XEOMIN Versus BOTOX: Challenging the Brand with Science – Part 1

By Kevin A. Wilson, Contributing Editor

Bringing a new product to an established market is a serious challenge. In the realm of aesthetic medicine it is no different, and as such product perception, molded by marketing, is a key determining factor in the battle for a slice of the market. Once a product is proven safe and effective, there begins the battle for the hearts and minds of customers.
Despite the American system of oversight centered on the FDA, there are certainly cases where successful marketing trumps the facts, and the better device or drug doesn't always win. In the case of neurotoxins specifically, the issue is the power of public perception, not safety or efficacy.

In aesthetic medicine there are two levels of customer: the physician user and the patient recipient of care. As Michael H. Gold, M.D., director of the Tennessee Clinical Research Center and Gold Skin Care Center (Nashville, Tenn.), explained, "Companies have to convince physicians that their product is safe and effective, among other things, and it helps to fill the proverbial fields by marketing to prospective patients as well. These days, consumers are bombarded with messages on all media fronts suggesting a need for some new drug or therapy. That isn't to be negative; companies owe it to themselves to promote their products by any legal means at their disposal. Despite the American system of oversight centered on the FDA, there are certainly cases where successful marketing trumps the facts, and the better device or drug doesn't always win. In the case of neurotoxins specifically, the issue is the power of public perception, not safety or efficacy, because in my opinion — based on years of research and clinical experience — the three big products are all safe and all work equally well in the hands of skilled practitioners."

"This hurdle is by no means small since BOTOX Cosmetic from Allergan (Irvine, Calif.) was first," Dr. Gold continued, "and they unintentionally made aesthetic medicine available to the 'Everyman,' shattering the invisible wall of perception that aesthetic medicine was only for the rich, and opening the door for the explosive growth of less invasive aesthetic medicine. In this they created a monster brand as well, not because BOTOX is necessarily better, but because it was first, has very good science behind it and great marketing."

For Merz Aesthetics (Raleigh, N.C.) the challenge of marketing its injectable neuromodulator XEOMIN has been a face-off with its main competitor, BOTOX Cosmetic, not to show superiority, but what is known as equivalence or non-inferiority. Despite a plethora of sound science showing XEOMIN to be equivalent to BOTOX, public perception seems to miss the facts. Another competitor rounding out the big three in neurotoxins is Dysport from Galderma Laboratories (Fr. Worth, Texas), which is fighting the same battle. "The fact is that all three of these products work, and work well, that is no secret. Different patients and physicians prefer particular products among the three for a variety of reasons, many being completely valid, but all three are safe and effective. That's why I offer all of them in my practice, and work with all three companies," stated Dr. Gold. whose facility is part of a large, multi-center, randomized and blinded clinical trial putting XEOMIN and BOTOX in a head-to-head test in an effort to dispel the wizardry of perception, at least within the medical aesthetic profession.

Cheryl Burgess, M.D., director of the Center for Dermatology and Dermatologic Surgery in Washington, D.C., echoed that sentiment. "I prefer XEOMIN because I prefer the look and feel of the result best, therefore that's what I use personally, but I offer and market all three products because in my experience they are basically equivalent in safety and efficacy, so why not be skilled in using all three to meet patient needs and demand?"

"I prefer XEOMIN because I like the look and feel of the result best, therefore that's what I use personally," she said, "but I offer and market all three products because in my experience they are basically equivalent in safety and efficacy, so why not be skilled in using all three to meet patient needs and demand? After all, given basic equality in safety and efficacy, it's the patient's choice and different patients have different experiences. However, when I offer neurotoxins at any price point the first question is whether or not they're as good, if they work as well or last as long as the others. In my clinical and research experience the answer is yes," Dr. Burgess' facility is also a study center in the new XEOMIN vs. BOTOX head-to-head clinical trial.

Where research is concerned, each company has sponsored studies specifically for their products, and there's always the expectation of revealing information the company can use to its advantage. "It is not about creating junk science to fool the public," Dr. Gold explained, "but even with the many ethical safeguards in place, there is bias and it affects even the most legitimate attempts at objective, evidence-based medicine. Not much can be done about this as it takes a lot of money to do research, and the companies are the ones with the money."

