Review Article

Which is the Ideal JAK Inhibitor for Alopecia Areata – Baricitinib, Tofacitinib, Ritlecitinib or Ifidancitinib - Revisiting the Immunomechanisms of the JAK Pathway

Kabir Sardana, Savitha Bathula, Ananta Khurana

Department of Dermatology, Venereology and Leprosy, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India

Abstract

Alopecia areata (AA) is an immune-mediated condition, clinically manifesting as non-cicatricial patches of alopecia. It is often a self-limiting condition; however, regrowth of hair can take a long period of time, resulting in significant psychological comorbidity. With the recent advances in pathomechanisms of AA, the therapeutic approach to the condition has become more specific, and targeted therapy with small molecules is probably the ideal intervention. Many therapies exist for AA, but none of the systemic agents were approved, until recently, when baricitinib (Janus kinase (JAK1 and JAK2 inhibitor) gained FDA approval for the treatment of adult patients with severe AA. JAK inhibitors (JAKibs) target the γc cytokine and interferon-gamma (IFN-γ) signaling pathway, which is critical to the immunopathogenesis of AA and thus can reverse the hair loss in AA. Although JAKibs are emerging as a promising treatment modality for AA, the ideal JAKib is not yet settled, as there is scant data on H-2-H (head-to-head) comparisons of JAK inhibitors in AA. Moreover, the response achieved with JAKibs is not sustained after treatment discontinuation, with many studies showing a high recurrence rate with tofacitinib and ruxolitinib post-treatment. Also, recent studies have hypothesized that JAK2, with its ubiquitous expression, can cause adverse effects, unlike JAK1, which is associated with multiple major cytokine receptor families and JAK3, which is exclusively associated with the γc cytokine receptor. Thus, JAK3ibs may be associated with a better side effect profile and, in conjunction with their specificity, may replace other JAKibs as the treatment of choice for AA. We herein discuss the role of the JAK/STAT (signal transducer and activator of transcription) pathway in AA, the intricacies of various JAKibs in the management of AA, and emphasize the need for studies on tissue JAK and cytokine expression before arriving at the ideal JAKibs for AA.

Keywords: *Alopecia areata, baricitinib, cyclosporine, deucravacitinib, hair cycling, ifidancitinib, IFN-γ, IL-15, JAK inhibitors, JAK/STAT, methotrexate, ritlecitinib, tofacitinib*

Introduction

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is an intracellular signaling network which is activated by multiple cytokine receptors and regulates the expression of various inflammatory mediators. JAK inhibitors (JAKibs) provide a targeted therapeutic approach for numerous chronic inflammatory cutaneous diseases, such as atopic dermatitis, alopecia areata, vitiligo, psoriasis, and lichen planus.

AA is a chronic, autoimmune, non-scarring alopecia that involves the destruction of hair follicles (HF) by autoreactive CD8+ T cells. JAK-STAT dependent cytokines, interferon-gamma (IFN-γ) and interleukin (IL)-15, contribute to the major signaling cascade which, via JAK1 and JAK3, leads to the proliferation of autoreactive CD8+ T cells [Figure 1]. Its use was heralded by a case of psoriasis with alopecia universalis (AU) reported by Craiglow BG *et al.*,[1] in 2014, wherein tofacitinib given for psoriasis resulted in dramatic improvement of AU as well. This seminal clinical observation opened the "flood gates" to the use of various JAK inhibitors in AA.

There are several studies endorsing the efficacy of various JAKibs in AA, including the recent drugs ritlecitinib and brepocitinib.[2] Tofacitinib, a JAK1/3

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Address for correspondence:
Dr. Kabir Sardana, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, 110 001, India.
E-mail: kabirijdvl@gmail.com

