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EDITORS WELCOME

Dear Canadian Dermatology Community,

We hope this current issue of Canadian Dermatology Today finds you, your loved ones and your patients all well during these difficult times.

As you may recall from our inaugural issue, this peer-to-peer initiative, written by Canadian clinicians for the Canadian dermatology community is meant to serve as an educational and informational resource with the goal of elucidating important and germane topics in the management of dermatological disease. With this said, our current issue highlights some fascinating topics from our authors including the diagnosis and management of granuloma annulare, the management of hidradenitis suppurativa in special populations and safe deoxycholic acid injection technique for submental fat reduction, to name a few.

We hope you find these articles illuminating and we thank you for your continued readership. Please let us know how we are doing by suggesting topics and feel free to share our registration link at canadiandermatologytoday.com with your peers so that, they too, can subscribe to future issues!

Best wishes,

Kim Papp, MD Jensen Yeung, MD Melinda Gooderham, MD Chih-ho Hong, MD



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ABOUT THE AUTHOR



Raed Alhusayen, MBBS, MSc, FRCPC

Dr. Alhusayen is Assistant Professor, Division of Dermatology, University of Toronto, Associate Scientist, Evaluative Clinical Sciences, Odette Cancer Research Program and Staff Physician, Division of Dermatology, Sunnybrook Health Sciences Centre. Dr. Alhusayen earned a Bachelor of Medicine, Bachelor of Surgery degree at the College of Medicine, King Saud University, Riyadh, Saudi Arabia. He then completed a residency in dermatology and a clinical fellowship in laser dermatology at the University of Ottawa. Dr. Alhusayen received a Master of Sciences degree in clinical epidemiology from the University of Toronto, where he also completed a clinical and research fellowship in advanced medical dermatology. As a dermatoepidemiologist, Dr. Alhusayen's areas of research interest include exploring prognostic indicators and measuring clinical outcomes, studying the risk of malignancy in patients with autoimmune skin disorders and assessing systemic comorbidities with skin diseases. Hidradenitis suppurativa is the main focus of Dr. Alhusayen's complex medical dermatology practice. He is the supervisor for clinical research in the advanced medical dermatology fellowship program. He is also the current president of the Canadian HS foundation.

MANAGEMENT OF HIDRADENITIS SUPPURATIVA IN SPECIAL PATIENT POPULATIONS

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease with an early age of onset. Medical therapies with anti-inflammatory properties are the mainstay of treatment. Tetracyclines, rifampicin plus clindamycin, and adalimumab are standard therapeutic approaches.[1] However, either due to lack of response or contraindications, many other medications are required in the management of the disease (Figures 1 and 2).[2,3]

This is especially true as HS patients are at higher risk for a growing list of comorbidities including metabolic syndrome, inflammatory bowel disease, malignancy, depression, pyoderma gangrenosum, and psoriasis.[4] Also, certain stages in life such as childhood and pregnancy can restrict treatment options. When appropriate, adjunct surgical interventions should be considered early to support the limited medical therapeutic options. In this article, we will discuss the management of HS in special patient populations (Table 1).

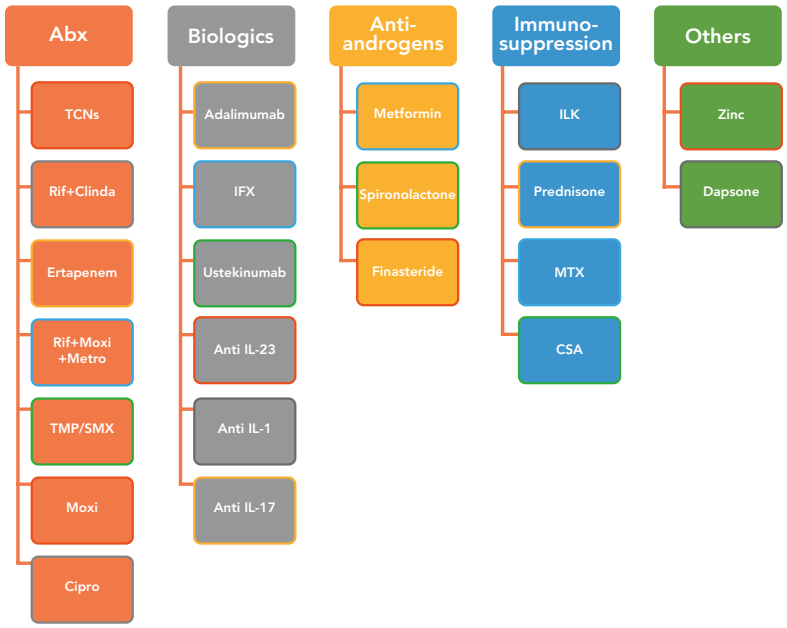


Figure 1. Treatment options for HS in special patient populations; table courtesy of Dr Raed Alhusayen

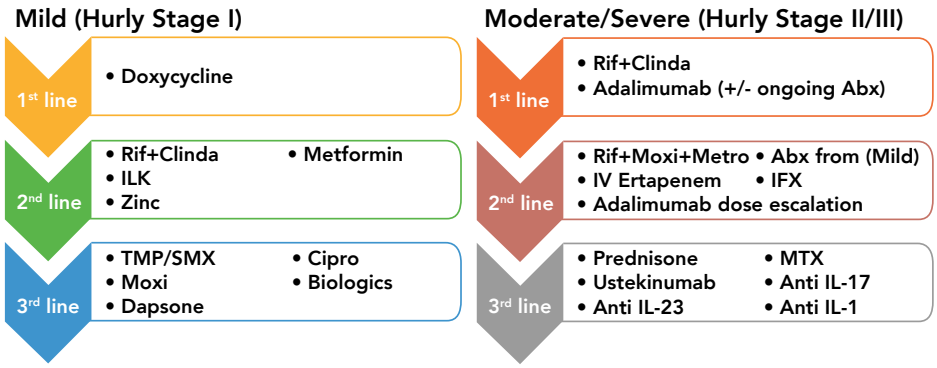


Figure 2. Stepwise approach for the management of HS; chart courtesy of Dr Raed Alhusayen

	POTENTIALLY GOOD OPTIONS	AVOID/CAUTION
PREGNANCY	ANTI-TNFS	TETRACYCLINES RIFAMPIN
INFLAMMATORY BOWEL DISEASE	METRONIDAZOLE CIPROFLOXACIN ANTI-TNFS ANTI IL-12/23	TETRACYCLINES CLINDAMYCIN ANTI IL-17
INFLAMMATORY ARTHROPATHIES	TETRACYCLINES ANTI-TNFS ANAKINRA SYSTEMIC STEROIDS	LEFLUNOMIDE
ADOLESCENCE	RIFAMPIN+CLINDAMYCIN CEPHALEXIN ANTIANDROGENS (METFORMIN, SPIRONOLACTONE, FINASTERIDE) ADALIMUMAB	TETRACYCLINES (UNDER THE AGE OF 8) SYSTEMIC STEROIDS
MALIGNANCY	TETRACYCLINES RIFAMPIN+CLINDAMYCIN SULFAMETHOXAZOLE/TRIMETHOPRIM ERTAPENEM	BIOLOGICS
PSORIASIS	ANTI-TNFS ANTI IL-12/23 ANTI IL-17 ANTI IL-23 CYCLOSPORINE	SYSTEMIC STEROIDS
PYODERMA GANGRENOSUM	DAPSONE MINOCYCLINE ANTI-TNFS ANTI IL-12/23 CYCLOSPORINE SYSTEMIC STEROIDS	

Table 1. Treatment options for HS in special patient populations; table courtesy of Dr Raed Alhusayen

Pregnancy

Only 20% of HS patients report symptom remission during pregnancy, with the majority (72%) reporting ongoing active disease and 8% experiencing worsening of symptoms.[5] Many HS patients prefer not to take any medications during pregnancy. This is a reasonable option if someone has mild stable disease. In these cases, intralesional triamcinolone injections can be used for localized flares. In more severe disease, systemic therapy is almost always required. Tetracyclines should be avoided during pregnancy due to the risk of impaired bone growth and staining of the teeth.[6–8] Antibiotics with a good safety profile in pregnancy include cephalexin, clindamycin, amoxicillin/clavulanate, and metronidazole.[9–14] Rifampin, although a category C drug, is routinely used in the treatment of tuberculosis during pregnancy but caution is required for use in HS as safer alternatives are available.[15,16] There are also case reports of using rifampin for the management of cholestatic pruritus in pregnancy.[17,18]

There is a growing body of evidence around the safety of anti-TNF biologics during pregnancy.[19–21] The majority of these drugs cross the placenta in the third trimester and patients should be counselled about the implications to the newborn baby.[21,22] The Centers for Disease Control and Prevention (CDC) recommends postponing live vaccines until the newborn is 6 months old if exposed to TNF-alpha inhibitors in the third trimester of pregnancy.[21] The decision to either avoid, discontinue use in the third trimester, or continue anti-TNF therapy throughout pregnancy should be personalized to each patient's needs and preferences.

