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

Elena Netchiporouk, MD, MSc, FRCPC, FCDA

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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Financial Disclosures

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Beyond Weight Loss: Practical Considerations for use of Glucagon-like Peptide-1 (GLP-1) and Incretin Therapy in Inflammatory Skin Disease

Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD

Introduction

The use of glucagon-like peptide-1 (GLP-1) based therapies has emerged as a topic in dermatology due to the strong bi-directional association between obesity and immune-mediated inflammatory skin disease. The expanding benefits toward cardiometabolic health with GLP-1 and other incretin therapies supports the existence of a "skin-heart-metabolic" axis, prompting a shift from purely skin-directed therapies to holistic and systemic patient management. Dermatologists should be aware of the mechanisms, clinical evidence, safety profiles, and practical prescribing considerations of existing and novel drugs.

History

Gastric inhibitory peptide (GIP) and GLP-1 were first isolated from gastric porcine extract in the 1970s and 1980s.[1] Early therapeutic use was limited by rapid enzymatic degradation. However, the discovery of exendin-4, an analogue GLP-1 receptor agonist against Gila monster venom, enabled the development of more stable synthetic peptide injectable analogues for clinical use. Successive generations of GLP-1 receptor agonists, including exenatide (2005), liraglutide (2010), dulaglutide (2014), and semaglutide (2017) demonstrated reductions in HbA1c in patients with Type 2 Diabetes Mellitus (T2DM). Although a modest weight loss signal was observed in clinical trials for all agents, efficacy improved substantially for newer formulations. Higher-dose liraglutide was the first GLP-1 receptor agonist approved for chronic weight management in 2014. Subsequent large-scale cardiovascular outcome trials revealed profound cardiovascular and renal protective benefits independent of glycemic control and weight. More recently, semaglutide and tirzepatide achieved mean weight reductions of 15% in the STEP-1 trial[2] and 20-22% in the SURMOUNT-1[3]

trial respectively. These results had demonstrated weight loss typically achieved with surgery, suggesting that obesity was treatable as a chronic metabolic disease rather than a consequence of lifestyle choices. As of 2024, an estimated 12% of American adults had used a GLP-1 medication.

Mechanism of Action

Incretins are gastric signalling peptides that include GLP-1 and GIP among others. GLP-1 receptors are expressed in multiple organs throughout the body, including the skin. In the gastrointestinal (GI) tract, GLP-1 enhances the regulation of insulin secretion, delays gastric emptying, and promotes the reduction of appetite. GIP stimulates glucagon secretion and increases triglyceride storage in adipose tissue. GLP-1 receptors are also expressed on a variety of immune cells, including T cells, B cells, monocytes, neutrophils, eosinophils, and hematopoietic stem cells.[4] GLP-1 receptor agonists have been shown to upregulate anti-inflammatory cytokine interleukin (IL)-10 and downregulate pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α), IL-1β, and IL-6.[5] Although mechanisms underlying their effects in skin disease are not fully understood, emerging evidence suggests the involvement of invariant natural killer T cells (iNKT), which shift immune responses toward T-helper (Th)1 or Th17 responses. In two psoriasis patients with T2DM, biopsy-proven plaque iNKT cell burden decreased following GLP-1 therapy.[4] A similar mechanism has been proposed in hidradenitis suppurativa (HS), in which GLP-1 receptor agonists may reduce the Th1/Th17-driven inflammatory cascade and reduce the production of IL-1β and TNF-α, with theoretical downstream effects on neutrophils, macrophages, and plasma cells.[6]

Review of Evidence

Currently, incretin-based therapies are generally accepted as part of adjunct therapeutic ladders for inflammatory skin disease including psoriasis and HS, although they have not yet been included in national-level treatment guidelines. In psoriasis, GLP-1 therapies have been evaluated in case reports, cohorts, and small clinical trials, primarily among patients with concomitant obesity or T2DM. Published case series describe patients aged 48–73 years with mild reductions in Psoriasis Area and Severity Index (PASI) scores ranging between 1.0–30.[6] and Physician Global Assessment (PGA) improvements of up to two points.[7] Cohort studies have demonstrated average reductions in PASI scores of 4.8–15.[7] improving to 2.2–9.2 after 12–18 weeks of treatment.[7] Overall improvement has been highly variable, with response rates ranging from 40–80%. In HS, case series have shown Dermatology Life Quality Index (DLQI) improvements, with scores decreasing from 12.3 to 9.7. However, individual case reports are more variable, showing improvements, including reductions of up to 10–11 points in overall DLQI scores.[7] The current evidence base is limited by small sample sizes, short-term use, typically below 6 months, and a lack of control groups.[8] A recent TriNetX retrospective cohort study of over 22,000 patients with HS has shown that GLP-1 therapy was associated with lower mortality, and reduced systemic complications including infection/sepsis and cardiovascular events.[8] Similarly, a TriNetX analysis of over 540,000 patients with atopic dermatitis had demonstrated similar benefits with lower odds of cardiovascular disease, heart failure, atherosclerosis, and ischemic heart disease.[9] The use of incretin therapies outside dermatologic conditions other than psoriasis and HS is not well-described. Evidence is currently limited to isolated case reports describing Hailey-hailey disease, acanthosis nigricans, and chronic spontaneous urticaria.[10]

Incretin therapy has been studied in combination with established biologic systemic treatment. In the phase IIIb TOGETHER-PsO trial of patients with psoriasis and obesity, 27.1% of participants receiving combination therapy achieved both PASI-100 and 10% or greater weight reduction with ixekizumab plus tirzepatide, compared to 5.8% with ixekizumab alone at 36 weeks.[11] Similarly, in the phase IIIb study TOGETHER-PsA trial, 31.7% of participants with psoriatic arthritis treated with ixekizumab plus tirzepatide achieved both a 50% improvement

in American College of Rheumatology response criteria and 10% or greater weight reduction, compared to 0.8% of patients receiving ixekizumab monotherapy over 36 weeks.[12] These trial results suggest that concomitant use of biologic immunomodulators with incretin therapy can produce synergistic improvements in both skin disease and cardiometabolic health.

Applications in Skin Disease

In Canada, semaglutide (GLP-1 receptor agonist) is currently indicated to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. It can be used in combination with oral metformin or other oral antihyperglycemic medications, or as monotherapy when other treatments are not tolerated or appropriate as standalone therapies. Special authorization and limited use criteria vary by province; however, coverage could require inadequate glycemic control on maximally tolerated doses of metformin/sulfonylurea or intolerance to first-line agents.

Higher-dose formulations were originally indicated for chronic weight management in adults with a body mass index (BMI) of greater than 30 kg/m^2 (class I obesity), or patients with a BMI of 27–30 kg/m^2 with one weight-related comorbidity, including hypertension, T2DM, dyslipidemia, or obstructive sleep apnea. Subsequent indications have been added or are underway for patients with established cardiovascular disease, including prior myocardial infarction, stroke, symptomatic peripheral artery disease, and a BMI greater than 27 kg/m^2, as well as for metabolic dysfunction–associated steatohepatitis. Pediatric use for chronic weight management is also indicated for those aged 12–18 years with a BMI above the 95th percentile for age who have not achieved weight reduction with lifestyle interventions alone. Both injectable and oral formulations are available however, injectable formulations generally produce greater weight loss than their oral counterparts.

