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LEADING ARTICLE

Updates on Botulinum Neurotoxins in Dermatology

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Abstract
Being the most popular non-surgical cosmetic procedure, botulinum neurotoxin (BoNT) injections are increasingly of interest to all cosmetic practitioners across the globe. This article serves to update readers on the new botulinum toxins that are currently in development or close to market in the USA and Canada, including daxibotulinumtoxin A, prabotulinumtoxin A, letibotulinumtoxin A, and botulinum toxin E. Despite having relatively similar characteristics and equivalent clinical efficacies, these neurotoxins manifest a multitude of unique potential advantages that will be explored in this review, including but not limited to a longer duration of action, the absence of animal-derived components or human albumin, and a rapid onset with short duration of action.

Key Points

Multiple neurotoxins have emerged in the market for use in treating facial rhytides.

Two particular additions with valuable advantages include daxibotulinumtoxinA, the first neuromodulator with a long-acting duration of 6 months, and botulinum toxin E, a neurotoxin with fast onset of action within 24 h and a shorter duration of activity of between 2 to 4 weeks.

Liquid toxins offer a convenient option for cosmetic use that does not require dilution, does not contain any animal-derived products, and has long-lasting effects.

1 Introduction

Botulinum neurotoxin (BoNT) injections are currently the most popular non-surgical cosmetic procedures on the market according to the American Society of Plastic Surgery. Before 1945, little was known about the chemical nature of BoNT, called the "most poisonous poison" [1]. In 1973, BoNT was used in an attempt to paralyze the extraocular muscles of monkeys, with eventual use for treating multiple ophthalmologic entities in humans including, but not limited to, strabismus [2]. It was not until 1991 that Dr. J. Carruthers and Dr. J.A. Carruthers first reported the use of BoNT for glabellar wrinkles at the annual meeting of the American Society for Dermatologic Surgery in Orlando [3].

BoNT is naturally produced by a Gram-positive, anaerobic, and spore-forming bacillus, *Clostridium botulinum* [4]. Seven serotypes of BoNT (named types A through G) have been identified so far, with only BoNT types A and B being available for therapeutic use. The therapeutic value of botulinum neurotoxin A (BoNT A) was first recognized in 1989 when the Food and Drug Administration (FDA) approved Oculinum for the treatment of strabismus and blepharospasm. It was not until April 2002 that the use of BoNT A (onabotulinumtoxinA) was approved for the treatment of glabellar lines by the FDA. In September 2013 and October 2017, the FDA eventually approved BoNT A for the treatment of lateral canthal lines and forehead lines, respectively. Since then, multiple BoNT formulations have been introduced to the market. This review will cover the new botulinum toxins that are currently in development, or close

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to market, in the USA and Canada, with an emphasis on their characteristics and potential advantages in treating rhytides.

2 Neurotoxin Serotypes

There are seven serotypes (A, B, C, D, E, F, and G) of BoNT. Each serotype has multiple subtypes that are based on a ≥ 2.6% difference in amino acid sequences [5]. Such variants in amino acid sequences confer different immunologic and biological properties on the neurotoxin.

Five subtypes of BoNT A have been described previously. In dermatology, three of the five subtypes of BoNT A are currently used for treating rhytides [6]. These three have similar affinities for binding SNAP25: onabotulinumtoxinA is marketed as Botox, Vistabel, and Vistabex (Allergan, Inc., Irvine, CA); abobotulinumtoxinA is marketed as Dysport and Azzalure (Ipsen Biopharm Ltd., Slough, Berks, UK); and incobotulinumtoxin A is marketed as Xeomin and Bocouture (Merz Pharmaceuticals Gmbh, Frankfurt, Germany). Additional subtypes of BoNT A have recently been in development, including prabotulinumtoxin A, daxibotulinumtoxin A, and letibotulinumtoxin A (Table 1). One subtype of BoNT B, rimabotulinumtoxin B, is also used in dermatology, and is marketed as Myobloc (Solstice Neurosciences, South San Francisco, CA, USA). It inhibits neurotransmitter release by cleaving synaptic vesicle associated membrane protein (VAMP, also known as synaptobrevin). Additionally, one subtype of BoNT E has been newly introduced with potential cosmetic and therapeutic use.