Anecdotally, the author has successfully used certolizumab,[23] an anti-TNF drug with a minimal placental transfer, to manage HS during pregnancy—although this use is off-label.

Inflammatory Bowel Disease

In a recent systematic review and meta-analysis which included 5 case-control studies, 2 cross-sectional studies, and 1 cohort study with a total of 93 601 unique participants, patients with hidradenitis suppurativa were found to have had a 2.12-fold increased odds for Crohn's disease (95% CI, 1.46-3.08) and a 1.51-fold increased odds for ulcerative colitis (95% CI, 1.25-1.82).[24]

Patients with concurrent diagnoses pose an unique therapeutic challenge. Tetracyclines and clindamycin, commonly used in the management of HS, are usually avoided in this patient population. Tetracyclines have been linked with increased risk of developing inflammatory bowel disease (IBD), while clindamycin is a major risk factor for C. difficile infection which is a special concern in the IBD population.[25,26] Good antibiotic options would be ciprofloxacin and metronidazole which are standard therapies for perianal IBD-related abscesses.[27]

Furthermore, a randomized controlled trial (RCT) found adalimumab plus ciprofloxacin (71% response rate) superior to adalimumab monotherapy (47%) in treating perianal fistulating Crohn's disease (p=0.047) from baseline to week 12 with no difference in safety issues observed between the two groups.[28]

Adalimumab is approved for HS and IBD. Both infliximab and ustekinumab are approved in IBD and were shown to be effective in the management of HS.[29–34] Also, there is anecdotal evidence that guselkumab may be effective in the management of HS and IBD.[35–37] Low dose systemic steroids can be used as monotherapy or in combination with anti-TNF biologics.[38,39] Methotrexate can also be added to anti-TNF biologics to prevent the formation of anti-drug antibodies.[40–42] Anti- IL-17 biologics should be avoided in this population due to the potential risk of IBD flare.[43–45]

Inflammatory arthropathies

In a retrospective case-control study, the unadjusted analysis showed that all comorbidities were diagnosed significantly more in the HS population as compared to the control population, including up to 52% of HS patients who have arthropathies (P<0.01).[46] There is a lack of awareness among clinicians about this association which could result in a delay in diagnosis and permanent joint damage. Seronegative spondyloarthritis is more common than rheumatoid arthritis in this group.[47–49]

Most HS treatments are safe to use in patients with inflammatory arthritis. Tetracyclines are effective in the management of mild rheumatoid arthritis making them a good first-line therapy in this patient population.[50] It is not clear if sulfasalazine, a standard treatment for inflammatory arthropathies, can be helpful in HS as it targets neutrophils which are major infiltrates in HS lesions.[51–53] A recent report described 2 patients who developed HS while on leflunomide for rheumatoid arthritis who improved a few weeks after discontinuation of the medication.[54]

Adalimumab and infliximab, but not etanercept, are good options in this patient group.[29,55–58] Also, in a small RCT (N=20), patients with Hurley stage II or III HS were randomized to received either anakinra, an anti IL-1ß antibody, or placebo. Results demonstrated that 78% of patients, in the anakinra arm, with moderate-to-severe HS achieved a Hidradenitis Suppurativa Clinical Response 50 (HiSCR 50) by week 12 (P=0.04).[59] The data on the efficacy of canakinumab, another anti IL-1ß antibody, is not conclusive with conflicting findings from case reports.[60–63] Systemic steroids may also help both conditions.[38,64]

Pediatric HS

Approximately 7% of HS patients have disease onset by age 12.[65] Patients with early-onset are more likely to have a family history of the disease.[65–67] As previously stated, tetracyclines are avoided in children under the age of 8 due to the impact on bone growth and teeth discoloration.[6,68] Rifampin and clindamycin combination may be used in this population.[66,67,69] Also, other antibiotics such as cephalexin and amoxicillin/clavulanic acid are alternative options. It has been suggested that hormonal abnormalities are more common in the pediatric HS population.[66,67] Hence, antiandrogen therapies including metformin, spironolactone, and finasteride may be especially helpful.[70–74]

Adalimumab is approved for use in adolescents 12 years or older in weight-based dosing. Children weighing 30 kg to less than 60 kg receive 80 mg at week 0 then 40 mg every other week starting at week 1. Children weighing 60 kg or more receive adult dosing.[75] There is real-world data using biologics off-label in pediatric populations for other inflammatory conditions and these same biologic agents may be used in recalcitrant HS cases as well. These include infliximab and ustekinumab.[76,77] Systemic steroids, although effective, should be avoided in the pediatric population due to the risk of

growth retardation.[78]

Malignancy

In general, biologic therapies are not recommended to be used in patients with active cancer due to risks of immunosuppression and cancer progression.[79,80] In patients with a past medical history of cancer, initiating biologic therapy depends on cancer type, time since remission, and HS severity.[79,80] The decision should be made, preferably in consultation with the treating oncologist, after weighing benefits and risks. Commonly prescribed antibiotics for the management of HS can be used in cancer patients with minimal concern. While the use of antibiotics immediately before initiating checkpoint inhibitor immunotherapy was associated with significantly shorter survival (2 vs 26 months for prior antibiotic therapy vs no prior antibiotic therapy, respectively; hazard ratio [HR], 7.4; 95% CI, 4.2-12.9) in a study involving 196 patients with a median age of 68 years and with non-small cell lung cancer (n = 119), melanoma (n = 38), and other tumor types (n = 39), there were no negative implications when antibiotics were prescribed concurrently with these agents.[81] In some cases, we can build on existing antibiotic therapy to achieve control of HS lesions. In a leukemia patient who underwent a stem-cell transplant and was placed on long-term sulfamethoxazole/trimethoprim prophylaxis, HS lesions developed after the dose of antibiotics was reduced to 3 times weekly. We were able to control the HS flare by restarting the daily dosing. In the most severe cases, a course of IV ertapenem is a reasonable choice.[82] Also, low dose prednisone is an option in severe recalcitrant cases.[38]

Psoriasis

Approximately 9% of HS patients have psoriasis.[47] For the most part, this creates an opportunity for HS patients to access medications approved for psoriasis that can also be effective in HS. Adalimumab is approved for both HS and psoriasis but the dosing in HS is double that for psoriasis.[55,83] While etanercept wasn't found to be effective in HS, infliximab can be helpful especially at higher doses and/or frequency.[56,84,85] Also, there are case series and phase II studies with positive results using ustekinumab, secukinumab, and guselkumab.[33–35,86] For moderate HS, 53% of patients taking apremilast achieved HiSCR50 in a small randomized controlled study.[87]

Cyclosporine is effective for both psoriasis and HS.[2,3] Patients should be closely monitored as HS patients are at higher risk for metabolic syndrome which may manifest itself through hypertension and dyslipidemia.[4] Antibiotics used to treat HS are generally safe to use in patients with psoriasis but they have no benefit in the latter condition. Similarly, systemic retinoids and methotrexate have a limited role in managing HS.[88] Finally, systemic steroids should be used with caution, if ever, due to the risk of psoriasis rebound upon medication withdrawal.[89]

Pyoderma gangrenosum

The rate of pyoderma gangrenosum among HS patients is not clear but appears to be higher than the general population.[90,91] Also, the 2 conditions could coexist as part of inflammatory syndromes such as PASH (PG, acne and suppurative hidradenitis) or PAPASH (pyogenic arthritis, acne, PG and suppurative hidradenitis).[92]

Dapsone, an antineutrophilic agent, is a good option for both HS and PG.[88,93–97] It can be used as monotherapy in mild cases or in combination for more severe cases. Similarly, there are several reports of successfully controlling PG using minocycline.[98–101] Systemic steroids and cyclosporine also are effective treatments.[1,93,102–105] Among biologics, adalimumab, infliximab, and ustekinumab have data to support their use for both conditions.[29,34,55,106–110] Finally, it is not clear if anakinra is effective in PG.[111,112]

Conclusion

HS is associated with many comorbidities which provides challenges as well as opportunities in managing these patients. If possible, the preference is to choose treatment modalities that address all existing comorbidities. When that is not possible, treating physicians should ensure the selected treatments don't negatively impact any of these comorbidities.