In the case of XEOMIN and their battle with BOTOX for market share, the competition is fierce. BOTOX branding is at the highest level of strength with the word 'BOTOX' used generically to describe the aesthetic use of injectable neurotoxins; the word 'Coke' is commonly used to refer to soft drinks in general. Nevertheless, the science as a whole seems to demonstrate that XEOMIN is quite similar to BOTOX, but Merz has made a strong case for itself in several ways.

An early battleground between XEOMIN and BOTOX was a difference in the potency of delivered toxin, and whether the presence or absence of complexing proteins in the drug formulation held significant benefit. "Often it was, 'Are the units equivalent,' versus questions about the protein that encapsulates the neurotoxin in BOTOX (not present in XEOMIN), which are both irrelevant since, to my knowledge, there hasn't been a single reported case of reaction to the protein to date in aesthetics, even with larger medical dosing," Dr. Gold noted. "Also, how equipotency translates into efficacy isn't perfectly understood, so many studies show both products to be effective for a variety of uses."

The two prominent studies' dealing with potency each suffer from the same basic hurdle: the assay used. "Each study addresses potency using that particular company's chosen assay, and different assays may yield slightly different results," Dr. Gold revealed. Hunt and Clarke in 2009 evaluated three unexpired lots of XEOMIN using the Allergan in-house L550 mouse potency bioassay, and found XEOMIN to be less potent than the BOTOX potency reference standard. Still, questions arose about whether XEOMIN had been reconstituted properly in this study. It has been established that if not reconstituted according to the manufacturer's recommendations (i.e. inverting the vial during reconstitution) some units of XEOMIN may be lost in the preparation, thus resulting in the differences noted in the study. Dresler in 2012 used the Merz standard batch release assay to test
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potency of five unexpired batches of BOTOX and XEOMIN, and found no statistical difference in potency; variability in potency for both was within the range allowed by European Pharmacopoeia, and the authors concluded that the two could be compared using a 1:1 conversion ratio. This study compared batches of actual product using identical assays, whereas Hunt 2009 compared XEOMIN to a preseed standard using an Allergan-approved assay. In each case both studies used the company's signature assay.

A meta-analysis of relative potency by Jandhyala in 2012 in the Journal of Drugs in Dermatology examined data from eight aesthetic studies in a network treatment analysis, and cited evidence from 11 other studies not directly addressing potency, and found no significant difference in relative potency, recommending that physicians continue to consider XEOMIN and BOTOX equally potent unless future evidence shows otherwise. "The issue with a study like this is always the criteria used to determine which studies to include in the analysis," Dr. Gold said.

**Head to Head General Efficacy, Tolerability and Spread**

A 2005 randomized, controlled, open-label study by Jost and colleagues measured compound action potential (CMAP) of extensor digitorum brevis muscles in feet, with each subject (N=14) receiving injections (4U each side) of both neurotoxins contralaterally. The study found XEOMIN and BOTOX comparable in efficacy, time to onset of action, duration of action and tolerability up to 90 days using a 1:1 dose ratio.

A similar, but larger study by Wohlfarth (2007), with data at each of 14 visits over one year, used varying doses of each XEOMIN and BOTOX – same dose within each subject (N=32) – finding that duration of effect was dose-dependent. Both neurotoxins were well tolerated and statistically significant reduction in CMAP was noted at all dose levels. Additionally, no significant effect in nearby muscles due to diffusion was noted.

"Early studies such as these have more to do with general efficacy of the product to prove the concept scientifically, so there is some limit to how this applies directly to aesthetic uses, but the value is still there," Dr. Gold pointed out.

A key single-center, double-blind, randomized, single dose trial by Kerscher in 2012 examined diffusion, or "spread," of the big three neurotoxins: XEOMIN, BOTOX and Dysport in a dosing ratio of 1:2.5 (5U:12.5U), with equal injection volume. Product was injected into the forehead and anterior tibialis muscles were measured at six weeks. The anterior tibialis associated with injection of BOTOX and XEOMIN were statistically equivalent over the study period, while spread with Dysport was significantly greater. All products were well tolerated.

"Spread isn't a major problem with the big three neurotoxins, despite it being singled out as a difference primarily between Dysport and the other two, which has been clearly demonstrated in the literature," Dr. Gold stated.

