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ABOUT THE AUTHOR

Marisa G. Ponzo, MD-PhD, FRCPC, FAAD

Dr. Marisa Ponzo is board certified in both the U.S. and Canada and is a community dermatologist in Toronto, Ontario. She completed her MD-PhD degree at McGill university followed by her dermatology residency at the University of British Columbia. She is currently working at North York Dermatology Clinic and has a busy Medical, Cosmetic and Clinical Trial practice. Prior to her recent move to Toronto, she was the Division Head of Dermatology at St Paul's Hospital in Vancouver, BC. In addition, she ran specialty clinics, including the Medsafe clinic, where patients with severe cutaneous adverse reactions to medications were assessed, and their culprit drugs were identified through specialized testing. She also ran a skin cancer screening clinic for patients with solid organ transplants.

Affiliations: North York Dermatology Clinic, North York, Ontario, Canada

Cicatricial Alopecias and the Role of Janus Kinase Inhibitors: A Novel Approach and Comprehensive Overview to a Challenging Problem

Marisa G. Ponzo, MD-PhD, FRCPC, FAAD

Cicatricial alopecias (CAs) represent a group of conditions that result in permanent hair loss due to the destruction of hair follicles and their replacement with scar tissue. Recently, Janus kinase (JAK) inhibitors have emerged as potential treatments for various alopecias, including scarring types. In this review, we will discuss CAs, their pathophysiology, diagnosis, and the evolving role of JAK inhibitors in their treatment.

Pathophysiology of Cicatricial Alopecia

The prevalence of cicatricial alopecias (CAs) is growing and is estimated to account for 7% of all alopecia cases.[1] These conditions include frontal fibrosing alopecia (FFA), lichen planopilaris (LPP), central centrifugal cicatricial alopecia (CCCA), discoid lupus erythematosus (DLE), and folliculitis decalvans. However, for the purpose of this review, we will focus on FFA, LPP and CCCA. Unlike non-CAs (e.g., alopecia areata, androgenetic alopecia, telogen effluvium), CAs result in irreversible follicular damage due to lymphocytic attack of the follicular bulge and scar tissue

formation, which prevents hair from regrowing due to irreversible damage to epithelial stem cells. Early diagnosis and treatment are imperative to help prevent scarring and the associated psychological burden.

The clinical presentation of CAs varies depending on the specific condition. However, patients will typically present with gradual hair loss, scarring, inflammation, perifollicular erythema, perifollicular hyperkeratosis, and follicular plugging. They may experience scalp dysesthesia and pruritus. The areas of the scalp affected develop shiny, smooth patches without visible follicular ostia. FFA primarily affects postmenopausal women and causes eyebrow loss and recession of the frontal hair line. Although distinct, LPP is thought to share an overlapping pathology and hence similar histological findings. LPP affects all genders and age groups, resulting in patchy hair loss throughout the scalp. Patients with LPP may experience more pruritis and scalp dysesthesia due to inflammation compared to those with FFA. CCCA is primarily observed in Afro-American women, and results in hair loss and tenderness at the vertex of the scalp.

The inflammatory process is central to the pathogenesis of these conditions. Some insights of this complex pathophysiological process can be gleaned. The inflammatory pathway is thought to involve the upregulation of T helper (Th) 1/interferon (IFN) g and fibrosis-related markers.[2-3] Studies have shown that the Th1 and Janus Kinase (JAK)/signal transducers and activators of transcription (STAT) pathways are upregulated in FFA.[4] Lesional skin of patients with CAs has shown enhanced fibrosis and STAT pathway-related genes.[5]

JAK Inhibitors: Mechanism of Action and Role in Cicatricial Alopecia

Treating CAs is challenging and aims to control inflammation and prevent further hair loss. Currently, there are no treatments approved by Health Canada or the Food and Drug Administration. While in-depth review of standard treatment protocols for CAs is reviewed elsewhere,[6] the focus of this review is on the novel use of JAK inhibitors (JAKi) for this condition. Previous treatment paradigms have shown inconsistent efficacy, which highlights an area of unmet need for CA therapies.

