Janus kinase inhibitors for alopecia areata: A narrative review

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Abstract

The Janus kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) pathway has been identified as a key player in the pathophysiology of alopecia areata and a potential target for therapy. Here, we give a narrative review of what is known about Janus kinase inhibitors in alopecia areata. Several clinical trials as well as smaller studies have demonstrated hair regrowth and remission with oral Janus kinase inhibitors therapy, even in patients who failed conventional treatment. Baricitinib is the only US FDA-approved treatment for alopecia areata but data for other oral Janus kinase inhibitors such as tofacitinib, ruxolitinib and ritlecitinib are also promising. Fewer clinical trials have investigated topical Janus kinase inhibitors for alopecia areata, with many of them terminated early due to unfavourable results. Overall, Janus kinase inhibitors are an efficacious addition to the therapeutic arsenal for treatment-refractory alopecia areata. Further work is needed to examine the effects of long-term usage of Janus kinase inhibitors, the efficacy of topical Janus kinase inhibitors, as well as to identify biomarkers that could predict differential therapeutic responses to the various Janus kinase inhibitors.

Keywords: JAK inhibitor, alopecia areata, autoimmune disease, hair loss

Introduction

Alopecia areata is a chronic autoimmune disease that causes non-scarring, discrete areas of hair loss and has unpredictable periods of remission and relapse. It has a lifetime incidence of 2%.[1] Although this condition affects all ages, the average age of onset is 25–37 years and it affects both males and females at equal rates.[1] The disease most commonly affects the scalp but can affect any hair-bearing area of the skin, sometimes progressing to complete hair loss on all areas of the scalp (alopecia totalis) or body (alopecia universalis). Due to the resulting disfigurement and unpredictable course, alopecia areata significantly reduces quality of life.[2] Individuals with alopecia areata are more likely to have comorbid psychiatric disorders such as anxiety and depression, and score lower on health-related quality of life measures.[2] Although it is widely accepted that the pathogenesis of alopecia areata is due to loss of immune privilege of the anagen hair follicle, less is known about mechanisms prompting loss of immune privilege in certain individuals. Its pathogenesis is thought to be multifactorial with genetic and environmental factors playing intricate roles. Recent evidence has identified the Janus kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) pathway as a key player in the pathophysiology of the disease and potential target for therapy. Herein, we give a narrative review of the role and future directions of Janus kinase inhibitors in the treatment of alopecia areata.

Pathogenesis of Alopecia Areata

Alopecia areata is characterised by inflammation and autoimmunity at the hair follicle. Normally, the anagen hair bulb is protected from the immune system by complex mechanisms and considered to be in a state of immune

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privilege. This is especially important during the anagen phase as new proteins are synthesized during this period of growth. The follicle is protected by its low levels of MHC protein and β2 microglobulin expression which decrease self-antigen presentation and prevent T-cell activation and proliferation. Anti-inflammatory molecules such as TGFβ-1, IL-10, α-MSH, MIF and somatostatin are also found in abundance within the hair follicle. In alopecia areata, cytokines such as IFNγ and common gamma chain cytokines (IL-2, IL-7 and IL-15) as well as inflammatory NKG2D+ CD8+ T cells and CD4+ T cells predominate. These T cells activate IFNγ, creating a positive feedback loop.[3] This influx of inflammatory cells leads to the premature end of the anagen phase and of the catagen phase, which is characterised by apoptosis of the hair cells.