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ABOUT THE AUTHOR

Fiona Lovegrove, MD



Dr. Fiona Lovegrove is a dermatologist based in London, Ontario where she runs an independent general dermatology practice. She has a special interest in medical and immuno-dermatology. Fiona is a graduate of the University of Toronto's combined MD/PhD program, obtaining her PhD in infectious disease research in 2008 and her MD in 2010. She remained at the University of Toronto for her dermatology residency, which she completed in June 2016. In her spare time, she enjoys cycling the riverside trails, sipping local craft beer and creating or consuming exciting food.

ADOPTING AN ORPHAN DISEASE: MANAGING SARCOIDOSIS IN THE ERA OF BIOLOGIC MEDICATIONS

Introduction

Sarcoidosis is a granulomatous immune-mediated inflammatory disorder. It remains a challenging disease to diagnose and treat because it has multiple cutaneous presentations, it can affect any organ system, and it is a diagnosis that can only be made when other granulomatous conditions, including infections, have been ruled out. However, making a diagnosis of sarcoidosis and providing effective treatment can be life-saving.

An increased understanding of this complex condition has led to new treatment options, including the innovative off-label application of biologic medications and small-molecule inhibitors (SMIs). This article will review key clinical aspects of cutaneous sarcoidosis, provide a quick refresher on necessary investigations for the busy dermatologist, and review the evidence for use of biologic medications and SMIs in the treatment of cutaneous sarcoidosis.

Etiology and pathophysiology:

Sarcoidosis is hypothesized to occur when an environmental exposure triggers an exuberant pro-inflammatory response in a genetically predisposed individual. Th1 cytokines are upregulated, Th2 cytokines are downregulated and regulatory T-cells are decreased, leading to granuloma formation and a persistently dysregulated inflammatory response[1]. Tumour Necrosis Factor alpha (TNF-α) is a Th1 cytokine that has been identified as pivotal in the development and maintenance of infectious granulomas[2]. In sarcoidosis,

TNF-α is a critical mediator of the inflammatory response, along with Interferon-gamma and the intracellular signal transducers and activators of transcription (STAT)1 [3–5]. An enhanced knowledge of what drives sarcoidal granuloma formation provides molecular targets for diagnostic purposes, monitoring disease progression, and ultimately, for treatment.

Clinical Variants:
Cutaneous sarcoidosis is notorious for its variety of morphologic presentations; hence it has been called a "great imitator". The classic presentation of sarcoidosis on the skin is red-brown papules or plaques with an "apple jelly" appearance on diascopy (Figure 1). But other common presentations include lupus pernio, subcutaneous or "Darier-Roussy" nodules, tattoo and scar sarcoidosis[6]. Recall, that although uncommon, cutaneous sarcoidosis can also display psoriasiform, annular, hypopigmented, or ulcerative morphology.

Work-up:
Certain clinical variants, such as lupus pernio and subcutaneous nodular sarcoidosis, are typically associated with systemic sarcoidosis[6], but a diagnosis of cutaneous sarcoidosis warrant a complete systemic work-up[7]. The goal of bloodwork is to evaluate systemic involvement, to anticipate management and for disease monitoring. Investigations should include CBC, liver function, renal function, thyroid stimulating hormone (TSH), calcium and vitamin D levels, and urinalysis[7]. Angiotensin-converting enzyme (ACE) which is produced by macrophages and other constituents of the granuloma, was originally thought to be positively correlated with a diagnosis of



Figure 1. A case of cutaneous sarcoidosis in a young man.

sarcoidosis[8], however, recent data suggest it has low sensitivity and specificity as a diagnostic marker[9]. In a high-volume practice, I rely on my electronic medical records – using macros and pre-populated bloodwork requisitions – to streamline this. Additionally, I ask the patient's primary care provider to organize an electrocardiogram (ECG), echocardiogram, chest X-ray, pulmonary function tests, and ophthalmic exam for the patient locally. Finally, since sarcoidosis is truly a multi-system disease, referrals to, and coordinated management with, multiple specialties is often required.

Approach to Treatment:
Treatment of cutaneous sarcoidosis follows a similar treatment ladder to other inflammatory skin diseases – topical therapies, intralesional injections, classic oral systemic treatments, biologics, and SMIs. Systemic treatment is usually considered when patients have failed topical and intralesional treatments or when their cutaneous disease is widespread or disfiguring[6]. Further, treatment is warranted if patients have certain systemic manifestations of sarcoidosis such as hypercalcemia, progressive pulmonary involvement, symptomatic cardiac involvement, ocular disease, or central nervous system involvement.

Classic systemic treatments:
Oral corticosteroids have been used to effectively treat sarcoidosis since the 1950's with early studies showing objective and subjective improvement to varying degrees in all patients treated (N=13)[10]. However, treatment of chronic disease with corticosteroids in the long-term can result in significant morbidity, and therefore having effective steroid-sparing treatment options is very important. In a small study of cutaneous sarcoidosis, 93% of patients showed subjective improvement and 86% showed objective improvement (N=14)[11]. Methotrexate appears to reach a maximal effect for cutaneous sarcoidosis at 6 months of treatment[12]. Numerous studies have examined antimalarial drugs, including chloroquine[13,14] and hydroxychloroquine[15], in the treatment of sarcoidosis. Hydroxychloroquine is effective for cutaneous sarcoidosis but not for pulmonary involvement as demonstrated in a cohort of 17 patients diagnosed with cutaneous sarcoidal granulomas and treated with hydroxychloroquine (2 to 3 mg/kg/day) in an open clinical trial[15]. Tetracycline antibiotics, including minocycline[16,17] and doxycycline[18], may also be effective in the treatment of cutaneous sarcoidosis. A prospective study showed improvement in 83% of patients (N=12) treated with minocycline at 200 mg/d, for a median duration of 12 months[17] and a retrospective study showed improvement in 74% of patients (N=27)[16] treated with minocycline with 6 (22%) having

complete remission;[14] (52%) having partial remission; and 7 (26%) having had no remission. Other agents, including allopurinol[19,20], leflunomide[21], mycophenolate mofetil[22,23], pentoxifylline[24], and thalidomide[25–29], have varying levels of evidence to support their use in sarcoidosis.

Novel systemic treatments – Biologic agents:

Since TNF-α is thought to be a key upstream mediator of granuloma formation, it follows that inhibition of TNF-α should be an effective therapeutic target for sarcoidosis[5,30]. Infliximab has the most data supporting its use in sarcoidosis with randomized control trials showing benefit in pulmonary[31,32], extrapulmonary[33] and cutaneous disease[34]. Infliximab treatment of twelve patients versus placebo showed a significant change between baseline and week 24 in desquamation ($p<0.005$) and induration ($p<0.01$) of cutaneous sarcoidosis, but no difference in erythema or area of involvement[34].

The data for adalimumab also support its use in pulmonary[35] and cutaneous sarcoidosis[36]. A randomized placebo-controlled trial of 12 weeks, followed by open-label treatment for an additional 12 weeks, followed by 8 weeks of no treatment, showed improvement in several measures of cutaneous disease, including dermatology life quality index (DLQI) ($P = .0034$), in the adalimumab treatment arm (N=10) compared to placebo (N=6) at 24 weeks; with some loss of response after 8 weeks of treatment withdrawl[36].

Lastly, golimumab may be another treatment option for cutaneous sarcoidosis in the TNF-α inhibitor class, with a trend towards improvement in the physician global assessment (PGA) score at 28-weeks compared to placebo with a nonsignificant numerically greater Skin Physician Global Assessment response observed following golimumab treatment (53%) when compared with the placebo group (30%)[37]. The same study found no significant differences in pulmonary sarcoidosis outcome with golimumab treatment and found no significant differences in pulmonary or cutaneous sarcoidosis outcomes with ustekinumab[37].

Etanercept does not have the same efficacy as other TNF-α antagonists in treating sarcoidosis. While case reports have shown improvement of cutaneous sarcoidosis with etanercept treatment[38,39], overall, the evidence is mixed and etanercept treatment of other diseases has been seen to paradoxically induce sarcoidosis[5].

The other biologic agent which has been proposed as treatment of sarcoidosis is rituximab. Again, the evidence is mixed, with limited benefit seen in a prospective early-phase trial in ten patients with refractory pulmonary sarcoidosis[40].

Novel systemic treatments – Small Molecule Inhibitors:

Small molecule inhibitors are oral medications that inhibit an intracellular signaling process and regulate downstream gene expression. There has been enormous interest in this therapeutic area for inflammatory diseases with a recent surge in drug development, especially in the janus kinase (JAK) inhibitor class of medications.

