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HIDRADENITIS SUPPARATIVA MANAGEMENT: AN OVERVIEW

Introduction

Hidradenitis Suppurativa (HS) is a chronic debilitating inflammatory skin disease characterized by the formation of recurrent nodules, abscesses, sinus tracts, fistulas and scarring within apocrine gland-bearing areas.[1] HS affects up to 3.8% of the Canadian population with a higher prevalence among females.[2] The condition is thought to be secondary to occlusion of the pilosebaceous unit and subsequent inflammation.[1]

The diagnostic criteria for HS includes the following: 1) *classic lesion morphology*, 2) *characteristic distribution of lesions*, 3) *recurrence of lesions*.[2] The Hurley staging system is commonly used for assessing the severity of disease in HS; however, there are several other staging systems that can be used as well. The Hurley staging system classifies HS into 3 stages. Hurley stage I indicates mild disease, with single or multiple lesions in affected areas, without scar formation. Stage II is classified as moderate disease and is characterized by recurrent lesions with sinus tract formation and scarring in affected regions. Stage III is considered severe disease and involves interconnected inflammatory lesions and sinus tracts in affected areas.[1] HS has an average delay of diagnosis of 7.2 years; consequently, patients often have higher stages of the disease by the time they are seen by a dermatologist.[3]

Unfortunately, HS is associated with a high burden of disease, with lesions that are often painful and can discharge, which can limit mobility.

Medical management is warranted to minimize inflammation and to reduce the burden of disease. Patients can benefit from procedural and surgical management as an adjunct to medical therapy through 1) *symptomatic relief*, which includes incision and drainage (I&D) and intralesional injections of Triamcinolone acetonide, 2) *prevention of disease*, which includes laser therapy, and 3) *managing recurrent and refractory lesions*, which includes surgical procedures such as deroofing and excisions.

At present, the mainstay for procedural management in HS consists of I&D, intralesional Triamcinolone acetonide, laser-assisted devices, deroofing, and excisions. Herein, we will review these adjunctive procedures that can assist in the management of HS patients.

Symptomatic relief

Incision & Drainage

I&D can be performed for symptomatic relief of lesions in acute flares of disease (**Figure 1**); however, this treatment does not modify the disease and the recurrence rate of lesions is almost 100%.[4]

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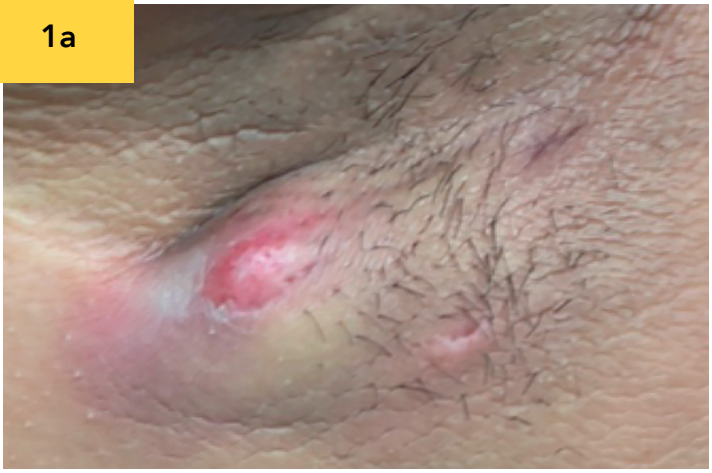

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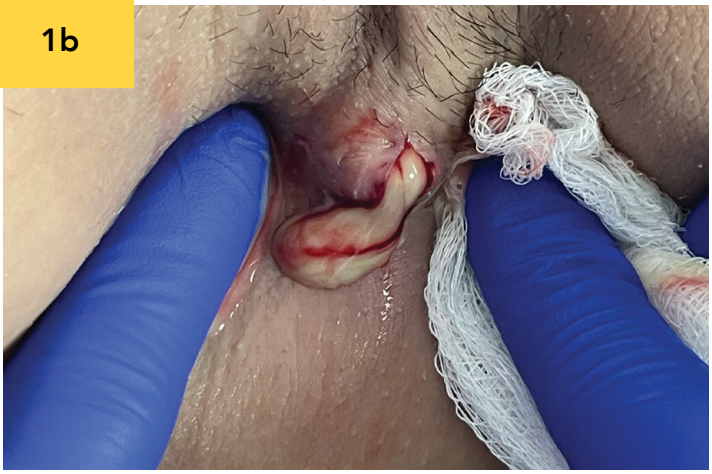

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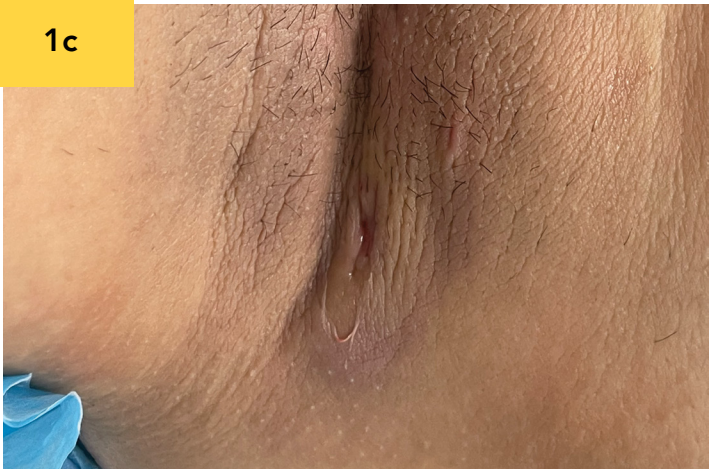

Figure 1. *Incision and drainage performed on a painful fluctuant nodule* ***a)*** *before,* ***b)*** *intra operatively, and* ***c)*** *immediately after the procedure. Incision and drainage was performed by Jessica Asgarpour, MD.*

Intralesional Triamcinolone acetonide

Intralesional Triamcinolone acetonide can help with pain relief and can hasten the resolution of lesions. Studies have reported mixed results. Typically, a concentration of 10mg/mL to 40 mg/mL is used per session.[2]

Preventative Therapy

Laser and light therapy

Laser and light-based therapies can be used to prevent and treat HS lesions. These therapies work mostly by reducing the amount of hair follicles and sebaceous glands as well as debulking of lesions.[5]

A systematic review compared the effectiveness of different light and laser therapies used to treat patients with HS. The review looked at neodymium-doped yttrium aluminum garnet (Nd: YAG), carbon dioxide (CO2) laser, psoralen plus ultraviolet A (PUVA), targeted phototherapy, photodynamic therapy (PDT), and others.[6]

Both Nd: YAG laser and CO2 laser therapies have shown effectiveness in the treatment of HS and included the highest number of patients.[6] CO2 laser therapy works at a wavelength of 10,600 nm. As an HS treatment, CO2 laser therapy is used for fractional ablation of scars or vaporizing and excising tissue and can be used instead of a scalpel for procedures such as deroofing and excisions. In addition, over 75% of patients who had undergone CO2 laser therapy showed improvement in their symptoms, had low recurrence rates, and over 90% of patients stated that they would recommend the procedure.[6]

Nd: YAG acts as a non-ablative laser at a wavelength of 1,064 nm. This laser works well for treating HS patients, especially to destruct the hair follicle. Many randomized controlled trials support the use of long-pulse Nd: YAG laser hair removal for conservative management of HS.[2] In fact, 85% of patients who underwent Nd: YAG therapy demonstrated improvement.[6] Patients were reported to have fewer flares and a reduced severity of disease. Combining Nd:YAG laser therapy with CO2 laser therapy has demonstrated better outcomes.[6]

Several studies have shown that targeted phototherapy improved HS lesions in more than 75% of treated patients.[6] Intense pulsed light therapy (IPL), which acts at a wavelength range of 500–1200 nm, led to improvement in 65% of HS patients.[6] Photodynamic therapy (PDT) was reported to be effective in ~70% of HS patients; however,

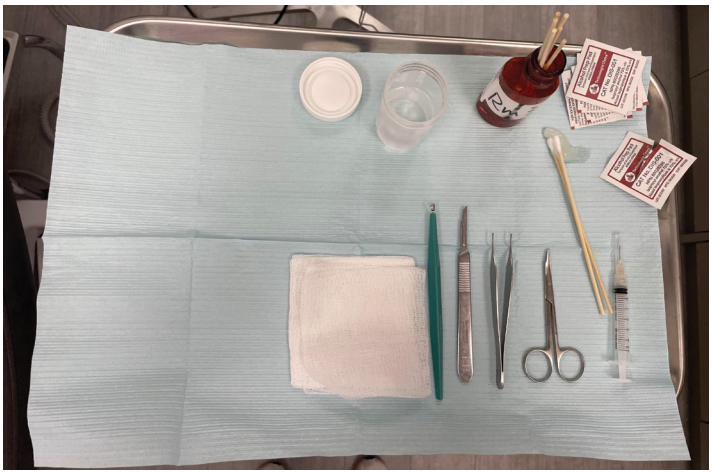

Figure 2. *Items included on the deroofing tray: Alcohol swabs for cleaning, lidocaine with epinephrine as an anesthetic, forceps and tenotomy scissors or scalpel to deroof, curette to remove the gelatinous tissue at the base, gauze and aluminum chloride for hemostasis, Vaseline for wound healing; image courtesy of Jessica Asgarpour, MD.*

several different photosensitizers were used.[6] PUVA was effective in 9/13 (69%) of HS patients in a single retrospective chart review.[6]

Overall, the systematic review noted that side-effects associated with all therapies were low.[6] PDT was associated with the highest proportion of adverse events (36%), followed by CO2 laser (26.2%), IPL (25%) therapies, targeted phototherapy (22.9%), and Nd:YAG laser (15%).[6]

Managing Static or Recurrent Lesions

Deroofing

Deroofing is a procedure that is typically performed in the clinic under local anesthetic (**Figure 2**). During this procedure, the surgeon removes the 'roof' of an inflammatory lesion or sinus tract along with curettage to remove the gelatinous granulation tissue (**Figure 3**).[3] Deroofing can be performed using blunt scissors, CO2 laser, or using electrosurgery.[4] Healing occurs through secondary intention because of higher rates of recurrence associated with primary closure.

