Botulinum neurotoxin A preparations side-by-side comparison

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Executive Summary

- In the United States, there are 4 BoNT-A products approved for non-cosmetic indications: aboBoNT-A (Dysport), daxiBoNT-A (Daxxify), incoBoNT-A (Xeomin), and onaBoNT-A (Botox).
- All BoNT-A products contain the same core 150-kDa neurotoxin but differ in the presence and composition of non-toxic accessory proteins (NAPs). AboBoNT-A and onaBoNT-A contain NAPs while incoBoNT-A and daxiBoNT-A do not. To account for the presence of inactive proteins, the potency of BoNT-A products is expressed in mouse units. One mouse unit corresponds to the calculated intraperitoneal medial lethal dose (LD_{50}) of reconstituted products in a biological mouse model. Due to differences in assays among manufacturers and the effect of exogenous factors on LD_{50} assay, BoNT-A preparations are not interchangeable on a unit-to-unit basis.
- Excipients also differ among the products. AboBoNT-A, incoBoNT-A, and onaBoNT-A contain human serum albumin for a stabilizer. In lieu of albumin, daxiBoNT-A contains a synthetic, proprietary stabilizing protein (RTP004) and polysorbate 20. Evidence from animal studies suggest that RTP004 may enhance binding of daxiBoNT-A to the nerve terminal, which in turn may enhance localization and facilitate increased internalization of the botulinum toxin.
- Despite differences in FDA-approved indications, it is assumed that BoNT-A products are therapeutically interchangeable because the pharmacological effect of the botulinum toxin class is mediated through the shared 150-kD neurotoxin. Evidence suggests dose conversion ratios are indication independent and at the appropriate dose conversion ratio, size and duration of effect and adverse event profile are similar among products.
- Results from multiple level 1 head-to-head studies suggest that incoBoNT-A is as effective as onaBoNT-A and has a comparable adverse event profile at a dose conversion ratio of 1:1.
- The optimal dose conversion ratio between aboBoNT-A and onaBoNT-A is uncertain because of the limited number of robust head-to-head comparisons. Collectively, results from preclinical and clinical studies suggest that at dose conversion ratios of ≤ 3:1, the effects of aboBoNT-A and onaBoNT-A are more comparable than the effects at higher conversion ratios.
- Due to limited comparative evidence, the optimal dose conversion ratio between daxiBoNT-A and onaBoNT-A is unknown. Evidence from a head-to-head trial and multiple single-arm trials suggests that daxiBoNT-A has an extended duration of action compared with onaBoNT-A. Additional comparative evidence in non-cosmetic indications is necessary to confirm that daxiBoNT-A has an extended duration of action when given at equipotent doses.
- All BoNT-A products may cause an effect at distant sites due to toxin diffusion from the site of injection. Multiple studies suggest that the key determinants of toxin diffusion are dose and volume and not molecular weight. When given at equipotent doses, there is little evidence to suggest that there are differences in toxin spread among aboBoNT-A, incoBoNT-A, and onaBoNT-A. While animal data suggests that daxiBoNT-A diffuses less, this needs to be confirmed in head-to-head studies.
- As with other biologically derived products, immunogenicity and the associated potential for antibody-induced treatment failure is a concern with BoNT-A products. The contribution of product characteristics (vs. patient or disease characteristics) to the development of immunogenicity is unknown because too few trials have prospectively evaluated rates of comparative immunogenicity. Immunogenicity may be lower with incoBoNT-A compared with other BoNT-A products; however, the potential for residual confounding in retrospective analyses creates uncertainty. Whether or not results can be extrapolated to other BoNT-A products without NAPs (eg, daxiBoNT-A) is unknown.

Botulinum neurotoxin A preparations side-by-side comparison[a]

	Generic name (brand name)			
	AbobotulinumtoxinA (Dysport) AboBoNT-A	**DaxibotulinumtoxinA (Daxxify) DaxiBoNT-A**	**IncobotulinumtoxinA (Xeomin) IncoBoNT-A**	**OnabotulinumtoxinA (Botox) OnaBoNT-A**
Manufacturer	Ipsen	Revance	Merz	Allergan
Approval date	2009	2022	2010	1989
Cosmetic and non-cosmetic indications (unless otherwise indicated, approval is in adults)				
Cosmetic indications	● (Glabellar lines < 65 y)	● (Glabellar lines)	● (Glabellar lines)	● (Glabellar, lateral canthal, forehead)
Blepharospasm			●	●
Cervical dystonia	●	●	●	●
Chronic migraine, prophylaxis				●
Detrusor overactivity, neurogenic				● (pediatrics ≥ 5 y, adults)
Hyperhidrosis, axillary				●
Overactive bladder				●
Sialorrhea, chronic			● (pediatrics ≥ 2 y, adults)	
Spasticity, lower limb	● (pediatrics ≥ 2 y, adults)			● (pediatrics ≥ 2 y, adults)
Spasticity, upper limb	● (pediatrics ≥ 2 y, adults)	Phase 2 (JUNIPER trial)	● (pediatrics ≥ 2 y excluding CP, adults)	● (pediatrics ≥ 2 y, adults)
Strabismus				● (pediatrics ≥ 12 y)

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Dosage				
Blepharospasm	Na	Na	Recommended initial dose is 50 units (25 units per eye). Do not exceed 50 units per eye	1.25-2.5 units into each of 3 sites per affected eye
Cervical dystonia	• Initial dose is 500 units given as a divided dose among affected muscles. • May re-treat at doses between 250-1,000 units every 12-16 wks or longer based on return of clinical symptoms. • Titrate in 250-unit steps according to patient response.	Recommended dose is 125 units to 250 units given intramuscularly as a divided dose among affected muscles.	Recommended initial dose is 120 units per treatment session	• Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients. • In most cases, do not exceed 50 units/site.
Chronic migraine, prophylaxis	Na	Na	Na	Recommended total dose is 155 units, given as 5-unit (0.1 mL) injections per each site divided across 7 head/neck muscles.
Detrusor overactivity, neurogenic	Na	Na	Na	Pediatrics • 0.5 mL injections across 20 sites into the detrusor. • ≥ 34 kg: Recommended total dose is 200 units. • < 34 kg: Recommended total dose is 6 units/kg. Adults • Recommended total dose is 200 units, given as 1 mL (≅ 6.7 units) injections across 30 sites into the detrusor.
Glabellar lines	50 units per treatment session, divided into 5 equal IM injections.	8 units into each of 5 sites, for a total dose of 40 units.	20 units per treatment session, divided into 5 equal IM injections (2 injections in each corrugator muscle and 1 injection in the procerus muscle).	20 units per treatment session, divided into 5 equal IM injections.

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Hyperhidrosis, axillary	Na	Na	Na	50 units per axilla
Overactive bladder	Na	Na	Na	Recommended total dose is 100 units, given as 0.5 mL (5 units) injections across 20 sites into the detrusor.
Sialorrhea, chronic	Na	Na	Pediatrics • The recommended dose is based on body weight administered in a 3:2 dose ratio into the parotid and submandibular glands, no sooner than every 16 wks; ultrasound guidance recommended. Adults • The recommended dose is 100 units per treatment session consisting of 30 units per parotid gland and 20 units per submandibular gland, no sooner than every 16 wks.	Na
Spasticity, lower limb	Pediatrics • Recommended dose is 10-15 units/kg per limb. The total dose administered per treatment session must not exceed 15 units/kg for unilateral limb injections, 30 units/kg for bilateral injections, or 1,000 units, whichever is lower. Adults • Recommended total dose is up to 1500 units. The total dose per treatment session (upper and lower limb) is 1,500 units.	Na	Na	Pediatrics • Recommended total dose is 4-8 units/kg (maximum 300 units) divided among affected muscles. Adults • Recommended total dose is 300-400 units divided across ankle and toe muscles.

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Spasticity, upper limb	Pediatrics • Recommended dose is 8-16 units/kg per limb. The total dose administered per treatment session must not exceed 16 units/kg or 640 units, whichever is lower. Adults • Recommended total dose is between 500-1,000 units. The total dose per treatment session (upper and lower limb) is 1,500 units.	Na	Pediatrics (excluding CP) • Recommended total dose is 8 units/kg (maximum 200 units) per single upper limb or 16 units/kg (maximum 400 units) in both upper limbs, divided among affected muscles. Adults • Recommended total dose is up to 400 units, divided among affected muscles.	Pediatrics • Recommended total dose is 3-6 units/kg (maximum 200 units) divided among affected muscles. Adults • Recommended total dose is up to 400 units divided among affected muscles.
Strabismus	Na	Na	Na	Dose is based on prism diopter correction or previous response to treatment with onaBoNT-A.
Route	IM	IM	IM or intraglandular	IM, intradetrusor, intradermal
Reconstitution	Yes: preservative-free 0.9% sodium chloride injection	Yes: preservative-free 0.9% sodium chloride injection	Yes: preservative-free 0.9% sodium chloride injection	Yes: preservative-free 0.9% sodium chloride injection
Stability after reconstitution	24 h under refrigeration	72 h under refrigeration	24 h under refrigeration	24 h under refrigeration
Dosage forms and availability				
Single-dose vial	Lyophilized powder	Lyophilized powder	Lyophilized powder	Vacuum-dried powder
Contraindications	• Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation. • Infection at the proposed injection site.			
	Hypersensitivity to cow's milk protein.	Na	Na	For intradetrusor injections: UTI or urinary retention.
Boxed warning	**Distant spread of toxin effect**: Botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These effects have been reported from hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and have resulted in death.			

