Efficacy and safety of botulinum toxin B injection for Raynaud's phenomenon and digital ulcers in patients with systemic sclerosis: single-blind, randomized trial

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Pathogenesis of systemic sclerosis

Raynaud's phenomenon (RP)

- Presence of episodic vasospasms of the peripheral blood vessels and ischemia of fingers in response to cold or emotional stress.
- It has been considered that cold- or stress induced norepinephrine stimulates the adrenergic receptor (AR)α on pericytes and/or vascular smooth muscle cells, thus resulting in vasoconstriction.
- ARα response are increased in the digital arteries in SSc patients, suggesting that norepinephrine is involved in the pathogenesis of RP in SSc.

Treatment of Raynaud's phenomenon

- Pharmacological treatments of RP have targeted the enhancement of vasodilation and/or reduction of vasoconstriction, such as calcium channel blockers, antiplatelet agents, sarpogrelate hydrochloride, cilostazol, and oral and i.v. prostanoil.
- The endothelin receptor antagonists bosentan and phosphodiesterase-5 inhibitor may benefit functional impairment in SSc-related RP patients.
- However, no satisfactory treatments for RP in SSc currently exist.

Several studies have recently shown the beneficial effects of botulinum toxin A (BTX-A) on RP in patients with SSc.

- Arch Dermatol 2012;148, 426-8.
- J Hand Surg 2010, 35A, 2085-92.
- Plast Reconstr Surg 2009, 124, 191-201.

Botulinum toxin

BTX-A or BTX-B enhanced the blood flow and survival of ischemic skin flaps using animal cutaneous flap models. (Wound Repair Regen 17, 411-417 (2009), J Surg Res 184, 1205-1213 (2013))

We identified that BTX-A or BTX-B enhanced the blood flow, and protected ulcer formation after cutaneous I/R injury using animal model.

- Uchiyama A et al. Scientific Reports 2015, Sekiguchi A et al. presenting in JSID; Poster#P08-08

The effect of botulinum toxin A on Raynaud's phenomenon in Japanese patients with systemic sclerosis: a prospective, open-label trial

Motegi S, et al. J Dermatol. 2016; 43(1): 56-62.

10U of BTX-A was injected into both sides of MP joint of the selected finger, targeting the neurovascular bundles.

Thermographic image at 20 min after cold water stimulation at 4 weeks after BTX-A injection.

Before treatment 4 weeks after treatment

BTX-A injected finger Epithelialization of digital ulcers

We identified the efficacy and safety of BTX-A on RP in Japanese SSc patients. J Dermatol. 2016; 43(1): 56-62.

We also identified that BTX-A inhibited the hypoxia-induced oxidative stress using cutaneous I/R injury mice model. Scientific Reports, 2015; 5: 9072

We have negotiated with manufacturing companies, but they did not intend to develop, we started a clinical trial using botulinum toxin type B (NerBloc®).

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COI Disclosure

Sei-ichiro Motegi

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Differences between type A and B botulinum toxin

- BTX-A and BTX-B cleave SNARE proteins SNAP-25 and VAMP, respectively.
- The efficacy of BTX-B treatment appeared sooner than that of BTX-A.
- BTX-B was more effective than BTX-A in patients with diseases regulated by the autonomic nervous system.
- It has been suggested that BTX-A and BTX-B at 1:20 to 1:40 dose ratios were equally effective in the treatment of several diseases

However, the efficacy of BTX-B injection for RP has never been examined.

The objective of this study

To assess the efficacy and safety of BTX-B for RP in SSc patients in a prospective, single-blind, randomized trial.

Study design

Method of administration

Only one-time injection of BTX-B into both sides of all fingers at 6 points.

(50 U, 200 U, and 400 U/ web space between fingers, and 25 U, 100 U, and 200 U/ radial side of the thumb and ulnar side of the small finger, respectively).

Clinical evaluation

Evaluate at 0, 2, 4, 8, 12, 16 weeks after treatment with Raynaud's score, pain / numbness VAS scale and skin temperature (cold water load test).

Demographic and clinical characteristics of 45 SSc patients with RP in the BTX-B-treated and no treatment control group.

