

Botulinum toxin type A treatment to the upper face: retrospective analysis of daily practice

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Background: Botulinum toxin type A treatment has been used for over 20 years to enhance the appearance of the face. There are several commercially available botulinum toxin type A products used in aesthetic clinical practice. The aim of this retrospective analysis was 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 an inspection of subject files for subjects 18 years of age or over 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 previous 2 years. Data on subject and physician satisfaction, treatment intervals, dosages, and safety were collected from 1256 subjects.

Results: There were no statistically significant differences between incobotulinumtoxinA and onabotulinumtoxinA with respect to physician and subject satisfaction, dosages, and adverse effects experienced. Both botulinum toxin type A preparations were well tolerated and effective in the treatment of upper facial lines. Due to low treatment numbers, abobotulinumtoxinA was not included in the statistical analysis.

Conclusion: The results of this retrospective analysis confirm the results of prospective clinical trials by demonstrating that, in daily practice, incobotulinumtoxinA and onabotulinumtoxinA are used at a 1:1 dose ratio and display comparable efficacy and safety.

Keywords: NT 201, incobotulinumtoxinA, onabotulinumtoxinA, abobotulinumtoxinA, upper face, retrospective analysis

Introduction

Botulinum toxins have been used for over 20 years for aesthetic procedures to improve the appearance of the face.^{1,2} Botulinum toxin type A injections are the most common nonsurgical procedures performed in the US with almost 2.5 million procedures carried out in 2010.³

There are several commercially available botulinum toxin type A products. OnabotulinumtoxinA (Botox®/Vistabel®; Allergan Inc, Irvine, CA) is indicated for the treatment of glabellar frown lines and is commonly used for the treatment of facial wrinkles.⁴ The terms “incobotulinumtoxinA”, “NT 201”, “Xeomin®”, and “Bocouture®” (Merz Pharmaceuticals GmbH, Frankfurt, Germany) all refer to the same botulinum toxin type A (150 kDa) that, unlike onabotulinumtoxinA, is free from complexing proteins. IncobotulinumtoxinA is currently licensed widely across Europe, the US, and parts of South America and Asia for aesthetic indications. IncobotulinumtoxinA

has demonstrated clinical efficacy in aesthetic indications in a number of clinical trials.⁵⁻⁷

In comparative, head-to-head trials in healthy volunteers, and in the therapeutic indications of blepharospasm and cervical dystonia, incobotulinumtoxinA had an identical time course of action (eg, time to onset, duration of effect, and time to waning of effect) as onabotulinumtoxinA.⁸ Furthermore, in a large head-to-head study comparing incobotulinumtoxinA with onabotulinumtoxinA for the treatment of glabellar frown lines, the percentage of responders 4 and 12 weeks after injection of the same number of units (U) of either preparation were similar, and demonstrated that both treatments were highly effective according to the assessment of independent raters, investigators, and subjects.⁷ No statistically significant difference in efficacy was observed in a proof-of-concept study in the treatment of crow's feet⁶ and in the treatment of forehead lines⁹ using a 1:1 dose ratio of the two products.

The aim of this retrospective analysis was to investigate the clinical efficacy of incobotulinumtoxinA compared with onabotulinumtoxinA or abobotulinumtoxinA (Dysport®/Azzalure®; Ipsen Ltd, Berkshire, UK) when used in daily practice by physicians to treat wrinkles of the upper face. IncobotulinumtoxinA was launched in Germany in 2005, making it the best suited location for this study by ensuring sufficient data could be obtained for this analysis including in off-label indications.

Parameters relating to subject and physician satisfaction, the time interval between doses administered (duration between treatment cycles), dosages used, and adverse effects experienced were investigated. Any differences in these parameters may indicate that the product with lower subject and physician satisfaction, shorter interval between treatments, or higher dosages was less clinically effective.

Materials and methods

The parameters used as indicators of clinical efficacy in daily practice were subject and physician satisfaction, the time interval between injections, dosage, and adverse effects. In order to collect the relevant data to address these questions, physicians known to use incobotulinumtoxinA at 41 sites in Germany were contacted and asked to complete questionnaires (Table 1) based on an inspection of files for those subjects who had received at least two consecutive botulinum toxin type A injections, but not more than three, in the upper face within 12 months during the last 2 years (ie, to treat glabellar frown lines, lateral periorbital wrinkles, and/or horizontal forehead lines, which includes common on- and off-label usage in clinical practice). A different questionnaire

Table 1 Components of questionnaire completed by physicians

Variables

Demographics and baseline characteristics

The following variables were considered as demographics and baseline characteristics:

- Gender (male/female)
- Age (years)
- Used botulinum toxin (Bocouture®/Xeomin®; Vistabel®/Botox®; Azzalure®/Dysport®)
- Treated indication (glabellar frown lines, horizontal forehead lines, crow's feet)

Side effects

Investigators were asked if any side effects occurred during the treatment period. If so, the nature of the side effects could be specified by choosing one or more of the following possible answers:

- Local pain
- Local hematoma
- Headache
- Ptosis of the upper eyelid
- Ptosis of the eyebrows
- Other

In addition, the severity of the most relevant side effect could be assessed (mild, moderate, severe)

Satisfaction with product

The investigator was asked to assess his/her satisfaction with the product (physician's satisfaction) as well as to transcribe the subject's satisfaction from subject documentation. The following answers were possible:

- Satisfied
- Not satisfied
- Unknown

Change of product

Participants were asked if the neurotoxin product was changed during the treatment period. If so, the following reasons could be assigned:

- Dissatisfaction with cosmetic result
- Dissatisfaction due to side effects
- Other

Treatment details

The treatment details were recorded for at least two but not more than three injections. The following data were collected:

- Treatment date
- Time interval until the next treatment in the same indication
- Overall dose for the treatment in this indication
- Individual doses for each injection point, where it was possible to choose between 24 different injection points

was filled in for each indication, giving a maximum of three completed questionnaires per subject. The selected subjects had therefore been treated according to the treatment flows shown in Figure 1. For the analysis, subjects were divided into two groups: subjects who did not change product and subjects who changed product (irrespective of whether the change occurred at visit 2 or visit 3 or both).

The documentation period was from March 2011 to June 2011 and data that would allow a subject to be identified were not collected. Male or female subjects aged 18 years and over

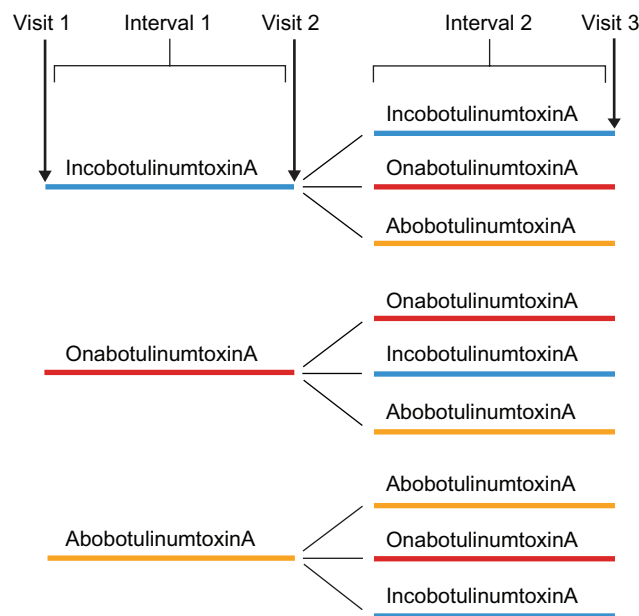


Figure 1 Diagram showing treatment flow.

Note: The three possible treatments and treatment intervals are shown, along with the nine possible treatment combinations.

who had received treatment with botulinum toxin type A were eligible for inclusion in this study. Initial treatments and touch-up treatments were reasons to exclude a subject from the study. No ethics committee approval was required for this retrospective study without invasive measures.

In daily practice, it is very common to treat “aesthetic units”, for example the “upper face”, rather than single isolated areas, such as forehead lines, the glabella or crow’s feet. Consequently, analysis was performed on all treatments of the upper face rather than single isolated areas. Differences between treatment groups were assessed using appropriate statistical analyses. Any differences in subject and physician satisfaction and adverse effects were analyzed using Fisher’s Exact test, while analysis of doses at each visit and treatment intervals used the Wilcoxon–Mann–Whitney test. The Student’s *t*-test was used to analyze the total mean dose across all visits. Data were collected from a sufficient number of subjects ($n = 1256$) to enable statistical analyses to be carried out.

Results

Of the 41 sites contacted, 21 sites returned completed questionnaires. In total, 2316 questionnaires were returned and 46 were excluded. Forty-five questionnaires were excluded because they only recorded one visit (rather than the required minimum of two) and one was excluded because it was a duplicate, leaving 2270 evaluable questionnaires. In total, data from 1256 subjects were included. Demographic and baseline

characteristics are shown in Table 2. Subject numbers in the incobotulinumtoxinA and onabotulinumtoxinA treatment groups were sufficient to ensure that robust statistical data could be obtained, but the number of abobotulinumtoxinA injections was so low (1.6%, which might reflect daily practice in Germany), that no statistical evidence could be conveyed. Hence, these were removed from the analysis. Most subjects received incobotulinumtoxinA injections and the majority of subjects did not change product within the time limits of this retrospective analysis (Table 2). The most common reason for product change given was that the usual product was unavailable at the time of treatment.

Subject and physician satisfaction

The vast majority of subjects were satisfied with their treatment (96.4% for incobotulinumtoxinA and 95.8% for onabotulinumtoxinA). There was no statistically significant difference in subject satisfaction between the two products ($P = 1.000$). Similarly, the rates of physician satisfaction were also very high for both products: 96.3% and 95.3% were satisfied with incobotulinumtoxinA and onabotulinumtoxinA, respectively ($P = 0.825$).

Interval between two treatments

Any difference in the mean treatment interval (ie, the time between the first and second injections [interval 1] or the

Table 2 Demographic and baseline characteristics

	n (%)
Total number of subjects	1256 (100)
Gender	
Male	105 (8.4)
Female	1151 (91.6)
Indication	
Glabellar frown lines	1096 (48.3)
Horizontal forehead lines	621 (27.4)
Crow’s feet	553 (24.4)
Product	
IncobotulinumtoxinA	1998 (88.0)
OnabotulinumtoxinA	236 (10.4)
AbobotulinumtoxinA	36 (1.6)
Product change	
Missing	3 (0.1)
No	2018 (88.9)
Yes	249 (11.0)
Age, years	
Mean	47.4
STD	10.91
Maximum	94.0
Median	46.0
Minimum	20.0

Abbreviation: STD, standard deviation.

second and third injections [interval 2]; Figure 1) was assessed separately in subjects who did not change product in order to give an indication of the duration of the effect. There was no statistically significant difference between the treatment intervals in subjects who did not change product (Table 3). The mean length of interval 1 was 25.25 weeks and 24.90 weeks for subjects treated with incobotulinumtoxinA and onabotulinumtoxinA, respectively ($P = 0.9646$). For interval 2, the mean length was 22.43 weeks and 21.95 weeks, respectively ($P = 0.8696$).

Because the group of subjects who did change product included subjects who changed product at visit 2 or visit 3 or both, no conclusions could be drawn from any differences between the lengths of the treatment intervals in this group of subjects.

Dosage

In order to analyze the dosages administered, subjects were again divided into two groups: those who did not change product and those who did. Within these two groups, the mean dosage of each product was calculated at each visit. For the subjects who did not change product, the mean dosages for incobotulinumtoxinA and onabotulinumtoxinA were 18.92 U and 18.79 U at visit 1 ($P = 0.4335$), 18.12 U and 18.44 U at visit 2 ($P = 0.4262$), and 18.20 U and 18.94 U at visit 3 ($P = 0.6900$), respectively. In the group of subjects who did change product, the mean dosages for incobotulinumtoxinA and onabotulinumtoxinA at each visit were 17.48 U and 16.99 U (visit 1; $P = 0.9138$), 17.13 U and 18.63 U (visit 2; $P = 0.3168$), and 17.97 U and 18.11 U (visit 3; $P = 0.7007$), respectively. 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 those who did not change product (Table 4). Furthermore, there was no statistically significant difference between the mean total dose of incobotulinumtoxinA and onabotulinumtoxinA across all visits ($P = 0.35$).

Safety

Adverse effects were analyzed in subjects who did not change product in order to assess any differences in adverse effects experienced by subjects receiving either product. In these subjects, all the adverse effects were mild or moderate in intensity. There were no severe side effects reported for either product. Of the subjects treated only with incobotulinumtoxinA, 6.7% experienced adverse effects compared with 9.5% of those treated with onabotulinumtoxinA, though this was not a statistically significant difference ($P = 0.178$). Localized pain was reported in 2.2% of subjects receiving incobotulinumtoxinA and 3.4% of subjects receiving onabotulinumtoxinA while local hematoma was reported in 3.0% and 2.7% of subjects, respectively. Headache was reported by 1.7% of incobotulinumtoxinA-treated subjects and 2.0% of onabotulinumtoxinA-treated subjects.

Discussion

This retrospective study, comparing use of botulinum toxin type A preparations in daily clinical practice, analyzed subject and physician satisfaction, the time interval between doses administered (duration between treatment cycles), dosages used, and adverse effects experienced, and found no differences between incobotulinumtoxinA and onabotulinumtoxinA. The low number of abobotulinumtoxinA injections meant that they were excluded from the analysis. This low number presumably reflects the habits of the physicians who responded to the questionnaire. Amongst these physicians, abobotulinumtoxinA is the least commonly used of the three products included in this study. More subjects were treated with incobotulinumtoxinA compared with onabotulinumtoxinA due to the fact that mainly incobotulinumtoxinA injectors were approached. However, all physicians were equally proficient and experienced in administering all products and both the subject and physician satisfaction were similar for incobotulinumtoxinA and onabotulinumtoxinA.

Subject and physician satisfaction levels were similarly high for both products, and product change was rare and

Table 3 Average interval between treatments in the upper face for subjects without product change

	Interval 1		Interval 2	
	IncobotulinumtoxinA	OnabotulinumtoxinA	IncobotulinumtoxinA	OnabotulinumtoxinA
Mean, weeks	25.25	24.90	22.43	21.95
STD	15.21	12.65	10.55	7.87
Median	22.43	23.29	20.57	20.86
	$P = 0.9646$		$P = 0.8696$	

Note: P value calculated using the Wilcoxon–Mann–Whitney test.

Abbreviation: STD, standard deviation.

Table 4 Mean total treatment doses in the upper face at each treatment visit for subjects with and without product change

Treatment visit	Subjects without product change		Subjects with product change	
	IncobotulinumtoxinA Dose (U)	OnabotulinumtoxinA Dose (U)	IncobotulinumtoxinA Dose (U)	OnabotulinumtoxinA Dose (U)
1				
Mean	18.92	18.79	17.48	16.99
STD	9.2	8.77	9.62	6.38
	$P = 0.4335$		$P = 0.9138$	
2				
Mean	18.12	18.44	17.13	18.63
STD	8.85	6.80	6.62	9.34
	$P = 0.4262$		$P = 0.3168$	
3				
Mean	18.20	18.94	17.97	18.11
STD	9.39	4.68	5.8	8.01
	$P = 0.6900$		$P = 0.7007$	

Note: P value calculated using the Wilcoxon–Mann–Whitney test.

Abbreviation: STD, standard deviation.

most often simply because the usual product was unavailable at the time, reflecting physician and subject confidence and satisfaction with both products.

The treatment intervals in subjects who did not change product were of a similar length. However, it should be noted that the length of time between two treatments is influenced by several factors, including financial and time constraints on the subject.

In this study no questions were asked relating to the reasons why subjects returned for subsequent treatments when they did, so the impact of the factors that may affect treatment interval could not be assessed here. In addition, the intention had been to analyze the different treatment areas separately, but this was not possible due to the confounding factor that allocation of individual injection points to a single isolated area was not necessarily possible (for example, some glabellar injection points also affect forehead lines and vice versa). Thus, the data were pooled and analyzed as “upper face”.

Similar clinical efficacy between incobotulinumtoxinA and onabotulinumtoxinA with regard to the other parameters tested suggests that these two products have similar clinical efficacy when used at the same dosage. In addition, the total dosages for both products were similar and low, as expected for cosmetic procedures in the face. Therefore, the results from this large retrospective study ($n = 1256$) are in line with published results of smaller prospective clinical studies which have shown similar efficacy of incobotulinumtoxinA compared with onabotulinumtoxinA in the treatment of glabellar frown lines in 381 subjects,⁷ crow’s feet in 21 subjects,⁶ and forehead lines in 12 subjects⁹ in aesthetic indications using identical dosages, as well as in therapeutic indications with similar dosages.^{10,11}

The results from the large number of subjects presented in this retrospective analysis of daily clinical practice support those observed in prospective, randomized, controlled trials. Therefore, evidence from both routine clinical practice and the clinical trial setting suggests that incobotulinumtoxinA and onabotulinumtoxinA have similar clinical efficacy in therapeutic and aesthetic indications. In addition, the results of this retrospective analysis demonstrated that the identical dosage (20 U) of both products for the treatment of glabellar frown lines is appropriate.

Conclusion

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.

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Disclosure

WP has served as a consultant and lecturer for Allergan Inc, Merz Pharmaceuticals GmbH and Galderma Pharma SA. MI has served as a consultant, speaker, and investigator in clinical trials for Merz Pharmaceuticals GmbH. UK received honoraria as an investigator in clinical trials and speaker for Merz Pharmaceuticals GmbH. L-PK has spoken at workshops and training sessions for Merz Pharmaceuticals

GmbH. WGP-D has acted as a consultant and lecturer for Allergan Inc, Merz Pharmaceuticals GmbH, and Galderma Pharma SA. TP has served as a consultant and speaker at workshops and meetings for Merz Pharmaceuticals GmbH and Galderma Pharma SA. She has received honoraria as an investigator in clinical trials for Merz Pharmaceuticals GmbH, Galderma Pharma SA, and Ipsen Pharma. Editorial assistance was provided by Ogilvy 4D and funded by Merz Pharmaceuticals GmbH.

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