Evaluation of botulinum toxin A injections for the treatment of refractory chronic digital ulcers in patients with systemic sclerosis

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ABSTRACT

Objective. *To evaluate the therapeutic benefit of botulinum toxin A (BTX-A) injections for digital ulcers (DU) in patients with systemic sclerosis (SSc).*

Methods. *A systematic literature review was performed and the identified articles were selected by two reviewers and analysed with respect to date of publication, inclusion and exclusion criteria, number and age of participants, volume of BTX-A, injection sites, outcomes, and adverse events. In addition, in the Zurich cohort, 7 SSc patients were eligible for the study and were assessed for the duration of DU to heal, duration of DU-free periods, changes in frequency and numbers of prescribed vasodilators, pain and blood flow.*

Results. *In five articles from the systematic review, at least 48% of DU had healed and up to 100% reduction in VAS for pain was reported. Our 7 patients (median age of 53 (47-82) years) had in median 2.5 (2-4) DU and were injected with a median BTX-A volume of 90 (50-100) units per hand. Of the 31 DU in all patients, 77% (n=24) healed. Time to wound closure was in median 8 (4-12) weeks and the DU-free duration was in median 8 (3-10) months. In 80% of the cases, at least one vasodilator was stopped or could be administered less frequently. An improvement of blood flow and pain was reported in 60% of the cases.*

Conclusion. *BTX-A injections might be of benefit for the treatment of chronic, refractory DU in selected SSc patients, yet a sufficiently powered prospective study will be needed as ultimate proof.*

Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterised by (peripheral) microangiopathy and fibrosis (1). The earliest sign of a disturbed microcirculation is Raynaud's phenomenon (RP) (2). Digital ulcers (DU) as indicators of ischaemia develop in about 50% of patients (3). Recurrent DU affect up to 30% of SSc patients (4). In SSc, DU substantially add to the burden of disease by causing considerable pain and by severely impairing every day functions and quality of life. Gigante *et al.* showed in a study with 27 patients that the parasympathetic activity increases in SSc patients with DU and promotes VEGF release leading to vasodilation (5). Current pharmacological or interventional treatment strategies also aim at the improvement of the microcirculation as recently reviewed by Barsotti *et al.* (6). For calcium channel blockers, often used as first-line therapy for RP (7), the effect on the healing of DU has not yet been sufficiently analysed (8, 9). Only one double-blinded randomised study showed a favourable effect on wound healing (10). Other unspecific vasodilators such as angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin-receptor inhibitors and anti-platelet aggregating agents are commonly prescribed, although there is so far no evidence for positive effects on the healing of DU (11). Treatment recommendations for DU include prostacyclin-analogues (7), based on a prospective observational study of 30 patients treated for a median of 3 years (12). However, in a meta-analysis, the use of prostacyclin-analogues showed only significant outcomes in preventing new DU and no effect on the healing of DU (8). Another option for vasodilating therapy of DU are phosphodiesterase type 5 inhibitors (PDE5-inhibitors). Although PDE5-inhibitors are not included in the European League Against Rheumatism/European Scleroderma Trials and Research Group (EULAR/

EUSTAR) guidelines, a favourable effect was found in a meta-analysis and in several other studies (8, 13, 14). For the prevention of recurrence of (multiple) DU, endothelin-receptor antagonists should be considered (7). In two randomised controlled studies, a significant effect on preventing new DU was shown, yet there was no evidence that endothelin-receptor antagonists had an effect on the healing of DU (15, 16). A recent study by Frech *et al*. provided some evidence that targeting molecules involved in endothelial shear stress, *i.e*. glycocalyx and tetrahydrobiopterin, in SSc patients might represent a novel therapeutic approach for the treatment of DU (17).

In situations with failed response to pharmacological therapy (18), surgical treatment, *i.e*. peripheral sympathectomy has been used to treat critical ischaemia. In a small retrospective analysis, 16 out of 17 patients experienced a favourable effect on the healing of DU (19). Another treatment option is an injection of BTX-A. BTX-A prevents sympathetic vasoconstriction of the vascular smooth muscle cells by blocking the transmission of the norepinephrine vesicle and therefore increases blood circulation (20). Additionally, it was found to reduce pain by decreasing the activity of chronically upregulated C-fiber nociceptors through blockade of alpha2-adrenoreceptors (20, 21). Data on BTX-A for the treatment of SSc-related DU are very limited (20-24). Thus, in this study, we performed a systematic review of the available literature and investigated the effects of BTX-A on DU in our local cohort of SSc patients.