All the aforementioned cytokines signal through the JAK-STAT signaling pathway. Janus kinase is a tyrosine kinase that exists in the cytoplasmic membrane of many different types of cells. Cytokines are one type of ligand that bind to the extracellular portion of the protein, triggering dimerization and transphosphorylation of Janus kinase proteins. This then triggers phosphorylation and dimerization of STAT proteins. STAT proteins have DNA-binding domains allowing them to initiate transcription of various downstream products. There are four different proteins in the Janus kinase family—JAK1, JAK2, JAK3 and tyrosine kinase-2 (TYK2), and many STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6). This allows for numerous combinations of JAK–STAT and in turn, various transcription products. Janus kinase inhibitors are small water-soluble molecules that cross the cytoplasmic membrane and bind to the ATP-binding domain on Janus kinase, preventing the Janus kinase protein from phosphorylating STAT proteins.[4]

Methods

A search was performed on PubMed in September 2022 including the search terms "alopecia areata" and "janus kinase inhibitor" or "JAK inhibitor." From this, a list of specific Janus kinase inhibitors was made, and searches of individual drugs and "alopecia areata" were performed to find any remaining studies. Systematic reviews, reviews, metanalyses and results not in English were excluded. The search yielded a total of 39 articles from 2015 to 2022, with no duplicate articles. A search was also conducted on ClinicalTrials.gov using the search term "alopecia areata," which resulted in 14 active, 18 completed, and 4 terminated clinical trials of oral and topical Janus kinase inhibitors. Eight articles in the PubMed search overlapped with studies found on ClinicalTrials.gov.

Oral Janus kinase inhibitors

Conventional first-line therapies for alopecia areata include topical corticosteroids, intralesional corticosteroids, systemic corticosteroids and less commonly, methotrexate, minoxidil, cyclosporine, mycophenolate mofetil or azathioprine for refractory disease. Janus kinase inhibitors are a potential novel addition to the therapeutic arsenal in alopecia areata. They have been widely used in and are approved by the US Food and Drug Administration (FDA) for other autoimmune and inflammatory conditions such as atopic dermatitis, psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and rheumatoid arthritis.[5] In June 2022, baricitinib became the first US FDA-approved treatment for alopecia areata. Other Janus kinase inhibitors have also been used off-label to treat alopecia areata, such as the first-generation Janus kinase inhibitors tofacitinib and ruxolitinib. There has been rapid development of more selective second-generation Janus kinase inhibitors. These include upadacitinib, brepocitinib, ritlecitinib, abrocitinib, jaktinib,deucravacitinib, ifidancitinib and delgocitinib. Table 1 summarizes all of the drugs that have been used in the literature to treat alopecia areata. Tables 2 and 3 summarize the completed and ongoing trials of oral drugs to date.

Table 1: A summary of Janus kinase (JAK) Inhibitors that have been reported in the literature for the treatment of alopecia areata

Drug	Mechanism of action	Dosing regimens
Baricitinib	JAK1/JAK2 Inhibitor	Oral • 4 mg or 2 mg once daily[6,7]
Tofacitinib	JAK1/JAK2/ JAK3 Inhibitor	Oral • 5 mg twice daily[8,9,11] • 10 mg twice daily[8] • 10–25 mg split twice daily[10] Topical • 2% twice daily[29]
Ruxolitinib	JAK1/JAK2 Inhibitor	Oral • 20 mg twice daily[14] • 5–15 mg twice daily[15] • 10–25 mg twice daily[16] Topical • 0.6% twice daily[28] • 1% twice daily[29] • 1.5% twice daily[32]
Ritlecitinib	JAK3/TEC Inhibitor	Oral • 200mg once daily for 4weeks, then 50mg once daily for 20weeks[18] • 50 mg, 30 mg, or 10 mg once daily[19]
Brepocitinib	TYK2/JAK1 Inhibitor	Oral • 60 mg once daily for 4 weeks, then 30 mg once daily for 20 weeks[18]
Upadacitinib	JAK1 Inhibitor	Oral • 30 mg daily[22,23]
Abrocitinib	JAK1 Inhibitor	Oral • 200 mg daily[24] • 100 mg or 200 mg once daily[25]
Ifidancitinib	JAK1/JAK3 Inhibitor	Topical • 0.5%[34-36] or 0.1% twice daily[34]
Delgocitinib	JAK1/JAK2/ JAK3/TYK2 Inhibitor	Topical • 30 mg/g twice daily[37]