Characteristic	Total patients	No treatment	BTX-B 250 U	BTX-B 1000 U	BTX-B 2000 U
No. of patients	45	8	9	10	18
Age (mean±SE)	60.7 ± 1.9	58.8 ± 3.2	55.4 ± 5.1	65 ± 3.9	61.7 ± 2.9
Female sex (%)	91.1 (41/45)	50 (4/8)	100 (9/9)	100 (10/10)	94.4 (17/18)
lcSSc / dcSSc	26 / 19	5 / 3	5 / 4	7 / 3	9 / 9
mRTSS (mean±SE)	11.7 ± 1.2	12.8 ± 3.3	14.5 ± 3.7	10.9 ± 2.7	10.5 ± 1.5
Autoantibodies					
Topo I (%)	26.7 (12/45)	25 (2/8)	22.2 (2/9)	20 (2/10)	33.3 (6/18)
ACA (%)	53.3 (24/45)	50 (4/8)	55.6 (5/9)	60 (6/10)	50 (9/18)
RNAP (%)	0 (0/45)	0 (0/8)	0 (0/9)	0 (0/10)	0 (0/18)
RNP (%)	6.7 (3/45)	0 (0/8)	11.1 (1/9)	10 (1/10)	5.6 (1/18)
Complications at baseline					
DU (%)	33.3 (15/45)	37.5 (3/8)	33.3 (3/9)	30 (3/10)	33.3 (6/18)
Total No. of DU	24	3	5	3	13
ILD (%)	42.2 (19/45)	50 (4/8)	44.4 (4/9)	30 (3/10)	44.4 (8/18)
PAH (%)	4.4 (2/45)	0 (0/8)	0 (0/9)	10 (1/10)	5.6 (1/18)
RE (%)	80 (36/45)	87.5 (7/8)	66.7 (6/9)	70 (7/10)	88.9 (16/18)

Raynaud's score

The changes in the severity of RP, including the frequency, pain, color, and duration, were assessed using the Raynaud's score

Raynaud's scores in 1,000- and 2,000-U-treated groups were significantly lower than those in control and 250-U-treated group.

Pain/numbness severity (VAS)

Pain/numbness severity was assessed using the 100-mm VAS

VAS scores in 1,000-U and 2,000-U-treated groups were significantly reduced 4 to 16 weeks after injection.

Skin temperature recovery after cold water stimulation

To assess the recovery of skin temperature in the treated finger, the skin temperature at the tip of the finger was measured just after and 10 minutes after an ice-bath immersion for 5 minutes.

BTX-B injection might enhance digital blood flow, leading to enhancement of skin surface temperature recovery after cold water stimulation.

The effect of BTX-B on the numbers of digital ulcers

The numbers of DUs in 1,000- and 2,000-U-treated groups were significantly lower than those in the control group 4 to 16 weeks after injection

Number of new DUs

Weeks	0	4	8	12	16	Total
No treatment (n=8)	0	4	1	1	1	7
BTX-B 250 U (n=9)	0	0	0	2	0	2
BTX-B 1000 U (n=10)	0	0	0	0	0	0
BTX-B 2000 U (n=18)	0	0	0	0	0	0

1,000 and 2,000 U of BTX-B injection might accelerate the healing of RP-related intractable DUs and prevent new DUs formation.

Adverse effects

Transient muscle weakness occurred in 1 patient in 2,000-U treated group from 5 days to 3 weeks after injection

- No systemic or local adverse events, such as an anaphylactic reaction, reduction in muscle contraction force, swallowing difficulty, dry mouth, and abnormal liver function were observed in any patients.

- Patients had pain at the injection sites, but this pain disappeared within a few hours.

Conclusion

- 1,000 U and 2,000 U/hand of BTX-B injection significantly improved the activity of RP in SSc patients.
- Neither serious systemic nor local adverse events of BTX-B was observed in our cases.
- BTX-B may have preventive and therapeutic potentials for RP and RP-related DU in SSc patients.
- A limitation of this study is the lack of a placebo control; therefore, further placebo-control studies are required.