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Novel In-Office Injectables for the Dermatology–Rheumatology Patient: Botulinum Toxin, Sodium Thiosulfate, and Hyaluronidase

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Abstract

Patients with systemic sclerosis (SSc) and related systemic autoimmune rheumatic diseases experience cutaneous complications that systemic immunosuppression and vasodilators frequently fail to control. These include refractory Raynaud phenomenon with digital ischemia, calcinosis cutis, and perioral fibrosis with microstomia. Three physician-administered injectable therapies can be readily incorporated in a routine dermatology office at modest cost using widely available equipment: botulinum toxin A (BoNT-A) for digital ischemia, sodium thiosulfate (STS) for calcinosis cutis, and hyaluronidase for microstomia. All three treatments are used off-label, and are supported primarily by observational evidence. This review summarizes the mechanistic rationale, current evidence, injection technique, dosing, and safety of each agent, supplemented by practical observations derived from five years of clinical experience.

Introduction

Current European League Against Rheumatism (EULAR) recommendations for the treatment of SSc address Raynaud phenomenon and digital ulcers in a stepwise fashion, beginning with dihydropyridine calcium channel blockers such as nifedipine as first line treatments, followed by phosphodiesterase-5 (PDE5) inhibitors and intravenous iloprost, with bosentan to reduce the number of new digital ulcers.[1] The 2023 EULAR update provides no recommendation for the treatment of calcinosis and explicitly identifies both calcinosis and local management of digital ulcers as priorities for future research.[1] In clinical practice, the use of systemic vasodilators is often constrained by limited efficacy, adverse effects such as hypotension and headache, treatment costs, and, in the case of iloprost, the need for infusion capacity.[2] Microstomia has no recommended therapy.

These unmet needs highlight a role for in-office procedural dermatology. This review provides a practical account of three injectable therapies, addressing their preparation, injection sites, dosing, and patient counselling for clinicians experienced in intralesional techniques.

Botulinum Toxin A (BoNT-A) for Raynaud phenomenon, Digital Ischemia, and Digital Ulcers

Rationale

BoNT-A is a zinc-dependent endopeptidase that cleaves SNAP-25, thereby preventing vesicle fusion at the presynaptic membrane.[3] This mechanism is relevant to digital vasospasm through two principal effects. First, BoNT-A produces sympathetic blockade by inhibiting norepinephrine release from synaptic nerve terminals. Experimental studies in rat cremaster arterioles and cultured sympathetic neurons have demonstrated dose-dependent inhibition of electrically evoked vasoconstriction, resulting in vasodilatory effects comparable to those observed with prazosin.[4] Second, BoNT-A exerts anti-neurogenic effects by blocking the evoked release of substance P, calcitonin gene-related peptide, and glutamate from sensory neurons, thereby attenuating neurogenic inflammation and pain.[5] A trophic or pro-angiogenic contribution has been proposed but remains unproven.

Evidence

A 2023 systematic review with meta-analysis of 13 studies reported significant improvements in both pain and functional outcomes following BoNT-A treatment, with pooled standardized mean changes of (−3.82; 95% confidence interval [CI], −6.62 to −1.02) for visual analog scale (VAS) pain scores and (−0.83; 95% CI, −1.47 to −0.19) for Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) scores among patients with Raynaud phenomenon, while noting that sample sizes were small.[6] Further support comes from a subsequent systematic review and individual patient data meta-analysis of 31 studies (119 patients) with refractory digital ischemia. Complete responses were observed in 93.1% of cases of acute digital ischemia, 90.1% of digital ischemic ulcers, and 87.5% of digital gangrene. Mean times to response were 11.8 days for acute ischemia, 24.5 days for gangrene, and 54.2 days for ulcers. Adverse events were limited to transient muscle weakness (7.6%) and injection-site pain (5.9%).[3] A decade-long single-centre cohort (n = 46) reported that 71.7% of patients experienced global Raynaud's improvement one month after treatment, with mean VAS pain scores declining from 7.65 to 3.48. Among 16 patients with digital ulcers, 13 showed improvement and five achieved complete ulcer remission. Although 86.2% required repeat treatment at a median of 12 months, 92% responded successfully to subsequent injections.[7]

Although these data are observational and subject to publication and selection bias, the beneficial effect has been substantial, consistent across heterogeneous cohorts, and reproducible in routine practice. Collectively, these findings support a genuine and clinically meaningful treatment benefit. The absence of an adequately powered randomized controlled trial remains the principal limitation, and reported complete-response rates should be interpreted as an upper bound rather than a guaranteed outcome.

