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Dutasteride Mesotherapy for Androgenetic Alopecia: What do we know?

Matt Sandre, MD, FRCPC

Introduction

Androgenetic alopecia (AGA) is a common dermatologic condition that can cause a significant amount of distress for some patients.[1-3] Dihydrotestosterone (DHT), an endogenous hormone, plays a major role in this form of hair loss, causing scalp hairs to undergo miniaturization and reducing the amount of time they spend in the anagen growth phase.[4,5] Dutasteride is one of several treatment options for AGA. It works by inhibiting 5-α reductase (5-aR) types I and II, ultimately reducing the levels of DHT in the scalp.[2,4] This can be contrasted to another 5-aR inhibitor, finasteride, which only inhibits the 5-aR type II.[4] Although dutasteride is potentially more potent than finasteride, its longer half-life (~5 weeks), similar side effect profile, and lack of Health Canada approval for AGA make some prescribers more likely to choose finasteride over dutasteride.[2,4]

Mesotherapy involves injections of a substance, such as vitamins or a medication, into the skin at the correct layer to achieve a desired therapeutic effect while minimizing systemic absorption and adverse effects.[4,6] The use of dutasteride mesotherapy for AGA has been described somewhat recently; however, a large pool of data is not available to determine its appropriate place in the AGA treatment ladder. Despite this, an increasing number of publications are appearing over time regarding dutasteride mesotherapy. This paper will provide a concise review of potential dosing and injection techniques, adverse effects, and outcomes of dutasteride mesotherapy.

Dosing and Injection Technique

Publications have reported using concentrations ranging from 0.005–0.05% for dutasteride mesotherapy.[6-11] Combinations of 0.01% dutasteride and 2% minoxidil have also showed positive results in both men and women with AGA.[12]

Given dutasteride's long half-life, a treatment interval of every 3 months could be a convenient option for patients, yet shorter treatment intervals ranging from weekly to monthly have also been described.[6-8] Reports have indicated that some providers commence with weekly injections, then slowly decrease the frequency to every 2 weeks, and eventually transition to a monthly treatment interval.[6,8]

Administration techniques vary between injecting 0.01–0.1mL of the solution at each location, leaving approximately 1 cm between injections, and a depth of injection of ~4 mm using fine/higher gauge needles.[13,14] Although not thought of as being mesotherapy in the traditional sense, a more recent publication assessed

the use of 2.5 mm depth microneedling to introduce a 0.01% dutasteride solution into the scalp.[15] These authors used a monthly treatment interval.[15]

Adverse Effects

A small number of studies have highlighted the lack of systemic side effects with dutasteride mesotherapy, including no significant difference in serum hormone levels after treatment.[4,13]

A systematic review conducted by Herz-Ruelas and colleagues was not able to identify any studies noting changes in libido, erectile dysfunction, or ejaculatory dysfunction associated with dutasteride mesotherapy.[4] The injection frequencies included in the review were as often as weekly, and there was no evidence of sexual side effects associated with dutasteride mesotherapy. In contrast, their review did highlight a decrease in libido, erectile dysfunction, and ejaculatory dysfunction with the use of oral dutasteride, although this increase was nonsignificant when compared to placebo.[4]

A report has described 2 cases of paradoxical nonscarring alopecia after dutasteride mesotherapy. The report noted that both patients who experienced this adverse effect had received a dutasteride solution using ethanol as the solvent.[11]

The first patient underwent one session of dutasteride mesotherapy with a 0.025% dutasteride solution and developed small patches of non-scarring alopecia 1 month later. She was lost to follow up to assess the progression or resolution of this adverse effect. The second case was a male who underwent treatment with dutasteride mesotherapy at the same injection concentration (0.025%) and technique of administration who later developed similar small patches of hair loss at the injection sites after 2 sessions. At the 3-month follow-up, no improvement was observed.[11]

The authors suggest that using ethanol as the solvent could have induced hair follicle toxicity and cell death leading to the secondary hair loss. Instead, they propose using dimethyl sulfoxide (DMSO) as the solvent for dutasteride mesotherapy over ethanol.[11] In Canada, it is crucial to be aware that there is no pre-formulated sterile dutasteride solution with a drug identification number available in pharmacies. Practitioners should therefore work with their compounding pharmacy colleagues to obtain a sterile dutasteride solution at the desired strength and in the most appropriate solvent.

Angioedema-like contact dermatitis secondary to dutasteride mesotherapy was reported in a woman who developed facial swelling and skin redness a day after her first mesotherapy session.[16] The swelling was quite extensive in the periorbital area despite the injections being administered locally on the scalp. Subsequent patch testing confirmed a strongly positive reaction to varying concentrations of dutasteride (0.001%, 0.01%, and 0.05%), as well as to 20% propylene glycol given that this was another ingredient in the dutasteride solution.[16]

Melo and colleagues described 10 patients who experienced frontal edema after mesotherapy with dutasteride; however, their solution was diluted with lidocaine.[17] Additionally, some, but not all, of the patients received platelet rich plasma injections in the same session. Treatments were spaced apart every 3 months. The edema lasted for approximately 1–4 days, improving with a cold compress and some improvements were noted with oral corticosteroids. The edema was most commonly seen after 2 sessions. It was unclear to the authors whether the adverse reaction was attributable to the dutasteride, or if it was secondary to the lidocaine, or the total volume injected in 1 session.[17]

Aside from localized pain, bleeding, and bruising from the injection itself, other side effects such as scarring alopecia, scalp abscesses, and fat necrosis have been mentioned infrequently in case reports with mesotherapy in general, but not specifically with dutasteride mesotherapy.[9,18,19] A retrospective study that included 541 patients who underwent dutasteride mesotherapy noted pain as the most frequently reported adverse effect in 45.5% of patients with no serious or sexual side effects observed.[9]

Potential side effects that have been discussed are outlined in **Table 1**.

Reported Adverse Effects of Dutasteride Mesotherapy
Pain
Bleeding
Bruising
Frontal Edema
Angioedema-like Contact Dermatitis
Nonscarring Alopecia at Injection Sites
** No current reports have indicated changes in serum hormone levels, changes in libido, erectile dysfunction, or ejaculatory dysfunction

Table 1. Reported Adverse Effects of Dutasteride Mesotherapy; *courtesy of Matt Sandre, MD, FRCPC.*

Outcomes

Available reports have shown favourable outcomes with dutasteride mesotherapy, yet, it appears to be less effective compared to oral dutasteride therapy.[4] For example, a study's pooled analysis has revealed a mean change in hair growth of 15.92 hairs per cm^2 with oral dutasteride, and 7.9 hairs per cm^2 with intralesional therapy.[4] The same analysis indicated that self-assessed improvement and treatment satisfaction with dutasteride mesotherapy had ranged from 7.1% to 92.9%, and 40% to 90%, respectively.[4]

The aforementioned multi-centre retrospective study of 541 patients utilized 0.01% dutasteride mesotherapy injections in men and women administered every 3 months.[9] Of note, 86 of those patients received dutasteride mesotherapy as monotherapy. Over 80% of the patients demonstrated a clinical improvement, and 33 of 86 patients (38.4%) who received dutasteride mesotherapy as monotherapy achieved a marked improvement.[9]

The authors conducted a 20-week randomized, double-blind, placebo-controlled study using 2.5 mm microneedling with 0.01% dutasteride. Participants received 3 monthly treatments with either microneedling with a dutasteride solution or microneedling with a saline solution.[15] Three dermatologists compared photographs taken at baseline to week 16. The dermatologists reported that 52.9% of the men in the microneedling-with-dutasteride-solution group had a statistically significant marked improvement in hair density compared to the microneedling-with-saline-solution group.[15]

My Approach

The area is cleaned with chlorohexidine or hypochlorous acid. A sterile solution of 0.05% dutasteride preserved with benzoyl alcohol is drawn up into BD 1mL syringes with Luer-Lok Tip using a 18G blunt-tipped needle. For injection, TSK STERiJECT Hypodermic 33G x 4mm needles are used. Given the use of 4mm needles, the desired depth is easily achieved by inserting the needle all the way to the hilt. Subsequently, 0.05mL per cm^2 of the desired treatment area is injected and treatments are repeated every 3 months. A minimum of 3 sessions are recommended to assess response and then, once desired response is achieved, a maintenance regimen of treatment every 6 months is recommended.

Combination treatment is always recommended with topical therapy such as 5% minoxidil, and consideration may be given to the addition of oral off-label minoxidil and/or finasteride in discussion with the patient. Based on personal preference, the author does not recommend oral dutasteride in those proceeding with dutasteride mesotherapy.

Patient selection may follow platelet-rich plasma injections; those with early changes of AGA would be more ideal candidates for trialing dutasteride mesotherapy than those with late-stage changes.