Material and methods

Systematic review

A search was performed in PubMed (Public Medicine), the Cochrane Library, and Google Scholar to identify studies on the use of BTX-A in the treatment of DU in SSc. The following search terms were used: "botulinum toxin" in combination with "Raynaud", "systemic sclerosis", "digital ulcers", "ischemia", "microangiopathy", "vasculopathy", "gangrene" or "necrosis". The structured search was last updated on the 30th of August 2017. We defined the following selection criteria: treatment with BTX-A, >3 participants, the majority of patients suffering from SSc, failed medical management of DU (*i.e*. systemic vasodilating therapy and local wound management), focus on healing rate/time of DU, and adverse events after BTX-A injections. Reviews and studies written in other languages than English or French were not included. All titles and abstracts generated by the search were screened by GL and BM. The final articles were selected after reading and judgement of the full text. When different opinions existed among the two reviewers on full text level, consensus was reached. Five studies were finally identified. The data were extracted and included the following relevant study details: date of publication, inclusion and exclusion criteria, number and age of participants, volume of BTX-A, injection sites, outcomes, and adverse events.

Patients

From our local SSc cohort (n=500) at the Department of Rheumatology, University Hospital Zurich, Switzerland, which is part of the EULAR Scleroderma Trials and Research (EUSTAR) registry (25), patients were extracted from the local database in August 2017. They were included, when they met the following inclusion criteria: classification of SSc (26), presence of DU (27), BTX-A injections, and stable vasodilating therapy for at least one year. Among 80 patients with DU, we identified 7 patients, who had been treated with BTX-A injections for chronic ulcers (≥3 months) with persistence despite vasodilating therapy. Since 3 patients had received BTX-A twice at intervals of 4, 13 and 24 months, finally 10 cases became eligible to assess the effect of BTX-A on the healing of DU, the development or recurrence of DU, the frequency of prescription of vasodilators, patient reported pain at follow up and blood flow judged by the treating physician (colouring, temperature of the digits) on physical examination. Furthermore, the volume, injection site and frequency of BTX-A injections were examined. In all patients, the BTX-A injections were carried out by MC at the Department of Plastic Surgery and Hand Surgery, University Hospital Zurich. The injection sites, *i.e*. 10–12 mm distal to the metacarpophalangeal joint of all digits and at the metacarpophalangeal joint of the thumb, were first disinfected, and then BTX-A was injected via a palmar approach. The volume ranged from 50 to 100 units (U) per hand. Written informed consent was obtained from all patients. The study has been approved by the institutional review board in Zurich (pre-BASEC-EK-839, BASEC KEK-Nr. 2016-01515, BASEC-Nr. 2018-02165).

Statistics

The statistical analysis was done using Excel v. 2016. As the data were non-parametric and not normally distributed, they were represented as median and interquartile range. Statistical significance was calculated using the one-sided Wilcoxon signed-rank test at $\alpha = 0.05$.

Results

Systematic review

In PubMed, the Cochrane Library, and Google Scholar numerous studies were identified using the same search terms (Supplementary Table S1). After excluding all studies which appeared more than once, analysed fewer than 3 patients, did not focus on the effect of BTX-A on DU in SSc, were reviews or written in another language than English or French, 5 studies were finally identified by two reviewers, GL and BM.

The majority of selected articles, presented in Table I, were open-label, uncontrolled case series. The inclusion criteria were similar in all articles, yet the exclusion criteria varied. In Uppal *et al*. and Van Beek *et al*., none were defined. In the other studies, patients with BTX-A allergy, pregnancy, and lactation were excluded. The number of patients and their age was comparable. However, the volumes of BTX-A injected differed from 10 to 200 U per hand. Furthermore, all studies chose different injection sites. Uppal *et al*. injected always into the non-dominant hand compared to Motegi *et al*., who injected only into the most affected digit (28, 29). Fregene *et al*. strategy was to

Table I. Selected studies from the systematic review process.