Technique

OnabotulinumtoxinA is reconstituted at a concentration of 100 U in 2 mL of normal saline (5 U/0.1 mL). A commonly described technique involves injecting 0.1 mL in each interdigital web space where the superficial digital arteries bifurcate.[8] Across the pooled literature, injections were most often administered at the interdigital neurovascular bundles, approached either palmarly or dorsally, with doses typically ranging from 5 to 10 U per digit side, with 10 U being the most common onabotulinumtoxinA-equivalent dose.[3] The neurovascular bundle was the most frequently targeted site (67.2%), and doses of 5 to 10 U per site accounted for two-thirds of treatments.[3] Higher doses (greater than 10 U per site) were associated with higher complete-response rates; therefore, approximately 50 U per limb (hand or foot) is a reasonable starting dose, with escalation to 100 U per limb in patients with a partial or absent response or in a limb threatening context.[3]

Adverse Events and Mitigation

BoNT-A is well tolerated when used for digital ischemia, with most common adverse events being transient intrinsic hand and thumb muscle weakness (~8%) and injection-site pain (~6%).[3] Both can be minimized through appropriate injection technique. Notably, most cases of muscle weakness occur in patients who received palmar injections, which supports a dorsal injection approach as the principal mitigation strategy.[3] Intrinsic muscle weakness, which most commonly affects thumb opposition and pinch strength, can be further minimized by placing injections closer to the neurovascular bundles than to the thenar musculature and by preferentially dosing the digits that are most symptomatic rather than treating all web spaces uniformly. Because digital ischemia most commonly involves the third through fifth digits, a practical distribution is 10 U per interdigital web space serving these digits and 5 U around the thumb and fifth digit, with the pattern adjusted to target the most symptomatic digits. Injection-site pain can be reduced with a 2% lidocaine (plain) block, a fine 32-gauge needle, and a vibration device applied adjacent to the injection site, together with slow injection. Topical lidocaine/prilocaine cream may be used, but is frequently insufficient as a sole analgesic measure in the author's experience. Lidocaine containing epinephrine should be avoided, as the vasoconstrictive effect of epinephrine can provoke digital vasospasm and compromise perfusion in an already ischemic digit.

Zinc Supplementation

Because BoNT-A is a zinc-dependent enzyme, zinc repletion is a mechanistically plausible adjunct. A double-blind, placebo-controlled crossover pilot study (n = 77) reported that 92% of participants receiving zinc citrate 50 mg plus phytase 3,000 PU experienced an average 30% increase in duration of BoNT-A effect.[9] However, the study was subsequently criticized for methodological limitations, including unmasking of the crossover, uncertain zinc dosing, absence of demonstrated baseline deficiency, and financial conflicts of interest.[10] A 2023 systematic review of four studies found that three reported significant benefits from zinc supplementation, although the authors emphasized the need for larger trials that include objective outcomes.[11] Given its low cost and favourable short-term safety profile, a reasonable approach is 50 mg elemental zinc daily for two weeks before injection, with the caveat that the supporting evidence is weak.

Cost

Cost is cited as a common objection to office-based BoNT-A therapy; however, the available economic data are favourable. In a five-year cost-effectiveness analysis comparing BoNT-A with traditional systemic vasodilator therapy for SSc-associated digital ulcers, BoNT-A was found to be economically dominant, providing both lower costs and greater benefit over the study period.[2] Total per-patient costs were approximately US$114,000 for BoNT-A versus US$285,000 for systemic vasodilators, representing a cost reduction of approximately US$170,000 per patient. These savings were attributed to higher complete-response rates, faster healing, fewer recurrent ulcer cycles, and reduced reliance on intravenous iloprost. Effectiveness was also modestly higher with BoNT-A, resulting in a gain of 0.06 quality-

