Title

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Tremor and Other Hyperkinetic Movements

Reviews

Systematic Literature Review of AbobotulinumtoxinA in Clinical Trials for Blepharospasm and Hemifacial Spasm

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Abstract

Background: The aim was to elucidate clinical trial efficacy, safety, and dosing practices of abobotulinumtoxinA (ABO) treatment in adult patients with blepharospasm and hemifacial spasm. To date, most literature reviews for blepharospasm and hemifacial spasm have examined the effectiveness of all botulinum neurotoxin type A products as a class. However, differences in dosing units and recommended schemes provide a clear rationale for reviewing each product separately.

Methods: A systematic literature review was performed to identify randomized controlled trials and other comparative clinical studies of ABO in the treatment of blepharospasm and hemifacial spasm published in English between January 1991 and March 2015. Medical literature databases (PubMed, Cochrane library, EMBASE) were searched. A total of five primary publications that evaluated ABO for the management of blepharospasm and hemifacial spasm were identified and summarized.

Results: Data included 374 subjects with blepharospasm and 172 subjects with hemifacial spasm treated with ABO. Total ABO doses ranged between 80 and 340 U for blepharospasm and 25 and 85 U for hemifacial spasm, depending on the severity of the clinical condition. All studies showed statistically significant benefits for the treatment of blepharospasm and hemifacial spasm. ABO was generally well tolerated across the individual studies. Adverse events considered to be associated with ABO treatment included: ptosis, tearing, blurred vision, double vision, dry eyes, and facial weakness.

Discussion: These data from 5 randomized clinical studies represents the available evidence base of ABO in blepharospasm and hemifacial spasm. Future studies in this area will add to this evidence base.

Keywords: AbobotulinumtoxinA, botulinum toxin, blepharospasm, hemifacial spasm

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Introduction

Blepharospasm and hemifacial spasm are disabling movement disorders involving the facial muscles that are routinely treated with botulinum neurotoxin type A (BoNT-A).

Blepharospasm is a focal dystonia characterized by excessive involuntary blinking or forceful closure of the eyelids. In the most common primary form (benign essential blepharospasm), symptoms are caused by spasm of the orbicularis oculi muscles.[1] Involuntary

closure of the eyelids can also be caused by failure of voluntary levator contraction, a condition known as "apraxia of lid opening"; the two conditions may co-exist.[2] Patients with mild blepharospasm can present with eyestrain and a sensation of dryness in the eyes that contributes to excessive blinking. These symptoms are sometimes difficult for physicians to distinguish from tic disorders, though tics involving the face are more likely to be suppressible for brief periods and generally do not improve with the use of a "sensory trick." With progression of the disorder some patients find it increasingly hard to keep their eyes open, leading to a functional blindness because of frequent and prolonged eyelid closure. In addition, the condition can be associated with depression, anxiety and social isolation.[3] Like other forms of dystonia, the pathophysiology of blepharospasm has not been clearly defined, but seems to be correlated with basal ganglia function and impaired neuroplasticity.[1]

Hemifacial spasm (HFS) is characterized by unilateral intermittent clonic or tonic contraction of the muscles responsible for facial expression. These muscles are supplied by the facial nerve, and the most likely cause of HFS is a blood vessel compressing the root of this nerve.[4] Other etiologies of HFS are similarly related to injury of the facial nerve, and may develop after facial reconstruction surgeries or Bell's palsy. The disorder typically begins around the eye and this often is the most symptomatic aspect to the disorder. HFS can have a significant impact on a patient's quality of life.[5]

The integral role of BoNT-A in the management of blepharospasm and HFS is recognized by guidelines from around the world.[6,7] The American Academy of Neurology (AAN) evidence-based treatment guidelines for blepharospasm and HFS recommend that BoNT should be offered as a treatment option to patients with blepharospasm (Level B) and hemifacial spasm (Level C).[6] At present, none of the BoNT-A is approved for the treatment of HFS in the United States.