Conclusion

Given how common AGA is in our patient population, it is important for practitioners treating this condition to stay informed about recently described therapies or innovative approaches to using established therapies. Although oral approved and off-label options are available, the potential for, and in some cases, unpredictable nature of systemic side effects may cause both patients and practitioners to feel uneasy about their use. Considering the currently available publications, dutasteride mesotherapy appears to show promise in providing benefit for patients with AGA. Importantly, its use with mesotherapy may avoid systemic side effects typically associated with oral administration of this drug. Given that dutasteride mesotherapy is not approved for AGA, practitioners should be aware of the potential side effects. This awareness can enable practitioners to engage in a candid discussion with patients before considering this relatively new treatment option.

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Financial Disclosures

None declared.

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Oral Lichen Planus: An Overview

Benoit M. Cyrenne, MD

Introduction

Oral lichen planus (OLP) is an inflammatory disorder of the oral mucosa with a prevalence of 0.5% to 2.2% among adults.[1,2] Disease onset tends to occur between the ages of 30 to 60 years and is observed more frequently among females than males.[2-4] In contrast to the cutaneous lesions of lichen planus, OLP is often chronic and patients are plagued with relapses and remissions.[5] OLP also often causes substantial morbidity, as it is considered to be a precancerous lesion owing to its associations with oral squamous cell carcinoma.[4,6] Rates at which OLP undergoes malignant transformation range from 0.4% to 1.4%, and these rates are highest for the atrophic and ulcerative clinical subtypes of OLP.[7]

Clinical Manifestations

While a bilateral, symmetrical pattern on the buccal mucosa is the most classic presentation of OLP,[4] there are six clinical subtypes that can be observed individually or in combination: reticular, erosive/ulcerative, plaque-like, papular, bullous, and atrophic (also known as erythematous).[5] The most recognized form of OLP is reticular lesions, which are frequently asymptomatic and can appear as multiple papules, plaque-like formations, or lacy patterns (Wickam striae).[4,5] Symptoms associated with OLP include pain, burning, swelling, irritation, and bleeding, especially with tooth brushing or eating. Symptoms are most common with the erosive or atrophic forms of OLP and are reported in approximately two thirds of patients.[2,4] Most patients with OLP experience "isolated" OLP, meaning they lack an associated cutaneous lichen planus or lichen planus affecting other mucosal sites.[8] Among OLP patients, approximately 15% report cutaneous lesions and 20% will have concomitant lesions in the genitalia. OLP may also involve the esophagus and lead to significant dysphagia.[2,9]

Diagnostic Criteria

Two main challenges have been identified in making the diagnosis of OLP: **1)** numerous other disorders either clinically and/or histopathologically resemble OLP, and **2)** the histopathologic features of OLP exist on a spectrum that is directly associated with the stage of disease at the time of biopsy, the clinical subtype, and the anatomic site.[2]

OLP shares overlapping features with oral lichenoid drug reaction, chronic ulcerative stomatitis, and lichenoid contact hypersensitivity reaction.[10] Erosive disease, especially erosive gingivitis,

Clinical Criteria	Histological Criteria
Presence of lesions that are bilateral and more or less symmetrical	Presence of a well-defined bandlike zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Presence of a lacelike network of slightly raised grey-white lines (reticular pattern)	Signs of liquefaction degeneration in the basal cell layer
Erosive, atrophic, bullous, and plaque-type lesions are accepted only as a subtype in the presence of reticular lesions elsewhere in the oral mucosa	Absence of epithelial dysplasia

Table 1. Modified WHO Criteria[11,12]; *courtesy of Benoit M. Cyrenne, MD.*

Clinical Criteria	Histological Criteria
Multifocal symmetric distribution of lesions	Band-like or patchy, predominately lymphocytic infiltrate that is found in the lamina propria and is confined to the epithelium–lamina propria interface
White and red lesions exhibiting one or more of the following forms: reticular/papular, atrophic (erythematous), erosive (ulcerative), plaque, bullous	Basal cell liquefactive (hydropic) degeneration
Lesions are not localized exclusively to the sites of smokeless tobacco placement	Lymphocytic exocytosis
Lesions are not localized exclusively adjacent to and in contact with dental restorations	Absence of epithelial dysplasia
Lesion onset does not correlate with the start of a medication	Absence of verrucous epithelial architectural change
Lesion onset does not correlate with the use of cinnamon-containing products	

Table 2. Cheng *et al.* Criteria[2]; *courtesy of Benoit M. Cyrenne, MD.*

may present with symptoms and features that are identical to other inflammatory dermatoses such as pemphigus vulgaris or mucous membrane pemphigoid.[2] Given the diverse features and anatomic specifications of OLP, its management and treatment is intrinsically multidisciplinary, involving professionals such as dentists, dermatologists, gastroenterologists, gynecologists, otolaryngologists, and ophthalmologists.[6]

The original World Health Organization (WHO) criteria for diagnosing OLP were proposed in 1978 and underwent subsequent modifications in 2003 (**Table 1**) owing to an absence of correlation between the clinical and histopathological criteria.[11,12] In 2016, a new set of criteria were proposed by the American Academy of Oral and Maxillofacial Pathology (**Table 2**).[2]

The severity of OLP can be measured using validated scoring systems such as the oral disease severity score (ODSS).[13] The ODSS provides a composite measure of the extent of disease intraorally as well as disease activity and degree of pain with high inter- and intra-rater reliability.

Treatments

Behavioural

Given the significant overlap in both the symptoms and histological features of OLP, oral lichenoid hypersensitivity reaction, and oral lichenoid drug reactions, the proper management of any patient with OLP should include a careful review of their medication and exposure history to ensure the correct identification of any modifiable factors. This thorough review may lead to a reduction in symptoms.

Oral lichenoid drug reactions can be caused by a number of different medications and may present with or without cutaneous lesions. The most common medications that may cause a reaction include anti-convulsants such as phenytoin, antibiotics, antihypertensives, antimalarials, and non-steroidal anti-inflammatory drugs (NSAID)s. Onset of symptoms after initiation of an offending medication ranges from weeks to over a year.[2] The most common causes of oral lichenoid hypersensitivity reaction include metals, flavouring agents such as cinnamon or peppermint, as well as dental restorative materials such as acrylates.[2]

Topical Therapies

Topical Corticosteroids

Topical corticosteroids are the first line treatment for all forms of OLP and are used widely to reduce pain and inflammation in the form of ointments and mouth rinses. Oral suspensions of triamcinolone have been demonstrated to be effective.[14] High-potency steroid mouth washes, which are of particular value for patients with widespread disease or posterior oropharyngeal lesions, may be used but care should be taken to avoid pituitary-adrenal axis suppression.[8]

Clobetasol propionate, the most potent topical steroid, is effective at treating OLP and has demonstrated superior efficacy compared to medium potency steroids such as fluocinonide or triamcinolone.[8] While steroid injections have demonstrated efficacy, due to the pain of administration and the association with atrophy, their utility in the treatment of OLP is limited.

Topical Calcineurin Inhibitors

Tacrolimus, a powerful immunosuppressive agent and calcineurin-inhibitor, has been found to have equal or greater efficacy in reducing pain and other symptoms compared to clobetasol,[7,15] and equal efficacy to topical pimecrolimus.[7] Further, despite warnings regarding the risk of carcinogenesis with topical and systemic tacrolimus, there is no evidence of an increased malignant potential of lesions treated with tacrolimus versus clobetasol.[15] Furthermore, tacrolimus is associated with lower rates of oral candidiasis.