TYK2: Tyrosine kinase 2, TEC: Tyrosine kinase expressed in hepatocellular carcinoma

Table 2: A summary of completed clinical trials of oral Janus kinase (JAK) inhibitors as listed on ClinicalTrials.gov

Drug	Mechanism of action	National clinical trial number	Phase	Number enrolled	Status	Results	Associated publication
ATI-501	JAK1/JAK3 Inhibitor	NCT03594227	II	87	Completed	The percent change in SALT Score at 24 weeks was −19.3 (P = 0.01) for the 400 mg arm, −24.1 (P = 0.001) for the 600 mg arm and −19.5 (P = 0.01) for the 800 mg arm.	Gold *et al*., 2020[38]
CTP-543	JAK1/JAK2 Inhibitor	NCT04797650	III	517	Completed	The proportion of patients reaching a SALT score of <20 at Week 24 was 38.3% in the 12 mg twice-daily arm and 33.0% in the 8 mg twice-daily arm, compared to 0.8% of patients receiving placebo (P < 0.0001).	Concert Pharmaceuticals, 2022[39]
CTP-543	JAK1/JAK2 Inhibitor	NCT04518995	III	706	Completed	The proportion of patients reaching a SALT score of <20 at Week 24 was 41.5% in the 12 mg twice-daily arm and 29.6% in the 8 mg twice-daily arm, compared to 0.8% of patients receiving placebo (P < 0.0001).	Concert Pharmaceuticals, 2022[40]
CTP-543	JAK1/JAK2 Inhibitor	NCT03941548	II	66	Completed	Not recorded	None
CTP-543	JAK1/JAK2 Inhibitor	NCT03811912	II	57	Completed	Not recorded	None
CTP-543	JAK1/JAK2 Inhibitor	NCT03137381	II	149	Completed	Percentage of participants achieving ≥50% relative reduction in SALT score from baseline after 24 weeks was 21.4% (P = 0.177) in the 4 mg dose group, 47.4% (P< 0.001) in the 8 mg dose group, and 58.3% (P < 0.001) in the 12 mg dose group compared to 9.3% in the placebo group.	King *et al*., 2022[41]
Ritlecitinib	JAK3/TEC Inhibitor	NCT03732807	II/III	718	Completed	The percentage of participants with a SALT score of <20 at Week 24 was 30.7% in the arm receiving 200 mg then 50 mg, 22.3% in the arm receiving 200 mg then 30 mg, 23.4% in the arm receiving 50 mg, and 14.3% in the arm receiving 30 mg compared with 1.5% in the placebo arm (P< 0.0001).	None
Ritlecitinib and Brepocitinib	JAK3/TEC Inhibitor, TYK2/JAK1 Inhibitor	NCT02974868	II	142	Completed	After 24 weeks, the percentage point change in SALT score from baseline, 31 in the ritlecitinib group and 49 in the brepocitinib group, was statistically different from placebo (P< 0.001).	King *et al*., 2021[17]
Ruxolitinib	JAK1/JAK2 Inhibitor	NCT01950780	II	12	Completed	The mean SALT score at baseline was 65.8%, 24.8% at 3 months and 7.3% at 6 months (P<0.005).	Mackay-Wiggan *et al*., 2016[14]
SHR302	JAK 1 Inhibitor	NCT04346316	II	94	Completed	Not recorded	None
Tofacitinib	JAK1/JAK2/JAK3 Inhibitor	NCT02299297	II	12	Completed	The percentage of participants achieving ≥50% relative reduction in SALT score from baseline was 67%.	Jabbari *et al*., 2018[8]
Tofacitinib	JAK1/JAK2/JAK3 Inhibitor	NCT02312882	N/A	40	Completed	The percentage of participants achieving ≥50% improvement in SALT score was 32% after 3 months.	Kennedy *et al*., 2016[9]
Tofacitinib	JAK1/JAK2/JAK3 Inhibitor	NCT02197455	II	30	Completed		
Tofacitinib	JAK1/JAK2/JAK3 Inhibitor	NCT03800979	IV	19	Completed	The percentage of participants achieving ≥50% change in SALT score was 47.4%.[42]	None