Tirzepatide, a dual GLP-1 and GIP receptor agonist, is indicated for the treatment of T2DM and chronic weight management using similar criteria. The same formulation and dosing regimen are used for both clinical indications.

The use of incretin therapies in skin disease remains off-label unless patients meet the criteria for T2DM or chronic weight management **(Table 1)**. In these cases, the primary therapeutic indication is the underlying disease, with any dermatologic improvement considered a secondary benefit. Emerging evidence suggests that these therapies can serve as useful adjuncts for the treatment of psoriasis or HS, potentially enhancing the efficacy of conventional and biologic systemic treatments.[13]

Indications (one of):	Clinical Information Required:
• T2DM with inadequate glycemic control on oral agents • Chronic weight management: BMI >30 kg/m^2 • Chronic weight management: BMI >27 kg/m^2 with one of hypertension, T2DM, dyslipidemia, obstructive sleep apnea • Chronic weight management: BMI >27 kg/m^2 with one of atherosclerotic cardiovascular disease (MI, stroke, symptomatic PAD), metabolic dysfunction–associated steatohepatitis • Pediatric chronic weight management: BMI >95th percentile for age	• T2DM: Hemoglobin A1c • Chronic weight management: height, weight, BMI, comorbidities • Supportive investigations: ambulatory blood pressure, random/fasting blood glucose, hemoglobin A1c, lipid panel, home/overnight sleep study, CT angiogram, coronary CT, liver ultrasound, and growth curves

Table 1. Indications for incretin therapy and clinical criteria necessary to support diagnoses for medication coverage; *courtesy of Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD*

Abbreviation: BMI: Body mass index; **CT:** Computed tomography; **MI:** Myocardial infarction; **PAD:** Peripheral artery disease; **T2DM:** Type 2 diabetes

In the author's opinion, incretin-based therapies may also have theoretical benefits in skin diseases related to friction (folliculitis, intertrigo, hyperhidrosis, lichen simplex chronicus), as well as skin diseases strongly associated with metabolic syndrome (acanthosis nigricans, polyendocrine metabolic ovarian syndrome, hirsutism).

Safety

In addition to known hypersensitivity and pregnancy, there are class-wide contraindications for GLP-1 and related therapies in patients with a personal history of Multiple Endocrine Neoplasia Syndrome Type 2, or a personal/family history of medullary thyroid carcinoma. This precaution is based primarily on findings from rodent studies, in which GLP-1 receptor activation stimulated proliferation of thyroid C-cells. However, human thyroid C-cells are thought to express fewer GLP-1 receptors and exhibit a lower proliferative ability.

GI adverse events were the most commonly reported in phase III clinical trials, including but not limited to nausea, diarrhea, vomiting, constipation,

Prescribing	Counselling	Monitoring
• Standing prescription with dose escalation protocol and refills • Instructions: "Monthly titration schedule, to hold and treat long-term at highest tolerable dose" • Completion of prior authorization paperwork (if applicable) ◦ Wegovy® (semaglutide) FlexTouch® 0.68 mg/mL, inject 0.25 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 1.34 mg/mL, inject 0.5 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 1.34 mg/mL, inject 1 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 2.27 mg/mL, inject 1.7 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 2.4 mg/mL, inject 2.4 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 10 mg/2.4 mL, inject 2.5 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 20 mg/2.4 mL, inject 5 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 30 mg/2.4 mL, inject 7.5mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 40 mg/2.4 mL, inject 10mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 50 mg/2.4 mL, inject 12.5 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 50 mg/2.4 mL, inject 15 mg Q1W x 1 mo	• Overall goal: balance weight loss with treatment tolerability • Eat and drink slowly • Stop when early satiety is reached • Expect decrease in bowel movement frequency • Increase fluid and fiber consumption if constipation occurs • Consume daily protein >0.8 g per kg of body weight per day • Resistance training 2-3 times per week is suggested • For tirzepatide, use additional contraceptive method in first 4 weeks of treatment for reproductive potential patients	• Body weight to guide medication renewal and dose escalation • Hemoglobin A1c, for medication renewal • Routine parameters for skin disease (e.g. PGA, BSA, PASI, HiSCR, AN count)

Table 2. Overview of prescribing information, key counselling points, and monitoring parameters for incretin treatment; *courtesy of Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD*

Abbreviation: AN count: Abscess and nodule count; **BSA:** Body surface area; **HiSCR:** Hidradenitis suppurativa clinical response; **mo:** month; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **Q1W:** Once weekly

dyspepsia, and abdominal pain. For semaglutide, nausea was the most frequent adverse event, occurring in 44.2% of treated participants. Most events were categorized as mild-moderate, transient, and often resolving after the dose escalation period. Treatment discontinuation due to adverse effects occurred in 4.5% of treated participants.[2] In trials of tirzepatide, although the incidence of nausea was lower, occurring in 33.3% of participants receiving the 10 mg dose, discontinuation due to adverse events occurred in 7.1% of treated participants.

Rare but notable side effects include, gall bladder disease, mood changes, worsening of diabetic retinopathy, non-arteritic anterior ischemic optic neuropathy, and severe lean muscle mass loss. While pancreatitis has been reported, current meta-analyses do not support an increased risk. Relative contraindications for use include older adults, frail individuals, or those planning to become pregnant.

Counselling and Practical Considerations

Semaglutide is available as a prefilled FlexTouch® pen in doses of 0.25, 0.5, 1, 1.7, and 2.4 mg, with needles supplied as part of the device. Tirzepatide is available as a KwikPen® in doses of 2.5, 5, 7.5, 10, 12.5, and 15 mg; needles are not included but are available without a prescription. For chronic weight management, doses are titrated at monthly intervals to the maximally tolerated dose, balancing weight loss with side effects. Although close follow-up is suggested, this may be impractical in dermatology practice. Therefore, a slower titration schedule with reassessment every 3–6 months may be preferable. Select patients may benefit from a "microdosing" strategy, particularly during dose escalation or de-escalation, when transitioning between agents, when experiencing severe GI side effects, or when medication costs are a concern. "Microdosing" refers to a patient-selected dose by counting pen clicks on compatible FlexTouch®/KwikPen® devices rather than delivering the full preset dose. This dosing strategy requires appropriate counselling and access to additional needles. Demonstration devices can be helpful for improving patient understanding and confidence. In the author's experience, prescribing multiple units of each dosage under a standing prescription can facilitate patient-directed dose titration **(Table 2)**. Prior authorization is commonly required by private insurance plans and can typically be completed using forms available through the insurer's website.