Cyclosporine has been evaluated as a topical treatment for OLP in the form of both a mouth rinse and gel with good effect; however, it has failed to demonstrate superior or equal efficacy in comparison with topical corticosteroids, which has limited its clinical use.[16]

Systemic Therapy

Hydroxychloroquine

Commonly used for cutaneous lichen planus or lichen planopilaris, there is limited evidence for the use of hydroxychloroquine in the treatment of OLP. However, some evidence suggests that erosive OLP can be effectively treated with hydroxychloroquine at doses ranging from 200–400 mg.[4] A recent retrospective case series demonstrated that 79% of patients who received hydroxychloroquine experienced a reduction of 25% or more in their ODSS, and that the median time to achieve this level of reduction was 6 months.[13]

Systemic Corticosteroids

Systemic corticosteroids are viewed as the most effective treatment for patients experiencing recalcitrant or erosive OLP, and are recommended as a first line therapy for extensive and/or erosive lichen planus in European guidelines.[16] While they induce rapid resolution of symptoms, the use of systemic corticosteroids is associated with a high rate of relapse, especially in comparison to other therapies.[17] Furthermore, a comparative treatment study did not observe differences in the response to systemic prednisone at a dose of 1 mg/kg/day compared to topical clobetasol; thus, systemic corticosteroids tend to be relied on when topical approaches are ineffective, when OLP is widespread, recalcitrant, erosive, or erythematous, or when other regions are exhibiting lichen planus.[5] While systemic prednisone can be used to treat ulcers and erythema in OLP, it has not demonstrated superiority to treatment with topical triamcinolone acetonide.[8]

Mycophenolate Mofetil

Mycophenolate mofetil is an immunosuppressive agent that has demonstrated effectiveness in treating recalcitrant erosive OLP.[5] Improvements in severe cases are typically observed over an extended period of many months and the treatment is generally well-tolerated.[4]

Azathioprine

Azathioprine is a purine analog that inhibits T-cell activation. The use of azathioprine treatment for OLP has been rarely reported; it is mainly used in predominantly severe or recalcitrant cases, especially when long-term corticosteroid use is contraindicated.[4] Its efficacy was demonstrated in an open-label single arm study in which seven of nine patients experienced a complete clearance of cutaneous and oral lesions after 12 weeks of therapy.[18]

Methotrexate

Methotrexate is an immunosuppressant that exerts its effects by inhibiting folic acid metabolism, which subsequently impedes DNA and cell replication. It has demonstrated efficacy in large case series. For instance, Torti *et al* included a series of 18 patients with erosive lichen planus who were treated with low dose (<12.5 mg/week) oral methotrexate. Ten of these patients demonstrated a 75% reduction in symptoms.[19] The efficacy of methotrexate was further supported in a randomized trial comparing its efficacy with oral prednisone. In this trial, an 8-week course of methotrexate exhibited superior efficacy with a complete response rate of 73.3% compared to a 60% response rate with an 8-week course of prednisone.[16,17]

Janus Kinase Inhibitors

Janus kinase inhibitors (JAKi) are potent and broad-acting immunosuppressive medications that have

been approved for a variety of inflammatory diseases including atopic dermatitis and psoriatic arthritis. They represent a promising new treatment modality for severe cases of OLP. Case reports have demonstrated several successful treatments of recalcitrant erosive OLP using either upadacitinib or tofacitinib.[9] The success of these treatments is attributed to the upregulation of JAK1 and JAK3 levels within OLP lesions.[9]

Systemic Retinoids

Systemic retinoids are vitamin A analogs that exert their effect through the activation of retinoic acid receptors, regulating epidermal proliferation and the cutaneous inflammatory milieu. Studies have examined the use of various systemic retinoids including acitretin, alitretinoin, isotretinoin, and etretinate. Both alitretinoin and etretinate have demonstrated success in treating OLP. Remission was observed in 64% of patients who received these medications orally at a dose of 30 mg daily, compared to the 13% remission rate in patients receiving a placebo at a dose of 30 mg per oral intake daily.[4] A trial comparing topical corticosteroid monotherapy with a combination of topical corticosteroids and acitretin demonstrated significantly improved response rates at 28 weeks. Furthermore, 88% of the combination treatment group achieved an ODSS reduction of 75% (ODSS75) compared to 47% in the group receiving topical triamcinolone alone.[20]

Cyclosporine

Cyclosporine is an immunosuppressant and calcineurin inhibitor that downregulates nuclear factor Kappa B (NF-κB). Most studies have examined its use as a topical formulation with demonstrated efficacy in erosive and atrophic forms of OLP.[21,22] The use of cyclosporine as a systemic agent has been shown to be effective in case reports and case series.[22]

Apremilast

Apremilast is an oral phosphodiesterase type 4 inhibitor that is approved for the management of psoriasis, psoriatic arthritis, and oral ulcers associated with Behçet's disease. Apremilast has demonstrated effectiveness in the treatment of OLP. After 12 weeks of therapy, 55% of the patients treated with apremilast showed improvement.[23] Crushed apremilast has been used to successfully treat OLP in a recent case report.[10]

Anti-psoriasis Biologics

Evidence regarding the efficacy of interleukin (IL)-17 and IL-23 blockade for treatment of oral or cutaneous lichen planus is limited; however, several case reports and small case series have demonstrated evidence of efficacy.[23] Solimani *et al* published a series that included 5 patients in which significant improvement in mucosal ulcerations was observed following the administration of secukinumab, ustekinumab, and or guselkumab.[24] Results of a phase II randomized placebo-controlled trial that evaluated secukinumab for the treatment of lichen planus including mucosal lichen planus (which includes OLP) demonstrated efficacy in the reduction of clinical symptoms, in which 37.5% of patients treated with secukinumab experienced a reduction of symptoms compared to 23.1% of patients treated with a placebo.[25] Of note, within the same trial, patients with cutaneous lichen planus did not demonstrate any improvement with secukinumab treatment.[25]

Light-Based Therapies

Laser Therapy

Low-level laser therapy has been used to effectively treat patients with symptomatic OLP. The following have all been used, with complete epithelialization within three weeks: 308 nm excimer laser radiation, 980 nm diode lasers, and CO_2 laser evaporation.[8] It appears to be an effective treatment when no further improvement is observed with steroids alone.

Photodynamic Therapy

Photodynamic therapy (PDT) uses photosensitizing compounds that, when activated by a specific wavelength of laser light, can destroy targeted cells using strong oxidizers. PDT has been shown to reverse the hyperproliferation and inflammation observed in OLP.[26]

Ultraviolet Irradiation

Photochemotherapy with long-wave ultraviolet light (PUVA) and 8-methoxypsoralen have been effective in treating recalcitrant OLP.[8] Photosensitization with topical 0.01% trioxsalen is recommended to avoid PUVA side effects. Erosive OLP may benefit from photochemotherapy especially if it has not responded effectively to conventional therapies, however, future research into this field would be valuable.[8]

Conclusion

OLP is a chronic, potentially debilitating disease which, in its severe form, requires treatment and clinical monitoring. Despite the high prevalence of this disease, there is a lack of high-quality clinical studies on treatment modalities, which limits our ability to rank treatment options among the myriad available. New treatments with novel mechanisms of action continue to be developed, suggesting substantial promise for the future management of OLP.

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* Clinical significance is unknown.

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Keloids: Review of Pathogenesis and Evidence-Based Treatment Modalities

Robert Bobotsis, MD, MSc SLI, FRCPC, DABD

Introduction

Keloids are fibroproliferative growths resulting from dysregulated healing following tissue injury with the subsequent deposition of excessive and disorganized collagen (**Figure 1**).[1] Prolonged chronic inflammation in the reticular dermis in particular during healing, is thought to precede the development of keloids. Experimental studies have demonstrated an increased release of growth factors, cytokines, and multiple immune cells.[2,3] The inflammatory cells secrete factors implicated in chronic inflammation, fibrosis and itch, among many others.[2]

Keloids demonstrate an autosomal dominant transmission with an incomplete penetrance, beginning most commonly in the 2nd and 3rd decades of life.[3] Keloids can be seen in all patients, but most frequently in those of skin of colour, particularly individuals from North Africa, South America, the Middle East, India, and China.[3] Areas of skin where keloids have the highest propensity to develop are related to other risk factors, including sites on the skin where an injury occurs due to dermatologic disease or external processes, high skin tension, and dense pilosebaceous content.[2,3] Hypertension and obesity also appear to be associated with the development of keloids at a systemic level.[2,3]

Keloids may present as a single lesion or a few lesions, or they can be widespread, developing without any known preceding trigger.[2,3]

In addition to distress from the physical appearance, keloids cause additional morbidity from pain (i.e. allodynia, burning, and stinging) and pruritus.[2] The Th2 cytokines, which are both profibrotic and pruritogenic, play a role and C-nerve fiber neuropathy ensues, producing pain and itch.[2]

Keloid Treatment Modalities

a) Preventative and Behavioural Strategies

Surgical Technique

To prevent keloid formation, especially in high tension areas of the body (eg. back, and shoulders, among others), surgeons should employ techniques that limit dermal tension, including broad undermining, placing scars along relaxed skin tension lines, dermal sutures, deep fascial plication sutures, local flaps, and Z-plasties.[5] There are no randomized controlled trials supporting this recommendation, however, the clinical

