An Introduction to a New Botulinum Toxin Type A Formulation

The first new botulinum toxin type A formulation to reach the US market in nearly two decades presents a new therapeutic option for cosmetic surgeons.

By Evan H. Schlam, MD

With last month's FDA approval of Dysport, dermatologic surgeons will soon have at their disposal a new option for chemodenervation. According to the FDA approval, the new formulation of abobotulinum toxin A (Dysport, Medicis—also to be distributed under the same name for neurologic indications by Ipsen, the European company that developed the formulation) is indicated for treatment of cervical dystonia and glabellar lines. However, like its US predecessor /competitor Botox (botulinum toxin A, Allergan), it will likely be used off-label for management of hyperhidrosis, other types of hyperdynamic wrinkling, wound healing, and more.

As Dysport progressed through the US approval process, speculation swirled regarding both financial and medical issues associated with the drug's introduction on the US market. Some factors remain undetermined. Here's what we know about Dysport and how it may be adopted into practice.

Distinct Products

Dysport is a distinct product from Botox, and the two are not interchangeable, as each manufacturer has emphasized. Dysport is formulated with 125µg human serum albumin with 2.5mg lactose; Botox contains 500µg human serum albumin with 0.9mg sodium chloride.[1] The molecular weights differ slightly. Botox has a consistent weight of 900kD, while Dysport's molecular weight ranges from 500kD to 900kD.

There is some speculation that the smaller relative size of the Dysport molecule could contribute to more rapid onset of action, anecdotally reported as early as three days post-injection. This size difference may also affect diffusion, discussed below.

While there is widespread agreement, there is still no official consensus regarding the ideal dosage conversion factor between the two agents. From a technical standpoint, some authors have pointed out, the conversion factor is not critically important because each manufacturer provides dosing information for its specific formulation. From a practical standpoint, however, conversion can be a key issue.[2] There is a natural desire among physicians to compare the efficacy, longevity, and safety of the agents—a feat only possible if they are weighed fairly. Patients/consumers, too, will want to know how the two products stack up.

Initial conversion recommendations dating back about 15 years to Dysport's European approval, suggested a Dysport:Botox ratio of 5:1 or 4:1. Today, many clinicians use a 3:1 conversion factor, though some suggest that dropping as low as 2.5:1

Botulinum toxin and Wound Healing

A growing area of interest has been the use of botulinum toxin to modulate scar formation and improve the healing of surgical wounds. A recent investigation in rats found that wounds treated with botulinum toxin (Botox) had less fibrosis and greater amounts of collagen than did control wounds. Treated wounds also demonstrated less infiltration of inflammatory cells and lower expression of TGF-beta1.

—Lee Bj, et al. Clin Exp Otorhinolaryngol. 2(1):20-7

Dysport At-a-Glance

Active agent: Botulinum toxin type A

Indications: Glabellar wrinkles (Medicis); Cervical dystonia in adults (Ipsen)

Formulation: 125μg human serum albumin with 2.5mg lactose

Molecular weight: 500kD to 900kD

Time to onset: May be more rapid than Botox

Diffusion: May diffuse more than Botox

Side effects: Same for all botulinum toxin type A formulations

may be more accurate.[3] One recent publication places the conversion ratio at 1.3-1.6:1.[4] However, Sampaio, et al. concluded that a "systematic review of head-to-head studies comparing Botox to Dysport suggest that the two formulations are not bioequivalent whatever the dose relationship."[2]

Glabellar Lines

Recently published data suggest that use of Dysport for glabellar lines is associated with minimal adverse events and good patient satisfaction.[5] Among 1,200 patients receiving up to five Dysport (then tentatively called Reloxin) treatments over 13 months, 72 percent of adverse events were determined not to be or not likely to be associated with treatment. Only 45 patients experienced ptosis, which typically lasted less than three weeks. A majority of patients (93 to 95 percent) reported onset of response by day seven. Response (no or mild glabellar line severity scale scores on day 30) as judged by investigators ranged from 80 to 91 percent during cycles 1 to 5.