SALT: Severity of Alopecia Tool, TYK2: Tyrosine kinase 2, TEC:Tyrosine kinase expressed in hepatocellular carcinoma

Baricitinib

Baricitinib is an oral first-generation JAK1/JAK2 predominant inhibitor approved at a dose of 1 mg, 2 mg or 4 mg for the treatment of alopecia areata. The first case report documenting its efficacy described the treatment of a 60-year-old woman with a 9-month history of alopecia universalis.[6] She was given 4 mg of baricitinib as monotherapy for 8 months, after the failure of intralesional corticosteroids, platelet-rich plasma and topical tofacitinib. She experienced 97% hair regrowth on the scalp and suffered no adverse effects. Two

Table 3: A summary of ongoing clinical trials of oral Janus kinase (JAK) Inhibitors as listed on ClinicalTrials.gov

Drug	Mechanism of action	National clinical trial number	Phase	Number enrolled	Status	Results	Associated publication
Baricitinib	JAK1/JAK2 Inhibitor	NCT03899259	III	546	Active, not recruiting	The percentage of patients with a SALT score ≤ 20 at week 36 was 38.8% in the 4 mg group, 22.8% in the 2 mg group, and 6.2% in the placebo group.	King *et al*., 2022[7]
Baricitinib	JAK1/JAK2 Inhibitor	NCT03570749	II/III	764	Active, not recruiting	The difference in the proportion of patients with a SALT score ≤ 20 at week 36 between the 4 mg dose group and the placebo group was 32.6% points (P < 0.001). The difference between the 2 mg dose group and placebo was 16.1% points (P < 0.001).	King *et al*., 2022[7]
CTP-543 (Deuruxolitinib)	JAK1/JAK2 Inhibitor	NCT04784533	II	300	Active, not recruiting	N/A	None
CTP-543 (Deuruxolitinib)	JAK1/JAK2 Inhibitor	NCT05041803	III	300	Active, not recruiting	N/A	None
CTP-543 (Deuruxolitinib)	JAK1/JAK2 Inhibitor	NCT03898479	II/III	1000	Enrolling by invitation	N/A	None
Deucravacitinib	TYK2 Inhibitor	NCT05556265	II	90	Not yet recruiting	N/A	None
Jaktinib	JAK1/JAK2/JAK3 Inhibitor	NCT05051761	III	420	Recruiting	N/A	None
Jaktinib	JAK1/JAK2/JAK3 Inhibitor	NCT05255237	III	210	Not yet recruiting	N/A	None
Jaktinib	JAK1/JAK2/JAK3 Inhibitor	NCT04034134	II	111	Recruiting	N/A	None
KL130008	JAK1/JAK2 Inhibitor	NCT05496426	II	176	Not yet recruiting	N/A	Li *et al*., 2022[43]
Ritlecitinib	JAK3/TEC Inhibitor	NCT04517864	II	71	Active, not recruiting	N/A	None
Ritlecitinib	JAK3/TEC Inhibitor	NCT04006457	III	1050	Active, not recruiting	N/A	None
SHR0302 (Ivarmacitinib)	JAK 1 Inhibitor	NCT05470413	III	330	Recruiting	N/A	None

SALT: Severity of Alopecia Tool, TYK2: Tyrosine kinase 2, TEC: Tyrosine kinase expressed in hepatocellular carcinoma

ongoing Phase 2–3 clinical trials, BRAVE AA1 and BRAVE AA2, have also demonstrated the efficacy of baricitinib in alopecia areata.[7] In both studies of 654 participants and 546 participants, respectively, participants were separated into groups receiving oral baricitinib 4 mg once daily, 2 mg once daily or placebo for 36 weeks. Their primary outcome was a Severity of Alopecia Tool (SALT) score of <20 at week 36. Participants in BRAVE AA1 met the primary end point in 39% of those who received the 4 mg dose, 23% of those who received the 2 mg dose and 6% of those who received placebo. The results for BRAVE AA2 were 36%, 19% and 3% respectively. Similar efficacies were reported for hair regrowth in eyelash and eyebrow involvement; the 4 mg dose yielded percentage point changes of 30 and 33 in eyebrow growth and 32 and 30 in eyelash growth compared with placebo in BRAVE AA1 and BRAVE AA2, respectively.

