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INCOBOTULINUMTOXINA: A UNIQUE AND PURE FORMULATION OF BOTULINUM NEUROTOXIN TYPE A FOR USE IN AESTHETIC AND THERAPEUTIC MEDICINE

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Introduction: Since the first botulinum neurotoxin (BoNT) was approved for the treatment of blepharospasm, hemifacial spasm, and strabismus in 1989, the range of licensed indications and the number of commercially available BoNT products has increased. IncobotulinumtoxinA (Xeomin®) was first approved for the treatment of cervical dystonia and blepharospasm in 2005 and for aesthetic applications (moderate-to-severe glabellar lines) in 2009. IncobotulinumtoxinA remains the only approved BoNT formulation containing the pure toxin, free from complexing/unnecessary proteins. Here we discuss the precision manufacturing and purification process used for incobotulinumtoxinA and describe its clinical relevance.
Methods: Applying different chromatographic procedures, a well-designed manufacturing process provides a pure BoNT/A with no other bacterial protein components. Consequently, incobotulinumtoxinA is free of complexing/unnecessary proteins and represents the state of the art in toxin development. The purification process of incobotulinumtoxinA ensures that only the active compound, needed to achieve clinical benefit, is included in the formulation. IncobotulinumtoxinA is produced as a lyophilized product requiring no refrigeration.
Results: No treatment-naive subjects in incobotulinumtoxinA clinical studies have developed neutralizing antibodies or demonstrated a secondary lack of treatment response. To date, no case of antibody development has been reported when treatment started and continued with incobotulinumtoxinA. In the published literature, subjects who developed neutralizing antibodies and secondary lack of response when treated with incobotulinumtoxinA were invariably pretreated with another toxin formulation.
Conclusions: The unique purification of incobotulinumtoxinA represents state-of-the-art BoNT development to minimize the risk of neutralizing antibody formation, which may lead to decreased clinical response. Neurotoxin protein load and absence of complexing/unnecessary proteins should be considered as subjects begin neurotoxin treatment earlier in their lives; especially patients who may be treated for multiple conditions and with higher doses.
Keywords: Botulinum neurotoxin type A; Formulation; Immunogenicity; Manufacturing; Precision; Purity

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EFFICACY AND SAFETY OF ULTRASOUND-GUIDED ADMINISTRATION OF INCOBOTULINUMTOXINA IN SUBJECTS WITH EPICONDYLITIS

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Introduction: Reversible inhibition of muscle contraction by injection of botulinum neurotoxin (BoNT) could play a role in the treatment of long-standing epicondylitis lesions, where surgery is often the only solution. The efficacy and safety of incobotulinumtoxinA, a BoNT type A free from complexing proteins, was assessed in adult subjects with epicondylitis resistant to other treatments.
Methods: Subjects ≥18 years of age with epicondylitis resistant to other treatments (including analgesics such as anesthetic injections, anti-inflammatory drugs such as corticosteroids, and physiotherapy), baseline pain intensity >4 on a Visual Analogue Scale (VAS; 0 [best] to 10 [worst]), and baseline functional impairment >30 points on the QuickDASH scale (0 [best] to 100 [worst]) received ultrasound-guided incobotulinumtoxinA 10 to 30 U/muscle, injected into the extensor carpi ulnaris, extensor digiti minimi, extensor digitorum longus, and extensor carpi radialis brevis muscles. Pain intensity and upper-limb functionality were assessed at baseline, 1, 3, and 6 months posttreatment. Secondary analyses stratified the patient population by baseline VAS and sex. Adverse events (AEs) were reported.
Results: Twenty-four subjects (mean [standard deviation, SD] age: 46.8 [9] years; baseline VAS score: 6.85 [1.8]; baseline QuickDASH score: 60.1 [20.9]) were included. Mean VAS and QuickDASH scores were improved from baseline at all follow-up visits ($P<0.001$ and $P=0.001$, respectively; repeated-measures analysis of covariance). There were significant differences between baseline and the 1-, 3-, and 6-month follow-up visits in subjects with baseline VAS ≥6, and in both males and females (all $P<0.05$, Tukey post hoc test). Third-finger weakness was the only AE reported (87.5% [21/24 subjects]), a known side effect of BoNT.
Conclusions: Ultrasound-guided incobotulinumtoxinA injections may be an effective treatment for epicondylitis in an appropriate subject population.
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Keywords: Botulinum neurotoxin A; IncobotulinumtoxinA; Lateral epicondylitis; Pain; Rehabilitation; Tennis elbow

