Clinical Equivalence of Conventional OnabotulinumtoxinA (900 KDa) and IncobotulinumtoxinA (Neurotoxin Free From Complexing Proteins – 150 KDa): 2012 Multidisciplinary French Consensus in Aesthetics

Bernard Poulain MD, Patrick Trevidic MD, Micheline Clavé MD, Claude Aharoni MD, Martine Baspeyras MD, Patrick Bui MD, Hugues Cartier MD, Marie-Hélène Charavel MD, Pierre Coulon MD, Serge Dahan MD, Jean-Marie Dallara MD, Denis Delonca MD, Laurent Dumas MD, Eric Essayagh MD, Olivier Galatoire MD, Nicolas Georgieu MD, Yann Grangier MD, Philippe Humbert PhD, Anne Le Pillouer–Prost MD, and Alain Mojallal MD

aInstitute of Cellular and Integrative Neurosciences, CNRS, University of Strasbourg, Strasbourg, France
bRue de Sontay, Paris, France
cAvenue de Flirey, Nice, France
dClinique Esthétique de Paris Spontini, Paris, France
eCentre Bordelais Dermatologie Esthetique, Bordeaux, France
fRue du Champ de Mars, Paris, France
gSquare Saint Jean, Arras, France
hCentre Esthétique et Anti-Age Médico-Chirurgical Paramédical et Laser de Bordeaux Triangle, Bordeaux, France
iRue Michelet, Aix, France
jkClinique Saint Jean–Languedoc, Toulouse, France
lCentro Laser Dermatologique Laser MD, Strasbourg, France
mClinique Esthétique Aquitaine, Bordeaux, France
nAvenue Carnot, Paris, France
oAvenue Saramartel, Antibes, France
pFondation Ophtalmologique Adolphe de Rothschild, Paris, France
qChirurgie Plastique Reconstruitce et Esthetique, Bayonne, France
rClinique de l’Ocean, Quimper, France
sUniversity of Franche-Comte, Besançon, France
tService de Dermatologie, Hôpital Privé Clairval, Marseille, France
uEdouard Herriot Hospital, Lyon, France

ABSTRACT

Botulinum neurotoxins are the most popular non-surgical treatments for aesthetic indications, but there is uncertainty about whether certain formulations are comparable in efficacy and safety and can be substituted for one another by a simple one to one dose conversion ratio. An expert panel of French practitioners was convened to establish a consensus on the clinical equivalence in efficacy and safety of OnabotulinumtoxinA (900 KDa) and IncobotulinumtoxinA (neurotoxin free from complexing proteins - 150 KDa). The consensus was divided into three sections incorporating a biological, bibliographic and clinical analysis of the two toxins. This included a review of the published data that have directly compared the two toxins for aesthetic indications and a survey of the panel’s extensive clinical experience with the two toxins in terms of efficacy and safety. All panel members reviewed and endorsed the content of each section. Among this expert panel of French aesthetic physicians and biologists there was consensus that OnabotulinumtoxinA and IncobotulinumtoxinA are clinically equivalent in terms of efficacy and safety, and that a switch from one drug to the other can be made using a simple 1:1 conversion ratio.


INTRODUCTION

The use of botulinum toxin as a therapeutic agent was pioneered by an ophthalmologist around 30 years ago for use in strabismus and blepharospasm. In the following decades, botulinum toxin became the standard of care for a number of disorders related to muscle dystonia. The potential aesthetic indications for botulinum toxin first became apparent in 1987, when it was found that treatment of blepharospasm also resulted in a smooth and relaxed appearance of the...
glabellar area. Since then, treatment of wrinkles with botulinum toxin has become the most popular non-surgical aesthetic procedure in many countries in the world.\textsuperscript{4,5}

**Why is This Expert Consensus Required in Aesthetics?**

The enormous popularity of botulinum neurotoxin injections among patients seeking non-invasive methods of facial rejuvenation has meant that physicians from diverse specialties have integrated botulinum toxin injections into their existing practices. With a large population of potential patients with individual preferences, anatomical variability, and the increasing number of botulinum neurotoxin type A products available it is likely that practitioners will be injecting more than one product. It is therefore important that they are familiar with all available preparations and are confident when switching between them. There is uncertainty among some practitioners about whether certain formulations are comparable in efficacy and safety and can be substituted for one another by a simple dose conversion ratio. In the absence of any published guidelines in this area, an expert panel was convened to establish a consensus on the clinical equivalence in efficacy and safety of OnabotulinumtoxinA, which is manufactured by the American laboratory Allergan (botulinum toxin 900 kDa [Botox\textsuperscript{®}/Vistabel\textsuperscript{®}; Allergan Inc, Irvine, CA, USA]) and IncobotulinumtoxinA, which is manufactured by the German laboratory Merz, in Dessau, Germany, (Xeomin\textsuperscript{®}/Bocouture\textsuperscript{®}; Merz Pharmaceuticals GmbH, Frankfurt, Germany).

**Consensus Methodology**

The consensus statement was developed by drawing on the combined expertise of a number of experienced users of botulinum toxin type A in France including dermatologists, oculoplastic surgeons, plastic surgeons, aesthetic physicians and a biologist. In 2012, the 20 expert panel members decided to undertake a biological, bibliographic and clinical analysis to determine whether there is clinical and biological equivalence between OnabotulinumtoxinA and IncobotulinumtoxinA.

The expert panel divided the consensus statement into three sections, with responsibilities for the individual sections shared between the group: (1) Structural and biological comparison, (2) bibliographic comparison of clinical studies, and (3) survey of practical and clinical experience of expert panel members. Each group nominated a team leader and all panel members reviewed and approved the methodology for each section to ensure the coherence and cohesion of this comparative approach.

**Structural and Biological Comparison**

For the first section, a keyword search for papers related to the structure, mechanism of action and biological activity of IncobotulinumtoxinA and OnabotulinumtoxinA was performed in addition to hand-searching references of published papers for additional citations, and contacting relevant experts. The literature search was conducted using the PubMed database (National Center for Biotechnology Information, US National Library of Medicine National Institutes of Health).