Tofacitinib

Tofacitinib is a JAK1/JAK2/JAK3 inhibitor with both oral and topical preparations. It is US FDA-approved for the treatment of many rheumatologic diseases such as rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, juvenile idiopathic arthritis and most recently, ankylosing spondylitis. Tofacitinib is one of the most cited drugs in the off-label use of Janus kinase inhibitors for alopecia areata. In a recent open-label pilot study by Jabbari *et al*., 12 participants were given a graduated dose of 5 mg twice daily to 10 mg twice daily of tofacitinib for at least 6–12 months.[8] Eight of the 12 (67%) patients met their primary endpoint of >50% hair regrowth from baseline, measured by SALT score.[8] Patch-type alopecia areata and alopecia totalis or alopecia universalis had similar responses. An earlier study evaluated the efficacy of 5 mg tofacitinib twice daily for 3 months in 66 patients, with 64% responding to the drug.[9] Unlike in the study by Jabbari *et al*., there were differences in

response by alopecia areata subtype. The median percentage change in SALT score was 70% in patch-type alopecia areata, 68% in ophiasis type alopecia areata, 11.8% in alopecia totalis and 10.5% in alopecia universalis.[8] These figures are not unexpected as alopecia totalis and alopecia universalis subtypes tend to be more treatment resistant. The larger sample size in the latter may explain the differences seen in the two studies. Patients were monitored for 3 months after cessation of drug and all of them experienced a return of alopecia areata within a median of 8.5 weeks.[8] In a smaller retrospective chart review of 13 patients by Ibrahim *et al*., patients were given a graduated dose based on treatment response as described in Jabbari *et al*., starting at 10 mg daily and up titrated to as much as 25 mg daily.[10] All patients had severe alopecia areata and the baseline mean scalp hair loss was 93%. Over half of the patients (53.8%) had a regrowth of >50%. The mean treatment response time was 4.2 months. In a 2019 retrospective study by Serdaroğlu *et al*., 63 patients who had alopecia areata involving >40% of scalp area (73% had alopecia universalis) received 5 mg twice daily for 6 months.[11] There were three patients classified as non-responders (5%; <5% change in SALT score). Of the 63 patients, 12% experienced minimal growth (% change in SALT score between 10–50%), 43% experienced partial growth (>50–90%) and 40% experienced complete growth (>90–100%).[11] Fifteen patients achieved 100% change in SALT score. Though many small case reports have been published with promising results and minor side effects, there have not been any larger scale trials. Investigators may be discouraged due to a recent US FDA warning for tofacitinib.[12] A large drug safety clinical trial showed an increased risk of major cardiovascular events and cancers in a population with cardiovascular risk factors.[13]

Ruxolitinib

Ruxolitinib is a JAK1/JAK2-predominant inhibitor with both oral and topical preparations that has been approved for the treatment of myeloproliferative disorders. Only one phase 2 clinical trial studying its efficacy in alopecia areata has been published.[14] A total of 12 patients were given 20 mg daily for 3–6 months and monitored for 3 months thereafter. In nine patients, hair regrowth was seen as early as 4 weeks after initiation of treatment, while the other 3 did not have any response. The mean baseline SALT score in the responder group was 65.8% which decreased to 7.3% at the end of treatment.[14] After discontinuation, three experienced significant hair loss but none returned to baseline levels in the 3-month follow-up period.