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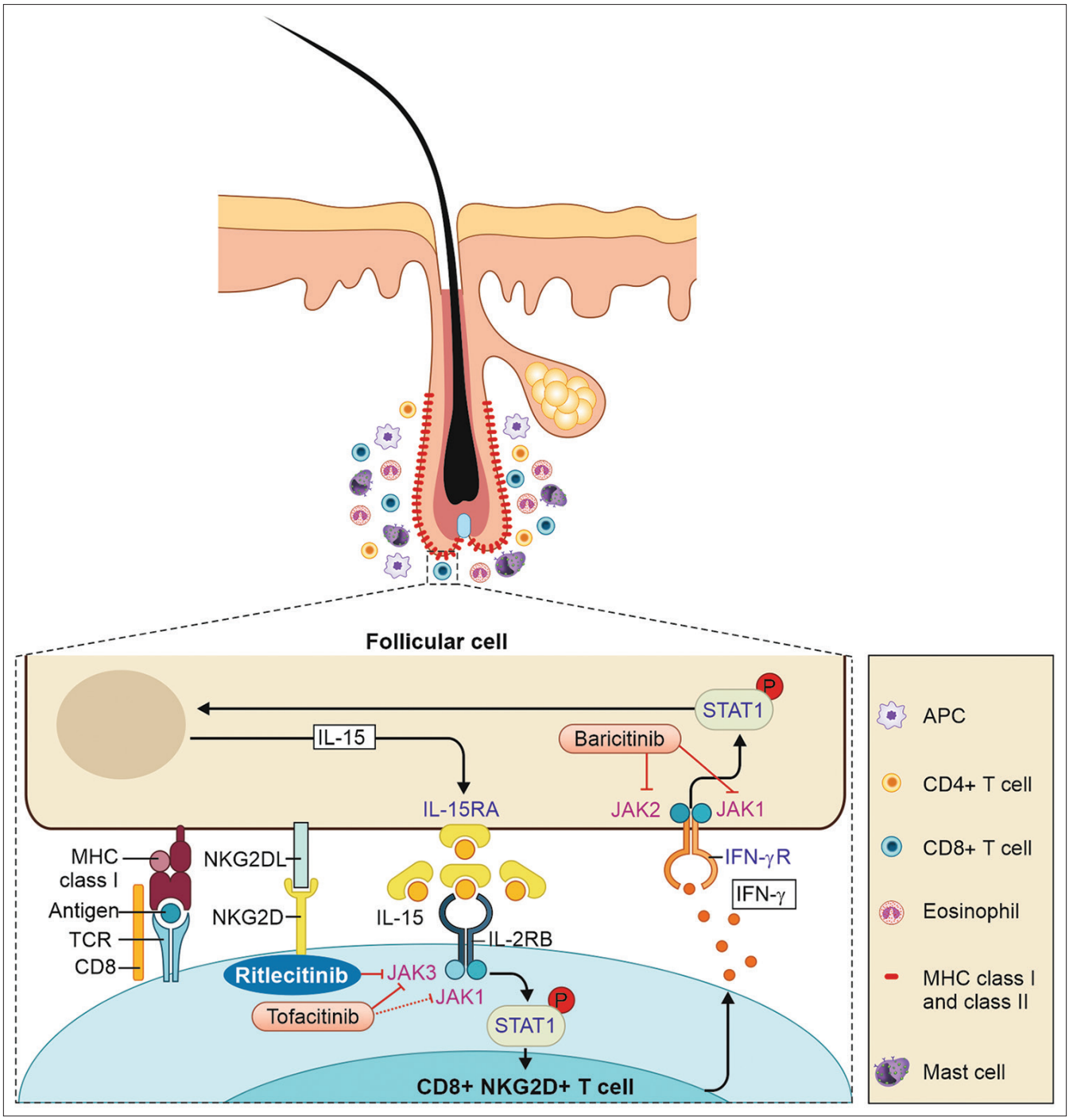

Figure 1: A depiction of role of JAK-STAT pathway, immune cells, and related cytokines in the immune-pathogenesis of alopecia areata. Specific targets of various JAKibs in alopecia areata are shown in the figure . The steps that predict AA , start with a loss of immune privilege leading to exposure of hair follicle antigens, which is followed by ingress of CD8+NKG2D+ T cell which interact with the follicular antigens through MHC class I The activated CD8+T cells then release IFN-γ which signals via JAK1 and JAK2 and releases IL 15 which mediates CD8+T cells induction. This is an autocrine loop that activates CD8+Tcells via JAK1 and JAK 3, to enhance the production of IFN-γ, amplifying the feedback loop. Apart from tofacitinib, specific JAK3 inhibitors including ritlecitinib and brepocitinib have been found to be effective and hold the potential of minimizing the side effects even though the efficacy may be similar. (APC: antigen presenting cells; TCR: T cell receptors; NKG2D: natural killer group 2D)

inhibitor, has shown excellent response but is believed to be associated with a higher adverse effect profile. Because of the ubiquitous expression of JAK 2, which accounts for side effects, baricitinib may not be the ideal JAKib of choice for AA. Also, the majority of the patients show recurrence soon after discontinuation of JAKibs.[3,4] Thus, an ideal JAKib for AA is yet to be determined and further studies are needed to assess the efficacy of JAKibs, taking into account the age, duration, severity of AA, and the predictable recurrence after stopping therapy.

Methodology

Electronic searches were performed using PubMed, Cochrane Library, and Evidence-Based Medicine Reviews. Search terms included 'alopecia areata', 'JAK inhibitor', 'JAK expression', 'tofacitinib', ruxolitinib', 'baricitinib', 'ritlecitinib' and 'ifidancitinib' as keywords. The search items were then analyzed for studies that included JAK tissue expression data. This identified 19 studies, out of which we excluded studies that did not look at JAKib drugs and then analyzed 14 studies published from 2014 to September 2022.

JAK receptors

Cytokine receptors of type I and type II receptor families engage signal transduction pathways that involve non-receptor tyrosine kinases called Janus kinases (JAKs) and transcription factors called signal transducers and activators of transcription (STATs). There are four known JAKs (JAK 1 to 3 and TYK2) and seven STATs (STAT 1 to 4, 5a, 5b, and 6)[5] [Table 1]. Receptor tyrosine kinases (TK) constitute membrane-bound receptors and have intrinsic TK activity, whereas non-receptor TKs need to recruit JAK to have kinase activity.

