IncobotulinumtoxinA for Upper Facial Lines

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Nottingham

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Before we start ….

• *Evidence wise* we are with all botulinum toxins on the good side as all toxins are drugs and drugs require clinical controlled trials

but let’s have a general look on botulinum toxin first!
At the moment we have three different toxins in Europe and the US

- *Abo* - BoNT-A (Dysport /Azzalure)
- *Inco* - BoNT-A (Xeomin /Bocouture)
- *Ona* - BoNT-A (Botox /Vistabel)
They are different, but they behave all similar when injected
And all three preparations have the same 150 kd component.
They decrease muscular activity*

- Botulinum toxin *specifically prevents neurosecretory vesicles from docking/fusing with the nerve synapse plasma membrane* and releasing their neurotransmitters to the adjacent muscle fibers.

* as well as sweating
Decrease of muscular activity and sweating around 2 injection points

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The area of the field of effect is influenced by the

- Units injected
- Muscles size and activity*

* Respectively the activity of the sweat glands
They are studied and licensed for ONE aesthetic indication mostly

• The glabella
Here one study with another botulinum toxin as comparator

Noninferiority of IncobotulinumtoxinA, Free from Complexing Proteins, Compared with Another Botulinum Toxin Type A in the Treatment of Glabellar Frown Lines

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BACKGROUND Use of botulinum toxin for esthetic purposes has rapidly expanded over the last 20 years. IncobotulinumtoxinA, also known as NT 201, is a new botulinum toxin type A (150 kDa) that is free from complexing proteins.

OBJECTIVES A prospective, multicenter, randomized, rater- and patient-blind, international Phase III trial to investigate the noninferiority of incobotulinumtoxinA to another botulinum toxin type A, onabotulinumtoxinA, in the treatment of glabellar frown lines.

METHODS A total of 381 patients were randomized in a 3:1 (incobotulinumtoxinA: onabotulinumtoxinA) ratio to receive 24 U incobotulinumtoxinA or onabotulinumtoxinA. Efficacy end points included the percentage of responders (patients with an improvement of ≥1 point on a 4-point facial wrinkle scale) at maximum frown at weeks 4 and 12 as assessed by the investigators, and a panel of independent raters based on standardized digital photographs.

RESULTS Four weeks after injection, response rates at maximum frown were 96.4% in the incobotulinumtoxinA group and 95.7% in the onabotulinumtoxinA group as assessed by independent raters. Analysis of the data confirmed the noninferiority of incobotulinumtoxinA. Response rates at rest were lower for both products. The rate of adverse events was low.

CONCLUSION IncobotulinumtoxinA is equally as effective as onabotulinumtoxinA in the treatment of glabellar frown lines. Both preparations were well tolerated.

This study was funded by Merz Pharmaceuticals GmbH. Editorial assistance was provided by Ogilvy 4D, Oxford, UK.
Results using a 4 point wrinkle scale

...but the glabella is just one indication ...
the toxins are injected all over the face

Sattler et al. 2011.
Dysport U

- 10 s.U.
- 5 s.U.
- 2-3 s.U.

Botox / Xeomin U

- 4 BU
- 2 BU
- 0.8 - 1.2 BU

So we need evidence beyond the glabella!
The first published trial on three facial areas

**Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Upper Facial Lines: Results From a Randomized, Double-Blind, Placebo-Controlled, Phase III Study**

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**BACKGROUND** Treating upper facial lines (UFL)—a combination of glabellar frown lines (GFL), horizontal forehead lines (HFL), and lateral periorbital lines (LPL)—is a common aesthetic practice.

**OBJECTIVE** To provide the first placebo-controlled evidence of the efficacy and safety of incobotulinumtoxinA for UFL.

**METHODS** Healthy subjects (≥18 years) with moderate-to-severe GFL, HFL, and LPL on the Merz Aesthetics Scales (MAS) at maximum contraction were randomized to incobotulinumtoxinA or placebo. For incobotulinumtoxinA, the recommended dose was 40 units of incobotulinumtoxinA, with the dose for each line determined by the investigator.

**CONCLUSION** IncobotulinumtoxinA demonstrated significant efficacy in treating GFL, HFL, and LPL separately and combined, as well as a good safety profile.

M. Kerscher has received research support and has conducted clinical trials for Merz Pharmaceuticals GmbH (as Head of the Division of Cosmetic Sciences, University of Hamburg, Germany) and has acted as a speaker and/or investigator for Merz, Kythera, Q-Med/Galderma, and Pierre Fabre. B. Rzany has acted as a speaker and/or advisor for IPSEN, Kythera, Merz, Q-Med/Galderma, Teoxane, and Sinclair. W. Prager has acted as a lecturer, advisor, and investigator for Merz, Galderma, and Allergan. P. Trevidic has acted as a speaker for IPSEN, Merz, and Teoxane. C. Inglefield has acted as an advisor and speaker for Merz, Syneron, Eternogen, and Q-Med Galderma. C. Turnbull has indicated no significant interest with commercial supporters.

So let’s look at this trial!
Methodology

- prospective
- randomized (2:1)
- double-blind (identical vials)
- placebo-controlled
- multicenter
Indication

- subjects with moderate-to-severe upper facial lines (UFL)
The Crow’s feet scale at maximum contraction

Flynn et al 2012
Patients were injected based on defined injection points and dosages.