Janus kinase inhibitors modulate the JAK/STAT signaling pathway, inhibiting STAT phosphorylation thereby regulating downstream pro-inflammatory cytokine production. Tofacitinib (a JAK 1/3 inhibitor approved for use in adult patients diagnosed with rheumatoid arthritis, psoriatic arthritis or ulcerative colitis) has been used to effectively treat a case of recalcitrant multiorgan sarcoidosis[41] and three cases of recalcitrant cutaneous sarcoidosis[42]. Use of ruxolitinib (a JAK 1/2 inhibitor), for on-label treatment of polycythemia vera rubra, demonstrated resolution of concomitant cutaneous sarcoidosis in a single case report[43]. Mechanistically, this makes sense since STAT1 appears to be a key mediator in the sarcoidosis pathway and therefore JAK inhibition warrants further investigation for sarcoidosis treatment.

As mentioned above, pentoxifylline, which is a phosphodiesterase (PDE) inhibitor and has weak anti-TNF-α activity, has been shown to be an effective treatment for sarcoidosis. Apremilast (a PDE4 inhibitor approved for use in moderate-to-severe psoriasis and psoriatic arthritis) has been examined as a treatment for cutaneous

DRUG CLASS	THERAPEUTIC AGENT
ORAL CORTICOSTEROIDS	VARIED
DMARD/IMMUNOMODULATORY AGENTS	METHOTREXATE; LEFLUNOMIDE; THALIDOMIDE
ANTI-MALARIAL	CHLOROQUINE; HYDROXYCHLOROQUINE
TETRACYCLINE ANTIBIOTICS	MINOCYCLINE; DOXYCYCLINE
XANTHINE OXIDASE INHIBITOR	ALLOPURINOL
IMMUNOSUPPRESSIVE AGENT	MYCOPHENOLATE MOFETIL
TNFα INHIBITOR	GOLIMUMAB; INFLIXIMAB; ADALIMUMAB
JANUS KINASE INHIBITORS	TOFACITINIB; RUXOLITINIB
PHOSPHODIESTERASE INHIBITOR	APREMILAST; PENTOXIFYLLINE

Table 1. Potential treatment options for sarcoidosis

sarcoidosis. Fifteen patients were treated with Apremilast 20 mg PO bid for 12 weeks and showed a significant improvement in induration of the index lesion compared to baseline ($p<0.02$); however no improvement was noted in erythema, desquamation or area of involvement[44].

Discussion and Conclusion

Cutaneous disease is one of the most common findings of sarcoidosis, and therefore dermatologists are often charged with making the diagnosis, directing systemic work-up and initiating treatment of this immune-mediated inflammatory disease. With many dermatologic diseases being relatively rare, with our comfort level understanding the immunology behind more common dermatologic conditions, and with so many of our treatments being "off-label", dermatologists are uniquely positioned to leverage immunological principles and novel therapies in the treatment of sarcoidosis.

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ABOUT THE AUTHOR



Matthew Karpman MD, FRCPC

Dr. Matthew Karpman is a board-certified dermatologist in his hometown of Edmonton. He completed his medical degree at the University of Calgary before pursuing his residency at the University of British Columbia. He is currently affiliated with the Division of Dermatology at the University of Alberta and is an advocate for the medical profession on many fronts.

TREATMENT OPTIONS FOR GRANULOMA ANNULARE

The few paragraphs devoted to granuloma annulare (GA) in classic dermatology textbooks do not provide justice to the volume of patients seen with this condition in clinical practice. The epidemiology of GA is such that it affects patients of all ages. Most cases of localized granuloma annulare are diagnosed in patients before 30 years of age. Incidence is highest in women, with a ratio of 2.3 to 1.0 over men[1]. Approximately 15 percent of all patients with granuloma annulare will have more than 10 lesions (i.e. disseminated granuloma annulare). These patients are usually children younger than 10 years or adults older than 40 years. Although uncommon, cases of granuloma annulare occurring in siblings, twins, and successive generations have been reported[2]. Seasonal peaks of granuloma annulare in the spring and fall also have been described[3]. The duration of the skin eruption varies. In more than one half of patients, it resolves spontaneously within two months to two years. However, cases of disseminated granuloma annulare may last three to four years or as long as 10 years. The eruption may recur as well, with 40% of children having recurrent lesions[4].

This leaves dermatologists with the task of sifting through the abundance of poor evidence in the literature for treatment options, or basing treatment on what has clinically worked in their own patients in the past. The paucity of good clinical data might also be attributed to the self-resolving nature of this condition, which can inflate successful outcomes in coincidental treatments. So, what are my options?

This non-infectious granulomatous skin disease has a wide array of clinical presentations. The most commonly encountered variant is the localized form, characterized by its annular pink-brown plaques, often on the dorsal hands or feet (Figure 1).



Figure 1. A case of granuloma annulare in a female

Although, localized GA starts off with a small cluster of coalesced papules, treatment is often sought by a patient after its centrifugal spread. The terms 'generalized' and 'disseminated' GA are used interchangeably in the literature and is usually defined by more than 10 papules or plaques on the body. Other rare morphologies include subcutaneous, perforating, and patch variants. GA can often be recognized clinically, but if in doubt, pathologic confirmation remains a valuable tool.

For a practical approach, treatments can be subdivided into those optimized for localized versus generalized disease. There are numerous treatment options described, but only one randomized controlled study to date involving eight patients which showed that super saturated potassium idode solution failed to demonstrate efficacy versus placebo[5]. This result may not be clinically informative given the limited access and limited use of this treatment by most dermatologists. For locally directed skin treatments, the most commonly used agents are topical corticosteroids. Despite the lack of formal evidence, the ease of application and high safety profile of these agents along with proper counselling make this first-line treatment well tolerated by patients. Potent Class I topical corticosteroids are favored for efficacy. Depending on the affected body site, topical pimecrolimus or tacrolimus can be considered and there are reports of topical dapsone having efficacy as well[6].

Intralesional triamcinolone dosed at 5mg/ml is another commonly used and efficacious modality. Nearly 70% of patients had resolution with this treatment compared to just 44% with normal saline injections[7]. Another option is cryosurgery with the application of liquid nitrogen to any erythematous papules or the annular rim of active plaques. Most anecdotal reports suggest 10-60 second freeze-thaw times, but this is somewhat dependent on the risk of blistering and scarring. When discussing treatment options with patients, I have found the progression from a topical to intralesional corticosteroid a logical idea to convey. Because of this, I have had more patients treated and more success with intralesional triamcinolone than cryotherapy thus far.

Resistant or more disseminated disease warrants consideration of systemic treatment options. Phototherapy is the most described therapy. Complete or partial clearance has been noted in up to 70% of patients using nbUVB[8]. Despite many of my patients having successes with nbUVB, recurrence can still be an issue and there may be a need for longer-term maintenance therapy. There are no phototherapy cessation guidelines for GA, so phototherapy holidays should be trialed to test whether or not sustained improvement has been achieved. The inconvenience of attending phototherapy or lack of accessibility to this treatment option itself has also been a noted barrier for some patients and should be considered when choosing this modality. Oral, topical, and bath PUVA, as well as UVA1 are also described for those who have access to one of these devices. For further elucidation of potential therapies for the treatment of generalized GA, Table 1 summarizes the key studies in this area.

For patients who require additional therapy, there are several oral options. Hydroxychloroquine at doses ranging from 200 mg to 400 mg daily have shown efficacy, although cutaneous response is often delayed by 3-6 months or more[9]. I have found it important to convey to patients the probable delayed cutaneous response to hydroxychloroquine and that no adequate clinical endpoints exist with regard to discontinuation. Despite having two cases of marked resolution on hydroxychloroquine, other patients have stopped treatment after several months because they had yet to notice a response. It is hard to counsel patients and set expectations around a formal treatment duration since response times are variable. To date, I have been individualizing the duration a patient's treatment course based on his or her motivation to achieve clear skin. If a patient has not noticed a cutaneous response after 6 months of therapy and has lost motivation to continue with an oral medication, I generally discontinue treatment.

Isotretinoin is another option with reports suggesting a starting does of 40 mg daily.