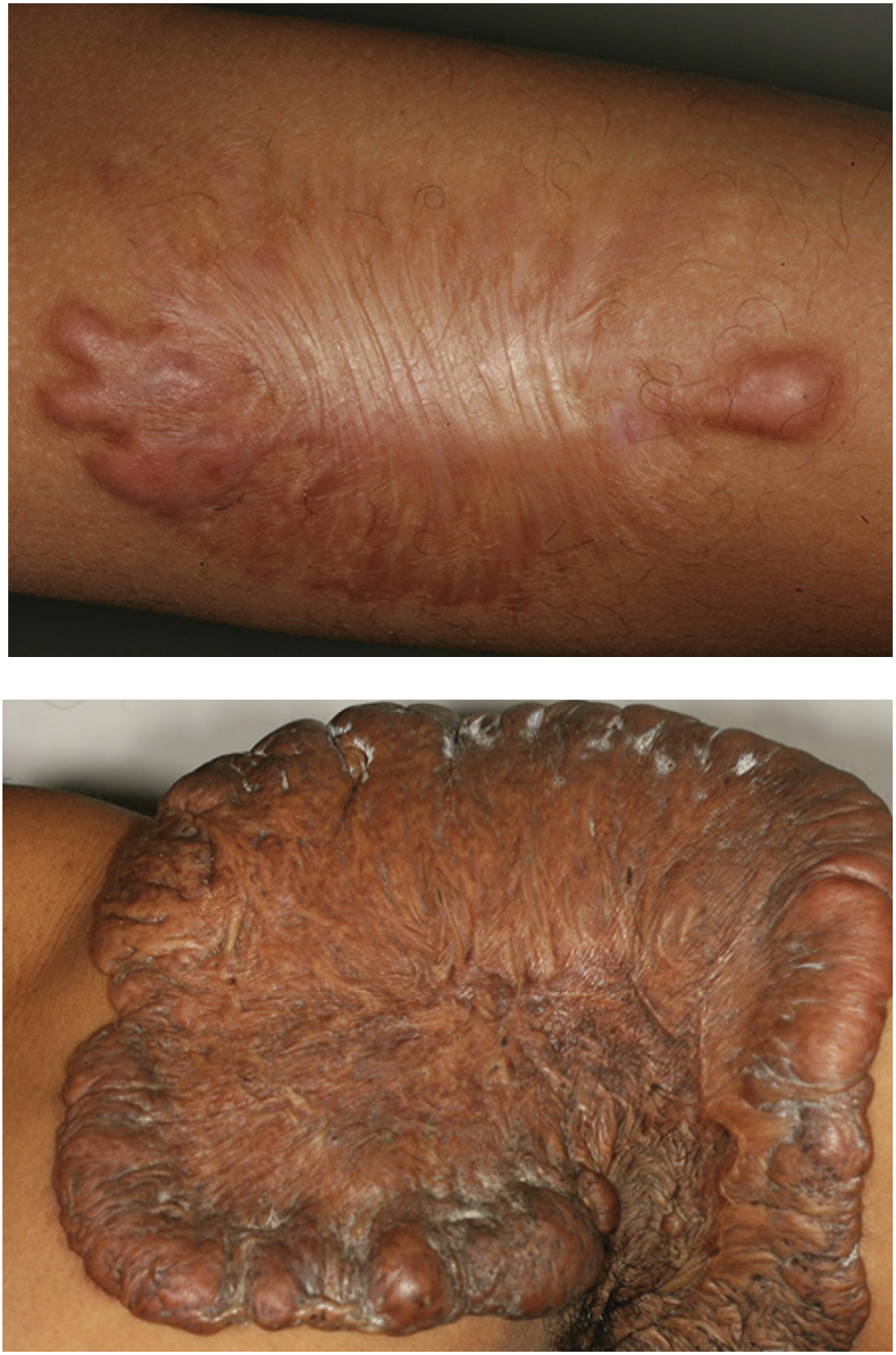

Figure 1. Keloids may appear with a sessile morphology (**top**) or a more nodular/exophytic morphology (**below**). The arrangement and anatomic location often provides a clue to the cause; *photos courtesy of* [4]*: (J. Delaleu, E. Charvet and A. Petit.Keloid Disease: Review with clinical atlas. Part 1: Definitions, history, epidemiology, clinics and diagnosis. Annales de Dermatologie et de Venereologie. 2023;150:3-15.)*

experience of most surgeons would suggest this as an expert opinion.

Silicone

Silicone based products are FDA approved for treating scarring and keloids, although they are used mostly as a preventative measure in clinical practice. The products are usually applied as either a topical gel or a sheet dressing 12–24 hours a day for 1–2 months post-operatively.

Patients commonly inquire about the use of post-procedural silicone products. The putative mechanism of action is not known, but its use may limit scar tension by decreasing skin stretching and promoting hydration through occlusion.[3,5] However, silicone has not been found to be an effective method of preventing keloids. A meta-analysis that included 10 trials comparing a silicone arm (gel or sheets) to a placebo arm did not find that silicone reduced the development of keloids in patients with a history of abnormal scarring.[6] Similarly, a Cochrane review of 20 clinical trials found that while silicone does reduce erythema and thickness, the evidence for reducing keloidal scarring is weak.[7]

b) Active Treatment Modalities

Surgical Excision

Excision alone is not recommended for keloids due to the very high risk of recurrence (up to 100%) and risk of lesions recurring at a larger size. Excision is combined effectively with other treatment modalities as outlined below.

Corticosteroids

Corticosteroids, intralesional kenalog (ILK) in particular, are the mainstay of keloid treatment by dermatologists. Corticosteroids are thought to work by reducing dermal inflammation, reducing oxygen via vasoconstriction, and inhibiting collagen synthesis.[3,5,8] Side effects include erythema, dyspigmentation, pruritus, pain, atrophy, telangiectasias, wound dehiscence and delayed healing.[8]

The literature presents a range of doses, frequencies, and injection timings for ILK treatment. A 2023 systematic review was conducted that compiled 16 studies, including 4 randomized-controlled trials and 12 prospective cohorts. They investigated the use of ILK monotherapy or in combination treatment with surgery or cryotherapy.[8] The dosage ranged from 10–40 mg/cc, administered through single injections either weekly or monthly, usually every 4–6 weeks.[8] Studies have found that ILK is most effective for treating sessile keloids (as opposed to pedunculated ones), with response rates between 50–100%, depending on the specific study, along with an overall recurrence rate of 33% and 50% at 1 year and 5 years, respectively.[8]

Studies using ILK as an adjuvant treatment to surgical excision are lacking control groups for the most part. For example, a recent meta-analysis that included 254 patients, pooled from 4 separate studies, did not demonstrate a reduction in the keloid recurrence rate.[9] The timing of ILK administration in the studies was inconsistent and no consensus recommendation was made.[9] However, the site of the keloid excision might have had an impact on the effectiveness of adjuvant ILK. A meta-analysis focusing on ear keloids reported a recurrence rate of 15.4% following excision. This was found to be of similar efficacy to the post-operative radiation group, which had a recurrence rate of 14%.[10]

Cryosurgery

Cryosurgery is another commonly employed keloid treatment modality, largely because dermatologists are comfortable with its use in many areas of practice. Cryosurgery causes tissue necrosis, however, it has also been shown to convert keloidal fibroblasts to a normal phenotype.[3] Side effects of cryosurgery include pain, bleeding, blistering, ulceration, dyspigmentation, and infection. While most dermatologists use spray cryosurgery, cryotherapy can also be administered by direct contact or intralesional needle methods. Intralesional cryosurgery, which involves applying the treatment to the core of the keloid, is considered to be the most efficacious cryotherapy modality.[11] A meta-analysis of 8 studies reported that intralesional cryotherapy was able to decrease the scar volume by 51–61%, with a recurrence range between 0–24%.[11] Intralesional cryosurgery is also more precise, as it allows one to limit the treatment area and minimize the amount of healthy skin that is frozen.[11]

Multiple published prospective cohorts and randomized-controlled trials have studied the combination of cryosurgery with other treatment modalities, including ILK, excision, or shave removal, and reported these techniques to be effective for the treatment of keloids (summarized here).[8]

Other Intralesional Treatments

5-fluorouracil (5-FU) has been used in various dermatologic indications. It is an anti-neoplastic drug that targets thymidylate synthase, thus inhibiting mitotically active keloidal fibroblasts.[8] Patients must be counselled on side effects including pain, bleeding, infection, ulceration, wound dehiscence, and poor healing. Meta-analyses and randomized-controlled trials (RCTs) have demonstrated its efficacy as a

monotherapy, in combination with ILK, and in reducing post-operative recurrences of keloids following excision.[3] An RCT that included 43 patients (with 50 keloids in total) compared the monthly administration of IL-5FU (50 mg/cc) to ILK (40 mg/cc), and reported that both treatment modalities were equally as effective at the 1 year follow up.[12] The former group however, had higher reports of telangiectasia and skin atrophy.[12]

By combining ILK with IL-5FU, the risk of steroid side effects can be reduced, potentially with greater efficacy. In two RCTs, one with 100 patients and one with 60 patients, ILK (40 mg/cc) monotherapy was compared to a combined treatment of IL-5FU (50 mg/cc) and ILK. The groups receiving combination treatment demonstrated a greater reduction in the Vancouver Scar Scale (VSS),[13] and a reduction in keloid volume.[14]

Just like 5-FU, bleomycin is another drug that has been used to treat other dermatologic diseases and is familiar among many dermatologists. It is an anti-neoplastic agent derived from *Streptomyces verticillus* that induces apoptosis in fibroblasts and inhibits collagen synthesis by targeting lysyl oxidase.[8] Similar to ILK, there are a wide range of reported recurrence rates following treatment of keloids with IL bleomycin monotherapy. In the largest available prospective study, 120 patients were treated with 15 units of bleomycin at 4-week intervals for an average of 4 months.[15] At the 18 month follow up, the reported recurrence rate was 14%.[15]

Bleomycin may be more effective than IL-5FU or ILK. In an RCT that included 164 patients, the authors found that IL bleomycin (1.5 IU/mL) was more effective in reducing the scores on the Patient and Observer Scar Assessment Scale (POSAS) compared to the ILK group.[16] In an RCT involving 60 patients, the authors compared treatment with either a combination of ILK (40 mg/cc) and 5-FU (1:9 mixture) or a combination of ILK (40 mg/cc) and bleomycin (1.5 IU/mL) in a 1:2.5 mixture.[17] The group receiving bleomycin and ILK showed a greater improvement in the VSS, and reported no recurrences.[17] The unique side effect of bleomycin that one must counsel patients about is hyperpigmentation, especially for patients with melanized skin. No systemic side effects were observed in these studies.