Reported dermatologic adverse effects include injection site reactions, altered skin sensation (dysesthesia and hyperesthesia), alopecia, and rare cases of keratinocyte carcinoma and drug hypersensitivity reactions.[14] Rapid weight loss may contribute to increased perceived facial aging through reductions in adipose-derived stem cell and fibroblast activity, as well as interactions with advanced glycation end products.[15]

Patient counselling should focus on setting goals for long-term use and strategies to maximize tolerability to achieve metabolic and cutaneous benefits.[16] Patients should be advised to adopt behavioural eating modifications including eating and drinking slowly and stopping when early satiety cues are reached to avoid acute nausea or vomiting. A decrease in bowel movement frequency is also expected due to slowed GI transit. Transient episodes of constipation can be managed with increased fluid intake and dietary fiber supplementation. Lean muscle mass loss can be minimized by prioritizing daily protein intake and engaging in resistance training. Daily protein intake should exceed 0.8 g/kg of body weight and can be achieved through nutritional supplement drinks/powders or lean meat consumption. Resistance training regimens are ubiquitous and should target major muscle groups and ideally be performed 2–3 times per week. Patients with reproductive potential who are taking oral contraceptives and tirzepatide should be advised to use additional contraceptive methods during the first four weeks of treatment due to reduced absorption of oral contraceptives.[17]

Future Directions

Emerging incretin therapies combine GLP-1 activity with additional mechanisms. In the phase III TRIUMPH-4 trial, patients with obesity and osteoarthritis achieved a mean body mass reduction of 28.7% and experienced improvements

in knee osteoarthritis pain scores (Eli Lilly, unpublished data, December 2025). Favourable changes were also observed in several secondary endpoints, such as reductions in markers of cardiovascular risk including non-high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein and systolic blood pressure. GI-related adverse effects (nausea, diarrhea, constipation, vomiting, decreased appetite) remained the most common side effects, although discontinuation rates (12.2–18.2%) were comparable to or lower than those reported with existing agents. Overall, the weight loss signal exceeded that observed in STEP-1[2] (15%) and in SURMOUNT-1[3] (20–22%).

Further studies are needed to investigate the cutaneous benefits of incretin-based therapies, including high quality meta-analyses and randomized double-blind clinical trials. Both translational and clinical research are required to clarify whether clinical improvements in psoriasis and HS are driven primarily by weight loss, drug concentrations, or a combination of these mechanisms.

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Beyond Cold Fingers: A Practical Approach to the Management of Raynaud's Phenomenon

Khalad Maliyar, MD, MScCH, FRCPC

Introduction

Raynaud's phenomenon (RP) is a vasospastic condition affecting the acral and digital arteries, characterized by well-demarcated colour changes of the fingers and toes, typically progressing from pallor to cyanosis and then reactive erythema. It is commonly triggered by exposure to cold temperatures or emotional stress. First described by Maurice Raynaud in 1862, RP remains one of the most frequently encountered vascular complaints in dermatology practice.[1] RP is classified into two distinct subtypes with markedly different clinical trajectories. Primary RP is relatively common, affecting approximately 2–12% of populations worldwide, with a notable female predominance and peak onset before the age of 30.[1,2] It follows a benign, nonprogressive course without structural endovascular pathology or tissue destruction, though it may significantly impair quality of life.

Secondary RP (SRP) occurs in association with a variety of conditions, most notably autoimmune connective tissue diseases (ACTDs), particularly systemic sclerosis (SSc), in which it affects 90–95% of patients.[1,3] Unlike primary RP, SRP is accompanied by biochemical and structural abnormalities within the microvasculature, including endovascular remodelling, intimal proliferation, fibrosis, and progressive luminal narrowing. These changes induce prolonged tissue ischemia with severe clinical consequences such as digital pitting, painful ulceration, gangrene, and in severe cases, auto-amputation.[3,4] Importantly, the vasculopathy of SRP extends beyond the digital circulation. Parallel vascular involvement of the heart, lungs, kidneys, and esophagus may contribute to major systemic manifestations,

including interstitial pulmonary fibrosis, pulmonary arterial hypertension, scleroderma renal crisis, and gastroesophageal reflux disease.[1,5]

Given that RP may serve as the earliest manifestation of an evolving systemic disease, with vasospastic symptoms predating overt ACTD by up to 20 years, dermatologists are uniquely positioned to identify, risk-stratify, and intervene early.[1] Distinguishing primary from secondary RP is essential and requires a careful history, review of systems, and physical examination for features of underlying ACTD, along with nailfold capillaroscopy and targeted serologic evaluation guided by clinical findings. This review provides a practical, evidence-based approach to the management of both primary and secondary RP, progressing from foundational lifestyle modifications through pharmacologic therapy and surgical intervention **(see Figure 1)**.

Lifestyle Modifications

Lifestyle interventions remain the foundation of RP management and should be recommended for all patients irrespective of the disease subtype. For many individuals with primary RP, conservative measures alone provide adequate symptom control, and pharmacotherapy may be deferred entirely.[6]

Patients should be counselled extensively on avoidance of cold exposure and other known triggers for vasospastic attacks, such as emotional stress. Practical measures include appropriate full body covering with particular attention to protecting the hands and feet in both cold outdoor weather conditions and air-conditioned indoor environments. Counselling should emphasize wearing additional layers of clothing, hats, thick socks, and mittens, which are preferred over gloves as they offer superior insulation through reduced individual finger surface area exposure.[6,7] Patients may benefit from covering the forehead, as exposure to cold air across this region produces a vasomotor "diver's reflex" that can induce peripheral vasospasm.[8] Hand or toe warmers or other portable warming devices may also help reduce the frequency and severity of attacks.

Smoking cessation is imperative for all patients with RP. Tobacco use is strongly associated with endothelial dysfunction and impaired vasodilatation, and smokers demonstrate a higher incidence of more severe phenotypes including digital ulcers and gangrene.[9] Medications known to exacerbate RP should be identified and, where clinically feasible, discontinued. These include but are not limited to nonselective β-blockers, ergotamine-containing migraine therapies, amphetamine/dextroamphetamine, caffeine, and oral contraceptives.[6,10] Notably, a meta-analysis including over 1,000 patients found that approximately 14% of individuals receiving β-blockers developed RP.[10]

Several physical manoeuvres may help patients abort acute attacks and are generally more effective in primary RP where structural vascular disease is absent. One technique, the "Frisbee manoeuvre," involves extending the arm laterally and repeatedly performing a rapid snapping motion of the wrist, generating centripetal force to restore digital blood flow.[11] Alternatively, a windmill or swing-arm technique is performed by rotating the arm rapidly in a softball pitching motion to achieve a similar effect.[12] Biofeedback training and relaxation techniques have also demonstrated benefit, particularly in patients whose attacks are primarily triggered by emotional stress rather than cold exposure.[13]

