Novel Uses of Botulinum Toxin in Limb Tremor

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Disclosures

- Grants/research support: Merz, Ipsen, Abbvie, Foundation for Peripheral Neuropathy
- Consultant: Merz, Ipsen, Abbvie

BoNT in Essential Limb Tremor: AAN QSS 2008 Review

- Prevalence: 0.5%-1.3% (≥ 65 y/o: 5.8%)
- Rx: propranolol, primidone (71% d/c), PN stim, focused US, DBS
- Two class 2 studies of BoNT in UL ET
- Conclusions: BoNT is probably effective should be considered
- Limitations: Challenges in producing sufficient neuromuscular blockade to relieve tremor without causing excessive weakness
- Inadequate evidence to suggest localizing technique

Simpson DM, et al. *Neurology.* 2008;70:1691-1698.

toxins

MDPI

Article

Tolerability and Efficacy of Customized IncobotulinumtoxinA Injections for Essential Tremor: A Randomized, Double-Blind, Placebo-Controlled Study

Mandar Jog [1,*], Jack Lee [1,2], Astrid Scheschonka [3], Robert Chen [4], Farooq Ismail [5], Chris Boulias [5], Douglas Hobson [6], David King [7], Michael Althaus [3], Olivier Simon [3,†], Hanna Dersch [3], Steven Frucht [8] and David M. Simpson [9] on behalf of the Essential Tremor Study Team

Jog, et al. Toxins 2020

Kinematic-Guided BoNT Therapy for ET

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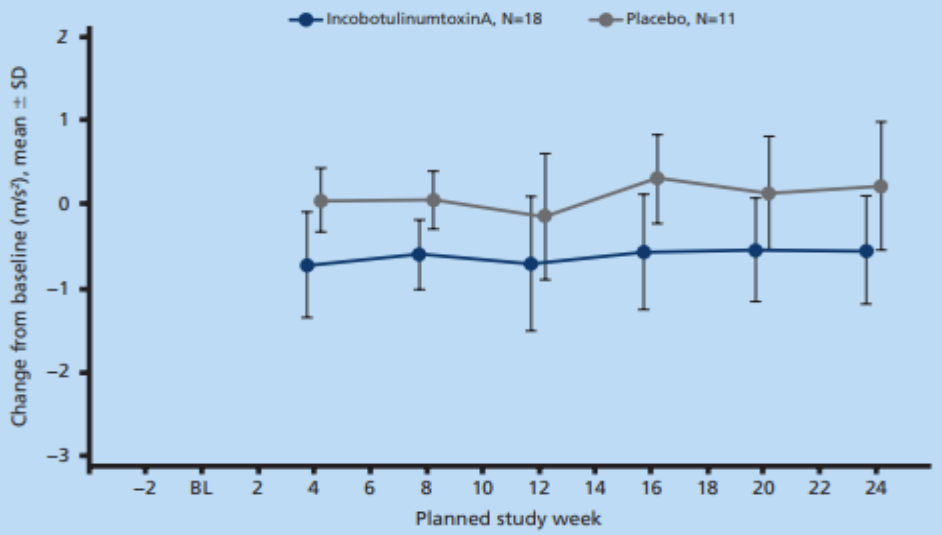
Kinematic-Guided BoNT Therapy for ET

Figure 3. Maximum log-transformed accelerometric tremor amplitude at wrist (injected limb); full analysis set, observed cases



Survey		IncobotulinumtoxinA N=18	Placebo N=11
Week 4 change from baseline	Mean ± SD (m/s²) p-value (ANCOVA) 95% CI (t-test)	−0.73 ± 0.63 0.004* −1.21, −0.34*	0.05 ± 0.38
Week 8 change from baseline	Mean ± SD (m/s²) p-value (ANCOVA) 95% CI (t-test)	−0.60 ± 0.42 <0.001* −0.95, −0.33*	0.05 ± 0.35

*p-value <0.05 for incobotulinumtoxinA versus placebo.
ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; SD, standard deviation.

