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CUTANEOUS DRUG REACTIONS (J BRIEVA, SECTION EDITOR)

Topical JAK Inhibitors for the Treatment of Alopecia Areata and Vitiligo

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Abstract
Purpose of Review Alopecia areata (AA) and vitiligo are dermatological autoimmune diseases that, until recently, have had no specifically targeted therapies. Here, we review the future of therapies specifically targeted to the treatment of alopecia areata and vitiligo, both of which have JAK-STAT signaling implicated in their pathogenesis.
Recent Findings With a greater understanding of disease mechanisms and pathogenesis, we are now able to target the immune dysfunction in autoimmune diseases with more precision than topical corticosteroids and calcineurin inhibitors. Inhibition of the JAK-STAT pathway has been shown to be effective in the treatment of AA, vitiligo, and in some patients with both diseases.
Summary In this review, we summarize the current molecular and immunological understanding of AA and vitiligo, how JAK inhibition is increasingly positioned as a new therapy for autoimmune diseases, and the future of topical JAK inhibitors in the field of dermatology.

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Introduction

Immune-mediated dermatological diseases encompass inflammatory conditions such as atopic dermatitis and psoriasis, as well as autoimmune disorders like alopecia areata (AA) and vitiligo. As a significant physical and immunological barrier between the body and the environment, the skin is the home of complex and intricate interactions between the epithelial and immune cells. Common first-line treatments for immune-mediated dermatological conditions include topical corticosteroids, which cause blanket immunosuppression and are replete with adverse effects. In this age of directed therapies and personalized medicine, we now have a more nuanced understanding of the various components of the immune system, along with the technology to disrupt them selectively. Thus, general therapies may soon be relegated to the archives, and research and development of directed therapies are now taking center stage. One such pathway that holds promise for therapeutic targeting in dermatology is the Janus Kinase (JAK)-Signal Transduction and Activators of Transcription (STAT) pathway.

JAK-STAT Signaling

JAK-STAT signaling is a ubiquitous and pleiotropic signaling pathway that is central to controlling multiple cellular processes. JAKs form non-covalent interactions with the cytoplasmic portion of cell surface receptors for over 50 growth factors and cytokines, most of which lack an intrinsic signaling apparatus, and ligand binding results in

their dimerization and trans-phosphorylation (Fig. 1). Phosphorylated JAKs recruit cytoplasmic proteins known as STATs via their Src-homology (SH2) domains. Phosphorylation of STAT proteins on a conserved C-terminal tyrosine residue leads to activation and dimerization of the STATs, and translocation to the cell nucleus where they bind to DNA elements to direct gene expression. In most eukaryotic systems, there are four different JAKs (JAK1, JAK2, JAK3, Tyk2) and seven STATs (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6).

JAK-STAT signaling was initially discovered as the main downstream pathway for interferon (IFN) signaling [1]. Subsequently, many other receptors have been found to employ a combination of JAKs for signaling, each system having preferential specificity for STAT proteins. Signal transduction is thus a product of the specific combination of JAKs and STATs present, and is lineage and context dependent in different cell types, leading to diverse patterns of gene expression. Details of the JAK-STAT pathway have been reviewed extensively by other authors [2•, 3].

JAK-STAT signaling is well characterized in the differentiation, maintenance, and activation of the healthy innate and adaptive immune system. JAK-STAT signaling has also been placed downstream of growth factor receptors, thus mediating cellular processes such as survival, differentiation, and proliferation in almost all cell types. In pathogenic states, constitutive or aberrant activation of JAK-STAT signaling may result in oncogenesis or dysfunction of the immune and hematopoietic system. As such, a new class of small-molecule drugs known as JAK inhibitors (JAKinibs) has been designed and developed to target these pathways. Ruxolitinib, a JAK1/JAK2 inhibitor, was the first JAKinib to be FDA approved, showing efficacy in the treatment of high-risk primary myelofibrosis [4]. Tofacitinib, a pan-JAK inhibitor, was later approved for the treatment of rheumatoid arthritis (RA) and has shown efficacy in the treatment of other immune-mediated diseases such as psoriasis, psoriatic arthritis (PsA), inflammatory bowel disease, and transplant rejection [5–7].