Pharmacologic Treatments

When lifestyle modifications prove insufficient, pharmacotherapy is warranted. In primary RP, pharmacologic agents should be introduced for patients whose symptoms substantially impair quality of life or who develop signs of tissue compromise. In contrast, SRP often warrants early and often aggressive pharmacotherapy to prevent irreversible tissue damage, with treatment tailored to the underlying etiology and the severity of digital ischemia.[2,6]

Calcium Channel Blockers

Calcium channel blockers (CCBs) are the preferred first-line systemic agents for both subtypes. They are effective at reducing the frequency, severity, and duration of attacks in both primary and secondary disease.[14] Dihydropyridine CCBs, particularly nifedipine

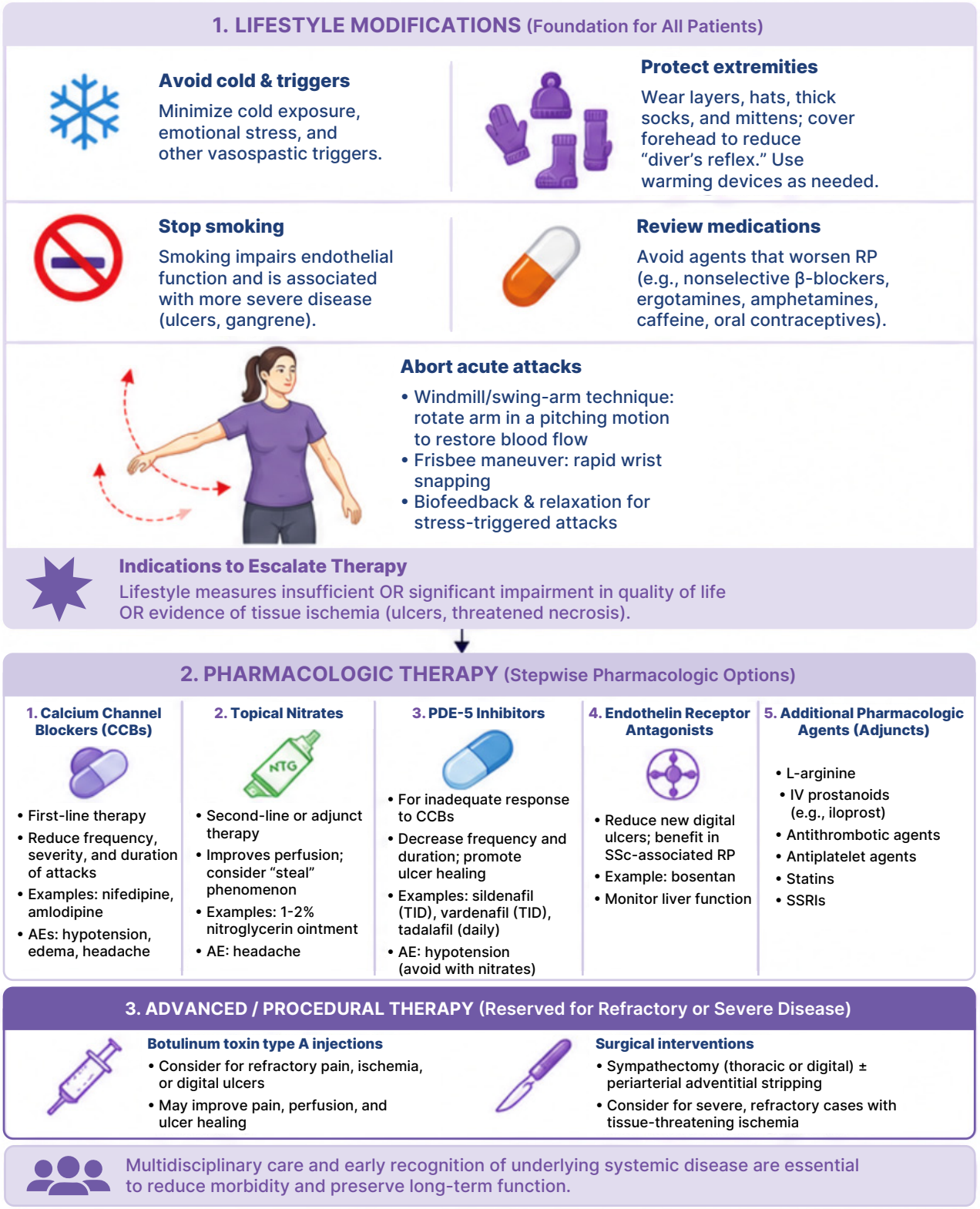

Figure 1. Approach to the Management of Raynaud's Phenomenon; *courtesy of Khalad Maliyar, MD, MScCH, FRCPC*

Abbreviation: AE: adverse effect; **CCB:** calcium channel blockers; **IV:** intravenous; **PDE-5:** Phosphodiesterase 5; **RP:** Raynaud's Phenomenon; **SSc:** systemic sclerosis; **SSRIs:** selective serotonin reuptake inhibitor; **TID:** three times daily

and amlodipine, are generally preferred over nondihydropyridine agents such as verapamil and diltiazem, as they exert more potent peripheral effects on vascular smooth muscle with less cardioselectivity. Common side effects include hypotension, peripheral edema, and headache.[14]

Topical Nitrates

Topical nitrates represent a useful second-line therapy in those with an inadequate response to CCBs, or are unable to tolerate CCB monotherapy. After application, topical nitroglycerin is metabolized to nitric oxide, providing potent exogenous vasodilation by increasing cyclic guanosine monophosphate concentrations in vascular smooth muscle. Several placebo-controlled trials have demonstrated improvements in digital artery perfusion and reducing symptom severity, and a systematic review and meta-analysis has confirmed the effectiveness of topical nitrates in both primary and secondary RP.[15] Topical nitroglycerin can be compounded as a 1–2% preparation in a hydrophilic ointment base and applied selectively to the affected digits or ischemic areas. Targeted application can help to reduce the "steal" phenomenon whereby less diseased vessels preferentially dilate and shunt blood from more severely affected digits.[6] Headache remains the most frequently reported adverse effect and limits tolerability in some patients.[15]

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors are reserved for patients who do not respond to CCB therapy. These agents inhibit the degradation of cyclic guanosine monophosphate, thereby potentiating the effects of both endogenous and exogenous nitric oxide. Evidence from randomized controlled trials (RCTs) and meta-analyses support the efficacy of PDE-5 inhibitors in decreasing the frequency and duration of attacks in SRP.[16] The landmark SEDUCE trial, a placebo-controlled study involving 83 patients with SSc, demonstrated a statistically significant benefit of sildenafil in healing ischemic digital ulcers at 8 and 12 weeks.[17] Available PDE-5 inhibitors include sildenafil and vardenafil, which may be administered up to three times per day and tadalafil, typically administered once per day.[2] Of note, a key side effect is that co-administration of PDE-5 inhibitors and topical nitrates can lead to profound hypotension.[2]

Endothelin Receptor Antagonists

Endothelin levels are pathologically elevated in SSc and are implicated in the underlying disease processes of severe RP phenotypes. Endothelin receptor antagonists limit endothelin-mediated vasoconstriction and pathologic vascular lumen remodelling. In particular, bosentan, a dual endothelin-1 and endothelin-2 receptor antagonist, has been evaluated in two major clinical trials—RAPIDS-1 and RAPIDS-2, where it demonstrated efficacy in reducing the formation of new digital ulcers, most prominently in patients with preexisting ulceration.[18] It is commonly initiated at a dose of 62.5 mg per day.