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BoNTA vs Placebo in Essential Tremor International Phase II Study

- Double-blind, placebo-controlled
- N = 75
- Inco-BoNT (Xeomin) 130-165U
- 8-14 upper limb muscle
- Cycle 1: Unilateral placebo-controlled; 24 wk
- Cycle 2: Bilateral open label; 16 wk

Intl PI: D Simpson, MD

Primary endpoint: Tremor Amplitude at Week 6

Baseline

Treatment	Mean (SD)
Xeomin (n=50)	**0.98** (1.12)
Placebo (n=26)	**1.16** (1.18)

SD = standard deviation

Change from baseline to Week 6 [RMS deg]

Treatment	LS Mean 95% CI	LS Mean difference (Xeomin – Placebo) 95% CI	p-value
Xeomin (n=46)	**-0.25** [-0.53; 0.04]	**0.21** [-0.18; 0.61]	**0.282**
Placebo (n=26)	**-0.46** [-0.83; -0.09]	**Changes < 0 indicate improvement**	

Analysis of covariance adjusting for baseline value and study site;
LS = least squares, RMS = root mean squares, deg = degrees of arc

Key secondary endpoint: TETRAS Performance Dominant UL

Baseline value

Treatment	Mean (SD)
Xeomin (n=50)	**13.0 (2.95)**
Placebo (n=26)	**12.3 (2.06)**

SD = standard deviation

Change from baseline to Week 6

Treatment	LS Mean 95% CI	LS Mean difference (Xeomin – Placebo) 95% CI	p-value
Xeomin (n=50)	**-1.98** [-2.79; -1.18]	**-1.29** [-2.19; -0.39]	**0.006**
Placebo (n=26)	**-0.69** [-1.47; 0.09]	Changes < 0 indicate improvement	

Analysis of covariance adjusting for baseline value and study site;
LS = least squares

Xeomin statistically significantly better than placebo

Inco-BoNT for ET Trial: Limitations and Future Directions

- Kinematic device as primary endpoint
  - Complex device reliability in multicentered study; quality control
  - Correlation with clinical endpoints
  - Practicality in Phase 3 trials and post-marketing clinical use
- Challenging BoNT injection paradigm in ET
  - Variable skill of injectors
  - Choice of muscles, doses, needle localization technique
  - Impact of local muscle weakness on efficacy measures and ADL
- Ph 2 multicentered placebo-controlled study underway with Ona-BoNT-A (Botox)

Results From the ELATE Trial: A Phase 2b Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of OnabotulinumtoxinA for the Treatment of Upper Limb Essential Tremor

Atul Patel[1], Kate Patterson[2], Dhira Khosla[2], Ronald DeGryse[2], Norman Huang[2], Rozalina Dimitrova[2], Michael C. Munin[3], Peter McAllister[4], Christine A. Cooper[5], David M. Simpson[6], Stuart H. Isaacson[7], Rajesh Pahwa[8], Richard L. Barbano[9], Lynn James[2]