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EFFECT OF CHEMODENERVATION AND SERIAL CASTING ON GAIT PARAMETERS IN ACQUIRED BRAIN INJURY PATIENTS WITH UPPER EXTREMITY SPASTICITY

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Introduction: A case series study was conducted to prospectively investigate the changes in temporospatial and kinematic gait parameters in acquired brain injury (ABI) patients treated for upper limb flexor pattern spasticity with botulinum toxin A injection, and adjunctive therapy involving stretching and casting. This study is intended to guide future research.
Methods: Once selected, patients were treated with ultrasound-guided incobotulinumtoxinA injection to the brachialis (100 units) and brachioradialis (75 units) muscles. Two weeks following injection, patients received a single upper-extremity stretching cast for a duration of 7 days. Outcome measures consisted of: Modified Ashworth Scale (MAS), Tardieu Spasticity Angle (TSA), maximum elbow extension range of motion (ROM), 2-minute walk test (2MWT), Edinburgh gait score (EGS), and a calculation of step length symmetry. Outcomes were selected to show the changes in functional gait parameters and how they compare to upper extremity spasticity attributes.
Results: Clinically important improvements of up to 9 points were noted in EGS results. Step length symmetry was also shown to normalize by greater than 5%, along with improvements in 2MWT results. These improvements corresponded with improvements in TSA results pre- and post-casting.

Conclusions: Combined intervention of toxin injection and stretching and casting to the upper extremity has been shown to effect improvements on functional gait parameters of ABI patients with spasticity.

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5-YEAR FOLLOW-UP AFTER FIRST BOTULINUM TOXIN TYPE A INJECTION IN REAL-LIFE POSTSTROKE SPASTICITY: A SINGLE-CENTER EXPERIENCE IN BARCELONA

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Introduction: Variability in botulinum toxin A (BoNT-A) injection practice is a common issue, and real-life practice data are scarce in the literature. In order to investigate practical clinical experience, we describe local practices at a public health clinic in Spain where poststroke spasticity patients were treated at least once with botulinum toxin type A.
Methods: This was a retrospective study of poststroke patients in a spasticity unit who started BoNT-A treatment during the years 2008 to 2011. Patients were included if 5-year follow-up data after first BoNT-A injection were available. Basic demographic data, treatment dynamics, and BoNT-A usage are reported.
Results: The study population comprised 43 patients (21 male, 22 female) ages 65.81±12.34 years (mRankin scale: 1[0], 2 [6], 3 [9], 4 [27], 5[1]). At 5-year follow-up, 22 patients were still receiving active treatment, whereas 21 patients were inactive (11 patients had died; 1 rejected treatment; 4 were lost to follow-up; in 3 cases, the physician considered continuation of BoNT-A to be unnecessary; and 2 patients had moved to another city). Of the 43 patients in the study, 36 (83.7%) had received a second BoNT-A treatment, with the mean time-to-second treatment being 198±82.9 days. The number of injection sessions per patient averaged 5.95±3.34 (range, 1 to 12 sessions). The average number of vials used per patient in 5 years was 18.72±13.73. The total amount of BoNT-A administered in this population over 5 years was as follows: onabotulinumtoxinA (Botox®), 55,505 U; incobotulinumtoxinA (Xeomin®), 20,840 U; and abobotulinumtoxinA (Dysport®), 10,100 U. The number of injection sessions for the active patients was statistically significant ($P>0.001$, student t test). The mean interval between injections was 208.7±96.1 days. The mean interval between the last injection and death was 519.6±508.8 days ($P=0.008$ using the Mann-Whitney test).
Conclusions: In our study, a high percentage of retreatment with BoNT-A was common in patients with poststroke spasticity. About a quarter of patients died during follow-up. No death could be directly attributed to botulinum toxin injection, attesting to a temporal plausibility. The study identified 2 subgroups of BoNT-A users: short-term users, defined by a smaller number of sessions; and long-term users, who received injections on a more regular basis. The long intervals between the last BoNT-A injection and death in our series suggests either that BoNT-A injection is not a priority in poststroke spasticity as patients enter the last period of life or that social or contextual factors preclude continuing injections.