Kerscher et al. 2015.
There was an exception for the forehead

- For this indication dosing could be adjusted based on muscular activity / grade of elastosis
As a high dosage will result in mostly unwanted moderate to severe brow ptosis.

So the study reflects real life injection decisions.

Nestor et al. 2011.
The inclusion and outcome criteria were based on 5-point MAS* scales

- These are thoroughly validated scales although for most other botulinum toxin studies 4-point scales have been used

* MERZ Aesthetic Scales
The Crow’s feet scales at maximum contraction

Flynn et al 2012
**Intra-rater reproducibility**

single scales upper face

D: Glabella lines dynamic, B: crow’s feet at rest, C: Crows feet dynamic

Flynn et al 2012
Overall *inter*-rater reproducibility
upper face

Flynn et al 2012
Methods

Outcome criteria

• The primary efficacy variables comprised
  – the rate of response as calculated by the proportion of investigator-assessed scores of “none” (0) or “mild” (1) on the 5-point MAS at maximum contraction on Day 30 for each individually treated area (GFL, HFL, and LPL)
  – and also the investigator-assessed combined MAS sum score of #3 at maximum contraction on Day 30 for the 3 treated areas combined (GFL, HFL plus LPL).

Kerscher et al. 2015.
Methods

Outcome criteria

• The secondary efficacy variables comprised
  – investigator- and subject-assessed responses on Day 30 for the overall appearance of the upper face according to the clinician’s and subject’s Global Impression of Change Scale (GICS);
  – …. so these are easier ones to reach

  \[ \text{least 1-point improvement} \] from baseline at rest and maximum contraction on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually

  – …. Kerscher et al. 2015.
Methods

Study schedule

Kerscher et al. 2015.
Results

Patient flow

Kerscher et al. 2015.
Results

Main outcome criteria

Figure 4. Response rates for investigator-assessed scores of “none” (0) or “mild” (1) on the 5-point MAS for GFL, HFL, and LPL and a sum score of 3 or lower in the UFL combination at maximum contraction on Day 30—observed cases, FAS. †Score of “none” (0) or “mild” (1); ‡sum score of 3 or lower.

Kerscher et al. 2015.
Results

Secondary outcome criteria at day 30

TABLE 3. Proportion of Subjects With a “Much Improved” (Increase of 2 Points) or “Very Much Improved” (Increase of 3 Points) Score on the GICS at Day 30—Observed Cases, FAS

<table>
<thead>
<tr>
<th></th>
<th>IncobotulinumtoxinA Group (n = 105)</th>
<th>Placebo Group (n = 51)</th>
<th>p (Logistic Regression Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator’s rating</td>
<td>86.4</td>
<td>2.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Subject’s rating</td>
<td>77.7</td>
<td>2.1</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Logistic regression model (including investigational site and treatment group as factors) for the treatment area combination (GFL, HFL plus LPL).
Rating according to the GICS: −3 = very much worse; −2 = much worse; −1 = minimally worse; 0 = no change; 1 = minimally improved; 2 = much improved; 3 = very much improved.

Kerscher et al. 2015.
Results for the glabella 1-point improvement over time (secondary criteria)

Kerscher et al. 2015.
Results for the forehead
1-point improvement over time
(secondary criteria)

Kerscher et al. 2015.
Results for the crow’s feet 1-point improvement over time (secondary criteria)

Kerscher et al. 2015.
Summary of efficacy

• Efficacy was good for all indications – but a bit weaker for the crow’s feet
What are the reasons for that?

- The zygomatic muscles, e.g. the smile is determined not only by the m. orbicularis oculi but by other muscles, too.

De Maio and Rzany 2007.
Results

Safety

- Treatment-emergent AEs of special interest
  - 2 cases of eyelid ptosis*, with one case being unilateral and the other being bilateral (n = 2; 1.9%), and 2 cases of dry eyes (n = 2; 1.9%).

*Both incidences of eyelid ptosis were considered to be mild

Kerscher et al. 2015.
What was a challenge of this trial!

- A very high proportion of screening failures!
Results

Patient flow

Kerscher et al. 2015.
Reason for screening failure

- Patients failed the questionnaire for significant psychological impact (FLQA-k)
What is the FLQA-k?

- The FLQA-k is a patient-reported outcome tool for the evaluation of self-perception of a subject’s body and aesthetic appearance. The questionnaire contains 44 items across several domains (body experience, body care, social contacts and avoidance, and self-confidence). A cutoff FLQA-k score of <0 was used in this study, which represents eligible subjects evaluated as having significant psychologic strain.

There are no published references for this tool and it had been never used before in an RCT.
So why was it used!

• Because of regulatory reasons
  – The inability of the German BfArM to accept that botulinum toxin is used beyond a clear disease definition
Summary

• Incobotulinumtoxin A proved to be efficacious and safe when treating three adjacent facial areas at the same time
Summary

• This study adds important evidence to the use of BoNT-A for this commonly used aesthetic indications
Summary

• The study is less comparable to other botulinum toxin studies because of several reasons
  – Outcome criteria: a 5 point score was used instead of a 4 point score
  – Inclusion criteria: by using a questionnaire as an inclusion criteria that deselected patients otherwise deemed fit to be treated
Summary

- The FLQA-k questionnaire was added because of the pressure of the German agency.
- This made the study less comparable to other studies and more expensive due to the high number of unnecessary screening failures.
Which raises the questions ....

Does this reflect real ethic concerns of the agency or is this more bigotry/paternalism towards aesthetic medicine?

;-)) and who controls the agency!