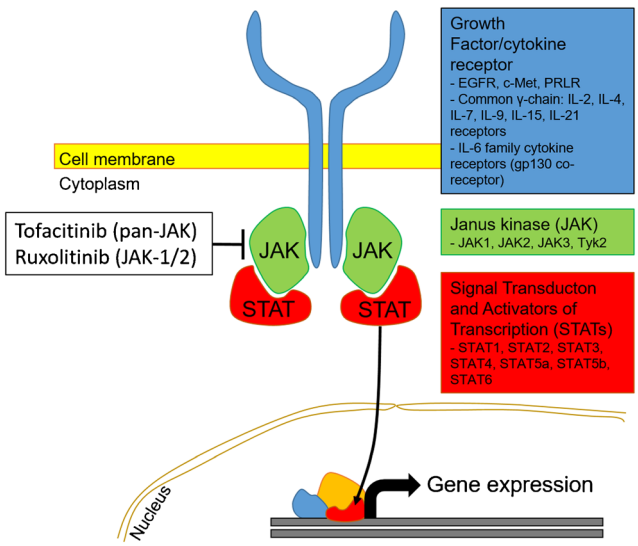

Fig. 1 Schematic of JAK-STAT signaling pathway. Specific cellular context will determine the combination of JAKs and STATs activated upon ligand binding. Recruitment of JAKs to the cytoplasmic portion of the receptor leads to auto-phosphorylation and activation, which in turn recruits and phosphorylates STAT proteins. Phosphorylated STATs translocate into the nucleus and bind to promoter sequences to enhance or repress gene expression. JAKinibs commonly used (tofacitinib, ruxolitinib) inhibit the kinase domain of the JAKs, preventing STAT protein phosphorylation and activation

Use of JAK Inhibitors in Dermatology

Compared to corticosteroids, JAKinibs provide a greater specificity to inhibit aberrant immune responses, while avoiding non-specific adverse effects associated with corticosteroids that may or may not be immune mediated (e.g., dermal atrophy, telangiectasia). Thus, as a class of drugs, JAKinibs have the potential to be applied to many dermatological conditions, due to their ability to inhibit many of the relevant signaling pathways.

Psoriasis

Because RA and PsA were hypothesized to share similar pathogenic Th1 cytokines with psoriasis, in particular those that signal via the common γ-chain (IL-2, IL-7, IL-9, IL-15, IL-21 and IFN-γ), JAKinibs were rationalized to be effective in psoriasis. Subsequent clinical trials have shown tofacitinib (as an oral medication) to be safe and effective in psoriasis and PsA [5, 8]. In a Phase 3 randomized non-inferiority trial of tofacitinib against etanercept and placebo for psoriasis, tofacitinib at a dose of 10 mg twice daily was as effective as etanercept twice weekly [9]. In contrast to biologics, small-molecule inhibitors like the JAKinibs can be orally administered, making them far more convenient and acceptable for the patient. Tofacitinib and ruxolitinib have also been topically formulated for psoriasis and have been shown to be effective in Phase 1–2 trials [8, 10, 11]. Topical JAKinibs will further improve on convenience and adherence to treatment, while reducing the risks of systemic exposure of the drug.

Atopic Dermatitis

Tofacitinib has been shown to have significant anti-pruritic effects on a mouse model of allergic contact dermatitis when given systemically, but had additional significant antagonistic effects on local pro-inflammatory cytokines and ear thickness when used topically [12]. Oclacitinib, a JAK-1/3 inhibitor,

also effective in this model, was recently approved by the FDA for veterinary in canine atopic dermatitis [13]. JTE-052, a novel pan-JAK inhibitor developed for treatment of inflammatory arthritis [14], has also been used topically to ameliorate the inflammation in a mouse model of atopic dermatitis [15] and allergic contact dermatitis (without a similar effect on croton oil-induced irritant contact dermatitis). A pilot study with six patients with moderate to severe AD showed oral tofacitinib to be effective in reducing disease severity where other treatments had failed [16]. Future studies will delineate the efficacy of JAKinibs in human AD, informing the potential therapeutic application and scope of the JAKinibs.

Pathogenesis of Alopecia Areata and Vitiligo

One of the prevailing theories surrounding the pathogenesis of AA involves the breakdown of immune privilege of the hair follicle, whereby "danger signals" in the form of MHC Class I or ULBP3 molecules are erroneously upregulated on the hair follicle [17••]. ULBP3 was identified by extensive genome-wide association studies to be a significant factor in AA pathogenesis [18••, 19], and its aberrant expression results in an attack by pathogenic $CD8^+$ cytotoxic effector T cells that also express NKG2D, the binding ligand of ULBP3 [17••]. This leads to destruction of the hair follicle, and a non-scarring hair loss that is initially noted to start in hairless patches, and may proceed to multifocal or universal involvement of the patient's hair-bearing skin.

Vitiligo, on the other hand, is due to a direct autoimmune attack as a result of sensitization of T cells to melanocyte autoantigens [20]. Abnormal cellular stress in melanocytes precipitated by genetic and environmental factors is believed to be a leading cause of melanocyte dysfunction [21–23]. This dysfunction activates innate immune inflammation and dendritic cell presentation of melanocyte autoantigens such as MART-1, gp100, tyrosinase, and tyrosinase-related proteins (TRP1 and 2) to T cells, hence sensitizing the T cells to target melanocytes for destruction, leading to depigmentation (reviewed in [24]).

