IncobotulinumtoxinA in Esthetics

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ABSTRACT

IncobotulinumtoxinA (Xeomin®/Xeomeen®/Bocouture®/XEOMIN Cosmetic™) is a botulinum toxin type A that differs from other commercially available botulinum toxin type A preparations in that it is free from complexing proteins ([150 kDa]/NT 201). The proven efficacy of incobotulinumtoxinA in various therapeutic indications preceded its use in the field of esthetic medicine, where it is widely approved for the treatment of glabellar frown lines on the basis of positive efficacy and safety findings from a number of clinical trials. Here, we discuss the characteristics of incobotulinumtoxinA and review the clinical data supporting its use in esthetics.

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INTRODUCTION

Characteristics of IncobotulinumtoxinA

IncobotulinumtoxinA (Xeomin®/Xeomeen®/Bocouture®/XEOMIN Cosmetic™; Merz Pharmaceuticals GmbH, Germany), along with onabotulinumtoxinA (BOTOX®/BOTOX® Cosmetic/Vistabel®; Allergan, Irvine, CA, USA) and abobotulinumtoxinA (Dysport®; Ipsen Ltd, Slough, Berkshire, UK / Azzalure®; Galderma UK Ltd, Watford, Hertfordshire, UK), is derived from the Hall strain of the anaerobic bacterium *Clostridium botulinum* type A. However, incobotulinumtoxinA is a formulation of botulinum neurotoxin type A that has undergone a purification processes that separates the 150-kDa neurotoxin from the high-molecular-weight (900 kDa) complex.[1,2] Therefore, the active ingredient of incobotulinumtoxinA represents the pure neurotoxin (150 kDa) that is free from complexing proteins.[1] In this respect, incobotulinumtoxinA differs from onabotulinumtoxinA and abobotulinumtoxinA, which both contain complexing proteins. IncobotulinumtoxinA is licensed in the United States, Canada, all major European countries, Argentina, and South Korea for the treatment of glabellar frown lines (GFL); in Russia and Mexico it is licensed for the treatment of mimic wrinkles and hyperkinetic facial lines, respectively.

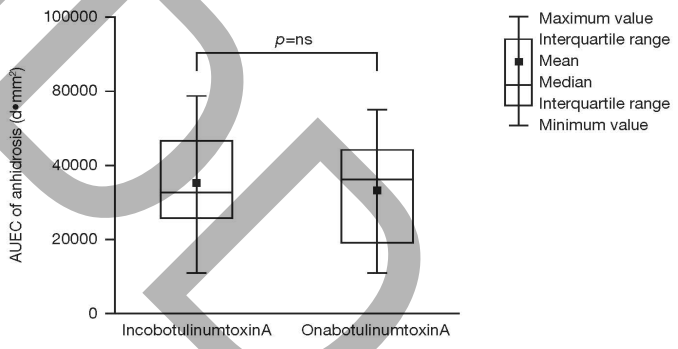
In a study by Frevert to determine the amount of neurotoxin present in pharmaceutical preparations of incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, the mean concentrations were observed to be 0.44 ng/100 U, 0.73 ng/100 U, and 0.65 ng/100 U, respectively. IncobotulinumtoxinA contains no other clostridial proteins, and, therefore, the specific biologic potency relative to the total foreign protein is 227 U/ng. Since the reported clostridial protein content per 100 U of onabotulinumtoxinA is 5 ng and of abobotulinumtoxinA is 0.87 ng, the equivalent specific biologic potency relative to the total foreign-protein load for onabotulinumtoxinA is 20 U/ng and for abobotulinumtoxinA is 115 U/ng.[3] Thus, the foreign-protein load delivered per unit of incobotulinumtoxinA is lower than that for both onabotulinumtoxinA and abobotulinumtoxinA.

Complexing proteins protect the neurotoxin from harsh environmental conditions (such as low gastric pH) after oral ingestion.[4,5] However, whether or not they are useful in commercially available preparations of botulinum neurotoxin serotype A (BoNT/A) is disputed as complexing proteins play no role in the clinical or therapeutic efficacy of BoNT/A. In real-time and accelerated-stability studies, incobotulinumtoxinA was stable without refrigeration for 48 months and was unaffected by short-term temperature stress up to 60°C, suggesting that a role for complexing proteins in stabilizing the neurotoxin outside the intestine is unlikely.[6] Furthermore, rapid dissociation of the BoNT/A complexes in onabotulinumtoxinA and abobotulinumtoxinA occurs at a neutral physiological pH, with a release of up to 80% of neurotoxin within 1 minute at neutral pH.[7] Such rapid dissociation at normal physiologic pH suggests that the complexing proteins cannot protect the neurotoxin postinjection, or limit its spread.

Spread of Effect/Field of Efficacy

The spread of different BoNT/A preparations is of crucial clinical relevance, especially in esthetics, where precise localization of the clinical effect is essential to avoid adverse events (AEs) caused by movement beyond the target muscle.[8] Six weeks after injection of dosages in line with those recommended for the treatment of GFL,[9-11] the mean maximal areas of anhidrosis (indicating the size of the field of efficacy) for incobotulinumtoxinA (5 U), onabotulinumtoxinA (5 U), and abobotulinumtoxinA (12.5 U) were 364.3 ± 138.1, 343.1 ± 110.7, and 459.1 ± 151.8 mm^2, respectively.[8] The maximal area of anhidrosis for inco-

FIGURE 1. The maximal area of anhidrosis of incobotulinumtoxinA and onabotulinumtoxinA within 6 weeks.[8] AUEC, area under the effect curve.



botulinumtoxinA was not significantly different from that of onabotulinumtoxinA and that of abobotulinumtoxinA.[8] (Figure 1). These results provide evidence that the absence or presence of complexing proteins does not affect neurotoxin spread.