Study	Van Beek *et al*. (32)	Fregene *et al*. (30)	Serri *et al*. (31)	Uppal *et al*. (28)	Motegi *et al*. (29)
Publication year	2007	2009	2013	2014	2016
Inclusion criteria	Failed MM of DU, chronic ulcers	Failed MM of DU, pain, chronic ulcers, gangrene	Failed MM of DU, limited daily living, following of dietary and hygienic rules	Failed MM of DU	Failed MM of DU, history of severe RP
Exclusion criteria	None	Sympathectomy, active infection	BTX-A allergy, pregnancy, lactation, denial of life-style changes	None	Pregnancy, <18 years, previous BTX-A injections
Number of patients (Male/Female)	11 (2/9)	26 (12/14)	18 (2/16)	20 (0/20)	10 (3/7)
Mean age and range (years)	51, 23-70	55, 37-72	46, 23-76	37, 22-57	63, NA
BTX-A dosage per injection (U)	20-200/hand	10-100/hand	100/hand	100/hand	10/digit
Injection sites	In 82% into finger root of digits 2-5, and of digits 1 if affected, and the palms, and in 18% finger root of the affected fingers only	In 38% finger root of the affected digits, in 83% the palms, and in 13% the distal volar wrist creases	In 28% the finger root of all digits and the palms, and in 72% finger root of all digits and PIP level of digits 2-5	Finger root of all digits of the non-dominant hand only	Proximal to the A1 pulley of the most affected digit
Results	80-100% reduction in VAS for pain was reported, 82% of DU healed	Mean 35% reduction in VAS for pain was reported, 48% of DU healed	Mean 67% reduction in VAS for pain was reported, 100% showed complete healing of DU	85% reported decrease in VAS for pain, 75% showed complete healing of DU	Mean 80% reduction in VAS for pain was reported, 100% of DU healed
Complications	27% temporary intrinsic muscle weakness	23% temporary intrinsic muscle weakness	17% temporary intrinsic muscle weakness	10% temporary intrinsic muscle weakness	None

MM: medical management; NA: not available; BTX-A: botulinum toxin A; U: units; PIP level: proximal interphalangeal level; VAS: visual analogue scale; DU: digital ulcers; RP: Raynaud's phenomenon.

inject into different sites depending on the location of the DU (30). Moreover, Serri *et al*. and Van Beek *et al*. changed their methods during the course of the study (31, 32). In Serri *et al*. study the injection sites changed to the proximal interphalangeal level instead of the palms, after intrinsic muscle weakness was reported (31). In Van Beek *et al*. study injections were made only into the affected digits until patients reported severe ischaemia of the other digits. Then, the injection site was changed to all digits and palms. Notably, in most of the studies, the majority of patients showed complete healing of the DU, and less than a third of the patients reported complications.

Baseline and clinical characteristics of the local systemic sclerosis cohort

Seven patients with SSc-associated refractory DU were treated in Zurich with BTX-A injections. Six of the patients were female and one male (Table II). The median age was 53 (47-82) years. Skin involvement was diffuse in 5 patients and limited in 2. All 7 patients suffered from RP and showed a late scleroderma pattern in nailfold capillaroscopy. Furthermore, all patients were ANA-positive and negative for ribonucleic acid polymerase III (RNA Pol III). Four patients had anti-topoisomerase 1 antibodies (anti-topo 1). Two patients were positive for anti-centromere antibodies (ACA). In 4 patients, lung fibrosis was diagnosed. The gastrointestinal system was affected in the majority of patients. They had mainly oesophageal symptoms and suffered to a lesser extent from intestinal symptoms. In none of the patients pulmonary hypertension or renal crisis was observed. The duration of SSc at the time point of BTX-A injections varied from 1 to 28 years and was in median 6.5 (4–15) years.

Effects of botulinum toxin A on chronic ulcers

The 7 patients had in median 2.5 (2-4) DU (Table II). Twenty-nine percent (n=9) were localised on the fingertips and 71% (n=22) on bony prominences. In 30% of the cases (n=3), ulcers were also observed on the lower limbs.