Radiation

The mechanism of action for radiation treatment of keloids includes inhibition of fibroblasts, inhibition of angiogenesis, along with downregulation of TGFβ and histamine from inflammatory cells.[3,8] Radiation is not often provided as a monotherapy, unless it is used for symptom control, in the aged population, or for very large keloids where surgery or intralesional treatment is not possible.[3] Instead, radiation is most useful as an adjunct therapy. A meta-analysis that included 72 studies totalling 9048 keloids revealed a 22% recurrence rate following surgery and post-operative radiation treament.[18] This meta-analysis revealed that monotherapy had a 37% recurrence rate, although pain and pruritus improved significantly in most patients.[18] The timing of radiation post-procedure appears to be important, with most studies documenting administration of radiation within 24 hours of the procedure yielding the best response (reviewed here).[8] There are however no clear recommendations on radiation dosing and scheduling.

The three main radiation modalities are: brachytherapy, electron beam therapy, and photon beam therapy.[19] While it is not clear which one is most effective, a systematic review that included 33 studies reported that adjuvant radiation with brachytherapy had a 15% recurrence rate while photon beam therapy and electron beam therapy both had a recurrence rate of 23% in their subgroup analyses.[18] Radiation can cause both acute (i.e. erythema, edema, pain, ulceration, and blistering) and chronic (i.e. telangiectasias and dyspigmentation) side effects. While radiation in general has been associated with the development of secondary malignancies, there is no definitive link between skin cancers and the short treatment protocols used in the adjuvant treatment of keloids.[18]

Lasers

While there is actually limited published data on lasers for the treatment of keloids, both ablative (CO_2, Erbium-doped yttrium aluminum garnet [Erb:YAG] and non-ablative lasers (pulsed dye laser [PDL], Neodymium-doped yttrium aluminum garnet [Nd:YAG], diode) have been described. Case series and small prospective cohorts have described laser treatment in combination with various intralesional therapies (ILK, 5-FU, interferon) or surgical excision. While there is very limited data, an interesting application of ablative lasers is as a method to improve the penetration of corticosteroids.

In one study, of 41 patients were treated with CO_2 followed by triamcinolone ointment under occlusion every 4 weeks for a total of 8 sessions and at 24-month follow up, there was a 10.5% recurrence rate.[20] In a split side-controlled prospective study, 30 patients were treated with ILK (10 mg/cc) compared to Erb:YAG (2940 nm) followed by application of betamethasone diproprionate ointment under occlusion 4 total times at 4 week intervals.[21] VSS reduction was statistically significant, but may not really be clinically significant (reduction from 6.90 to 2.63 vs. 2.07) at 12-week follow up after completing the last session.[21]

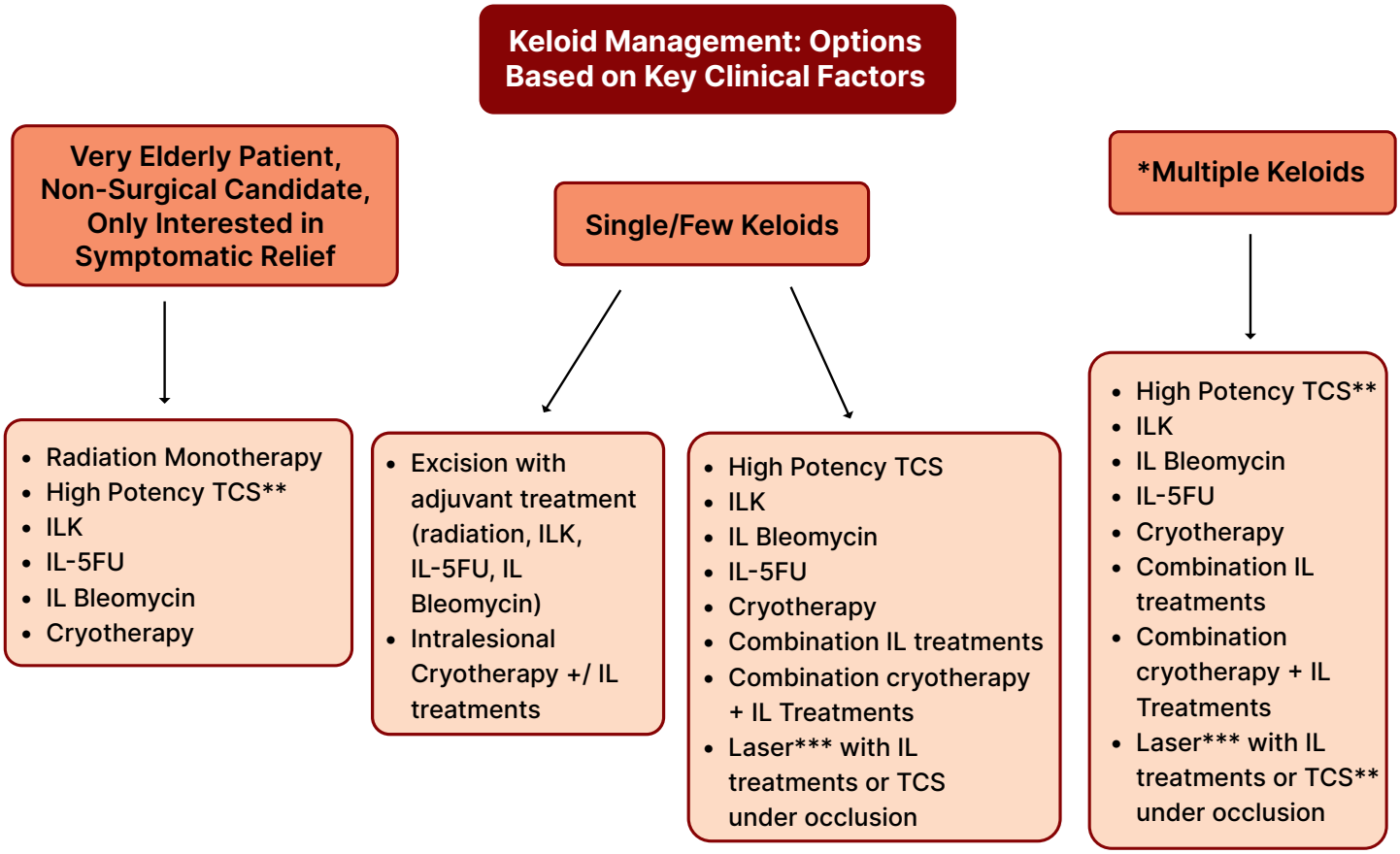

Figure 2. Algorithm for keloid management; *courtesy of Robert Bobotsis, MD, MSc SLI, FRCPC, DABD.*

***Multiple keloids (eg. involving a regional area of the body such as the chest) should be differentiated from widespread keloidal disease, the latter of which is extremely difficult to treat. Treatment options should be reviewed with patients along with honest discussion around realistic expectations.

****Corticosteroid ointments and creams can also be used to treat keloids over many months (usually under occlusion) and have the benefit of being painless.