While the triggering events in AA and vitiligo are likely to be distinct, both processes result in the activation of the Th1 adaptive immune response, and the recruitment of $CD8^+$ effector T cells into the skin [25]. In AA, IFN-γ induces the production of CXCL10, which is a central chemokine in the recruitment of the effector T cells to the skin to drive alopecia. IFN-γ has been shown to be significantly upregulated in circulating PBMCs and lesional skin of AA patients [26, 27]. Likewise, IFN-γ is also a critical component of vitiligo pathogenesis [28, 29], inducing CXCL10 in lesional vitiligo skin to promote autoreactive T cell recruitment and effector function [30••]. Serum CXCL10 has been shown to correlate with disease activity in vitiligo and may be useful as a clinical biomarker in this disease [31••, 32, 33]. In the case of AA, interleukin 15 (IL-15) has also been shown to be a supporting cytokine for the $CD8^+$ $NKG2D^+$ T cells [17••]. Both IFN-γ and IL-15 bind to cytokine receptors that employ the common γ-chain, which in turn signals via the JAK-STAT pathway.

Current Therapies for AA and Vitiligo

Despite their considerable clinical burden, both AA and vitiligo have no FDA-approved therapies that reverse or target the disease process. Randomized controlled trials (RCTs) are rare, and those that are published are often poorly designed (usually underpowered or insufficient follow-up), and rank low on the American College of Physicians (ACP) grading system for clinical trials [34].

Topical corticosteroids, a mainstay of dermatological therapies, are normally first-line treatment for vitiligo. Intralesional injections of corticosteroids are generally preferred in AA, where the pathogenic immune infiltrate is deeper in the dermis [25]. Corticosteroids have a global suppressive effect on all immune cells, causing reduced cellular proliferation and attenuation of cytokine production and chemotaxis. Corticosteroids also have effects on other cell types in the skin, such as fibroblasts and keratinocytes, and their suppressive effects in these cell types lead to adverse side effects such as atrophy and skin fragility [35]. Other topical immunosuppressants include the calcineurin inhibitors (e.g., cyclosporin, tacrolimus, pimecrolimus), which disrupt the NFAT-calcineurin signaling pathway and interfere with the activation of T cells, decreasing production of IL-2. While adverse effects are less severe compared with corticosteroids, calcineurin inhibitors come with a US FDA Black Box warning for potential malignancies resulting from immunosuppression [36]. Thus, it is imperative that safer and more specific therapies are developed for dermatological conditions such as AA and vitiligo.

The era of directed therapies began with biologics, which revolutionized the treatment of immune-mediated diseases by targeting specific cytokine-receptor interactions. The most successful example is the treatment of psoriasis [37] with TNF-α (Tumor Necrosis Factor-α) inhibitors, and more recently with IL-12/23 inhibitors that target common or unique subunits (p40, and soon p19 [38]) of the cytokines produced by Th17 skewed T cells, and the upcoming biologic therapies to IL-17, the driving force for Th17 differentiation [39]. However, biologics, which are essentially proteins (either antibodies or modified receptor subunits), require parenteral administration and are potentially immunogenic with repeated exposure. While there was some genetic evidence that TNF-α might play a role in the pathogenesis of AA and vitiligo [40, 41], subsequent case reports and case studies revealed that

TNF-α inhibitors were not effective in the treatment of either disease [42, 43] and, in many cases, they have been shown to precipitate disease [44–46]. The development of small-molecule inhibitors of multiple signaling pathways relevant to dermatological disease has undergone significant growth in the pharmaceutical industry.

Success Stories: Treatment of AA and Vitiligo with JAK Inhibitors

Recent studies on the immunopathogenesis of AA and vitiligo also uncovered a potential role for targeting the JAK-STAT pathway in these diseases. Following the work that identified the pathogenic $CD8^+$ $NKG2D^+$ T cells in AA, oral ruxolitinib given at a dose of 20 mg twice daily for 3 to 5 months resulted in full regrowth of hair in three patients who were previously treatment-resistant [17••]. Other JAKinibs, tofacitinib and baricitnib, were subsequently also found to be highly effective in patients with treatment-resistant AA [47, 48]. Serendipitously, one patient in a pilot study of ruxolitinib for the treatment of AA had concomitant vitiligo that also responded to treatment [31••]. This was supported by an additional case report describing the efficacy of systemic tofacitinib in the treatment of vitiligo [49•]. These findings have been confirmed in recent open-label trial of 12 patients with moderate-to-severe AA, where 75% of patients experienced at least 50% regrowth (compared to the expected rate of 12% spontaneous remission in a matched population) [50].