The sequence of events in the JAK-STAT signaling pathway is now well defined [Figure 2]. The inactive JAK enzymes are non-covalently attached to the cytoplasmic domains of type I (which includes receptors for IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, erythropoietin, thrombopoietin, prolactin, and growth hormone) and type II (receptors for IFN-α, IFN-β, IFN-γ, IL-10, and IL-22) cytokine receptors. When two receptor molecules are brought together by binding a cytokine molecule, associated JAKs are activated

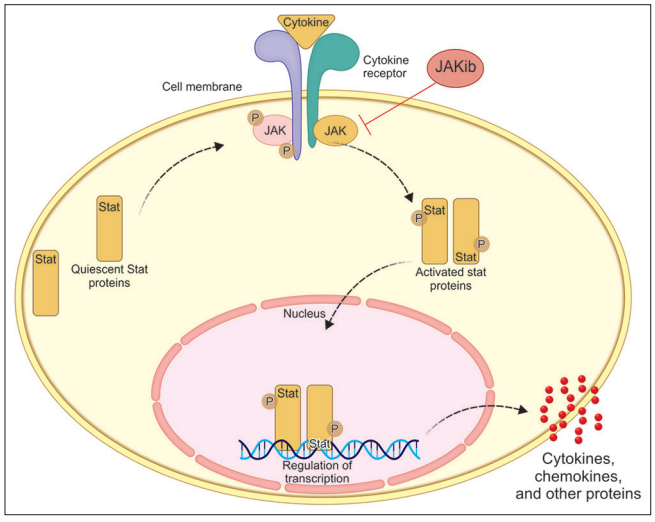

Figure 2: Schematic representation of the JAK/STAT pathway. Upon binding of cytokine to receptors, there is phosphorylation of JAK/STAT proteins and the pathway is activated. The dimerization and translocation of STAT into the nucleus result in signal transduction and expression of various inflammatory mediators

and phosphorylate the tyrosine residues in the cytoplasmic portions of the clustered receptors. These then interact with the SH2 domains of monomeric cytosolic STAT proteins, which in turn lead to the phosphorylation of the STAT proteins. The STAT dimers that are generated migrate to the nucleus, where they bind to specific DNA sequences in the promoter regions of cytokine-responsive genes and activate gene transcription[5,6] [Figure 2].

The JAK receptors mediate the function of immune cells and thus determine the action of the main CD4+ T cells, including T helper 1 (Th1), Th2, Th17, and T regulatory (Treg) cells[6] [Figure 3], amongst other cells. Thus, they mediate the action of immune-mediated cells that play a role in the autoimmune processes of varied skin disorders. The interaction between the cytokines and JAK-STAT receptors leads to a significant amount of combinatorial diversity in the signaling sequence that can be generated from the limited number of JAK and STAT proteins. The subset of type I cytokine receptors that use common cytokine receptor γ chain (γc) utilizes the JAK3 kinase for signaling. Cytokines which belong to γc family include IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. γc cytokines activate three major signaling pathways, which include the PI-3-K-Akt (phosphoinositide-3-kinase–Akt) pathway, the RAS-MAPK (mitogen activated protein kinase) pathway, and the JAK-STAT pathway, and promote cellular survival and proliferation.[7] JAK3 is the only JAK kinase that is not expressed ubiquitously, with its expression largely restricted to immune cells, and it is only activated by γc-containing receptors.

Effects of JAK-STAT on hair cycling

Animal models have demonstrated the role of the JAK-STAT pathway in HF stem cell quiescence, apart from the immune-mediated mechanism discussed above. This is in line with the similar role of the pathway in skeletal muscles, hematopoietic cells, adipose tissues, etc.[8-11] Harel *et al.*[12] demonstrated that JAK inhibitor–mediated hair growth may also occur independent of the T lymphocyte effect and likely represents an intrinsic property of hair. Key genes in the JAK-STAT pathway, such as *Stat5A/B, Stat3, Jak1, Jak3, and Socs2/3,* are expressed at high levels in catagen and telogen and are repressed in early anagen. JAK-STAT signaling may thus prevent anagen re-entry and JAK blockade relieves this inhibition to allow for normal hair cycle progression.[12] Apart from the direct

Table 1: Overview of JAK and the linked cytokines

JAK	Cytokines
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-15, IL-21, INF-α, IFN-β, IFN-γ
JAK2	Erythropoietin, thrombopoietin, granulocyte-monocyte colony stimulating factor, IL-3, IL-5, IFN-γ
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
TYK2	IFN-α, IFN-β, IL-6, IL-10, IL-12, IL-13, IL-23