A Canadian prospective study assessed efficacy and pain reduction in patients who underwent deroofing of HS lesions. The study included 43 patients and 123 lesions deroofed. After 3 months, only 7% of deroofed sites had one recurrence, 41% of patients reported no erythema, and 43% of patients reported no discharge at the surgical site. Of note, pain and Dermatology Life Quality Index scores were significantly reduced.[7] A meta-analysis of 22 articles

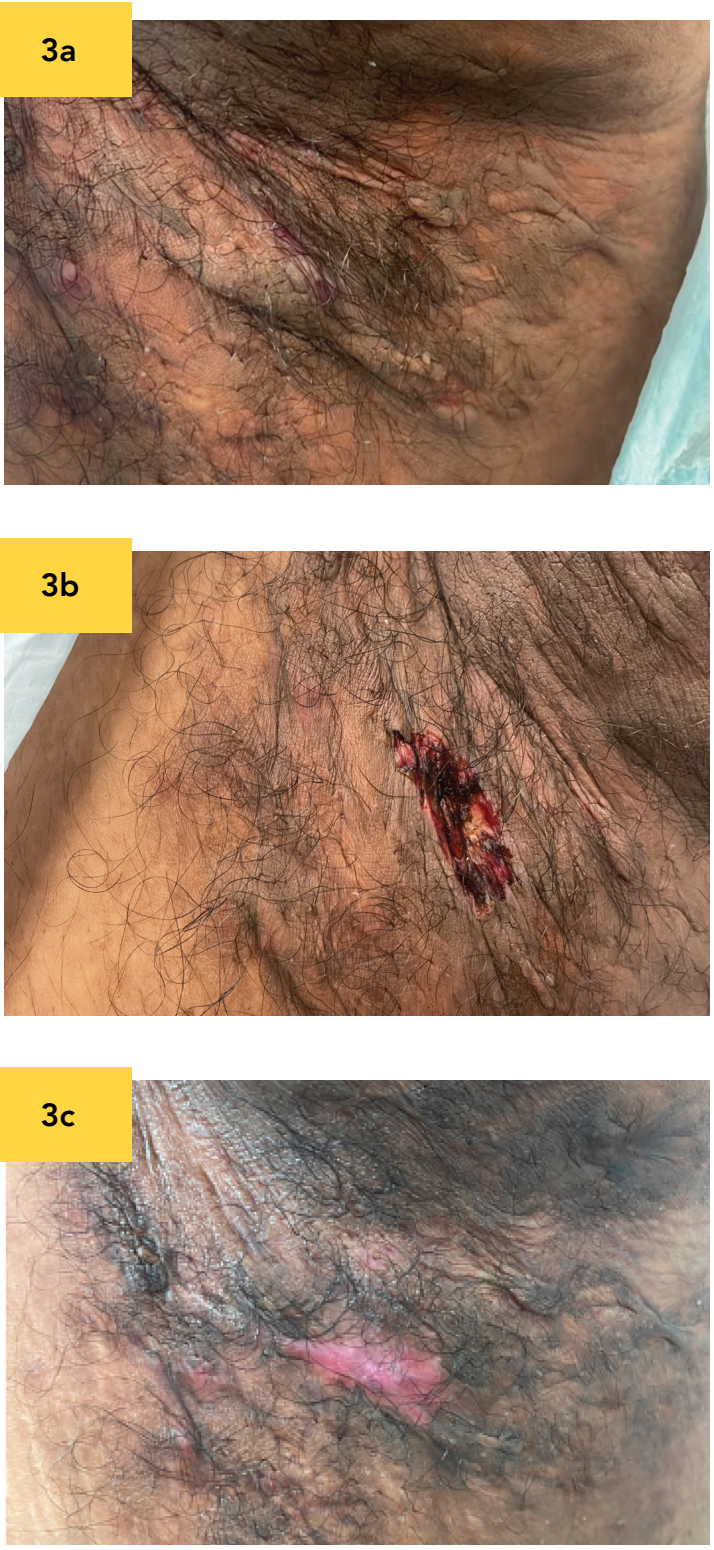

Figure 3. *Axilla deroofing images were taken at* ***a)*** *baseline,* ***b)*** *immediately after deroofing, and* ***c)*** *at week four of follow-up. Axilla deroofing performed by Jessica Asgarpour, MD.*

Prevention	Symptomatic relief	Management of static lesions
• Light therapy: IPL, PDT, targeted phototherapy, PUVA • Laser therapy: Nd:YAG	• Incision and drainage • Intralesional Triamcinolone acetonide	• Deroofing • Excision (scalpel vs CO2 ablation): the excision can be limited, wide or radical

Table 1. *Summary of procedural therapies useful as an adjunct to medical management for Hidradenitis Suppurativa; courtesy of Jessica Asgarpour, MD.*

Abbreviations: CO2*: carbon dioxide;* ***IPL****: intense pulsed light therapy;* ***Nd:YAG****: neodymium-doped yttrium aluminum garnet;* ***PDT****: photodynamic therapy* ***PUVA****: psoralen plus ultraviolet A.*

revealed an overall recurrence rate for deroofing of 27%; follow-up was variable.[8]

Excision

Excisions represent a more invasive surgery for patients. Depending on the extent of disease, local or general anesthetic may be used. Excisions can be defined as limited, wide, or radical. The intent of limited excisions is to leave clear margins. Wide excisions remove additional margins of skin. Radical excisions remove the entire hair bearing region down to the fascia.[3] There is limited data assessing recurrence rates for excisions in HS; however, the common perception is that more extensive procedures are associated with a lower recurrence.[3] A meta-analysis of 22 articles revealed an average of 22% recurrence with limited excisions and 13% for wide excisions.[8] Recurrence rates were highest with primary closure (15%); followed by flaps (8%) and grafts (6%). The rate of recurrence for excision with secondary intention was said to be the lowest; however, the rate was not reported.[8]

Conclusion

In conclusion, procedural management is key in the management of HS patients and serves as a useful adjunct to medical management. Procedural management aids in prevention and severity of disease, symptomatic relief, and in the treatment of static, recurrent, and refractory lesions. Furthermore, these procedures may all be conducted in a clinic setting under local anesthetic, and, notably, reports of adverse events are relatively low. Overall, these treatments are associated with success and high patient satisfaction.

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Financial Disclosures

Amgen, Abbvie, Bausch Health, Beiersdorf, Boehringer, Celltrion, Eli Lilly, Fresenius Kabi, Galderma, ICPDHM, Janssen, Johnson & Johnson, L'Oreal, Medplan, Novartis, Pfizer, RBC Consultants, Sanofi, SUN Pharma, UCB

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Malignancies: lymphoma and other malignancies were observed in patients taking JAK inhibitors to treat inflammatory conditions and were more frequently observed in patients with rheumatoid arthritis (RA) during a clinical trial with another JAK inhibitor versus TNF inhibitors.

Thrombosis: including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients taking JAK inhibitors to treat inflammatory conditions. Many of these events were serious; some resulted in death. Consider risks and benefits prior to treating patients who may be at increased risk. In a clinical trial in patients ≥50 years of age with RA, a higher rate of all-cause mortality and thrombosis occurred in patients treated with another JAK inhibitor versus TNF inhibitors. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

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AD=atopic dermatitis; JAK1=Janus kinase 1.
* Clinical significance unknown.

Reference: CIBINQO Product Monograph, Pfizer Canada ULC.

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Dr. Toni Burbidge is a is a dermatologist based in Calgary, Alberta where she practices medical and surgical dermatology. She is board-certified in both Canada and the United States. She completed her medical degree at the University of Toronto, and dermatology residency at the University of Calgary. She has a special interest in cutaneous oncology and is involved in melanoma research with the multi-disciplinary Cutaneous Oncology team at the Tom Baker Cancer Centre in Calgary. She also teaches medical residents and other learners in her affiliation with the University of Calgary as a clinical lecturer.