TABLE 1
Summary of Publications on Treatment of Generalized Granuloma Annulare

TREATMENT TYPE	NUMBER OF PATIENTS	DOSAGE AND DURATION	OUTCOME	SIDE EFFECTS
DAPSONE				
Steiner, 1985	10	100 mg daily for 2 to 18 weeks	Four had complete resolution, three had partial response	Headache or weakness
Czarnecki, 1986	6	100 mg daily for 4 to 12 weeks	All resolved	Fatigue
Saied, 1980	2	100 to 200 mg daily for 4 to 44 weeks	One had complete resolution, one was resolving	None
ISOTRETINOIN (ACCUTANE)				
Schleicher, 1985	1	40 mg once to twice daily for 12 weeks	90 percent resolution	Dry lips, elevated triglyceride levels
Tang, 1996	1	30 to 50 mg daily for 16 weeks	Complete response	None
Buendia-Eisman 2003	1	50 mg daily for eight weeks	90 percent resolution	None
Schleicher, 1992	7	40 mg daily for 10 weeks	100 percent response; three recurred after initial clearing, and drug discontinued	Elevated liver function test results
HYDROXYCHLOROQUINE (PLAQUENIL)/CHLOROQUINE (ARALEN)				
Carlin, 1987	1	Hydroxychloroquine 200 mg twice daily for 12 weeks	Near complete clearing	None
Simon, 1994	1	Two hydroxychloroquine, 6 mg per kg daily for six weeks	Complete clearing	None
		Four chloroquine, 3 mg per kg daily for six weeks		
CYCLOSPORINE (SANDIMMUNE)				
Fiallo, 1998	2	3 mg per kg daily for 12 weeks	Complete clearing	None
NIACINAMIDE				
Ma, 1983	1	1,500 mg daily for 24 weeks	Complete clearing	None
NARROWBAND UVB (NB-UVB)				
Cunningham et al	10	12 courses of treatment	clearance or minimal residual disease (MRD) in seven patients	None
Pavlovsky et al	13	20 treatments	54% of patients had complete response(defined as complete clearance of the lesions) or partial response (defined as >50% clearance of lesions)	None
VITAMIN E/ZILEUTON (ZYFLO)				
Smith, 2002	3	Vitamin E, 400 IU daily	Complete clearing	None
		Zileuton, 600 mg daily for eight to 12 weeks		
TOPICAL TACROLIMUS 0.1% OINTMENT (PROTOPIC)				
Harth, 2004	4	Apply twice daily for eight weeks	Two patients had healing of inflammation.	Burning, itching
TOPICAL PIMECROLIMUS 1% CREAM (ELIDEL)				
Rigopoulous, 2005	1	Apply twice daily for 12 weeks	Partial clearing	None
POTASSIUM IODIDE				
Smith, 1994	8	3 to 10 drops three times dailyfor 24 weeks	No benefit over placebo	Rhinorrhea, metallic taste, acneform eruption
INFLIXIMAB (REMICADE), ADALIMUMAB (HUMIRA), TUMOR NECROSIS FACTOR α INHIBITOR,				
Hertl, 2005	1	5 mg per kg intravenously at 0, 2, and 6 weeks and monthly for four months	Near complete clearing	None
Min and Lebwohl, 2016	7	Initial 80 mg dose, followed by 40 mg every other week	An average of 87% BSA improvement	None

IU = international units

The advantage with this treatment is that results can be seen as soon as one month[10]. I have had several patients trial this medication, with many showing marked early success. Unfortunately, several patients who showed improvement have relapsed after cessation of isotretinoin. The prospect of re-experiencing mucocutaneous side effects has been a barrier to restarting this otherwise good option.

Given its use in other inflammatory cutaneous diseases, many dermatologists would be comfortable prescribing doxycycline at 100 mg daily to try and clear GA. The mechanism of action is likely associated with its anti-inflammatory effect, but given the pathologic similarities of GA and infectious granulomas, researchers have speculated that there may be an unknown infectious etiology implicated in GA. The limiting factor with using an antibiotic would be duration of treatment in an effort to control antimicrobial resistance, but its safety profile warrants consideration. Studies of average treatment duration are sparse, as is my personal long-term use with this medication in GA.

Lastly, a new and interesting frontier in the treatment of GA includes biologic therapies with anti-TNFα agents being the most widely used. However, it should be noted that the cost of off-label biologic medication utilization would be a major barrier for most patients in Canada. Keeping access and cost in mind, there are reports of improvement in as little as 2-6 weeks and follow up showing that efficacy is sustained.[11,12]

In summary, therapeutic choice should be guided by a combination of the available data, clinical efficacy, and patient preference. Of course, given that GA has no known systemic complications, observation is an option for those who decline treatment. Generally, high-potency topical corticosteroids are a worthwhile starting point for treatment with a subsequent transition to serial intralesional triamcinolone injections or cryotherapy for those who are more motivated to see results. If desired efficacy is not achieved or if the GA is more generalized in its manifestation, nbUVB is likely the most effective and easiest next line of treatment if available. Hydroxychloroquine and isotretinoin can also be used in the right patient after discussion of expectations for improvement and potential side effects. As more biologics enter the market and costs decrease, it will be interesting to see if anti-TNFα or other immunomodulatory agents become mainstream options for off-label disease use in the future.

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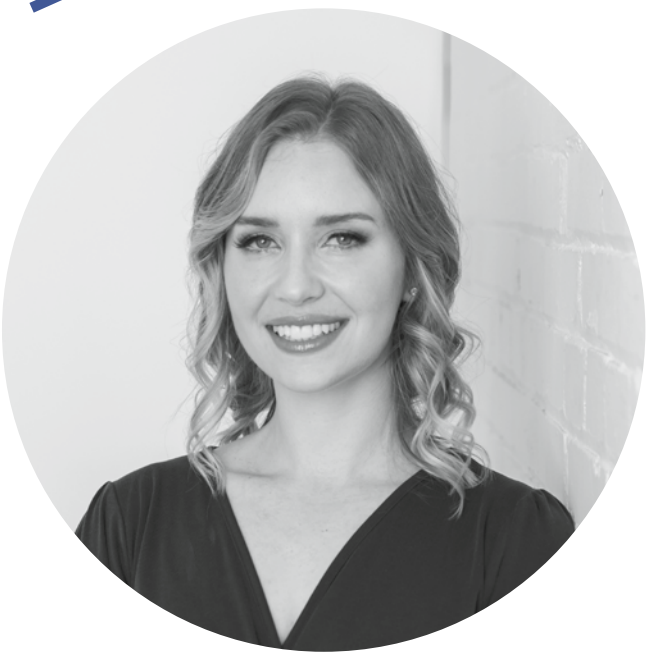
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ABOUT THE AUTHOR

Dorota Kadlubowska, BSc, MDCM, FRCPC



Dr. Dorota Kadlubowska is a dermatologist with the SKiN Centre for Dermatology in Cobourg, Ontario and the SKiN Laser Clinic in Peterborough, Ontario. She has a mixed medical and cosmetic practice, and also serves as a clinical trials sub-investigator. She completed medical school and dermatology residency at McGill University, then went on to pursue further subspecialty training at the University of Toronto where she completed a year-long fellowship in dermatologic laser surgery and cosmetic dermatology.

SAFE DEOXYCHOLIC ACID INJECTION TECHNIQUE FOR SUBMENTAL FAT REDUCTION

Introduction

Body contouring is gaining popularity in the aesthetic world, as many patients are opting for non-surgical treatments to reduce fat and to improve their appearance. Prior to 2015, patients seeking cosmetic enhancement to reduce submental fat (SMF) typically underwent submental liposuction. Health Canada and the United States Food and Drug Administration approved deoxycholic acid for the reduction of moderate-to-severe SMF in 2015. Deoxycholic acid (BELKYRA™, Allergan, Madison, NJ) is a minimally invasive injectable treatment for the non-surgical reduction of submental adipose tissue. It is a synthetic bile acid that acts on adipocytes by emulsifying fats. Upon injection in the submental fat, it disrupts plasma membranes and ultimately induces adipocyte cell lysis. This is followed by an inflammatory reaction, with a subsequent reduction in fat.[1] The swelling takes up to a week to resolve, and then tissue remodelling takes place over months. In one of the early randomized controlled trials (RCT) comparing deoxycholic acid to placebo, between 64 – 69% of patients (n=360) were highly satisfied with the appearance of their face and chin using the Subject Self-Rating Scale (SSRS score ≥4) after up to 4 treatments compared to 29% in the placebo group ($P < 0.001$).[2] Deoxycholic acid injection can be a safe and effective addition to a dermatologist's cosmetic practice, with a high rate of patient satisfaction.

The first portion of this article will address the safety concerns of deoxycholic acid treatment, outlining not only the common adverse effects (AEs) but also highlighting rare side effects that have been reported in case reports and case series. The second portion of the article will review patient selection, anatomic considerations, and injection techniques to achieve a safe outcome.

Adverse events associated with deoxycholic acid injection

Multiple phase III clinical trials have established the safety profile of deoxycholic acid and have reported the most common AEs'.[2-5] Since coming to market, a growing body of literature regarding real-world AEs after injection have come to light.