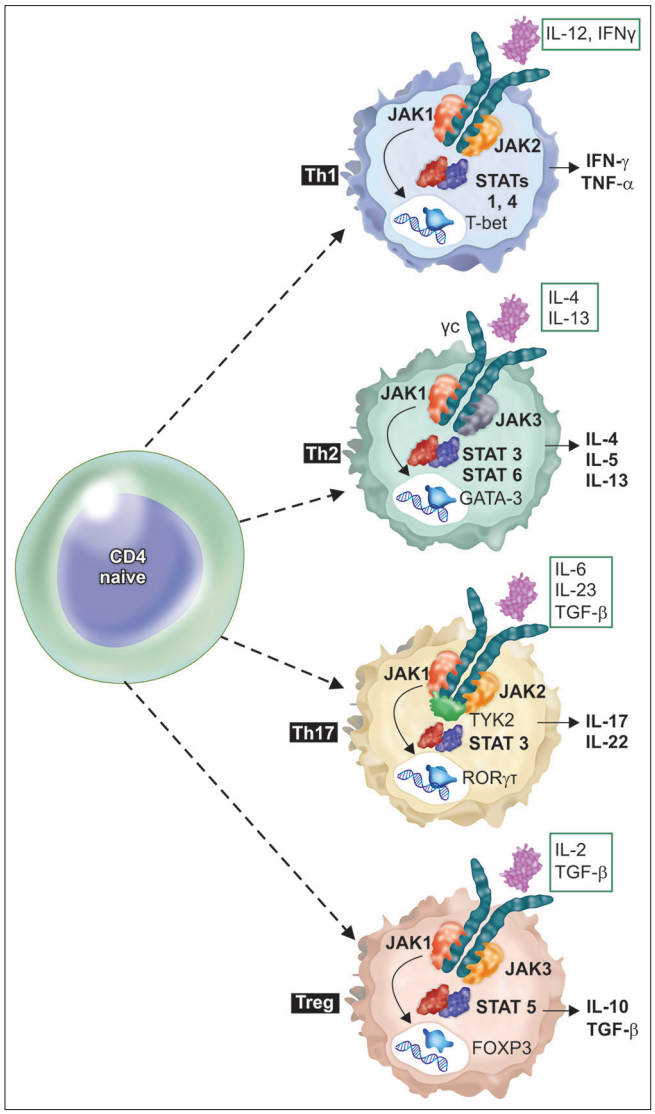

Figure 3: A diagrammatic depiction of the cytokine and Th cell interaction and the role of JAK/STAT. The interaction leads to activation of JAK/STAT pathway which releases cytokines that mediate various diseases. (GATA-3: GATA binding protein-3; FOX3P: forkhead box P3; IL: interleukin; PI3K: phosphoinositide 3-kinase; RORγT: retinoic acid-related orphan nuclear hormone receptor; T-bet: T-box containing protein; TGF-β: transforming growth factor β; TNF-α: tumor necrosis factor-α)

role, JAK inhibition by tofacitinib has been shown to promote anagen re-entry by inducing expression of other anagen-inducing factors such as transforming growth factor (TGF) β2, fibroblast growth factor (FGF) 7/10, lymphoid enhancer-binding factor-1 (LEF-1), and members of the NOTCH family.

Alopecia areata pathogenesis

Alopecia areata (AA) is believed to be mediated by CD4+ and CD8+ cytotoxic T lymphocytes, which results in damage to the HF due to antigenic recognition. The latter occurs due to a breakdown of the immune privilege of the HF, leading to selective targeting of the hair in the anagen phase. This breakdown is mediated by varied mechanisms, including a genetic predisposition. The predominant cell implicated in AA is the cytotoxic CD8+ NKG2D+ T cell.[13,14] Genome-wide association studies of AA have shown the upregulation of MHC class I or ULBP3 (UL-16- binding protein 3) molecule, an NKG2D ligand in the hair follicle, to play an important role in the pathogenesis of AA, as subsequent immune recognition initiates the attack by CD8+NKG2D+T cells on hair follicles.[15] This results in a premature transition of anagen to catagen and telogen phases in the hair cycle, resulting in alopecia.

The immune privilege of the HF is maintained in the anagen phase by various mechanisms, including major histocompatibility complex (MHC) class I molecules' downregulation and expression of natural killer (NK) and CD8+ T cell inhibitors such as macrophage migration inhibitory factor (MIF) and transforming growth factors (TGF) β1 and β2, increased expression of Fas ligand (which serves to eliminate autoreactive T cells), and impaired function of antigen-presenting cells. The major steps involved in the pathogenesis include the collapse of the HF immune privilege, exposure of the auto-antigen which is believed to be a part of the HF, and the prominent role of the local IFN-γ-IL-15 axis. Binding of the IFN receptors results in increased production of inflammatory signaling molecules, including IL-15, and increased release of cytotoxic granzymes. IL-15 then activates the JAK-STAT pathway in the CD8+ T-cells, resulting in further release of IFN-γ and thus setting up a positive feedback loop. Notably, IFN-γ mediates its effect via the JAK1/2 receptors and IL-15 via JAK1/3 receptors, which forms the rationale for the use of JAKibs in AA [Figure 1]. It seems that the major cytokine, IFN-γ, induces the JAK/STAT signaling and thus leads to the recruitment of CD8+ T cells through CXCL9 and CXCL10 mediated mechanisms. This possibly interferes directly with the hair growth cycle via suppression of the proliferation and activation of hair stem cells and reduction of angiogenesis.[12,16] In addition, IL-15, via the JAK-STAT pathway, increases the production of perforin and cytotoxic granzymes from CD8+ T cells. Also, NKG2D+ NK cells and CD4+ T cells can bind with NKG2D ligands on the HF, which further release perforin and granzymes, resulting in HF cell apoptosis.