Botulinum Toxin Type A

Botulinum toxin type A (BoNT-A) has emerged as an increasingly popular adjunctive therapy for RP. Its therapeutic effects appear to result from both vascular and neuromodulatory mechanisms including inhibition of sympathetic vasoconstriction and blockade of pain-associated neurotransmitters, such as substance P and calcitonin gene-related peptide.[4,19] Numerous studies have reported improvements in pain, perfusion, colour change, and ulcer healing following treatment.[19] There is no consensus regarding optimal dosing, dilution, or injection sites. A commonly used approach involves slowly injecting five units of BoNT-A into the bilateral interdigital web spaces at the bifurcations of the superficial digital arteries surrounding each affected digit, for a total dose of 50 units per hand.[2] Some clinicians avoid thumb injections unless symptoms are substantial. Clinical benefits can be observed within days to one week. Adverse effects are generally mild and transient, most commonly localized injection-site discomfort or temporary hand weakness.

Additional Pharmacologic Agents

Several adjunctive therapies with a more limited evidence base warrant consideration in select patients. L-arginine, an amino acid and nitric oxide precursor, is particularly useful for patients

who cannot tolerate conventional vasodilators due to low systemic blood pressure.[20] Intravenous prostanoids, notably iloprost, have shown efficacy in SSC-related SRP, with a Cochrane meta-analysis of seven RCTs reporting improvements in attack frequency and severity as well as digital ulcer healing and prevention.[2] In patients with SRP associated with underlying hypercoagulable states, such as antiphospholipid syndrome, consideration may be given to antithrombotic therapy, including anticoagulants (e.g., low-molecular-weight heparin) and antiplatelet agents such as aspirin.[2] Losartan has also shown superiority to nifedipine in one RCT for reducing RP attack severity and frequency, making angiotensin II receptor blockers a reasonable adjunct.[2] Statins may also improve endothelial dysfunction in SSc through pleiotropic effects. Finally, selective serotonin reuptake inhibitors remain an option in patients with concurrent low blood pressure, although higher quality evidence is needed before their routine use can be recommended.[2]

Surgical Interventions

Surgical intervention is generally reserved for patients with severe refractory SRP who have failed medical therapy or who develop threatened digital viability, including impending digital necrosis or progressive ischemic ulceration. Historically, sympathectomy procedures involved the ligation of sympathetic fibers at the thoracic level and were used to reduce vasospastic activity. Contemporary use of this procedure is increasingly performed using minimally invasive endoscopic techniques in order to minimize surgical morbidity, although long-term recurrence remains a concern.[2] Peripheral digital sympathectomy with periarterial adventitial stripping is another method used to improve blood flow and help with ulcer healing in severe cases. This approach aims to restore vascular compliance and address the fixed obstructive component of advanced SRP that pharmacotherapy alone cannot overcome.[2]

Conclusion

RP is far more than a benign inconvenient reaction to cold exposure or a cosmetic concern; particularly in its secondary form, it can be associated with substantial morbidity. Early distinction between primary and secondary disease is paramount, as SRP may herald serious systemic pathology that extends well beyond the digital vasculature. Effective management requires a stepwise approach guided by disease subtype, severity, and associated comorbidities. This approach begins with comprehensive lifestyle modifications, progressing through evidence-based pharmacotherapy, and incorporating procedural or surgical interventions when necessary. Given their role in early recognition of connective tissue disease and cutaneous vasculopathy, dermatologists are uniquely positioned to identify, risk-stratify, and longitudinally manage patients with RP. A comprehensive and multidisciplinary treatment strategy addressing both vascular dysfunction and systemic disease remains central to reducing morbidity and preserving long-term function and quality of life.

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Better by Design: Guide to Micro-Interventions for Optimizing the Dermatology Appointment

Irina Oroz, MD, FRCPC, DABD

The corporate world has long recognized the impact of interpersonal dynamics, communication, and behavioural economics on business outcomes. Countless books are written on leveraging behavioural science and psychology to optimize negotiations, build alliances, and improve customer experiences. Publications such as the *Harvard Business Review* exist to translate evidence and ideas in leadership, management, and psychology into practical insights that help business professionals lead and communicate effectively.

Yet, this wealth of evidence and insight remains largely untapped by the Dermatology world. At the crux of it, the dermatology appointment is a powerful and complex encounter. Dermatologists must establish trust and rapport almost immediately, creating an environment that supports open communication and safety. Only then can they effectively provide patient education, and the intricate negotiation and shared decision-making required for patient centred care.

Dermatologists spend years mastering what to say to patients, yet receive far less training on how to deliver the information. As a result, dermatologists rely on intuition and role models during training to shape the way we interact with patients, and once in practice we rarely have the opportunity to see how our practice differs from our peers. Yet, small physician behaviours, often lasting only seconds, shape first impressions, trust, satisfaction, and our patient's willingness to follow our recommendations.

First impressions play a critical role in shaping a patient's trust, comfort level, and perceptions of physician competence. While a number of factors contribute to these judgements, evidence suggests that **what a physician wears has a significant impact**.

Evidence from two North American image-based studies has shown that the colour of a physician's scrubs matters. In an online photographic survey with 562 responses, evaluating male and female plastic surgeons,

navy and blue scrubs were associated with higher ratings than black scrubs across several domains. For female surgeons, navy and blue scored significantly better than black for skill, representativeness, trustworthiness and compassion. For male surgeons, navy and blue scored better than black for knowledge, skill, representativeness, trustworthiness and compassion.[1] Similar findings were reported in another study, showing that **physicians in blue were perceived as the most caring**, whereas those in black were most frequently rated as the least knowledgeable, skilled, trustworthy, and caring for both men and women.[2] Scrub colour aside, patients also seemed to have opinions on scrub style, with fitted scrubs being preferred over the traditional loose hospital style scrubs.[1]

A 2025 *BMJ* systematic review relayed fascinating insights regarding physician attire. "Gender-specific findings indicated that male physicians were perceived as more professional when wearing formal attire with white coats, while **female physicians in similar attire were often misidentified as nurses or assistants**."[3]

When dermatology-specific publications are examined, the findings suggest that patients prefer white coats.