Feature	Botulinum Toxin A	Sodium Thiosulfate	Hyaluronidase
Indication	Refractory Raynaud phenomenon, digital ischemia, digital ulcers, digital gangrene	Calcinosis cutis (SSc, dermatomyositis)	Perioral fibrosis/microstomia (SSc, MCTD)
Preparation	100 U onabotulinum-toxinA in 2 mL normal saline (5 U/0.1 mL)	Intralesional: commercially available intravenous formulation at a concentration of 150 to 250 mg/mL (no compounding). Topical: 25% in Aquaphor, petrolatum, or 20% zinc oxide (compounded)	150 to 200 IU/mL
Dose	5 to 10 U per digit side (10 U most common); approximately 50 U per limb (hand or foot); escalate to 100 U per limb if partial response is observed	Intralesional: 0.5 to 1 mL per digit; 1 mL per cm of lesion at other sites	1 mL per session at a concentration of 150 to 200 IU
Typical Injection Sites	Interdigital neurovascular bundles of affected digits; dorsal approach preferred	Directly into and around calcific deposits	Ring of small aliquots around the perioral region
Anesthesia	2% lidocaine (plain) block; avoid lidocaine with epinephrine; vibration device; 32-gauge needle; slow injection (topical inadequate)	2% lidocaine digital/ring block (essential)	Topical EMLA with infraorbital and submental nerve blocks
Interval / Sessions	Every 2 to 6 months guided by the patient's response and symptoms	Weekly to monthly for 4 to 6 sessions; topical nightly for 3 to 6 months	Monthly, benefit plateaus after 3 to 5 sessions
Time to Response	12 days (acute ischemia), 25 days (gangrene), 54 days (ulcers)	Weeks to months; topical mean 4 ± 5 months to improvement	18 to 48 days
Most Common Adverse Effects	Transient intrinsic hand/thumb weakness (reduced by dorsal approach and selective digital dosing), injection-site pain	Procedural pain; inflammatory extrusion of calcium through skin; local ulceration	Injection-site pain, mild bruising
Evidence Level	Systematic reviews of observational data; no evidence from adequately powered RCTs	Observational data	Observational data

Table 1. In-office injectables for cutaneous complications of systemic sclerosis and related autoimmune disease: indications, preparation, dosing, technique, and expected outcomes; *courtesy of Elena Netchiporouk, MD, MSc, FRCPC, FCDA*

Abbreviation: MCT: mixed connective tissue disease; **MHISS:** Mouth Handicap in Systemic Sclerosis Scale; **RCT:** randomized controlled trial. All uses described are off-label.

adjusted life-years (QALYs); a QALY represents one year of life in full health. Although this gain was small, it reflects an improvement in health-related quality of life per patient in addition to the cost savings. When an intervention is both less costly and more effective, it is the preferred strategy from a health economic perspective regardless of a payer's willingness-to-pay threshold.

Sodium Thiosulfate for Calcinosis Cutis

Rationale

Calcinosis cutis is a complication of SSc and dermatomyositis, leading to pain, functional loss, ulceration, and secondary infection, yet no established therapy exists.[12] STS is proposed to exert its effects through chelating calcium to form the more soluble calcium thiosulfate, thereby promoting dissolution of ectopic calcium deposits. In addition, it has antioxidant and vasodilatory properties that may contribute to symptom and pain relief.[12,13] These mechanisms are inferred largely from its use in systemic calciphylaxis and remain incompletely characterized for cutaneous calcinosis.[12–14]

Evidence

In a systematic review of 30 studies including 288 patients, the majority of treatment options for calcinosis cutis were classified at level IV evidence. Low-dose warfarin was specifically discouraged based on level 1B evidence, whereas intralesional STS emerged as a promising alternative with level IV evidence.[12] Contemporary reviews continue to describe only heterogeneous, often partial efficacy for medical therapies, with more favourable responses observed in patients with early or localized disease. When technically feasible, surgical excision remains the most effective treatment option.[15,16] For topical STS, a systematic review (n = 45) reported complete response in 20% and partial response in 58%, with a mean time to improvement of 4 ± 5 months and a mean time to resolution of 5 ± 4 months. Response rates were highest for small, superficial lesions and diminished with increasing lesion size.[17] The overall evidence base is observational, with no controlled trials; therefore, effect estimates should be interpreted with appropriate caution.