A handful of studies have compared Dysport to Botox for treatment of glabellar lines. One study involved 24 evaluable patients who received bilateral injections of Dysport and Botox (randomly assigned) with photographic assessments conducted by a three-expert panel.[3] EMG muscle activity assessment was also recorded. The conversion factor was 3:1. Beginning at 10 weeks and through the remainder of the 20 week total trial period, Botox began to show statistically significantly loss of effect compared to Dysport.

A larger study using a 2.5:1 Dysport to Botox ratio for treatment of glabellar lines found better results for Botox.[6] Patients were randomly assigned to receive treatment with either formulation with 20 percent of the dose injected into the procerus muscle and 80 percent into the corrugator muscles. At week 12, 77 percent of Botox patients had an improvement of wrinkling of 1-grade or more, versus 59 percent of Dysport patients. At week 16, 1-grade or better response was evident in 53 percent of the Botox group and 28 percent of the Dysport group. The estimated rate of relapse at week 16 was 23 percent for Botox versus 40 percent for Dysport.

Hyperhidrosis

In one study comparing the safety and efficacy of Dysport versus Botox for the management of palmar hyperhidrosis, researchers found that Dysport may show a trend toward greater improvement but with a higher incidence of adverse events.[7] The study involved eight patients treated in the same session with intradermal injection of Dysport into one palm and Botox in the other, at a 4:1 ratio. The study was double-blinded and randomized. At one month, Dysport-treated sides had a 78.6 percent decrease in sweating versus baseline sweating area (BSA), and Botox-treated patients had a 56.6 percent reduction versus BSA. The difference was not statistically significant. At three months, average reduction from BSA in the Dysport group was 69.4 percent, compared to 48.8 percent in the Botox group. Patient self-evaluations reflected similar perceived efficacy for both agents, with one-month and three-month patient ratings of 77 percent and 75 percent improvement for Dysport and 68 percent and 72 percent improvement for Botox. Weakness of thumb-index pinch, the lone reported adverse side effect, occurred in four Dysport patients (lasting eight to 30 days) and two Botox patients (lasting 15 to 21 days).

In a study assessing the effects of Botox and Dysport for the management of axillary hyperhidrosis, data revealed a similar trend.[8] Using a Dysport:Botox conversion factor of 3:1, researchers injected each axilla with a different formulation. At one month, the mean rate

of sweating decreased 99.4 percent in the Dysport group and 97.7 percent in the Botox group. At four months, the treatment success (greater than 50 percent reduction in sweat) rate for Botox was 77.8 percent compared to a statistically non-significant 88.9 percent for Dysport.

Diffusion, Antibodies, and Other Considerations

Beyond difference in dosing, another significant difference between these two distinct formulations may be rate of diffusion. Some data and reports of clinical experience suggest that Dysport may diffuse more readily than Botox does. Kranze, et al. reported similar diffusion characteristics for both agents in their human skin model test of Botox and Dysport.[4] And in a recent publication, an Ipsen researcher notes that, "The active neurotoxin in Type A products is the same and therefore diffusion is equal when equal doses are administered."[9]

Following their cervical dystonia trial, however, Ranoux, et al. suggested that a slightly higher incidence of side effects associated with Dysport compared to Botox may have been due to increased diffusion of the former (which also showed slightly better efficacy at 3:1 and 4:1 dosing).[10] When Cliff, et al. investigated the effects of Dysport and Botox on sweat production following injections into the forehead, they found larger areas of anhidrosis associated with Dysport injections, suggesting a greater range of migration.[11]

As with onset of action, diffusion may be associated with molecule size, several theories suggest. Pickett disagrees, stating, "Diffusion of botulinum toxin products is not related to the size of the toxin complex in the product since the complex dissociates under physiological conditions, releasing the naked neurotoxin to act."[9] This may become an issue settled through cumulative clinical experience rather than pure science.

There are theoretical concerns about development of antibodies to botulinum toxin, regardless of the formulation. Botox has a reported anti-body induced failure rate of less than one percent.[12] It seems likely that Botox and Dysport would have a similar rate of anti-body induction, as their biological activity is rated at 100 MU-EV/ng and 60 MU-EV/ng, respectively. Botulinum toxin type B (Myobloc, Solstice), by comparison, has a biological activity of 5 MU-EV/ng and an antibody-induced therapeutic failure rate of 44 percent in cervical dystonia. Generally, dermatologists need not worry about antibody development.