In one study, 54% of patients preferred their dermatologist to wear a white coat, with female patients placing greater importance on the appearance of the physician than male patients.[4] Similarly, a 2019 survey of 834 patients, including 140 dermatology patients, has shown that the combination of white scrubs with a white coat received the highest composite rating for knowledge, trust, caring, approachability, and comfort. Dermatology and neurology patients were also more likely than infectious-disease patients to report that physician attire mattered (41% vs 32%; p=0.038).[5]

Once a clinician enters the room in their blue scrubs, the next step is to sit down. In a randomized controlled trial, patients perceived physicians who sat at the bedside as having spent more time with them versus those who stood, despite no difference in the actual duration of the encounter. **When a physician sits, patients report a more positive interaction, a better understanding of their condition, and improved compliance to treatment recommendations**.[6]

When taking a seat, consider adjusting the height of your chair to the patient's eye level. This non-verbal cue conveys attentiveness and availability. One trial has shown that **patients were significantly more likely to report that physicians seated at eye level "always" carefully listened to them** and explained things in an easy-to-understand manner, and almost all patients stated the time the physician spent with them was "just right".[7]

Introducing yourself clearly is a simple act that is highly impactful. In a survey of 353 hospital patients, 89.7% reported that a physician introducing themselves positively influenced their healthcare encounter. **Addressing patients by name early in the encounter signals recognition and personalization**. In a prospective inpatient study, use of the patient's name was significantly associated with higher Hospital Consumer Assessment of Healthcare Providers and Systems scores, with most preferring to be addressed by their first name.[8]

Having introduced yourself, resist the temptation to look at the computer. Make eye contact with the patient first. Video analysis of 100 primary-care encounters found that physicians with a technology-centred communication style spent significantly less time making mutual eye contact with the patient. When physicians looked at the computer, patients were more likely to look away, potentially disengaging.[9]

A strong start to the appointment matters because patient satisfaction depends largely on whether their doctor understands and responds to what the patient had hoped to accomplish during the visit.

Begin the appointment by asking about the patient's goals and expectations. Understanding what they hope to learn, improve, or achieve helps to make sure that both physician and patient develop a mutually agreed-upon agenda for the visit, and provides an opportunity to manage patient expectations.

This is particularly important in dermatology, where patients often arrive with numerous concerns and expectations about diagnostic certainty, treatment speed, skin clearance, and

long-term disease control. A simple invitation at the start of the visit, such as, "What would you like to make sure we address today?"—can significantly reduce unaddressed concerns. Importantly, **appropriately phrased agenda-setting has been shown to reduce unmet concerns by 78%, counterintuitively without significantly increasing the visit duration**.[10]

Explicitly asking for a patient's expectations has been shown to more than double the likelihood that patients felt their clinician understood what they hoped to achieve.[11] In my clinic I often ask, "what are you hoping for today".

Importantly, patient-centred care does not require fulfilling every request. Studies have shown that **patients generally tolerate an expectation not being fulfilled as long as it is acknowledged, discussed, and replaced with a credible alternative plan**.[12]

Dissatisfaction arising from a mismatch between patient expectations and what can realistically be provided can be reduced by identifying the patient's underlying goals, setting clear expectations, and offering an appropriate alternative when the requested investigation or treatment is not indicated. Early discussion about goals and expectations creates an opportunity to prioritize concerns, define realistic outcomes, and develop a shared plan.

As the appointment moves beyond the first few minutes, effective communication is paramount. Yet, physicians are rarely given practical guidance on what empathy, validating concerns, and engaging in shared decision-making should sound like in everyday practice. Although these skills are vital, translating them into language that feels comfortable, efficient, and normal-sounding during a busy dermatology visit can be challenging.

Drawing on evidence from communication, business, psychology, and medical literature, we can use and adapt the following evidence-informed "micro-scripts" to optimize both communication and efficiency in the clinic.

Improving patient satisfaction is not the only goal of optimizing communication. There is much power in the therapeutic relationship itself, with evidence showing doctor-patient relationships can have a therapeutic effect, regardless of prescribed drugs or treatments. In a randomized trial involving 719 patients with the common cold, **encounters rated as highly empathic were associated with lower symptom severity and shorter illness duration**.[13] "Physicians who adopt a warm, friendly, and reassuring manner are more effective than those who keep consultations formal and do not offer reassurance."[14]

Practically, phrases such as "That must be exhausting," and "it sounds like you've been through a lot" can show empathy, along with techniques such as emotion labelling, for example: "That sounds incredibly frustrating." Mirroring, or repeating the patient's last few words or key phrases is also strongly supported in the psychology and communication research, and helps to convey understanding. Showing empathy strengthens the therapeutic relationship and has the potential to improve a patient's health beyond the effects of any treatment we prescribe.

In dermatology, where most conditions are chronic, setting expectations around outcomes is key. Unclear expectations can lead to a disappointed patient and follow-up appointments become much more challenging. Without a clear timeline, patients may interpret the lack of immediate improvement in their skin as treatment failure.

Specifically, **patients should be told when they can expect to see improvement, and when peak improvement will occur**. For example, when treating acne, I tell my patients "I expect that in 3 months your acne should be about 20–25% better, and it will get even better after a year". Explaining to patients that little visible change is expected after a week of topical steroid use helps them understand that meaningful improvement requires time, compliance with medication use, and persistence.

For more challenging chronic conditions such as lichen planopilaris, it is important to define success in realistic terms by saying "our goal is control, not perfection." Patients can also be reassured by knowing there is a backup plan by briefly describing next steps if the current treatment fails. Setting realistic positive expectations can improve both patient-reported and physical outcomes.[15]

Finally, the last 60 seconds of the appointment provide an ideal opportunity to implement several evidence-supported micro-interventions that can optimize both the patient experience and clinical outcomes. A 2025 study of 718 dermatology patients reported that adherence was significantly lower for topical therapies compared with systemic treatments, with complex topical regimens and insufficient physician instructions among the factors associated with lower adherence.[16] Instructions should be concise and clear. Dermatologists should eliminate ambiguity by explaining what medication goes where, how often it should be used, and for how long.

One of the most strongly recommended communication strategies is the use of teach-back techniques to confirm understanding. Using phrases such as "Just so I know I explained it clearly; can you tell me how you're going to

Clinical purpose	Evidence-supported phrasing	Compared with	What the evidence specifically shows	Dermatology example
Make a collaborative treatment proposal	**"How about we…?"**	"I'll start you on …?."	"How about we…" invites collaboration and gives the patient more agency.	"How about we start with phototherapy?"
Offer control	**"Would you like me to prescribe ___?"**	"I'm going to prescribe ___."	"Would you like me to…" gives the patient greater decisional authority and options.	"Would you like me to prescribe something for the itch while we wait for the biopsy results?"
Give a clear professional recommendation	**"I recommend ___ because ___."**	Listing options without stating a recommendation.	"I recommend…" clearly communicates clinical judgement while allowing for discussion.	"Given the severity of your eczema, I recommend starting a biologic therapy because topical treatments alone are unlikely to provide adequate control."
Personalize a recommendation	**Use the patient's own words: "Because you told me the itching is keeping you awake…"**	A generic description of the clinical problem.	Using the patient's own words in the recommendation has been associated with greater treatment acceptance and reinforces that the plan reflects their priorities.	"Because you said you'd like your acne clear for your wedding, the best next step is…"
Recommend against an unnecessary treatment	**First state what you recommend: "For the symptoms, I recommend ___. Antibiotics will not help because this is viral."**	Leading with "You don't need antibiotics."	Patients are more likely to accept a non-antibiotic plan when an alternative is offered first, followed by an explanation of why antibiotics are unnecessary.	"For this tinea infection, I recommend an anti-fungal treatment. Antibiotics are not likely to help since it's caused by a fungus."