To date, most literature reviews for blepharospasm and HFS have examined the effectiveness of all BoNT products as a class.[6,8,9] However, differences in dosing units and recommended schemes provide a clear rationale for reviewing each product separately. In the United States, this principle is emphasized by mandatory Food and Drug Administration (FDA) labeling stating that BoNT subtypes are not interchangeable and no standard dose adjustments should be used to substitute one subtype for another. Indeed, education on the specifics of each product is a key unmet need in the medical community, as the lack of direct product comparability leads to confusion and therefore potentially sub-optimal treatment. AbobotulinumtoxinA (ABO) has been used to treat blepharospasm and HFS in many countries outside the United States for many years.[10–12] We have previously reported on a systematic review evaluating the use of ABO in the management of adult upper limb spasticity.[13] Here we report the results of a parallel systematic review of clinical studies of ABO in blepharospasm and HFS.

Methods

The systematic literature review presented here is one part of a larger systematic review of all potential indications for ABO, the results of which will be presented separately per each relevant indication. The literature search strategy and methods for this systematic review were specified in advance and previously described in a protocol.[13] Components of the protocol include the literature search strategy, screening criteria, data extraction methods, and risk of bias appraisal used to assess studies selected for inclusion.

Screening criteria

Specific study characteristics of interest were defined in the protocol. They include study type—randomized controlled trials (RCTs) and other comparative clinical studies; patient population—adult patients with blepharospasm and HFS; treatment—ABO; and outcomes—primary and secondary efficacy, safety, and dosing.

Literature search strategy and data sources

The literature search strategy was developed using a combination of Medical Subject Heading (MeSH) terms and keywords. Keywords of relevance to the review of blepharospasm and HFS were abobotulinumtoxinA (alternative spellings included: abobotulinumtoxin A and abobotulinum Toxin A), Dysport, hemifacial spasm, blepharospasm, and clinical trial. Language (English only) and date limits (January 1991 to January 2013) were also applied.[13] Subsequently, the search was updated to include blepharospasm and HFS papers published between January 2013 and March 2015. Searches were performed in three foundational and comprehensive electronic medical literature databases (PubMed, Cochrane Library, EMBASE). Bibliographic reference lists of systematic reviews identified during screening were searched to identify any relevant studies that were not identified through the electronic database searches.

Study selection

At Level 1 screening, all publications reporting preclinical, Phase 1, prognostic/biomarker, genetic retrospective, registry, case report, and/or non-comparative studies were excluded, as were letters, consensus reports, editorials, and non-systematic reviews. Although, systematic reviews and meta-analyses were not included in their own right, they were used for identification of additional primary studies. At Level 2 screening, all publications that reported only biochemical or immunologic endpoints were excluded. Also at this stage, non-randomized, controlled Phase 2 or 3 clinical trials, comparative long-term follow-up studies (e.g., open-label follow-up of randomized controlled clinical trials) and comparative prospective Phase 4 post-marketing trials were excluded, provided that adequate information from randomized Phase 2 and Phase 3 trials had been identified.

Data extraction

Study methodology, patient, and treatment-level data were extracted from the full text publications under predefined headings. Each included study underwent quality assessment for risk of bias based on Cochrane metrics. The quality assessment for RCTs systematically addresses six types of bias: selection, performance, detection, attrition, reporting, and other sources of bias not covered by other domains. If

non-RCTs or other study types were deemed relevant for data extraction, quality assessment was performed using Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) appraisal criteria for non-RCTs.[14]

Role of the funding source

The study was partially funded by Ipsen for data collection and editorial support. K.D. developed the protocol and data collection was coordinated by RTI Health Solutions and designates. Aside from procuring the data collection and editorial support, Ipsen did not contribute to the study conduct or reporting of results.