The pivotal randomised controlled trials, REFINE-1, authored by Jones et al. and REFINE-2, authored by Humphrey et al., reported the common adverse events observed after deoxycholic acid injeciton.[4,5] They reported that AEs were common, mostly transient, and for the most part, mild-to-moderate in nature. The four most common reported AEs were swelling (87%), bruising (72%), pain (70%), and numbness (67%). These common effects lasted for an average of about four days. Somewhat less common were erythema (27%), induration (23%), paresthesia (14%), nodule formation (13%), and pruritus (12%). Notably, dysphagia was observed in 2% of patients, with a median duration of 3 days. Marginal mandibular nerve injury was reported in 4% of treated subjects, with a median duration of about 44 days (ranging from 1-298 days to resolution). Other less common side effects included site warmth, skin tightness, nausea, and headache. Most of the reported adverse events occurred around the injection site and were easily managed by using ice packs and oral analgesics.

Post-marketing studies and case series described uncommon AEs that were not originally reported in the phase III randomised controlled trials. Shridharani (2017) was one of the first to report mild transient alopecia at the injection sites in 8 of 39 male patients; 5 of 21 [23.8%] who underwent multiple sessions versus 3 of 18 [16.7%] who underwent a single session (p = .702).[6,7] In this series, all the cases of alopecia resolved within six weeks of the last treatment session. Five additional cases of localized non-scarring alopecia at injection sites were subsequently reported.[8-11] Some of the affected patients experienced re-growth, while others did not. One male developed patchy alopecia in the treatment area one week after injection, which eventually resolved at the seven month mark.[8] Another patient with beard alopecia reported only a 60% improvement in the alopecia fourteen months after his first treatment.[8] Sebaratnam et al. (2019) performed a biopsy on a patient with post-treatment beard alopecia which was suggestive of a localized telogen effluvium as the likely responsible mechanism.[11]

Four cases of skin necrosis or vascular injury have been reported after deoxycholic acid treatment.[12-15] Most cases presented with pain upon injection and immediate visible skin blanching, followed by the development of retiform purpura, papular or vesicular lesions following the procedure. Some of the cases of skin necrosis resolved without sequelae, while others resulted in scarring. One case of skin necrosis and ulceration along the mandible healed with an indurated red plaque, which was improved using pulsed dye laser and fractionated CO2 laser.[14] There was one reported case of hypertophic scar formation after resolution of a vascular event and another case of atrophic, depressed scars on the neck which persisted at a follow up visit one month after injection.[15]

Most of the AE's of deoxycholic acid treatment are expected, tolerable, transient, and easily managed. Although rare, skin necrosis and beard alopecia have been reported in post-marketing reports. An understanding of the possible side effects of the procedure are needed for informed consent to take place and may help set expectations for post-procedure discomfort.

Patient selection

Proper patient selection is the first step to achieving a safe and aesthetically desirable outcome. Deoxycholic acid injection is indicated for improvement in the appearance of moderate-to-severe convexity or fullness associated with SMF in adults via the reduction of pre-platysmal fat, which is located between the platysma and the dermis. Patients with excess adipose or soft tissue in the post-platysmal area will not benefit from treatment. Excessive skin laxity in the submental area is another sign that the patient may not be an ideal candidate for treatment. Further reduction of SMF in these patients may accentuate the skin laxity and result in an aesthetically undesirable outcome. It is important to palpate the submental area to assess the location and amount of adipose tissue, as well as to assess for the presence or absence of excessive skin laxity.

Safe injection technique

When delineating a safe treatment area, it may be useful to visualize or draw a treatment zone that is bordered superiorly by the submental crease, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone (at the cervicomental angle). The injection points should be 1.5 cm away from the inferior border of the mandible to avoid injecting near

the marginal mandibular branch of the facial nerve (Figure 1). Doing so can lead to neuropraxia or transient asymmetrical smile.

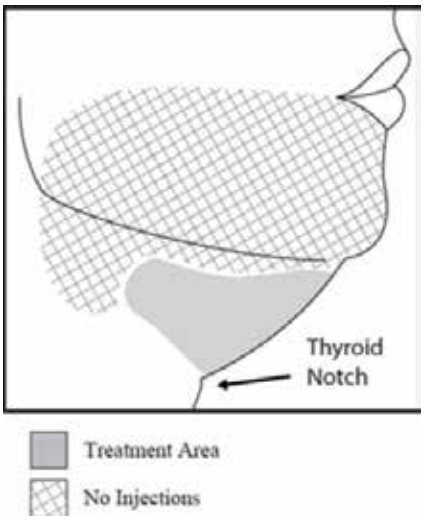


Figure 1. Avoid the Marginal Mandibular Nerve Area; BELKYRA™ product monograph, March 2016

A 1x1 cm grid is marked on the area to be treated, so that each injection point is 1 cm apart. As per the product monograph, 0.2 ml is injected next to each grid marking, spaced 1 cm apart, with a 30G (or smaller) 0.5-inch needle. Pinch the subcutaneous tissue between two fingers to isolate the fat prior to injection. Consider aspirating prior to injecting the product to avoid intravascular injection. Up to 50 injection points or a maximum of 10 mL of product is advisable in one session. Repeat treatments should be spaced at least 1 month apart for a maximum of 6 sessions.[16]

In addition to avoiding injecting near the mandible and near the course of the marginal mandibular nerve, try to visualize the approximate locations of other important anatomical structures. These include the mental and submental arteries, the submandibular glands (these lie close to the mandible and are the second largest salivary glands after the parotid gland), as well as

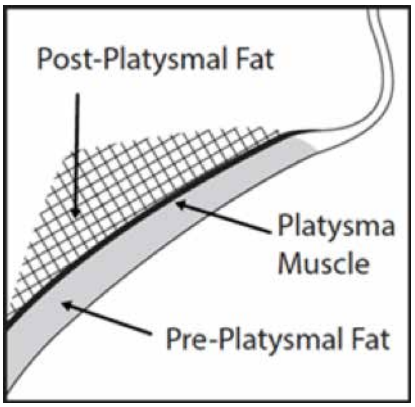


Figure 2. Sagittal View of Platysma Area; BELKYRA™ product monograph, March 2016

the digastric, sternocleidomastoid and platysma muscles. Try to be mindful of the most likely locations of the lymph nodes in the submental, submandibular, and cervical areas. If you meet resistance with your needle, withdraw and reposition. Inserting your needle into adipose tissue should not give a feeling of resistance.

Safe injection techniques for deoxycholic acid injections of the submental region

- Inject at least 1.5 cm away from important structures i.e. the mandible, the marginal mandibular branch of the facial nerve, arteries, and salivary glands
- Do not exceed 0.2 ml per injection site
- Avoid intradermal injections to avoid skin necrosis
- Consider aspiration prior to injection to avoid intravascular injection
- Pinch the adipose tissue between your fingers to isolate it prior to injection

Table 1. Safe injection techniques for deoxycholic acid; courtesy of Dorota Kadlubowska, MD

Conclusion

Dermatologists are sought out in the aesthetic world for their expertise, their regard for safety, as well as their ability to manage complications associated with cosmetic treatments. Accordingly, it is important to have a solid understanding of not only the common, but also the rare complications of the cosmetic treatments they provide. In order to achieve a desirable outcome, the understanding of adverse events, proper patient selection, knowledge of anatomy and safe injection techniques are of utmost importance.

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ABOUT THE AUTHOR

Aaron Wong, MD, FRCPC

Dr. Aaron Wong is the residency program director in the Department of Dermatology and Skin Science at UBC where he is also a clinical assistant professor. His clinic is based at St. Paul's Hospital and focuses on HIV Dermatology and he also has a community practice in New Westminster, B.C.



CASE FOR CONSIDERATION: A 30-YEAR-OLD HIV-POSITIVE MAN WITH PSORIASIS

You are seeing a 30-year-old man with a history of established psoriasis in your outpatient dermatology clinic. The patient has well-controlled human immunodeficiency virus (HIV) and he takes a new antiretroviral (ARV) medication, Biktarvy®. The patient's HIV in the blood is undetectable and his CD4 T-cell count is normal. His health is otherwise good. During the clinical workup, he mentions that his partner is HIV-negative and is on pre-exposure prophylaxis (PrEP) medication and has developed brown facial spots and is wondering if the PrEP medication may have caused this and also wants to see a dermatologist.

The patient starts on combination calcipotriene / betamethasone dipropionate foam and considers phototherapy. Upon reviewing the data on Biktarvy®, you become aware that it causes "rash" and wonder about interactions with acitretin, cyclosporine, or methotrexate. Biktarvy® contains bictegravir, emtricitabine and tenofovir alenamide. It does not contain ritonavir.