Other factors may influence neurotoxin spread, such as injection volume or depth, and injection accuracy. However, one study of incobotulinumtoxinA showed no significant differences between 2 different injection volumes to administer 25 U for the treatment of GFL,[12] and a pilot study in subjects with forehead hyperhidrosis revealed that size of the area of anhidrosis was unaffected by injection depth (intradermal versus intramuscular).[13]

Immunogenicity

Complexing proteins and inactive neurotoxin serve no therapeutic or beneficial purpose, and, consequently, increase the foreign-protein load delivered with onabotulinumtoxinA and abobotulinumtoxinA above that represented by the active neurotoxin. Any foreign protein is potentially immunogenic, and, if neutralizing antibodies are generated, treatment failure can result.

Antibody-induced treatment failure has long been recognized in therapeutic uses of BoNT/A, such as for cervical dystonia or spasticity, where doses can be considerably higher than in esthetics. For example, 4.3% of 559 subjects treated with onabotulinumtoxinA (cumulative dose >450,000 U) for torticollis between 1984 and 1992 developed neutralizing antibodies.[14] From 1998, the level of clostridial proteins in onabotulinumtoxinA was reduced by 20 ng/100 U to 5 ng/100 U; one study found that this reduced protein load decreased the risk of antibody formation by a factor of 6.[15] However, cases of antibody-induced treatment failure have still been reported with the 5-ng/100-U formulation of onabotulinumtoxinA when used for therapeutic indications.[16, 17]

In a preclinical study, repeat injections of incobotulinumtoxinA, in contrast to onabotulinumtoxinA and abobotulinumtoxinA, did not induce neutralizing antibodies in New Zealand rabbits.[18] Eight intradermal injections of 16 U incobotulinumtoxinA or onabotulinumtoxinA were performed 2 to 8 weeks apart with an additional 25-U dose administered 10 weeks after the eighth injection. AbobotulinumtoxinA was administered over a 13-week period at a starting dose of 40 U/kg for the first 5 injections followed by a final, sixth injection of 20 U/kg. No animal had neutralizing antibodies after incobotulinumtoxinA injection, but 15 and 4 rabbits, respectively, had neutralizing antibodies following abobotulinumtoxinA and onabotulinumtoxinA injections.[19] This preclinical evidence is supported by clinical data from a study of subjects with upper limb spasticity who were treated with one injection of either placebo or incobotulinumtoxinA followed by 5 injections of incobotulinumtoxinA (maximum cumulative dose: 2,395 U); no subjects developed neutralizing antibodies during the 89 weeks of the study.[20]

The development of neutralizing antibodies has not been extensively studied in esthetics, but there have been several reports of immunity or resistance to cosmetic applications of onabotulinumtoxinA and abobotulinumtoxinA,[21-26] and the possibility of the formation of neutralizing antibodies in esthetics should not be dismissed. In order to minimize the risk of complete secondary treatment failure due to neutralizing antibodies, "booster injections" are best avoided.[23] However, in esthetics, it is a common practice to assess subjects at 2 weeks post-treatment in case touch-up injections are necessary.[27] Therefore, a short injection interval is often inevitable after the initial treatment.

IncobotulinumtoxinA in Neurology

BoNT/A preparations have been used extensively in neurologic indications (Table 1) prior to their expansion into esthetic medicine, with incobotulinumtoxinA demonstrating efficacy, good tolerability, and non-inferiority to onabotulinumtoxinA in the treatment of cervical and focal dystonias, and blepharospasm at similar dosages.[28-30] In addition, Phase 3 clinical trial data have shown a comparable duration of effect for incobotulinumtoxinA and onabotulinumtoxinA in blepharospasm and cervical dystonia (Figure 2).[1]

Clinical Efficacy of IncobotulinumtoxinA in Esthetic Indications

Glabellar Frown Lines

Placebo-controlled studies

In esthetics, there have been several randomized, placebo-controlled trials investigating the efficacy of incobotulinimtoxinA in treating GFL. Two identically designed, randomized, double-blind, placebo-controlled Phase 3 studies in 547 subjects (≥18 years old) with moderate-to-severe GFL at maximum frown on the Facial Wrinkle Scale (FWS: 0 = none, 1 = mild, 2 = moderate, and 3 = severe) investigated the efficacy of a single treatment of 20 U incobotulinumtoxinA or placebo over 120 days.[31,32]

TABLE 1.

Summary of Clinical Trials of IncobotulinumtoxinA in Neurologic and Esthetic Indications

	Indication	Comparator	Total Number of Subjects	Number of Subjects Treated With IncobotulinumtoxinA	Number of Subjects in Comparator Group	Reference #
Therapeutic	Cervical dystonia	OnabotulinumtoxinA	463	231	232	28
	Cervical dystonia	Placebo	233	159	74	55
	Blepharospasm	OnabotulinumtoxinA	300	148	152	29
	Post-stroke upper-limb spasticity	Placebo	148	73	75	56
Esthetic	GFL	OnabotulinumtoxinA	381	284	97	35
	GFL	Placebo	271	182	89	32
	GFL	Placebo	276	184	92	31
	GFL	None	801	796		40
	GFL	None	105	105		34
	Crow's feet	OnabotulinumtoxinA	21	21	21	41

GFL, glabellar frown lines.