3 New Botulinum Neurotoxins

3.1 Prabotulinumtoxin A-xvfs

Prabotulinumtoxin A-xvfs is marketed as Jeuveau (Evolus, Inc.). It is a 900-kDa purified BoNT A that has been recently approved by the FDA and Health Canada for moderate to severe glabellar lines in adults. It was developed by Daewoong Pharmaceutical Co., Ltd. of Seoul, South Korea and licensed to Evolus, Inc. of the United States for clinical development and distribution in several countries including the USA, Europe and Canada [7]. It is commercially available as a vacuum-dried product with an excipient that includes 0.5 mg human serum albumin (HSA) and 0.9 mg sodium chloride (NaCl) per 100-U vial. It is to be reconstituted with 2.5 mL of 0.9% sterile saline. The Korean version, known as Nabota, is lyophilized (freeze-dried).

Table 1 New botulinum neurotoxins currently in development

Serotype	Prabotulinumtoxin A-xvfs	Daxibotulinumtoxin A	Letibotulinumtoxin A	Botulinum toxin E	Liquid toxins
Trade name	Jeuveau, Nuceiva, Nabota	N/A	Botulax, Regenox, Zentox, Reage, Magnion, Hugel Toxin, Juvenlife, Botulim, Botoshot	N/A	1. Innotox
Alternative name	DWP-450	RT002		EB-001	2. QM-1114 3. MT10109L
Manufacturer	Evolus, Inc. (USA)	Revance Therapeutics (USA)	Hugel Pharma (Korea)	Bonti, Inc. (USA)	1. Medytox (Korea) 2. Galderma (Switzerland) 3. Allergan (USA)
FDA approved	February 2019	No	No*	No	No
Advantages	Similar efficacy to 20 U of Botox at day 30 Lower cost	No animal-derived components or human albumin Long-lasting duration of effect (23.6 weeks)		Effect seen within 24 h	Lower risk of error in preparation Improved office efficiency
Disadvantages			Lower specific potency than Xeomin due to significant amount of inactive neurotoxin	2–4 week duration of action**	Cost Inability to adjust the volume of reconstitution

FDA Food and Drug Administration, *N/A* Not applicable

*LetibotulinumtoxinA was approved in South Korea in March 2010

**The short duration of effect could potentially be considered advantageous in the setting of first-time users who are interested in a short-term outcome

Two identical USA phase III, randomized, multicenter, double-blind, placebo-controlled clinical trials, involving 330 and 324 participants, respectively, confirmed efficacy compared with placebo in reducing the severity of glabellar lines, defined as a 2-point composite improvement agreed upon by physician and patient, at day 30. In one study (EV-001), 67.5% of subjects met the primary endpoint, compared to 1.2% of patients in the placebo arm, after a single treatment at 5 months follow-up. In a second study (EV-002), 70.4% of subjects met the primary endpoint, compared to 1.3% of patients in the placebo arm, after a single treatment at 5 months follow-up [8]. In a third multicenter, phase III, Canada/Europe study (EVB-003), involving 540 participants and comparing prabotulinumtoxin A to onabotulinumtoxin A for the treatment of glabellar lines, a single treatment of 20 U of prabotulinumtoxin A, administered as five injections of 4 U/0.1 mL each in adult subjects for the treatment of moderate to severe glabellar lines, was found to be superior to placebo and non-inferior to 20 U of onabotulinumtoxin A (Botox). Three prabotulinumtoxin A subjects (1.2%) had serious adverse events (SAEs): worsening of a conjunctival cyst; spontaneous abortion at 114 days; and spasms and severe pain of the facial muscles at 151 and 164 days [8]. None of the SAEs were considered to be study drug related.