HIV and its treatment have changed significantly over the past 30 years. The virus can be fully suppressed with antiretroviral therapy (ARV), formerly known as highly active antiretroviral therapy (HAART). If ARVs are accessible and started early, collaborative cohort studies across Europe and North America demonstrate improved survival & life expectancy. There are now no threshold levels for initiation of ARVs based on CD4 T-cell count or viral load, if the ARVs are accessible to the patient. Treatment is generally recommended after diagnosis of HIV.[25]

Questions to Ponder:

- What are the relevant updates with regard to the newer anti-retroviral therapies and acronyms?
- Should we be concerned about intralesional or topical steroids and protease inhibitors such as ritonavir?
- What about using systemic medications such as acitretin, methotrexate, and cyclosporine together with ARVs?

Updates in HIV Acronyms

HIV-related cutaneous reactions can be due to initial infection with the virus itself, opportunistic infections (OI), or because of treatment of the virus or OIs themselves.

Immune reconstitution inflammatory syndrome (IRIS) is a phenomenon whereby the inflammatory response is exaggerated towards an infectious organism as host immunity recovers (i.e. T helper or CD4+ cells increase) following treatment with ARVs. Those diagnosed at a later stage of HIV are more susceptible and typically this can manifest in the form of extensive infections such as herpes simplex virus infections, herpes zoster, warts, molluscum, candida, and dermatophyte infections. Non-infectious sequalae can include lupus, extensive alopecia areata, or folliculitis.[1]

The use of PrEP in landmark, well-conducted randomized controlled trials have demonstrated efficacy of combination tenofovir disoproxil fumarate and emtricitabine (TDF-FTC or Truvada®) in preventing HIV transmission and has been approved by Health Canada for this indication.[2-4]

Post-exposure prophylaxis (PEP) can be non-occupational (nPEP) or occupational. Combination tenofovir disoproxil fumarate and emtricitabine (generic or branded Truvada®) is also used for this purpose. Lifestyle and behavioral interventions still remain key to HIV prevention even with the availability of PEP and PrEP.[5]

Antiretrovirals – New and Old

HIV antiretroviral therapy has consisted of combinations of the following[8]:

1) Nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI)
2) Non-nucleoside reverse transcriptase inhibitors (NNRTI)
3) Protease inhibitor (PI)
4) Integrase inhibitors
5) CCR5 antagonists

Antiretroviral therapy has moved towards combining different types of ARVs into one convenient pill, taken once a day including branded medications such as:

- Genvoya® (elvitegravir + cobicistat + emtricitabine + tenofovir alafenamide)
- Odefsey® (emtricitabine + rilpivirine + tenofovir alafenamide)
- Biktarvy® (bictegravir + emtricitabine + tenofovir alafenamide)
- Stribild® (cobicistat + elvitegravir + emtricitabine + tenofovir disoproxil)
- Atripla® (efavirenz + emtricitabine + tenofovir disoproxil)
- Complera® (emtricitabine + rilpivirine + tenofovir disoproxil)

Many of the newest QD regimens contain the nucleotide reverse transcriptase inhibitor (NRTI), tenofovir alafenamide (TAF), instead of tenofovir disoproxil fumarate (TDF). TAF has some advantages over TDF, including selectively activating within the cell (whereas TDF activates in the bloodstream), less nephrotoxicity & less reduction in bone mineral density. TDF, however, may lead to less elevations of cholesterol and may be beneficial in those with dyslipidemia.[6,7]

Generally, most ARVs are well-tolerated by patients and mucocutaneous adverse events tend to be the exception, rather than the norm. Non-nucleoside reverse transcriptase inhibitors (NNRTI) are the most common class of ARVs to cause cutaneous toxicity, particularly morbilliform eruption. The morbilliform eruption tends to resolve even when the medication is continued; thus, physicians can treat through the rash with agreeable patients. Nevirapine, in particular, has been associated with morbilliform eruption, drug hypersensitivity and Stevens–Johnson syndrome/ toxic epidermal necrolysis (SJS/ TEN).[9] In the developing world, nevirapine is a common cause of SJS / TEN in HIV / AIDS patients. The observed cluster of adverse

events recorded as "rash" were used non-specifically in clinical trials that formed the basis for bringing these drugs to market, so characterization of cutaneous adverse events remains imprecise for many of these medications.

HIV & Lipodystrophy

Antiretroviral lipodystrophy manifests through a variety of changes in body and facial fat composition. Metabolic abnormalities often accompany the lipodystrophy including dyslipidemia and impaired glucose tolerance. Lipoatrophy occurs in the facial temporal and buccal fat pads, limbs and buttocks while lipohypertrophy occurs in the abdomen, dorsocervical region ("buffalo hump"), and breast tissue (gynecomastia). These findings were initially attributed to protease inhibitors (PI) but now are strongly related to NRTIs, particularly stavudine and didanosine as well as NNRTIs such as efavirenz.[10,11,13]

Protease Inhibitor Drug Interactions

Ritonavir is protease inhibitor that boosts the function of other PIs by inhibition of the cytochrome P450 3A4 pathway. This inhibition reduces breakdown of other PIs, thus providing the aforementioned "boosting" effect. Other drugs metabolized by this pathway, such as corticosteroids and cyclosporine, both of which are used with relative frequency in dermatology, should be approached with caution. Iatrogenic Cushing's syndrome (ICS) has been reported with single epidural, intra-articular or intramuscular injections of 40 mg or more of triamcinolone acetonide (TAC). There are no published reports of this occurring with intralesional or topical corticosteroids. However, iatrogenic Cushing's syndrome can occur with topical steroids in patients without HIV so the effects of ritonavir should not be disregarded.[14-16]

There are currently no guidelines or data to suggest a safe dose. Consultation with the patient's HIV provider to determine if an alternate, non-boosted regimen is advisable if intralesional therapy is being considered, particularly if the anticipated dosage is large or injections are to be given on a regular basis. If intralesional therapy is initiated, the author suggests dilution of the TAC to 2.5 mg / ml or lower, keeping the total administered dose below 15 mg and spacing out injections by 8-12 weeks. If there is a clinical suspicion of adrenal suppression or iatrogenic Cushing's syndrome, these patients should be further investigated.

Cyclosporine is similarly affected by ritonavir-induced cytochrome P450 3A4 inhibition. Lower doses and monitoring of cyclosporine levels may be necessary to prevent toxicity if it must be used. Based on pharmacokinetic data, daily doses of cyclosporine should be

Table 1.
Mucocutaneous adverse events of anti-retroviral therapy.[10,11,12]

DRUG CLASS	COMMON MUCOCUTANEOUS FINDINGS
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)	
Zidovudine	Nail & mucous membrane hyperpigmentation
Abacavir*	Abacavir hypersensitivity syndrome: "maculo-papular rash", urticaria, diffuse erythema, erythema multiforme, targetoid eruption, morbilliform eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) *Screening for HLA B5701 allele positivity significantly reduces development of the abacavir hypersensitivity syndrome
Stavudine	Lipodystrophy
Emtricitabine	Xerosis and eruptions of various morphology (macules-papules, vesicular, pustular)
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	
Tenofovir	Self-limited rash with morbilliform eruption, vesicular eruptions & urticaria; overall incidence is low
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)	
Nevirapine	Morbilliform eruption (up to 28%) and DRESS, SJS, TEN; oral ulcers & acute generalized exanthematous pustulosis
Efavirenz	Morbilliform eruption
Etravirine	Morbilliform eruption
PROTEASE INHIBITORS (PI)	
Ritonavir	Circumoral paresthesia
Fosempranavir	Morbilliform eruption; drug contains a sulfa moiety
Atazanavir	Jaundice & scleral icterus (due to increased unconjugated bilirubin)
Darunavir	Self-limited morbilliform eruption
Indinavir	Morbilliform eruptions, retinoid like effects (hairloss, cheilitis, xerosis & paronychia) and lipohypertrophy; not commonly used
INTEGRASE INHIBITORS	
Elvitegravir	Not commonly reported with this group
Bictegravir	
Raltegravir	
ENTRY & CCR5 FUSION INHIBITORS	
Enfuvirtide	Injection site reactions
Maraviroc	Undefined "rash" in up to 16.5% in preclinical trial

reduced by 5-20%. This poses a challenge for weight-based dosing of cyclosporine which may range from 2-5 mg / kg, depending on the indication. The old adage of "start low, go slow" should be adopted, along with the monitoring of levels when ritonavir and cyclosporine are being used concomitantly.[17]
Stribild® contains cobicistat, elvitegravir, emtricitabine and tenofovir. Cobicistat is also a cytochrome P450 3A4 (CYP3A4) inhibitor and there have been reports of adrenal suppression with concurrent inhaled, intranasal or intra-articular corticosteroids.[18,19]

Other Systemic Medications and HIV

Acitretin is an established immune-modulating retinoid for treatment of psoriasis in HIV. It is not metabolized through the cytochrome P450 pathway.[20] Methotrexate (MTX) use in HIV showed poor safety outcomes or opportunistic infections in the published literature from 1987-1995.[21-24] This was before advent of regular ARV therapy and thus, patients may have had poorly controlled HIV. In some cases, methotrexate doses were higher than what is normally used in dermatology. If the patient has well controlled HIV, MTX can be used provided that regular clinical and laboratory monitoring are followed. Online drug interaction checkers are helpful as well.