Affiliations: Skin Health and Wellness Centre, Calgary, AB
Cumming School of Medicine, University of Calgary, Calgary, AB

TREATMENT OF FIELD CANCERIZATION: BEYOND TOPICAL AGENTS

Introduction

Field cancerization (FC) is defined at the cellular level as the growth of a mutant clone that creates a field of cells predisposed to subsequent tumour growth.[1] Cutaneous FC is a phenomenon that occurs in areas of the skin exposed to chronic ultraviolet radiation (UVR), including the face, balding scalp, forearms, and dorsal hands.[2] This then leads to fields of clonal proliferations of p53-mutated keratinocytes and is characterized by multifocal actinic keratoses (AK), squamous cell carcinomas in situ (SCCis), and cutaneous squamous cell carcinomas (CSCC).[3] Risk factors for FC are similar to those for AKs and CSCCs, including exposure to UVR, lighter skin types, increasing age, male sex, and immunosuppression.[3] Topical therapies for FC were previously discussed in a previous article in this journal.[4] This review will therefore focus on field ablation treatment options and oral medications.

Field Ablation

Field ablation with chemical peels or laser resurfacing has been studied for the treatment of AK and FC. Unlike topical treatments discussed previously,[4] field ablative options are non-selective and treat the entire area to which they are applied, not just atypical cells.

Chemical Peels

Chemical peels are indicated in the management of AK and work by nonspecific chemical ablation of defined skin layers followed by regeneration of the epidermis and superficial dermis. Chemical peels that have been studied for AK include 70% glycolic acid peels, 30–35% trichloroacetic acid (TCA) peels, and peels combining Jessner's solution with 35% TCA.[5] Studies have demonstrated that glycolic acid alone did not provide a significant improvement in AK, and that combination treatment with 5-fluorouracil (5-FU) was required to achieve a 91% clearance of AK lesions. For instance, Jessner's solution combined with 35% TCA achieved AK clearance rates of 75–78%, and 30–35% TCA alone achieved 48–89% clearance rates of AK.[5] Studies that included comparator arms have shown that chemical peels were not as effective in clearing AK lesions or decreasing the recurrence of AK as that of photodynamic therapy (PDT) or 5-FU.[5,6] Side effects of chemical peels can include discomfort, bacterial superinfection, and scarring.[6] However, chemical peels require only one application in a clinician's office, which can be helpful for patients where compliance may be an issue. However, the relative lack of specificity of treatment with chemical peels may lead to a larger area of the skin requiring

aftercare and has a higher risk of scarring compared with more targeted medical field therapies.

Laser Resurfacing

Laser resurfacing works by removing the superficial layers of skin (epidermis and dermis) that contain actinic damage, which promotes re-epithelialization of healthy skin. Laser resurfacing can be conducted as monotherapy with fully ablative lasers (CO2 and erbium-doped yttrium aluminum garnet [Er:YAG]) or with non-ablative fractional lasers (e.g. CO2, Er:YAG, Thulium).[7] A review article that summarized the findings of several small studies has demonstrated that laser resurfacing monotherapy had comparable efficacy to 5-FU and 30% TCA peel for reducing AK lesions, although it was inferior to PDT.[7] A major limitation of these studies is the small number of patients analyzed and the use of different protocols and lasers in each study.[7] Several studies have shown that PDT coupled with laser resurfacing increases clearance rates of AK compared with PDT monotherapy or ablative laser resurfacing monotherapy alone, especially with hyperkeratotic AK lesions or on sites such as the limbs.[8] This finding is thought to be achieved by facilitating the delivery of photosensitizers into the skin. Side effects include pain, edema, temporary hyperpigmentation, erythema, itching, and peeling. In rare instances, patients can develop scarring or hypopigmentation. It is important to keep in mind that laser resurfacing is not typically covered by insurance plans; consequently, the cost to patients may be prohibitive. Similar to chemical peels, a benefit of laser resurfacing is that it is often a "one-time" treatment in comparison to many topical therapies. However, further study is required to determine if this treatment is more effective than topical therapies to justify its higher cost.

Oral Medications

Nicotinamide

Nicotinamide (also known as niacinamide), is a vitamin B3 derivative that augments the repair of UV-induced DNA damage and reduces UV-associated immunosuppression.[9] Nicotinamide taken at a dose of 500 mg orally twice daily is generally considered safe, with no concerning side effects being reported with this dosing. Three small phase 3 studies have demonstrated that oral nicotinamide reduced the rates of AK and keratinocyte carcinoma (KC) (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC] combined) in immunocompetent patients. Notably, in the landmark clinical trial by Chen et al., the number of AK lesions was reduced by 13% ($P<0.001$) at 12 months, and the number of KC lesions was decreased by 23% ($P=0.02$).[9] However, no evidence of benefit was found after nicotinamide was discontinued, suggesting that nicotinamide treatment must be continued long term.

The evidence for benefit of nicotinamide treatment in immunosuppressed patients is mixed. Some small case-control studies have shown improvement in AK, but not SCC. Furthermore, a 2023 phase 3 trial on nicotinamide did not demonstrate a decrease in the number of KCs or AKs in solid-organ transplant recipients, though this study was closed early owing to low recruitment and was underpowered.[10] While the benefits of nicotinamide therapy are promising, current evidence is not definitive, especially in the immunosuppressed population. In addition, longer-term prospective studies are lacking. Nicotinamide treatment is however a low-risk option that may be helpful in treating high-risk individuals and should be considered as an option for these patients.

Acitretin

Acitretin is an oral retinoid used for chemoprevention that works by normalizing keratinocyte differentiation in the epidermis, as well as hindering the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), migration inhibitory factor-related protein 8 (MRP-8) and interferon-γ (IFN-γ).[11] Acitretin has been studied for chemoprevention in solid organ transplant recipients (SOTRs), and guidelines suggest consideration of acitretin in patients with >5 KCs over the course of 2 to 3 years, significant field disease with diffuse AKs/SCCis despite treatment, high-risk KCs, or metastatic KCs.[12]

A 2021 systematic review showed a 56% reduction in KC formation,[13] and several small retrospective studies have demonstrated sustained efficacy and safety for up to 5 years of treatment with acitretin.[14] Similar to nicotinamide, continuous treatment is required to maintain chemoprevention, with some studies noting a "rebound effect" of a rapid increase in KC lesions after discontinuation of acitretin.[14] Dosing is 10–30 mg daily, depending on side effects. Common side effects include hypertriglyceridemia, liver function test abnormalities, headache, mucocutaneous xerosis, myalgias, and alopecia.[11] Most studies have been conducted in SOTRs[15] and patients with genodermatoses such as xeroderma pigmentosa. As such, while acitretin is a common medication to use in the SOTR population, its benefit in immunocompetent individuals requires further study.

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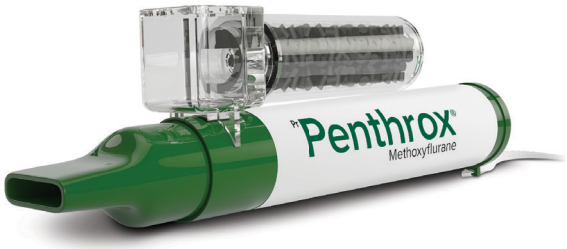

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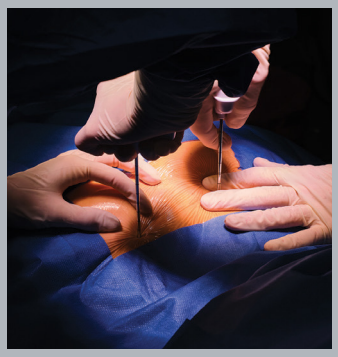

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- Use as an anesthetic agent

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Nephrotoxicity: Supratherapeutic doses of methoxyflurane inhalation have been shown to lead to serious, irreversible nephrotoxicity in a dose-related manner. Dosing limitations should be followed meticulously to prevent or limit risk of nephrotoxicity. Consecutive day use of PENTHROX® is not recommended because of nephrotoxic potential. The lowest effective dose should be administered, especially in the elderly or in patients with other known risk factors of renal disease.

Hepatotoxicity: Very rare cases of hepatotoxicity have been reported with methoxyflurane inhalation when used for analgesic purposes. Use with care in patients with underlying hepatic conditions or having risk factors for hepatic dysfunction. PENTHROX® must not be used in patients who have a history of showing signs of liver damage after previous methoxyflurane use or halogenated hydrocarbon anesthesia.

OTHER RELEVANT WARNINGS AND PRECAUTIONS:

- Administer with caution in elderly patients with hypotension and bradycardia due to possible reduction in blood pressure
- Drug dependence
- May influence the ability to drive and operate machinery
- Potential CNS effects
- Do not administer concomitantly with alcohol ingestion
- To reduce occupational exposure to methoxyflurane, the PENTHROX® Inhaler should always be used with the activated carbon chamber to adsorb exhaled methoxyflurane
- Drug interactions - inducers of CYP 2E1 and CYP 2A6
- Local skin reactions or irritation to the eyes and mucous membranes
- Exercise caution if administering to a nursing mother

FOR MORE INFORMATION:

Please consult the Product Monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for important information relating to adverse reactions, drug interactions, patient counselling, and dosing/disposal information (regarding the total maximum dose for a single administration or over the first day of treatment, in a single 48-hour period and entire treatment course) which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-888-867-7426.