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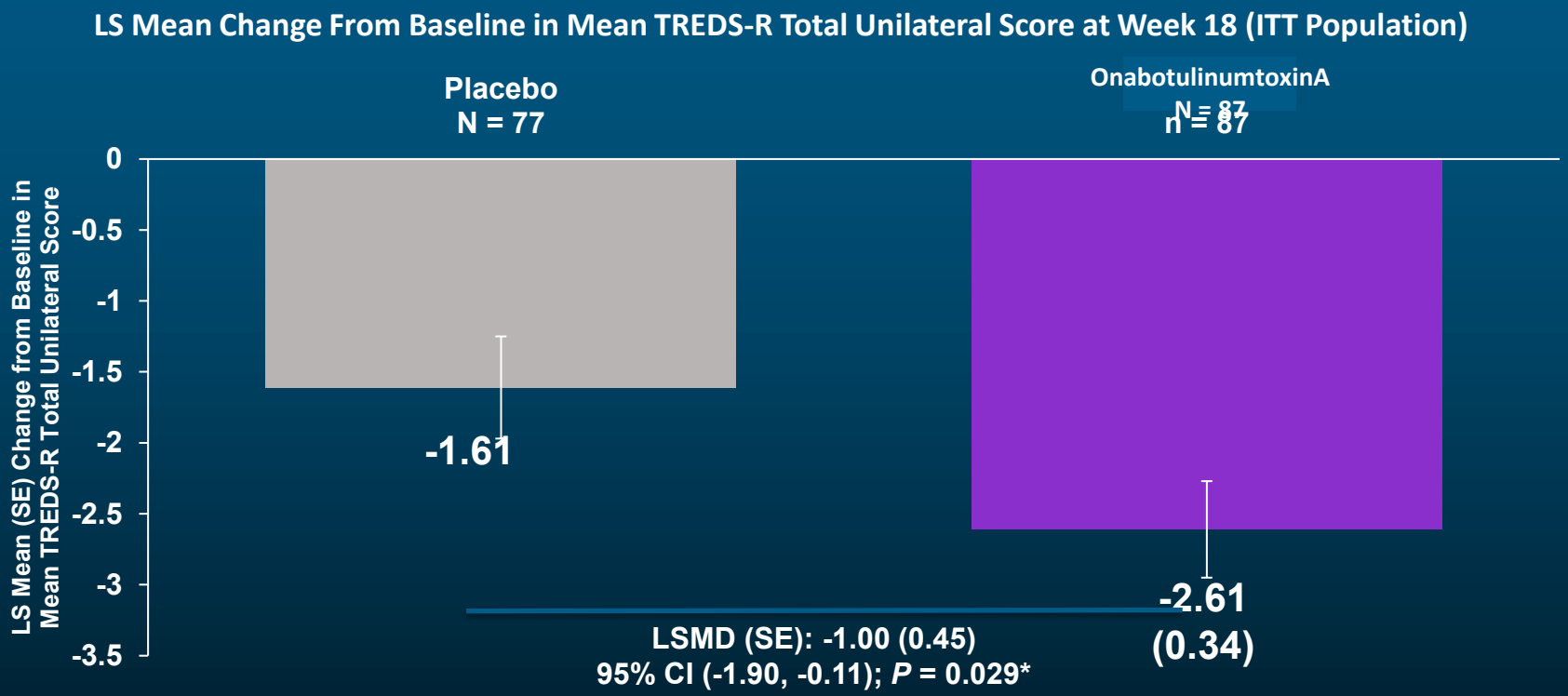
Presented at MDS 2025

Efficacy Outcomes

OnabotulinumtoxinA demonstrated statistical superiority compared with placebo on the primary and all secondary endpoints in the intent-to-treat (ITT) population

OnaBoNTA Demonstrated Significant Improvement in TREDS-R (Primary Endpoint)



The change from baseline was calculated from the average TREDS-R total unilateral score across Weeks 15, 18, 21. Between group differences were calculated for onabotA minus placebo with P-value and 95% CI obtained from a mixed-effects model repeated measures (MMRM) across double-blind treatment period adjusting for treatment, weeks, site, and treatment by week interaction as fixed effects, with baseline as covariate, and subject and residual errors as random effects.

CI, confidence interval; ITT, intent-to-treat; LS, least squares; LSMD; least squares mean difference; SD, standard deviation; SE, standard error; TREDS-R, Tremor Disability Scale-Revised.

*$P \leq 0.05$ significant.

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OnabotulinumtoxinA Demonstrated Significant Improvement in All Secondary Endpoints

Secondary Efficacy Endpoints assessed at week 18	*P*-value
Change from baseline in TETRAS ADL score across 5 unilateral items	0.001
Change from baseline in TETRAS Archimedes Spiral score	<0.001
Change from baseline in TETRAS Handwriting score	0.007
Change from baseline in Clinical Global Impression of Severity (CGI-S)	<0.001
Change from baseline in Patient Global Impression of Severity (PGI-S)	0.001
Change from baseline in TETRAS UL Score	<0.001

ADL, activities of daily living; TETRAS, TRG essential tremor rating assessment scale; TREDS-R, tremor disability scale-revised; TRG, Tremor Research Group; UL, upper limb.

Conclusions

OnabotulinumtoxinA demonstrated statistical superiority compared with placebo on primary and all secondary endpoints in the intent-to-treat (ITT) population

The overall safety results are consistent with the known safety profile of onabotulinumtoxinA

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