Technique

Intralesional STS therapy uses the commercially available intravenous STS formulation typically at concentrations of 250 mg/mL. A practical evidence-based regimen uses injections of STS at concentrations of 150 to 250 mg/mL, administered as 0.5 to 1.0 mL per digit or 1.0 mL per centimetre of lesion at other sites, with treatments repeated weekly to monthly for four to six sessions.[12] For patients who cannot tolerate injections or who have widespread superficial disease, compounded topical STS is a reasonable alternative.[17] Based on the author's experience, a representative compounded formulation consists of 25% STS in Aquaphor, petrolatum, or 20% zinc oxide, applied nightly under a hydrocolloid dressing for at least three to six months. Efficacy is partial, and ulcerated lesions remain painful.[17]

Adverse Events and Mitigation

The principal adverse effect of intralesional STS is procedural pain, which may be exacerbated by the pro-inflammatory transcutaneous extrusion of calcium that accompanies a therapeutic response. Patients should be counselled in advance about the potential for both of these effects to occur.[12] In the author's experience, a digital or ring block using 2% lidocaine is essential given the pain of injection. In a case series of topical STS, the only reported adverse event was localized pain from a presumed allergic reaction in one patient, however, the author has observed that this discomfort seems to correlate with the transcutaneous elimination of calcium.[17] Several measures may help reduce procedural pain and the associated local inflammation, although none have been evaluated in controlled studies. In the author's experience, when a lesion is about to ulcerate, prior enucleation may reduce post-procedural pain. Adjunctive measures that may help include doxycycline 100 mg twice daily for one to two weeks for its anti-inflammatory effect, consistent with the reported use of tetracyclines in calcinosis cutis; a short course of prednisone 20 mg daily for five days in patients at low risk of scleroderma renal crisis; and topical anti-

inflammatory therapy, such as a Janus kinase (JAK) inhibitor or betamethasone/fusidic acid, applied under a silicone foam or hydrocolloid dressing. JAK inhibitors have shown preliminary benefit for calcinosis in a real-world SSc cohort, with improvement observed in 45.5% of affected patients, providing a rationale for topical use despite the absence of direct evidence in calcinosis.[18]

Hyaluronidase for Microstomia

Rationale

Perioral fibrosis in SSc and mixed connective tissue disease restricts the oral aperture, compromising nutrition, dental hygiene, and speech, and is a major contributor to mouth-related disability. Hyaluronidase degrades hyaluronan in the extracellular matrix, providing a potential therapeutic approach to mouth-related disability. Beyond simple matrix remodelling, hyaluronan is required for transforming growth factor-β1-dependent maintenance of the myofibroblast phenotype, and its degradation may interrupt the fibrotic loop.[18,19] Although this antifibrotic rationale is mechanistically plausible, it has not been directly demonstrated in perioral scleroderma tissue.

Evidence

Although the clinical literature is limited, it is consistent. A single-patient case report described improvement in peroral fibrosis after serial intradermal hyaluronidase injections to the lips over a seven month period.[20] A four-patient case series using 200 IU of hyaluronidase diluted in 6 mL of saline and administered monthly reported a mean increase in maximal oral commissure distance of 0.9 cm (19.1%) and a mean reduction in the Mouth Handicap in Systemic Sclerosis (MHISS) score of 19.3 points (61.9%), with clinical benefits plateauing after three to five months and was maintained for at least six months following treatment.[20,21] Further support comes from a systematic review and case series of eight patients with limited SSc, diffuse SSc, mixed connective tissue disease (MCTD), and scleromyxedema. Most patients received 150 IU per treatment session, with gains in vertical oral aperture of up to 15 mm, together with improvements in MHISS scores of up to 10 points after one to four monthly treatments.[22] However, it should be noted that all evidence is uncontrolled and derived from small numbers.

Technique

A representative regimen is 1 mL of hyaluronidase at a concentration of 150 to 200 IU/mL, injected in a ring of small aliquots around the perioral region, repeated at monthly intervals.[22]

Adverse Events and Mitigation

Reported adverse events have been limited to injection-site pain and mild bruising, with no serious events observed.[22] In the author's experience, topical EMLA alone often provides insufficient analgesia, whereas infraorbital and submental nerve blocks substantially reduce pain while adding only a few minutes to the procedure.[22] Bruising is minimized by using a fine-gauge needle (e.g., 32G) and administering small aliquots.

Conclusion

BoNT-A, STS, and hyaluronidase offer dermatologists practical treatment options for ischemic digits, calcinosis, and microstomia, respectively, conditions that are often refractory to other therapies. While the evidence base remains observational, these interventions are inexpensive, low risk in trained hands, with botulinum toxin showing favourable economic outcomes. Careful attention to technique and dose, more than agent selection, appears critical to achieving optimal results.

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