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† A phase IV, randomized, double-blind, single-centre, placebo-controlled study to evaluate the efficacy and safety profile of PENTHROX® for the treatment of incident pain in adult patients requiring analgesia associated with a planned bone marrow biopsy (BMB) procedure. 49 patients were randomized to PENTHROX® and 48 patients to placebo. All patients received local anaesthetic as well as study drug.

NRS = numeric rating scale

Capecitabine

Oral capecitabine can be considered as an option for patients with FC who continue to develop large numbers of KC lesions despite the use of field-directed therapies and other chemopreventative agents. Capecitabine is a prodrug of 5′-deoxy-5-fluorouridine, which is converted to its active metabolite 5-FU, and has been used off-label for prevention of KC.[12] Case reports and small case series have shown that capecitabine treatment reduces both SCC and BCC, as well as AK in SOTRs.[16] Capecitabine is typically administered at a dose ranging from 0.5–1.5 g/m^2 daily for days 1 to 14 of a 21-day treatment cycle.[17] The treatment cycles are repeated until disease progression or the development of intolerable side effects, which occur in up to 30% of patients.[16] Side effects include fatigue, diarrhea, hand-foot syndrome, febrile neutropenia, and stomatitis.[16] Although capecitabine shows promise as a chemopreventative agent for KC, studies have only been conducted in a small population of SOTR and further larger studies are needed to truly determine efficacy.

Conclusion

Patients with FC are at higher risk of developing multiple CSCCs and often experience significant morbidity and mortality from their disease. Early intervention to treat FC with field ablative methods, as well as chemoprevention with oral medications, can potentially prevent progression to CSCC and decrease the cost to the individual and the health care system. Further studies will need to be conducted in both immunosuppressed and immunocompetent individuals to discover the most effective treatments, both in terms of cost and improved patient outcomes.

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Financial Disclosures

Advisory Boards: Abbvie, Bausch Health, Leo, Lilly, Janssen, Sun Pharma, UCB, Novartis
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DERMATOLOGIC CARE FOR THE LGBT POPULATION: TERMINOLOGY, STRATEGIES & SELECT DISEASES

Introduction

Canada is home to approximately 1 million people who are lesbian, gay, bisexual or transgender (LGBT).[1] Improving access to care and health for LGBT persons is a public health focus. Dermatology has a longstanding history of providing care to the LGBT community. For instance, in the 1980s, dermatologists diagnosed opportunistic infections and Kaposi sarcoma in young gay men; this contributed to the recognition of the HIV/AIDS epidemic.[2] The role of dermatologists in caring for the LGBT population has continued to grow over time.

LGBT populations experience increased disparities in health compared with others. These disparities are evident in both physical and psychosocial conditions. In Canada, these disparities stem from inequities related to healthcare accessibility, quality of care, and inclusivity.[3] The fear of stigmatization, coupled with previous negative healthcare experiences, may cause LGBT patients to delay or avoid accessing healthcare.[4]

Ongoing awareness and education of LGBT health needs is integral for providing culturally competent care. This article will review important terminology pertaining to LGBT patients, approaches to caring for LGBT populations, and a brief overview of a few dermatologic conditions within the LGBT population.

Terminology

Understanding and applying appropriate terminology is important when approaching LGBT healthcare. Clinicians must be aware of and understand the different concepts of sex, gender identity, sexual orientation, sexual behaviour, and gender expression (**Table 1**). The terminology related to the LGBT population is ever evolving and requires that clinicians commit to ongoing education to stay current with the latest terms and concepts.

Sex refers to biological and physiological qualities, such as the reproductive system and hormones of males and females, which are assigned at birth. **Gender identity** refers to a person's personal and individual sense of their gender, which may be different from the sex they were assigned at birth. People may identify as a man, woman, neither, other, or along the spectrum between man and woman. One's gender identity may or not may align with the sex they were assigned at birth. The term "**cisgender**" is used for those whose sex and gender identity are aligned, and the term "**transgender**" describes those whose sex and gender identity

Concept	Description	Examples of Terms (including but not limited to)	Additional Notes
Sex	Based on biological and physiological properties, such as genitalia and chromosomes	• Female • Male • Intersex (chromosomal pattern that varies from XX female or XY male)	• Assigned at birth. • May not align with gender identity. • 'Cisgender' describes a person whose gender identity aligns with the sex they were assigned at birth. • 'Transgender' describes those whose assigned sex at birth does not align with differs from their gender identity.; (see below for more information)
Gender identity	A person's personal and individual sense of gender	• Woman • Man • Gender non-conforming; (examples include: non-binary, gender-queer, agender, bigender, two-spirit, fluid)	• May not align with the assigned sex at birth. • May not align with their sexual orientation and/or behaviour. • Pronouns (he/him, she/her, they/them) are how individuals identify themselves.
Transgender	A person whose gender identity does not align with their assigned sex at birth	• Transgender man (female to male);), or trans man • Transgender woman (male to female);), or trans woman	• May not align with/differ to varying degrees from the sex they were assigned sex at birth. • The term "transgender" can be applied regardless of medical or surgical interventions. • The term "transgender" should be used as an adjective, not as a noun. • "Transitioning" or "gender affirmation" refers to the process of recognizing and expressing a gender different from the assigned sex assigned at birth. The process includes medical/surgical treatments, behavioural changes, and/or legal processes. The process is individualized for each person tailored to each individual.
Sexual orientation	A person's physical, emotional, and sexual attraction to others	• Straight • Gay • Lesbian • Bisexual • Asexual	• Might not correlate with sexual behaviour. • The term "homosexual" is a historical term which and is now considered a derogatory term and thus should not be used.
Sexual behaviour	The person's sexual behaviour of a person relatingin relation to the gender(s) of their sex partner(s)	• MSM: men who have sex with men • MSW: men who have sex with women • WSW: women who have sex with women • WSM: women who have sex with men	• These terms are used in clinical settings and are not used by patients to describe themselves. • These terms are not all-encompassing. For example, some MSM also have sex with women, or a WSW may have sex with men.

Table 1. *Terminology for LGBT persons[4,5]; adapted from Yeung et al.[4]*

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OTHER RELEVANT WARNINGS AND PRECAUTIONS:
- Prescribers are to register in the SILIQ Patient Support Program before prescribing SILIQ, be educated on the appropriate use of SILIQ, and educate patients on benefits and risks of treatment, especially the risk of suicidal ideation and behaviour.
- Discontinue SILIQ if the patient develops Crohn's disease while taking SILIQ.
- SILIQ may increase risk of infections.
- Exercise caution when considering the use of SILIQ in patients with a chronic infection or a history of recurrent infection.
- Evaluate patients for tuberculosis (TB) prior to initiating SILIQ treatment. Do not administer SILIQ to patients with active TB. Initiate treatment for latent TB prior to administering SILIQ. Monitor SILIQ patients for signs and symptoms of active TB.
- Live vaccines should not be given concurrently with SILIQ. Patients may receive inactivated or non-live vaccinations.
- Discontinue and initiate appropriate therapy if anaphylactic or other serious allergic reaction occurs.
- No adequate and well-controlled studies have been conducted in pregnant women.
- Caution in nursing women.

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do not align. The term "**transgender**" is an adjective, as opposed to a noun – i.e. an individual should be referred to as a "**transgender person**" as opposed to "**a transgender**."[4] Notably, the term "transgendered" is considered outdated.[4] **Gender affirmation**, also known as "**transitioning**," is the process of recognizing and expressing a gender identity that does not align with one's sex. "**Drag**" or **cross-dressing** refers to a person wearing clothing linked to a gender that differs from their sex assigned at birth. It is important to note that cross-dressing is not indicative of being transgender. **Sexual orientation** is a person's identity in relation to the gender(s) to which they are sexually attracted. Sexual orientation may not align with sexual behaviour. For example, a self-identified straight man might have sex with women and men. The term "**homosexual**," previously used to describe same-sex sexual behaviours or attraction, is considered derogatory, and thus should not be used.[4]

Strategies for Inclusive Care

Given the disparities in health for the LGBT population, dermatologists should create a welcoming space and cultivate relationships with LGBT patients. According to Yeung et al, implementing 3 key strategies can help dermatologists to provide care for LGBT patients, which include (1) *use of inclusive terminology*, (2) *obtaining an appropriate history*, and (3) *creating a trusting space for patients*.[4]

The first strategy can be applied by using inclusive language and embedding it throughout the patient experience; by this means, dermatologists and their clinical teams can demonstrate recognition and appreciation of diversity. Inclusive language also addresses the prejudice and discrimination that LGBT populations face by acknowledging their presence and identities.[5] The use of inclusive language is thus essential in building rapport with patients. Inclusive language should be employed when directly communicating with a patient, when describing someone who is present, as well as throughout the provision of services and virtual communications.[5] It is important to avoid assumptions when meeting and providing care to all patients. In addition, physicians should pay close to attention to the language used by a patient and respectfully seek clarification when needed.

An intake form can be used to obtain this information prior to the visit. Suggestions for the intake form include:

What sex were you assigned on your birth certificate? Select all that apply:

- Male
- Female
- Decline to answer

What is your current gender identity? Select all that apply:

- Man
- Woman
- Transman
- Transwoman
- Non-binary
- Other (please specify)
- Decline to answer

What is your sexual orientation? Select all that apply:

- Heterosexual
- Lesbian
- Gay
- Bisexual
- Other (please specify)
- Decline to answer

What pronouns do you use? Select all that apply:

- He/Him
- She/Her
- They/Them
- Decline to answer

The following are potential questions or phases that could be used during the initial visit:[4,5]

- "To be respectful, how many I address you?"
- "What pronouns do you use?" instead of "what pronouns do you prefer?"
- "I apologize in advance for any errors in addressing you. Please correct me at any point."