Mouse models have highlighted the role of CD4+ T cells in extensive lesions of AA. While injections of CD8+ T cells alone induced localized hair loss, injections of CD4+ T cells alone showed induction as well as promotion of AA.[17] Also, T regulatory cells (Tregs) are found to be defective in patients with AA, as they fail to suppress high levels of serum cytokines including IL-2, IL-13, IL-15, IL-17, and IFN-γ.[18] An imbalance between Th17 and Treg cells is demonstrated in patients with AA, with Th17 levels exceeding the Treg levels during active stages of the disease.

JAK inhibitors in alopecia areata: present data and drawbacks

The therapeutic role for JAKibs was originally suggested by experiments in C3H/HeJ murine models of AA, in which hair regrowth was seen consequent to the administration of either JAK1/2 or JAK1/2/3 inhibitors, with demonstrable effects on type I cellular immunity. There is also a role of various other cytokines, including IL-12 and IL-23–mediated T-cell responses, which can lead to downstream T-cell activation via IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21[13,19] [Table 1]. Various immunosuppressive agents (ISA) used in AA act by modulating immune responses, but none of the existent drugs target the JAK/STAT pathway [Table 2].

Studies on scalp tissue and/or serum of patients with AA have shed light on the cytokine pathways that drive AA, including those associated with Th1/NK/T-cell activation (IL-2, IL-15), Th1 (IFN-γ, IL-12/IL-23p40, CXCL10), and Th2 (CCL13, CCL18) pathways, as well as inhibition of hair keratins (KRTs) and keratin-associated proteins (KRTAPs).[20] The importance of this is that the ideal study is one that examines the therapeutic intervention based on the improvement of these pathogenic parameters. Such exacting standards have not been met for a large number of non-JAKib systemic drugs used in AA and can account for failures in severe AA.

While the role of various JAKibs in AA has been increasingly reported, with the predominant literature on tofacitinib, baricitinib, ruxolitinib, and recently, the selective JAK3ibs, it is pertinent to point out that it is not yet clear which is the ideal JAKib for AA[21,22] [Table 3].

JAKibs can be divided into two generations. The first-generation includes small molecules such as baricitinib and tofacitinib, which act as non-selective inhibitors of JAKs. On the other hand, second-generation drugs such as filgotinib and upadacitinib have selective inhibitory activity against JAKs. This difference in the selectivity of the two generations is associated with some differences in their safety and efficacy. There is yet another classification based on their binding mode and the type of interactions with the amino acids that divides JAKs into reversible (competitive) and irreversible (covalent) inhibitors.

Table 2: Mechanism of action of immunosuppressive agents (ISA) used in alopecia areata

Drugs	Mechanism of action
Methotrexate (MTX)*	MTX polyglutamates inhibit dihydrofolate reductase - inhibits purine synthesis - leads to a buildup of adenosine - leads to a reduction in TNF-α and IFN-γ synthesis
Cyclosporine*	Inhibits calcineurin - inhibits Th cell activation and suppresses IFN-γ production
Azathioprine*	Inhibits purine synthesis and impairs T cell function and decreases IL-2
JAK/STAT inhibitors	Inhibition of JAK/STAT suppresses downstream signal transduction pathways

*The existent ISAs used in AA do not target the JAK STAT pathway except a minor JAKib in vitro action of MTX

A drug that inhibits a selective JAK receptor is ideal, as it would lead to fewer side effects as some JAK receptors are ubiquitously expressed. Notably, the JAK2 receptor is ubiquitous, and thus, a non-JAK2ib drug is ideal. Also, the large majority of clinical data is derived from study populations which is heterogeneous, with variation in the type of AA, extent, severity, and even dosages of drugs employed for AA. Some authors have combined tofacitinib with steroids, which is unnecessary and also obviates the role of JAKibs and is not the ideal method of prescribing JAKibs in AA. We do not combine tofacitinib with oral steroids and achieve favorable results in the vast majority of our patients. Also, studies do not look at complete improvement, which is more important to the patient than a partial response, which is the reason why most trials may not be clinically translatable in real-world scenarios in a dermatology clinic. And importantly, data on the maintenance of response achieved with JAKibs in AA are scarce.

There is a need for studies that analyze *in vivo* gene and cytokine expression in biopsy specimens of cases of AA, pertinently those that examine the expression of JAK 1, 2, and 3 in scalp biopsies, which is the ideal basis for a therapeutic intervention. Also, the effect of JAKib on the various pathogenic steps that lead to AA should ideally be studied.