A smaller case series by Lui and King in 2019 followed eight patients with severe alopecia areata (SALT score >50) who had been given ruxolitinib 10–25 mg for a total of 5–31 months.[16] Five patients achieved almost complete regrowth with an average improvement in SALT score of 98%. Four of those patients achieved this on a lower dose of ruxolitinib, 10 mg twice daily, which had not yet been seen in the literature.[16] Another report by Vandiver *et al*. in 2017 described two patients who were successfully treated with ruxolitinib, doses being up-titrated to 30 mg daily for complete remission and, for one of the patients, results were maintained on 20 mg daily.[15]

Ritlecitinib and Brepocitinib

Ritlecitinib is a JAK3 selective inhibitor and an inhibitor of several tyrosine kinases expressed in the hepatocellular carcinoma (TEC) kinase family. Brepocitinib is a TYK2 and JAK1 selective inhibitor. They were compared in one large phase 2a trial, ALLEGRO. In this study, 142 patients with severe alopecia areata, defined as >50% scalp hair loss, were randomly assigned to either ritlecitinib 200 mg once daily for 4 weeks, then 50 mg once daily for 20 weeks, brepocitinib 60 mg once daily for 4 weeks, then 30 mg once daily for 20 weeks, or matching placebo.[17] After 24 weeks, the percentage point change in SALT score from baseline was 31 for the ritlecitinib group and 49 for the brepocitinib group.[17] Near-complete hair growth was seen in 25% of patients in the ritlecitinib group, 34% of patients in the brepocitinib group, and 0% of patients in the placebo group.[17] Scalp biopsies were taken from a subset of this study group for a subsequent study, wherein 46 patients were included.[18] Lesional and non-lesional scalp biopsies were taken at baseline, week 12, and week 24. Immunohistochemistry showed a significant decrease in CD3+, CD8+ and NKG2D+ T cells in lesional skin after treatment.[18] Changes in the inflammatory skin markers correlated with clinical improvement and changes in serum biomarkers such as reduced expression of TH1 (IFN-γ, CCL5), TH2 (CCL17, CCL18, IL-5), TH22 (IL-32), and increased expression of KRT86, KRT85, KRT75 after 12 weeks of treatment. Gene expression also changed significantly after treatment with gene profile shifting towards non-lesional phenotype. Genes involved in pathways of T cell activation, TH1/NK/T-cell activation, TH1/IFN-γ–related were downregulated in treated groups. These changes were most profound in the ritlecitinib group. It was also noted that patients with a longer durations of alopecia areata showed lesser improvements in biomarkers and gene expression.[18]

In a second study, ALLEGRO 2b/3, the safety and efficacy of ritlecitinib alone was studied. This randomized, placebo-controlled, double-blind study included 718 patients 12 years of age and older with severe alopecia areata (SALT score >50). They were randomized to receive 50 mg, 30 mg or 10 mg of ritlecitinib, or placebo. A greater proportion of patients who took ritlecitinib 30 mg or 50 mg once daily met the primary endpoint of SALT score ≤20 after 24 weeks compared with placebo.[19] There is an active Phase 2a clinical trial for ritlecitinib which is set to be complete in 2023. Because of these promising results, on September 2022, the US FDA accepted for filing the new drug application for ritlecitinib in alopecia areata for adults and adolescents 12 years of age and older.[20]

Upadacitinib

Upadacitinib is a second-generation JAK1-selective inhibitor approved for the use of treating atopic dermatitis (AD). Recent case reports have documented positive responses in hair regrowth in patients with concurrent alopecia areata and atopic dermatitis. In one report a 59-year-old with a 35-year history of alopecia areata and atopic dermatitis was treated with upadacitinib after failing to respond to baricitinib in the preauricular and eyebrow areas.[21] The preauricular areas of the scalp and eyebrows showed regrowth within 4 weeks. In another case study, a 24-year-old with a 10-year history of atopic dermatitis and alopecia areata was treated with upadacitinib 30 mg daily.[22] Her baseline SALT score was 89.2 affecting scalp, eyebrows and eyelashes. She showed clinical improvement in 3 months without any sign of disease activity on trichoscopy. The only case report documenting the use of upadacitinib specifically for alopecia areata was by Gori *et al*. in 2022.[23] This was a 25-year-old with a 4-year history of alopecia universalis which had been refectory to conventional therapy. She was given upadacitinib 30 mg daily. By week 4, minimal clinical improvement and sporadic vellus hairs were noted on trichoscopy and by week 12 diffuse hair regrowth on the scalp, jawline area, eyebrows, eyelashes were noted (SALT score of 9).[23]

