was evaluated by UPDRS section 16, which showed significant change in the IncoA group compared with the placebo group at 4 and 8 weeks ($P=.01$). On the tremor severity scale (NIHCGC), the IncoA group had significant improvement compared with the placebo group at 4 and 8 weeks ($P<.001$). Patient perception of change (PGIC) also showed significant improvement at 4 and 8 weeks ($P<.001$) in the IncoA group

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TABLE 2. Baseline Demographic and Clinical Characteristics of the IncoA and Placebo Groups[a]

Variable	IncoA/placebo group (n=14)	Placebo/IncoA group (n=16)	*P* value
Age (y), median (range)	62 (51-81)	68.50 (57-87)	.25[b]
Male sex (No. [%])	12 (85.7)	11 (68.8)	.39[c]
Duration of symptoms (y), median (range)	5 (1-11)	4.5 (1-28)	.87[b]
Duration of PD diagnosis (y), median (range)	3.25 (0.5-10)	3 (1-27)	.84[b]
UPDRS section 20 score (median [range])	3 (3-4)	3 (2-4)	.18[b]
UPDRS 16 score (median [range])	3 (1-4)	2 (1-4)	.16[b]
UPDRS section 21 score (median [range])	3 (0-4)	2 (0-3)	.17[b]
NIHCGC tremor severity score (median [range])	3 (2-4)	3 (2-4)	>.99[b]
PDQL score (median [range])	131 (53-177)	118.5 (74-167)	.76[b]
Grip strength score (median [range])	64.5 (20-90.4)	46.3 (21.8-87.4)	.19[b]

[a]IncoA = incobotulinumtoxinA; NIHCGC = National Institutes of Health Collaborative Genetic Criteria; PD = Parkinson disease; PDQL = Parkinson's Disease Quality of Life Questionnaire; PGIC = Patient Global Impression of Change; UPDRS = Unified Parkinson's Disease Rating Scale.
[b]Mann-Whitney *U* test.
[c]Fisher exact test.

compared with the placebo group. More patients in the IncoA group showed improvement in quality of life (PDQL) at 4 and 8 weeks, but the difference from placebo was not significant (*P*=.09).

Grip strength was measured using an ergometer at baseline and 4 weeks after the injections. The weakness in the IncoA group was not statistically significant compared with the placebo group. Overall, 10 out of 27 patients (37%) in the IncoA group and 6 out of 27 (22%) in the placebo group demonstrated decreased strength in ergometric assessment (≥10 points). There was no carryover effect of IncoA in the placebo arm after crossover (*P*=.54). Of the 10 patients in the IncoA group, 5 did not perceive the hand weakness, 3 found it subtle and noninterfering, and 2 found it moderate to severe and interfering. In the placebo group, 1 patient reported having moderate to severe hand weakness. The hand weakness lasted 6 to 8 weeks.

DISCUSSION

This study is the first randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy of a BoNT in PD tremor. There are 2 double-blind studies that have

TABLE 3. Comparison of Outcomes Between Patients Receiving IncoA and Placebo at 4 and 8 Weeks[a]

Scale	Comparison of difference	IncoA/placebo median (range of difference)	Placebo/IncoA median (range of difference)	*P* value
UPDRS section 20	At 4 wk[b]	1 (−1 to 4)	0 (−2 to 1)	<.001
	At 8 wk	1 (0 to 4)	0 (−1 to 1)	<.001
UPDRS section 16	At 4 wk[b]	0 (−2 to 2)	0 (−2 to 1)	.01
	At 8 wk	0 (0 to 2)	0 (1 to −3)	<.001
UPDRS section 21	At 4 wk[b]	1 (−3 to 3)	0 (−3 to 2)	.076
	At 8 wk	1 (0 to 3)	0 (−3 to 3)	.01
NIHCGC tremor severity	At 4 wk[b]	1.00 (−1 to 2)	0 (−2 to 1)	<.001
	At 8 wk	1 (−1 to 2)	0 (−2 to 2)	<.001
PGIC	At 4 wk[b]	3 (1 to 7)	2 (1 to 6)	<.001
	At 8 wk	5 (2 to 7)	2 (1 to 3)	<.001
PDQL	At 4 wk[b]	0 (−55 to 13)	0 (−12 to 33)	.14
	At 8 wk	0 (−55 to 14)	0 (−11 to 33)	.09
Strength score at 4 weeks (median [range])[b]		6.8 (−45.4 to 21.3)	−1 (−12.4 to 41.6)	.32

[a]IncoA = incobotulinumtoxinA; NIHCGC = National Institutes of Health Collaborative Genetic Criteria; PDQL = Parkinson's Disease Quality of Life Questionnaire; PGIC = Patient Global Impression of Change; UPDRS = Unified Parkinson's Disease Rating Scale.
[b]Wilcoxon signed rank test.