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BREAKING A DOGMA: HIGH DOSES OF INCOBOTULINUMTOXINA TO TREAT SEVERE LIMB SPASTICITY WITH COMPLEX CLINICAL PATTERNS: A RETROSPECTIVE, MULTICENTER STUDY

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Introduction: Botulinum neurotoxin (BoNT) is the treatment of choice in patients with severe spasticity. The use of dosing schedules is controversial; therefore, the management of treatment is often operator-dependent. Recently, the TOWER study (*Neurology*. 2017) demonstrated the safety and efficacy of incobotulinumtoxinA (Xeomin®) doses up to 800 U. The aim of this study was to ascertain whether there is any evidence of recurring dosage schemes and how they relate to current recommendations.
Methods: This is a retrospective study concerning BoNT therapy administration over the past 3 years in 4 centers in the south of Italy. We collected data on patients with severe upper- and/or lower-limb spasticity due to encephalic or medullary lesions who regularly receive incobotulinumtoxinA at intervals of ~3 months.
Results: Seventy-four patients (31 females) were included in this study, with a mean age of 50±18 years (range, 3 to 85 years). A total of 364 injections was analyzed, with an average of 5 sessions/patient. Dosage schemes (mean±standard deviation [SD] units/visit) in adults were: total body (n=342), 323±131 (from 80 to 830); upper limb (n=261), 274±114 (from 65 to 780); lower limb (n=217), 179±106 (from 50 to 550). Dosage schemes in pediatric patients were: total body (n=22), 144±85 (from 65 to 290); upper limb (n=17), 25±11 (from 15 to 40); lower limb (n=22), 125±78 (from 50 to 260). Sites from 5 to 7 and from 2 to 5 in the upper and lower limb, respectively, were simultaneously treated in at least 50% of patients during the same visit.
Conclusions: Our findings show that incobotulinumtoxinA is regularly used at high dosages both at a focal and, above all, a global level, which reflects the complexity of clinical patterns. Indeed, the safety and efficacy of this innovative approach allows patients with severe limb spasticity to be injected in more muscle sites at the same visit than is routinely recommended.
Keywords: IncobotulinumtoxinA; Multicenter; Scheduling: Spasticity
Reference

Wissel J, Ferreira JJ, Molteni F, et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity. *Neurology*. 2017;88(14):1321-1328.

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SYNAPTIC REMODELING OF HUMAN ORBICULARIS OCULI MUSCLES FROM PATIENTS TREATED WITH BOTULINUM TOXIN TYPE A

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Botulinum neurotoxin type-A (BoNT/A) is the most common medical treatment for blepharospasm. The mode of action of BoNT/A involves several well characterized steps and neurotoxin domains, contributing to the paralysis of the skeletal neuromuscular junction (NMJ) through the specific block of acetylcholine (ACh) release from motor nerve terminals. In blepharospasm, periodic BoNT/A administration every two to three months is necessary to maintain a satisfactory, spasm-free state. The ability of intramuscular axons and nerve terminals to sprout new processes and form additional synapses in response to muscle inactivity induced by BoNT/A constitutes a remarkable example of synaptic plasticity in adult animals and humans.
In the present work we have analyzed upper orbicularis oculi muscles from 12 patients undergoing surgical myectomy for essential blepharospasm. These patients had been previously injected, for varying times, with two commercially available BoNT/A products (Dysport® [abobotulinumtoxinA], Ipsen, and Xeomin® [incobotulinumtoxinA], Merz), and the last injection ranged from 4 days to 3 months before myectomy. Control orbicularis oculi muscles were obtained from patients undergoing functional surgery who had never been exposed to BoNT/A. The immunostaining with both β-III