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Warnings/precautions	• Botulinum toxin preparations are not interchangeable. Units of biological activity of one botulinum toxin preparation cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method. • Serious hypersensitivity reactions that may include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea have been reported. • Botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. • The recommended dose and frequency of administration should not be exceeded. • Concomitant neuromuscular disorder(s) may exacerbate clinical effects of treatment.			
	• Product contains albumin and therefore may carry an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease. • The possibility of an immune reaction when injected intradermally is unknown. • Dry eye may occur with glabellar line treatment; if symptoms persist, consider referring patient to an ophthalmologist.	Reduced blinking from injection of botulinum toxin products in the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. To decrease the risk of ectropion, toxin should not be injected into the medial lower eyelid area.		
		• Use caution when administering to patients with pre-existing cardiovascular disease.	• Product contains albumin and therefore may carry an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease.	• Product contains albumin and therefore may carry an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease. • Retrobulbar hemorrhage and compromised retinal circulation may occur with botulinum toxin treatment of strabismus. • Bronchitis and URTI have been reported in patients treated for upper limb spasticity. • Autonomic dysreflexia in patients treated for detrusor overactivity has been reported and requires prompt medical therapy. • May increase the incidence of UTI and the risk-benefit of

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				using in patients with multiple UTIs should be assessed. • Due to the risk of urinary retention in adults treated for bladder dysfunction, only treat patients who are willing and able to initiate catheterization posttreatment, if required, for urinary retention.
Adverse reactions	• Glabellar Lines (≥2%): nasopharyngitis, headache, injection site pain, injection site reaction, upper respiratory tract infection, eyelid edema, eyelid ptosis, sinusitis, nausea, and blood present in urine. • Cervical dystonia (≥5%): muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain and eye disorders. • Spasticity in adults (4-5%): Muscular weakness (upper, lower), falls (lower), pain in extremity (lower) • Spasticity in pediatrics (≥10%): URTI (upper), pharyngitis (upper), nasopharyngitis (lower), cough (lower), pyrexia (lower).	• Glabellar Lines: headache (6%), eyelid ptosis (2%), facial paresis (1%). • Cervical dystonia (≥5%): headache (9%), injection site pain (8%), injection site erythema (5%), muscular weakness (5%), and URTI (5%).	• Cervical dystonia (≥5%): dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain. • Chronic sialorrhea (adults, ≥4%): tooth extraction, dry mouth, diarrhea, and hypertension. (pediatrics, ≥1%): bronchitis, headache, and nausea/vomiting. • Spasticity in adults (≥2%): seizure, nasopharyngitis, dry mouth, and URTI. • Spasticity in pediatrics (≥3%): nasopharyngitis and bronchitis. • Blepharospasm (≥10%): eyelid ptosis, dry eye, visual impairment, and dry mouth.	Incidence ≥5% and >placebo (if applicable) • Cervical dystonia: dysphagia, URTI, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis. • OAB: UTI, dysuria, urinary retention • Detrusor overactivity (adults): UTI, urinary retention. (pediatrics): UTI, leukocyturia, bacteriuria. • Chronic migraine: neck pain, headache. • Spasticity in adults: pain in extremity. • Spasticity in pediatrics: URTI • Axillary hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome.
Drug interactions	Aminoglycosides or other agents interfering with neuromuscular transmission may potentiate effects; anticholinergic drugs may potentiate anticholinergic effects.			
Description and properties[b-d]				
Molecular weight, kDa	300-500	150	150	900

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Accessory proteins present	Yes	No	No	Yes
Excipients	HSA (125 mcg/vial), lactose (2.5 mg/vial)	PS20, sugar, buffer, excipient peptide (RTP004, Peptide Exchange Technology)	HSA (1000 mcg/vial), sucrose (4.7 mg/vial)	HSA (500 mcg per 100 units), sodium chloride
Total protein mass (including accessory proteins)	4.35 ng per 500 units	NR	0.44 ng per 100 units	5 ng per 100 units
Active neurotoxin protein mass	0.65 ng per 100 units	0.18 ng per 40 units	≅ 0.44 – 0.6 ng per 100 units	0.73 ng per 100 units
How supplied/storage handling				
SDV	Lyophilized powder: 300 units, 500 units	Lyophilized powder: 50 units, 100 units	Lyophilized powder: 50 units, 100 units, 200 units	Vacuum-dried powder: 50 units (Cosmetic), 100 units (Botox, Cosmetic), 200 units (Botox)
Storage (unopened vial)	2-8° C until expiration date on the vial	20-25° C or 2-8° C	≤ 25° C until the expiration date on the vial	2-8° C for up to 36 mos
Disease-Specific Guidelines [e,f]				
Blepharospasm (AAN 2016)	Weak evidence: may be considered as a treatment option (Level C)	Na	Moderate evidence: should be considered as a treatment option (Level B)	Moderate evidence: Should be considered as a treatment option (Level B)
	Clinical context: “All three type A toxins appear to have similar efficacy and can continue to be efficacious over long periods”			
Cervical Dystonia (AAN 2016)	Strong evidence: should be offered as a treatment option (Level A)	Na	Moderate evidence: should be considered as a treatment option (Level B)	Moderate evidence: should be considered as a treatment option (Level B)
	Clinical context: “Although evidence levels may differ across BoNT serotypes and brands, all formulations have regulatory approval and are commonly used. There is an extensive clinical history of onaBoNT-A and incoBoNT-A use, but the lack of additional Class I studies led to only a Level B recommendation.”			
Adult Spasticity, Upper Extremity (AAN 2016)	Strong evidence: should be offered as a treatment option (Level A)	Na	Strong evidence: should be offered as a treatment option (Level A)	Strong evidence: should be offered as a treatment option (Level A)

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Adult Spasticity, Lower Extremity (AAN 2016)	Strong evidence: should be offered as a treatment option (Level A)	Na	Insufficient evidence: to support or refute a benefit (Level U)	Strong evidence: should be offered as a treatment option (Level A)
	Clinical context: "Because of lack of comparative trials, there is insufficient evidence to indicate that any of the BoNT formulations is superior to the others."			
Pediatric Spasticity, CP (AAN 2010)[g]	Strong evidence: "for localized/segmental spasticity in the upper and lower extremities of children with CP that warrants treatment, BoNT-A should be offered as an effective and generally safe treatment (Level A). Different formulations are not bioequivalent and may have different therapeutic efficacy and safety profiles.			
Chronic Migraine (AAN 2016)	Na	Na	Na	Strong evidence: should be offered as a treatment option (Level A)
	Clinical context: "Although the reduction of headache days with onaBoNT-A was statistically superior to placebo in 2 Class I studies, the magnitude of the difference is small."			

Abbreviations: AAN = American Academy of Neurology; BoNT = botulinum toxins; CP = cerebral palsy; HSA = human serum albumin; kDa = kilodalton; IM = intramuscular; OAB = overactive bladder; PS = polysorbate; Na = non-applicable; NR = not reported; NAPs = nontoxic accessory proteins; SDV = single-dose vial; URTI = upper respiratory tract infection; UTI = urinary tract infection

Footnotes

[a] Includes only the BoNT-A preparations approved for or under evaluation for non-cosmetic indications. PrabotulinumtoxinA (Jeuveau) is only approved for cosmetic indications. The information in the table, unless otherwise noted is from the product labeling.

[b] Solish N, Carruthers J, Kaufman J, Rubio RG, Gross TM, Gallagher CJ. Overview of daxibotulinumtoxinA for injection: A novel formulation of botulinum toxin type A. *Drugs*. 2021;81(18):2091-2101.

[c] Carr WW, Jain N, Sublett JW. Immunogenicity of botulinum toxin formulations: Potential therapeutic implications. *Adv Ther.* 2021;38(10):5046-5064.

[d] Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. *J Neural Transm*. 2013;120(2):275-290.

[e] Simpson DM, Hallet M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818-1826.

[f] AAN guidelines – published in 2016 and reaffirmed in 2022 - do not discuss the use of the use of daxibotulinumtoxinA.

[g] Delgado MR, Hirtz D, Aisen M, et al for the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2010;74(4):336-343.