TABLE 4. Review of the Literature: Double-Blind and Open-Label Studies on Evaluation of Botulinum Toxin in the Treatment of PD Tremor and ET

Reference, year	Patients	Study type	Tremor type	Toxin type	Evaluation period (wk)	Measure outcome	Results	Adverse effects
Jankovic and Schwartz,[12] 1991	4 ET, 1 DyT, 3 Dyt-ET, 1 PD, 1 peripheral-induced	OL	Mixed	OnaA	~12	Clinical rating	No statistical improvement. Improvement in 60% of patients.	6/10 hand weakness
Trosch and Pullman,[13] 1994	12 PD, 14 ET	OL	ET, PD	OnaA	6	Subjective functional improvement, global disability, computer-assisted quantitative assessments	2 PD (17%) and 3 ET (21%) had >50% reduction on tremor amplitude. 5 PD and 5 ET had moderate to marked subjective improvement in functional benefit. No scale statistically significant.	Digit extension weakness in 1 patient with PD
Jankovic et al,[20] 1996	25	R DB PC	ET	OnaA	16	Unified Tremor Rating and Assessment for functional severity, severity of rest, action postural tremor, sickness impact profile, accelerometry	Significant improvement in tremor severity rating scale. No significant improvement in functional rating scale.	Mild (50%) to moderate (42%) weakness at week 4 in extensor muscles
Pullman et al,[14] 1996	15 PD and 17 ET	OL	Mixed	OnaA	6-8	Clinical rating, disability score, tremor amplitude/ frequency	No statistically significant improvement. 2/15 PD and 7/15 ET had significant improvement.	Not available
Pacchetti et al,[21] 2000	20	OL	ET	AboA	4, 12, 20	Daily living self-questionnaire and severity tremor scale, accelerometer	Significant improvement in all scales at 4 and 12 wk.	15% of patients had finger extensor weakness
Brin et al,[19] 2001	133	R DB PC Parallel group	ET	OnaA	6, 12, 16	Severity rating, functional disability, quality of life, grip strength	Significant improvement in postural tremor at 6, 12, and 16 wk in low- and high-dose groups and kinetic tremor improvement at 6 wk.	Hand weakness in 30% (13/43) of the low-dose group and in 70% (31/45) of the high-dose group
Rahimi et al,[15] 2015	38	OL	PD	IncoA	6, 16, 22, 32, 38	UPDRS section 20, Fahn-Tolosa-Martin tremor scale, kinematic analysis	Significant improvement of tremor at 6, 32, and 38 wk.	25% mild grip weakness, 57% mild third finger weakness

Continued on next page

TABLE 4. Continued

Reference, year	Patients	Study type	Tremor type	Toxin type	Evaluation period (wk)	Measure outcome	Results	Adverse effects
The present study	30	R DB PC crossover	PD	IncoA	4, 8	UPDRS sections 20, 21, 16; NIHCGC tremor severity, PGIC, PDQL, accelerometer	Significant improvement in UPDRS (sections 16 and 20), PGIC, NIHCGC tremor severity score at 4 and 8 wk, UPDRS section 21 at 8 wk. Trend toward improvement in PDQL at 4 and 8 wk but not statistically significant.	Hand weakness (P=.32)

AboA = abobotulinumtoxinA; ET = essential tremor; DyT = dystonic tremor; IncoA = incobotulinumtoxinA; NIHCGC = National Institutes of Health Collaborative Genetic Criteria; OL = open label; OnaA = onabotulinumtoxinA; PD = Parkinson disease; PDQL = Parkinson's Disease Quality of Life Questionnaire; PGIC = Patient Global Impression of Change; R DB PC = randomized double-blind placebo-controlled; UPDRS = Unified Parkinson's Disease Rating Scale.

reported on the effects of onabotulinumtoxinA (OnaA) on essential tremor (ET). In 1 study,[19] 133 patients were randomized to receive low-dose (flexors: 15 U, extensors: 10 U), high-dose (flexors: 30 U, extensors: 20 U), or placebo injections. There was a significant improvement in postural tremor, but hand weakness occurred in 30% of the low-dose group and 70% of the high-dose group and was a limiting factor. In the second study,[20] 25 patients with ET were randomized to receive placebo or BoNT injections into the wrist flexors and extensors. Four weeks after OnaA injection, tremor scores improved (75% vs 27% in the BoNT and placebo groups, respectively; P<.05). Again, 50% of the patients who received BoNTs experienced muscle weakness, which lasted for 4 weeks.