Results

Publications identified

We have previously reported the overall results of the larger systematic survey.[5] The current search identified five primary publications that evaluated ABO for the management of adult blepharospasm and HFS and met our search criteria.[15–19] Two studies included only patients with blepharospasm,[15,17] two studies included patients with HFS,[18,19] and one study included patients with both blepharospasm and HFS.[16] Studies used a wide range of outcome measures including the Blepharospasm Rating Scale (and subscales), quality of life, and frequency of involuntary movements. Three of the studies also evaluated the efficacy of onabotulinumtoxinA (ONA; Botox)[15,16] and one also included another formulation not available in the United States (Neuronox).[19]

Efficacy in blepharospasm and HFS

All studies demonstrated the efficacy of ABO versus placebo in the management of blepharospasm and HFS; Table 1 provides an overview of efficacy and safety outcomes from each of the studies. The studies comparing the efficacy of ABO with other BoNT products generally showed equivalent efficacy, including latency and duration of action.[15,16,19]

To evaluate the efficacy and safety of ABO in patients with blepharospasm, Truong and colleagues[17] conducted a Phase 2, multicenter, double-blind, randomized, parallel-group, placebo-controlled study in 120 patients. Patients were randomized to receive a single treatment of ABO (with a total dose of 40, 80, or 120 U per eye) or placebo injected subcutaneously into the medial and lateral upper and lower lids of each eye. The primary efficacy variable was functional disability as measured by the percentage of normal activity achieved on the Blepharospasm Disability Scale (BDS). Secondary efficacy outcome measures included the Frequency of Involuntary Movement (FIM) scale and severity of oculofacial spasms using the Severity Rating Scale (SRS). After 4 weeks, functional disability was significantly lower following ABO treatment at all doses than placebo ($p \leq 0.006$). Efficacy was dose-related and maintained through week 12 for all active treatment groups. Similarly, significant improvement in the FIM scale and SRS scores were observed after 4, 8, and 12 weeks for all ABO doses compared to placebo ($p \leq 0.001$) and 16 weeks for patients treated with 80 and 120 U ($p < 0.05$).[17]

Nüssgens and Roggenkämper[15] compared the clinical profile of ONA and ABO (given at a dose ratio of 1:4) in 212 patients with essential blepharospasm. Patients received one injection of ABO and one injection of ONA in two separate treatment sessions (at the first session patients randomly received one of the drugs, at the second the other drug was given). The mean dose of ABO was 182 ± 55 U (range 100–340 U) and the mean dose of ONA was 45 ± 13 U (range 25–85 U). The study found that the mean duration of effect was similar between the two formulations (ABO: 8.0 ± 4.6 weeks vs. ONA 7.98 ± 3.8 weeks; $p=0.42$).

Sampaio et al.[16] performed a single-blind, randomized, parallel, comparative study to test the hypothesis that the optimal conversion factor for ABO to ONA is approximately 4:1 for adult patients with blepharospasm (n=42) or HFS (n=49). The primary outcome measures were the duration of effect, defined as the interval between the day of treatment and the date the patient reported a waning of effect, and the number of boosters needed. Secondary outcome measures were latency of effect, defined as the interval between the day of treatment and the start of symptomatic relief; clinical efficacy, measured as the relative percent improvement in the Blepharospasm Rating Scale, and frequency of adverse reactions. Eligible patients were randomized into two groups: one group received treatment with ABO using 10 U per point according to predefined schemes (blepharospasm: 5 points per eye giving a total dose of 100 U; HFS: 5 points around the affected eye and 2 points to the lower face giving a total dose of 70 U). The other group received ONA according to a similar injection pattern using 2.5 U per point. At this dose ratio, both ABO and ONA groups produced similar clinical efficacy and tolerability. For patients showing a positive response without the need of a booster, the duration of effect was 13.3 ± 5.9 weeks for the ABO group and 11.2 ± 5.8 weeks for the ONA group. The frequency of booster treatments was 23% in the ABO group and 12% in the ONA group ($p=0.26$), with the booster dose always the same or similar to the one given in the first treatment.

In contrast to the studies by Nüssgens and Roggenkämper[15] and Sampaio et al.,[16] the study reported by Kollewe et al.[18] used a lower dose ratio of ONA: ABO of 1:2.56. This was an observational of patients with HFS (n=97) and reinnervation synkinesias (n=36) who were treated with either ONA (n=78) or ABO (n=55) for 6 years (range 2–12 years); all patients received eight consecutive treatments. For HFS, injections were administered at three or four sites of the orbicularis oculi of the upper and lower eyelid. If residual contractions remained, additional injections were administered into the zygomaticus major, the buccinators corrugator, or the frontalis muscles. The mean $\pm$ SD ONA dose for HFS was 22 ± 10 U and the mean ABO dose 51 ± 24 U. The benefits of treatment were similar between the two HFS groups: the therapeutic effect started within the first week (5.9 ± 3.4 days with ABO and 6.1 ± 3.2 with ONA) and lasted for at least 12 weeks (12.2 ± 3.7 weeks with ABO and 12.1 ± 3.1 weeks with