The aim of the second strategy is to obtain a thorough history related to sex and gender-affirming procedures, which is an important component of the diagnosis, and may improve the management of skin diseases.[6] While clinicians may hesitate to ask questions about sex and gender affirming procedures, most patients understand the importance of sharing this information and are willing to participate. A recent study in the USA surveyed patients and emergency department clinicians about obtaining a sexual history. Interestingly, nearly 80% of clinicians thought patients would refuse to provide their sexual orientation, whereas only 10% of patients reported they would refuse to provide their sexual orientation.[7]

When it is suitable and appropriate for clinical management, the patient's sexual history should be obtained. It is important to be mindful of the time it may take to build rapport before a patient is comfortable sharing their sexual history. It also may be helpful to ask anyone accompanying the patient to step out of the room to provide the privacy needed for the patient to feel comfortable sharing their sexual history.

Obtaining a sexual history can be normalized with the following phrases/questions:[4]

- "I routinely ask patients about their sexual history."
- "Are you sexually active?"
- "Do you have sex with women, men, or both?"

With regards to transgender patients, it is necessary to ask about medical and surgical interventions. Specifically, dermatologists should be aware of any hormone therapies that the patient is using, because these therapies can have cutaneous side effects. Not all patients will report hormone therapy as a "medication" on intake forms or during the initial visit; thus, this information may need to be specifically requested.[4]

The third strategy is to create a safe and welcoming environment for LGBT patients. It is important to recognize a patient's sex and gender identity, and to acknowledge the patient's name and pronouns. If the name/gender does not match insurance or other forms, dermatologists and clinic staff should ask patients how they wish to be addressed and make a note in the electronic medical record for future visits. In addition, inclusive imagery can be utilized throughout the clinic.[8]

Dermatological Diseases

This section provides a brief overview of a few dermatological diseases within the LGBT population. Please see the article by Yeung et. al for a comprehensive review of dermatological conditions common in LGBT persons.[8]

Transgender patients have distinct skin health needs in the context of gender-affirming surgical treatments and cross-sex hormone therapies. Dermatologists can treat cutaneous side effects of these treatments and contribute to screening and preventive care for transgender individuals.

Acne vulgaris is a potential side effect for transgender men receiving testosterone.[8] Over 85% of patients will develop acne within 4–6 months of initiating testosterone therapy.[9] Acne vulgaris can be treated with topical and oral antibiotics and retinoids. It is important to note that oral isotretinoin is a teratogen, and pregnancies have been reported in transgender men who are amenorrheic and on testosterone therapy.[9] As such, clinicians must consider the potential for pregnancy when treating transgender patients with isotretinoin, discuss contraception, and facilitate pregnancy testing. Melasma is a concern for transgender women receiving estrogen cross-sex therapy.[8] In addition, these patients may have facial hair that is resistant to hormonal therapy. Laser hair removal is a common procedure among transwomen.

Dermatologists can also use tools in the cosmetic armamentarium to provide gender-affirming care. For example, neuromodulators can be used to shape the eyebrows or to reduce masseter hypertrophy for a feminine appearance. Hyaluronic acid fillers can be used to contour cheeks, lips, and the jawline.

Compared to women who have sex with women (WSW), men who have sex with men (MSM) are at high risk for infectious conditions including but not limited to sexually transmitted diseases (STDs), viral hepatitis, MRSA skin infection, Kaposi sarcoma, and skin cancer.[4] The latter is linked to increased tanning bed exposure.[4] Appropriate screening and vaccinations, including human papilloma virus (HPV), hepatitis A, hepatitis B and meningococcal vaccines, should be considered.

While understudied in the literature, WSW are also at risk for HIV and other STDs.[4] However, WSW believe they require less screening for STDs. They also have lower rates of pap smear screenings as well as HPV vaccinations.[4] Clinicians for WSW should focus on safe sex counselling and encourage safer sex and health practices, including screening and vaccination.

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Financial Disclosures

Consultant/Advisory Boards: Allergan, Galderma, L'Oreal, NAOS, Neutrogena

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- Avoid use of other dermatologic medications and potentially irritating topical products that have a strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes
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- Treatment area should not be covered with dressings or bandages
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RAR-γ, retinoic acid receptor gamma

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ABOUT THE AUTHOR

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AUTOIMMUNE RHEUMATIC DISEASE WITH CUTANEOUS MANIFESTATIONS IN NORTH AMERICAN INDIGENOUS POPULATIONS: A REVIEW OF REGIONAL PREVALENCE DATA AND DISEASE CHARACTERISTICS

Abbreviations: SLE: Systemic Lupus Erythematosus, **SSc**: Systemic Sclerosis, **NAI**: North American Indigenous, **MCTD**: Mixed Connective Tissue Disease, **ACR**: American College of Rheumatology, **IHS**: Indian Health Services (US).

Introduction

Patients with cutaneous findings of systemic autoimmune rheumatological disease often require a multidisciplinary approach to diagnosis and management. In general, the first signs of systemic rheumatological diseases may be skin manifestations, which prompt those affected to visit the dermatology clinic. The basis and presentations of conditions such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) are complex, and involve genetic and environmental influences that are embedded in broad and overlapping factors of the socioecological model. This review recognizes that North American Indigenous (NAI) peoples are diverse, by region, language, culture, home environment, and more; therefore, generalizations are not intended. Furthermore, interpretations of the literature are limited by factors such as region and location (e.g., remote-rural vs. urban), sample size, study design, and statistical interpretations. Additionally, knowledge of biological and genetic predispositions of autoimmune diseases in the NAI population is lacking and beyond the scope of this article. The use of racial and ethnic terminologies can vary greatly and is often based in social concepts. These terms are also used in the context of current categorizations employed by the US Census or as categories that

are often used in clinical trials. Thus, further use of the term "North American Indigenous" (NAI) in this article takes this into account. It is worth noting that commonalities surrounding historical contexts and barriers to care are found for many NAI individuals and communities, for example for those living rurally and remotely. The purpose of this review is to provide a broad overview of what is known about mostly regional prevalence data and disease characteristics of autoimmune diseases such as SLE and SSc in the NAI population. Unique considerations surrounding barriers to care reported to be faced by some NAI populations will also be explored.

Discussion

Many observational regional studies across Canada and the United States (US) have demonstrated generally higher prevalence rates of SLE[1-8] and SSc[4,9] in NAI population samples. These studies are summarized in **Table 1**. Higher risks of other autoimmune diseases in NAI populations have been reported. For instance, a cross-sectional study from multiple regions of the US has demonstrated that Native Americans have a higher risk of Sjogren's syndrome and may present with less typical features, higher levels of disease activities, and extraglandular findings (**Table 1**).[10] In the US southwest, Behçet's disease may be more prevalent in the NAI population who may commonly present with a variety of skin manifestations (**Table 1**).[11] Mixed-connective tissue disease may also have a higher prevalence in NAI than in other populations.[12]

A considerable amount of data was found on the clinical manifestations of SLE in the NAI population. Notably, clinical manifestations of SLE may vary among individuals. Common clinical manifestations for example can include positive antinuclear antibody (ANA) positivity, arthritis, malar rash, and photosensitivity.[1,6,13]

Disease activity, manifestations, or outcomes of SLE or SSc may be worse or may not present in the typical manner, such as those described in the box below:

- A population-based study from southern Manitoba has demonstrated an association of NAI with higher severity index scores and younger age at diagnosis, more frequent vasculitis and renal complications, along with being more likely to receive immunosuppressive drugs or prednisone, and having increased mortality.[1]
- A Canadian cross-sectional study has found that NAI ethnicity is an independent risk factor for Raynaud's severity and gastrointestinal symptoms in those with SSc.[14]
- A population-based Indian Health Services (IHS) registry study that included the Oklahoma, Phoenix, and Alaska areas has shown that the three most common American College of Rheumatology (ACR) criteria met by Native Americans with SLE includes ANA positivity, hematologic disorder, and arthritis, with discoid rashes and neurologic disorders being the least common criteria met.[6]

With regards to potential genetic or hereditary predispositions, little is known. However, a genetic or family history risk for SLE may be present in some Indigenous populations.[3,6] For example, one of the highest prevalence rates of SLE worldwide has been identified in the Nuu-Chah-Nulth, an Indigenous group located in the Canadian Pacific Northwest.[2] SLE incidence rates may be higher in those of Crow, Arapahoe, and Sioux background, all of whom share regional commonalities and reside in the northern half of the US.[15] The highest worldwide prevalence rate of SSc has been identified in the Choctaw, and those with SSc who received care at the Oklahoma IHS had a higher prevalence of SSc compared with other Native American or white populations in the region. Among those with SSc, the disease phenotype was homogenous, and included diffuse scleroderma, pulmonary fibrosis, autoantibodies to topoisomerase-I, and associations with certain human leukocyte antigen (HLA) haplotypes.[9] Antifibrillin antibodies,[16] fibrillin-1,[17] and fibroblast gene[18] expression polymorphisms have been identified in those with native North American ancestry and have been associated with SSc in the Choctaw. These disease expressions may influence the disease course or be associated with increased susceptibility for

SSc,[18] or poorer survival.[16] In the context of Behçet's disease, mutations in the HLA-B51 gene family may be common in some regional Indigenous groups such as the Navajo and Pueblo.[11] Such studies raise questions as to whether there are genetic linkages unique to certain Indigenous groups with regards to prevalence findings and disease phenotypes.