Safety and efficacy of JAK inhibitors in alopecia areata

Tofacitinib: Liu *et al.*[4] conducted a retrospective study of 90 AA, AU, or alopecia totalis (AT) patients on oral tofacitinib 5-10 mg with or without prednisone and demonstrated >50% regrowth in 77% of patients (evaluated using the severity of alopecia tool (SALT) scoring system). Of the 90 patients, 20% were complete responders (>90% reduction in SALT), whereas 56.9% were intermediate to moderate responders (51%-90% reduction in SALT for intermediate responders and a 6%-50% reduction in SALT for moderate responders), and 23.1% were non-responders (≤5% reduction in SALT). Localized disease with AA and the duration of disease with AU or AT ≤10 years had a good prognosis. An open-label single-arm trial by Jabbari *et al.*[23] consisting of 12 patients with moderate to severe AA or its variants on oral tofacitinib ≥10 mg daily for 6–12 months showed ≥90% regrowth.

However, a retrospective study of 13 recalcitrant AA and AU patients found that while all 3 AA patients responded to oral tofacitinib, treatment was unsuccessful in 5/10 AU patients.[24] Furthermore, relapse was noted in 5 patients;

Table 3: An overview of the JAK inhibitor drugs

JAK Target	Drug	Indication	Use in AA
JAK1	Filgotinib	Rheumatoid Arthritis (RA), Ulcerative Colitis (UC)	No
	Abrocitinib	Atopic Dermatitis (AD)	No
	Itacitinib	Graft Versus Host Disease (GVHD)	No
	Solcitinib	UC	No
JAK2	Fedratinib	Myeloid Proliferative Tumor	No
		Myelofibrosis	
	Gandotinib	Myeloproliferative Neoplasms	No
	Pacritinib	Acute Myeloid Leukemia (AML)	No
JAK3	**Ritlecitinib**	RA	Yes
TYK2	**Deucravacitinib**	Psoriasis	Yes
	Ropsacitinib		
JAK1/JAK2	**Baricitinib**	AD	Yes
	Ruxolitinib	Myeloid Proliferative Tumor	Yes
		GVHD	
	Momelotinib	Myelofibrosis, Polycythaemia Vera, Thrombocythaemia, AML	No
JAK1/JAK3	Decernotinib	RA	
	Ifidancitinib	RA	Yes
JAK1/TYK2	**Brepocitinib**	Severe Ulcerative Colitis, Cicatricial Alopecia	Yes
JAK1/JAK2/	Oclacitinib	Dermatitis	No
JAK3	**Tofacitinib**	RA, Psoriatic Arthritis, UC, Juvenile Idiopathic Arthritis	Yes
JAK1/JAK2/	**Delgocitinib**	AD	Yes
JAK3/TYK2	Gusacitinib	AD	No
	Peficitinib	RA	No

one of the relapses occurred during treatment, two occurred after the second month of treatment completion, and one occurred after 1 year of treatment completion. Most studies report no adverse effects in patients on tofacitinib.[25-27] Side effects reported were transient and limited to mild infections such as upper respiratory infections, urinary tract infections, herpes zoster, folliculitis, and conjunctivitis; liver enzyme abnormalities, thrombocytopenia, neutropenia, and hypercholesterolemia were rarely observed.[28]

The response rates of tofacitinib monotherapy versus combination therapy with oral steroids is pertinent for clinicians, especially with emerging data that shows the promising efficacy of oral tofacitinib monotherapy in AA.[29,30] In a retrospective study of 61 patients with moderate-to-severe AA who had been treated with at least 3 months of monotherapy of tofacitinib or steroids, or their combination, and analyzed using SALT50, there was no significant difference among these three groups.[31] An open-label comparative study to evaluate the efficacy of JAKibs in 75 AA (>30% hair loss), AU, and AT patients revealed a robust improvement with a mean change in SALT score of 93.8 ± 3.25 and 95.2 ± 2.69 in tofacitinib and ruxolitinib groups, respectively.[32] Thus there is no need to combine JAKib with systemic steroids.

The black box warning for tofacitinib, forewarns about serious infections (active tuberculosis, invasive fungal infections including cryptococcosis and pneumocystosis, and viral infections including herpes zoster), malignancy (including lymphomas and solid tumors), major adverse cardiovascular events (defined as cardiovascular death, myocardial infarction, and stroke), and thrombosis.[33]

Ruxolitinib: The literature on the efficacy of ruxolitinib in AA is limited mostly to case reports and series. In one open-label, single-arm trial by Mackay-Wiggan *et al*.,[34] 12 patients with moderate to severe AA were administered 20 mg ruxolitinib twice daily for 3–6 months. Of the 12 patients, 9 (75%) had ≥50% regrowth at 12 weeks, and at the end of 6 months, 7 of these 9 patients had >95% regrowth. No serious adverse effects have been reported with ruxolitinib in the literature.[34,35] Risks for serious infections, major adverse cardiovascular events (MACEs), thrombosis, and cancer are the boxed warnings issued by the FDA.[36]

