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Clinical Research Paper

A cross-sectional structured survey of patients receiving botulinum toxin type A treatment for blepharospasm☆

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ABSTRACT

To characterize satisfaction with current standard-of-care botulinum neurotoxin type A (BoNT/A) treatment for blepharospasm, we performed a cross-sectional, structured survey in subjects with blepharospasm who had received ≥2 BoNT/A cycles. Subjects were interviewed immediately before re-injection to evaluate treatment satisfaction, time course of treatment effects, preferred injection intervals, Jankovic Rating Scale (JRS), and Blepharospasm Disability Index (BSDI).

Subjects' ($n = 114$) last treatment was onabotulinumtoxinA ($n = 78$), incobotulinumtoxinA ($n = 35$), or abobotulinumtoxinA ($n = 1$). The most frequent injection interval was 12 weeks (46.5% subjects); 30.7% had an interval >12 weeks. The main rationale for interval choice was "to maintain treatment efficacy" (44.7%). However, 36.6% reported that treatment effects usually declined within 8 weeks; 69.6% within 10 weeks. JRS and BSDI scores indicated re-emergence of symptoms before re-injection, with 70.2% and 73.7% of subjects reporting difficulties to drive and read, respectively. Overall, treatment satisfaction was high, but declined at the end of the cycle. Many subjects (52.3%) would prefer an injection interval of <12 weeks; 30.6% of <10 weeks.

In conclusion, the survey results indicate that blepharospasm symptoms, such as difficulties to drive and read, re-emerge at the end of a BoNT treatment cycle and that flexible, individualized treatment intervals may improve treatment satisfaction and outcomes.

1. Introduction

Blepharospasm is a focal dystonia characterized by excessive involuntary closure of the eyelids caused by contraction of the *orbicularis oculi* and other facial muscles [1]. Blepharospasm is a chronic, disabling condition that affects patients' quality of life, social interactions, employment status, and may lead to depression [2–5]. With prevalence estimates ranging from 16 per million (in Japan) to 133 per million (in Southern Italy), primary blepharospasm is one of the most common forms of adult-onset dystonia [6]. It predominantly occurs in patients in their fifties and sixties, and affects women more than men [6,7]. It is estimated that at least 50,000 individuals in the USA are affected by blepharospasm, corresponding to a prevalence of approximately 50 per million, with a female preponderance of 1.8:1 [8].

The recommended treatment option for blepharospasm, based on US and European treatment guidelines as well as expert consensus, is repeated intramuscular injections of botulinum neurotoxin (BoNT) [9–11]. In the USA and Europe, three BoNT type A (BoNT/A) formulations (abobotulinumtoxinA, Dysport®, Ipsen Biopharm Ltd., UK; incobotulinumtoxinA, Xeomin®, Merz Pharmaceuticals GmbH, Germany; onabotulinumtoxinA, Botox®, Allergan, Inc., USA) are currently available commercially. At present, all three formulations are licensed for the treatment of blepharospasm in Europe [12–14], while only incobotulinumtoxinA and onabotulinumtoxinA are licensed for the treatment of blepharospasm in the USA [15,16]. These formulations are derived from the Hall strain of *Clostridium botulinum*; in

Abbreviations: BoNT, botulinum neurotoxin; BoNT/A, botulinum neurotoxin type A; BSDI, Blepharospasm Disability Index; CD, cervical dystonia; JRS, Self-administered Jankovic Rating Scale; SD, standard deviation.

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incobotulinumtoxinA, the active neurotoxin has been purified from neurotoxin-associated complexing proteins [17].

The efficacy and safety of BoNT/A formulations for the treatment of blepharospasm have been demonstrated in a number of controlled clinical trials [18–24]. However, treatment effects are temporary and patients require repeat injections. Current US and European prescribing information for approved BoNT/A formulations recommend minimum injection intervals of 12 weeks for the treatment of blepharospasm, mainly due to concerns that shorter intervals might promote the development of neutralizing antibodies and adverse events, with eyelid ptosis and dry eyes being described as the most common adverse effects of BoNT/A treatment for blepharospasm [13–16,25]. To date, only one prospective clinical trial has been conducted in blepharospasm allowing BoNT treatment intervals shorter than 12 weeks [19,26]. This study included a randomized, placebo-controlled main period with one incobotulinumtoxinA treatment followed by an open-label extension period with up to five incobotulinumtoxinA treatments at flexible intervals ≥6 weeks, with a total treatment duration of up to 68 weeks. In this study, injection intervals <12 weeks were not associated with a higher incidence of adverse events than intervals ≥12 weeks [27] and no patients developed neutralizing antibodies based on the sensitive mouse hemidiaphragm assay [26]. Importantly, the study also revealed that treatment intervals <12 weeks were clinically indicated in a considerable proportion of patients with blepharospasm, based on the clinical need for re-injection as established by the investigator and confirmed by a Jankovic Rating Scale (JRS) severity subscore ≥2 [26]. Hence, many patients with blepharospasm experienced recurrence of symptoms before the end of the current standard-of-care 12-week interval, which may reduce quality of life.