*****The literature on laser treatment for scarring mostly focuses on hypertrophic scars.

Abbreviations: TCS: topical corticosteroids, **IL:** intralesional, **5-FU:** 5-fluorouracil

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Figure 3. International guidelines on the management of keloids.[22-26]; *courtesy of Robert Bobotsis, MD, MSc SLI, FRCPC, DABD.*

Discussion

When reviewing the available literature, it is difficult to assess efficacy because of several factors, such as the variability in the quality of studies, the scarcity of direct comparisons between combination treatments and monotherapy, lack of control groups, or poor control for numerous factors including keloid size, skin type, previous treatments, and the body site of the keloid, among many other factors. Also, most studies did not use validated outcome measures such as the VSS or POSAS. Importantly, many studies did not reliably differentiate between hypertrophic scarring and keloids, for which natural history, prognosis, and treatment are vastly different. There is minimal evidence for which treatments work best based on the anatomic site. An exception is perhaps ear keloids, which have the most data supporting the use of combination treatments. It is possible that anatomic factors play a role in ear keloids, which appear to have lower recurrence rates across multiple types of maintenance therapies (i.e. compression and intralesional treatments). While IL-5FU and IL bleomycin look promising as both monotherapy and adjuvant treatment to prevent the recurrence of keloids, unlike ILK, there is a lack of long term (i.e. 5 year) follow up data in the literature for these treatments.

While this review is limited by its non-systematic nature, it does summarize available RCTs, systematic reviews, and meta-analyses to provide practical, up-to-date, and efficacious keloid treatment options. The most effective keloid management likely necessitates a multimodal approach. However, the optimal treatment plan will need to be individualized to patient specific factors, taking into account adherence, cost, their ability to tolerate procedures, and their expectations. **Figure 2** provides an approach to treating keloids based on the data summarized in this paper. In addition, **Figure 3** lists international guidelines that the interested clinician can reference.

Conclusions

Keloid treatments can be categorized into topical, intralesional, surgical, radiation, and laser options. Unfortunately, there is no single treatment approach one can apply that guarantees consistent results and no risk of recurrence. While ILK remains the most commonly used treatment by dermatologists, there are a wide array of other options we can offer our patients who are seeking symptomatic and cosmetic treatments for this disabling condition.

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Update on Chronic Hand Eczema

Sonja Molin, MD

Introduction

Hand eczema is an inflammatory skin disease that often has a chronic course. Chronic hand eczema (CHE) is defined as eczema on the hands with a disease duration of longer than three months or two or more relapses per year.[1] During the COVID-19 pandemic, hand eczema gained attention due to the increased risk of developing particularly irritant contact dermatitis in the context of a change in hand hygiene habits and frequency of hand washing.[2]

This has once more highlighted how important skin protection continues to be for prevention of the disease. Beyond this, new and updated guidelines are available,[1,3] and a multitude of high-quality studies on hand eczema prevalence, pathogenesis and treatment have furthered our understanding of the disease and its management.

This article aims to provide an overview on recent information about hand eczema with a focus on epidemiology, quality of life, and new treatment options.

Epidemiology

Two recent systematic reviews and meta-analyses provide updated estimates on the prevalence and incidence of hand eczema in the general population[4] and in healthcare workers.[5] Their results show that healthcare workers are at a higher risk of developing hand eczema, with pooled lifetime (33.4%), 1-year (27.4%) and point prevalence (13.5%) numbers higher than the results in the general population (14.5%, 9.1%, 4.0%, respectively).[4,5] In addition, the incidence rate of hand eczema was found to be higher in healthcare workers with 34 cases/1000 person-years compared to 7.3 cases/1000 person-years in the general population.[4,5]

Knowledge about hand eczema in children and adolescents is limited, although many adult patients describe onset of their disease early in life. Pediatric hand eczema is common, although reports about frequency of hand eczema in children vary (lifetime prevalence: 6.5%–13.3%; 1-year prevalence 5.2%–10.0%).[6] Allergic contact dermatitis is a contributing factor in the development of pediatric hand eczema with the most commonly reported allergens being nickel, methylisothiazolinone, and methylchloroisothiazolinone.[6]

Sources of exposure specific for the young age group include toys, slime, and bubble solutions.

A recent study from Denmark explored hand eczema among 15-19-year olds and found point-prevalence in this cohort to be 4.9%, with 1-year prevalence of 12.1% and lifetime prevalence of 18.3%.[7] A total of 60.2% of the adolescents were working either part-time or full-time and 38.2% of the participants with hand eczema believe that occupational exposures were contributing to their skin disease.[7] Silverberg *et al* described sixfold higher odds of developing hand

	Mechanism of action	Route of administration
Delgocitinib	Pan-JAK inhibitor	Topical
Ruxolitinib	JAK 1/2 inhibitor	Topical
Dupilumab	IL-4/IL-13 inhibitor	Subcutaneous injection
Tralokinumab	IL-13 inhibitor	Subcutaneous injection
Upadacitinib	JAK 1 inhibitor	Oral
Gusacitinib	JAK/spleen tyrosine kinase (SYK) inhibitor	Oral

Table 1. Selection of treatments studied for hand eczema (not exhaustive); *courtesy of Sonja Molin, MD.*

eczema in children and adolescents in the context of employment.[8] These results emphasize the need for early promotion of skin care and protection to prevent development of eczema in young workers.

Impact on Quality of Life

Quality of life is significantly impacted by hand eczema, which is a result of limited hand function, visible skin lesions and associated stigma, and negative consequences of not being able to fully participate in life or work.

Several recent studies analyzed quality of life impairment in people living with hand eczema as well as the presence of anxiety and depression.[9-11] A Finnish study confirmed a significant association of (self-reported) hand eczema and symptoms of anxiety and depression in a working age general population cohort.[10] A study from Poland measured the quality of life impairment in 100 hand eczema patients using the Dermatology Life Quality Index (DLQI) and found a mean value of 11.62, which translates into "very large effect on patient's life".[11] The severity of anxiety and depression in patients was linked to hand eczema severity.[11] A nationwide cross-sectional study from Denmark sent questionnaires about hand eczema to a random sample of 100,000 adults. In a group of 2,176 respondents with current hand eczema, they observed moderate impairment in several domains of the questionnaire that was used (Quality Of Life in Hand Eczema Questionnaire, [QOLHEQ]) including symptoms, treatment, and prevention. The authors report that severe, chronic and work-related eczema, as well as female sex were strongly associated with moderate-to-severe impairment of quality of life.[9] The most bothersome symptoms related to hand eczema are itch and pain. Zalewski *et al* studied the prevalence and characteristics of itch in hand eczema patients, itching was reported by 81.0% of the participants and pain in 53.0% during the three days before the examination.[12] They found both itching and pain more frequently among female participants, and both correlated positively with the severity of hand eczema.[12] Treatment approaches for hand eczema need to target these key symptoms and ideally provide fast relief.

New Treatment Options for Hand Eczema

Traditional treatment of hand eczema included topical moisturizing creams, topical steroids and systemic agents for severe cases. With new therapeutic targets emerging, and some of the advanced therapies for atopic dermatitis (AD) starting to cross over for use in hand eczema it is likely that our approach to the management of the disease will change significantly in the nearer future. Interleukin (IL)-4/IL-13 inhibitors and Janus kinase (JAK) inhibitors are two classes of drugs emerging for the treatment of CHE. The following paragraph highlights some of the newer data relevant for management of hand eczema without raising the claim of completeness. It will discuss delgocitinib, dupilumab and upadacitinib in more detail. More compounds are currently in clinical development for hand eczema and further results are to be expected (**Table 1**).

Topical treatment options for hand eczema are limited and topical corticosteroids (TCS) are still considered the gold standard for management of flares. Long-term use of TCS is limited by their safety profile.[13] A recent study from Denmark reported that in their cohort, 76.4% of hand eczema patients would prefer a nonsteroidal topical treatment.[14] Steroid fatigue is common in patients with chronic inflammatory skin diseases and these results emphasize the need for steroid-free treatment options to broaden the therapeutic armamentarium.

The topical pan-JAK inhibitor delgocitinib is currently being studied for hand eczema. Its Phase 3 clinical trial program has been completed and the regulatory approval process is underway in several countries. The role of JAK inhibitors in the development of hand eczema is not yet fully understood. They are relevant in immune cell signalling and activation of

keratinocytes and the skin's inflammatory response.[13] It was reported that topical delgocitinib application may contribute to improvement of skin barrier function by suppressing STAT3 activation and the subsequent increase in levels of barrier proteins like filaggrin.[15]

In a pooled data analysis from the Phase 3 trials with twice daily application of delgocitinib cream 20 mg/g compared to cream vehicle in adults with moderate to severe CHE, a greater proportion of delgocitinib-treated patients achieved treatment success (IGA [Investigator's global assessment] -CHE score of 0 or 1 with an improvement of at least 2 points from baseline) versus cream vehicle at week 16 (24.3% vs 8.4%; P<0.001). For the evaluation of these results, it is important to know that 'clear/almost clear' would only allow for no/barely perceptible erythema and no other signs of hand eczema.[16]

Adverse events leading to treatment discontinuation were reported in 0.5% of delgocitinib-treated patients compared to 3.4% in the cream vehicle group. The most frequent adverse events (≥ 2% in any treatment group) were COVID-19 infection (delgocitinib: 11.1%, vehicle cream: 10.6%) and nasopharyngitis (delgocitinib: 6.9%, vehicle cream: 7.5%).[16]