Table 1. **Summary of Completed Clinical Trials for Blepharospasm and Hemifacial Spasm**

Study Identifiers, Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
Nüssgens and Roggenkämper[15] Design: Randomized, double-blind, study Objective: To find the bioequivalence between ONA and ABOport	Patient population: Patients with essential blepharospasm Sample size: N=212 Intervention • ABO (182.1±55.1 U) • ONA (45.4±13.3 U)	**Primary outcome** Duration of effect • ABO (n=212): 8.03 weeks±4.6 (range, 0–22 weeks) • ONA (n=212): 7.98 weeks + 3.8 (range, 0–16 weeks) No statistically significant differences in the duration of the two treatments (p=0.42)	**Safety outcomes** AEs (ptosis, tearing, blurred vision, diplopia, hematoma, foreign body sensation) per group: • ABO: 51 of 212 patients (24.1%) • ONA: 36 of 212 patients (17.0%) Moderate significant difference ($p<0.05$) observed Ptosis (ABO vs. ONA): 14 cases (6.6%) vs. 3 cases (1.4%) $p<0.01$

Table 1. Continued

Study Identifiers, Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
Sampaio et al.[16] Design: Single-blind, randomized, parallel, comparative trial Objective: Compare the efficacy and the tolerability of ABO and ONA, using a conversion factor 4:1	Patient population: Patients with blepharospasm (n=42) or HFS (n=49) Sample size: N=91 Intervention • ABO - 100 U/side, blepharospasm - 70 U, HFS • ONA - 25 U/side, blepharospasm - 17.5 U, HFS	**Primary outcomes** For all patients **ABO (n=48)** / **ONA (n=43)** / **p** Duration of effect in patients with no boosters[1] (weeks): 12.8±5.6 / 13.1±11.8 / 0.91 Frequency of booster treatments: 11 (24%) / 5 (12%) / 0.26 [1]Intention-to-treat analysis. For patients with HFS alone **Intention-to-treat** / **ABO (n=27)** / **ONA (n=22)** / **p** Duration of effect (mean weeks±SD): 13.0±6.3 / 12.8±6.6 / NR Frequency of booster treatments: 2 (7.4%) / 1 (4.5%) / NR **On treatment** / **ABO (n=15)** / **ONA (n=16)** / **p** Duration of effect (mean weeks±SD): 13.9±7.0 / 13.4±6.5 / NR Frequency of booster treatments: 2 (13.3%) / 1 (6.3%) / NR **Secondary outcomes** Values reported for the ITT population for ABO and ONA, respectively: • Onset Latency (mean days±SD): 5.3±6.7; 4.4±4.1; p=0.45 • Efficacy score: 47.2±35.9; 46.5±26.8; p=0.35 • Functional score: 48.6±41.9; 33.8±34.4; p=0.2	**Safety outcomes** No differences between groups • AEs: 50% (ABO), 47% (ONA) • Most prevalent AEs • Facial paresis (in HFS)