FIGURE 2. Duration of treatment effect of incobotulinumtoxinA and onabotulinumtoxinA in Phase 3 studies in blepharospasm and cervical dystonia.[1]
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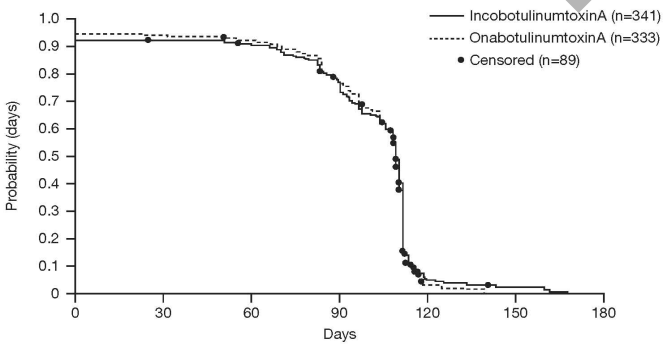
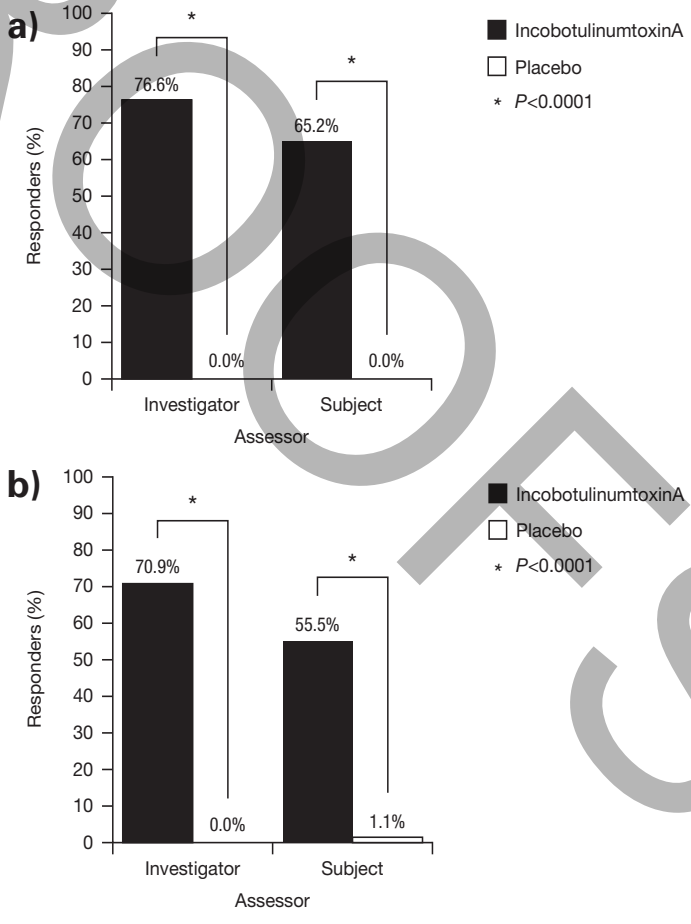


Efficacy was assessed using a new composite endpoint of treatment success (CETS) to reflect the US Food and Drug Administration's (FDA's) recent increased interest in identifying substantial improvements after BoNT/A treatment. Importantly, CETS responders were defined as subjects with an improvement of ≥2 points (investigator-assessed) at maximum frown on the FWS at day 30 compared with baseline, as well as an improvement of ≥2 points at maximum frown on a subject-assessed 4-point scale (responses: 0 = no muscle action at all, 1 = some even slight muscle action possible, 2 = moderately strong muscle action possible, 3 = strong muscle action possible that may cause local pallor) compared with baseline. IncobotulinumtoxinA was superior to placebo ($P<.0001$) at day 30 postinjection according to the CETS in both studies (Carruthers et al[31] 60.3% vs 0%; Hanke et al[32] 47.8% vs 0%). Breakdown of the CETS revealed the superiority of incobotulinumtoxinA to placebo in both the investigator and subject assessments in both studies

FIGURE 3. Percentage of responders (subjects with a ≥2-point improvement from baseline) according to a 4-point scale assessed by the investigators as subjects at day 30 in **a)** placebo-controlled trial by Carruthers et al[31] and **b)** the placebo-controlled trial by Hanke et al.[32]



(Figure 3). In addition, the investigator-rated FWS score of none (0) or mild (1) at maximum frown at day 30 postinjection revealed superiority of incobotulinumtoxinA to placebo (P<.0001) in both studies, with responder rates for incobotulinumtoxinA and placebo of 79.9% vs 0%, respectively[31] and 76.4% vs 0%, respectively.[32] The subjects' assessment at maximum frown at day 30 using a definition of a responder as an improvement of ≥1 point on the subjects' 4-point scale also confirmed the superiority of incobotulinumtoxinA compared with placebo in both studies (P<.0001), with responder rates of 87.5% vs 9.8%, respectively[31] and 83.5% vs 11.2%, respectively.[32]

Importantly, these 2 studies are the first clinical trials to implement these efficacy criteria in line with the FDA's preference for rigorous efficacy assessments of BoNT/A. In contrast to other studies where responders were often defined as subjects with a ≥1-point improvement from baseline or subjects with a score of 0 or 1 on the FWS, in these studies the definition of a responder set the threshold much higher. Not only did subjects have to achieve a ≥2-point improvement from baseline for them to qualify as a responder on the CETS, but this improvement had to be simultaneously achieved in the investigator and subject assessments, making these new assessments the most stringent applied to date.[31,32] It is important to note that the subject assessment of the CETS was also on a 4-point scale and therefore more difficult to achieve than a 2-point improvement on the commonly used 9-point Likert-type scales. If the CETS is employed in other trials in the future, it will provide valuable standardization to BoNT/A efficacy assessments.