As a further corroboration on these findings, AA patients who had received systemic ruxolitinib for the treatment of other diseases like plaque psoriasis, essential thrombocythemia [51] and chronic mucocutaneous candidiasis [52] also were reported to have concomitant resolution of their alopecia. Further case reports confirming the efficacy of tofacitinib in the treatment of alopecia universalis also appeared in the literature [53, 54].

In a recent single-arm pilot study of tofacitinib for AA, it was noted that the starting dose of 5 mg BID was sufficient for effective hair regrowth in as soon as 4 weeks [55]. While there were no adverse events reported with the higher dose regimen in AA, topical formulations have been considered for delivery of higher concentrations of JAKinibs to the hair follicle microenvironment, so as to spare patients the potential side effects of prolonged systemic exposure, which may include immunosuppression.

The Future for Topical JAK Inhibitors in AA and Vitiligo

Targeting the JAK-STAT pathway with small-molecule inhibitors has many advantages over systemic biologic therapy. For skin diseases, higher local concentrations can be achieved with a topical formulation compared with systemic dosing so as to modulate local immune dysfunction. One of the earliest proof-of-concept studies used an intranasal topical inhibitory peptide to STAT6 to prevent Th2 differentiation in the airways in an experimental model of asthma, preventing development of allergic airway disease [56]. By avoiding systemic administration, the use of JAKinibs topically might avoid reported adverse effects such as increased risk of infections, hyperlipidemia, myelosuppression, and potential systemic malignancy.

Preclinical studies of topical ruxolitinib have shown it to be an effective modulator of the local immune response in an animal model of contact hypersensitivity [57] and have been shown to be effective for psoriasis in a small pilot study [11]. Topical 0.6% ruxolitinib cream was also recently shown to be effective in treating a case of alopecia universalis (complete loss of hair including scalp, eyebrows), and even though a larger surface of application was used in this case, there were no adverse effects on complete blood count, renal, or liver biomarkers [58]. This success has spurred several pharmaceutical companies to develop topical JAK inhibitors for AA, which are currently in Phase 1 and 2 clinical studies (please refer to www.clinicaltrials.gov for updates).

The safety profile of topical JAK inhibitors have thus been proven during these trials or other conditions. Topical tofacitinib has been shown to be efficacious and safe in both psoriasis and atopic dermatitis in Phase 2 clinical trials [10, 59]. Although there have not been any published data on the topical bioavailability of FDA-approved JAKinibs, preclinical studies on mouse skin have suggested that increased local concentrations have a more robust effect on hair regrowth in the mouse model of AA than systemic treatment [17••]. Further exploration into this effect has raised the possibility of a direct effect on hair follicle stem cells, promoting hair growth in normal mice [60]. Notably, in these studies in both AA and normal mice, topical treatment with JAKinibs only induced hair growth at the site of application, arguing against systemic absorption. In human patients using topical ruxolitinib for psoriasis, systemic JAK inhibition was ruled out by showing negligible inhibition of pSTAT3 in peripheral blood cells [61].

A recent study reported that chemokine production in the skin of a mouse model of vitiligo during disease progression predominantly originated from the keratinocytes [62•]. Selectively eliminating IFN-γ signaling only in keratinocytes abrogated disease, suggesting that specifically targeting this pathway only in the epidermis could be a highly effective treatment strategy. Thus, topical JAK inhibitors hold at least theoretical promise in the treatment of vitiligo as well. While AA and vitiligo may share certain pathogenic traits, the culprit inflammatory infiltrate is much deeper in the dermis for AA [25]. Thus, bioavailability and drug penetration may be a

legitimate concern for AA to target the anatomical site of inflammation and will be addressed in preclinical and Phase 1 clinical trials.

Conclusion

Future studies of topical JAKinibs for AA and vitiligo will interrogate and open new avenues of treatment for these diseases. New formulations and subsequent generations of the JAKinibs for topical use will expand their use beyond these diseases and may also find their place in the treatment of other dermatological diseases like psoriasis, allergic and atopic skin diseases, and possibly some forms of cutaneous malignancies.

Compliance with Ethical Standards

Conflict of Interest Etienne CE Wang declares no conflict of interest.

Dr. Christiano reports grants from National Institutes of Health, grants from Locks of Love Foundation, during the conduct of the study; personal fees from Aclaris Therapeutics, other from National Alopecia Areata Foundtion (NAAF), outside the submitted work. In addition, Dr. CHRISTIANO has a patent issued.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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