Overview

Introduction

Botulinum neurotoxins are derived from various strains of *Clostridium botulinum*.[1] There are 8 distinct serotypes (A-H) of botulinum neurotoxins that differ in clinical applicability.[1] When considering only serotype A, there are 3 botulinum neurotoxin type A (BoNT-A) products available in the United States for the treatment of non-cosmetic indications: abobotulinumtoxin A (Dysport, aboBoNT-A),[2] incobotulinumtoxin A (Xeomin, incoBoNT-A),[3] and onabotulinumtoxinA (Botox, onaBoNT-A).[4] A novel BoNT-A product, daxibotulinumtoxinA-lanm (Daxxify, daxiBoNT-A) was approved by the FDA in 2022 for the treatment of glabellar lines.[5] Ongoing studies are evaluating its use for non-cosmetic indications. BoNT-A is used to treat a variety of neurologic conditions. Expanded Food and Drug Administration (FDA)-labeled indications, mounting evidence for the efficacy of off-label indications, and cost differences have led to a renewed interest in the potential for therapeutic interchange among the 3 agents. Based on the available data, experts postulate that no differences in efficacy exist among products and any efficacy and safety differences observed in clinical trials are likely due to inappropriate dosing.[1,6,7] This summary provides an overview of conversion considerations, while Appendix A provides a comparative evidence summary of the 4 BoNT-A preparations for common uses. While use for migraine is the leading indication for onaBoNT-A use, comparative evidence and off-label studies are limited for the other BoNT-A products and this common use is not addressed.

Relative potency

In nature, botulinum neurotoxins are transcribed by bacteria as protein complexes that are comprised of a core neurotoxin (150 kD) that is complexed to nontoxic accessory proteins (NAPs).[1] The NAPs help stabilize and protect the core neurotoxin from changes in temperature, low pH, and enzymatic degradation. At physiologic pHs, the neurotoxin progenitor complex is cleaved, leaving the 150-kD neurotoxin,[1] which is the active moiety responsible for the pharmacological effect of botulinum neurotoxins, namely inhibition of acetylcholine release from the motor terminals.[1] All commercially available BoNT-A preparations contain the same 150-kD active neurotoxin, but differ in terms of the presence and composition of NAPs. Both aboBoNT-A and onaBoNT-A include NAPs, although the preparations differ in molecular weight and 3-dimensional structure because each contains a different complement of NAPs.[8] NAPs are removed during the manufacture of incoBoNT-A and daxiBoNT-A; therefore, the incoBoNT-A and daxiBoNT-A preparations are free of any accessory proteins and only contain the core neurotoxin.[8]

To account for the presence of inactive proteins, the potency of BoNT-A products is expressed in mouse units.[1] One unit of BoNT-A corresponds to the calculated intraperitoneal median lethal dose (LD_{50}) of reconstituted product in a biological mouse model.[9] Many factors affect the LD_{50} assay, including the type of assay, mouse strain, gender and age, route and volume of injection, time of examination post injection, and delivery vehicle or reconstitution buffer.[10] Because of the assay's sensitivity to exogenous factors, proprietary manufacturing methodologies, and the lack of bioassay standardization among manufacturers, a mouse unit of 1 BoNT-A preparation is not equivalent to a mouse unit of another preparation.[9] The FDA-approved prescribing information for all BoNT-A preparations warns that preparations are not interchangeable on a unit-to-unit basis.[2-5]

Although bioassays are proprietary, there are known differences between the bioassays used to quantify the potencies of aboBoNT-A and onaBoNT-A. One of these known differences is diluent selection. The assays for aboBoNT-A and onaBoNT-A use a phosphate buffer that contains gelatin and saline as the diluent, respectively.[1] An early experiment that evaluated the potencies of onaBoNT-A and aboBoNT-A using the opposite assay (eg, onaBoNT-A assay for aboBoNT-A potency determination and vice versa) suggested that the onaBoNT-A assay may be less sensitive than the aboBoNT-A assay.[11] In this experiment, 2 onaBoNT-A batches (labeled 100 LD_{50} units per vial) assayed by the aboBoNT-A method had potencies of 270 and 360 LD_{50} units per vial. Conversely, aboBoNT-A (labeled 500 LD_{50} units per vial) had a mean potency of 470 and 277 LD_{50} units per vial when assayed by the aboBoNT-A and onaBoNT-A methods, respectively.[11] Results of this experiment suggest that the relative potency of a unit of onaBoNT-A versus a unit of aboBoNT-A is in the range of 2 to 3.[6]

Similar experiments conducted with incoBoNT-A and onaBoNT-A suggest that a labeled unit of incoBoNT-A is roughly equivalent to a labeled unit of onaBoNT-A.[12,13] Results of a comparative study that used the incoBoNT-A assay to evaluate 5 lots of each toxin revealed no significant differences between labeled potencies.[12] Lots of incoBoNT-A ranged

in potency from 99 to 114.6 LD_{50} units per vial and lots of onaBoNT-A ranged in potency from 96.6 to 111.0 LD_{50} units per vial.[12] Conversely, results of a comparative study using the onaBoNT-A assay to determine potency demonstrated that the average potencies of 3 incoBoNT-A lots were significantly lower than the potency of the onaBoNT-A reference. In this study, the relative potency of a unit of incoBoNT-A versus a unit of onaBoNT-A ranged from 0.69 to 0.84.[13] The reasons for the disparate results between the studies are unclear but may be attributable to methodological differences between the LD_{50} assays.[12]

At the time of this review, no similar experiments have been published between daxiBoNT-A and other BoNT-A toxins.

Conversion considerations and dose equivalence

Although prescribing information warns that commercial BoNT-A preparations are not interchangeable on a unit-to-unit basis,[2-5] practitioners must establish approximate dose equivalence among BoNT-A preparations so that a switch among preparations can be made if necessary. While the 150-kDa neurotoxin that is common to all the products is responsible for the clinical effect, efficacy (effect size and duration of effect) is a function of the amount of the 150-kDa neurotoxin in the administered dose and likely is also a function of the efficiency of delivery of the 150-kDa neurotoxin to the nerve terminals. Formulation may affect the latter, but the effect has not been quantified; therefore, doses of BoNT-A products that contain an identical amount of the 150-kDa neurotoxin may or may not have the same effect size. Except for daxiBoNT-A, all BoNT-A products are formulated with human serum albumin (HSA), which functions as a stabilizer to limit the loss of activity through protein aggregation and protein adsorption. It is uncertain if differences in albumin concentration among the BoNT-A products are clinically meaningful. In lieu of albumin, daxiBoNT-A contains a synthetic, proprietary stabilizing protein (RTP004) and polysorbate 20. Animal studies suggest that RTP004 may enhance binding of daxiBoNT-A to the nerve terminal, which in turn may enhance localization and facilitate increased internalization of the botulinum toxin.[14]

IncoBoNT-A and onaBoNT-A dose equivalence

It is generally accepted that incoBoNT-A is as effective as onaBoNT-A and has a comparable adverse event profile and duration of effect when a clinical conversion ratio of 1:1 is employed.[1] Evidence to support this conversion is based on the results of pivotal registration trials conducted in patients treated for blepharospasm (BPS)[15] and cervical dystonia (CD).[16] In these trials, incoBoNT-A was noninferior to onaBoNT-A when incoBoNT-A was given at a fixed dose equal to the patient's previous stable dose of onaBoNT-A.[15,16] Results of clinical data are largely consistent with preclinical data.[12,13]

AboBoNT-A and onaBoNT-A dose equivalence

The conversion ratio between aboBoNT-A and onaBoNT-A is uncertain. Though aboBoNT-A and onaBoNT-A have been used clinically for more than a decade, no expert consensus has been reached on the conversion ratio between aboBoNT-A and onaBoNT-A.[1,6,7,17] In 1993, Brin and Blitzer suggested that 1 unit of onaBoNT-A was equivalent to approximately 4 to 5 units of aboBoNT-A based on anecdotal evidence and expert opinion.[18] Subsequently, several trials evaluated aboBoNT-A and onaBoNT-A at a fixed dose conversion ratio of 4:1 in various conditions.[19-23] In these studies, aboBoNT-A was often associated with higher efficacy, longer duration of action, and a higher frequency of adverse effects than onaBoNT-A, indicating that a ratio of 4:1 is not an equipotent ratio. Several studies have examined conversion ratios of aboBoNT-A to onaBoNT-A of ≤ 3:1; the results of most of these studies suggest that a conversion ratio of ≤ 3:1 is more appropriate than higher conversion ratios. However, in these studies, conversion ratios ranged from 1.7:1 to 3:1[24-28]; thus, their results offer no definitive conclusions on the optimal conversion ratio. More recent systematic reviews of the literature suggest that a conversion ratio of aboBoNT-A to onaBoNT-A between 2:1 and 3:1 is most appropriate.[1,7,9,17,29] Results from LD_{50} assay,[11] preclinical,[30] and healthy volunteer[31] studies support this more conservative dose conversion ratio.