**Bibliographic comparison of clinical studies**

In the second section of the consensus an analysis and comparison of OnabotulinumtoxinA (900 kDa) and IncobotulinumtoxinA (neurotoxin free from complexing proteins -150 kDa) in terms of the published clinical data was performed. The methodology agreed by the experts for this section of the consensus took the following steps:

- Conduct a comprehensive literature search using the PubMed database and the following keywords: aesthetic AND ([Bocouture] OR [Xeomin] OR [IncobotulinumtoxinA]) AND ([OnabotulinumtoxinA] OR [Botox] OR [Vistabel]) AND (botulinum toxin A free from complexing proteins) AND (glabellar lines OR crow's feet OR forehead lines) AND (head-to-head) study.
- Research and identification of all published studies or presented posters comparing OnabotulinumtoxinA (900 kDa) with IncobotulinumtoxinA (free from complexing proteins -150 kDa).
- Selection restricted to already published studies or presented posters on aesthetic indications.
- Distribution of studies to all members of the working group for review and analysis of each article according to a predetermined and agreed summary grid (Appendix 1)

**Survey of Practical and Clinical Experience of Expert Panel Members**

In the third section of the consensus, French panel experts determined whether there is clinical equivalence in efficacy and safety between OnabotulinumtoxinA and IncobotulinumtoxinA based on their extensive clinical experience with the two neurotoxins. The group comprised two dermatologists and six plastic surgeons – all having extensive experience with the use of botulinum toxin in all its forms and indications. Each member of the group agreed to provide a comparison of the two toxins based on experience from their own practice, using their individual techniques for injection and their own personnel. The methodology for the preparation of this section of the consensus was as follows:

- Development of questionnaire (see Appendix 2) by group leader and clinical comparison working group
- Approval of questionnaire by all working groups involved in the development of the consensus statement
- Completion of questionnaire by all members of the clinical comparison working group
• Analysis of responses by all members of the working group under the direction of the group leader
• Development of a consensus for presentation to the other working groups.

Consensus Preparation
A preliminary summary was compiled and presented to the group at a consensus meeting held in Paris in June 2012. The material was discussed and the contents of each section revised after the meeting in the light of the discussions. Authors then reviewed and endorsed the content of the revised presentations, which provided the basis for the first draft of the statement. The manuscript subsequently underwent review and revision by each member of the consensus group. The following text summarizes the findings of the expert panel whose goal was to develop a consensus on whether OnabotulinumtoxinA and IncobotulinumtoxinA are equivalent in terms of efficacy and safety and can be substituted for one another by a simple one to one dose conversion ratio.

Throughout the consensus and depending on nomenclature and author preference, the following terminology may be used to identify the two botulinum toxins:

• for IncobotulinumtoxinA: botulinum toxin free from complexing proteins (150 kDa), as well as its brand names: Bocouture® or Xeomin® Cosmetic™

• for OnabotulinumtoxinA: conventional botulinum toxin (900 kDa), conventional botulinum toxin complex 900 kDa or conventional botulinum complex 900 kDa, as well as its brand names: Vistabel® or Botox®.

RESULTS

Structural and Biological Comparison
Characterization of OnabotulinumtoxinA (900kD) and IncobotulinumtoxinA (150kD)
With a number of botulinum neurotoxins now available for injection, it is important to characterize their individual molecular and biological characteristics. The first section of this consensus statement will describe the properties of two products that share the same neurotoxin: conventional OnabotulinumtoxinA (900 kDa) and IncobotulinumtoxinA (neurotoxin free from complexing proteins - 150 kDa).

Neurotoxin is one of the components of botulinum toxin
Botulinum toxin type A was purified in crystalline form in 1946 when it was assumed that it was a single protein. This crystalline toxin with a molecular weight of 900 kDa has two distinct biological actions: on the one hand it preferentially inhibits acetylcholine release, and on the other hand it has hemagglutinating properties. The notion that a complex of several molecular entities was responsible for the diverse biological actions of the 900 kDa toxin quickly became established.

A single protein (150 kDa) possesses neurotoxic activity, the other proteins are not pharmacologically active on nerve terminals and consist of several hemagglutinating (HA) proteins and a single non-toxic, non-hemagglutinating (NTNH) protein. NTNH resembles the 150 kDa neurotoxin, but is devoid of biological activity. HA and NTNH are often grouped under the acronym NAPs (Neurotoxin Associated Proteins) or under the term complexing proteins. The 150 kDa neurotoxic protein usually refers to the pure botulinum neurotoxin as opposed to the 900 kDa toxin complex formed by the association of botulinum neurotoxin with the NAPs.

The commercial toxin preparations correspond to the 900 kDa toxin complex (OnabotulinumtoxinA: a 150 kDa neurotoxin molecule complexed with NAPs) and the 150 kDa neurotoxin (IncobotulinumtoxinA: pure neurotoxin without complexing proteins), respectively.

Diversity of type A botulinum neurotoxins
Botulinum neurotoxin (150 kDa) is a dichain, fully active protein consisting of 1296 amino acids. It consists of a light chain (L, ~50 kDa) connected by a disulfide bond to a heavy chain (H, ~100 kDa). Gene sequencing of numerous strains of C. botulinum producing type A toxin has identified at least five subtypes of neurotoxin type A (A1 to A5), which can differ in their amino acid sequences from 10% to over 25%. The commercial type A toxins/neurotoxins (OnabotulinumtoxinA, IncobotulinumtoxinA) are produced from the Hall reference strain for C. Botulinum (strain ATCC3502). The 150 kDa neurotoxins present in the two products are therefore identical and of subtype A1.

Stability and dissociation of the toxin complex
At acidic pH, the individual component proteins of the complex including the neurotoxin are degraded or altered in structure, but when associated in the toxin complex they are stable at pH 3.5 to 6.8. Above this pH the different forms of type A toxin complex in OnabotulinumtoxinA dissociate. At physiological pH, >80% of neurotoxin associated with NAPs (complex) is rapidly released from the complexing proteins and can therefore act on the nerve terminals.