The efficacy and safety of incobotulinumtoxinA for GFL treatment has also been investigated in another prospective, multicenter Phase 3 clinical trial conducted in Germany. The study was designed according to the recommendations of the local authority to gain approval in Germany for this indication. The main, randomized phase was 120 days, followed by an open-label extension period (Merz Pharmaceuticals GmbH, data on file). The subjects enrolled were males and females aged ≥18 years with moderate-to-severe GFL on the FWS and a sum score below cut-off based on the Quality of Life, Skin and Cosmetics Questionnaire ('Fragebogen zur Lebensqualität, Haut und Kosmetik' [FLQA-k]).[33]

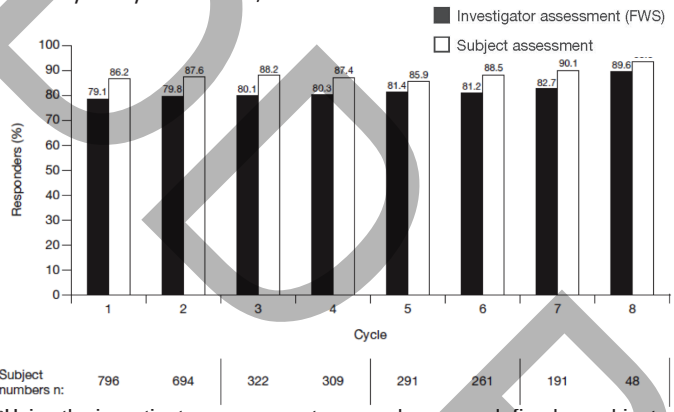
The impact of the FLQA-k as an inclusion criterion

In clinical trials, subject selection is usually based on wrinkle severity as assessed on a wrinkle scale. In this study, however, the additional inclusion criterion of a sum score below cut-off on the FLQA-k was required by the German regulatory authority (BfArM). The FLQA-k questionnaire was designed to assess health-related quality of life in subjects with various skin conditions, and included topics such as social life and emotional status.[33] Its use resulted in a more challenging study population; of note, 108 subjects were not randomized and 78.8% (85/108) of these dropouts were because of screening failure due to the lack of a sum score below cut-off resulting in most subjects (79.9%) in the full analysis set having severe GFL (a score of 3) at maximum frown at baseline, while the remainder had a score of 2 (moderate). This differs from other BoNT/A trials where the mean score at baseline in the BoNT/A groups (where subjects had to have a score of ≥2 at maximum frown on a 4-point scale) was 2.59, meaning that approximately 40% of subjects had a score of 2.[34,35] The use of this questionnaire may also select a study population more in line with the intended subjects for whom the severity of their wrinkles poses an important psychological impact.[9-11] Its use meant that most subjects would have to achieve a 2-point improvement in order to qualify as a responder when assessed by the investigator (responder = subject with a score of 0 or 1). Therefore, the rating by the subject on the Patient Global Assessment (PGA) may be a more useful measure in this study because this scale is designed to measure the relative improvement from baseline, which is the important outcome for the subject.

"IncobotulinumtoxinA is highly purified and free from complexing proteins and is a potent and well-tolerated botulinum toxin serotype A with proven efficacy in neurological and esthetic indications."

Subjects received one 20-U dose of incobotulinumtoxinA or placebo during the main phase and one 20-U dose of incobotulinumtoxinA during the open-label extension period. In the main period, 256 subjects were randomized 2:1 and treated with the study medications (incobotulinumtoxinA: 169 subjects [19.5% male]; placebo: 87 subjects [23% male]). The percentage of responders on the FWS (subjects with a score of 0 or 1 at maximum frown) at day 30 postinjection during the main period was significantly higher for incobotulinumtoxinA (51.5%) compared with placebo (0.0%; P<.0001). In addition, the percentage of responders on the 9-point PGA scale (subjects with a score of >2, moderate improvement) was significantly higher for incobotulinumtoxinA (67.5%) compared with placebo (1.1%) at day 30 postinjection (P<.0001) (Merz Pharmaceuticals GmbH, data on file). The relatively low response rate of 51.5% compared with other incobotulinumtoxinA studies may be due to the more severely affected study population and the high proportion of males (20%) compared with, for example, the all-female study by Sattler and colleagues and the open-label study of incobotulinumtoxinA by Imhof in which only 5% of the study population was male.[36,37] The number of men is significant since, probably due to their larger muscle mass, they require higher doses of BoNT/A than women for GFL treatment,[38,39] and therefore the 20-U dose

FIGURE 4. Overall responder rates according to investigator (none or mild wrinkles) and subject assessments[a] (one grade improvement) *at maximum frown* at the 'Evaluation Visit' (day 30 postinjection) in Cycles 1-8 (full analysis set, n=796).[40]



[a]Using the investigator assessment, responders were defined as subjects with a Facial Wrinkle Scale (FWS) score of 'none (0)' or 'mild (1)'. Using subject assessment, responders were defined as subjects with ≥1-point improvement on the 4-point scale compared with day 0.