According to the studies thus far, prabotulinumtoxin A-xvfs (Jeuveau) constitutes a new competitor to onabotulinumtoxin A (Botox) given that it is not inferior to it in clinical efficacy. It even might be at an advantage given it is expected to be priced 20–25% lower than Botox [9].

3.2 Daxibotulinumtoxin A

Daxibotulinumtoxin A (DAXI) corresponds to the investigational drug RT002. It was developed by Revance Therapeutics, a Silicon Valley biotechnology firm. It is a novel 150-kDa protein complex composed of BoNT A and a stabilizing peptide excipient designed to be a long-lasting, injectable neurotoxin with no animal-derived components or human albumin. Its peptide excipient is unique due to its small molecular weight, 5 kDa, and its highly positively charged amino acid sequence that forms an electrostatic interaction with the 150-kDa neurotoxin. This allows for the prevention of aggregation of BoNT and prevents its adsorption to container surfaces. It is formulated in a sugar and polysorbate 20 buffer, making it the only botulinum toxin product formulation without human blood- or animal-derived proteins [10]. RT002 is the only neurotoxin using this stabilizing excipient peptide technology, which provides 2-year product stability requiring no refrigeration. Additionally, daxibotulinumtoxin A used to be available as a topical gel, RT001. The REALISE 1 trial investigated its use in potentially treating crow's feet topically. Unfortunately, RT001 did not achieve its co-primary and other endpoints in improving lateral canthal lines, so it is no longer in clinical development [11].

In two phase III, double-blinded, active and placebo-controlled studies (SAKURA 1 and 2), the duration of effect in treating glabellar lines with DAXI was 27 weeks [12]. The BELMONT study, presented at the American Academy of Dermatology in March 2016, showed a median duration of $\geq$ 1-point improvement on the Investigator Global Assessment—Facial Wrinkle Severity (IGA-FWS) scale with RT002 40 U lasting 23.6 weeks versus onabotulinumtoxin A 20 U at only 18.8 weeks [13]. Daxibotulinumtoxin A was generally well tolerated in all doses, with no SAEs, except for a possible migraine in one patient receiving the 20-U dose [13]. It was concluded that the 40-U dose of daxibotulinumtoxin A had the most favorable risk/benefit profile, with significantly greater response rate and significantly longer duration of response than the 20-U onabotulinumtoxinA treatment ($P = 0.03$).

In a prospective, 84-week, open-label, repeat-dose, phase III study (SAKURA 3) evaluating the safety and effectiveness of daxibotulinumtoxinA in treating moderate-to-severe glabellar lines, efficacy exceeded or was comparable to that seen in the SAKURA 1 and 2 studies with daxibotulinumtoxinA at a dose of 40 U [14]. Efficacy was highly consistent across sequential treatment cycles and multiple endpoints evaluating response rates and duration of effect. The highest responder rates and longest duration of effect were observed in registration trials for moderate to severe glabellar lines. Additionally, effectiveness of DAXI was maintained beyond a single treatment, with a very high proportion of subjects meeting the treatment goal of none or mild wrinkle as early as week 1. The most frequent treatment-related adverse events were headache (4.6%), injection site pain (3.6%), and injection site erythema (3.0%). A low rate of eyelid ptosis was observed (less than 1% per treatment).

Given its significantly longer duration of response compared to onabotulinumtoxinA, daxibotulinumtoxinA represents the first long-acting neurotoxin, possibly allowing for fewer treatments per year. In addition, it is an attractive option given that it may not require refrigeration during storage and is produced without any animal or human blood products, which can potentially be a source of disease transmission.