Table 1. Continued

Study Identifiers, Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
Truong et al.[17] Design: Phase 2, multicenter, double-blind, randomized, parallel-group, placebo-controlled study Objective: Evaluate the efficacy and safety of three doses of ABO in patients with bilateral blepharospasm	Patient population: Patients with blepharospasm Sample size: N=120 (85 evaluable) Intervention • PBO • ABO 40 U • ABO 80 • ABO 120 U	**Primary outcome** Functional disability=PNA on the BDS (the median difference in PNA between active treatment and PBO): • Significantly lower after treatment with all doses (ABO 40 U [n=23], ABO 80 U [n=25], ABO 120 U n=27]) compared with PBO (n=10); p<0.01 (values and 95% CIs depicted in a figure) • Statistically significant functional benefit was dose related, and was maintained through week 12 for all doses and up to week 16 for the ABO 80 U and 120 U groups (p≤0.001) **Secondary outcomes** Frequency of involuntary movements (FIM score): • Significantly improved in all ABO groups compared with PBO • Median of differences in scores between each ABO group (40 U, 80 U, 120 U) and PBO - Week 4: –2.0, –3.0, –3.0 (p<0.001 for all) - Week 8: –2.0 (p<0.001), –3.0, –2.0 (p<0.001, for ABO 80 and 120) - Week 12: –2.0, –2.0 (p=0.001, for ABO 40 U and 80 U), –3.0 (p<0.001) - Week 16: –1.0 (p=0.107), –1.0 (p=0.032), –1.0 (p=0.044) Severity of oculofacial spasms (Severity Rating Scale) • Significantly improved in the ABO groups • Median of difference in severity of oculofacial spasm scores between each ABO group (40 U, 80 U, 120 U) and PBO: - Week 4: –1.0, –2.0, –2.0 (p<0.001 for all) - Week 8: –1.0, –2.0, –2.0 (p<0.001 for all) - Week 12: –1.0 (p=0.001), –1.0, –1.0 (p<0.001 for ABO 80 U and 120 U) - Week 16: –0.0 (p=0.104), –1.0 (p=0.003), –1.0 (p=0.011) Severity of global impairment (measured by changes in the VAS scale from baseline) improved with all three ABO doses. At week 16, the mean change from baseline was lower than that for previous weeks	• ABO was well tolerated and the AEs were mild • AEs as n (%) related to treatment per group (PBO, ABO 40U, 80U, 120U): • Eyelid ptosis: 1 (4), 4 (13), 12 (39), 18 (58) • Blurred vision: 1 (4), 7 (23), 6 (19), 13 (42) • Lagophthalmos: 0, 3 (10), 2 (6), 7 (23) • Diplopia: 0, 3 (10), 5 (16), 5 (16) • Increased lacrimation: 1 (4), 5 (17), 3 (10), 2 (6) • Dry eyes aggravated: 0, 1 (3), 4 (13), 0

Table 1. Continued

Study Identifiers, Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
Kollewe et al.[18] Design: Observational study Objective: Report long-term efficacy and safety of ABO and ONA using the ratio ABO:ONA=2.56:1	Patient population: Patients with HFS (n=97) and RS (n=36) Sample size: N=133 HFS Intervention: • ABO 51±24 U, HFS • ONA 22±10 U, HFS	**Primary outcomes** **ABO (n=55)** / **ONA (n=78)** **Primary outcomes** — **HFS (n=44)** / **RS (n=11)** / **HFS (n=53)** / **RS (n=25)** Onset latency (days): 5.9±3.4 / 5.9±3.7 / 6.1±3.2 / 6.9±3.4 Duration of effect (weeks): 12.2±3.7 / 12.1±3.1 / 12.1±3.1 / 11.2±2.7 GCI[1]: 2.6±0.4 / 2.6±0.2 / 2.6±0.3 / 2.6±0.4 [1]GCI scale: 0=no effect, 1=slight, 2=moderate, 3=marked improvement in severity and function. No statistically significant differences in all analyzed parameters between either patient groups or both drugs (*P* values NR) **Secondary outcomes** Treatment outcome between the third and last injection: stable in 91% of all patients	**Safety outcomes** AEs were mild and transient. AEs (% of injection series) in ABO and ONA groups: • Ptosis: 2.8%, 2.3% • Dry eye: 1.7%, 1.1% • Facial weakness: 1.5%, 0.9% • Diplopia: 0.2%, 0.2% • None were statistically significant

