Botulinum toxin in topical form draws interest
By Nancy A. Melville

**National report** — Much about it is still somewhat of a mystery, but early findings on a topical form of botulinum toxin have been compelling enough to earn a $20 million show of support from Medicis and catapult the research onto the cosmetic medicine radar.

The botulinum toxin molecule is large — very large — and just how the molecule could penetrate the stratum corneum and make its way deep enough under the skin to have the same effect as injected botulinum toxin has many scratching their heads.

Even the company behind the research, Mountain View, Calif., Revance Therapeutics, hasn't quite figured it out yet.

"There's a lot more that we don't know than we do know, but our approach is driven by scientific data, and what we've seen so far in preclinical and clinical trails outside of the U.S. has been very encouraging," says Dan Browne, president and CEO of Revance.

The details of what Revance does know about the vehicle are still largely under wraps, but a preliminary study that is the first published research on the formulation refers to the vehicle as a "proprietary transport peptide molecule that binds the toxin in a noncovalent manner."

In that study, researchers used the topical formulation of botulinum toxin type A (BTX-A) to treat 12 patients with primary axillary hyperhidrosis.

The randomized, blinded, vehicle-controlled study yielded impressive results: A 65 percent mean reduction of sweating on 10 axillae treated with the BTX-A (200 U) was observed after four weeks of treatment, compared with a 25 percent mean reduction in sweating on the vehicle-controlled axillae (Derm Surg. 2007 Jan;33(1 Spec No.):S76-80).

Lead author Richard Glogau, M.D., says the results offered an encouraging indication of the mechanism's potential.

"The issue we were concerned about was whether the material would actually get deep enough to reach the muscle," says Dr. Glogau, a clinical professor of dermatology at the University of California, San Francisco.

"But we obviously got to the bottom of the dermis, because that's where the endocrine sweat glands are."
Another concern, particularly in cosmetic use of the product, was the possibility of migration, but Dr. Glogau says so far, that doesn't appear to be an issue.

"It really appears to behave in a similar fashion as an injectable, and when applied topically, it stays local," he says.

According to Mr. Browne, "The initial formulations were sort of water-based, but that had the tendency to run away from the treatment site, so we moved to a gel base.

"(This) gives the control to apply the drug product exactly on the treatment site for targeted local superficial delivery."

U.S. trials awaited

Early clinical trials in Korea and Mexico have shown encouraging results, and Mr. Browne says he expects phase 2 clinical trials to begin in the United States sometime this year.

A big vote of confidence indicating that Revance may be more than just another bogus "better than Botox" product was Medicis' $20 million investment in the company, made in December.

The investment gave Medicis preferred stock in Revance, equivalent to about a 10 percent ownership of the company. Medicis also purchased an option to acquire Revance or gain exclusive North American licensing rights during an option period to extend through the end of phase 2 testing in the United States.

According to Medicis' executive vice president Mitchell S. Wortzman, Ph.D., even though the research is preliminary, the potential impact that a topical botulinum toxin product could have on the market is compelling.

"Conventional wisdom suggests that the botulinum toxin molecule is too large to penetrate the skin, but the preliminary data that Revance has produced certainly makes one sit up, and say these guys may be on to something," he says.

Dr. Wortzman is also Medicis' chief scientific officer.

"Time will tell if they can really deliver targeted doses in a therapeutic way, but it's interesting — it causes one to question conventional wisdom, and that's sometimes where the greatest breakthroughs come from," he says.

"Medicis' injectable botulinum toxin product Reloxin is expected to compete in the aesthetic market with Botox, but what Medicis doesn't have rights to on the injectable side is the therapeutic distinction," said Ken Trbovich, a stock analyst with RBC Research in Denver, Colo.

"The potential for Revance to have a therapeutic indication such as hyperhydrosis could, therefore, be a big advantage for Medicis."
Medicis 'cautious'

The relatively small size of the investment underscores that Medicis' optimism is cautious, Mr. Trbovich says.

"Medicis has made similar investments in the past on things that didn't work out, but this is an opportunity for them to dip their feet in the water without dropping a huge amount of capital," he says.

Allergan, meanwhile, may be keeping an eye on its botulinum toxin competition, but in a statement, the company tells Dermatology Times that a topical botulinum toxin formulation is not something it recognizes as even approaching the efficacy of its signature product, Botox.

"Allergan has been researching various formulations of botulinum toxin and does not believe that a topical form of botulinum toxin can quickly and consistently penetrate deep into the skin and muscle to produce the desired effect," says Allergan spokesman Leslie A. Bryant.

"Based on our research, we believe that a topical botulinum toxin, regardless of the delivery mechanism in the cream or gel, can't come close to the results seen with an injection of Botox Cosmetic," she says.

Revance moves ahead

Nevertheless, Revance research is moving full speed ahead, and therapeutic as well as cosmetic indications are indeed a big part of the company's plans, according to Mr. Browne.

"We're very attracted to both facial aesthetics and hyperhidrosis indications, but we also think there could be potential opportunities for acne, a potential toxin for pain and even podiatry," he says.

"Right now, indications (such as acne) are more observational, and whether a topical approach will work is something we currently don't know yet."

As far as what kind of niche the topical product might fill in the facial aesthetics marketplace, the jury is also still out, especially when the phenomenal success of Botox in the mass market can largely be credited to highly mastered injection techniques that constitute a virtual art form.

Benefits may differ

Even though Botox injections use tiny needles and tend to fall on the low end of the pain scale, needle-phobic patients may still represent an ideal market for a topical botulinum toxin formulation. But those patients will need to be warned not to expect all of the aesthetic benefits of an injectable, says Ranella Hirsch, a Cambridge, Mass., dermatologist and president of the American Society of Cosmetic Surgery and Aesthetic Dermatology.
"There is a subset of patients for whom the injectable process may be out of reach and who would prefer a topical application, but the issue right now is that with the current state of technology, nothing approximates what you can predictably expect with injectable Botox," she says.

"That said, it will be exciting to see what the future brings with the topical application."

When it comes to hyperhidrosis, however, Dr. Hirsch says the prospects for a topical botulinum toxin are intriguing.

"People who hesitate at the larger number of Botox injections in the underarms and hands would truly find a topical application to be a boon, so this could really be an exciting development in that area," she says.

Dr. Glogau agrees that a topical formulation may not be able to substitute for injectable Botox, but it still could find a significant fan base of its own.

"For people who have no problem getting injections in the lateral crow’s feet area, it’s hard to beat injectable toxins," he says. "But I think there is a market out there for people who maybe don't want to get stuck and who would be willing to take a lesser effect in order to avoid a shot."

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