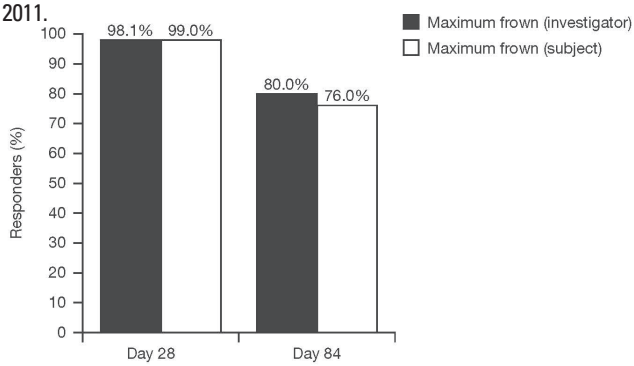
used in this study would be unlikely to achieve optimal results in 20% of the study population.

Open-label studies

The first study to investigate the repeated usage of incobotulinumtoxinA in the clinical setting was a prospective, open-label, multicenter, repeat-dose Phase 3 trial,[40] which enrolled subjects from the two Phase 3, placebo-controlled trials,[31,32] along with subjects from 2 other randomized, placebo-controlled trials (www.clinicaltrials.gov identifiers: NCT00430963 and NCT00430586; Merz Pharmaceuticals GmbH, data on file). This large study included a total of 801 subjects with moderate-to-severe GFL on the FWS at maximum frown. Subjects received up to 8 repeated cycles of treatment with 20 U incobotulinumtoxinA with treatment intervals of at least 85 days. Efficacy was assessed at maximum frown on day 30 of each cycle as the percentage of responders: subjects with glabellar-line severity of none (0) or mild (1) on the FWS (investigator assessment) or subjects with ≥1-point improvement compared with day 0 on a 4-point scale (subject assessment). Investigator-assessed response rates were high and remained high throughout a maximum of 8 cycles (range 79.1%–89.6%), as were subject-assessed responder rates (range 85.9%–93.8%), demonstrating the long-term efficacy of incobotulinumtoxinA. This study also demonstrated that repeat dosing of incobotulinumtoxinA was effective, with a trend towards increasing response rates that were consistently high for up to 8 regular cycles of treatment (Figure 4).

The efficacy of incobotulinumtoxinA in GFL treatment has also been demonstrated in a prospective, open-label, Phase 3

FIGURE 5. Investigator and subject assessments of responder rates (subjects with an improvement of ≥1 point compared with day 0 on a 4-point scale) at days 28 and 84 postinjection with 20 U incobotulinumtoxinA.[36] Adapted from Imhof M, et al. *Journal of Clinical and Aesthetic Dermatology.* 2011.



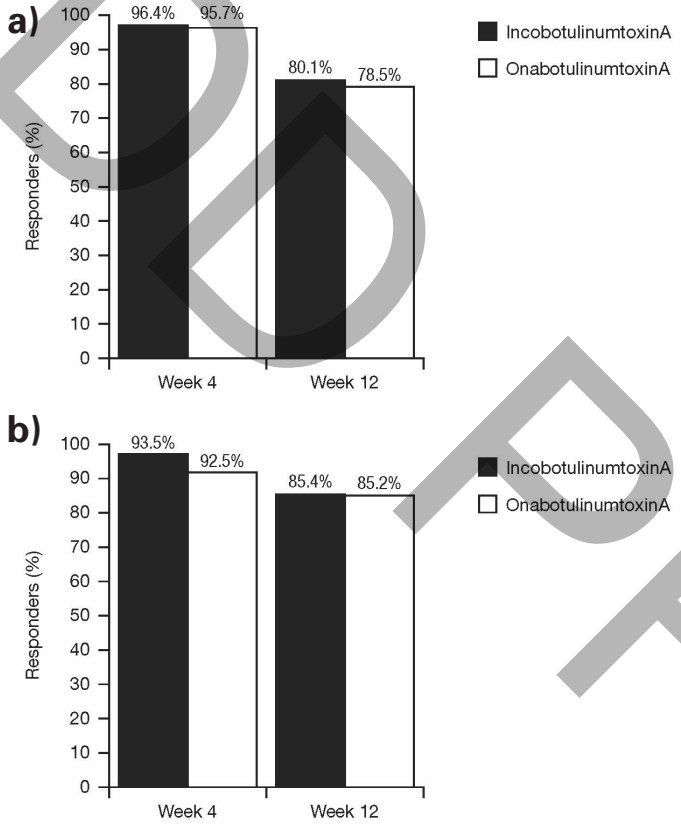
single-arm study.[36] A total of 105 subjects (18–65 years of age) with moderate-to-severe GFL at maximum frown on the FWS were treated with 20 U incobotulinumtoxinA and assessed over 84 days. At 28 days post-treatment, 98.1% of subjects showed an improvement of ≥1 point on the investigator-assessed FWS compared with day 0 and, after 84 days post-treatment, a high percentage of subjects (80%) remained responders (Figure 5). Subject-assessed responder rates were consistent with investigator assessments, with 99% and 76% of subjects achieving an improvement of ≥1 point on the 4-point subject-assessment scale at maximum frown on days 28 and 84, respectively.