DaxiBoNT-A and onaBoNT-A dose equivalence

To date, daxiBoNT-A has only been compared with onaBoNT-A for the treatment of glabellar lines in a phase 2, dose-ranging trial.[32] The trial was not designed a priori to draw inferential conclusions about comparative effectiveness between active treatments. Nevertheless, daxiBoNT-A at doses of 20 units, 40 units, and 60 units was compared to the approved onaBoNT-A dose of 20 units for treatment of glabellar lines and inferential statistics were performed with no adjustments for multiplicity. At the week 16 assessment point, the approved dose of daxiBoNT-A 40 units was statistically superior to onaBoNT-A 20 units for multiple investigator- and subject-assessed efficacy endpoints, respectively while daxiBoNT-A 20

units demonstrated an inconsistent trend of numerical superiority for the same endpoints. At the week 24 assessment point, a numerically greater proportion of patients treated with daxiBoNT-A 40 units experienced a 1- or 2-point improvement on the Investigator Global Assessment-Facial Wrinkle Severity scale (IGA-FWS) compared with onaBoNT-A 20 units, but for the same endpoints rated by the subject, no differences were noted. A similar discrepancy occurred between investigator and subject ratings for the percentage of patients rated as having none or mild glabellar lines at week 24. The median duration of response, defined as the duration of at least a 1-point improvement on the IGA-FWS, was similar between daxiBoNT-A 20 units and onaBoNT-A 20 units (20 and 18.8 weeks, respectively), but significantly longer with daxiBoNT-A 40 units (23.6 weeks; *P* = .03 for comparison). The only adverse event reported with greater frequency with daxiBoNT-A 40 units vs. onaBoNT-A 20 units was facial asymmetry. The occurrence of headache and eyelid ptosis was lower in daxiBoNT-A-treated subjects; however, only 1 case of eyelid ptosis was reported in the onaBoNT-A treatment group.

Investigators chose to compare 40 units of daxiBoNT-A to 20 units of onaBoNT-A because the doses contain a roughly comparable amount of the 150-kDa neurotoxin. However, investigators of an animal study that compared daxiBoNT-A to onaBoNT-A at a 1:1 ratio found no significant differences in peak paralytic effect between the toxins, suggesting that a conversion ratio of daxiBoNT-A to onaBoNT-A of 2:1 is not equipotent.[33] Study investigators suggest that the incremental effectiveness of daxiBoNT-A 40 units that was achieved in the glabellar line trial without an increase in diffusion-related safety issues is attributable to its unique formulation rather than dose non-equivalency. If this assertion is validated in additional studies, determination of a dose conversion ratio between daxiBoNT-A and other BoNT-A products will be challenging. It is generally assumed that at the correct dose conversion ratio, BoNT-A products have a similar effect size and duration of effect. Results from the dose-ranging trial in glabellar lines appear to demonstrate that daxiBoNT-A is associated with incremental benefits in effect size and duration of treatment effect compared with onaBoNT-A when given at doses containing a comparable quantity of the 150-kDa neurotoxin. Due to limited evidence, caution is warranted. The phase 2 trial was not designed to evaluate the comparative effectiveness between daxiBoNT-A and onaBoNT-A and the sample size was small with a substantial number of subjects excluded from the per-protocol analysis. Additionally, response rates in glabellar line trials may be affected by outcome definitions and instruments/methods used for outcome measurement. Additional comparative evidence in non-cosmetic indications is necessary to establish with higher certainty the appropriate dose conversion ratio between daxiBoNT-A and onaBoNT-A and to establish that daxiBoNT-A has an extended duration of action compared with onaBoNT-A when given at doses to achieve the same therapeutic effect.

Toxin spread

All BoNT-A products contain a boxed warning regarding the potential for toxin spread from the area of injection, which may produce untoward toxin effects that include life-threatening swallowing and breathing difficulties.[2-5] While life-threatening distant spread is uncommon, toxin spread to contiguous areas occurs more frequently. Practitioners generally accept that BoNT-A preparations diffuse to some extent after injection[34]; however, debate remains about whether commercial preparations of BoNT-A differ in their propensity to diffuse.

AboBoNT-A, incoBoNT-A, and onaBoNT-A

A persistent misconception in the literature is that the size of the toxin complex affects toxin diffusion and that higher weight complexes diffuse more slowly.[35,36] Results of clinical comparisons that show higher rates of diplopia, dysphagia, or ptosis with aboBoNT-A (500-900 kDa complex) compared with onaBoNT-A (900 kDa complex) perpetuate this misconception.[34,36] Animal and human studies that specifically evaluated the toxin spread of BoNT-A preparations did not demonstrate differences in the potential for toxin spread among the agents.[30,31,37,38] Results of these studies are not surprising, given that the neurotoxin core that is common to all BoNT-A commercial preparations dissociates from the toxin complex in less than 1 minute at physiologic pH values.[1] Rather, multiple studies suggest that the key determinants of diffusion are dose and volume. In healthy volunteers, diffusion zones increase linearly with increasing dose and injection volumes.[30,31] Injection depth/technique, target site, muscle hyperactivity, and post injection massage are all factors that may contribute to a lesser extent to the degree of toxin spread observed clinically.[1] As such, in comparative studies that demonstrated a higher incidence of toxin spread with aboBoNT-A versus onaBoNT-A, the cause was likely the use of an incorrect dose conversion rather than any true diffusion differences between preparations.

DaxiBoNT-A

It is theorized that daxiBoNT-A may diffuse to a lesser extent because of the novel RTP004 stabilizer. At physiological pH, RTP004 is positively charged and forms strong noncovalent, electrostatic bonds with the anionic surfaces of the core 150-kDa neurotoxin and with negatively charged extracellular surfaces such as neuronal cells. Enhanced binding of the RTP004-neurotoxin complex to nerve cells may reduce diffusion from the injection site and facilitate internalization of the neurotoxin. In turn, greater internalization of the neurotoxin into the neuron may be associated with gains in effect size and duration of effect vs. neurotoxins that do not form such a complex.[14] Results from a study performed in mice suggests that daxiBoNT-A and onaBoNT-A are equipotent at a 1:1 dose ratio based on the comparative peak paralytic effect at the target muscle, but are equipotent at a 2.5:1 dose ratio – coined a "diffusion dose ratio" - based on comparative paralytic effect on muscles adjacent to the target muscle. Not surprisingly, when dosed at a 2.5:1 dose ratio, daxiBoNT-A had a greater and more extended paralytic effect at the target muscle than onaBoNT-A.[33]

Preclinical results that suggest daxiBoNT-A diffuses less than onaBoNT-A have not been validated in human comparative studies. In the phase 2 dose-ranging trial that evaluated the effect of daxiBoNT-A for the treatment of glabellar lines, the occurrence of diffusion-related adverse events such as eyelid ptosis and facial asymmetry was low and not significantly different between daxiBoNT-A 40 units and onaBoNT-A 20 units (3 events vs. 1 event, respectively). Because "equipotent" doses of daxiBoNT-A and onaBoNT-A were not assessed, it is unknown if there is a difference in diffusion because dose and volume may influence the extent of diffusion.[32]

Data from phase 2[39] and phase 3[40] trials that have evaluated daxiBoNT-A for the treatment of CD suggest that daxiBoNT-A has an extended duration of effect and a lower occurrence of diffusion-related adverse events compared with other BoNT-A preparations, which investigators attribute to differences in diffusion characteristics among BoNT-A products. In the phase 2 dose-escalation trial in CD, the median duration of response of daxiBoNT-A (100 to 450 units) was 25.3 weeks (95% CI, 20.14 to 26.14 weeks).[39] Similarly, in the pivotal, single-dose phase 3 trial in CD, the median duration of response ranged from 20 weeks in the daxiBoNT-A 250-unit group up to 24 weeks in the daxiBoNT-A 125-unit group.[40] In comparison, results from clinical trials suggest a median duration of response of 13 weeks with incoBoNT-A[41] and 18.5 weeks with aboBoNT-A.[42] Of note, these observed differences are not based on data generated from head-to-head trials, but rather indirect comparisons across trials. Indirect comparisons have limitations; foremost is that duration of response is defined differently across BoNT-A trials with trial-specific criteria for retreatment. DaxiBoNT-A likely has an extended duration of action, but without head-to-head evidence, it is largely uncertain if there are meaningful gains in the duration of effect unless measured per a standardized definition.

Likewise, the occurrence of dysphagia, a diffusion-related adverse event commonly reported with botulinum toxin treatment for CD, was low in the phase 3 daxiBoNT-A trial with only 1.6% and 3.9% of participants reporting dysphagia in the 125-unit and 250-unit groups, respectively during the 36-week trial.[40,43] In the phase 2 dosing-ranging trial, 14% of subjects treated with 100 to 240 units of daxiBoNT-A reported dysphagia as an adverse event during the 20-week trial,[39] which aligns more closely to the 10.3% rate reported with incoBoNT-A[41] and the 16% rate reported with aboBoNT-A.[42] It is unclear if the low occurrence of dysphagia in the phase 3 trial was due to less diffusion, adverse event ascertainment, or an isolated result.