Access to care remains a challenge for many individuals who reside rurally and remotely. Many studies include a rural population. Notably, rural populations, including some IHS catchment areas, face an uneven distribution of, and limited access to, specialists such as rheumatologists.[19] Barriers to care found in these studies include availability of healthcare (e.g., services provided at an urban-based tertiary care hospital such as direct-access to a rheumatologist, nephrologist, or in-house dialysis), and transportation barriers in which long-distance travel is required from remote communities.[3,6,18] Findings from these studies indicate that disparities reflected in disease outcomes are likely related to similarly identified barriers. For example, a review of 320 patients with SLE who received care within three IHS regions demonstrated that almost one-quarter of these patients were diagnosed by a primary care provider compared to urban-based specialists. However, specialist diagnosis of SLE was associated with better outcomes including a higher probability of an earlier diagnosis, receiving appropriate laboratory tests, having their SLE criteria classification documented, being tested for biomarkers of disease, and ever being treated with hydroxychloroquine.[19]

Most US data included in this review is gathered from IHS databases. It is important to keep in mind that the IHS represents a federally-operated rural healthcare delivery system that operates under the Department of Health and Human Services for status American Indian and Alaska Natives.[20] Therefore, many IHS-based studies likely represent more ruralized populations. However, recent US Census Bureau data indicates increasing representation of Native Americans, which shows that a majority of Native Americans now reside in urban areas and thus may be better represented in federal and state programs (e.g., Medicaid and Child Health Insurance Program) in which they may seek healthcare.[21] However, in Canada, a relatively higher proportion of Indigenous peoples live rurally.[22] Therefore, a limited diversity of the NAI population may have been captured in this data. Additional information is required to clarify characteristics of those seeking care outside of these registries, or those who have not participated in the studies included in this review. However, regardless of this issue, this review uncovered important themes. In particular, for rural-based NAI individuals who face barriers to care that are often based on the geographical location of their residence and the proximity and access to care.

Conclusions

This review has some limitations. First, this review provides a non-systematic summarization of heterogenous findings on the prevalence and disease outcomes of autoimmune diseases such as SLE and SSc in the NAI population. Analyzing and comparing differences in factors including regional location, study design, sample size, and statistical interpretation, among others is beyond the scope of this article. It remains unclear whether differences in these factors in the NAI population are related to a fundamental predisposition to these conditions, or to external factors such as systemic differences in health care access.

Knowledge of prevalence rates of SLE and SSc indicates the need for an increased awareness among clinicians of these diseases in the NAI population, and encourages further research initiatives to assess disease severity and outcomes, and to address gaps in treatment access.[6] This knowledge can potentially aid in screening of high-risk populations, which may facilitate early diagnosis and treatment, ultimately resulting in decreased morbidity.[3] In addition, better specialist access and primary care education for those who provide care to individuals with SLE are indicated.

Increased representation of the NAI population in clinical trials such as those for SLE may help clarify disease characteristics and therapeutic response. Despite the documented high population-based estimates of SLE, Indigenous peoples remain under-represented in randomized controlled trials of SLE, although their representation is increasing over time.[23] Any future Indigenous community-based studies should engage community input and approval using culturally competent research methodology frameworks.[19] Ultimately, gathering such knowledge and acknowledgement of population-specific differences in autoimmune and rheumatologic diseases in NAI peoples may help guide further studies on potentially diverse pathophysiology, and address barriers to care. On a practical level, it may assist clinicians in making more accurate diagnoses, thereby improving patient care.

Study/Country /Region	Study Design	Case Definition	Sample Size	Estimated Prevalence/Incidence**	Notes
(Peschken & Esdaile, 2000)[1] CAN Southern Manitoba	Regional arthritis center database search, medical record review (prevalence, disease course, survival)	SLE diagnosis (ACR criteria; diagnosed by rheumatology, hematology, nephrology, and general internal medicine)	n=49/257 Indigenous (19%) with SLE	Prevalence 42.3/100,000 Indigenous (twice-fold higher than general population at 20.6/100,000)	Indigenous ethnicity associated with: • Higher SLE disease severity index scores at diagnosis • Younger age • More frequent vasculitis and renal involvement • More likely to receive immunosuppressives or prednisone at most recent clinic visit • Four-fold increased likelihood of death
(Atkins et al., 1988)[2] CAN Pacific Northwest (Vancouver Island)	Retrospective, medical records	SLE	n=157 total requiring rheumatologist referral	Prevalence 348/100,000	Highest worldwide rates of SLE identified in the Nuu-Chah-Nulth Original article (abstract only*): Details extracted from Systematic review of rheumatic disease epidemiology in the Indigenous populations of Canada, the United States, Australia, and New Zealand (McDougall et al., 2017)[19]
(Houghton et al., 2006)[3] CAN British Columbia	Retrospective chart review	Pediatric (< 18) patients with SLE (ACR criteria) seen at the province's only tertiary care pediatric rheumatology clinic	n=6/40 Indigenous with SLE	Prevalence 8.8/100,000 (~2.5 fold higher compared to the pediatric general population at 3.3/100,000)	Family history of rheumatic disease more common in the Indigenous compared to non-Indigenous. Arthritis, myositis, and gastroenteritis common in the Indigenous. Limited by small sample size, and potential under-estimation of Indigenous case definitions.
(Barnabe et al., 2012)[4] CAN Alberta	Population-based registry stratified by FN status	SLE and SSc (ICD-9 codes)	Not specified	SLE prevalence (FN) 32.2/10,000 females, 3.2/10,000 males SSc prevalence (FN) 7.9/10,000 females, 1.3/10,000 males	Overall, prevalence of SLE and SSc comparable to FN and non-FN populations. On age stratification, FN females >age 45 had a two-fold higher prevalence of either SLE or SSc vs. non-FN females. Trend toward higher SLE prevalence in urban, and higher SSc prevalence in rural areas.
(Izmirly et al., 2021)[5] US National (CDC National Lupus Registry) and one Indian Health Services registry	Population-based registry	SLE (ACR criteria)	n=5,417 SLE cases (total)	Prevalence American Indigenous/ Alaska Native population: females 270.6/100,000, and males 53.8/100,000	American Indigenous/Alaska Native population "had the highest race-specific SLE estimates, both among females and males". [5] Multi-racial data included. Overall pooled prevalence from state registries was 72.8/100,000 py.
(Ferucci et al., 2014)[6] US Alaska, Phoenix area and Oklahoma regions	Population-based registry from IHS	SLE (ACR criteria)	n=285 cases	Prevalence 178/100,000 py (for females alone 271/100,000) Incidence 7.4/100,00 py (for Indigenous; females alone 10.4/100,000)	Estimates exceed most general population estimates. Female Indigenous adults found to have highest prevalence, most prominent in Phoenix area.

Study/Country /Region	Study Design	Case Definition	Sample Size	Estimated Prevalence/Incidence**	Notes
(Feldman et al., 2013)[8] US National (Medicaid database from 47 states)	Medicaid database (administrative billing claims/ICD-9 codes for SLE and demographics including self-reported race/ethnicity)	SLE (ICD-9 codes)	n=515/310,736 with SLE (Native American)	Prevalence 165.7/100,000 SLE, lupus nephritis 36.4/100,000 Incidence highest among African American females (38.6/100,000 py and Native American females (37.3/100,000 py)	Multi-racial data included. High SLE prevalence in Native American females (213.3/100,000) vs. males (48.9/100,000).
(Boyer et al., 1991)[7] US Alaska Native (Southeast coast; Tlingt, Haida, Tsimshian)	Patient care database	SLE	Not specified	Prevalence 112/100,000	High frequencies of both SLE and rheumatoid arthritis observed. Prevalence of SLE in Alaskan Natives approximately double vs. most white populations.
(Arnett et al., 1996)[9] US Oklahoma	Population estimates from an Oklahoma IHS database	SSc (ACR criteria)	n=28 Oklahoma Choctow cases	Prevalence 469/100,000 (full Choctaw), overall prevalence 66/100,000	Significantly higher prevalence in full blood quantum Choctaws (documentation of ancestry) – the highest prevalence documented. Homogeneity of phenotype: diffuse scleroderma, pulmonary fibrosis, autoantibodies to Topoisomerase-I, association with HLA haplotypes Other Native Americans in Oklahoma showed similar prevalence to white populations.
(Ferucci et al., 2017)[12] US IHS, Three regions of the US	Population-based registry from IHS	MCTD – (three case definitions encompassing rheumatologist diagnosis/ Alarcon-Segovia criteria)	n=61 Native American cases (all case definitions)	Prevalence 6.4 to 26.3 per 100,000 depending on definition used	MCTD prevalence higher in females. Authors concluded prevalence 'appears higher' than that in other populations.