Biological Activity
Biological activity and role of NAPs in botulinum intoxication
NAPs are not neuroactive, they have no synergistic role with the neurotoxin on the synapses and there is no evidence that they can alter the dissemination of neurotoxin within tissues. In mice, no difference in toxicity is observed between the 150 kDa neurotoxin, the purified 900 kDa complex, or crude preparations of toxin (mixture of complexed), administered by intraperitoneal injection whose concentrations is adjusted to the content of the 150 kDa neurotoxin. All the effects of the purified 150 kDa neurotoxin are strictly identical to those of the toxin (complex). On the other hand, NAPs
do play an essential role in foodborne botulism by allowing the passage of neurotoxin into the gastrointestinal tract without degradation.

Neurotoxin is the pharmacologically active entity on nerve terminals Our knowledge of the cellular and molecular mode of action of botulinum toxins has been established using purified 150 kDa neurotoxins that for the most part have been produced from the Hall A strain of C. botulinum ATCC 3502 (ie, the strain producing OnabotulinumtoxinA and IncobotulinumtoxinA). The cellular and molecular mechanisms of action of OnabotulinumtoxinA and IncobotulinumtoxinA neurotoxins are therefore identical to those that have been established with the purified 150 kDa neurotoxins by academic laboratories.

Neurotoxin A binds to the nerve terminal membrane by the C-terminal half of its heavy chain. Two co-receptors are recognized on the nerve terminal membranes: a protein (SV2) and a ganglioside. Recycling by endocytosis of the empty synaptic vesicles causes the internalization of neurotoxin molecules bound to their receptor. The translocation is caused by acidification of the vesicles containing the neurotoxin. A pore or translocation channel in the vesicular membrane allows the linearized light chain to enter the cytosolic compartment. At the same time, the disulfide bond linking the two chains is reduced allowing the light chain to diffuse freely in the cytosol.

The neurotoxin inhibits acetylcholine release by an intracellular action driven by its light chain. This is a zinc metalloprotease that specifically cleaves the protein SNAP-25. Neurotransmitters are released into the synapse when Ca²⁺ ions entering the nerve trigger fusion of docked vesicles with plasma membrane. By cleaving SNAP-25, neurotoxin A prevents the fusion of the synaptic vesicle with the presynaptic membrane, thereby blocking the release of acetylcholine in the synaptic cleft resulting in myorelaxation. The proportion of SNAP-25 cleaved determines the degree of inhibition.

Duration of intraneuronal light chain activity
Once internalized by the nerve terminals, the neurotoxin molecules are protected from extracellular mechanisms of exogenous protein elimination and also from possible antibody neutralization. The intraneuronal half-life of the neurotoxin light chain (catalytic domain) is the principal factor determining duration of action, and as OnabotulinumtoxinA and IncobotulinumtoxinA share the same neurotoxin they have an identical molecular duration of action. As long as light chain molecules persist in the neuronal cytosol, they will continue to cleave SNAP-25, which is continuously synthesized in the neuron. Recovery of synaptic function only occurs when the neurotoxin light chain molecules have been eliminated.

Formulations of OnabotulinumtoxinA (900 kDa) and IncobotulinumtoxinA (150 kDa)
Botulinum toxin formulations contain an amount by weight of 900 kDa toxin complex (OnabotulinumtoxinA) or 150 kDa neurotoxin free from complexing proteins (IncobotulinumtoxinA) as well as excipients (Table 1). Both products are in the form of a dry powder for dilution.

Neuroactive entity
One hundred Units of OnabotulinumtoxinA corresponds to 5 ng of toxin, of which one-sixth (150 kDa/900 kDa) would be neurotoxin type A, ie, 0.833 ng. A similar neurotoxin load is measured by ELISA (0.73 ng). The latter observation is consistent with the presence of one molecule of neurotoxin per 900 kDa toxin complex. However, formulated botulinum complex (OnabotulinumtoxinA) has been found partially disassembled at pH 5.5 (with ~80% of the neurotoxin being dissociated from the NAPs), while this is not the case for non-formulated complexes. This raises questions about the impact of the dry powder preparation (vacuum drying) and/or the effect of the formulation on the stability of the toxin complex.

One hundred Units of IncobotulinumtoxinA corresponds to 0.6 ng of neurotoxin A. By ELISA, the neurotoxin load is 0.44 ng for 100 U.

### Table 1

<table>
<thead>
<tr>
<th>Name of toxin or neurotoxin</th>
<th>Name of product</th>
<th>Protein complex load per vial</th>
<th>Neurotoxin load (ng)</th>
<th>Neurotoxin load by ELISA (ng)</th>
<th>MW</th>
<th>Excipients</th>
<th>Units/ pack</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Botox</td>
<td>2.5 mg</td>
<td>0.833 ²</td>
<td>0.73</td>
<td>900 kDa complex</td>
<td>HSA</td>
<td>100 AU</td>
</tr>
<tr>
<td></td>
<td>Vistabel</td>
<td>-</td>
<td>0.417 ²</td>
<td>ND</td>
<td>250</td>
<td>NaCl 0.9 mg</td>
<td>50 AU</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Xeomin</td>
<td>-</td>
<td>0.6 ³</td>
<td>0.44</td>
<td>150 kDa neurotoxin</td>
<td>Sucrose</td>
<td>100 U</td>
</tr>
<tr>
<td></td>
<td>Bocouture</td>
<td>-</td>
<td>0.3 ³</td>
<td>ND</td>
<td>1000</td>
<td>4.7 mg</td>
<td>100 U</td>
</tr>
</tbody>
</table>

1. Manufacturer indication.
2. Estimated on the basis of one neurotoxin molecule (150 kDa) per 900 kDa complex (=1/6 of toxin complex load).
3. Manufacturer indication.
4. Frevert.
Excipients and their role

The excipients present (NaCl or sucrose, and human serum albumin) are added to allow vacuum evaporation or freeze-drying while minimizing denaturation of the toxin/neurotoxin. The type of excipient strongly influences preservation of activity during freeze-drying.36 Thus, NaCl is used in vacuum drying of Botulinum37 but its crystals would denature the neurotoxin during freeze drying.35

Once reconstituted in solution, human serum albumin prevents the non-specific binding of the toxin/neurotoxin and adherence to the vial wall or syringe.36,38 The load of human albumin in commercial toxins (0.5 to 1 mg for 100 U toxin) is minimal with respect to its physiological content (4 to 5 g/kg of body weight, of which 40% to 45% is found in the intravascular space) and very small in terms of quantities used in other medical applications.

