ABOUT THE AUTHOR

Cathryn Sibbald, MSc, MD, FRCPC

Dr. Cathryn Sibbald is a dermatologist who completed her residency training at the University of Toronto and is board certified in Canada and the US. She completed fellowship training in pediatric dermatology at the Children's Hospital of Philadelphia. She has an MSc in Epidemiology from the London School of Hygiene & Tropical Medicine and a BSc Ph.M. from the University of Toronto. She is a staff physician with research and clinical activities at the Hospital for Sick Children, and recently joined the pyoderma gangrenosum clinic at Women's College Hospital. She is an assistant Professor at the University of Toronto in the Department of Pediatrics with a cross appointment to the Department of Medicine. Her clinical interests are broad and include alopecia, morphea, and laser treatment of vascular lesions.

Affiliations: Assistant Professor, Cross Appointment, Division of Dermatology, Department of Medicine, University of Toronto, Assistant Professor in Department of Paediatrics, Faculty of Medicine, University of Toronto

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]

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.

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.

Correspondence

Dr. Cathryn Sibbald
Email: cathryn.sibbald@sickkids.ca

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