The reported serious adverse events (delgocitinib: 1.7%, vehicle cream: 1.9%) were all assessed as unrelated to the study drug. No adverse events of special interest (ie. eczema herpeticum, deep vein thrombosis, or pulmonary embolism) were observed, with no changes or differences of clinical relevance between treatment groups in laboratory parameters, vital signs, or electrocardiogram.[16] The pooled data analysis showed statistically significant improvement in health-related quality of life measured by DLQI and EQ5-D (EuroQol-5 Dimension) in patients treated with delgocitinib compared to cream vehicle.[17,18] A significant mean reduction in itch was detected 1 day after the first application of delgocitinib cream and for pain 3 days after the first application of delgocitinib cream.[19]

Moderate and severe hand eczema can be challenging to treat and might require systemic treatment. Recent data on systemic treatments used for AD like IL-4/IL-13 inhibitors and oral JAK inhibitors confirms their potential for use in patients with hand eczema. IL-4/IL-13 inhibition moderates the TH2 response to improve pruritic immune-mediated inflammatory skin diseases and has been shown to be effective in AD.[13] A recent Phase 3 multicentre trial studied dupilumab in adult and adolescent patients with atopic hand and foot dermatitis compared to placebo.[20] The mean duration of atopic hand/foot dermatitis in all participants (n=133) was 15.6 years. This underlines how long-lasting the course of the disease is for many patients. At Week 16, a significant number of patients reached the primary endpoint (HF [hand foot]-IGA 0/1) with dupilumab (40.3%) compared to placebo (16.7%).[20] The adverse events and safety profile were consistent with those of previous reports on the use of dupilumab in AD.[20]

Treatment of patients with atopic hand eczema with the selective JAK1 inhibitor upadacitinib at a daily dose of 15 mg or 30 mg compared to placebo was studied over 16 weeks in the context of two Phase 3 multicentre trials.[21] Efficacy was measured by change in the Hand Eczema Severity Index (HECSI). A 75% or greater HECSI improvement was observed in both dosing groups compared to placebo, with short timelines and maximum improvement already achieved after 4 weeks.[21] The adverse event and safety profile were consistent with those of previous reports on the use of upadacitinib in AD.[21]

Perspective

Chronic hand eczema continues to be a bothersome disease with significant impact on patients' quality of life and work productivity, and effective treatment options are needed to expand our therapeutic armamentarium. New treatments are emerging that will likely change our approach to the disease and allow the clinician to move away from the topical steroid-only approach.

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Similarities and Differences in Biosimilars: A Literature Review and Summary

Lauren Lam, MD, BScH, FRCPC

Introduction

The use of biosimilars is becoming standard practice for Canadian dermatologists. However, most of these clinicians most likely graduated prior to their adoption of biosimilars and, as a result, are likely to have minimal to no experience with biosimilars. Considering this limited prior experience, it can be challenging to gain a full understanding of how one biosimilar differentiates from another. The objective of this paper is to educate clinicians so that they are well-informed on how to select the appropriate biosimilar for the patient at hand. This literature review and summary will review the current biosimilar landscape in Canada; review nuances between adalimumab biosimilars; and review available clinical experience data of adalimumab switch to biosimilar and vice versa for the treatment of hidradenitis suppurativa (HS). It also aims to highlight methodologies for improving biosimilar patient compliance when switching to alternative agents.

Literature Review

With the objective of providing additional context for the decision-making process in selecting an adalimumab biosimilar, a literature review was conducted with a focus on use in HS, as this is the most likely condition for which Canadian dermatologists would initiate a bio-naïve patient on a biosimilar. Biosimilars for ustekinumab are now on the market in Canada; however, for the purposes of this article the focus was limited to adalimumab.

Dermatologists may not be aware that in clinical trials it is only necessary to demonstrate non-inferiority and safety in one licensed indication of the originator product (most often rheumatoid arthritis). This is noteworthy, as the presumption that a biosimilar works with equal statistical significance in other disease states has not actually been substantiated with clinical trial evidence. No biosimilar molecules have randomized clinical trials for HS. Therefore, unfortunately, there is no clinical trial data to review, nor comparator studies between biosimilars. The data available for biosimilars in the treatment of HS in general is sparse, thus two relevant publications from Europe were reviewed in detail.

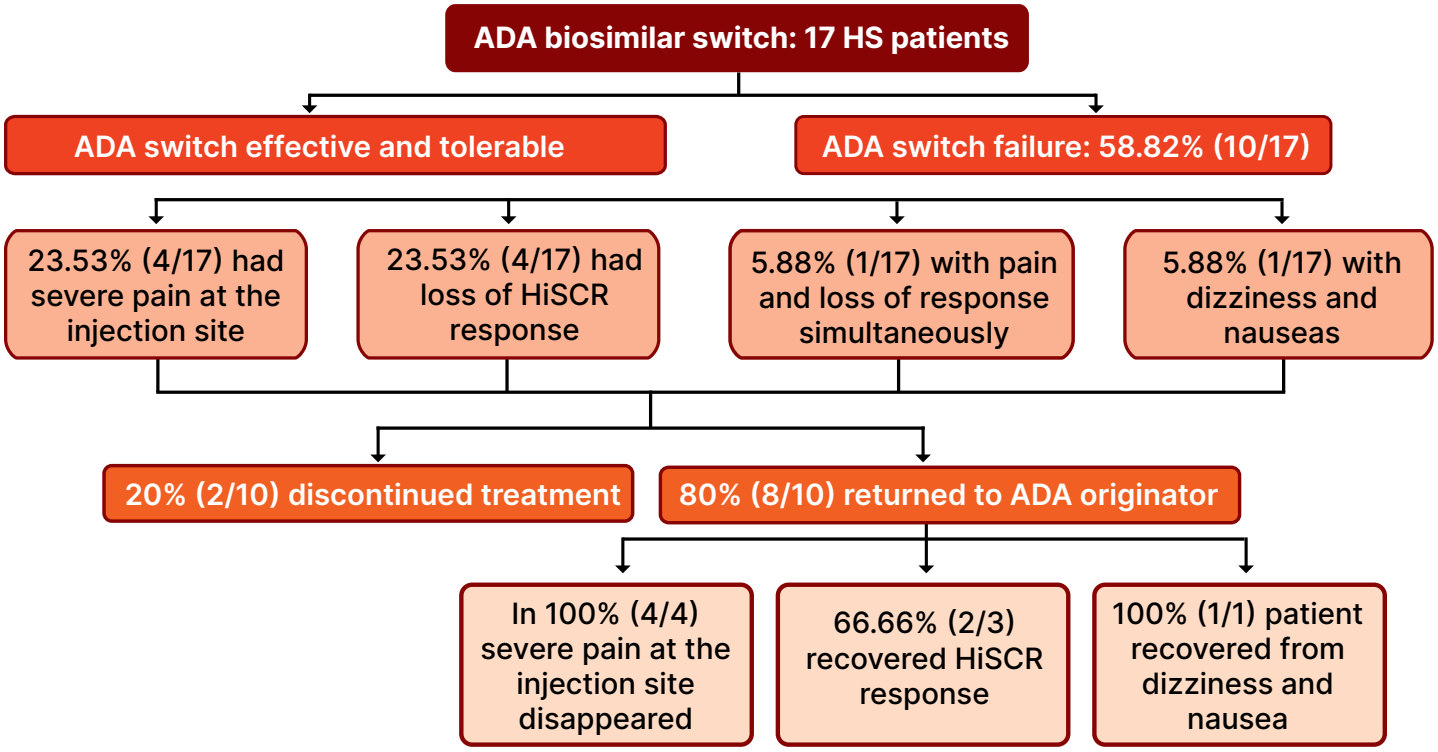

Figure 1. Patients switching flow chart; *adapted from Montero-Vilchez, T., et al, 2022.*

Abbreviations: ADA: Adalimumab, **HiSCR:** Hidradenitis Suppurativa Clinical Response, **HS:** Hidradenitis Suppurativa

Nuances in Biosimilars

Qualities of Biosimilars

It is important to highlight that biosimilars are similar to already licensed biotherapeutic products in quality, safety and efficacy. Heterogeneity of the production process and variations in manufacturing can potentially result in similar efficacy, non-inferiority, or even improved efficacy than that of the originator drug. By definition, biosimilars are required to perform similarly in quality, safety, and efficacy to an already licensed biotherapeutic product.

Biosimilars are Disease Specific

The literature contains clinical trial data substantiating the efficacy and tolerability of originator and biosimilar agents in the treatment of psoriasis. However, these results are not transferable between different biosimilars or diseases, therefore extrapolations regarding efficacy between biosimilar agents should be avoided. In addition, biosimilars may not perform equally in all diseases[1] and positive outcomes are not transferrable between disease states.