Immunogenicity

As with many other biologically-derived products, the potential exists for antibody production to lead to a decreased response to BoNT-A treatment over time.[1] There are numerous factors that contribute to immunogenicity, including: product-related factors (manufacturing processes, toxin source, inactive toxin, antigenic protein load, accessory proteins, and excipients) and treatment- and patient-related factors (duration of treatment, cumulative dose, previous exposure, reinjection interval, dystonic condition, and vaccinations).[8,44] All commercial preparations contain the same core neurotoxin, a 150-kDa protein. In addition, aboBoNT-A and onaBoNT-A contain NAPs, which are absent from incoBoNT-A and daxiBoNT-A. Neutralizing antibodies (NAbs; those that inhibit biological activity) develop against the neurotoxin core, while non-neutralizing antibodies (those that do not affect biological activity) may develop against NAPs.[15] The contributory role of NAPs to the immunogenicity of commercial preparations remains unclear and manufacturers of commercial preparations often attempt to influence the debate. One camp suggests that the antigenic protein load only consists of 150-kDa active neurotoxin core,[15] while the other camp suggests that NAPs can increase the antigenicity of

BoNT preparations.[45,46] Evidence to support the latter argument is based on the results of 2 preclinical studies, which demonstrated that NAPs behave as immunological adjuvants that increase the antigenicity of BoNT preparations.[47,48] Experts have raised questions about the validity of both studies' conclusions because some of the study methods may have contributed to the increased observation of immunogenicity.[8,49] Both studies used formaldehyde-treated proteins that are known to enhance immunogenicity; administered higher concentrations of botulinum neurotoxin at a greater frequency than occurs in clinical practice; and used BoNT-A preparations of unknown purity.[8]

In the prescribing information, rates of antibody development in pivotal trials for non-cosmetic indications range from 0% to 1.2% with onaBoNT-A, 0.2% to 3.6% with aboBoNT-A.[2,4] and 0.3% with incoBoNT-A.[3] Of note, most of these studies were of limited duration and may not represent the rate of antibody development with extended use. The immunogenicity of daxiBoNT-A is not fully established; immunogenicity has only been characterized in the cosmetic phase 3 clinical program for glabellar lines.[50] The glabellar line development program included 2 single-dose studies of 36 weeks duration and a multiple-dose study of 84 weeks duration. Overall, there was a low incidence of antibody formation; 21 (0.8%) subjects developed anti-daxiBoNT-A binding antibodies and 35 (1.3%) subjects developed anti-RTP004-binding antibodies. None of the antibodies were neutralizing and of the 19 subjects who were retested, 18 subjects tested negative for antibodies, suggesting that antibodies that develop are transitory. There was no evidence that antibody development impacted clinical response or duration of treatment effect.[50] Because lower doses are used for cosmetic indications, the low immunogenicity of daxiBoNT-A observed in cosmetic development program needs to be confirmed in studies evaluating higher doses that are commonly used for the treatment of non-cosmetic indications.

The scarcity of comparative immunogenicity literature adds to the lack of clarity about the contribution of product characteristics to the development of immunogenicity. Results of a single preclinical study in rabbits suggest that the incidence of NAbs is greatest with aboBoNT-A; however, this finding needs to be verified in human studies.[51] While many studies have evaluated the incidence of antibody formation in patient cohorts, it is inappropriate to estimate comparative immunogenicity from non-comparative literature because of potential differences in confounders that may influence NAb formation including assay sensitivities and variations in administered dose per session, inter-injection intervals, duration of treatment, dose per session, and clinical indication.[15] In a meta-analysis[52] combining studies with different methodologies and clinical populations, NAb development in BoNT-A treatment responders across all clinical indications did not significantly differ among BoNT-A preparations with frequencies of 1.5% (95% CI, 0.3 to 7.1%), 1.7% (95% CI, 0.4 to 7.4%), and 0.5% (95% CI, 0.1 to 2.5%) reported for onaBoNT-A, aboBoNT-A, and incoBoNT-A, respectively. Heterogeneity was considerable in the results for onaBoNT-A and aboBoNT-A, but not for incoBoNT-A. This may suggest that incoBoNT-A is associated with a consistently low degree of antigenicity across clinical indications, or it may be reflective of a shorter duration of use and fewer FDA-approved clinical indications. In secondary non-responders, NAb formation was high with a reported frequency of 56.7% (95% CI, 45.2 to 67.5%) and 32.5% (95% CI, 22.8 to 43.9%) with aboBoNT-A and onaBoNT-A, respectively. Heterogeneity was low. In a second, recently published meta-analysis[53] that excluded studies with the more antigenic onaBoNT-A preparation marketed prior to 1997, aboBoNT-A was associated with the highest frequency of NAb development at 7.4% (95% CI, 5.3 to 9.6%; I^2 = 97.24%) followed by incoBoNT-A (0.3%, I^2 = 0%) and onaBoNT-A (0.3%, I^2 = 53.47%). Once again, there was no heterogeneity in the results for incoBoNT-A.

Due to limitations noted with cross comparing immunogenicity rates from studies with different designs and clinical populations, a meta-analysis is limited in its ability to determine the comparability of immunogenicity profiles among the BoNT-A products. Results from 3 single-center, observational studies suggest that incoBoNT-A may be less antigenic than other preparations, but limitations of these studies need to be acknowledged. Two of the 3 studies were cross-sectional studies that measured the prevalence of NAbs at study entry by means of the mouse hemi-diaphragm assay (MHDA). The first study[54] examined patients who had been exclusively treated with incoBoNT-A or who had received 9 or fewer treatments with another BoNT-A preparation before switching to incoBoNT-A and who received at least 14 incoBoNT-A treatments after the switch. In the overall cohort, the average duration of incoBoNT-A treatment was 5.3 years. Two patients (both in the switch group) had a positive MHDA test for an overall NAb prevalence of 2.2% in the cohort and an estimated NAb incidence of 0.37% per year (assuming a constant rate of development over time). Both patients with a positive MHDA test had previously been treated with aboBoNT-A for CD. The study included patients who were treated for various clinical indications but did not account for potential differences in NAb development across indications nor did it evaluate the prevalence of NAbs with other BoNT-A preparations. The second cross-sectional study[55]

evaluated the prevalence of NAbs in treatment responders across 5 clinical indications and 3 BoNT-A preparations. The most common clinical indication for treatment was CD and the most common BoNT-A preparation was aboBoNT-A. In the interim analysis, NAb rates were similar between aboBoNT-A and onaBoNT-A at 6% and 7%, respectively, while patients who had switched between BoNT-A preparations had a NAb rate of 33%. No NAbs were observed in patients treated exclusively with incoBoNT-A; however, the duration of incoBoNT-A treatment was significantly shorter. When the aboBoNT-A and onaBoNT-A cohorts were censored to match the incoBoNT-A-licensed period, BoNT-A preparation become the main risk factor for NAb induction; however, in the uncensored cohort, BoNT-A preparation lost significance and life-time dose and dose per treatment session emerged as the primary risk factors. In the final analysis of this study,[56] none of the patients exclusively treated with incoBoNT-A (n = 70) had a positive MHDA test. In those treated with either aboBoNT-A or onaBoNT-A without a switch (n = 392), 5.9% had a positive MHDA test (6% if censored to match the licensed period for incoBoNT-A). Like the results of the interim analysis, 33% of patients initially treated with aboBoNT-A or onaBoNT-A and switched to another BoNT-A preparation (n = 183) had a positive MHDA test. This study was not randomized, and it is important to note that distribution of clinical indications (and doses) was slightly different between groups, which may have contributed to differences in NAb development. Additionally, it may not be appropriate to group aboBoNT-A and onaBoNT-A in the same cohort. The third study[57] retrospectively evaluated 471 patients for the presence of NAb-induced complete secondary treatment failure (cSTF) and risk factors for developing cSTF across 5 different clinical indications. In this study, none of the 49 patients treated exclusively with incoBoNT-A over a mean of 8.4 ± 4.2 years (range, 1-14 years) developed NAb-cSTF; however, 2 patients treated exclusively with incoBoNT-A had a transient positive MHDA test. Independent risk factors for development of NAb-cSTF were high BoNT-A dose per treatment, switching from onaBoNT-A to aboBoNT-A, and treatment of neck muscles.

Collectively, results from these studies along with evidence that shows that there is a reduction in NAb antibody titers when patients with NAb-induced partial secondary treatment failure with another BoNT-A preparation are switched to incoBoNT-A, provide a signal that immunogenicity may be lower with incoBoNT-A compared with other BoNT-A preparations. However, the potential for residual confounding in retrospective analyses continues to create uncertainty. Results need to be confirmed in prospective, multicenter studies with properly matched cohorts. In addition, as there is not always an absolute correlation between development of NAbs and treatment resistance, the clinical meaningfulness of studies that assess NAb prevalence over time without also evaluating treatment responsiveness is unclear. Whether or not results can be extrapolated to other BoNT-A formulations without complexing proteins is unknown.

Conclusion

The 4 BoNT-A preparations that are commercially available are not bioequivalent on a unit-to-unit basis. Preclinical and clinical data suggest that incoBoNT-A and onaBoNT-A demonstrate similar safety and efficacy at an approximate 1:1 ratio while the optimal dose conversion ratio of aboBoNT-A and onaBoNT-A or incoBoNT-A is unknown. Published evidence collectively demonstrates that at conversion ratios of 3:1 or less, the effects of aboBoNT-A and onaBoNT-A are more comparable than at higher ratios. Limited evidence precludes determining a conversion ratio between daxiBoNT-A and other BoNT-A products. Uncertainty exists about diffusion and immunogenicity differences among BoNT-A products.