Baricitinib: BRAVE-AA1 and BRAVE-AA2 phase randomized controlled studies which enrolled 654 and 546 adult patients of AA with SALT score ≥50, respectively, demonstrated beneficial effects with baricitinib in severe AA.[37] Patients were randomly assigned in a 3:2:2 ratio to receive once-daily baricitinib at a dose of 4 mg, 2 mg, and placebo respectively. The proportion of patients with a SALT score of ≤20 at week 36 were 38.8% with 4 mg baricitinib, 22.8% with 2 mg baricitinib, and 6.2% with placebo in BRAVE-AA1, and 35.9%, 19.4%, and 3.3%, respectively, in BRAVE-AA2. Side effects such as acne,

elevated levels of creatine kinase, and increased levels of low- and high-density lipoprotein cholesterol were noted in patients of the baricitinib group. Black box warnings by the FDA include serious infections, malignancy, and thrombosis.[38]

Deuruxolitinib (CTP-543): It selectively inhibits JAK1 and JAK2, is under trial as an oral treatment for adult patients with moderate-severe AA, and the knowledge on the efficacy and safety profile of the drug is limited. A phase 2 randomized control trial evaluating the efficacy of deuruxolitinib in 149 patients with moderate-severe AA versus 147 placebo patients found a dose-related increase in the percentage of patients who achieved SALT50 scores at week 24 (9% with placebo, 21% with 4 mg twice daily, 47% with 8 mg twice daily, and 58% with 12 mg twice daily).[39] The response rate was statistically significant for the 8 mg twice daily and 12 mg twice daily groups versus placebo and differences were observed as early as 12 weeks after the treatment initiation. The safety profile of the drug was similar to the known safety profiles of JAKibs. However, as discussed earlier, JAK2ibs would not be an ideal choice for the treatment of AA as they have a universal expression and may lead to more side effects. Recently, the US FDA stopped the trial of 12 mg dose of the drug in AA but the 8 mg dose trial is continuing and its results are awaited.

Novel JAK inhibitors in AA

Here, it is pertinent to mention that experimental *ex vivo* data on AA has shown that JAK 3 seems to be the predominant determinant of AA and thus an ideal target for the disease. The initial data shows that inhibition of JAK 3 is effective and impacts favorably on the suppression of cytokines, JAK receptors, and Th cell subtypes in AA.[40,41] Notably, baricitinib does not target JAK 3 and while the drug has attained FDA approval, it might not be the ideal JAKib for AA. Tofacitinib is a pan JAKib and while there is growing data on its efficacy, mechanistically, it would possibly have more side effects than a specific JAKib.

Ritlecitinib and Brepocitinib: Recent data suggest that both ritlecitinib (an inhibitor of JAK3 and TEC kinase family) and brepocitinib (a TYK2/JAK1 inhibitor) showed a significant reduction in inflammatory markers including Th1 (IFN-γ, IL-12/IL-23p40, IL-12RB1, CXCL9/CXCL10, STAT1, CCL5), Th1/NK/T-cell activation (IL-2RA, IL-15RA, IL-16), Th2-related (CCL13, CCL18), IL-23 (IL-23p19), Th22 (IL-32), Treg cells (IL-10, FOXP3), and JAK3 in scalp biopsy samples at weeks 12 and 24 of treatment.[42] As per the 24 week results of this randomized placebo-controlled trial evaluating the efficacy and safety of ritlecitinib and brepocitinib, SALT90 was achieved by 25% of patients in the ritlecitinib group and by 34% of patients in the brepocitinib group, compared with 0% in the placebo group and both drugs were well tolerated.[2] The most common adverse reactions seen in the phase 2b/3 trial were nasopharyngitis, headache, and upper respiratory tract infection.[43] There were no MACEs, deaths, or opportunistic infections in the trial. Long-term efficacy and safety results and the effect of treatment withdrawal are, however, still awaited. However, considering the mechanistic advantages and seemingly favorable adverse effect profile, these two drugs have the potency to supplant the existing drugs for AA in the future.[42]

Winnette *et al*.[44] analyzed the results from the use of the Alopecia Areata Symptom Impact Scale (AASIS) in the phase 2a ALLEGRO trial, which was conducted to evaluate the efficacy and safety of ritlecitinib and brepocitinib in 142 AA patients. At 24 weeks of treatment, the mean AASIS global score and SALT score showed improvement in active treatment groups compared to placebo. Also, the relationships between AASIS scores and SALT scores at baseline and week 24 were assessed, which showed small correlations between the SALT score and the AASIS global score ($r = 0.18$) at baseline, whereas large correlations were found between the SALT scores and the AASIS global score at 24 weeks ($r = 0.51$).

Existing data suggest that if dual JAK1 and JAK3 inhibition can be achieved, it can effectively suppress downstream signal transduction pathways in AA and the additional advantage of avoiding unwanted JAK2-mediated side effects would make it an ideal drug for AA.[45] A recent study found that the JAK1/3 inhibitor, ifidancitinib, has potent effects and suppresses IFN-γ signaling, which is responsible for the collapse of HF immune privilege. In addition, the drug inhibited the *in vitro* differentiation of naive CD8+ T cells to NKG2D+CD8+T cells, which are critical to AA pathogenesis and also affected the memory T cells that are associated with AA.[13,46]

Relapses and nonresponsiveness

The reason for non-responsiveness to JAKibs and relapse is a pertinent issue and it has been noted that a disease duration of more than ten years leads to a delayed and incomplete response. This is the most consistent determinant, while other factors like age of onset, atopy, the severity of AA, and associated autoimmune disorders have also been suggested as determinants of responsiveness to systemic therapy.