Units of Biological Activity of the Toxin

Biological units are not interchangeable between different neurotoxin products because the units used by each manufacturer are not the same. According to European Pharmacopoeia and legal requirements, no consensus statement on biological activity can therefore be drawn. This section will describe how the biological activity of the two botulinum toxins is measured.

Measuring the biological activity of the toxin

The process of toxin/neurotoxin purification leads to a very pure product in terms of molecular entities, but comprising both active and non-active proteins; the same applies with the process of freeze drying, which can cause denaturation of part of the neurotoxin.35,39 Therapeutic use is based on injection of a «quantity of biological activity» expressed by a number of units.

The test used until recently by Allergan and the test used by Merz to measure biological activity of the toxin/neurotoxin in batches launched in the market at an early stage (see published clinical studies) or those currently on the market (note that new tests in use or under development) is based on the determination of the median lethal dose of toxin/neurotoxin after intraperitoneal injection in mice (mLD50 assay).12,18 On this basis, 1 unit of toxin is defined as one mouse LD50, ie, the dose of toxin/neurotoxin capable of killing 50% of a group of mice. Variations in the practical implementation of the mLD50 assay can impact evaluation of the number of mLD50 and therefore the number of units.36,37

The evaluation of IncobotulinumtoxinA complies with the European Pharmacopoeia: the formulated toxin is diluted in a saline solution with an additional quantity of serum albumin whose purpose is to prevent non-specific binding of the neurotoxin to the walls of the vial or the syringe.40 In this condition, the test allows the actual bioavailable quantity of biological activity in the vials to be evaluated. In the OnabotulinumtoxinA test, the formulated toxin is diluted in a saline solution without added protein or gelatin.41 As a result, a fraction of the neurotoxin present may be lost by non-specific adsorption, ie, it evaluates the quantity of activity which is injected when the formulation is reconstituted as in the clinic. With this protocol it is not possible to ascertain the entire biological activity contained in the vial.

Formulations of OnabotulinumtoxinA and IncobotulinumtoxinA have been subjected to studies aimed at comparing the units in the formulations. Using the same mLD50 assay used by Allergan, Hunt and Clarke41 estimated that 1 U of IncobotulinumtoxinA corresponded (on average) to 0.74 (0.69, 0.75, 0.78) Allergan U after standardization of the potency of IncobotulinumtoxinA to that of OnabotulinumtoxinA. On the other hand, based on the test used by Merz, Dressler et al.50 showed that 100 nominal U of OnabotulinumtoxinA correspond to an average potency of 103.1 mLD50 (five batches analyzed) and that 100 U of IncobotulinumtoxinA correspond to an average potency of 101.7 mLD50 (five batches analyzed).

Specific biological activity of the products

Based on the amount by weight of neurotoxin present in 100 U, the specific biological activity (number of units of biological activity / units of mass of neurotoxin) of the products is different, and should be calculated on the basis of (a) the supposed quantity of neurotoxin in the vial or (b) measured by ELISA (Table 1):

- OnabotulinumtoxinA = (a) 120 U.ng⁻¹ or (b) 137 U.ng⁻¹; IncobotulinumtoxinA = (a) 167 U.ng⁻¹ or (b) 227 U.ng⁻¹). Therefore, although the amount of units of neurotoxin is the same when OnabotulinumtoxinA or IncobotulinumtoxinA is administered to a patient, the amount of neurotoxin protein administered is different. IncobotulinumtoxinA contains the highest specific neurotoxin activity.50 The difference in specific activity between the two products may arise from either a different implementation of the mLD50 by the two manufacturers (1 U Allergan being different from 1 U Merz), or because a fraction of the OnabotulinumtoxinA neurotoxin is inactive. The latter possibility has been proposed based on the observation that the specific activity described by Allergan is 2 x 10⁻⁷ mLD50/mg toxin complex compared with a value of 3.7 x 10⁻⁷ mLD50/mg toxin complex published in the scientific literature.33,39

Data from scientific studies highlighting the identical character of the neurotoxin strain in the two products, and the identical mode of action and duration of action of the neurotoxin at the neuromuscular junction, support findings from clinical practice, in which a conversion ratio of 1:1 is reported.42-46

Bibliographic Comparison of OnabotulinumtoxinA and IncobotulinumtoxinA

Head-to-head studies

In total, nine studies40,41,46-52 and two posters53,54 comparing OnabotulinumtoxinA (900 kDa) with IncobotulinumtoxinA (neurotoxin free from complexing proteins - 150 kDa) were identified in the literature and analyzed by the expert group (Table 2), which included four plastic surgeons, an ophthalmologist, an oculo-
### TABLE 2.