No blinded trial has been conducted on the effect of BoNTs on the resting tremor of PD before the present study. There have been 5 open-label trials, summarized in Table 4. Trosch and Pullman[13] treated 12 individuals with PD and 14 with ET with BoNT injections into the forearm muscles. They measured tremor amplitude and frequency with accelerometric recording. The mean amplitude reduction for the PD tremor group was 15%, with 5 patients demonstrating more than 50% amplitude reduction and 1 showing 98% reduction. The mean frequency reduction was 1 for the PD group. Five patients (38%) reported moderate to marked functional improvement. In another study from Columbia University,[14] investigators reported the effect of OnaA injections in 187 patients with limb disorders, of whom 15 had PD tremor. Only 2 of 15 patients (13.3%) had major quantitative changes in tremor amplitude (>50% reduction) after OnaA treatment and reported satisfactory functional improvement. More recently, Rahimi et al[15] evaluated the use of IncoA in 28 patients with PD tremor in an open-label study over 38 weeks. Patients received IncoA injections at weeks 0, 16, and 32 and had 6 clinical visits at weeks 0, 6, 16, 22, 32, and 38. The total dose of IncoA per session varied from 200 to 360 U. Using the tremor subsets of the UPDRS (sections 20, 21, and 23), the authors noted significant improvement of tremor (measured by kinematics and clinician scores) at weeks 6, 32, and 38 (P<.05). Seven

patients who had major problems with eating and dressing at baseline showed marked improvement of these functions. Patients demonstrated a 25% decrease in grip strength after the first injection, but this was perceived and rated as subtle, grade 1 (of 4) weakness and not interfering. A subtle weakness of the third finger was noted in 57% of the patients. The authors attributed the absence of significant and interfering weakness in their study to the careful kinematic identification of involved muscles and to a flexible injection approach, unlike the fixed injection approach of the previous studies. Patients were not formally evaluated for patient perception of improvement through validated scales such as the PGIC.

The results of the present randomized, double-blind, crossover, placebo-controlled trial are promising. In particular, the low incidence of disabling hand weakness (6.6% vs ≥50% in previous ET and PD studies) is of note and has practical value. There is a possibility that this study is underpowered to detect a statistically significant difference in grip strength. This low incidence resulted from application of a customized approach with muscle selection by needle EMG, which allowed inclusion of a larger number of muscles in the plan of injection, reducing the applied dose per muscle (eg, flexor digitorum superficialis). Furthermore, the inclusion of lumbrical muscles (not included in previous studies of PD or ET) in the plan of injection might have helped to achieve better results because the metacarpophalangeal joint is almost always involved in the resting hand tremor of PD.

The present study has limitations. First, the duration of the study arms (3 months) was short, since the clinical effect of BoNTs on movements sometimes lasts more than 3 months. Therefore, it is conceivable that in some patients who were injected first with IncoA, the results of subsequent saline injection might have been influenced by the IncoA effect, which may have lasted beyond 3 months. Thus, it will be helpful to have a longer washout period in designing crossover studies in the future. Second, although 50% of the patients who received IncoA (vs 26% in the placebo group) expressed satisfaction with the results, only one-third of the patients reported substantial improvement of tremor and significant improvement of their lifestyle. Nonetheless, considering that patients of this cohort had not responded to various medications and had disabling tremors, the degrees of satisfaction presented by patients is of clinical value.

CONCLUSION

To summarize, this is the first double-blind, randomized, placebo-controlled, crossover study evaluating the efficacy and safety of customized injection of IncoA in PD tremor. There was significant improvement in resting tremor and patient impression of change at 4 and 8 weeks and improvement in action/postural tremor at 8 weeks, without significant hand weakness 4 weeks after the IncoA injections. Future expanded studies using further refinement of a customized technique implemented in a larger cohort are necessary for optimal results.

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Abbreviations and Acronyms: **AboA** = abobotulinumtoxinA; **BoNT** = botulinum neurotoxin; **DyT** = dystonic tremor; **EMG** = electromyography; **ET** = essential tremor; **IncoA** = incobotulinumtoxinA; **NIHCGC** = National Institutes of Health Collaborative Genetic Criteria; **OL** = open label; **OnaA** = onabotulinumtoxinA; **PD** = Parkinson disease; **PDQL** = Parkinson's Disease Quality of Life Questionnaire; **PGIC** = Patient Global Impression of Change; **R DB PC** = randomized, double blind, placebo controlled; **UPDRS** = Unified Parkinson's Disease Rating Scale

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