Resident memory T cells (T_{RM}) persist in peripheral tissues for long periods and play an important role in host defense against infections and tumors. In the skin, these cells have been noted in psoriasis, vitiligo, and atopic dermatitis.[18] While these cells have been noted in AA, their role remains undefined. Most skin infiltrating CD8+ T cells in C3H/HeJ AA mice also co-express markers characteristic for T_{RM} (CD69+, CD103+). It has been shown that treatment with JAK1ibs or JAK3ibs significantly decreased the frequency of these cells, but the same was not noted with JAK2ibs treatment.[18] The persistence of

these cells can explain why many patients of AA begin to relapse and lose hair after successful ruxolitinib or tofacitinib treatment.[23,32] Liu *et al*.[4] found 100% relapse within 3 months of discontinuation of tofacitinib. In a study by Mackay-Wiggan *et al.,* relapse was noted in all patients within 12 weeks of stopping treatment with oral ruxolitinib treatment.[34]

Thus, there is a need for a therapeutic strategy that not only inhibits the function of pathogenic T_{RM} but also eliminates them from lesional skin, which may lead to durable disease remission in AA.[47] JAK3ibs, thus may be useful in the durable remission of AA. Also, Ifidancitinib is able to induce T cell exhaustion and this is characterized by loss of effector function and the expression of multiple inhibitory receptors such as PD-1 (programmed cell death 1 receptor), TIM-3 (T cell immunoglobulin and mucin-domain containing-3), and LAG-3 (lymphocyte activation gene-3), as well as changes in transcriptional signature.[48] Such drugs can achieve long-term remissions.

In the absence of long-term T cell exhaustion, the need for a long-term maintenance dose remains an existential issue, especially in severe variants like alopecia totalis, and this indefinite therapy with JAKibs raises concerns about adverse effects.[49] However, up to 2.5 years of safe continuous use of tofacitinib has been reported with the maintenance of results, and the safety in a pediatric case is a good reason to suggest its replicative dose and duration in adult patients.[50]

Conclusion

It is clear that JAKibs are the future of therapeutics, especially in AA. Overall, current data suggest the oral JAK inhibitors (baricitinib, ritlecitinib, deuruxolitinib, brepocitinib) as a promising new class of agents that can induce significant hair regrowth, with mild to moderate adverse effects. While Baricitinib recently received US FDA approval for the treatment of severe AA, ritlecitinib and deuruxolitinib have received the breakthrough therapy designation for AA. However, there is a need for even more targeted drugs, which would ensure fewer side effects and maximize results, and the JAK3ibs/JAK1 and JAK3ibs largely fulfill this criterion. Recent data suggests that this class of drugs has exquisite efficacy and a low propensity for side effects. JAKibs are the first class of systemic drugs to be given US FDA approval in AA, which is proof enough of their efficacy based on translation data on JAK expression. Also, they are superior to existing drugs used in AA, which do not modify the JAK-STAT pathway. The advantage is that this class of drugs can help replace the wide-spread use of steroids with its myriad regimens and doses, which lead to side effects, and this is an excellent reason to graduate to the use of JAKib.[51] Also, it has been shown that they are superior to corticosteroids in AA which highlights its steroid-sparing ability.[31] Ultimately, the goal should be the use of JAKibs that reflect the JAK expression in AA and the use of drugs that maintain T cell exhaustion after treatments to effect long-term results and fewer relapses.[47]

JAKibs are being tried in various immune-mediated inflammatory disorders such as atopic dermatitis, alopecia areata, vitiligo, psoriasis, lichen planus, and interfernopathies. In fact, such is a ubiquitous expression of JAK receptors, that disorders mediated by Th1, Th2, and Th17 cells can be effectively treated by JAKibs.[6]

Of course, like biologicals, there would be other issues relevant to clinical practice, including the cost of the treatment and the availability of drugs. These also include the need for head-to-head inter- and intra-class comparison trials in patients with identical clinical severity of AA, which have not yet been performed. The *in vitro* selectivity of JAKib may not always translate to *in vivo* selectivity and despite differences in JAK-selectivity, the cytokine inhibition profiles of currently approved JAKinibs are highly similar with preference for JAK1-mediated cytokines.[52]

It would also be particularly interesting to note the longevity of response, drug survival rates, and side effect profiles outside the rubric of a clinical trial. The ideal study model should include the study of tissue JAK and cytokine expression. Also, most trials are sponsored by the industry, where the aim is to dwell on the "positives" and not "comparative analysis". A real-world assessment with a comparison of existing systemic drugs for AA with JAK3ibs would be ideal, but there is good quality translative "bench to bedside" data that shows that the future of AA lies firmly in the domain of JAKibs, and it's our opinion that JAK3ibs would replace the existent JAKib drugs for AA.

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Conflicts of interest

There are no conflicts of interest.

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