Table 1. *Summary of SLE, SSc Disease Prevalence and Characteristics in North American Indigenous Peoples; courtesy of Rachel Asiniwasis, MD.*

*****Abstract only, Unable to locate or retrieve full text; therefore, information is based on the abstract.*
*******Confidence intervals, p-values and other statistical measures are not included in this table; details can be found in the primary source.*

Abbreviations: ***ACR:*** *American College of Rheumatology;* ***CAN:*** *Canada;* ***CDC:*** *Centers for Disease Control and Prevention;* ***FN:*** *First Nations;* ***HLA:*** *human leukocyte antigen;* ***IHS****: Indian Health Services;* ***MCTD:*** *mixed connective tissue disease;* ***SLE:*** *Systemic lupus erythematosus;* ***SSc:*** *Systemic sclerosis;* ***py:*** *person-years;* ***US:*** *United States*

Notes: *In the US, IHS represents a federally run health service within the Department of Human and Health Services for American Indigenous peoples and Alaska Natives, in recognition of the relationships between the federal government and tribes based on Article I, Section 8 of the 1787 Constitution, and being reflected in numerous treaties, laws, supreme court decisions and executive orders. It consists of 12 physical areas in the US, each having a base office located in Alaska, Albuquerque, Bemidji, Billings, California, Great Plains, Nashville, Navajo, Oklahoma, Phoenix, Portland, and Tucson. There are currently 170 IHS and tribally managed health centres based both in urban areas in urban areas and on-reserve, servicing approximately 2.6 million Native Americans belonging to 574 federally recognized tribes in 37 states. It largely represents a rural healthcare delivery system (IHS, 2021; KFF).*

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CANADIAN DERMATOLOGY TODAY: HIGHLIGHTS FROM THE INFLAMMATORY SKIN DISEASE SUMMIT 2023 IN VIENNA, AUSTRIA

Introduction

The Inflammatory Skin Disease Summit (ISDS) 2023 conference was packed with many scientific presentations on current and future innovations in dermatology. At the forefront were cytokine profiling, targeting, and monitoring. Although much of this work is conducted in study settings, it will inevitably be incorporated into clinical practice in the coming years.

Janus kinase Inhibitors

Dr. Gadina presented a review of current Janus kinase inhibitors. He pointed out that 4 different "generations" of Janus kinase (JAK) inhibitors have been outlined, partly based on a recent publication.[1] The first generation orthosteric inhibitors of JAKs are non-specific and include tofacitinib and baricitinib. Second generation inhibitors are more specific, and include upadacitinib (JAK1), abrocitinib (JAK1), and ritlecitinib (JAK3/TEC). In theory, this specificity could translate to fewer adverse effects arising from blockage of kinases with reduced affinity, although absolute in vivo confirmation of this theory is still lacking. In addition to the many indications for these agents, off-label uses are expanding, including genetic interferonopathies and morphea associated with signal transducer and activator of transcription 4 (STAT4) mutation.[2,3]

The third and fourth generations of JAK inhibitors include novel agents still in development. The "third generation" includes itaconate, which is a metabolite of the Krebs cycle that accumulates in macrophages and inhibits phosphorylation of JAK1. Itaconate is currently being studied for its potential use in treating asthma, allergic diseases, and alopecia areata (AA) (in topical form).[4]

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- **EASI 90**: **53.1%** (n/N=149/281) **vs. 8.1%** (n/N=23/281) of patients achieved EASI 90 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

A rapid improvement in skin clearance was achieved for RINVOQ 15 mg compared to placebo (defined as EASI 75 by Week 2; secondary endpoint)[1,2]

- **EASI 75**: **38.1%** (n/N=107/281) **vs. 3.6%** (n/N=10/281) of patients achieved EASI 75 at Week 2 with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

A greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful itch reduction (≥4-point reduction in Worst Pruritus NRS; secondary endpoint) compared to placebo treatment group at Week 16

- **≥4-point reduction in Worst Pruritus NRS**: **52.2%** (n/N=143/274) **vs. 11.8%** (n/N=32/272) of patients achieved a ≥4-point reduction in Worst Pruritus NRS with **RINVOQ 15 mg vs. placebo** (p<0.0001, multiplicity-controlled).

At Week 16, a greater proportion of patients treated with RINVOQ 15 mg achieved clinically meaningful improvement in emotional state (ADerm-IS emotional state domain score improvement from baseline; secondary endpoint) vs. placebo group (RINVOQ 15 mg [n/N=142/227]: 62.6%; placebo [n/N=42/212]: 19.8%; p<0.0001, RINVOQ vs. placebo, multiplicity-controlled).

RINVOQ is only indicated in patients not adequately controlled with a systemic treatment or when it's inadvisable; majority of the study subjects were treated with systemic therapy or phototherapy before starting RINVOQ.

* Comparative clinical significance has not been established.
† Please see Product Monograph for additional dosing and administration information.
‡ MEASURE UP 1 was a 16-week, randomized, double-blind, multicentre, placebo-controlled study that included adolescent and adult patients with refractory moderate to severe atopic dermatitis not adequately controlled by topical medication(s). At baseline, patients had an vIGA-AD score ≥3 in the overall assessment of AD (erythema, induration/papulation, and oozing/crusting) on an increasing severity scale of 0 to 4, an EASI score ≥16 (composite score assessing extent and severity of erythema, edema/papulation, scratches and lichenification across 4 different body sites), a minimum BSA involvement of ≥10%, and weekly average Worst Pruritus NRS ≥4. Patients received RINVOQ 15 mg or RINVOQ 30 mg once daily, or placebo.

ADerm-IS: Atopic Dermatitis Impact Scale; BSA: body surface area; EASI: Eczema Area and Severity Index; JAK: Janus kinase; NRS: Numerical Rating Scale; vIGA-AD: validated Investigator's Global Assessment for Atopic Dermatitis.

References: 1. RINVOQ Product Monograph. AbbVie Corporation. **2.** Guttman-Yassky E, Teixeira HD, Simpson EL, *et al.* Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet* 2021;397(10290):2151-68.

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Finally, the "fourth generation" of JAK inhibitors were presented, which include small interfering RNAs (siRNAs) that offer sequence-specific gene silencing of JAK1.[5] For example, in a mouse model, injection of siRNA resulted in significant downregulation of JAK1 mRNA that lasted for 5 weeks. Clearly, these innovations require human studies and further development. However, it is important to note that these agents represent a trend toward therapeutics that are more specific, potentially safer, and more effective.

Alopecia Areata

Dr. Paus discussed two pathobiologic mechanisms of AA, in which non-autoimmune and auto-immune attack of the hair follicle resulted in interferon-gamma signalling and the collapse of hair follicle immune privilege.[6] This hair follicle collapse results in hair dystrophy, premature catagen, and the AA phenotype. He mentioned new data which suggests that interleukin-15 (IL-15) antagonizes this hair follicle immune privilege collapse ex vivo.[7] This finding could weaken the argument for JAK3 inhibition in the treatment of AA. However, human studies looking at IL-15 treatment are needed, and JAK3 inhibition has been associated with effective regrowth of hair in patients with AA.[8]

Recent research has confirmed a critical role for epidermal growth factor receptor (EGFR) to restrain hair follicle intrinsic inflammatory JAK-STAT1 signalling. Disruption of JAK-STAT1 signalling was associated with the prevention of scarring tissue destruction, suggesting a novel role of JAK inhibitors for early scarring alopecia, and topical JAK inhibitors for adverse effects in EGFR-inhibitor treated cancer patients.

Data from the Phase 2 trial that evaluated the efficacy and safety of ritlecitinib demonstrated a decrease in expression of C-C motif chemokine ligand (CCL) 17, CCL-16 and IL-6 at week 12, and decreases in CCL-17, IL-9 and IL-13 expression at week 24, which was correlated with improvement from baseline in Severity of Alopecia Tool (SALT) scores.[9]

Atopic Dermatitis

Data was presented from a study that included a small group of 14 patients with atopic dermatitis (AD) and a history of eczema herpeticum (EH), and patients with AD without a history of EH. Both groups received treatment with dupilumab.[10] A history of EH was associated with elevated herpes simplex 1 (HSV1)-specific immunoglobulin E (IgE) levels, which had decreased after 12 weeks of dupilumab treatment. These findings add to the multiple currently accepted benefits of dupilumab.

A presentation included data for a new treatment approach, RPT193 (zelnecirnon), which is a potent and selective oral chemokine receptor 4 (CCR4) antagonist. RPT193 targets CCR4-mediated migration of Th2 cells to inflamed tissues, with subsequent secretion of IL-4, IL-5, and IL-13 cytokines. Results from a Phase 1b study were presented, with treatment being associated with changes in biomarkers measured in lesional skin that paralleled improvements in clinical scoring systems.

Another targeted treatment presented at the conference was amlecitinib, an anti-OX40 ligand monoclonal antibody, which prevents the interaction of OX40 on antigen presenting cells to T cells. The placebo-controlled study of patients with AD included 4 different subcutaneous dose regimens administered every 4 weeks. Treatment with amlecitinib was associated with a decrease in Eczema Area and Severity Index (EASI) scores of up to 60% at week 16, and a 73% decrease in EASI scores at week 24. Side effects in the drug vs placebo arms included nasopharyngitis (11% vs 9%), HSV (2.3% vs 2.5%). Of note, no severe injection site reactions, chills/aphthous ulcers, or pyrexia/flu-like symptoms were reported.

Linking Alopecia Areata to Atopic Dermatitis

Dr Guttman proposed that AA is joining the atopic march. Potential Th2 activation in some patients with AA is evidenced by several factors, such as increased IgE levels, seasonal flaring of AA, response to antihistamines, and presence of eosinophils and mast cells around AA-affected hair bulbs in 31–87.5% of patients.[11-15] Dr. Guttman also referenced data from a study that used OLINK proteomics to demonstrate a systemic Th2 inflammation response in the serum of adult AA patients similar to that seen in AD patients.[11]

Dr Guttman went on to present data on the benefit of JAK inhibitors in AA. While topical JAK inhibitors have shown promise in mouse models for treating AD, the results from three large human studies have not shown statistically significant effects, which Dr Guttman attributes to the thicker epidermal skin in humans. She also presented cytokine data from 18 patients who received ritlecitinib in a Phase 2 study, which demonstrated significant decreases in CCL-17, CCL-18 and IL-5 at week 12 as well as CCL-17, IL-9 and IL-13 at week 24 that were correlated with improved SALT scores.[9]

Psoriasis

Dr. Gudjonsson from Ann Arbor, Michigan provided an update on the current understanding of the immunogenetics of psoriasis, with an emphasis on cytokine signalling as a critical component of disease pathogenesis. He presented the latest data that implicates a subset of activated fibroblasts as a key driver of psoriasis, which resulted in IL-36 amplification and production of IL-17A and tumour necrosis factor (TNF) alpha.[16] Dr. Gudjonsson proposed a new framework to describe psoriasis pathogenesis by 4 main pathways: IL-23/IL-17, Type 2 interferons (IFN-gamma, which is shown to amplify IL-17 inflammation), IL-36 (associated with cutaneous lesion severity), and fibroblasts.

Hidradenitis Suppurativa

Dr. Kreuger presented an update on hidradenitis suppurativa (HS) and encouraged clinicians to consider targets for study in the superficial and deep layers of lesions.

He presented an analysis of epidermal lesional skin samples which demonstrated high levels of TNF alpha and IL-6 primarily from keratinocytes and not dermal cells, with the depth of inflammatory infiltrate correlating with HS severity.[17] The expression levels of elevated IL-1B, IL-12, IL-23 and IL-36 gamma in keratinocytes was mitigated by topical ruxolitinib. This data provides a rationale for novel topical treatments targeting these cytokines in superficial/early lesions.

Dr. Kreuger also presented data from dermal tunnel skin samples obtained in deroofing procedures, which showed that type 17 T (T17) cells in HS expressed lower levels of IL-23R, and higher levels of IL-1R1 and IL-17F, compared with psoriasis T17 cells ($P < 0.05$).[18] Both IL-1A from keratinocytes in dermal tunnels and IL-1B from semimature

dendrocytes can stimulate IL-1R, and can stimulate IL-6 secretion from fibroblasts, which taken together contributes to TH-17 induced production of IL-17A and IL-17F. The data presented above could expand the therapeutic candidates for HS.

Vitiligo

Three systemic JAK inhibitors have shown promising results for effectiveness in treating non-segmental vitiligo in adults compared with placebo, which includes (1) *ritlecitinib*, a Phase 2b study, (2) *povorcitinib,* a Phase 2b study, and (3) *upadacitinib*, a Phase 2 dose-finding study that was presented at the 2023 EADV congress in Berlin.

New therapeutics under study include auremolimab, an antibody to IL-15. Another advance involves star-shaped particles, termed stratum corneum to enhance drug penetration (STAR), which are vehicles containing tiny metal particles with micron-scale projections that create microscopic pores in the stratum corneum.[19] In addition, data was shown that demonstrates reduced CD8+ T cells and epidermal depigmentation in a mouse model of vitiligo using siRNAs.[5]

Autoimmunity

Dr. Payne reviewed autoimmune disorders that have increased in prevalence in recent years. She presented data showing that stem cell transplantation has been effective in a case series of patients with pemphigus vulgaris (PV), which led to complete remission lasting 12–16 years in some patients, along with 2 deaths related to preconditioning treatment and transplantation.[20] In addition, the DesCAARTes Phase 1 trial is enrolling patients with mucosal PV refractory to immunosuppressives to determine the optimal dose of desmoglein 3 (DSG3) chimeric autoantibody receptor T-cells (DSG3-CAART).[21] The goal of the trial is to deplete anti-DSG3 B-cells and simultaneously produce memory CAART cells that can persist, leading to long-term remission.[22]

Lupus

First line treatments for cutaneous lupus remain antimalarials, methotrexate, mycophenolate, and azathioprine. Anifrolumab, a type 1 interferon receptor antagonist indicated for moderate-to-severe systemic lupus, was associated with a significantly improved Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) response compared with placebo from week 8 through week 52.[23] Most recently, deucravacitinib, which blocks interferon type 1 elevation, was associated with a >50% decrease in CLASI scores at week 48 in 62–70% of patients who had a minimum baseline CLASI score of 10.[24]

Artificial Intelligence in Dermatology

A review of the possibilities of artificial intelligence in dermatology was presented, with studies demonstrating that digital image analysis conducted by artificial intelligence consistently performs at the level of a novice practitioner, although it is less accurate than an expert.[25] Resources were presented including Seamless M4T (Massive Multilingual Multimodal Machine Translation), which can input text or audio in 35 or more languages and translate the data into text or audio. For those interested in an alternative to ChatGPT, consider using HuggingChat, which is an opensource alternative to ChatGPT that uses large language models with more recent date cut-offs.

Urticaria

The final topic, presented by Dr. Maurer, was chronic spontaneous urticaria (CSU). Dr. Maurer presented new data reporting elevated levels of IgE anti-tissue tranglutaminase 2 in up to 20% of CSU patients.[26] Dr. Maurer shared information on the CRUSE app, which is a free program that allows patients with chronic urticaria to track their urticaria scores. In addition, treatments for CSU can be characterized based on 4 different mechanisms of action (**Table 1**). Notably, data recently presented at EAACI 2023 reported that dupilumab has shown significant benefits in patients with CSU in urticaria scores and IgE levels at 24 weeks. Barzolvolimab, a receptor tyrosine kinase type III (KIT) antibody, was associated with mast cell depletion and improved CSU symptoms, although Dr Maurer acknowledged adverse effects including development of poliosis, likely related to the presence of KIT on melanocytes and other cells.

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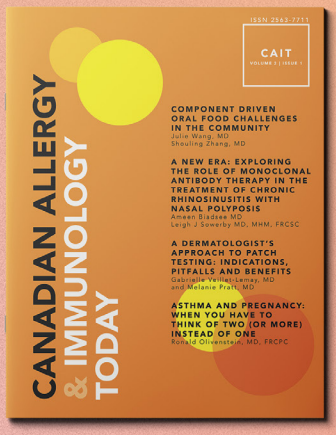

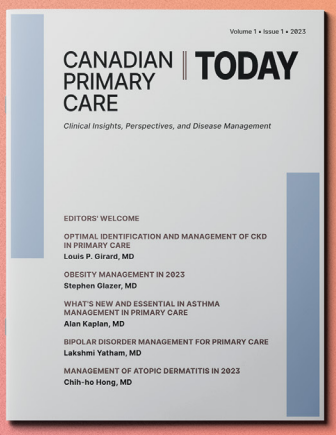

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Method of targeting Mast Cells	
Inhibition of mediators	Antagonists/ antibodies of IL-4 IL-13, IL-17/23, histamine 4R
Inhibition of activation	Antagonists/ antibodies to FCER1*, TSLP, C5aR, MRGPRX2, BTK/SYK/JAK/STAT
Silencing	Blocking of Siglec-8, (only present on mast cells + eosinophils)**
Depletion	Antibody to KIT (barzolvolimab)

Table 1. *Treatments for Chronic Spontaneous Urticaria; courtesy of Cathryn Sibbald, MD.*

***BTK inhibitors remibrutinib and rilzabrutinib*
****Antibody to Siglec8: lirentelimab*

Abbreviations: Histamine 4R: *histamine 4 receptor,* ***IL:*** *interleukin,* ***FCER1:*** *Fc epsilon RI,* ***TSLP:*** *thymic stromal lymphopoietin,* ***C5aR:*** *complement 5a receptor,* ***MRGPRX2:*** *Mas-related G protein-coupled receptor X2,* ***BTK:*** *Bruton's tyrosine kinase,* ***SYK:*** *spleen tyrosine kinase,* ***JAK:*** *Janus kinase,* ***STAT:*** *signal transducer and activator of transcription,* ***Siglec-8:*** *sialic-acid-binding immunoglobulin-like lectin 8,* ***KIT:*** *receptor tyrosine kinase type III.*

Conclusion

Although only in its fifth year, this conference has quickly become a well recognized forum for presentation of the most recent advances in our profession. For those interested in attending, the conference is held biannually with the location alternating between Vienna and New York.

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