**Bibliographic Comparison of OnabotulinumtoxinA and IncobotulinumtoxinA**

<table>
<thead>
<tr>
<th>Article title</th>
<th>Author(s)</th>
<th>Reviewer</th>
<th>Study objectives and methods</th>
<th>Conclusion of author(s)</th>
<th>Conclusion of reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines</td>
<td>Sattler G, Callander MJ, Grablowitz D, et al.</td>
<td>Dr P. Trevidic</td>
<td>OBJECTIVES: To investigate noninferiority of incobotulinumtoxinA to onabotulinumtoxinA for treatment of glabellar frown lines. METHODS: In a prospective, multicenter, randomized, rater-and patient-blind, Phase III trial, 381 patients were randomized in a 2:1 ratio to receive 24 U incobotulinumtoxinA or onabotulinumtoxinA. Efficacy endpoints included percentage of responders (patients with ≥1 point improvement on 4-point facial wrinkle scale) at maximum frown at weeks 4 and 12 as assessed by investigators, and a panel of independent raters based on standardized digital photographs.</td>
<td>IncobotulinumtoxinA is as effective as onabotulinumtoxinA in the treatment of glabellar frown lines over at least 12 weeks. The high satisfaction rates that the treated patients reported supported the independent panel's and investigators' assessments of high treatment success. Both preparations were well tolerated.</td>
<td>This study confirms what many previous studies have shown: equivalence of incobotulinumtoxinA and onabotulinumtoxinA.</td>
</tr>
<tr>
<td>Is there a difference in the persistence, efficiency and efficacy of three botulinum toxin A-containing products? A double-blind, randomised study</td>
<td>Rappel T, Kranzelbinder B, Wiedner M, Scharnagl E.</td>
<td>Dr P. Coulon</td>
<td>OBJECTIVES: To compare the persistence, efficiency and efficacy of three toxins for the treatment of glabellar frown lines or hyperhidrosis axillaris. METHODS: Double-blind, randomized, controlled trial of 84 patients: For glabellar frown lines each patient received one of the three products (5 injection points), in a randomised allocation: – total dose 21 U Botox® (OnabotulinumtoxinA) (n = 21) or 21 U Xeomin® (IncobotulinumtoxinA) (n = 21) or 63 U Dysport® (AbobotulinumtoxinA) (n = 21). For hyperhidrosis axillaris 21 patients received identical protocol of 15 points of injection with 45 U of Botox® or 45 U of Xeomin® per armpit.</td>
<td>This is one of the few studies to directly compare different botulinum toxin type A products. Of the three tested for the treatment of glabellar frown lines, Xeomin® had the most rapid onset (mean 2.8 days) and maintained 100% response in a greater number of patients at Day 120 than both the other preparations. In the treatment of hyperhidrosis, Xeomin® and Botox® were similarly effective. During production, Xeomin® undergoes purification to remove complexing proteins. This suggests that Xeomin® could be associated with a lower incidence of neutralizing antibodies and hence a lower incidence of secondary nonresponse. The data support previous studies showing that botulinum toxin type A is effective and has a good safety profile for the treatment of glabellar frown lines and hyperhidrosis.</td>
<td>The relevance of this study is primarily that rapidity of onset was clearly in favor of Xeomin® vs Botox® or Dysport®. Only mean values and standard deviations were calculated: 2.8 ± 0.8 days for Xeomin®, 6.4 ± 1.1 and 6.7 ± 0.9 respectively, for Botox® and Dysport®. With low but still sufficient numbers (n=83 glabellar frown lines), it would have been very easy to perform simple significance tests (Xi 2) that would most likely have confirmed significant differences. The absence of these tests is regrettable.</td>
</tr>
<tr>
<td>Botulinum toxin type A treatment to the upper face: retrospective analysis of daily practice</td>
<td>Prager W, Huber-Vorländer J, Taufig AZ, et al.</td>
<td>Dr P. Trevidic</td>
<td>OBJECTIVES: Retrospective analysis to compare the clinical efficacy of the most commonly used botulinum toxin type A preparations in daily practice. METHODS: Physicians from 21 centers in Germany completed questionnaires based on records for 1256 subjects aged ≥18 years who had received at least two, but not more than three, consecutive treatments with incobotulinumtoxinA, onabotulinumtoxinA or abobotulinumtoxinA within a 12-month period in the last 2 years. The number of abobotulinumtoxinA injections was so low (1.8%) that they were not included in the analysis. Data on subject and physician satisfaction, treatment intervals, adverse effects and toleration were recorded. In daily aesthetic practice, similar clinical efficacy between incobotulinumtoxinA and onabotulinumtoxinA in terms of subject and physician satisfaction, dosage given and safety were observed. These data support comparable and similar therapeutic efficacy of these two products and clinicians may alternate between incobotulinumtoxinA and onabotulinumtoxinA as product availabilities dictate.</td>
<td>The results show that in daily practice there is no significant difference between the two toxins at a dose ratio of 1:1. Prospective study led by MERZ in Germany on two competing products with standard statistical bias for a retrospective examination of files, with subjective criteria at the discretion of the physician. In spite of that, this study is important and the conclusion is in agreement with those of published double-blind studies.</td>
<td>The results show that in daily practice there is no significant difference between the two toxins at a dose ratio of 1:1. Prospective study led by MERZ in Germany on two competing products with standard statistical bias for a retrospective examination of files, with subjective criteria at the discretion of the physician. In spite of that, this study is important and the conclusion is in agreement with those of published double-blind studies.</td>
</tr>
</tbody>
</table>
TABLE 2.

Bibliographic Comparison of OnabotulinumtoxinA and IncobotulinumtoxinA continued

Comparison of two botulinum toxin type A preparations for treating Crow’s feet: a split-face, double-blind, proof-of-concept study


Dr A Le Pillouer Prost

OBJECTIVES: To compare the clinical effectiveness of botulinum toxin type A free of complexing proteins with a botulinum toxin type A complex for the treatment of crow’s feet. METHODS: In a double-blind, randomized, proof-of-concept study, 12 U of each product were compared in 21 participants with a facial wrinkle score (FWS) of 2 to 3. Evaluations were performed for up to 4 months. Subjects with an improvement of at least 1 point on the FWS were considered responders.

The outcome of a 4-month intra-individual, double-blind comparison of periorbital lines (crow’s feet) demonstrated that both botulinum toxin A products (used in a 1:1 dose ratio) offer good efficacy and tolerability. Small differences observed between the products were statistically not significant. Both botulinum toxin type A free of complexing proteins and the botulinum toxin type A complex have been found to be long-lasting, effective, safe therapeutic options for periorbital lines, without a significant difference between them.

Comparison of the spread of three approved botulinum toxin type A preparations


Pr P. Humbert

OBJECTIVES: To investigate the spread of three approved botulinum toxin type A preparations, with and without complexing proteins. METHODS: In this double-blind, randomized study, 29 healthy women were randomized to receive two of the study medications on contralateral sides of the forehead at doses of 5U incobotulinumtoxinA, 8U onabotulinumtoxinA and 12.5U abobotulinumtoxinA in an identical injection volume. Spread was evaluated by analysis of the area of anhidrosis of each product.