Abrocitinib

Abrocitinibis a second-generation JAK1 selective inhibitor recently approved for the treatment of atopic dermatitis. Studies of its efficacy in alopecia areata have been limited to a few case reports in those with concurrent alopecia areata and atopic dermatitis. In one report, a 14-year-old girl with a history of atopic dermatitis and 3-year history of alopecia universalis was given a course of abrocitinib 200 mg daily after failing topical steroids and oral antihistamines.[24] Hair regrowth was noticed after 12 weeks of this treatment, and after 2 years on abrocitinib, she had complete regrowth. In another report of two adults enrolled in a trial evaluating abrocitinib in the treatment of atopic dermatitis, one patient with severe atopic dermatitis and alopecia universalis achieved complete remission after 34 weeks and the second patient with treatment-resistant alopecia universalis also achieved remission by week 36.[25]

Topical Janus kinase Inhibitors

Although there has been success in clinical trials of oral Janus kinase inhibitors in adults, these drugs may be associated with adverse effects such as increased risks of infection, malignancy, anemia, thrombocytopenia and hyperlipidemia.[26] This is especially a concern in the pediatric population, for which there are no US FDA-approved treatments despite it being the second largest age group affected by alopecia areata.[1] Topical corticosteroids are useful in treating those with limited disease; however, long-term use can lead to atrophy of sensitive areas like the eyelid and eyebrows. Consequently, there is a need for other types of topical therapy.

Most of the literature to date on topical Janus kinase inhibitors are case reports and case series in the paediatric population. In a case series of 6, patients aged 3–17 were treated with either topical 1% ruxolitinib, 2% ruxolitinib, or 2% tofacitinib for 3–18 months. Cases varied on the type of alopecia areata diagnosis, areas the topical was applied to, and the base of the formulation. All but two patients experienced some regrowth.[27] In another case report, a teenager with alopecia universalis that had been refractory to treatment with systemic steroids, intralesional steroids, sulfasalazine, topical squaric acid dibutyl ester and topical anthralin was treated with topical 0.6% ruxolitinib cream twice daily and achieved almost complete eyebrow regrowth and 10% hair regrowth on the scalp after 12 weeks.[28]

In a randomized control trial of adults, 16 patients with alopecia universalis were given four different tubes: 2% tofacitinib, 1% ruxolitinib, 0.05% clobetasol ointment and placebo which were randomized to the bilateral eyebrows and temples.[29] After 12 weeks of treatment, 38% of patients had partial regrowth in the area treated with 2% tofacitinib, 31% in the area with 1% ruxolitinib, 62% in the area with clobetasol and no regrowth in the areas treated with placebo.[29] In another report, topical 2% tofacitinib treatment was given to a woman with alopecia areata affecting the upper eyelashes.[31] She had near complete regrowth at 4 months.[31] Table 4 summarizes completed and ongoing clinical trials of topical Janus kinase inhibitors to date.

Despite encouraging results in scattered case reports, a review conducted in 2021 suggested that the literature on topical Janus kinase inhibitors may be misleading because of publication bias.[31] They identified a total of eight topical Janus kinase inhibitors trials, four of which were terminated, likely due to unfavourable results, compared with none of the oral Janus kinase inhibitor trials being terminated. Our search yielded similar results—of the nine studies in Table 4, 4 were terminated. In the two completed studies of ifidancitinib and delgocitinib, results in the treatment arm were not significantly different from placebo or vehicle alone.