All patients were under therapy with in median 2.5 (1–3) specific vasodilators as well as 2 (1–2) unspecific vasodilators (Supplementary Table S2). Six out of 7 patients were treated with an anti-platelet aggregating agent. The injected volume of BTX-A was 90 (50–100) U per hand (Table III). None of the patients reported negative side-effects during or after the treatment. Except for one patient, all patients received BTX-A injections into both hands. Three patients received BTX-A injections a second time for newly developed or recurrent DU. Out of 31 DU in all patients, 77% (n=24) healed (Fig. 1) ir-

Table II. Patients' main characteristics at time point(s) of botulinum toxin A injections.

Patient no.	Sex	Age (years)	Skin involvement	Raynaud's phenomenon at time point(s) of BTX-A injections	Nailfold capillaroscopy pattern at time point(s) of BTX-A injections	ANA and SSc-specific antibodies	Duration of SSc time point(s) of BTX-A injections (years)	Number of chronic ulcers on atdifferent locations at time point(s) of BTX-A injections		
								Lower limbs	Upper limbs	
									Fingertips	Bony prominences
1	F	54	Limited	+	Late	ANA, ACA	12	0	0	2
2	F	55	Diffuse	+	Late	ANA, anti-topo 1, anti-PM Scl 100	28	0	1	1
3	F	88	Limited	+	Late	ANA, ACA	1	0	2	0
4	F	47/49	Diffuse	+/+	Late/late	ANA, anti-topo 1	4/6	0/0	1/0	3/1
5	M	52	Diffuse	+	Late	ANA, anti-topo 1, anti-PM Scl 100	7	1	1	2
6	F	39/39	Diffuse	+/+	Late/late	ANA, anti-topo 1, anti-PM Scl 100	15/15	0/3	2/0	2/1
7	F	82/83	Diffuse	+/+	Late/late	ANA, anti-PM Scl 100	4/5	0/1	2/0	4/6

M: male; F: female; ANA: antinuclear antibodies; ACA: anti-centromere antibodies; anti-topo 1: anti-topoisomerase 1 antibodies; anti-PM Scl 100: anti-polymyositis/systemic sclerosis 100 antibodies; SSc: systemic sclerosis; BTX-A: botulinum toxin A.

Table III. Usage and effects of botulinum toxin A injections on chronic ulcers.

Patient no.	Volume (U per hand)	Frequency of injection	Location of injection	Injection site	Number of chronic ulcers on the fingertips		Number of chronic ulcers on the bony prominences		Healing duration (weeks)	Duration of ulcer-free periods (weeks)	Duration of SSc at time point(s) of BTX-A injections (years)
					Before BTX-A injections	After BTX-A injections	Before BTX-A injections	After BTX-A injections			
1	100	1	Both hands	Finger roots	0	0	2	0	12	40	12
2	50	1	Both hands	Finger roots	1	0	1	0	20	20	28
3	100	1	Left hand	Finger roots	2	2	0	0	-	0	1
4	50/50	2	Both hands/ both hands	Finger roots/ finger roots	1/0	0/0	3/1	0/0	8/12	4/48	4/6
5	50	1	Both hands	Finger roots	1	0	2	0	8	40	7
6	100/100	2	Both hands/ both hands	Finger roots/ finger roots	2/0	0/0	2/1	0/1	1/-	12/0	15/15
7	90/90	2	Both hands/ both hands	Finger roots/ finger roots	2/0	0/0	4/6	0/4	4/-	32/0	4/5

U: units; BTX-A: botulinum toxin A; SSc: systemic sclerosis; -: no or reduced healing.

respective of the location (fingertips/ bony prominences). Time to wound closure was in median 8 (4–12) weeks and the ulcer-free duration was in median 8 (3-10) months (Table III). In 8 out of 10 cases, at least 1 vasodilator was stopped or could be administered less frequently after BTX-A injections (Table IV). An improvement of blood flow and pain was reported in 6 out of 10 cases (Table IV). The late SSc pattern as observed in the nailfold capillaroscopy did not change after median 13 (9.5–25) months of follow-up. In two patients out of three, repeated injections did not improve wound healing compared to the prior injections (Table III). The third patient in contrast had a prolonged ulcer-free period.

