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Topical Botulinum Toxin Will Turn Market 'Upside Down'

By: BRUCE JANCIN, Skin & Allergy News Digital Network

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WAIKOLOA, HAWAII – Topically applied botulinum toxin type A may no longer be a pipe dream, as it is now likely full speed ahead for proposed phase III trials of the agent.

The completed phase II program consisted of 11 clinical studies in which 553 patients had their lateral canthal lines treated with the investigational topical product known for now as RT001, under development by Revance Therapeutics. The results were highly impressive, according to Dr. Alastair Carruthers, a dermatologist at the University of British Columbia, Vancouver.

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"Watch out for topical botulinum toxin. I think Revance is going to turn the neurotoxin market upside down," he predicted at the Hawaii Dermatology Seminar, sponsored by Skin Disease Education Foundation (SDEF).

Revance has developed a proprietary platform that enables transcutaneous flux of large medicinal payloads. The company has reported successful proof-of-concept studies for topically delivered insulin, growth factors, and numerous other macromolecules with applications in fields ranging from cardiovascular disease to cancer. But it's the topical botulinum toxin project that has captured Dr. Carruthers' attention.

"Their technology enables you to get the neurotoxin across intact skin, which is something I never thought that we would see. But it really works," he said.

No significant adverse events occurred in the phase II studies. There was no evidence of diffusion of neurotoxin away from the target muscle, and no effect upon the cranial nerves, he said. Laboratory monitoring and ECGs did not yield any evidence of systemic exposure.

The median duration of therapeutic effect was 113 days. The response rate was up to 89% based upon a stringent composite end point requiring a 2-point improvement as assessed independently by investigator and patient, he said.

The key to this technology is a synthetic peptide carrier which contains protein transduction domains and a backbone core that attaches to the neurotoxin molecule. This peptide carrier can be set to achieve different depths of penetration.

The proposed commercial product that will undergo phase III testing entails mixing the viscous topical gel in a one-step applicator, which is then used in treating the lateral canthal lines. The mixing and application takes only a couple of minutes. The gel is left on for perhaps 30 minutes – the optimal time is yet to be determined – and then removed with a proprietary cleanser.

Dr. Carruthers said that as many know, increasing competition has arrived among the manufacturers of the three Food and Drug Administration–approved injectable botulinum toxin type A products.

"I doubt that the battle, such as it is, will be fought on intellectual, scientific issues. I think it will be fought based upon cost, marketing, and other intangibles," he predicted.

Brand loyalty, company sponsorship of medical education, appeals to nationalism – one manufacturer is U.S.-based, the others German and French – these are the sorts of issues he expects to see brought forth.

That's because the things that really matter to clinicians, such as onset of therapeutic effect, its spread, duration, and side effects, are all a function of dose – and there is no agreement as to what the comparable dose is between the various commercial preparations. Despite manufacturers' claims, it's not possible to detect small differences in effectiveness, immunogenicity, or other end points without doing studies that would require enormous numbers of patients, according to Dr. Carruthers.

He advised that given the uncertainty regarding dosing comparability, the best practice is to have only one botulinum toxin type A product in the office. This avoids the thorny issue of trying to use comparably effective dilutions.

Dr. Gary D. Monheit

In a separate presentation at the annual meeting of the American Society for Dermatologic Surgery, Dr. Gary D. Monheit, a dermatologist in private practice in Birmingham, Ala., agreed that the topical botulinum toxin could be practice changing.

He said that RT001 is best for superficial musculature such as crows' feet, and possibly in the future for perioral and forehead wrinkles.

The investigational product affects pore size and helps smooth the skin, he said. And since the product is mostly absorbed in the superficial musculature, it could eventually be used on the eyelids and lips for superficial wrinkles and to brighten up dull skin.

Dr. Carruthers reported that he has no financial relationship with Revance. He is a consultant to, and paid investigator for, Allergan and Merz, which market Botox (onabotulinumtoxinA) and Xeomin (incobotulinumtoxinA), respectively.

Dr. Monheit is a consultant and clinical investigator for Revance.

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Naseem Miller was a contributing writer.