Finally, side effects associated with botulinum toxin injection include injection site reactions, headaches, muscle weakness, and ptosis associated with periocular injections. Side effects tend to be transient and are not specific to any formulation. It is also important to note that the FDA has ordered a black box warning for botulinum toxin products regarding adverse effects that could occur if the effects of the toxin extend outside the injection site. FDA also has mandated a Risk Evaluation and Mitigation Strategy (REMS) be put in place for all botulinum toxin products. Reportedly, most instances of distant spread of toxin happened in adult patients who received Botox or Myobloc for approved or unapproved neurologic indications.

Implications for Practice

Although the question of dose conversion remains unanswered, the data taken together indicate that the final "resolution" to this question may involve two different conversion scales—one for small muscles and one for large muscles. As Ranoux and his team point out, their cervical dystonia trial supported the much-discussed 3:1 ratio, while most studies for hyperdynamic wrinkles favor lower conversion ratios. It will also be important for cosmetic surgeons to consider the issue of diffusion, which future studies may help elucidate.

Importantly, physicians should avoid over-emphasizing comparisons between Botox and Dysport, as fair, balanced head-to-head trials are nearly impossible at this time. Rather, as Sampaio, et al. suggest, indirect comparisons may offer more insight, supporting that "intrinsic differences are present in the two products."[2]

At this time, the most compelling difference between Dysport and Botox may be cost. The price-point for Dysport in the US has not been publicized, but analysts suspect that Medicis will employ competitive pricing in efforts to gain market share. ■

1. Monheit GD in Benedetto AV, ed. Botulinum Toxin in Clinical Dermatology. Taylor & Francis, 2006.

2. Sampaio C, Costa J, Ferreira JJ. Clinical comparability of marketed formulations of botulinum toxin. Mov Disord. 2004 Mar;19 Suppl 8:S129-36.

3. Karasi, Adrian R, Hammes S, Thimm J, Raulin C. A randomized double-blind study of the effect of Botox and Dysport/Reloxin on forehead wrinkles and electromyographic activity. Arch Dermatol. 2007 Nov;143(11):1447-9.

4. Kranz G, Haubenberger D, Voller B, Posch M, Schnider P, Auff E, Sycha T. Respective potencies of Botox and Dysport in a human skin model: a randomized, double-blind study. Mov Disord. 2009 Jan 30;24(2):231-6.

5. Moy R, Maas C, Monheit G, Huber MB; Reloxin Investigational Group. Long-term safety and efficacy of a new botulinum toxin type A in treating glabellar lines. Arch Facial Plast Surg. 2009 Mar-Apr;11(2):77-83.

6.Lowe P, Patnaik R, Lowe N. Comparison of two formulations of botulinum toxin type A for the treatment of glabellar lines: a double-blind, randomized study. J Am Acad Dermatol. 2006 Dec;55(6):975-80.

7. Simonetta Moreau M, Cauhepe C, Magues JP, Senard JM. A double-blind, randomized, comparative study of Dysport vs. Botox in primary palmar hyperhidrosis. Br J Dermatol. 2003 Nov;149(5):1041-5.Click here to read

8. Talarico-Filho, Mendonça DO Nascimento M, Sperandeo DE Macedo F, DE Sanctis Pecora C. A double-blind, randomized, comparative study of two type A botulinum toxins in the treatment of primary axillary hyperhidrosis. Dermatol Surg. 2007 Jan;33(1 Spec No.):544-50.Click here to read

9. Pickett A. Dysport: Pharmacological properties and factors that influence toxin action. Toxicon. In Press.

10. Ranoux D, Gury C, Fondarai J, Mas JL, Zuber M. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. J Neurol Neurosurg Psychiatry. 2002 Apr;72(4):459-62.

11. Cliff SH, Judodihardjo H, Eltringham E. Different formulations of botulinum toxin type A have different migration characteristics: a double-blind, randomized study. J Cosmet Dermatol. 2008 Sep;7(3):230.

12. Dressler D, Hallett M. Immunological aspects of Botox, Dysport and Myobloc/NeuroBloc. Eur J Neurol. 2006 Feb;13 Suppl 1:11-5.