**Non-inferiority of XEOMIN versus BOTOX was demonstrated for both primary and secondary variables.**

**Medical Indications**

"Looking at studies of non-aesthetic treatments has some value, especially when we're dealing with examining the overall equivalence of two products," Dr. Gold expressed. "The weight of the evidence doesn't have the same impact as it might in investigations of aesthetic use. A commonly cited potential confounding factor is that medical use of neurotoxin usually involves greater doses than ever seen in aesthetic medicine, so studies of aesthetic indications may be more sensitive to change and thus more powerful for indicating differences between products. In the case of XEOMIN versus BOTOX the overall picture seems to indicate equivalence, but that's how people view the use of non-aesthetic studies in this context."

Benecke 2005 studied XEOMIN and BOTOX for cervical dystonia (n=463) in a double-blind non-inferiority trial using a 1:1 dose ratio, with dosing based on treatment history (70U to 3000U intramuscula injection, mean doses virtually equivalent). In this case the design involved using patients who were already responding to treatment successfully using BOTOX for the first treatment, and then received a second treatment with BOTOX and also exhibited a good response. For the third and final round of treatments the patients received either BOTOX or XEOMIN (randomized) at the same dose. There were no statistically significant differences between mean and median duration of effect. Both formulations demonstrated safety and tolerability.

In 2006 a similar investigation by Roggenkämper (n=256) examined XEOMIN versus BOTOX in a non-inferiority trial for blepharospasm with a design similar to that of the Benecke 2005 study in several key instances, including using a 1:1 dose ratio with dosing based on treatment history; patients experienced successful treatments using BOTOX for two rounds of therapy, with the third round randomized between XEOMIN and BOTOX. As with the Benecke study, non-inferiority of XEOMIN versus BOTOX was demonstrated for both primary and secondary variables. Median duration of effect was 110 days for both products, and efficacy was virtually the same as well. One key difference between the two trials is the significantly lower dosage used in the Roggenkämper study. While higher doses are often a hallmark of medical (rather than aesthetic) investigations, it was not the case in this study and the outcomes still clearly demonstrate non-inferiority in a similar fashion.

Dressler also performed a large study (n=263) in 2009 investigating patients previously treated for a variety of movement disorders including hyperhidrosis (n=57), hemifacial spasm plus reinnervation synkinesis (n=17), hyperhidrosis (n=64), spasticity (n=84) and dystonia (n=91). The dose ratio was 1:1 with a maximum dose of 840U. Looking at onset of effect, duration of effect, adverse effect profile and diffusion with identical parameters and definitions of response, investigators reported no objective or subjective differences between products, concluding that the 1:1 exchange between BOTOX and XEOMIN would be valid.
“We need to study these neurotoxins in head-to-head comparisons, blended fashion and in numbers where significance can be determined.”

A smaller double-blind, randomized, parallel-group pilot study by Wobbeles, et al. in 2011 (n=65) of the safety and efficacy of XEOMIN and BOTOX for blepharospasm treated patients at a 1:1 dose ratio and assessed at weeks four, eight, and 14. Global assessments and adverse events between formulations were not significantly different. Positive changes on the two rating scales used were not statistically different at week eight, and there was no difference in duration of effect noted.

**Aesthetic Indications**

According to Dr. Gold, this is where the rubber meets the road as far as comparisons go. “We need to study these neurotoxins in head-to-head comparisons, blended fashion and in numbers where significance can be determined.”

In 2010 Sattler and colleagues compared XEOMIN and BOTOX for globellar lines in what has since been considered a landmark study. This prospective, multicenter, randomized, rater- and patient-blind international trial is among the strongest studies available because of its size and robust design. A 1:1 dose ratio was used in this study as well. In Dr. Gold’s opinion, the total dose was somewhat large by U.S. standards (24U), however, did involve injection in the same five point pattern across the forehead. Study authors were looking for responses of at least one point on a four point facial wrinkle scale via independent physician rating of photographs. The response rates for XEOMIN and BOTOX, respectively, were 96.4% and 95.7% at week four; response rates at week eight were 80.1% and 78.5%, respectively, denoting efficacy in both products were well tolerated.