Head-to-head studies

IncobotulinumtoxinA vs onabotulinumtoxinA

In the largest comparative Phase 3 study conducted to date, the non-inferiority of incobotulinumtoxinA to onabotulinumtoxinA for GFL treatment was demonstrated.[37] A total of 381 females aged 18 to 50 years with moderate-to-severe GFL according to the FWS were randomized in a 3:1 (incobotulinumtoxinA: onabotulinumtoxinA) ratio to receive 24 U incobotulinumtoxinA or onabotulinumtoxinA to allow for adequate safety monitoring of this novel BoNT/A. This dose was the average dose used for GFL treatment in clinical practice in a survey of physicians at the time the study was initiated and it lies towards the middle of the recommended range on the European label for incobotulinumtoxinA.[10] Assessments were made from standardized digital photographs by both the subjects and a panel of 3 independent expert raters. A response was defined as an improvement of ≥1 point at weeks 4 and 12 compared with baseline, as assessed by investigators and subjects on the FWS. For the 9-point PGA scale, response was defined as a score of ≥2 at weeks 4 and 12 compared with baseline. Comparable high response rates at maximum frown at 4 weeks post-treatment were observed with incobotulinumtoxinA and onabotulinumtoxinA according to the investigator using the FWS (96.4% vs 95.7%, respectively) and the PGA (93.5% vs 92.5%, respectively), and were maintained at 12 weeks post-treatment (FWS: 80.1% vs 78.5%; PGA: 85.4% vs 85.2%, respectively)[37] (Figure 6). At weeks 4 and 12, the lower

FIGURE 6. Percentage of responders at maximum frown at weeks 4 and 12. **a)** Independent rater assessment on the Facial Wrinkle Scale from standardized digital photographs. **b)** Patient Global Assessment.[37]



bound of the 95% confidence intervals for the differences between treatment groups exceeded the predefined non-inferiority margin of –15%, confirming the non-inferiority of incobotulinumtoxinA to onabotulinumtoxinA at weeks 4 and 12.[37]

Non-inferiority trials can be used to assess whether a new treatment is no worse than an existing active comparator by a specified margin called the "equivalence margin," and any improvement still fits within the definition of non-inferiority.[41] Therefore, the conclusion of non-inferiority does not rule out possible superiority of the new treatment.[42]

Another recent study compared the efficacy of incobotulinumtoxinA and onabotulinumtoxinA in 35 subjects with GFL.[43] Two 4-U injections of incobotulinumtoxinA were compared with 2 injections of 6 U onabotulinumtoxinA in the corrugator muscles in a split-face trial design. To enable intra-individual comparison, the procerus muscle was not injected. Results of the study revealed that the 50% higher dose of onabotulinumtoxinA (equivalent to a 30U dose if all 5 common injection sites in the glabellar region were similarly treated) was non-superior to an incobotulinumtoxinA dose equivalent to 20 U. This suggests that in the majority of subjects there is no need to increase the dose of BoNT/A above the recommended 20 U. Similar results were demonstrated in a study of GFL treatment in African-American women, which showed no statistically significant differences in efficacy between 20-U and 30-U doses of onabotulinumtoxinA.[44] Occasionally, the dose may need to be tailored to the individual: in men, who tend to have a larger muscle mass, or subjects with very strong mimic muscle activity, a larger dose may be required.

IncobotulinumtoxinA vs onabotulinumtoxinA and abobotulinumtoxinA

Onset and durability of effect influence the cost and convenience of BoNT/A treatments for subjects, and they impact their overall satisfaction. The onset and durability of effect of incobotulinumtoxinA versus onabotulinumtoxinA and abobotulinumtoxinA was investigated in a large, Phase 3, double-blind, randomized study that included 120 subjects (Rappl et al, Poster presented at IMCAS Asia, 10–12 July 2010, Hong Kong). Subjects received 21 U incobotulinumtoxinA, 21 U onabotulinumtoxinA, or 63 U abobotulinumtoxinA. Comparable efficacy was seen for all 3 products; however, incobotulinumtoxinA showed the most rapid onset of effect, followed by onabotulinumtoxinA and abobotulinumtoxinA. The duration of effect was longest with incobotulinumtoxinA, but this result was not statistically significant.

Other Esthetic Indications

Lateral periorbital wrinkles (crow's feet)

In a double-blind, randomized, proof-of-concept, intra-individual study comparing the clinical effectiveness of incobotulinumtoxinA with that of onabotulinumtoxinA in the treatment of lateral periorbital wrinkles, 21 subjects with a FWS score of 2 or 3 were treated with 12 U incobotulinumtoxinA and onabotulinumtoxinA, with each product administered to one side of the face.[45] Subjects were monitored for up to 4 months post-treatment. Responders were defined as subjects with an improvement of ≥1 point on the FWS compared with baseline. No significant difference in response rate was seen between incobotulinumtoxinA and onabotulinumtoxinA at maximum contraction 1 month post-treatment (95% vs 90%, respectively), and comparable efficacy was maintained for ≤4 months (84% response rate for both products). After 4 months, 15% of participants in both treatment groups rated their crow's feet as 'markedly' or 'very markedly' improved. Thus, incobotulinumtoxinA showed no differences in efficacy from onabotulinumtoxinA when used at the same dosage to treat lateral periorbital wrinkles.

A similarly designed study in 22 subjects compared the efficacy of incobotulinumtoxinA with abobotulinumtoxinA in a 1:3 dose ratio for the treatment of lateral periorbital wrinkles.[46] There were no statistically significant differences in response rate between the 2 products after 4 weeks and 4 months post-treatment.

TABLE 2.