We conducted a cross-sectional, structured survey in the USA in subjects who received BoNT/A injections for blepharospasm. We assessed BoNT/A treatment history, treatment intervals, physicians' rationale for intervals, time course of patient-reported therapeutic effects, treatment satisfaction, patient-preferred treatment intervals, Blepharospasm Disability Index (BSDI), and self-administered JRS scores.

2. Material and methods

2.1. Ethics and regulatory requirements

The study protocol, informed consent, and other appropriate study-related documents were reviewed and approved by an independent ethics committee/institutional review board. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines and applicable regulatory requirements. Written informed consent was obtained from each subject prior to enrollment (i.e. prior to completing the survey). The trial was registered with ClinicalTrials.gov. (NCT01686061).

2.2. Subjects

Subjects who were eligible for participation included 18- to 80-year-old men and women with blepharospasm who had completed ≥2 treatment cycles with abobotulinumtoxinA, incobotulinumtoxinA, or onabotulinumtoxinA. The survey focused on BoNT/A treatment only and subjects were excluded if they had received rimabotulinumtoxinB during any of the previous two treatment cycles.

Subjects were recruited at five clinical sites in the USA. All subjects attending study sites to receive BoNT/A treatment for blepharospasm were invited to enroll. Interviews took place immediately prior to subjects' next scheduled treatment, i.e. just before a re-injection. However, the survey was a non-interventional study and no treatments were administered as part of the study. Survey data were collected via interviews conducted by study staff other than treating physicians; the same member of staff conducted all interviews at each site, whenever possible.

2.3. Patient survey

Demographics, baseline disease characteristics, medical history, previous BoNT/A treatment history and reasons for the chosen treatment interval were retrieved from subjects' medical records. The reasons for the chosen treatment interval could be selected from a pre-defined list in the case report form (included as supplementary material), but study staff had the option to specify other reasons if applicable. The study then collected the following information about subjects' perspectives of BoNT/A treatment.

2.3.1. Botulinum toxin treatment – historical and current cycle

Subjects were asked to recall their BoNT/A treatment history (usual treatment interval, reasons for the interval, and usual time to onset, peak, and decline in effect) and experiences over the current injection cycle (time to onset, peak, and decline in effect). Subjects were asked when they would have preferred to have their next injection, if given the choice.

2.3.2. Treatment satisfaction

Subjects rated their current satisfaction with BoNT/A treatment using a numerical rating scale ranging from 1 to 10, where 1 was defined as *not at all satisfied* and 10 as *very satisfied*. Subjects were also asked to recall their satisfaction at the peak effect of BoNT/A treatment during their current cycle. Subjects with a rating of 1–3 were classified as *not at all satisfied*, those with a rating of 4–7 as *somewhat satisfied*, and those with a rating of 8–10 as *very satisfied*.

2.3.3. Blepharospasm disability index

Subjects completed the BSDI, a validated scale assessing functional impairment in activities of daily living [21,28]. Items were rated on a 5-point scale from 0 (no impairment) to 4 (no longer possible due to blepharospasm), or rated as non-applicable. Subjects were also asked to recall their level of impairment at the peak of BoNT/A treatment effect.

2.3.4. Jankovic rating scale

The JRS is a validated physician rating scale that includes a severity item and a frequency item that are both scored from 0 (best) to 4 (worst) [18,28]. In this survey, we have used the JRS as a self-administered instrument that was completed by subjects under the guidance of clinic staff to rate blepharospasm symptoms (current and at the peak of BoNT/A treatment effect).

2.4. Statistical methodology

Descriptive statistics were used to summarize all data. Continuous variables were summarized by number, mean and standard deviation (SD), and median value and range. Categorical variables were summarized as counts and percentages. Percentages were based on non-missing values. Statistical analysis was performed using the SAS® software package (SAS Institute Inc., Cary, NC).

3. Results

The survey took place between September 2012 and April 2013. Overall, 124 subjects participated in the survey and 91.9% (114/124) were included in the final analysis. The other 8.1% of subjects (10/124) were excluded as they had not met the inclusion criterion for age.