Appendix A. Comparative evidence summary

In the following summary sections, onaBoNT-A is considered the standard of care and emphasis has been placed on the safety and efficacy data of aboBoNT-A and incoBoNT-A in select labeled and off-labeled indications. When available, results of proof-of-concept trials and comparative literature are presented. The sections do not attempt to determine place in therapy of BoNT-A, but rather the interchangeability among marketed products.

Blepharospasm

OnaBoNT-A and incoBoNT-A are FDA approved for the treatment of BPS.[3,4] While incoBoNT-A was originally approved for use in patients previously treated with onaBoNT-A for BPS, in 2019 the indication was expanded to include treatment of BPS in both previously treated and toxin-naïve patients.[3] AboBoNT-A, while approved for BPS in European countries, is not FDA approved for the treatment of BPS.

All 3 BoNT-A products are effective for treatment of BPS. In its 2016 practice guidelines (re-affirmed in April 2022), the American Academy of Neurology (AAN) suggests that any of the BoNT-A preparations can be considered a treatment option, with a higher level of recommendation given to onaBoNT-A and incoBoNT-A compared with aboBoNT-A due to the availability of more robust clinical trial data with the former.[59]

Presently, incoBoNT-A has been evaluated in 2 randomized, placebo-controlled, phase 3 trials. In the initial trial, a fixed dose of incoBoNT-A equal to the stable dose of previous onaBoNT-A therapy (up to a maximum of 50 units/eye), significantly improved symptom severity (assessed by the Jankovic Rating Scale [JRS]), significantly reduced functional impairment (assessed by the Blepharospasm Disability Index [BSDI]) and was associated with greater improvements in patient- and investigator-rated global assessments of response to therapy at 6 weeks versus placebo.[60] In toxin-naïve patients, a fixed dose of incoBoNT-A of 25 units/eye (total dose of 50 units) given at a flexible treatment interval significantly improved symptom severity (assessed by JRS) and numerically but not significantly reduced functional impairment (assessed by BSDI). The median duration of treatment effect was 20 weeks. During this trial, there was a more pronounced effect in the placebo group than in the previous trial, likely because patients had been treatment free for at least 12 months. The effect in the placebo group may have diminished the difference in effect size between active and placebo treatment groups and contributed to the non-significant difference for functional outcomes. Patients who experienced a waning of effect after the first injection were eligible to receive a second injection of incoBoNT-A during an open-label period in which both the dose and treatment interval were flexible. Of the 39 patients who received a second injection, 36 were given a dose of 25 units/eye and in those, the median treatment duration was 20 weeks.[61,62] Despite some limitations, it is notable that the level of evidence for incoBoNT-A is more robust than that for onaBoNT-A.

Similarly, in a phase 2 trial, a single fixed dose of 40, 80, or 120 units of aboBoNT-A per eye was associated with significant improvements in functional disability (assessed by the percentage of normal activity on the Blepharospasm Disability Scale [BDS]), frequency of involuntary movements (assessed using the Frequency of Involuntary Movement scale [FIM]), and severity of oculofacial spasms (assessed using the Severity Rating Scale [SRS]) at weeks 4, 8, and 12 compared with placebo. Doses of 80 and 120 units/eye maintained significant responses as measured by the BDS, FIM, and SRS compared with placebo through week 16, suggesting a dose-response relationship.[63]

Conversion considerations

There are several published comparisons of the BoNT-A products. Unfortunately, the rating scales used to assess symptom severity or functional disability in BPS are not sensitive enough to detect small differences between active treatments.[64] Thus, rating scales are inherently biased against detecting a difference in comparative trials and therefore uncertainty cannot be eliminated. Additionally, most comparator trials compare fixed doses of toxins, which makes it difficult to determine if potency differences exist.[64] For example, if a toxin has a dose ceiling at 1.25 units/site and the comparator toxin has a dose ceiling at 2.5 units/site, at an evaluated dose of 2.5 units/site, the toxins will be similarly effective despite a potency difference.

The noninferiority of incoBoNT-A compared with onaBoNT-A at a dose ratio of 1:1 was established in a single trial.[15] In this trial, the difference between BoNT-A products in the sum score of the JRS at 3 weeks post injection did not exceed

the a priori-defined noninferiority margin of 0.8. As stated earlier, the JRS is likely not sensitive enough to detect minor differences between products because it was originally developed to detect differences between active treatment and placebo.[64] Results of multiple secondary endpoint comparisons that included mean BSDI score, patients' evaluation of global response, investigators' assessment of efficacy, median latency, median duration of effect, and tolerability also did not differ significantly between treatment groups.[15] Results from a prospective, randomized, split-face comparison in patients with bilateral BPS previously controlled on a stable onaBoNT-A dosing regimen provide further evidence for comparative effectiveness between onaBoNT-A and incoBoNT-A at a dose conversion ratio of 1:1 unit.[65] An additional report from a single site experience suggests no loss of efficacy at 1:1 unit dose ratio, but a trend toward a greater duration of treatment effect with onaBoNT-A.[66]

A subsequent pilot trial that compared incoBoNT-A with onaBoNT-A at a dose ratio of 1:1 showed a consistent, nonsignificant trend toward greater improvement with onaBoNT-A at weeks 4 and 8 on both the BSDI and JRS. Despite numerical differences in these measures, there was no difference between groups in patient global assessment with both groups rating improvement as moderate for symptoms, but no change in function. This may have been due to small differences in baseline disease severity in an overall small population. More patients randomized to incoBoNT-A vs. those randomized to onaBoNT-A had a BSDI total score greater than 4 at baseline. In a post hoc analysis, a significantly higher percentage of patients treated with onaBoNT-A were considered responders based on a threshold of achieving a 4-point and 0.67 change in total BSDI score and BSDI mean item score, respectively, at week 4.[67] These results should be viewed as hypothesis generating because the pilot trial only enrolled 64 patients and the post hoc analysis was limited to 43 patients. While the conclusion of this real-world utilization study suggests that patients who switched from onaBoNT-A to incoBoNT-A required a higher dose, the requirement for higher doses was not validated by comparative efficacy assessments. Additionally, as a multinational study, the dosing differences were driven by a single site.[68]

Most trials that compared aboBoNT-A with onaBoNT-A for BPS treatment are low quality. Several retrospective trials in which a single patient switched between BoNT-A preparations for various reasons have attempted to determine a dose conversion ratio at which the BoNT-A products are similarly efficacious. Results of these trials are disparate, with dose ratios of aboBoNT-A to onaBoNT-A ranging from 3:1 to 5:1.[69-71] The different ratios likely resulted from imprecise efficacy measures (eg, latency and duration) or an absence of efficacy measures, the highly variable nature of BPS, dose creep that occurred as a function of time or disease progression, and limitations associated with retrospective data collection.

Several studies of BPS have compared aboBoNT-A with onaBoNT-A at a fixed dose ratio of 4:1.[19-21] All of these studies showed a statistically significant difference between the BoNT-A preparations in at least 1 outcome. In a crossover trial that evaluated a single switch from aboBoNT-A to onaBoNT-A, significant differences in favor of onaBoNT-A were reported for symptomology improvement as assessed by the JRS, duration of effect, and tolerability.[19] The washout period in this study was likely inadequate, which biased results in favor of onaBoNT-A. In the remaining 2 studies, the primary efficacy outcome—duration of effect—was not significantly different between the BoNT-A products at a 4:1 ratio.[20,21] However, in one of these trials aboBoNT-A was associated with a significantly higher incidence of adverse events,[21] and in the other trial, there was a nonsignificant trend toward an increased requirement for unscheduled boosters in the aboBoNT-A treatment group.[20]

Cervical dystonia

All BoNT-A preparations – aboBoNT-A, daxiBoNT-A, incoBoNT-A, and onaBoNT-A - are FDA approved for the treatment of CD[2-5] due to their demonstrated safety and efficacy in placebo-controlled trials.[59] Botulinum toxin is accepted as a first-line treatment option for CD, and the AAN recommends that aboBoNT-A should be offered for treatment (Level A recommendation); in addition, onaBoNT-A and incoBoNT-A should also be considered options for treatment (Level B recommendation).[59] The difference in evidence level is due to fewer Class I studies of onaBoNT-A and incoBoNT-A. The AAN also states that aboBoNT-A and onaBoNT-A are probably equivalent in terms of CD treatment.[59]

The noninferiority of incoBoNT-A compared with onaBoNT-A at a dose ratio of 1:1 unit was established in a comparative trial that investigated 463 patients with the predominantly rotational form of CD.[16] All enrolled patients had a stable therapeutic response to onaBoNT-A therapy and the mean study doses of incoBoNT-A (140.4 ± 51.4 units) and onaBoNT-A (138.9 ± 46.8 units) were based on the dosages of onaBoNT-A received by participants in 2 consecutive visits that occurred prior to the start of the study. The primary endpoint—the change from baseline in Toronto Western