Table 1. Continued

Study Identifiers, Design, Objective	Patient Population, Sample Size Intervention	Efficacy Outcomes	Safety Outcomes
Kongengdao and Kritalukkul[19] Design: Double-blind, randomized, cross-over study Objective: To compare post-treatment QoL in HFS patients treated with ABO and Nx	Patient population: Patients with HFS Sample size: N=26 Intervention: • ABO 60 U • Nx 12.5 U	**Outcomes** **ABO** / **Nx** **Primary** HFS-30: 27.3±22.8 / 27.2±22.1 **Secondary** SF-36: 112.1±8.0 / 109.7±9.9 AIMS: 10.3±7.5 / 10.7±6.7 CES-D: 17.2±7.7 / 16.5±7.4 No statistically significant differences in all analyzed parameters (*P* values NR) **Tertiary outcomes** ABO vs. Nx • HFS Total intensity score (6.62±0.7 vs. 8.04±0.2; p<0.001) • Duration of facial muscles spasm per day (3.64±0.4 vs. 4.7±0.4 hours/day; p<0.001) • Duration of functional impairment per day (1.25±0.1 vs. 1.73±0.2 hours/day; p<0.001)	None reported

Abbreviations: ABO, AbobotulinumtoxinA; AE, Adverse Effect; AIMS, Abnormal Involuntary Movement Scales; BDS, Blepharospasm Disability Scale; CES-D, Center for Epidemiological Studies Depression Scale; CIs, Confidence Intervals; FIM, Frequency of Involuntary Movements; GCI, Global Clinical Improvement; HFS, Hemifacial Spasm; HFS-30, Hemifacial Spasm 30 Questionnaire; Intention to Treat,; Not Relevant,; Nx, Neuronox; ONA, OnabotulinumtoxinA; PBO, Placebo; PNA, Percentage of Normal Activity; QoL, Quality of Life; RS, Reinnervation Synkinesia; SD, Standard Deviation; VAS, Visual Analog Scale.

Table 2. Dose Ranges of ABO by Individual Study

	Nüssgens and Roggenkämper[15] (Blepharospasm)	Truong et al.[17] (Blepharospasm)	Sampaio et al.[16] (Blepharospasm and HFS)	Kollewe et al.,[18] 2010 (HFS)	Kongsengdao and Kritalukkul[19] (HFS)
Dilution used	10 U/0.1 mL	200 U/1 mL	500 U/2.5 mL	200 U/1 mL	15 U/0.075 mL
Total	182 ± 55 U (100–340 U)	40 U per eyeand 8O U per eye and 120 U per eye	100 U for blepharospasm 70 U for HFS	46 ± 22 U	60 U
Orbicularis oculi	NR	40U per eye and 80 U per eye and 120 U per eye (all divided between 6 points)	10 U per point[1] 5 points per eye for blepharospasm 5 points on affected eye for HFS	NR	15 U per point 2 points
Orbicularis oris			–		15 U per point 2 points
Lower face[2]			10 U per point 2 points		

[1]Some patients required injections into other muscles (not reported).
[2]Injection points in the lower face were not specified.
Abbreviations: ABO, AbobotulinumtoxinA; HFS, Hemifacial Spasm; Not Relevant,

ONA). Treatment outcomes between the third and last injection were stable in 91% of all patients.

The most recent study was a 24-week, double-blind, randomized, cross-over comparison of quality of life in 26 HFS patients after being treated with ABO and Neuronox reported by Kongsengdao and Kritalukkul.[19] The study used the hemifacial spasm-30 questionnaire (HFS-30), the SF-36 to assess quality of life as well as the Abnormal Involuntary Movement Scale (AIMS), and center for epidemiologic studies-depression (CES-D) questionnaire. Both treatments reduced mean HFS-30, AIMS, and CES-D scores without any difference between the two groups; neither treatment had an effect on mean SF-36 scores. Of interest the study showed that the total intensity score of HFS (6.62 ± 0.7 vs. 8.04 ± 0.2), duration of facial muscles spasm per day (3.64 ± 0.4 vs. 4.7 ± 0.4 hours/day) and duration of functional impairment per day (1.25 ± 0.1 vs. 1.73 ± 0.2 hours/day) in the ABO group were all significantly lower than the Neuronox group ($p < 0.001$).[19]

Safety

The most common adverse effects (AEs) reported were ptosis for patients with blepharospasm and facial paresis for HFS patients.[15–19] Other AEs included blurred vision, lagophthalmos, diplopia, foreign body sensation, increased lacrimation, and aggravated dry eyes.[15–19]