Conclusion

Janus kinase inhibitors represent a step towards more targeted treatment in alopecia areata. Oral Janus kinase inhibitors have been proven to be efficacious, particularly baricitinib, tofacitinib, ruxolitinib and ritlecitinib. Trials of oral Janus kinase inhibitors in alopecia areata have reported limited side effects but a safety study of tofacitinib in rheumatoid arthritis has raised concerns.[13] Janus kinase inhibitors with even more selectivity towards specific Janus kinase subtypes are already being formulated, which may improve their safety profile. There is no conclusive evidence regarding the efficacy of topical preparations as the literature is lacking in large scale randomized controlled clinical trials and fraught with publication bias. There has been some work on identifying biomarkers that predict treatment

Table 4: A summary of ongoing and completed clinical trials of topical Janus kinase (JAK) Inhibitors as listed on ClinicalTrials.gov

Drug	Mechanism of Action	National Clinical Trial Number	Phase	Number Enrolled	Status	Results	Associated Publications
Tofacitinib	JAK1/JAK2/ JAK3 Inhibitor	NCT02812342	II	10	Completed	Not recorded	None
Ruxolitinib	JAK1/JAK2 Inhibitor	NCT02553330	II	90	Terminated	A ≥50% decrease in SALT score was seen in 25% of participants at Week 12, 33.3% of participants at Week 18, and 50% of participants at Week 24. The study was terminated early based on the results of a planned interim analysis.[33]	None
Delgocitinib	JAK1/JAK2/ JAK3/TYK2 Inhibitor	NCT02561585	II	40	Completed	The mean percentage point decrease in SALT score from baseline to Week 12 was 3.8 in the treatment group and 3.4 in the vehicle group (P = 0.97).[37]	None
Delgocitinib	JAK1/JAK2/ JAK3/TYK2 Inhibitor	NCT03325296	II	13	Terminated	N/A	None
Ifidancitinib	JAK1/JAK3 Inhibitor	NCT03354637	II	56	Terminated	N/A: "Only 8 of the 56 enrolled participants had efficacy measures on Day 169 (primary endpoint) of the ATI-502-AA-203 study. Based on this limited data set, the maintenance of, or new hair regrowth cannot be adequately assessed from this study. The ATI-502-AA-203 study was terminated early due to lack of efficacy in a similarly designed study with ATI-502 Topical Solution."[34]	None
Ifidancitinib	JAK1/JAK3 Inhibitor	NCT03759340	II	129	Terminated	The percent change from baseline in SALT score at Week 24 was 13.9 (P = 0.38) in the 0.1% arm, 9.3 (P = 0.16) in the 0.5% arm.[35]	None
Ifidancitinib	JAK1/JAK3 Inhibitor	NCT03551821	II	1	Completed	N/A	None
Ifidancitinib	JAK1/JAK3 Inhibitor	NCT03315689	II	11	Completed	The amount of drug in scalp biopsies taken at Visits 3 (day 2) and 7 (day 29) were 579.7 ng/g and 5710.0 ng/g, respectively.[36]	None
Jaktinib	JAK1/JAK2/ JAK3 Inhibitor	NCT04445363	I/II	120	Recruiting	N/A	None

SALT: Severity of Alopecia Tool, TYK2: Tyrosine kinase 2, TEC: Tyrosine kinase expressed in hepatocellular carcinoma

response to Janus kinase inhibitors;[14,18] however, further studies on differential responses to Janus kinase inhibitors would enable clinicians to use scalp biopsies or serum tests to select appropriate treatment. Janus kinase inhibitors appear to result in only temporary cessation of disease activity, as rebound hair loss within weeks has been reported after discontinuation of the drug in several studies.[8,14,32] As there are currently no curative treatments available, patients may need long term Janus kinase inhibitor therapy to maintain hair regrowth. Future studies should examine optimal maintenance dosage regimens once patients achieve remission and adverse effects of long-term treatment for this chronic condition.

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