Journey of a therapeutic poison: Botulinum toxin A and its biosimilars

The history of botulinum toxin dates back to 1822 when a German physician, Dr. Kerner, identified it as a "fat poison" derived from "sour sausages." After self-administering the toxin, he reported marked drying of the palate and pharynx. He suggested that the toxin interrupted nerve conduction, reduced hyperexcitability, and caused what was later described as clinical botulism. Subsequently, in 1869, another German physician, John Müller, coined the term *botulism* from "botulus," the Latin word for sausage. The source was identified to be anaerobic bacteria, *Clostridium botulinum*, and seven different subtypes (A–G) were discovered. Subtype A of the botulinum toxin (BoNT-A) was chemically purified in 1928, paving the way for its therapeutic use.[1]

The first published use of BoNT-A was for correcting induced strabismus in rhesus monkeys by Scott *et al*. in 1973.[2] They commercialized onabotulinumtoxinA as "Oculinum" (Oculinum, Berkeley, USA), which gained the U.S. Food and Drug Administration (FDA) approval for blepharospasm and strabismus in 1989 and was further rebranded as "Botox™" (Allergan Inc. Irvine, CA, USA). Concurrently, a team in the United Kingdom independently purified the toxin and gained European approval for their product abobotulinumtoxinA (Dysport™: *Dys*tonia/*Port*on Down; Ipsen Ltd., Slough, UK). A third type of BoNT-A, incobotulinumtoxinA (Xeomin™, Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany), has been marketed from 2005 onward.[2] The use of BoNT-A in aesthetic medicine was first described in 1988. In 2002, the FDA additionally approved Botox™-Cosmetic for glabellar lines. The approval recommended rebranding of the products when used for cosmetic indications to provide a differentiation – Botox™ (functional [f]) and Botox®-Cosmetic (cosmetic [c]); Xeomin™ (f) and Bocouture™ (c), and Dysport™ (f) and Dysport™-Cosmetic (c).

All three above-mentioned compounds contain the core neurotoxin weighing 150 kDa and varying amounts and types of nontoxin accessory proteins. This is reflected in the total molecular weights, which range from 900 kDa for onabotulinumtoxinA, 500 to 900 kDa for abobotulinumtoxinA, and 150 kDa for incobotulinumtoxinA; the latter contains only the core neurotoxin protein. Their bioavailability differs, and thus the neurotoxin load per hundred units varies. Specific potencies are 137 units/ng for onabotulinumtoxinA, 154 units/ng for abobotulinumtoxinA, and 227 units/ng for incobotulinumtoxinA. As a result, in 2009, the FDA issued a statement that the units cannot be converted from one product to another due to their pharmacological differences.[1,3]

The drug is costly, and for resource-poor countries with poor federal health insurance coverage, it may remain unaffordable for a majority of the population. In addition, the single-use vials (after reconstitution) and the need for repeat injections add to the cost of treatment. Besides the rare but potentially serious complication of iatrogenic botulism, a more commonly seen side effect is the failure of response due to antibody formation, often occurring when high doses are used at frequent intervals.[4] IncobotulinumtoxinA had been designed without complexing proteins to overcome this immunogenicity.

For improving the cost-effectiveness as well as reducing the side effects, indigenous BoNT-A biosimilars have been designed. All the newer formulations contain a lesser amount of protein to reduce the risk of immunogenic responses. These are available in restricted markets from a range of manufacturers: Chinese BTXA-Prosigne/Lantox; Korean alternatives such as Neuronox (Meditoxin), Coretox, Botulex, Innotox, Wiztox, and Nabota; and the Indian biosimilar Botogenie™ (Biomed Private Ltd., India). It is important to understand that the potency units of each product are specific and are not interchangeable.[3,5] This fact is heavily stressed by the regulatory authorities and is mandated to be included as clear statements on the package inserts and prescriptions. Minor changes between the reference product and biosimilars, including the type of stabilizers, affect the clinical efficacy, tolerability, and immunogenicity. Reports of urticaria and allergic reactions leading to anaphylaxis have been documented with Chinese BTXA, which contains dextran and gelatin as stabilizers.[6]

DaxibotulinumtoxinA for injection (DAXI, Revance Therapeutics, Inc., Newark, CA) is yet another biosimilar formulation composed of BoNT-A complexed with a novel peptide excipient, is devoid of human or animal components, and is stable at room temperatures before reconstitution. DAXI has undergone three extensive clinical trials (SAKURA 1, 2, and 3) and is awaiting an FDA approval. Once approved, this may be the first FDA-approved BoNT-A biosimilar that offers a significantly longer duration of response and high efficacy as compared with Botox™.[7,8]

Biosimilars are revolutionary and improve the outreach of the product. However, caution must be exercised to ensure the dosage of the active BoNT-A compound. Legislation, due diligence, and postmarketing surveillance will go a long way in improving the quality of these products.

Limited literature is available detailing the efficacy of the "Make in India" indigenous Botogenie™. Pandey *et al*.[9] have successfully used this product for infantile esotropia. The authors of the present study in this journal issue have described their experience with the same product in the treatment of essential blepharospasm and hemifacial spasms. Although they have reported a successful outcome with a good safety and efficacy profile, in the absence of a control arm, their study does not elucidate how Botogenie™ fares in comparison with the FDA-approved molecules.[10]

The future looks promising, and further research including comparative trials can help elucidate the applications, dose standardization, efficiency, and toxicity of the BoNT-A biosimilars.

We hope to see long-lasting, efficacious, reliable BoNT-A biosimilars, with an enhanced safety profile, for ever-expanding applications in the fields of functional as well as aesthetic medicine.

Kasturi Bhattacharjee, Aditi Mehta

Department of Ophthalmic Plastic and Reconstructive Surgery, Sri Sankaradeva Nethralaya, Guwahati, Assam, India.
E-mail: kasturibhattacharjee44@hotmail.com

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About the author

Dr. Kasturi Bhattacharjee

Dr. Kasturi Bhattacharjee is the Director (Clinics and Academics) and Head, Department of Orbit, Ophthalmic Plastic Reconstructive Surgery and Oculofacial Aesthetics at Sri Sankaradeva Nethralaya, Guwahati.

She is a pioneer ophthalmologist and has performed the first navigation guided transorbital optic canal decompression surgery. She is actively involved in research, has over 65 peer-reviewed publications, and is the recipient of 38 awards including the Col. Rangachari Award (2008). She is on the editorial board for AAO-EyeNet magazine, is the section editor of IJO and is a reviewer for several international journals. She is also a global examiner for FRCS (Glasgow) for the past 15 years.