In facial aesthetics, where precise localization of clinical effect is essential, a botulinum toxin type A preparation with limited and predictable spread potential is preferable.

Phase IV study comparing incobotulinumtoxinA and onabotulinumtoxinA using a 1:1.5 dose-conversion ratio for the treatment of glabellar frown lines


Dr M. Bassewicz

OBJECTIVES: To investigate whether a 50% higher dose of onabotulinumtoxinA was nonsuperior to incobotulinumtoxinA in the treatment of glabellar frown lines in the short and long term. METHODS: This Phase IV study enrolled subjects with symmetrical moderate-to-severe glabellar frown lines (score: 22 on a validated Merz 5-point scale) at maximum frown. Corrugator muscles on both sides were treated with two injections of either 4 U incobotulinumtoxinA or 6 U onabotulinumtoxinA (equivalent to a total dose of 20 and 30 U, respectively, if corrugator muscles on both sides and the procerus are treated) allowing intra-individual comparison. Glabellar frown line severity was assessed from standardized photographs every 4 weeks for 4 months and, in a subset of subjects, for up to 6 months post-treatment. The primary efficacy endpoint was the percentage of subjects with an improvement of 1 point on the 5-point scale at week 4. Nonsuperiority was assessed by comparing the response rates of each product.

Although different doses of incobotulinumtoxinA and onabotulinumtoxinA were used, the clinical effect was the same with respect to percentage of responders 4 weeks post-treatment. The 50% higher dose of onabotulinumtoxinA was nonsuperior to the dose of incobotulinumtoxinA for the treatment of glabellar frown lines in this study. As the same doses of incobotulinumtoxinA and onabotulinumtoxinA are commonly used in the clinical setting and are recommended for treatment of glabellar frown lines, the authors conclude that there is no reason to increase the dose for this indication above 20 U for either product.

This is an excellent and original methodology study whose findings will certainly be useful to clinicians.
Among the 11 comparative studies (between 2, 3 or 4 toxins) could be divided into non-inferiority studies (1), studies on the onset of action, duration of action and efficacy (2), tissue dissemination (1), efficacy (3), dose-ranging studies (2), and pharmaceutical studies (2). This summary focuses on aesthetic indications.

Among the 11 studies, three studies sponsored by ALLERGAN concluded that there was no clinical equipotency between IncobotulinumtoxinA and OnabotulinumtoxinA; however, one clinical study was comparing different doses. In contrast, eight studies demonstrated non-inferiority of IncobotulinumtoxinA to OnabotulinumtoxinA, concluding that the two toxins were clinically similar in terms of efficacy and safety with a 1:1 conversion ratio. Six of these studies were sponsored by Merz; for two studies the sponsor, if any, was not indicated.

Based on a review of studies comparing OnabotulinumtoxinA with IncobotulinumtoxinA the consensus is that there is clinical equivalence between the two neurotoxins at a 1:1 dose ratio. These findings are in agreement with the results of a recent meta-analysis of clinical and preclinical studies that directly compared OnabotulinumtoxinA and IncobotulinumtoxinA, and
 Submission data review  

The rigor of analysis of clinical endpoints and adverse events for submission approval is generally much higher than in published reports and therefore to supplement the bibliographic comparison the authors have also compared the OnabotulinumtoxinA and IncobotulinumtoxinA data that resulted in US FDA approval of these products for the treatment of glabellar lines.

OnabotulinumtoxinA received FDA approval in 2002 based on a review of three studies: two multicenter, double-blind, randomized, placebo-controlled trials and an open-label study that included only those subjects who had completed one of the controlled studies and qualified for re-injection. In both placebo-controlled studies, patients with moderate to severe glabellar lines at maximum frown received intramuscular injections of 20 U OnabotulinumtoxinA or placebo into five glabellar sites. Patients were followed up for 120 days after injection. The two primary endpoints were investigator assessment of glabellar

<table>
<thead>
<tr>
<th>TABLE 2.</th>
<th>Bibliographic Comparison of OnabotulinumtoxinA and IncobotulinumtoxinA continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A randomised, double-blind comparison of 20 units of onabotulinumtoxinA with 30 units of incobotulinumtoxinA for glabellar lines</strong></td>
<td><strong>OBJECTIVES:</strong> To explore relative efficacy of different labelled doses of onabotulinumtoxinA and incobotulinumtoxinA for the treatment of glabellar lines in a clinical setting. <strong>METHODS:</strong> In a randomized, double-blind study, 224 subjects with moderate/severe glabellar lines were randomized to 20 U of onabotulinumtoxinA or 30 U of incobotulinumtoxinA. Physicians rated lines at maximum contraction at 28, 84, 98 and 112 days using the facial wrinkle scale (FWS). Primary endpoint was the proportion of responders based on injector’s rating at Day 28. Treatment response was defined as achievement of ≥1 point improvement on FWS. <strong>RESULTS:</strong> 20 U of onabotulinumtoxinA were as effective as 30 U of incobotulinumtoxinA in reducing the severity of glabellar lines 28 days post-injection, and demonstrated a trend in favor of onabotulinumtoxinA at days 84, 98 and 112. These results were obtained despite a 50% higher dose of incobotulinumtoxinA. This result reinforces previously reported biological activity data, demonstrating that unit doses of the two toxins are not interchangeable and has a significant error in the study design. Once binding sites on nerve terminals have become saturated with 20 U, a further 10 or 20 U has no added effect on the glabellar muscles, i.e. the outcomes will be the same, although perhaps longer lasting. (Cf. Carruthers et al., 2005) – In this dose-ranging study, there was no significant difference in efficacy between 20, 30 and 40 U of onabotulinumtoxinA for reducing glabellar lines. <strong>CONCLUSION:</strong> The conclusion of this study cannot be accepted because of the questionable methodology and the small number of patients.</td>
</tr>
<tr>
<td><strong>Comparison of the timeframe until first effect and the duration of action of two botulinum toxins in the forehead</strong></td>
<td><strong>OBJECTIVES:</strong> To analyse differences in efficacy and duration of action between two commercially available type A botulinum neurotoxins (Vistabel® [OnabotulinumtoxinA 4U/50U KDa] and Xeomin® [IncobotulinumtoxinA – pure neurotoxin 150 KDa]) in the forehead region. <strong>METHODS:</strong> In a randomized, double-blind (face design), 12 female volunteers received three injections of 4U Vistabel® each into the left or right forehead area (12 U total dose). The alternate forehead area received three injections of 4U Xeomin® each (12 U total dose). Efficacy was determined by analysing results of brow position photography, facial asymmetry photography and subjective evaluation by the patients. <strong>RESULTS:</strong> This study confirms that the effect of Vistabel® (OnabotulinumtoxinA – conventional toxin 900 KDa) and Xeomin® (IncobotulinumtoxinA – pure neurotoxin 150 KDa) at a 1.1 conversion ratio is not equivalent and favors Vistabel® in terms of efficacy and duration.<strong>CONCLUSION:</strong> The conclusion of the study was that despite a 50% difference in dose, the clinical difference was an average of only 1 point on the facial wrinkle scale. However, this study was sponsored by Allergan, the manufacturer of onabotulinumtoxinA and has a significant error in the study design. Once binding sites on nerve terminals have become saturated with 20 U, a further 10 or 20 U has no added effect on the glabellar muscles, i.e. the outcomes will be the same, although perhaps longer lasting. (Cf. Carruthers et al., 2005) – In this dose-ranging study, there was no significant difference in efficacy between 20, 30 and 40 U of onabotulinumtoxinA for reducing glabellar lines. <strong>CONCLUSION:</strong> The conclusion of this study cannot be accepted because of the questionable methodology and the small number of patients.</td>
</tr>
</tbody>
</table>