Spasmodic Torticollis Rating Scale (TWSTRS) severity score (range, 0-35) at 28 ± 7 days post injection—was 6.6 and 6.4 points in the incoBoNT-A and onaBoNT-A groups, respectively. The upper limit of the 95% CI for the difference between groups did not exceed the a priori-defined noninferiority margin of 1.3 (data not provided). The mean onset of effect (7.3 ± 4.3 vs. 7.2 ± 4.1 days), waning of effect (9.9 ± 3.8 vs. 10.0 ± 3.9 weeks), and duration of effect (95.9 ± 30 vs. 94.3 ± 31.4 days) did not differ significantly between incoBoNT-A and onaBoNT-A, respectively. Dysphagia was the most reported adverse event, with a frequency of 10.8% and 8.2% in the incoBoNT-A and onaBoNT-A groups, respectively.[16] The therapeutic equivalency between onaBoNT-A and incoBoNT-A was further documented in a single-center, cross-over trial that observed 40 patients with CD over a mean of 7 years who were transitioned from onaBoNT-A to incoBoNT-A at a 1:1 unit dose conversion.[72] In this trial, patients were treated with onaBoNT-A for a mean of 18.4 ± 12.4 treatment cycles and incoBoNT-A for a mean of 9.2 ± 4.5 treatment cycles. Differences between BoNT-A toxins for mean treatment duration and injection interval were within the pre-defined equivalence margin of ± 1.5 weeks. The mean treatment durations for onaBoNT-A and incoBoNT-A were 11.2 ± 1.1 weeks and 11.4 ± 1.3 weeks, respectively (difference: 0.3 weeks; 95% CI, -0.3 to 0.9) while the mean injection intervals were 14.7 ± 1.6 weeks and 15.0 ± 2.2 weeks, respectively (difference: 0.5 weeks; 95% CI, -0.4 to 1.4). Note, treatment response was assumed to be consistent across treatment periods with changes in treatment duration a signal for potential differences in efficacy.

There are 4 prospective comparisons of onaBoNT-A and aboBoNT-A.[22,24,26,73] Three of the 4 comparisons used a randomized, double-blind, crossover design due to the individual variability of CD. In each of these comparisons, the BoNT-A dose was determined on a per patient basis and onaBoNT-A and aboBoNT-A were given at a fixed dose ratio that corresponded to the determined dose.[22,24,73] In 2 of the comparisons, patients participated in 3 treatment periods.[22,24] In the first comparison, each patient (n = 54) received onaBoNT-A at the patient's usual effective dose, aboBoNT-A at 3 times the dose of onaBoNT-A (3:1 fixed dose ratio), and aboBoNT-A at 4 times the onaBoNT-A dose (4:1 fixed dose ratio). Injection volume and protocol were consistent among the treatment periods. Pooled results from the three 16-week treatment periods demonstrated a mean improvement in Tsui score at 4 weeks of 3.22 for onaBoNT-A, 4.32 for aboBoNT-A given at 3 times the dose, and 4.89 for aboBoNT-A given at 4 times the dose. Both doses of aboBoNT-A were statistically superior to onaBoNT-A. The secondary endpoint—reduction in TWSTRS pain score—was also significantly in favor of aboBoNT-A at both dose ratios. Compared with onaBoNT-A, duration of effect was numerically greater with the 3:1 aboBoNT-A dose and statistically greater with the 4:1 aboBoNT-A dose. The incidence of dysphagia was also significantly greater with both aboBoNT-A dose ratios.[26]

The second comparison had 3 treatment periods that evaluated an individualized dose of aboBoNT-A, onaBoNT-A at 33% of the individualized dose of aboBoNT-A (3:1 ratio), and onaBoNT-A at 59% of the individualized dose of aboBoNT-A (1.7:1 ratio). Dilution was consistent among treatment periods. The primary endpoint— reduction in total TWSTRS pain score from baseline to week 4 in the pooled 3:1 aboBoNT-A to onaBoNT-A comparison—favored aboBoNT-A, but the difference between groups was not significant. Additionally, the difference in the 4-week TWSTRS total pain score in the pooled 1.7:1 aboBoNT-A to onaBoNT-A comparison was not significant.[24] Conclusions drawn from the results of this comparison are limited because the study was underpowered, and a carryover effect was likely due to 12-week treatment periods.

The final crossover trial evaluated the noninferiority of aboBoNT-A compared with onaBoNT-A at a fixed dose ratio of 2.5:1 in 94 patients during separate 16-week treatment periods.[73] Although a noninferiority margin of 1.5 was selected for the upper limit of the one-sided 95% CI, the investigators did not consider the noninferiority margin in the interpretation of results. The mean change from baseline in Tsui score at 4 weeks was 4.8 ± 4.1 units and 4 ± 3.9 units for onaBoNT-A and aboBoNT-A, respectively (95% CI for mean change of -0.1-1.7) While the upper limit exceeded the noninferiority margin, the investigators stated that the difference between groups did not reach statistical significance. Toxin preparation preference did not differ, with 36, 34, and 22 patients stating preference for aboBoNT-A, onaBoNT-A, and neither, respectively. A similar incidence of adverse events occurred with both formulations.[73]

A randomized, parallel comparison of aboBoNT-A and onaBoNT-A in 73 patients with rotational CD demonstrated no statistical or clinically meaningful differences between aboBoNT-A and onaBoNT-A at a fixed dose ratio of 3:1 for the following outcomes: adjusted posttreatment Tsui scores (4.8 vs. 5.0, respectively); mean time to re-treatment (84 days vs. 81 days, respectively); investigator-rated global efficacy (76.3% vs. 65.7%, respectively); and adverse events (58% vs. 69%, respectively).[22]

Studies suggest that at a dose conversion ratio of 1:1, incoBoNT-A to onaBoNT-A is comparatively effective for treatment effect and duration. While all comparative studies of aboBoNT-A and onaBoNT-A are flawed, collective results suggest that the conversion ratio of aboBoNT-A to onaBoNT-A is 3:1 or less.

At present, the conversion ratio between daxiBoNT-A and other BoNT-A preparations is unknown. The phase 3 development program for daxiBoNT-A in CD consisted of the pivotal phase 3 ASPEN-1 trial[43] and an extension trial, ASPEN-OLS.[74] High-level results have been presented in poster format. Briefly, ASPEN-1 was a 36-week, double-blind, placebo-controlled, single-dose trial in which 301 patients with isolated, moderate-to-severe CD were randomized 3:3:1 to receive daxiBoNT-A 125 units, daxiBoNT-A 250 units, or placebo. The primary endpoint, the mean reduction from baseline in the TWSTRS total score averaged over weeks 4 and 6 was 12.7 points (31% change), 10.9 points (27% change), and 4.3 points (12% change) with 125 units, 250 units, and placebo, respectively. The primary endpoint was statistically significant compared with placebo at both daxiBoNT-A doses, but the difference was not significant between doses. The secondary endpoint, median time to the loss of at least 80% peak treatment effect, was 24 weeks for the 125-unit dose and 20 weeks for the 250-unit dose. Overall, both doses were well tolerated with a low occurrence of muscular weakness (4.8% and 2.3% for 125 unit and 250 unit-dose respectively) and dysphagia (1.6 and 3.8%, respectively).[43]

Subjects who completed the ASPEN-1 trial (n = 271) in addition to de novo enrollees (n = 86) were eligible to receive up to 4 additional open-label treatment cycles of daxiBoNT-A during ASPEN-OLS trial. During cycle 1, patients were treated with daxiBoNT-A 125 units or 250 units based on disease severity and previous treatment history. During cycles 2 through 4, patients could receive the same dose as during cycle 1 or the investigator could increase or decrease by 1 dose step per cycle based on patient's response in previous cycle (flexible dosing: 125 units, 200 units, 250 units, or 300 units). The primary endpoint, the mean reduction from baseline in the TWSTRS total score averaged over weeks 4 and 6 was 15.4 points (n = 357), 17.7 points (n = 329), 17.9 points (n = 234), and 19.9 points (n = 65) during treatment cycles 1, 2, 3, and 4 respectively, demonstrating no reduction in efficacy across repeated treatment cycles.[74] Investigators placed 87% of subjects on ≥ 1 dose above 125 units (≥ 250 units, 77%; 300 units, 37%).[75] The median duration of effect across doses, defined as time to loss of at least 80% of peak treatment effect, ranged from 19.9 to 26 weeks. Across all treatment cycles, 9.8% and 8.7% of patients reported dysphagia and muscular weakness, respectively with a rate per treatment cycle of 4.2 and 4.9, respectively.[74]