JAKi are a class of medications that target specific intracellular signalling pathways crucial for the immune response. JAKs are enzymes that mediate the activity of cytokines involved in immune responses. Specifically, they are critical for the signalling of interleukins and interferons, which are implicated in inflammation and autoimmunity. The most well-known JAKi include tofacitinib, ruxolitinib, upadacitinib, abrocitinib, and baricitinib. These medications are approved and are commercially available for other dermatologic conditions, namely nonsegmental vitiligo, atopic dermatitis, and alopecia areata. By blocking the signalling of pro-inflammatory cytokines, they help reduce the immune-mediated inflammation observed in various conditions, including autoimmune skin diseases such as alopecia. In conditions such as CAs, particularly those with autoimmune or inflammatory mechanisms such as LPP and DLE, JAKi have shown promise as novel treatments due to their ability to target the inflammatory pathways directly.

Clinical Evidence for JAK Inhibitors in Cicatricial Alopecias

Data from retrospective analyses, case series, and case reports show promising results in blocking the JAK pathway for CAs. Several clinical trial programs are underway to provide larger-scale datasets.

Interestingly, some early studies have reported the use of topical JAKi as an effective treatment option for CAs. Given the potential toxicity of systemic JAKi, this offers a valuable addition to our treatment armamentarium. A retrospective chart review with 41 patients demonstrated that topical tofacitinib, a JAK-1/3 inhibitor, applied as a 2% cream twice daily in patients with LPP and FFA, resulted in a 48% decrease in the Lichen Planopilaris Activity Index (LPPAI) score at 9 months.[6]

In 2024, Desai et al. published a case study on the use of topical ruxolitinib 1.5% cream in a 55-year-old male with FFA.[7] Ruxolitinib is a selective JAK1 and JAK2 inhibitor, approved in Canada and the US for treating atopic dermatitis and nonsegmental vitiligo. In this case report, the patient presented with a 4-year history of frontal hairline tenderness and recession, followed by eyebrow pruritus and loss, along with facial papules. The patient applied topical ruxolitinib 1.5% cream generously to the frontal scalp/forehead for 3 months. He reported an improvement in pain, stabilization of his frontal hair line, and resolution of his facial papules. These findings were confirmed by clinical evaluation and trichoscopy. A case series in 2023 has shown similar findings.[8] In 2025, a retrospective cohort study showed an average 34% improvement in the LPPAI after a mean usage period of 8.5 months.[9]

In a phase 2a randomized clinical trial, patients with CA (LPP/FFA/CCCA) were randomized in a 3:1 ratio to receive either brepocitinib, an oral JAK1/2 inhibitor, at a dose of 45 mg once daily for 24 weeks or a placebo. After this period, all participants were re-randomized to receive brepocitinib for another 24 weeks.[10] The coprimary endpoints were changes in lesional expression of C-C motif chemokine ligand (CCL5), changes in lesional expression of fibrosis-related markers, and safety at week 24. Patients receiving brepocitinib showed significant downregulation of CCL5 expression at week 24. Analysis of placebo patient data showed an enrichment of fibrosis-related markers. Brepocitinib was well tolerated. Key secondary clinical efficacy outcomes showed significantly improved clinical severity scores. Patients with LPP receiving brepocitinib showed a significant mean percent change in LPPAI of -51% (90% confidence interval [CI], -79.5, to -30.2) compared to baseline at week 24. Further improvement was noted at week 48 with a mean percent change of -79.2% (90% CI, -100 to -53.6). Similar improvements were noted in the FFA and CCCA groups. Phase III trials are underway and are expected to be informative.

Overall, emerging evidence suggests a role for JAKi in the treatment of CAs. However, it remains uncertain whether the results can be maintained once topical or systemic JAKi are discontinued.

Challenges and Future Directions

While JAKi show promise as a treatment option for CAs, several challenges and areas for further investigation remain. JAKi can cause side effects, including immunosuppression, which can increase the risk of infections, and potential adverse effects on cholesterol and liver function. The long-term effectiveness of JAKi for CAs is still under study. Given the chronic nature of many CAs, ongoing trials are essential to assess whether JAKi can provide sustained benefits. Due to the heterogeneous nature of CAs, personalized treatment approaches, including the use of JAKi, need to be tailored to each patient's specific condition and response to therapy.

Correspondence

Marisa G. Ponzo, MD-PhD, FRCPC, FAAD
Email: Marisa.Ponzo@vch.ca

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