which concluded that there was no difference in the relative potency of the two products.65
The purpose of the open-label study of OnabotulinumtoxinA was to determine if the previous results could be maintained over repeated cycles of treatment, and if the safety profile remained unchanged. A total of 373 out of 514 subjects who had completed the two placebo-controlled studies and whose glabellar lines were at least mild in severity at the time of exit from those studies were eligible to enroll. Two treatments of OnabotulinumtoxinA were administered. Thirty days after the first and second treatments the responder rates were at least 86% for both the investigator’s rating of glabellar line severity at maximum frown and the subject’s global assessment of change in appearance of glabellar lines. Adverse events were reported for 137/277 (49.5%) subjects treated in the preceding studies with OnabotulinumtoxinA and for 46/96 (47.9%) subjects treated with placebo. Blepharoptosis was reported for 11 subjects (2.9%) during the two injection cycles (seven subjects [2.5%] were previously treated with OnabotulinumtoxinA and four subjects [4.2%] were previously treated with placebo).

IncobotulinumtoxinA gained FDA approval for the treatment of glabellar frown lines in July 2011 based on data from two trials that used a revised FDA responder definition. Both studies were multicenter, double-blind, randomized, placebo-controlled trials with a duration of 120 days. Patients with moderate to severe glabellar lines at maximum frown (severity score of 2 or 3 on the facial wrinkle scale [FWS]), as assessed by the investigator, were randomized in a 2:1 ratio to 20 U IncobotulinumtoxinA or placebo. The entire 20 U of IncobotulinumtoxinA dose was reconstructed in a total injection volume of 0.5 mL to be injected at five glabellar sites (0.1 mL per site).
ite endpoint to satisfy FDA requirements. The new composite endpoint defines a treatment response as an improvement of 2 points or more from baseline, as assessed by the investigator and the subject on separate 4-point scales, instead of the previously used response definition of improvement of 1 point or more from baseline or a FWS score ≤1. Only a subject fulfilling these two criteria was counted as a responder in the CETS, making these new assessments the most stringent to date.

In both studies, the primary efficacy endpoint of CETS at maximum frown on Day 30 was achieved in a significantly higher number of patients treated with IncobotulinumtoxinA (47.8% and 60.3%) than placebo, none of whom achieved CETS (Table 3). As in the OnabotulinumtoxinA trials, the most common treatment-emergent adverse event was headache: 7.1% and 3.8%, respectively, in the IncobotulinumtoxinA groups and 1.1% in both studies for placebo. One case of blepharospasm was reported in each study in the IncobotulinumtoxinA group.

As a secondary endpoint, the trials also reported data in which a responder was defined as a subject with a score of 0 (none) or 1 (mild) on the FWS at Day 30 according to the investigator. This endpoint is comparable to those in the two OnabotulinumtoxinA FDA submission trials, which also had similar inclusion and exclusion criteria and identical dose and injection volumes into the five glabellar sites. Although the efficacy of two different treatments for the same indication can only be directly compared in head-to-head comparative randomized studies, the similarities between the studies allow cautious comparisons to be made. The response rates in the IncobotulinumtoxinA trials at maximum frown were 76.4% and 79.9% compared with 83.7% and 76.7% in the two OnabotulinumtoxinA trials.

This review of the FDA submission data for OnabotulinumtoxinA and IncobotulinumtoxinA supports the results of the five glabellar sites. Although the efficacy of two different treatments for the same indication can only be directly compared in head-to-head comparative randomized studies, the similarities between the studies allow cautious comparisons to be made. The response rates in the IncobotulinumtoxinA trials at maximum frown were 76.4% and 79.9% compared with 83.7% and 76.7% in the two OnabotulinumtoxinA trials.

The experience of this working group in relation to OnabotulinumtoxinA consists of more than 18,000 injections over a period of 6 to 10 years, and for IncobotulinumtoxinA nearly 2,250 injections over a period of 1 to 2 years, since its launch in France in 2010.