While the decrease in TWSTRS total score in the ASPEN-1 trial is slightly higher than reported in pivotal phase 3 trials with the approved doses of incoBoNT-A and aboBoNT-A,[41,42] the most obvious difference in results among studies is the longer duration of effect reported with daxiBoNT-A in the ASPEN-1 and ASPEN-OLS trials. Caution is warranted as each trial measured duration of treatment effect differently. In the incoBoNT-A trial, duration of treatment effect was measured as time between initial injection and retreatment, with retreatment need defined as a TWSTRS total score ≥ 20 and a spontaneous request for retreatment.[41] Flexible injection intervals combined with nonspecific criteria for retreatment in the incoBoNT-A extension study may have contributed to a shorter duration of treatment effect. In the aboBoNT-A trial, duration of effect was measured as time between initial injection and return of TWSTRS total score to within 10% of baseline, which yielded a longer duration of treatment effect than with incoBoNT-A.[42] Conversely, the ASPEN-1 and ASPEN-OLS trials measured duration of effect as the median time to loss of at least 80% of peak treatment effect.[43,74] In the ASPEN trials, it is unknown if patients requested retreatment prior to loss of 80% of peak treatment effect. The other notable difference is the lower occurrence of dysphagia with daxiBoNT-A in the single-dose ASPEN-1 trial and a low incidence per treatment cycle in the ASPEN-OLS trial.[43,74] As noted, occurrence of dysphagia was much higher in the phase 2 trial that evaluated daxiBoNT-A for treatment of CD and similar to rates reported with other BoNT-A preparations. It is uncertain if this is a true difference, a dose-related effect, or if different methods of soliciting adverse events among trials contribute to differences. For example, in incoBoNT-A trials, patients were questioned about the presence of dysphagia and asked to rate the severity of dysphagia on a scale of 1 to 5 at each follow-up visit.[76]

Limb spasticity, adult

Upper

AboBoNT-A, incoBoNT-A and onaBoNT-A are FDA-approved for the treatment of adult and pediatric upper extremity spasticity[2-4]; the AAN recommends that any of 3 preparations can be offered to treat focal manifestations of adult spasticity involving the upper limb (Level A recommendation).[59] Results of multiple randomized, controlled trials support the use of aboBoNT-A, incoBoNT-A, and onaBoNT-A to treat upper limb spasticity to reduce muscle tone and improve passive function. Results are equivocal about whether or not BoNT-A preparations improve active function; however, results of several trials suggest a trend toward improvement with aboBoNT-A.[59] To date, there are no comparative studies to determine a dose conversion among the BoNT-A preparations.[29,77] The optimal dosage regimen of each of the BoNT-A preparations is unknown, which further complicates the determination of a correct conversion ratio between aboBoNT-A and onaBoNT-A.[77] Although pediatric upper extremity spasticity is not discussed in detail here, the approval for aboBoNT-A and onaBoNT-A is inclusive of cerebral palsy (CP) while incoBoNT-A has not been approved for CP-associated spasticity due to marketing exclusivity granted to other BoNT-A preparations; however, incoBoNT-A has been evaluated for the treatment of CP-associated spasticity.[78,79]

Top-line results of the phase 2 JUNIPER trial – a randomized, double-blind, placebo-controlled trial - that evaluated daxiBoNT-A at doses of 250 units, 375 units, and 500 units for the treatment of adult upper limb spasticity after stroke or traumatic brain injury were presented in oral format at the International Congress of Parkinson and Movement Disorder Society in September 2022. Briefly, the 500-unit dose met one of the co-primary endpoints at week 6 and in a post-hoc analysis, met both co-primary endpoints at week 4. The median duration of response was reported to be 24 weeks.[80]

Lower

Both aboBoNT-A and onaBoNT-A are FDA approved for the treatment of adult and pediatric lower limb spasticity.[2,4] Based on the availability of randomized, controlled trials, the AAN recommends that aboBoNT-A and onaBoNT-A be offered as treatment for the focal manifestation of adult spasticity involving the lower limb (Level A recommendation).[59] Only results from a single-arm, open-label study that evaluated the efficacy of incoBoNT-A in treating lower limb spasticity in 71 patients with post-stroke spasticity are published.[81] A phase 3 trial that evaluated incoBoNT-A at a dose of 400 units for the treatment of post-stroke leg spasticity failed to demonstrate a statistical difference compared to placebo for the change from baseline in the Ashworth Scale for plantar flexors at week 4; these results are not published.[82] Due to the absence of randomized, placebo-controlled comparisons, the AAN states that there is insufficient evidence to support or refute the use of incoBoNT-A to treat lower limb spasticity.[59]

The approval of onaBoNT-A to treat adult lower limb spasticity was based on the results of a phase 3 trial of 468 adults with post-stroke ankle spasticity.[83] All patients randomized to onaBoNT-A received 300 units, divided among specified muscles. Patients could receive an additional 100 units (total dose, 400 units) if needed. The coprimary endpoints were the average of the change from baseline to weeks 4 and 6 in the modified Ashworth Scale (MAS) ankle score (0-5 point grade) and the Physician Global Assessment of Response (clinical global impression [CGI], 9-point scale ranging from -4-+4) at weeks 4 and 6. Compared with placebo, onaBoNT-A was associated with a significant reduction in the mean change on the MAS (-0.6 vs. -0.8, respectively) and a significant improvement in the mean CGI (0.7 vs. 0.9, respectively).[83] OnaBoNT-A (dose range: 100 units to 540 units) has been evaluated in multiple additional studies for the treatment of post-stroke lower limb spasticity[84-89] and for lower limb spasticity secondary to CP[90] and severe brain injury.[91] In these studies, onaBoNT-A given at total doses of 200 to 300 units reduced muscle tone, but had variable effects on different measures of functional improvement.[84,85, 90,91] Recently, an expert panel of 10 clinicians in neurology and physical medicine and rehabilitation reached a consensus on dosing recommendations for 3 common aggregate post-stroke postures: equinovarus foot (typical starting dose: 400 units; total maximum dose: 600 units); extended knee, plantar flexed foot/ankle (typical starting dose: 400 units; total maximum dose: 600 units); and plantar flexed foot/ankle, flexed toes (typical starting dose: 300 units; total maximum dose: 500 units).[92]

The approval of aboBoNT-A to treat adult lower limb spasticity was based on the results of a phase 3 trial in 381 adult patients with lower limb spasticity secondary to stroke or traumatic brain injury.[93] Patients randomized to aboBoNT-A received 1000 or 1500 units. The primary endpoint—change in the MAS at the ankle joint from baseline to week 4—was

-0.6, -0.8, and -0.5 with 1000 units of aboBoNT-A, 1500 units of aboBoNT-A, and placebo, respectively. Only the difference between aboBoNT-A 1500 units and placebo reached statistical significance. Both doses of aboBoNT-A were associated with a 0.9-point increase in CGI compared with a 0.7-point increase with placebo. Muscle weakness occurred in a higher percentage of patients that received 1500 units (7%) versus those that received 1000 units (2%); the difference was more pronounced in women than men.[93] An additional 6 randomized, controlled trials evaluated aboBoNT-A for the treatment of lower limb spasticity in adults,[94-99] including 4 placebo-controlled comparions.[94,97-99] Two of the placebo-controlled studies were also dose-ranging, and assessed aboBoNT-A at total doses of 500 units, 1000 units, and 1500 units[97,99] and are the only results discussed in further detail. In 234 patients with post-stroke calf spasticity causing spastic equinovarus deformity, 1000 units and 1500 units of aboBoNT-A significantly reduced patient dependence on walking aids compared with placebo. Additionally, 1500 units of aboBoNT-A was associated with significant improvements in calf spasticity measured by the MAS at weeks 4, 8, and 12 compared with placebo. For other outcome measures, including gait velocity, stepping rate and step length discrepancy, and Rivermead Motor Assessment, there were no significant differences among placebo and aboBoNT-A groups or among the multiple doses of aboBoNT-A.[96] Results of the second dose-ranging study, conducted in 74 patients with definite or probable multiple sclerosis and disabling spasticity of the hip adductor muscles, demonstrated a significant increase in the maximum distance between knees in the 1500-unit aboBoNT-A group compared with placebo. All aboBoNT-A doses improved muscle tone, but the differences between active groups and placebo did not reach statistical significance. Patients treated with 1000 units and 1500 units of aboBoNT-A reported a 1-point improvement in the median hygiene score, while patients treated with 500 units of aboBoNT-A and placebo reported no change in score during treatment.[99] In both dose-ranging studies, there was a trend toward a greater incidence of adverse events with the 1500-unit dose of aboBoNT-A compared with lower doses.[97,99]

In published randomized control trials, total doses of aboBoNT-A used to treat lower limb spasticity ranged from 500 to 2000 units.[100] FDA approved prescribing information recommends doses of up to 1500 units.[2] Though it is tempting to compare the FDA-approved doses of aboBoNT-A with onaBoNT-A and conclude that the conversion ratio is 5:1 for the treatment of lower limb spasticity, this conclusion is flawed because the optimal doses of BoNT-A preparations for the treatment of lower limb spasticity are unknown. The pivotal onaBoNT-A trial evaluated a single dose, and the pivotal aboBoNT-A trial compared each aboBoNT-A dose with placebo, but doses were not compared to one another. Based on the available evidence, the dose range for onaBoNT-A is 300 to 500 units and the corresponding range for aboBoNT-A is 1000 to 1500 units.

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