3.3 Letibotulinumtoxin A

Letibotulinumtoxin A is marketed as Botulax. It was developed by Hugel, Chuncheon, South Korea, and was first approved in South Korea on March 2010. It is a 900-kDa complex comprised of BoNT A, 0.5 mg HSA as a stabilizer, and 0.9 mg NaCl as a tonic adjuster. It is commercially available in a sterile 100-U vacuum-dried form without a preservative. It should be stored at 2–8 °C, like other BoNT

A forms, and has a shelf life of 3 years in freeze-drying conditions.

In a study conducted by Merz Pharmaceuticals comparing different BoNT type A formulations in Asia, Botulax was shown to have more neurotoxin (844 pg of neurotoxin protein) than Xeomin (incobotulinumtoxinA) in an equivalent volume [15]. However, Botulax contained greater amounts of inactive neurotoxin (103%) than Xeomin in an equivalent volume. Unfortunately, those inactive neurotoxins cannot be taken up by neurons and might infer an immunogenic impurity stimulating the production of antibodies. In such instances, these inactive components could reduce the clinical efficacy of the neurotoxin and increase the risk of becoming a nonresponder due to their immunoreactive properties. Additionally, Xeomin, which has 416 pg/vial of purified neurotoxin and 0.240 U of efficacy per pg of neurotoxin, had the lowest neurotoxin protein content and consequently the highest specific potency compared to the four Asian BoNT A preparations (Botulax, Meditoxin, Nabota, and Relatox) in this study [15]. This suggests that Xeomin is the most potent among other BoNT A formulations being used in Asia. Additionally, given that it contains the least amount of inactive neurotoxin, it could be advantageous due to its lower risk of inducing immunoreactions and secondary nonresponse to BoNT A.

Further clinical studies would have to be conducted to assess the efficacy and safety of Botulax in treating glabellar lines. One randomized, double-blind, active-controlled, multicenter, phase I/III clinical trial (ClinicalTrials.gov identifier: NCT03408236) is currently recruiting participants in South Korea to evaluate the safety and efficacy of Botulax as compared to Botox in patients with moderate to severe crow's feet lines [16].

Given that it contains higher amounts of inactive neurotoxin, letibotulinumtoxinA might be at a disadvantage due to its lower specific potency and higher risk of potentially inducing immunoreactions.

3.4 Botulinum Toxin E

BoNTs, mainly serotypes A and B, are the most widely used neurotoxins for cosmetic purposes. However, serotype E has been recently introduced for use due to its faster onset and shorter duration of effect. Specifically, EB-001 is a proprietary purified form of BoNT E that was formulated as a liquid for injection initially by Bonti, Inc., Newport Beach, California [17]. In September 2018, Allergan acquired Bonti, Inc. and obtained global rights to both its product candidates, EB-001A (aesthetic indications) and EB-001T (therapeutic indications). BoNT E has a structure similar to BoNT A, consisting of two protein chains, a 100-kDa heavy chain linked by a disulfide bond to a 50-kDa light chain.

In a randomized, double-blinded, placebo-controlled, cohort study, EB-001 was shown to be safe, tolerable, and efficacious, with a two-grade investigator-rated improvement in glabellar frown line severity at maximum frown [18]. This primary outcome was equivalent to maximal 80% response rate observed at the highest dose. Additionally, the clinical effect with EB-001 was seen within 24 h and lasted between 14 and 30 days. There were no SAEs or ptosis reported in this study. This distinct profile of BoNT E might be favorable for aesthetic or therapeutic procedures where quick onset and short duration of effect are desired.

In addition to its efficacy in treating glabellar lines, BoNT E is being investigated in scar reduction following Mohs surgery in the Scar Healing Improvement with Neurotoxin E (SHINE) clinical program [19]. EB-001A or placebo was administered to the frontalis muscle directly after Mohs surgery for skin lesions on the forehead in 12 participants. Based on the visual analog scale, EB-001A–treated subjects reported 50% improved scar appearance as compared to scars in the placebo group. The EB-001A-treated group reported no itching, compared to 75% of the placebo group who reported itching, based on Scar Cosmesis Assessment and Rating (SCAR) scores. The majority of the placebo subjects reported pain at 24 h and 8 days after surgery, while a smaller percentage of the EB-001A-treated group reported pain, based on SCAR scores. Additionally, improved scar color and scar stiffness was reported in the EB-001A group as compared to the placebo group, based on Patient and Observer Scar Assessment Scale (POSAS) scores.