Across the same conditions of treatment, and using the varying techniques and anatomical approaches specific to each practitioner, the findings of the experts from the clinical comparison were the following:

1. All consensus panel experts use a dose conversion ratio of 1:1 when switching from one toxin to another.

2. The onset of action of the two toxins is almost clinically equivalent in the majority of patients in the two cohorts and across all treatment indications. The onset of action is on average 2.8 days for IncobotulinumtoxinA and 3.4 days for conventional botulinum toxin (900 kDa), but varies according to patient.

3. The intensity of action of the two toxins is clinically equivalent in the majority of patients in the two cohorts and across all treatment indications. The equivalence in intensity of action between the two toxins was confirmed at 15 days, 30 days, 3 months and 4 months by all of the experts.

4. The duration of action of the two toxins is clinically similar in the majority of patients in the two cohorts and across all treatment indications. According to the clinical experience of the experts and their retrospective and respective analyses, the duration of action is equivalent between the two toxins at 3 months, 4 months and beyond 4 months. The experts also confirmed that the duration of action for botulinum toxin varies from one patient to another.

5. The aesthetic effect of the two toxins is similar from the point of view of the expert as well as the patient in the majority of patients in the two cohorts and across all treatment indications. Certain experts noted a more flexible effect and natural effect with IncobotulinumtoxinA, despite the absence of any mirror effect (smooth, shiny) on the skin. Some members have observed that the mirror effect on the skin is greater with conventional botulinum toxin (900 kDa). The consensus was that the choice of agent should be at the request of the patient.

6. The spread of the two toxins is clinically similar at equivalent concentrations and dilutions for all treatment indications.

7. The safety profile in the short-, medium- and long-term is similar between the two toxins for all treatment indications. The patients’ impressions in terms of safety were also similar for the two toxins.

8. The rupture of the cold chain necessary for the storage and for the transport of OnabotulinumtoxinA (900 kDa) is, according to the experts, the most common cause of decline in efficacy and safety of OnabotulinumtoxinA. A positive advantage of IncobotulinumtoxinA is that it does not require refrigeration for transportation and storage as it is stable at ambient temperature (<25°C) for up to 3 years before reconstitution.
CONCLUSION

This consensus statement was prepared by an expert panel of 20 members in response to uncertainty surrounding the equivalence in efficacy and safety of OnabotulinumtoxinA (botulinum toxin complex - 900 kDa) and IncobotulinumtoxinA (pure neurotoxin free from complexing proteins - 150 kDa).

Structural and Biological Comparison

Summarizing the biological activity of the two products, the expert panel noted that IncobotulinumtoxinA is derived from the same strain of *C. botulinum* as OnabotulinumtoxinA, but contains only the active neurotoxin moiety (150 kDa). The neurotoxin in the 900 kDa OnabotulinumtoxinA complex and the neurotoxin that constitutes IncobotulinumtoxinA (150 kDa) are therefore identical, sharing the same mode of action, synaptic effects and molecular longevity. The complexing proteins (NAPs) are not required for either the stability of the 900 kDa toxin complex or for limiting the spread of the 150 kDa neurotoxin. Due to the absence of complexing proteins, IncobotulinumtoxinA contains a lower amount of botulinum neurotoxin with respect to units compared with OnabotulinumtoxinA and therefore has a higher specific potency. The fast dissociation of the toxin complex (>80% in less than 1 min at physiological pH) means that regardless of whether OnabotulinumtoxinA or IncobotulinumtoxinA is injected, the only neuroactive protein that disseminates is the 150 kDa neurotoxin, which is the only protein of the complex to possess pharmacological activity on the neuromuscular junction.

The expert panel observed that the protocols for evaluating the biological activity of OnabotulinumtoxinA and IncobotulinumtoxinA are identical, and that it is not possible to state that the units of measure used by Allergan and Merz are identical. However, in clinical practice a 1:1 unit exchange between OnabotulinumtoxinA and IncobotulinumtoxinA is reported.

Bibliographic Comparison

The expert panel identified 9 published studies and 2 published posters directly comparing OnabotulinumtoxinA and IncobotulinumtoxinA in aesthetic indications. Eight of these 11 studies demonstrated non-inferiority of IncobotulinumtoxinA to OnabotulinumtoxinA in terms of efficacy and safety over a variety of treatment indications including forehead lines, glabellar frown lines and crow’s feet. These data have been supplemented by a review of the FDA submission data for OnabotulinumtoxinA and IncobotulinumtoxinA. Although the submission data for IncobotulinumtoxinA use the more stringent new FDA criteria for defining a responder, a secondary efficacy assessment conducted at Day 30 used the same responder definition as the earlier OnabotulinumtoxinA trials with very similar responder rates, further supporting the findings from head-to-head studies.

Survey of Practical and Clinical Experience

In the final section, expert panel members drew on their own extensive clinical experience to provide information on the clinical equivalence of OnabotulinumtoxinA and IncobotulinumtoxinA. The consensus of the group was that OnabotulinumtoxinA (900 kDa) and IncobotulinumtoxinA (150 kDa) are clinically equivalent in terms of efficacy and safety parameters.

The absence of complexing proteins in IncobotulinumtoxinA does not hinder its performance, and the pure form of neurotoxin may potentially reduce sensitization and antibody formation, which has been a concern with past formulations containing complexing proteins. Furthermore, IncobotulinumtoxinA does not need to be refrigerated, which makes it easier to store and transport.

In conclusion, among this expert panel of French aesthetic physicians and biologists, there is consensus that OnabotulinumtoxinA and IncobotulinumtoxinA are clinically equivalent in terms of efficacy and safety and that a switch from one drug to the other can be made using a simple 1:1 conversion ratio. Properties that differentiate IncobotulinumtoxinA from other botulinum toxins are its pure neurotoxin free from complexing proteins and its stability at ambient temperature for up to 3 years before reconstitution.

CONTRIBUTIONS

All the authors contributed to concept development, writing and critical review of the manuscript.

ACKNOWLEDGMENTS

The authors wish to acknowledge the contribution of Jenny Grice for translation of the French text and for helping to finalize this manuscript. This activity was supported by an unrestricted educational grant provided by Merz Pharmaceuticals GmbH.

DISCLOSURES

None of the authors have any relevant conflicts to disclose.

REFERENCES