Summary

HIV treatments have come a long way and there continue to be medical advances which generally herald improved outcomes for patients, but adverse cutaneous events from existing and new medications should not be overlooked.

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ABOUT THE AUTHOR



Shanna Spring, MD

Dr. Shanna Spring is a board-certified dermatologist in both Canada and the United States. After completing her undergraduate Bachelor of Science degree at McGill, she studied medicine at the University of Toronto. Upon completion of her MD, she moved back to her hometown of Ottawa for her residency in dermatology. An interest in pediatric dermatology sent her on a year-long fellowship to the University of California - San Francisco (UCSF) and the University of Toronto (SickKids). Now settled back in Ottawa, she splits her time between CHEO, Bruyere Hospital and The Ottawa Hospital with a continued interest in pediatric dermatology.

RETHINKING CONVENTIONS IN PEDIATRIC ATOPIC DERMATITIS

Antihistamines in atopic dermatitis

During my residency training, we were taught to encourage parents to use Benadryl® (diphenhydramine) or Atarax® (hydroxyzine) at night to help their itchy children sleep better. Parents were instructed to use higher doses than labelling on the bottle suggested, as the clinical intent was to use it for its sedating side effects rather than any sort of specific treatment for their child's atopic dermatitis.

This past year, the Canadian Society for Allergy and Clinical Immunology (CSACI) came out with a position statement on proper antihistamine use, directly in opposition to this practice.[1] First generation H1 antihistamines have side effects like sedation and impairment with decreased cognitive function. Although they may help initiate sleep, they have been shown to cause poor sleep quality. These antihistamines cross the blood brain barrier and cause significant CNS suppression. Some studies have shown a decrease in school performance in patients regularly taking this medication.[2] Previous use of first generation antihistamines has a possible association with increased ADHD symptoms in children with atopic dermatitis.[3]

Second generation antihistamines are more efficacious and safer than first generation antihistamines.[5] These second generation drugs are now our first line therapy for urticaria and rhino-conjunctivitis. There is evidence that rupatadine, one of the newer second generation antihistamines, may even have some antipruritic effects in atopic dermatitis.[4] Despite its long history of use in acute type I allergic reactions, pediatric hospital protocols for anaphylaxis no longer include oral Benadryl®. CSACI has recommended that all first generation antihistamines be made available by prescription only, so as to discourage use by the general population.

It has been my clinical experience that many families still reach for Benadryl® (diphenhydramine) when their child is itchy, no matter the etiology. It is our responsibility, along with our pharmacy colleagues, to discourage the use of this outdated medication. CSACI strongly recommends that the "use of first-generation antihistamines should be significantly curtailed."[1]

Bleach baths

Another controversy in our day-to-day practice is whether or not to suggest bleach baths to our patients with recurrent *Staphylococcus aureus* infection. A recent systematic review found that bleach baths are effective in decreasing AD severity but are not more effective than water baths alone.[5] This study confirms that regular bathing is better than infrequent bathing in AD. A Cochrane review in 2010 found no benefits of using anti-staphylococcal interventions (i.e. bleach baths) to decrease the density of *S. aureus* on the skin of AD patients when compared to the regular use of anti-inflammatory medications we use to treat AD.[6]

In addition, a recent basic science publication looking at various laboratory models of *staph* eradication highlighted that the clinical concentration of dilute bleach baths we recommend to patients is actually not inhibitory to the survival or growth of *S.aureus* or *S.epidermidis*.[7] In reality, bactericidal effects were only seen at higher concentrations of bleach, levels that would be cytotoxic to human cells and could not be safely used in practice.

Dr Amy Paller, a prominent pediatric dermatologist in Chicago, has an interest in the microbiome and atopic dermatitis. In a recent study with Majewski et al, the investigators evaluated sodium hypochlorite (NaOCL) body wash in a 6-week, prospective, open label study which included 50 patients (ages 6 months to 17 years) with moderate-to-severe AD and proven *S. aureus* skin colonization. Patients were instructed to use the bleach-based body wash daily, in addition to their regular medicated creams. Primary endpoints included Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) scores. At the end of the 6-week study, there was improvement in all outcome measures comparing baseline to 2-week and to 6-week evaluations. Interestingly, 64% of individuals were still positive for *S. aureus* at the conclusion of the study. The authors postulated that bleach baths and washes "involve a mechanism beyond its oxidative capability and bactericidal activity against *S. aureus*", suggesting that they may be anti-inflammatory without affecting bacterial dysbiosis.[8]

With all of this conflicting data, it is still difficult to know what to suggest to the patient and family sitting in front of you. The Canadian consensus statement on pediatric atopic dermatitis probably sums it up best: "bleach baths have not been consistently shown to improve outcomes in AD and may be used at the discretion of the treating health care provider."[9]

Early emollient use as primary prevention in atopic dermatitis

In 2014, Simpson et al published a paper which sent ripples of excitement throughout the dermatology world. A small pilot randomized controlled trial of 124 infants at high risk for AD looked at daily emollient use from <3 weeks to 6 months of age vs control and the subsequent development of AD. Parents in the intervention arm were instructed to apply full-body emollient therapy at least once-per-day starting within 3 weeks of birth. Parents in the control arm were asked to use no emollients. The primary clinical outcome was the cumulative incidence of atopic dermatitis at 6 months, as assessed by a trained investigator. At the conclusion of the study, regular emollient use showed a statistically significant protective effect on the cumulative incidence of AD with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017).[10] A similar small Japanese study showed another favourable result of 32% risk reduction of development of AD with daily emollient use.[11]

These findings spurred on the funding and recruitment of two larger cohort studies, one in the UK and one in Sweden.

The Barrier Enhancement for Eczema Prevention (BEEP) study was a multicenter, double-arm, parallel group randomized controlled trial recruiting patients from 16 sites across the UK[12], whose findings were recently published in *The Lancet*. In this study, 1394 infants with a high risk of developing AD were randomized 1:1 into application of petrolatum based emollients once a day in the first year of life vs standard skin care advice only (control). The primary outcome reported was development of AD at 2 years of age. The findings were somewhat surprising: 23% of children in the emollient group developed eczema vs 25% in the control group (adjusted relative risk 0.95 [95% CI 0.78 to 1.16], p=0·61; adjusted risk difference –1.2% [–5.9 to 3.6]) and 15% of

children in the emollient group had skin infections vs only 11% in the control group. The authors postulate the higher risk of infection may be due to increased inoculation of pathogens during emollient application, possible disturbance of the microbiome or possibly that emollients can make the skin more adhesive to bacteria. The authors concluded that there is no evidence to support daily emollient use in the prevention of AD in high risk infants, and that this might actually cause harm in the form of an increased risk of skin infections. "This practice should stop unless new evidence suggests otherwise".

In the same *Lancet* publication, the findings of the PreventADALL population-based study were also presented[13]. This study followed 2394 newborn infants for the first year of life, randomized into one of four groups: a control group (controls with no specific advice on skin care while advised to follow national guidelines on infant nutrition), a skin emollient group (bath additives and facial cream), a food intervention group (early complementary feeding of peanut, cow's milk, wheat, and egg), and a combined skin and food intervention group. The skin intervention consisted of the intervention 4 days a week, from age 2 weeks to 8 months of age. Even with this low level of intervention required, patients still had a low adherence to the full protocol. The primary outcome of AD at 12 months of age showed the highest rate of occurrence in the skin intervention group (11%) and the lowest rate in the combined skin and food intervention group (5%). This interesting and novel finding in the combined intervention group highlights the possibility that multiple interventions may work synergistically. This will hopefully be further elucidated when the extension of the study looks at allergy outcomes at age 3.

Taking these two large studies into consideration, there is no strong published evidence that daily use of an emollient in population-based or high-risk groups of infants in the first year of life can delay, suppress or prevent AD. These two studies used infrequent oil baths or daily petrolatum based products so it is possible that ceramide containing, low pH emollients may confer more of a benefit. The PEBBLES study is an ongoing large randomized controlled trial looking at similar outcomes but with a more sophisticated emollient used twice a day[14]. Even if this does show a positive outcome, it is unclear if a more costly cream and a more intensive regime would be a possible and realistic population-based strategy for reducing AD incidence.

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