The study reported by Nüssgens and Roggenkämper[15] used a dose ratio of 1:4 to compare the safety of ONA and ABO, and found that the total number of side effects was lower with ONA than with ABO ($p < 0.05$); ptosis was observed in three cases of ONA treatment and 14 cases of ABO treatment ($p < 0.01$).[15] This higher level of AE was not noted in the studies by Sampaio et al.,[16] which used the same dose ratio and found AEs to occur in about half of patients (ABO 50% vs. ONA 47%), nor in the study by Kollewe et al.,[18] where rates were similar between the ABO and ONA groups (ptosis 2.8% vs. 2.3%, dry eye 1.7% vs. 1.1%, facial weakness 1.5% vs. 0.9% and diplopia 0.2% vs. 0.2%, respectively).

Dosing

Dose ranges by individual study are given in Table 2. The main muscle injected was the orbicularis oculi, although patients in the HFS study reported by Kongsengdao and Kritalukkul[19] also received injections into the orbicularis oris and patients in the study reported by Sampaio et al.[16] also received injections into the lower face (injection point not specified). Patients in the Kollewe et al.[18] study could also receive into the zygomaticus major, buccinator, corrugator, or frontalis muscles if there were residual contractions after the orbicularis oculi injections. Investigators in this study avoided making injections into the orbicularis oris muscle in order to prevent paralysis of the mouth.

Discussion

The main aim of this systematic review is to summarize the relevant data on efficacy and safety profile of ABO in blepharospasm and HFS. Other reviews are available regarding assessment of BoNT for treatment of blepharospasm and HFS with no emphasis on the practical dosing of ABO.[6,8] This is essential information as dosing units of one BoNT-A product are not interchangeable.

In this review, all studies showed the efficacy of ABO in managing both blepharospasm and HFS. The studies generally showed that clinical improvements were seen within a week of injection and that the therapeutic effect lasted at least 3 months. Three of the five studies attempted to compare ABO with another BoNT-A product using a "dose ratio." Such ratios are notoriously hard to estimate,[20,21] and while a large number of studies have attempted to evaluate various dosing ratios in focal dystonias, dermatologic conditions, and in healthy volunteers, they have differed in design and quality and, as a result, report a wide range of conversion ratios.[20,21] Two of the studies used an ABO:ONA dose ratio of 4:1;[15,16] however, recent clinical and dermatological studies have suggested that the most appropriate ABO:ONA comparison ratio is less than 3:1.[21] Indeed, the study by Kollewe and colleagues supports equal efficacy when the products are given in a dose ratio of ABO:ONA of $<3{:}1$.[18] At higher doses, clinical efficacy and duration of effect might be observed as equivalent in studies of specific fixed dose relationships, but the same is not true for rates of AEs.[22] A key reason for this is that there is little to no increased therapeutic effect above an optimally effective dose, but the presence of excess toxin is associated with an increased risk of AEs, including unwanted spread of the toxin to other facial regions.

The studies presented in this review provide the available evidence for the safetly profile of ABO for both blepharospasm and HFS. In the Nüssgens and Roggenkämper study, the higher incidence of ptosis in the ABO vs. ONA groups may well represent overdosing due to use of both a higher starting ONA dose and the high conversion ratio (as discussed above).[15] The review provides the dose ranges of ABO that have been safely used in the various trials. In this respect it should be noted that the dosing table provided here is based on the published studies, and does not mean that other doses should not be applied; physicians should always use clinical judgment on dosing schedules dependent on the severity of impairment.

This systematic literature review is part of a larger review where the use of ABO in other indications has also been evaluated.[13] When comparing the present results with the strength of the literature for blepharospasm and HFS, it is apparent that more high quality studies with ABO are required to inform practice. Based on our strict inclusion criteria a number of uncontrolled, exploratory studies were excluded and affected our sample size. While this obviously eliminated some clinically relevant information, this established methodology is considered necessary to avoid bias by using explicit, systematic methods.

In summary, this systematic review provides the current evidence regarding safety and efficacy of ABO injection for blepharospasm and HFS. However, the review also revealed the lack of large trials of ABO to manage these two separate conditions.

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