Discussion

Our study showed that in a limited number of SSc patients with chronic, refractory DU, BTX-A injections had an added therapeutic benefit. In contrast to previously used vasodilating agents a relevant reduction of perceived pain was reported. Most importantly, 77% of DU healed after injecting a median of 90 U BTX-A injections per hand. In average, the effect lasted 8 months and in the majority of patients 1 vasodilator could either be stopped or administered

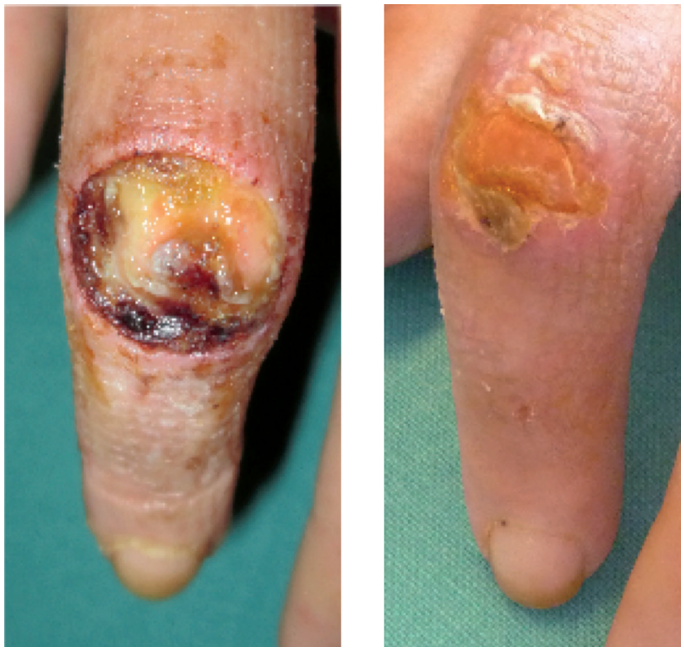

Fig. 1. Digital ulcer before (left) and after (right) botulinum toxin A injection. 86 x 78mm (300 x 300 DPI).

less frequently after BTX-A injections. Studies with a comparable design, patient numbers, and dosing showed similar effects of BTX-A injections on wound healing rate and time of BTX-A injections on SSc-associated DU (28, 31, 32). Also in Bello *et al*. study, the only randomised, double-blind, placebo-controlled study on BTX-A injections in SSc patients, the number of active DU per physical examination was evaluated as a tertiary outcome (24). Although the result was not significant, the healing rate was slightly better in the hand with BTX-A treatment than in the hand with placebo-treatment (injections with 2.5ml of sterile saline per hand) (24). The number of DU decreased in a period of 4 months from 0.53 to 0.28 in hands allocated to BTX-A treatment compared to the decrease from 0.55 to 0.36 in hands allocated to placebo treatment (24). However, the study was underpowered for the analysis of BTX-A effects on healing of DU (24).

The injection sites in the following studies with similar outcomes differed. Whereas Uppal *et al*. injected BTX-A into the same sites as in our study (28), Serri *et al*. chose a different approach. They injected both hands on the level of the metacarpophalangeal joints and in addition 4 sites of the palm in 5 patients and 8 sites on the level of the proximal interphalangeal joints of digits 2-5 of 13 patients (31). Van Beek *et al*. injected BTX-A into the superficial palmar arch and the common and proper digital arteries of all fingers (thumb only, if symptomatic) in 9 patients (32). Two patients received injections of the affected fingers only (32). Whether the localisation of the injection site affect-

Table IV. Additional effects of botulinum toxin A.

Patient no.	Vasodilator with change in frequency of prescription after BTX-A injections	Duration until vasodilators frequency change of prescription after BTX-A injections (weeks)	Frequency of prescription (days/month)		Vasodilator started after BTX-A injections	Time of vasodilators start after BTX-A injections (weeks)	Reported pain after BTX-A injections	Reported blood flow after BTX-A injections	Nailfold capillaroscopy pattern	
			Before BTX-A injections	After BTX-A injections					Before BTX-A injections	After BTX-A injections
1	Prostacyclin-analogues	4	3	3 every second month	0	0	NA	Better	Late	Late
2	Prostacyclin-analogues	20	30	7	0	0	Better	Better	Late	Late
3	0	0	0	0	PDE5-inhibitors	4	Better	NA	Late	Late
4	Prostacyclin-analogues/ prostacyclin-analogues	4/4	30/30	3/3	0/0	0/0	Better/NA	Better/NA	Late/late	Late/late
5	0	0	0	0	0	0	NA	NA	Late	Late
6	Prostacyclin-analogues/ prostacyclin-analogues, ERA	6/4, 1	30/30, 30	3/7, 0	Anti-platelet aggregating agents/ 0	3/0	Better/ better	Better/ better	Late/late	Late/late
7	Prostacyclin-analogues, PDE5-inhibitors/ anti-platelet aggregating agents	4, 4/8	3, 30/30	0, 0/4	0/0	0/0	NA/better	Better/ better	Late/late	Late/late