Scarcity of Switching data

Regulatory agencies typically do not require switching studies to approve a biosimilar; therefore, extensive clinical trial data on the effects of non-medical switching and switching between biosimilar agents is not available. However, two real-world studies examining biosimilar switches (**Figure 1**) provide some insight into clinical experiences, response rates and reasons for discontinuation. Clinical trial data shows that discontinuation rates post non-medical switching vary from 6.1% to 55.9%.

A large proportion of patients initiated on a biosimilar will likely be transitioned from the originator molecule for cost reasons (i.e., a non-medical switch).

Characteristics of Biosimilars

Differences in formulation, packaging and excipients are the most tangible variances between biosimilar agents. In selecting a biosimilar, it is important to consider its formulation; packaging (latex vs latex-free), and excipients (citrate vs citrate-free) (**Table 1**). In particular, excipients associated with injection site reaction can contribute to higher levels of discontinuation in patients undergoing a non-medical switch. As excipients, citrates and phosphates are well-known causes of injection site reaction. Other aspects of formulations that can cause increased injection site pain include non-physiologic pH, higher viscosity, and higher volume.[2]

	Amgevita	Abrilada	Hulio	Hadlima	Hyrimoz	Idacio	Simlandi	Yuflyma
Citrate Free	X							
Latex & Citrate Free		X	X				X	X
Latex Free				X				
Contains Citrate					X	X		

Table 1. Current Canadian landscape for adalimumab biosimilar agents; *courtesy of Lauren Lam, MD, BScH, FRCPC.*

Literature Review

Switching from Adalimumab Originator to a Biosimilar: Clinical Experience in Patients with HS

Study #1

The first study reviewed was a single-centre, retrospective cohort study conducted in Spain in 2022.[1] The study focused on clinical experience switching from the adalimumab originator molecule to a biosimilar and, in some cases, switching back again to the originator molecule.

The study comprised 17 HS patients (age 18+) on originator adalimumab who were switched to a biosimilar for non-medical reasons. The patients had all achieved HiSCR after >12 weeks on the originator molecule. No repeat induction dose was administered upon switching to the biosimilar agent. The population was quite reflective of a typical HS practice, with younger patients (mean age 31) who had tried multiple treatments prior to adalimumab, and the majority of patients were Hurley Stage II (23%) or III (70%).

Study #1 Design

- Evaluated q12w post-switch
- Switch-back offered if efficacy or tolerability issues
- Continued evaluation q12w post-switch back
- Only 1 female patient received additional treatment:
  - Metformin 850 mg OD
  - Spironolactone 50 mg OD

Patients were offered the option of switching back to the originator molecule if issues with efficacy or tolerability arose. If a switchback was made, the patient continued to be monitored q12w after this second switch.

All but one patient was receiving adalimumab monotherapy. The single patient receiving combination therapy was also on metformin 850 mg QD, and spironolactone 50 mg QD.

Study #1 Results

- The majority of patients (10/17) experienced a switch failure.
- Of those 10 patients, an equal proportion of patients (4/10) experienced either severe pain at the injection site or loss of HS clinical response (HiSCR).
- One patient experienced both. Unfortunately, 2 of those who had a switch failure completely discontinued biologic treatment altogether.
- Of the remaining patients who returned to the originator molecule, injection site pain resolved in each case.
- Two of three patients recovered HiSCR response.

Study #2

Seven Years-Experience of Adalimumab Therapy for HS in a Real-life Dermatologic Setting

The second study was a single-centre, retrospective review conducted in Italy in 2020.[3] Its focus was clinical experience switching from the adalimumab originator to a biosimilar agent, in addition to initiating bio-naïve patients on a biosimilar agent.

The study comprised 10 patients. Of these, 4 patients were switched for non-medical reasons, while 6 bio-naïve patients were initiated on a biosimilar agent. Two of the four patients switched from the adalimumab originator to a biosimilar agent were switched back to the originator agent due to injection site reaction.

Variables	Total Sample (*n* = 17)	Switch Effective and Tolerable (*n* = 7)	Switch Failure (*n* = 10)	*P*
Age (years)	31 (19–51)	43 (17–50)	26.5 (19–53.5)	0.675
Sex				
Male	12 (70.59%)	5 (71.43%)	7 (70%)	1
Female	5 (29.41%)	2 (28.57%)	3 (30%)	
Smoking habit (yes)	8 (47.06%)	2 (28.57%)	6 (60%)	0.335
Age of onset (years)	15 (15–22.5)	16 (15–33)	15 (14.25–18)	0.085
Family history (yes)	8 (47.06%)	4 (57.14%)	4 (40%)	0.637
Hurley stage				
I	1 (5.88%)	1 (14.29%)	0	0.394
II	4 (23.53%)	1 (14.29%)	3 (30%)	
III	12 (70.59%)	5 (71.43%)	7 (70%)	
AN count	2 (0.5–6.5)	2 (0–9)	3 (0.75–5.75)	0.588
Draining tunnels count	3 (2–4.5)	3 (1–9)	2.5 (2–3.25)	0.129
Number of affected areas	4(3–4)	4(2–4)	4 (3.75–4.25)	0.473
Number of previous treatments	4 (2.5–4.5)	4(3–5)	4 (2–4.25)	0.429
Follow-up time before switching (weeks)	48 (28–80)	32 (20–80)	48 (43–87)	0.167

Table 2. Sociodemographic and clinical characteristics of the patients; *adapted from Odirici, G. et al, 2023.*

Abbreviations: AN: total abscess and inflammatory nodule count

Data are expressed as relative (absolute) frequencies and median (interquartile range). Student's *t*-test for independent samples or the Wilcoxon test were used to compare continuous variables, depending on the normality of the variable. The chi-square test or Fisher's exact test, as appropriate, were applied to compare categorical data. A two-tailed $p < 0.05$ was considered statistically significant for all tests.

Study #2 Design

- Single-centre, retrospective review in Italy in 2020
- Clinical experience switching from adalimumab originator to biosimilar and initiating bionaive patients on biosimilar

Study #2 Results

- 4 patients switched from the adalimumab originator to a biosimilar agent for non-medical reasons
- 6 patients were initiated on a biosimilar
- 2 patients who switched to a biosimilar switched back to originator product due to *injection site reaction*

No patient characteristics were statistically significant to predict the likelihood of biosimilar failure or success (**Table 2**).

Study Summaries

Both studies highlight two important considerations when switching patients to a biosimilar. First, injection site pain is the most likely cause of discontinuation of biosimilar treatment, sometimes leading to discontinuation of all biologic treatment as a result. This would ultimately be to the patient's detriment, as without systemic treatment, further progression of the disease will occur. Therefore, choosing an agent with the fewest excipients that may cause pain could potentially help avoid this.

Second, ensuring that injection site pain protocols have been adhered to is critical in reducing the likelihood of intolerable injection site pain reaction (**Box 1**).

Conclusion

Biosimilars are exactly that – similar, but not equivalent to the originator, and not equivalent to one another. Biosimilar agents have safety and non-inferiority data, but not necessarily for every disease, unlike their originator molecule.

Two key considerations when comparing biosimilar agents are their excipients and packaging. As the most common cause for discontinuation of biosimilar agents is injection site pain, consider a biosimilar agent's excipients and, where possible, select the agent with the lowest excipient load to help reduce the likelihood of injection site pain.

Unfortunately, to date there are no clinical studies demonstrating statistically significant patient characteristics that help predict a higher likelihood of achieving HiSCR with biosimilars.

As Canadian practitioners continue to gain experience with biosimilar agents, perhaps further studies could explore these important clinical concerns.

- Apply a topical anesthetic or ice 30 minutes prior to injection
- Apply a topical steroid 2–3 days to anticipated site prior to injection
- Inject at 45 or 90 degrees
- Inject slowly
- Use an auto-injector, which can reduce patient-related injection techniques that are inadvertently causing increased pain
- Allow medication to warm up to room temperature for 30–45 minutes prior to injection
- Inject abdomen rather than thigh
- Alternate injection sites
- Advise patients to take antihistamine or NSAID/acetaminophen 1 hour prior to injection

Box 1. Injection Protocols and Patient Counselling; *courtesy of Lauren Lam, Md, BScH, FRCPC.*

Key Clinical Pearls
Biosimilar but not equivalent
• Biosimilars have safety and non-inferiority data, but *not necessarily for every disease indication* as with the originator
Not all biosimilars are the same
• Each biosimilar contains its own unique excipients and packaging. *Consider this during switching, if injection site pain becomes a concern*
Pain equates to reduced patient compliance
• Pain is the primary cause for patients discontinuing a biosimilar
Lack of predictability
• No particular factors have been established to predict achieving HiSCR with biosimilar use

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