“In any controversy surrounding this investigation concerns the larger dose administered,” Dr. Gold pointed out. “In Europe they regularly use larger doses of neurotoxin, which is why the study was set up this way as with the standard of the time, so the criticism is about whether or not larger doses make it harder to reveal the key differences between products, in what has been termed a ‘threshold’ effect regarding sensitivity. This is similar to how medical studies of neurotoxin aren’t as useful for product comparison.”

Another study that gets a lot of press is the Moers-Carp study for globellar lines, originally a poster, but later published in the Journal of Cosmetic and Laser Therapy (2012). This randomized, double-blind, multicenter trial (n=224, 112 for each product) used reconstituted product given in equal injection volumes at five sites. As with the Sattler study and others, the primary endpoint was improvement of one point on a four point facial wrinkle scale. In this case efficacy was equal at 28 days, a trend favoring BOTOX was noted at days 84, 98, and 112, but differences were not statistically significant.

“The issue with this large and often cited study is the different dosing, which seems to favor BOTOX because study results are equivalent, but less BOTOX is used over the five injections sites, Dr. Gold reported. “If there is a dose threshold, does that mean one might have had similar results with 20U of XEOMIN rather than 30U? Either way this is a landmark trial, although not truly head-to-head because doses were not equal.”

In 2010 Prager performed a double-blind, randomized, split-face proof-of-concept study of efficacy between BOTOX and XEOMIN for crow’s feet. Both products demonstrated tolerability and strong efficacy at four months with no statistical difference noted between agents.

In 2012 Prager conducted a multicenter split-face trial of 35 subjects undergoing two injections into the corrugator muscle, using 6U of BOTOX and 4U of XEOMIN. The primary endpoint was greater than or equal to one point improvement on a five point scale at four weeks, four months and six months, with a secondary endpoint of improvement greater than two points. Response rates were basically equivalent for both primary and secondary endpoints at all three time points. As with the Moers-Carp study, the differing dosages tend to confound the comparison somewhat, making it difficult to truly classify this study as head-to-head as well.

Previous to that, in 2010, Prager performed a double-blind, randomized, split-face proof-of-concept study of efficacy between BOTOX and XEOMIN for crow’s feet, again using the classic definition of improvement as an increase of one point on a four point facial wrinkle scale, as rated by independent physicians (in this case looking at photographs at two, three and four months). The dose ratio was 1:1 (12U). Both products demonstrated tolerability and strong efficacy at four months, with no statistical difference noted between agents. Response rates were nearly identical and investigators concluded that the excellent response rates at the four month endpoint suggested efficacy would persist.

In 2012 Prager also published a retrospective chart review study including patients (n=1256) receiving two to three consecutive treatments with XEOMIN or BOTOX within a specific 12 month period. In that time about 11% of patients switched products during their treatment course, but regardless, dosage was virtually the same throughout (1:1 BOTOX/XEOMIN). No significant differences were noted between products in mean or median treatment intervals, dosage, adverse effects or patient satisfaction; both formulations were well tolerated and effective. Investigators concluded that in daily practice the two products may be used in a 1:1 dose ratio with comparable expectations of safety and efficacy. “While not a randomized, double-blind study, there is strength in the large patient population,” Dr. Gold stated.

Although it may seem confusing Dr. Gold makes it perfectly clear; “Overall the collection of trials raises a lot of questions that would be answered by large-scale, well designed studies, but XEOMIN’s status as non-inferior to BOTOX isn’t really one of them. Nevertheless, the debate is still open, which is the impetus behind the large clinical trial we’re working on.” While not a head-to-head randomized, double-blind study features a robust design with ten study centers enrolling 230 healthy female patients (median age 41).

Dr. Gold, it still comes down to the clinical reality of the big three neurotoxins. “To the best of my knowledge, all of the big three neurotoxin offerings in the U.S. are safe, effective, legitimate alternatives for aesthetic use, and the
"To the best of my knowledge, all of the big three neurotoxin offerings in the U.S. are safe, effective, legitimate alternatives for aesthetic use, and the literature shows it. There will always be variation, but when you look at the overall picture they all work well in the hands of injectors who know what they're doing."

In part 2, Dr. Gold and colleagues will discuss the new clinical trial currently in progress in greater detail, as well as address other factors surrounding the proposition of those challenging the market share of BOTOX.

References: