UK Registry for Botulinum Toxin Type A use in Cosmetic Practice

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ABSTRACT

Background: The United Kingdom Society for the Study of Aesthetic Medicine (UKSSAM) set-up a national registry on the routine use of botulinum toxin type A (BoNT-A) for the aesthetic indication.

Methods: 51 practitioners contributed usage, efficacy and safety data to this analysis of the first 3,500 BoNT-A treatment episodes captured in the registry (January 2011 to October 2013).

Results: 53% of episodes were routine, repeat treatments, 33% were new/first-time visits, and 14% were top-ups. The vast majority (81%) of treatments included the glabella, crow’s feet and/or forehead lines. OnabotulinumtoxinA was the most widely used type of BoNT-A (53% of visits), followed by abobotulinumtoxinA (32%), and incobotulinumtoxinA (15%). 55% of practitioners used only one type of BoNT-A, 33% used two types, and 12% used all three. The ratio of top-up treatments to routine (new/repeat) visits was 1:10 for incobotulinumtoxinA, 1:7 for onabotulinumtoxinA, and 1:4 for abobotulinumtoxinA. IncobotulinumtoxinA (mean 3.9 days) and abobotulinumtoxinA (4.1 days) had a significantly quicker onset of action than onabotulinumtoxinA (4.4 days; both P < 0.05). Duration of action was significantly longer for incobotulinumtoxinA (mean 17.8 weeks) than for abobotulinumtoxinA (15.8 weeks; P < 0.05) and onabotulinumtoxinA (15.4 weeks; P < 0.05). Patients receiving incobotulinumtoxinA (mean score 8.8, where 0 = unsatisfied and 10 = completely satisfied) and onabotulinumtoxinA (8.6) had a significantly higher level of satisfaction than those receiving abobotulinumtoxinA (8.0; both P < 0.05). A total of 173 adverse events (AEs) were reported across all products (incidence 4.9%). The most frequently reported AE was brow ptosis (34% of total AEs), which was most commonly associated with abobotulinumtoxinA.

Conclusion: The UKSSAM registry represents the largest collection of real-life data of BoNT-A use for cosmetic improvement worldwide. The registry has an important role in informing practitioners on how treatment with BoNT-A performs in routine clinical practice and has the potential to support best practice.

Keywords: Aesthetic; wrinkles; onabotulinumtoxinA; incobotulinumtoxinA; abobotulinumtoxinA; real-world data

Date received: 1 November 2014; accepted 1 December 2014

INTRODUCTION

Botulinum toxin type A (BoNT-A) injections are one of the most popular cosmetic interventions for improving the appearance of facial lines. BoNT-A and other non-surgical interventions are currently estimated to account for nine out of 10 cosmetic procedures undertaken in the UK and represent 75% of the market value. Several formulations are now available and three are licensed in the UK for the treatment of glabellar lines: Clostridium botulinum toxin (type) onabotulinumtoxinA (Botox®/Vistabel®, Allergan Ltd., Marlow, UK), incobotulinumtoxinA (Bocouture®/Xeomin®, Merz Pharma UK Ltd.), and abobotulinumtoxinA (Azzalure®, Galderma (UK) Ltd. Watford, UK/Dysport®, Ipsen Ltd., Slough, UK). However, despite increasing demand for BoNT-A for cosmetic purposes, there remains a relatively limited evidence-base for their use, particularly in terms of real-world experience.

The United Kingdom Society for the Study of Aesthetic Medicine (UKSSAM) is an academic organisation set-up for and by surgeons, physicians, dentists and nurses who use BoNT-A, dermal fillers and LASER in their aesthetic treatments. The primary aim of the UKSSAM is to promote best practice in the use of non-surgical aesthetic interventions, achieved by the collection of real time observations and reviewing outcomes of current practices. Herein we report on the first results of a UK registry aimed at collecting data on adverse events and efficacy across all BoNT-A products used for the aesthetic indication. The UKSSAM registry is the first and only BoNT-A registry of use and represents the largest observational study of BoNT-A in existence.

METHODS

Study design and data collection

A total of 51 practitioners contributed data to this analysis of the first 3,500 BoNT-A treatment episodes for the aesthetic indication captured in the UKSSAM registry (data collected between January 2011 and October 2013).

The following data were collected for each treatment episode of BoNT-A at the participating centres: baseline
characteristics (gender, age); previous history of BoNT-A use; site of treatment; onset and duration of action; patient satisfaction; and adverse events. Onset (how long before the patient noticed their treatment working) and duration (how long it lasted for) of action for each product was rated by the subject based on their previous treatment (i.e. available only for ‘repeat’ and ‘top-up’ treatment episodes). A ‘repeat’ treatment was defined as a routine, subsequent treatment at an interval consistent with the normal duration of action of the product (i.e. 3 months). A ‘top-up’ was defined as a request for additional treatment to augment that already provided much sooner than would be expected for a ‘repeat’ (i.e. around 2 weeks); this was primarily due to a less than optimal result from the primary treatment. Patient satisfaction was rated on previous treatment using a visual analogue scale (VAS), where 0 = totally unsatisfied and 10 = completely satisfied.

All data were anonymised such that individual records could not be ascribed to a particular patient. Ethical review was deemed unnecessary according to the National Research Ethics Service (NRES) guidance document. As such, the study was registered with the UKSSAM research department as a service evaluation [SEv/BnTR-1/11].

**Study outcomes & statistical analysis**

The primary outcomes were the patterns of usage of BoNT-A for facial rejuvenation, including an evaluation of efficacy (onset and duration of action and patient satisfaction) and adverse events. Data were evaluated on an overall basis and also split by type of BoNT-A (onabotulinumtoxinA, abobotulinumtoxinA or incobotulinumtoxinA). Chi-squared tests were used to analyses differences in the use of BoNT-A. Onset and duration of action and patient satisfaction data were analysed by Tukey’s Studentized Range (HSD) test, whilst a disproportionate analysis and patient satisfaction data were analysed by Tukey’s test.

**RESULTS**

**Baseline data, details of visits and BoNT-A usage**

Of the 3,500 BoNT-A treatment episodes, patients predominantly attended for repeat injections (53%), followed by new/first-time visits (33%), and for top-ups (14%) (Chi-squared \( P < 0.0001 \)). The vast majority of injections were given to women (86%) and the mean age was 45 (20–84) years. The most popular area for treatment was the glabella, covering 74% of visits, followed by Crow’s feet (60%) and forehead lines (55%) (Table 1).

Of the 51 practitioners, the majority (55%) used only one of the three types of BoNT-A (onabotulinumtoxinA, abobotulinumtoxinA or incobotulinumtoxinA), with 33% using two of the three types, and 12% utilising all three types in their practice. OnabotulinumtoxinA was the most frequently administered BoNT-A, representing 53% of the total visits, compared to 32% for abobotulinumtoxinA, and 15% for incobotulinumtoxinA. Whilst onabotulinumtoxinA was used most frequently for repeat visits (67% of visits vs. 18% for abobotulinumtoxinA and 14% for incobotulinumtoxinA), patients receiving treatment for the first-time typically received abobotulinumtoxinA (49% vs. 31% for onabotulinumtoxinA and 20% for incobotulinumtoxinA). For the vast majority of top-up visits, patients typically received either onabotulinumtoxinA or abobotulinumtoxinA (both 45% of visits) rather than incobotulinumtoxinA (10%). The ratio of top-up visits to routine (new and repeat) visits was 1:10 for incobotulinumtoxinA, 1:7 for onabotulinumtoxinA, and 1:4 for abobotulinumtoxinA.

For most areas of the face, including the glabella, crow’s feet and forehead, onabotulinumtoxinA was the most frequently administered type of BoNT-A, followed by abobotulinumtoxinA and incobotulinumtoxinA (Table 1). AbobotulinumtoxinA, however, was most frequently used for treatment of the orbicularis (52% of treatments vs. 34% for onabotulinumtoxinA and 17% for incobotulinumtoxinA) and depressor anguli oris (45% vs. 35%)

**TABLE 1.**

<table>
<thead>
<tr>
<th>Area of Face</th>
<th>Glabella n (%)</th>
<th>Crow’s feet n (%)</th>
<th>Forehead n (%)</th>
<th>Orbicularis n (%)</th>
<th>Nasalis n (%)</th>
<th>DAO n (%)</th>
<th>Mentalis n (%)</th>
<th>Masseter n (%)</th>
<th>Others n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>1,359 (52%)</td>
<td>1,145 (54%)</td>
<td>948 (49%)</td>
<td>56 (34%)</td>
<td>71 (58%)</td>
<td>23 (20%)</td>
<td>55 (80%)</td>
<td>7 (19%)</td>
<td>354 (34%)</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>847 (33%)</td>
<td>643 (30%)</td>
<td>600 (31%)</td>
<td>84 (52%)</td>
<td>31 (25%)</td>
<td>52 (45%)</td>
<td>10 (14%)</td>
<td>3 (8%)</td>
<td>498 (48%)</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>398 (15%)</td>
<td>328 (16%)</td>
<td>372 (19%)</td>
<td>23 (14%)</td>
<td>21 (17%)</td>
<td>41 (35%)</td>
<td>4 (6%)</td>
<td>27 (73%)</td>
<td>188 (18%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>2,604 (74%)</strong></td>
<td><strong>2,116 (60%)</strong></td>
<td><strong>1,920 (55%)</strong></td>
<td><strong>163 (5%)</strong></td>
<td><strong>123 (4%)</strong></td>
<td><strong>116 (3%)</strong></td>
<td><strong>69 (2%)</strong></td>
<td><strong>37 (1%)</strong></td>
<td><strong>1,040 (30%)</strong></td>
</tr>
</tbody>
</table>

*more than one area of the face could be treated in a single treatment episode; DAO: depressor anguli oris (triangularis)
for incobotulinumtoxinA and 20% for onabotulinumtoxinA). Despite being the least used of the three types of BoNT-A, incobotulinumtoxinA appeared the treatment of choice for injection into the masseter, representing 73% of episodes (vs. 19% for onabotulinumtoxinA and 8% for abobotulinumtoxinA).

The brand of onabotulinumtoxinA most frequently administered was Botox at 97% versus 3% for Vistabel. Azzalure (89%) was the main brand of abobotulinumtoxinA used (vs. 11% for Dysport), whilst Bocouture (71%) was the preferred brand of incobotulinumtoxinA (vs. 29% for Xeomin).

### Onset of action
The mean onset of action following injection of BoNT-A was 4.3 (0–28) days. AbobotulinumtoxinA (4.1 days) and incobotulinumtoxinA (3.9 days) had significantly quicker onsets of action compared to onabotulinumtoxinA (4.4 days; P < 0.05 for both) (Table 2). There was no significant difference in speed of onset for abobotulinumtoxinA versus incobotulinumtoxinA.

### Duration of action
The mean duration of action for BoNT-A treatment was 15.8 (0–120) weeks. IncobotulinumtoxinA had a significantly longer duration of action than the other two types of BoNT-A (17.8 weeks vs. 15.8 weeks). IncobotulinumtoxinA had a significantly longer duration of action than the other two types of BoNT-A (17.8 weeks vs. 15.8 weeks). The mean duration of action for BoNT-A treatment was 15.8 (0–120) weeks. IncobotulinumtoxinA had a significantly longer duration of action than the other two types of BoNT-A (17.8 weeks vs. 15.8 weeks). OnabotulinumtoxinA appeared the treatment of choice for injection into the masseter, representing 73% of episodes (vs. 19% for onabotulinumtoxinA and 8% for abobotulinumtoxinA).

### Adverse events
A total of 173 adverse events were reported, resulting in an overall incidence of 4.9% across the 3,500 treatment episodes. The most common adverse events were ptosis of the brow and bruising, representing 76% of the total reported (Table 3). Failure of effect was also considered an adverse event, affecting 1.3% of treatment episodes (45/3,500). The incidence of adverse events was around twice as high for abobotulinumtoxinA (7.7%) than for onabotulinumtoxinA (3.9%; OR 2.1, confidence interval [CI] 1.5–2.9) and over double the rate for incobotulinumtoxinA (3.0%; OR 2.7, 95% CI 1.6–4.7). The chances of an adverse event were broadly similar between incobotulinumtoxinA and onabotulinumtoxinA, although slightly in favour of the former (OR 0.761, 95% CI 0.4–1.3). The most frequently reported adverse event associated with abobotulinumtoxinA was ptosis (67% of reported events), whilst onabotulinumtoxinA and incobotulinumtoxinA were more commonly associated with bruising (56% and 50%, respectively, of events).

### Discussion
The UKSSAM registry provides the largest dataset of real-life clinical experience with BoNT-A for cosmetic purposes extant. As expected, the vast majority of BoNT-A treatments were for the improvement of glabella, crow’s feet and/or forehead lines (81%). OnabotulinumtoxinA was the most widely used type of BoNT-A (55%), with the vast amount of practitioners using the Botox brand (97%). Approximately half (49%) of new patients, however, were treated with abobotulinumtoxinA, which might indicate a move by practitioners to preferentially using this type of BoNT-A. There was some variability in the

### TABLE 2.

<table>
<thead>
<tr>
<th>Onset of action, duration of action and patient satisfaction across all patients and split by type of BoNT-A used</th>
<th>n</th>
<th>Onset Mean days (min-max)</th>
<th>Duration Mean weeks (min-max)</th>
<th>Satisfaction Score* (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>1,838</td>
<td>4.4 (0–20)</td>
<td>15.4 (0–36)</td>
<td>8.6 (0–10)†</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>1,123</td>
<td>4.1 (0–21)*</td>
<td>15.8 (0–43)</td>
<td>8.0 (0–10)</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>539</td>
<td>3.9 (0–28)*</td>
<td>178 (0–120)†</td>
<td>8.8 (0–10)†</td>
</tr>
<tr>
<td>All</td>
<td>3,500</td>
<td>4.3 (0–28)</td>
<td>15.8 (0–120)</td>
<td>8.6 (0–10)</td>
</tr>
</tbody>
</table>

*VAS scale where 0 = totally unsatisfied and 10 = completely satisfied; SD: Standard deviation; †P < 0.05 vs. onabotulinumtoxinA; ‡P < 0.05 vs. abobotulinumtoxinA/OnabotulinumtoxinA; ††P < 0.05 vs. abobotulinumtoxinA.
type of BoNT-A chosen depending on the area of the face to be treated, with onabotulinumtoxinA being used most frequently for the glabella, crow’s feet and forehead (52% of treatments), abobotulinumtoxinA for treatment of the orbicularis (52%) and depressor anguli oris (45%), and incobotulinumtoxinA for injection into the masseter (73%). Whether this relates to perceived differences in effectiveness or tolerability between the products in different facial areas or is an artefact of the numbers, requires further elucidation. It is apparent that most practitioners (55%) tended to use just one type of BoNT-A, with only a small percentage using all three (12%).

The onset of action of incobotulinumtoxinA and abobotulinumtoxinA at around 4 days is slightly slower than the 2–3 days reported in their respective Summary of Product Characteristics (SmPC). At 4.4 days, onabotulinumtoxinA had significantly the slowest onset of action compared to the other two types (both P < 0.05), although this is in line with its SmPC, which reports an improvement in wrinkle severity (of the glabellar) within 1 week of treatment. The products all displayed a mean duration of action of over 3 months, with incobotulinumtoxinA having significantly the longest effect at around 4 months (P < 0.05 vs. both other types of BoNT-A). This is all in accordance with the SmPCs and provides real-world experience to support that the interval between repeat treatments should not be more frequent than every three months.

Satisfaction was, on average, generally high following treatment with BoNT-A (8.8 on a scale of 0–10), highlighting the beneficial impact that such cosmetic interventions can have on patient wellbeing. Patients receiving incobotulinumtoxinA (8.8 on a scale of 0–10) and onabotulinumtoxinA (8.6) had significantly (P < 0.05) higher satisfaction than those receiving abobotulinumtoxinA (8.0). This might relate in part to patients receiving abobotulinumtoxinA more frequently requiring top-up visits, on average 1 top-up per 4 patients treated, compared to a ratio of 1:10 for incobotulinumtoxinA and 1:7 for onabotulinumtoxinA. Having to return for a top-up and go through the procedure again, taking time out for this, and the perception that the treatment has not worked effectively, particularly for patients who are self-funding, might influence overall satisfaction with treatment and the lower scores for abobotulinumtoxinA.

The apparent differences between the three types of BoNT-A in terms of onset, duration of action and requirement for top-up treatment might be related to protein load, as this is the main differentiator between the products.Whilst available evidence suggests that complexing proteins do not contribute to the stability of the drugs and do not directly contribute to their therapeutic effects, they may be associated with a secondary nonresponse due to the development of neutralising antibodies. Since incobotulinumtoxinA is free from complexing proteins, this might explain it having the longest duration and the lowest requirement for top-up treatments of the three types of BoNT-A.

The overall incidence of adverse events was low at 4.9%, reaffirming the good tolerability of BoNT-A in routine clinical practice. AbobotulinumtoxinA was twice as likely to deliver an adverse event as onabotulinumtoxinA and incobotulinumtoxinA. The main adverse event was brow ptosis, which represented 57% of the adverse events for abobotulinumtoxinA, but only 13% and 11% for incobotulinumtoxinA and onabotulinumtoxinA, respectively. Historical discussions have centred on the observation that the migration characteristics of abobotulinumtoxinA mean that the product moves further into surrounding tissues than onabotulinumtoxinA and incobotulinumtoxinA. It had been postulated that this...
may be responsible for an increase in adverse event rates,\textsuperscript{13,14} though this link remains speculation. Migration of abobotulinumtoxinA and consequent complete, temporary denervation of the frontalis suspending the eyebrow may be responsible for the rates of brow ptosis seen. Preservation of a minimum suspensory muscle function to the brow is important in reducing this particular type of side effect.

The UKSSAM registry has an important role in informing practitioners on how treatment with BoNT-A performs in routine clinical practice. Data from the registry may well go on to support best practice in the use of BoNT-A for cosmetic improvement.

\section*{Acknowledgements}

The author received no remuneration for the article and has no conflicts of interest to declare. Statistical support was provided by Lovemore Gakava.

\section*{References}


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