Aside from its role in improving scars, botulinum toxin E embodies a unique neurotoxin due to its quick onset of action within 24 h and its short duration of action of between 2 and 4 weeks. It would be an appealing treatment option when a shorter duration of response than that of BoNT A (3–4 months) is required.

4 Liquid Toxins

Most forms of botulinum toxin type A are freeze-dried and thus require reconstitution, which can be difficult for users. A new formulation, called the liquid-type BoNT A, has been developed in Korea by Medytox under the name of Innotox that simplifies the procedure and avoids contamination. A similar liquid-type toxin named MT10109L is being developed in North America and is in its early stages of phase III clinical trials in Canada and USA [20]. It is being evaluated for safety and efficacy in treatment of moderate to severe glabellar and lateral canthal lines. Its estimated date of completion is January 2021. MT10109L does not contain any animal-derived products or albumin. In a double-blind, randomized, phase III study of 168 patients, there was no significant difference in the improvement rate at maximum

frown and at rest by both live and photographic assessment between the MT10109L and Botox groups at week 4 [20].

Another liquid toxin in its early stages of development is QM-1114 by Galderma [21]. A phase II, randomized, double-blind controlled trial with 359 participants evaluated three doses of botulinum toxin (total dose: 30 [102 subjects], 45 [103 subjects], and 60 units [103 subjects]) versus placebo (51 subjects) in the treatment of moderate to very severe glabellar frown lines. Decrease in wrinkle severity from maximal frown was significantly higher throughout 6 months for all QM-1114 groups versus placebo. The clinical response, defined as the median time to return to baseline score at maximum frown, was at least 175 days or longer. No serious treatment-related adverse events were reported. Treatment with the new liquid formulation QM-1114 thus represents a suitable alternative to the traditional BoNT A products that require reconstitution before use given its high efficacy, long durability, and adequate safety profile.

Finally, rimabotulinumtoxin B is a BoNT serotype B manufactured by Solstice Neurosciences (South San Francisco, CA, USA) as a liquid formulation under the name of Myobloc in the United States and Neurobloc in Asia and Europe [22]. Myobloc comes in the form of a colorless to light-yellow sterile solution. Each 3.5-mL vial of formulated Myobloc contains 5000 units of botulinum toxin type B per milliliter in 0.05% HSA, 0.01 M sodium succinate, and 0.1 M sodium chloride at pH 5.6. Myobloc is currently approved for the treatment of cervical dystonia and chronic sialorrhea in adults. It has been shown, however, to have a more rapid onset of action, greater area of diffusion, more painful injections, and shorter duration of action when used for cosmetic purposes [23].

Additional advantages of liquid toxins are the reduced risk of error in preparation and the improved office efficiency. However, the disadvantages would be the cost to the patient and the inability to adjust the volume of reconstitution if a more concentrated form is desired. Further studies would have to be carried out to assess for differences in patient outcomes.

5 Conclusion

Being the most popular noninvasive procedure, botulinum injections constitute a growing worldwide interest. It is only natural that the market will continue to expand and avidly welcome the introduction of newer botulinum toxins with more exciting features such as a faster onset of action or a longer duration of action. This review serves to highlight the wide diversity of BoNTs that are currently marketed and in development along with their potential advantages and disadvantages. This diversity, however, entails the importance of making an informed decision when selecting the proper toxin for a particular patient. Botulinum toxin has proven to be versatile over the years, and further randomized controlled studies would have to be performed in order to clarify whether such newer toxins actually exhibit superiority, equivalence, or non-inferiority in terms of clinical efficacy.

Compliance with Ethical Standards

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