Table 1. Evidence supported phrases for clinical encounters; *courtesy of Irina Oroz, MD, FRCPC, DABD*

use these creams?" avoids testing the patient. This approach allows physicians to assess understanding and improve patient education. Teach-back is supported in both the general medical literature and dermatology-specific research.[17]

5 S's of the final 60 seconds

1. **Signpost**
   "Before we wrap up, is there anything important we haven't covered?"
2. **Summarize**
   "You have eczema, and our goal is to get the inflammation under control with cream."
3. **Simplify**
   "Use this cream once daily on red, rough areas for two weeks, and moisturize twice daily."
4. **Show understanding**
   "Just so I know I explained it clearly, tell me how you're going to use the two creams."
5. **Specify next steps**
   "If it isn't better in four weeks, contact us; otherwise, I'll see you in three months."

For complex treatment plans, give the patient a written action plan. This evidence-based intervention counterintuitively improves efficiency by reducing time spent counselling and repetition, while making patients feel more comfortable. An effective action plan should include what treatments to use, where and how often to apply them, how long to continue treatment, what to do if symptoms improve or worsen, and when follow-up is recommended. In a randomized trial evaluating a pre-printed eczema action plan, parents receiving the plan had significantly greater understanding of atopic dermatitis treatment.[18] While written action plans may not be necessary or relevant for all dermatology patients, the concept can be applied to complex treatment plans, elderly patients with memory challenges, and parents managing chronic skin condition in young children. For dermatologists already using artificial intelligence-assisted documentation tools, creating a patient treatment summary can be a practical way to implement this approach.

Clear, understandable instructions from the dermatologist are the most important factors for treatment adherence. Conversely, inadequate instructions are associated with poorer medication adherence.[19]

The **5 S technique** creates an intentional closing sequence that uses the final 60 seconds of the visit to make sure that the patient leaves feeling heard, understands the treatment plan, knows how to carry it out, and is clear about the next steps. A recent paper on optimizing the conclusion of clinical encounters highlights the concept of "Signposting:" explicitly telling your patient that the visit is drawing to a close before you begin the closing sequence.[20] The key point is that you avoid the abrupt transition from discussion to departing. This is particularly relevant in dermatology, where last minute "doorknob" concerns frequently emerge, which can derail the flow of an appointment.

When considering strategies to optimize the patient experience, it is important to recognize the limitations of the available evidence. The patient experience is difficult to study, and many available investigations measure outcomes such as trust, satisfaction, perceived empathy, or understanding rather than objective measures such as medication adherence or clinical outcomes. In addition, the evidence is distributed across multiple specialties and disciplines, with relatively few studies specific to dermatology. While many of the strategies discussed here are supported by randomized or interventional studies, others are based on observational data or principles extrapolated and interpreted from communication science, psychology, and other fields.

Not all patients value the same communication approaches. Preferences vary with age, culture, specialty, clinical setting, and the individual. These recommendations are not meant to be used as a script or a checklist for every appointment, but rather as a collection of practical evidence-informed tools that can be adapted to the patient sitting across from us. Further dermatology-specific research is needed to determine which of these small interventions translate into meaningful improvements in patient experience, adherence, and clinical outcomes.

As dermatologists, we rely on evidence to guide our investigations, treatment decisions, and our approach to disease management. We have the same opportunity to apply an evidence-

based mindset to how we deliver care. The patient experience is not simply about making patients happy; it can influence trust, understanding, engagement, adherence, and ultimately outcomes and the quality of care we provide. Many of the behaviours that contribute to a positive patient experience are also specific, teachable, and remarkably simple. No single phrase, clothing choice, or communication technique will completely transform a patient encounter. Rather, it is the combination of small, intentional choices throughout the visit that matters. Improving the patient experience does not require more time with patients, but greater intentionality in how we use the time we already have.

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Off-Label Uses of Topical Ruxolitinib

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Introduction

Janus kinase (JAK) inhibitors, such as ruxolitinib, have emerged as promising therapeutic agents in dermatology. These small-molecule inhibitors target and disrupt the inflammatory Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, critical to inflammatory and autoimmune skin disorders.[1] Topical formulations allow localized treatment while minimizing the systemic side effects commonly associated with oral JAK inhibitors. Ruxolitinib, a selective JAK1/JAK2 inhibitor, is approved for the treatment of atopic dermatitis (AD) and non-segmental vitiligo in individuals 12 years and older as of 2022.[1-4] The therapeutic effects of ruxolitinib in AD and vitiligo are primarily mediated through inhibition of JAK1/JAK2 signalling, which regulates cytokines implicated in AD such as interferon (IFN)-γ, interleukin (IL)-13, and IL-31, as well as IFN-γ-driven melanocyte destruction in vitiligo.[5]

Beyond these approved indications, off-label uses for oral and topical ruxolitinib are rapidly emerging, particularly for conditions with underlying inflammatory or autoimmune mechanisms. While systemic treatment has demonstrated good efficacy in a variety of conditions, the potential for associated side effects can limit the feasibility of their widespread use.[6] For topical administration, the data is promising; however, its broader adoption is limited by a lack of large-scale trials, optimized dosing, and long-term safety data. This review examines the evidence to date, highlights knowledge gaps, and explores the potential for broader clinical applications of topical JAK inhibitors in dermatology.

Mechanism of Action in Select Conditions

The success of ruxolitinib cream across a variety of conditions can be attributed to its targeted inhibition of the JAK/STAT pathway. This pathway plays a critical role in regulating immune responses and inflammatory cytokines implicated in numerous dermatological diseases.

- **Alopecia Areata:** Characterized by peri-follicular lymphocytic infiltration involving natural killer cells and T cells, which are targets of ruxolitinib's inhibitory action. By reducing this peri-follicular infiltration, ruxolitinib addresses the autoimmune processes driving hair loss.
- **Psoriasis:** Driven by dendritic cell activation and cytokine dysregulation, processes that are effectively countered by ruxolitinib's action on the JAK/STAT pathway. Ruxolitinib suppresses these pathogenic pathways by suppressing dendritic cell activation and cytokine overproduction, interrupting the cycle of inflammation and keratinocyte hyperproliferation, decreasing lymphocytic infiltration, and acanthosis.[7,8]

These mechanisms support ruxolitinib as a logical therapeutic candidate for a broad range of inflammatory and autoimmune skin conditions.

