European Journal of Neurology 2012, 19: 355–356 doi:10.1111/j.1468-1331.2011.03560.x

EDITORIAL

Editorial comment on '5 year experience with incobotulinumtoxinA (Xeomin®) the first botulinum toxin drug free of complexing proteins'

See paper by Dressler, on page 385.

In this issue, Dr. Dressler reviews his experience with a new botulinum toxin type A product, incobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals, Frankfurt/M, Germany), since its market introduction in 2005. This editorial seeks to provide a different perspective to some of the assertions made in the paper. The following major points will be discussed, and the evidence supporting each point will be evaluated.

1 Potency equivalence of incobotulinumtoxinA with onabotulinumtoxinA
2 Stability of the incobotulinumtoxinA drug product
3 Immunogenicity of incobotulinumtoxinA and the proposed role of accessory proteins in antibody-induced failure of botulinum toxin therapy

Potency equivalence

The author asserts that as incobotulinumtoxinA vials have identical potency labeling to onabotulinumtoxinA (i.e., 100 U) and, as the description of dosing is similar in some clinical indications, that this implies that clinical dosing would be identical in all indications (i.e., a unit per unit equivalence or a 1:1 dose ratio). However, similar product potency labels can lead to a misunderstanding of the appropriate clinical dose. This is especially important because each drug product has specific dosing, efficacy, and safety characteristics for each clinical indication. As evidence, the author cites two published clinical trials, designed for non-inferiority, used to evaluate incobotulinumtoxinA (Xeomin) for cervical dystonia and blepharospasm. There are four important points to consider when discussing the clinical comparability between two products:

1 The European Summaries of Product Characteristics (SPC) for all botulinum toxin products have statements, which caution the user on the units and conversion. For example, the Merz December 2009 United Kingdom SPC for Xeomin states 'One unit corresponds to the medial lethal dose (LD50) when the reconstituted product is injected intraperitoneally into mice under defined conditions. Due to differences in the LD50 assay, these units are specific to Xeomin and are not interchangeable with other Botulinum toxin preparations'.
2 Non-inferiority trials do not 'confirm identical potency labeling and identical diffusion properties of both drugs' only that one product is not worse than or inferior to the standard treatment by more than an arbitrary amount. Factors such as the drug formulation, dose, patient population, and the sensitivity of the outcome measure selected can significantly bias the outcomes of non-inferiority trials. For example, the outcome scales used in blepharospasm trials are valuable in distinguishing a botulinum toxin treatment from placebo, but not between products [1]. In addition, the specific trials in question assessed treatment results at two time points, 3–4 and 16 weeks. These trials provide no data on the duration or decay of the clinical response, and therefore, conclusions of comparability can only be drawn based on the peak of response.
3 It is suggested that all botulinum toxin-based products rapidly disassemble, liberating the neurotoxin component. If this was the case, then all botulinum toxin products would have exactly the same clinical profiles (assuming equivalent amounts of the 150-kDa neurotoxin moiety administered). However, it is long established that botulinum toxin products have differing dose, efficacy, and safety profiles; therefore, additional factors must influence the release of the neurotoxin from the complex *in vivo*.
4 Drug potency is defined by the assays utilized by each manufacturer and is an important reason for the SPC warnings on the product unit definition. A study is cited, reporting that incobotulinumtoxinA contained less activity than onabotulinumtoxinA with an *in vivo* assay [2]. Hunt *et al.* [3] followed with additional data, which confirmed the reduced activity of incobotulinumtoxinA with an *in vitro* method and identified an unexplained SNAP25 cleavage product. These results support the regulatory statements, which caution the user on the comparability of units and the lack of interconversion.

Stability of incobotulinumtoxinA

The statement that incobotulinumtoxinA has a product shelf life of 4 years without temperature restriction is incomplete. For example, the Merz UK SPC for Xeomin cites a 4-year shelf life for an unopened vial and restricts storage to <25°C, while the US package insert restricts storage to specific windows of −20 to

EUROPEAN JOURNAL OF NEUROLOGY
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−10, 2–8, or 20–25°C. On the basis of the storage requirements for incobotulinumtoxinA, it was suggested that accessory proteins are unnecessary for stability of the drug product. However, it is well established dogma that the 150-kD neurotoxin is a very labile protein and therefore the stability of incobotulinumtoxinA is likely derived from the albumin and sucrose excipients in the formulation.

What is, perhaps, more relevant to clinicians is the stability of the drug products after reconstitution. Both incobotulinumtoxinA and onabotulinumtoxinA are required to be refrigerated after reconstitution and can be both used for up to 24 h after reconstitution when stored under these conditions.

Immunogenicity of incobotulinumtoxinA and the proposed role of accessory proteins in the clinical immune response

As botulinum toxins are bacterially derived proteins, therapy with any botulinum toxin product has the risk of the stimulation of a humoral immune response. It is well accepted that only neutralizing antibodies that form against the 150-kD neurotoxin component lead to treatment non-response. Dr. Dressler claims that incobotulinumtoxinA is less immunogenic than the other marketed products and that this results from the removal of the accessory proteins in the manufacturing of incobotulinumtoxinA. However, the US FDA package insert for incobotulinumtoxinA reports a seroconversion rate of 1.1% in clinical trials in CD, blepharospasm and upper limb spasticity.

Large studies are required to determine the rate of neutralizing antibody formation. One example of the level of evidence desired is a meta-analysis of five indications, which demonstrated that 11/2240 (0.49%) onabotulinumtoxinA (BOTOX®, BOTOX® Cosmetic, Vistabel®Allergan, LLC. Irvine, CA, USA.)-treated patients demonstrated neutralizing antibodies at one or more post-treatment time points and 4/2240 (0.2%) were positive at study completion. However, only three patients became non-responsive to onabotulinumtoxinA therapy [4]. Thus, the immunogenicity of onabotulinumtoxinA is considered very low. Therefore, to claim a lower immunogenicity for incobotulinumtoxinA would require, at minimum, a similar number of *de novo* Xeomin-treated patients in the same indications studied for a similar period (i.e., up to 15 treatment cycles for cervical dystonia). No long-term immunogenicity data have been published for incobotulinumtoxinA.

The work of Lee *et al.* was used to claim an immunologic adjuvant effect of the accessory proteins (CPs). However, this was a non-clinical study using high quantities of inactivated botulinum toxin B in animals to study the formation of neutralizing antibodies. In a published response to this paper, Prof. Atassi highlighted the experimental flaws and the weakness in the logic in applying the non-clinical results to patients [5]. On the basis of the US package insert for Xeomin® and the available peer-reviewed data, claims of immunogenicity superiority cannot be substantiated. The statement by Dr. Dressler that 'robust clinical data are required for confirmation of this hypothesis' is appropriate.

The introduction of additional products in this therapeutic class is valuable and provides the clinician with options in treating their patients. It is important that factual descriptions of each product are communicated to provide physicians with scientifically based information to make appropriate clinical decisions.

Disclosure of conflict of interest

K. Roger Aoki is an employee of Allergan, LLC, the manufacturer of BOTOX®.

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