Summary of the Incidence of Treatment-Related Adverse Events Reported in Clinical Trials of IncobotulinumtoxinA

Study	Treatment-Related AEs (%)			Most Frequent Treatment-Related AEs (%)		
	Placebo	Incobotulinum-toxinA	Onabotulinum-toxinA	Placebo	Incobotulinum-toxinA	Onabotulinum-toxinA
Sattler et al[37]	N/A	3.2	5.2	N/A	Headache (1.8)	Headache (2.1)
Imhof and Kuhne[36]	N/A	3.8	N/A	N/A	Headache (2.9)	N/A
Carruthers et al[31]	2.2	7.1	N/A	Headache (1.1)	Headache (3.8)	N/A
Hanke et al[32]	2.2	12.1	N/A	N/A	Headache (7.1)	N/A
Rzany et al[40]	N/A	6.3	N/A	N/A	Headache (3.5)	N/A

AEs, adverse events; N/A, not available.

Despite the high responder rate in this study at 4 months post-treatment, it is frequently noticed in clinical practice that the duration of action of BoNT/A treatment is longer for the treatment of GFL than for lateral periorbital wrinkles (T. C. Flynn, personal communication).

Forehead lines

Results have been reported from an intra-individual, split-face, controlled study assessing the efficacy of four BoNT/A preparations in only 12 male subjects with moderate-to-severe hyperdynamic forehead lines as assessed on the FWS.[47] Each subject was treated with 2 of the 4 BoNT/A formulations (17 U incobotulinumtoxinA, 17 U onabotulinumtoxinA, 17 U Chinese BoNT/A [Prosigne®, Lanzhou Biological Products Institute, Lanzhou, China], or 51 Speywood U abobotulinumtoxinA) applied to each side of the forehead and assessed for 150 days. Responders were subjects who achieved forehead line severity of none (0) or mild (1) on the FWS 30 to 60 days post-treatment. All treatments resulted in a positive response (100%) and no statistically significant differences were seen between treatments in the reduction of forehead line severity and the maintenance of improvement, suggesting comparable efficacy of incobotulinumtoxinA and onabotulinumtoxinA when used at the same dosage for this indication.

Safety of IncobotulinumtoxinA in Esthetic Indications

IncobotulinumtoxinA is generally well tolerated.[2] The incidence of treatment-related AEs in clinical trials is low (Table 2), and AEs of special interest are rare. In the large head-to-head study conducted by Sattler and colleagues, only one case of eyelid ptosis was reported in the onabotulinumtoxinA group.[37] This is particularly significant because the 3:1 ratio of subjects randomized to incobotulinumtoxinA and onabotulinumtoxinA, respectively, increased the probability of discovering an AE occurring in the incobotulinumtoxinA group. Eyelid ptosis occurred in only 2 subjects in a repeat-dose study of incobotulinumtoxinA and there was no evidence to suggest that the incidence of AEs increased with cycle number, indicating that the safety profile of incobotulinumtoxinA remains stable following repeat dosing.[40] Importantly, there have been no reports of new neutralizing antibody production during esthetic trials of incobotulinumtoxinA.[31,32,36,37,40]

Subject Perspectives

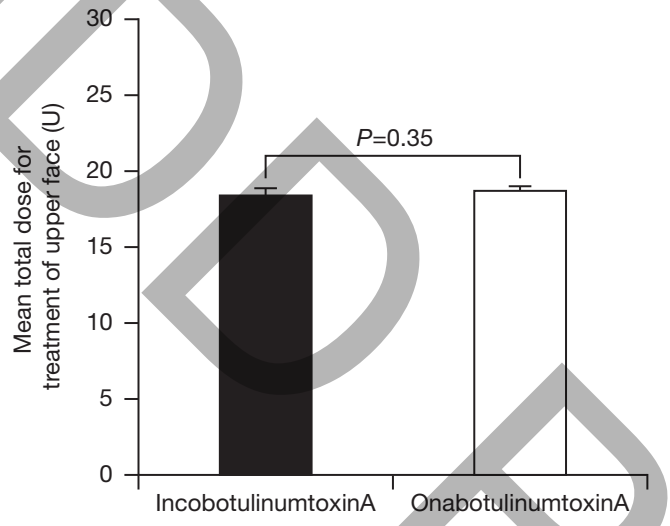
Subject-reported outcomes are particularly important in the field of cosmetic medicine, where the subject's opinion is the most relevant for judging treatment success. Numerous subject-assessed scales are reported in the literature, the most common being those using Likert-type scales (amongst other measures) in addition to subject satisfaction.[48]

In a prospective, open-label Phase 3 study of incobotulinumtoxinA, 9-point PGA scale assessments were performed at days 28 and 84 post-treatment; 97.2% and 84.8% of subjects, respectively, reported a score of >2 (ie, a complete, marked, or moderate improvement in the appearance of their GFL compared with baseline).[36] Sattler and colleagues also reported results of a similar PGA (9-point scale) at weeks 4 and 12 post-injection, when 93.5% and 85.4% of subjects, respectively, reported at least a moderate improvement (score of >2) compared with baseline.[37]

In a study investigating the treatment of lateral periorbital wrinkles, 70% of subjects in the incobotulinumtoxinA group and 65% of subjects in the onabotulinumtoxinA group rated the improvement of their lateral periorbital wrinkles as 'markedly improved' or 'very markedly improved' at 1 month post-treatment.[45]

In a study of 28 women who received treatment with incobotulinumtoxinA (mean dose 36 U) to the upper third of the face for glabellar, periorbital, and forehead lines, subjects were asked to assess their facial appearance via a self-perception questionnaire. After injection, subjects felt they looked more attractive, younger, and less tired (Luebberding et al, Poster presented as the 20th EADV Congress, 20–24th October, 2011, Lisbon, Portugal).