BTX-A, botulinum toxin A; PDE5-inhibitors, phosphodiesterase type 5 inhibitors; ERA, endothelin-receptor-antagonists; NA, not available.

ed the healing rate, was so far only addressed in one study. Fregene *et al*. injected BTX-A into 3 different sites depending on the location of the DU (30). For distal locations, BTX-A was injected along the track of the digital vessels, for more proximally located DU, they injected BTX-A at the web space and at the level of the superficial palmar arch, on either side of the involved digit (30). If several digits were affected, BTX-A was injected close by the radial or ulnar arteries at wrist level (30). The comparison of the three injection sites did not show significantly differences in healing rates (30), which could be due to the small number of patients (n=26).

Concerning the safety of BTX-A injections, in our 7 patients no complications during or after the treatment occurred, which was probably due to the chosen distal injection sites. In contrast, Van Beek *et al*. reported muscle weakness in 27% of all patients and in Serri *et al*. study 17% of the patients suffered from reversible intrinsic paralysis (31, 32). Whereas the BTX-A dosages were comparable to our study, the injection sites differed as specified above. In contrast to our study, Van Beek *et al*. and Serri *et al*. injected BTX-A also into the palm (31, 32). After 3 out of 5 patients reported intrinsic paralysis, Serri et al. changed the injection location from 4 sites in the palm to 8 sites in digits 2-5 on the level of the proximal interphalangeal joints (31). Thereafter, no further complications were reported, suggesting that injections into the palm might have been responsible for the muscle weakness (31). In Motegi *et al*. study also injections into the palm were made with no local or systemic adverse effects reported (29). This may be explained by the fact, that half of the dosage of BTX-A used by Serri *et al*. was injected (29, 31). The intrinsic muscle weakness was always reversible (24, 28, 30-32).

Recently another method for decreasing complication rate, namely a dorsal approach of BTX-A injection, gained interest (24, 33). Dhaliwal *et al*. examined 40 patients, who received BTX-A injections via a dorsal approach (33). None of the patients reported hand weakness after BTX-A injections (33). This result was explained by the authors with the theory that the lumbricals were protected from the effects of BTX-A due to the muscle anatomical location (33). However, as none of the patients suffered from DU, the effect on healing rate of DU was not analysed (33).

Apart from the beneficial effect of BTX-A on the improved wound closure, there was also reduction of pain. In our study, in 60% of the cases an improvement in pain was reported. This result was confirmed by several other studies from the systematic review (28, 30). In Uppal *et al*. study 85% of the patients reported decrease in visual analogue scores (VAS) for pain (28). The methods of BTX-A injections, number of patients and exclusion criteria were comparable.

The most important novelty of our study compared with previous studies is the analysis of vasodilator use after BTX-A therapy. In median one vasodilator was either stopped or administered less frequently. Furthermore, in 3 patients the effect of a second BTX-A injection after the development of new or recurrent DU was analysed. Compared to 2 patients, whose DU persisted after second BTX-A injections, in one patient all DU healed with a longer healing rate than after the first BTX-A injections and a longer ulcer-free duration. Thus, further studies are needed to estimate whether the repetition of the treatment is as effective.

Certain limitations exist in our study. First, the sample size with only 7 patients is very small. The reasons for the few patients receiving BTX-A injections are that a cost credit was requested for the treatment as well as the first line therapy needed to have failed. However, most of the studies on this issue included less than 50 patients, analogous to our study. Furthermore, as the nailfold capillaroscopy examined only the morphology, a Doppler ultrasound to assess the tissue perfusion would have been a good objective endpoint. Prospective, randomised, placebo-controlled trials are needed to confirm the promising effects of BTX-A on the healing of DU in patients with SSc since the only available study had change in blood flow at 1-month follow-up as primary endpoint (24). In addition, future studies should also address the ideal injection sites and volumes of BTX-A for best results with the lowest rate of adverse events.

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