Advantages of Topical Ruxolitinib Cream

Ruxolitinib cream offers several key benefits compared to approved systemic treatments[5]:

1. **Localized Action:** As a topical agent, it provides targeted treatment with minimal systemic absorption, reducing risks such as malignancy or immunosuppression-related infections. However, some systemic absorption may occur, as evidenced by reports of relative leukopenia upon treatment initiation.[8]
2. **Rapid Symptom Relief:** Patients often experience sustained symptomatic improvement within days to weeks of initiating treatment.
3. **Convenience and Compliance:** Unlike oral JAK inhibitors (e.g., tofacitinib), injectable biologics, or oral antibiotics, ruxolitinib cream is user-friendly, and may enhance patient adherence.

4. **Long-Term Tolerability:** Its limited systemic side effects make it suitable as a long-term treatment option.

Safety Profile and Reported Side Effects

Reported side effects for ruxolitinib cream are mild and self-limited. Some examples of mild adverse events include pruritus, irritation, pain, localized dryness, erythema, and headaches. Ruxolitinib does carry a boxed warning regarding serious infections, malignancies, major adverse cutaneous events, thrombosis, and mortality. However, the topical application results in limited-to-negligible systemic absorption and the steady-state plasma concentration of ruxolitinib remains well below the thresholds associated with systemic JAK-inhibitor toxicities.[8] Consequently, the risk of systemic adverse effects is not deemed to be clinically significant.

Methods

A literature search was conducted using PubMed, OVID Medline, and Embase with the search terms "ruxolitinib," "JAK inhibitors," "Janus kinase inhibitors," and "topical." Twenty-six studies, encompassing a total cohort of 520 patients, met the inclusion criteria and were analyzed. The identified studies included randomized controlled trials, open-label studies, retrospective analyses, and case reports. The clinical characteristics, distribution patterns, and observed therapeutic efficacy profiles across these 26 extracted protocols are systematically outlined below in **Table 1**. In addition to the above-mentioned literature review, Turchin et al[18] have also previously published a review of topical, off-label uses of ruxolitinib. They have cited its effective use in the following conditions: atopic dermatitis, vitiligo, alopecia areata, psoriasis, lichen planus (LP), necrobiosis lipoidica, discoid lupus erythematosus, and seborrheic dermatitis.

Limitations of the Current Evidence

Although ruxolitinib cream has shown promise across a range of off-label dermatologic applications, several limitations remain:

1. **Small Sample Sizes:** Many studies rely on case reports or small cohorts, limiting the generalizability of the results.
2. **Short Study Durations**: Most trials have follow-up durations of only 6–12 months, limiting the assessment of long-term efficacy and safety for chronic diseases.
3. **Unoptimized Dosing Protocols:** Available concentrations (e.g., 0.075% or 2%) have not been systematically compared to refine treatment strategies.
4. **Limited Peer-Reviewed Data:** Many findings remain unpublished or have not undergone peer review, restricting interpretation and validation by the broader scientific community.

Future Directions

To address these limitations and expand the clinical utility of ruxolitinib, further research is needed:

1. **Large-Scale Randomized Trials:** These are essential to validate efficacy and safety across broader populations.
2. **Long-Term Studies:** Chronic conditions require data on outcomes extending beyond 12 months.
3. **Dose Optimization Studies:** Comparative trials investigating different concentrations and regimens could help tailor treatment for specific conditions.
4. **Broader Applications:** Exploration of topical ruxolitinib efficacy should be further explored to determine its full therapeutic potential.

Currently, active clinical trials are evaluating topical ruxolitinib across several off-label conditions (ClinicalTrials.gov). There are trials being conducted in adult and adolescent patients with hidradenitis suppurativa (NCT07049575), children 6 to <12 years of age with non-segmental vitiligo (NCT06804811), refractory cutaneous dermatomyositis (NCT06857240), and participants with discoid lupus (NCT06261021).

Conclusion

Ruxolitinib cream has demonstrated significant promise in both approved and off-label dermatological indications. Its localized action, rapid symptom relief, and favourable safety profile

make it an attractive alternative to systemic treatments. However, current evidence is limited by small sample sizes, short follow-up periods, and unoptimized dosing protocols. Addressing these gaps through larger-scale, long-term research will be critical to understanding its full potential as a safe and effective therapy for diverse inflammatory and autoimmune skin diseases.

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Dermatological Condition	Number of Studies	Reported Clinical Effect / Efficacy Notes	Primary Literature Sources
Alopecia Universalis	3	Shows potential for systemic regrowth, though highly prone to relapse upon withdrawal	Solimani et al., 2019[5] Craiglow et al., 2016[9]
Alopecia Areata	4	Stimulates hair regrowth by reducing peri-follicular T-cell infiltration.	Bayart et al., 2017[10] Gordon et al., 2019[11] Deeb et al[12], Olsen et al., 2012[13]
Psoriasis	3	Significantly decreases epidermal acanthosis and limits cytokine overproduction.	Carmona-Rocha et al., 2024[7]; Punwani et al., 2012[8]
Cutaneous Graft-Versus-Host	3	Controls localized, resistant sclerodermatous skin flares.	Solimani et al., 2019[5]
Frontal Fibrosing Alopecia	2	Slows down or stabilizes the progression of frontal hairline scarring.	Hosking et al., 2018[3] Desai et al., 2024[15]
Seborrheic Dermatitis	2	Reduces erythema and scaling via localized anti-inflammatory pathway blocks.	Gong et al., 2021[2] Pope et al., 2022[14]
Lichen Planus	2	Flattens classic violaceous papules and eases localized pain/pruritus.	Solimani et al., 2019[5], Brumfiel et al., 2022[16]
Cutaneous Lupus	2	Calms active discoid or subacute cutaneous lesions without systemic toxicity.	Hosking et al., 2018[3]
Hidradenitis Suppurativa	2	Decreases nodular inflammatory burden in early Hurley stages.	Hosking et al., 2018[3]
Necrobiosis Lipoidica	1	Promotes granulomatous ulcer healing and stabilizes plaque margins.	Solimani et al., 2019[5] Nugent et al., 2022[17]
Total Encompassed	**24 Studies**	**Cumulative Clinical Cohort: 520 Patients**	**Extracted Literature Set**

Table 1. Off-Label Applications of Ruxolitinib Cream; *courtesy of Parbeer Grewal, MD, FRCPC, FAAD*

J&J/Janssen, JAMP Pharma, Leo Pharma, Med Plan, Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme, Sandoz, Sun Pharmaceuticals, Takeda, and UCB. Investigator for: AbbVie, Amgen, Anacor, Apogee, Arena Pharmaceuticals, Avillion, Bausch Health, Biogen, BMS, Boehringer Ingelheim, Celgene, CorEvitas, Dermavant, Eli Lilly, Galderma, Innovaderm, J&J/Janssen, Leo Pharma, Meiji Seika Pharma, Moonlake Immunotherapeutics, Novartis, Pfizer, Regeneron, Sanofi-Aventis/Genzyme, Sandoz, Takeda, UCB, and Vitae.

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