FIGURE 7. The mean total dose for incobotulinumtoxinA and onabotulinumtoxinA in treatment of the upper face across all visits in subjects who did not change product.[49]



Although investigator assessments are of key importance as objective expert assessments of treatment efficacy, subject assessments usually correlate well with investigator assessments.[31,36,37]

Clinical Practice

The use of incobotulinumtoxinA and the other BoNT/A preparations is increasing in cosmetic medicine, and off-label usage is commonplace. A retrospective analysis by Prager and colleagues was based on findings from 1,256 subjects who had received at least 2 or 3 consecutive BoNT/A injections in the upper face within 12 months during the previous 2 years, to treat GFL, lateral periorbital wrinkles, and/or horizontal forehead lines (which includes common on- and off-label usage in clinical practice).[49] Physicians completed a total of 2,316 questionnaires, of which 2,270 were evaluable, giving information regarding physician and subject satisfaction, dosages, treatment interval, and product change. Results revealed that most subjects were satisfied with their treatment (96.4% for incobotulinumtoxinA and 95.8% for onabotulinumtoxinA); similarly, the rates of physician satisfaction were also very high for both products (96.3% and 95.3%, respectively). There were no statistically significant differences in subject or physician satisfaction between the 2 products. The mean total treatment dose for the upper face at each treatment visit did not differ significantly between incobotulinumtoxinA and onabotulinumtoxinA for subjects who did and did not change product, and neither did the mean treatment dose across all visits for subjects who did not change products (Figure 7). All side effects were mild to moderate, with no severe AEs reported for either product in subjects who did not change product.[49] The results of this large analysis echos those reported from prospective, randomized, controlled clinical studies and provide further robust clinical evidence that incobotulinumtoxinA and onabotulinumtoxinA have similar clinical efficacy in esthetic indications in daily practice.

This large retrospective analysis provides a useful comparison between incobotuliumtoxinA and onabotulinumtoxinA in daily practice, but head-to-head trials provide the best data with which to compare the efficacy of the 2 products because results from different clinical trials cannot be compared due to differing subject demographics and dose and injection site variations; and the photographic scales used in the assessments can also differ.

Though different BoNT/A preparations are not interchangeable unit-for-unit because of the different assays used by manufacturers to check biologic potency and consistency in product quality, the same or similar doses are commonly used for incobotulinumtoxinA and onabotulinumtoxinA in clinical trials for esthetic[34-37, 45] and therapeutic indications[28,29] as well as in esthetic clinical practice.[49] In addition, the strength of action of incobotulinumtoxinA has been reported as being 1:1 with onabotulinumtoxinA.[50] However, there is no single widely accepted ratio for the use of abobotulinumtoxinA in comparison with onabotulinumtoxinA or incobotulinumtoxinA and abobotulinumtoxinA. The ratio ranges from 1:2.5 to 1:3 for cosmetic procedures.[51]

Future Perspectives

Between 1997 and 2011, there was an almost 4,000% increase in the number of treatments with BoNT/A,[52] demonstrating the enormous growth in demand for BoNT/A injections. In addition, the growing evidence for the efficacy and safety of topical BoNT/A preparations in cosmetic medicine indicates the beginning of an exciting new chapter in the story of BoNT/A in esthetics.[53] However, to date, such advances cannot compete with the wealth of experience that has accumulated over the years with BoNT/A injections, which has led to esthetic treatments becoming more sophisticated and refined. There has been a move towards an approach that treats the whole face rather than isolated areas to achieve beautification and a natural look relying on an understanding of the processes underlying facial aging and precise injection of target muscles. Moreover, individualization of therapy is also essential for a successful outcome. For example, different types of GFL have been classified, enabling identification of the most important muscles for each pattern, and improving tailored treatment.[54] This emphasizes the fact that injection sites should be adapted for each subject and a fixed injection scheme is not universally appropriate.

The tendency for subjects to seek treatment at an earlier age, and the increasing preference for a more holistic approach to facial rejuvenation, has resulted in larger treatment areas and consequently larger doses of BoNT/A. IncobotulinumtoxinA, as

one of the second generation BoNT/As, is uniquely suited for this evolving usage due to its established efficacy, precise localization, and favorable safety profile and, crucially, its lack of complexing proteins, which reduces the foreign-protein load, helping to minimize the risk of secondary treatment failure.

CONCLUSION

IncobotulinumtoxinA is highly purified and free from complexing proteins and is a potent and well-tolerated botulinum toxin serotype A with proven efficacy in neurological and esthetic indications. A 20-U dose of incobotulinumtoxinA has consistently proven effective for the treatment of GFL, including under a new composite endpoint for assessing treatment success in this indication. Comparative studies have shown that incobotulinumtoxinA has comparable clinical potency to onabotulinumtoxinA and these 2 products are routinely used at a 1:1 dose conversion ratio.

DISCLOSURES

Dr. Martina Kerscher has received research support and has conducted clinical trials for Merz Pharmaceuticals GmbH. Dr. Timothy Flynn has received research support and honoraria, and has participated in clinical trials with the following manufacturers of botulinum toxin: Allergan Inc, Medicis Pharmaceutical, Merz Pharmaceuticals GmbH, and Solstice Neurosciences Inc. He holds common stock in Allergan Inc. Dr. Yana Yutskovskaya has no conflicts of interest to report.

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