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REVIEW



JAK inhibition in the treatment of alopecia areata – a promising new dawn?

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ABSTRACT

Introduction: Alopecia areata (AA) is a T-cell-mediated disease which produces circular patches of non-scarring hair loss and nail dystrophy. Current treatment options for AA are limited and often yield unsatisfactory results. Pharmacologic inhibition of the Janus kinase (JAK) enzyme family is regrowing hair and reversing nail dystrophy in a number of patients with hitherto refractory AA. The six JAK inhibitors which have been successful in treating AA are tofacitinib, ruxolitinib, baricitinib, CTP-543, PF-06651600 and PF-06700841.

Areas covered: This review reports randomized-controlled trials, open-label trials, case series and case reports published in the literature to date and describes the epidemiology and pathophysiology of AA, the mechanism of action of JAK inhibitors and the adverse effects identified. Electronic searches were performed using Medline Ovid, PubMed, Embase, Cochrane Library and Evidence-Based Medicine Reviews.

Expert opinion: The discovery of JAK inhibition represents a major breakthrough in the treatment of AA. Positive results in early phase 1 and phase 2 clinical trials have enabled the commencement of phase 3 clinical trials and there is now a growing sense of optimism among patients with long-standing, treatment-refractory AA. Further work is required to determine the optimal dose and treatment duration and whether maintenance therapy is universally required.

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1. Introduction

AA is an immune-mediated disorder which produces non-scarring hair loss. It classically presents with asymptomatic, well-defined circular patches of hair loss which may be single or multiple [1]. Patchy scalp alopecia can progress to total scalp hair loss (alopecia totalis, AT) or total body hair loss (alopecia universalis, AU) [1].

AA can be classified as acute or chronic. Forty percent of patients develop a solitary patch of AA that regrows spontaneously within 6 months [2]. Twenty-seven percent develop additional patches, however still achieve complete and persistent remission at 12 months [2]. Chronic AA is defined as AA that continues beyond 12 months [2]. These patients develop additional areas of alopecia and have persistent hair loss. In patients with chronic AA, 30% develop AT and 15% develop AU [2]. In patients with AT or AU, 17% achieve complete hair regrowth [3].

The lifetime incidence of AA has been reported to be 0.7–4% and is similar in both genders [4,5]. The majority of patients with AA are relatively young, with up to 66% being younger than 30 years [6]. People with AA have an increased overall risk of other autoimmune diseases [6].

AA can occur in children and has been reported in infants as young as 1 month of age [7]. In children under the age of 16 years, the mean age of diagnosis is approximately 11 years of age [8]. Earlier age of onset of AA, particularly before the age of 6 years, is associated with poorer prognosis and increased likelihood of refractory disease [8,9]. Positive family

history has been reported in 8.4% to 51.6% of children with AA [7,8,10,11].

Other possible indicators of poor prognosis include disease duration of more than 1 year, multiple discrete patches of hair loss, extensive hair loss affecting >50% of the scalp, ophiasis pattern of alopecia, associated nail disease, Trisomy 21, atopy and a positive family history of AA or other autoimmune disorders [9].

There is an increased lifetime prevalence of psychiatric disorders, particularly depression and generalized anxiety disorder, in people with AA [12]. This may be linked to the impact that AA can have on health-related quality of life [13,14]. The Dermatology Life Quality Index (DLQI) scores are similar in people with AA to other chronic relapsing skin diseases such as atopic dermatitis and psoriasis [13].

The aims of treatment of AA are to arrest disease progression and reverse hair loss. Treatment options include conservative management, topical therapy (with corticosteroids, minoxidil and immunotherapy), intralesional corticosteroids and systemic therapies including corticosteroids and steroid-sparing agents [9].

An Australian expert consensus statement outlined a treatment algorithm for AA, including the indications for and choice of systemic treatment [9]. Patients with a solitary active patch of AA or a solitary stable patch of AA which is impacting their mood or social function should be treated with topical high-potency corticosteroids in children and intralesional corticosteroid injections in adults [9]. All patients with

Article highlights

- The JAK family is a group of four intracellular enzymes: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). The JAK-STAT pathway is activated when extra-cellular cytokines bind to cell surface cytokine receptors. Cytokine receptor binding and subsequent activation of the JAK/STAT pathway is involved in the pathogenesis of AA
- The most common adverse effect associated with JAK inhibitors is increased risk of infection. Other adverse effects include increased risk of venous thromboembolic events and laboratory abnormalities including elevated liver enzymes, lipids and creatine phosphokinase (CPK)
- Oral tofacitinib, a pan-JAK inhibitor, is the most commonly used JAK inhibitor for AA to date. Numerous open-label trials, large case series and case reports have described successful treatment of AA with oral tofacitinib
- Oral ruxolitinib, a JAK1/JAK2 inhibitor, has shown promising results for the treatment of AA in small case series and case reports
- CTP-543 (deuterated ruxolitinib), an oral JAK1/2 inhibitor, has recently been shown to be efficacious in patients with moderate to severe AA in a Phase 2 randomised, placebo-controlled trial
- PF-06651600, an oral JAK3 inhibitor, and PF-06700841, an oral TYK2/JAK1 inhibitor have recently been shown to be efficacious and well-tolerated in patients with AA in a randomised double-blind, placebo-controlled trial
- It is likely that maintenance therapy with JAK inhibitors is necessary sustain the response in AA. There have been numerous reports of relapse following discontinuation of treatment with JAK inhibitors

multiple patches of AA or ophiasis alopecia should be treated with topical or intralesional corticosteroids and if no significant response is observed after 6 months, topical immunotherapy or systemic therapy should be considered [9]. Rapid progressive hair loss, or AT/AU, are indications for systemic therapy [9].

2. Methods

Electronic searches were performed using Medline Ovid, PubMed, Embase, Cochrane Library and Evidence-Based Medicine Reviews from their dates of inception to September 2019. Search terms included 'alopecia areata', 'JAK inhibitor', 'Janus kinase Inhibitor', 'ruxolitinib', 'tofacitinib' and 'baricitinib' as key words.

3. Pathophysiology of alopecia areata

The hair follicle is a site of relative immune privilege [15,16]. Immune privilege enables antigens in the hair follicle to evade immune surveillance and escape immune attack through several mechanisms [16]. Abnormalities in hair follicle immune privilege are inherent in people susceptible to autoimmune diseases including AA [16,17]. In AA, inflammatory cells attack anagen hair follicles. Anagen hair bulbs that are in the process of active pigment production are attacked preferentially, but all anagen follicles are susceptible [16]. Although AA may present as localized patches, the biochemical features of AA may extend significantly beyond the areas that are clinically affected [17,18].

AA susceptibility is inherited as a polygenic trait [19,20]. Murine models have furthered our understanding of the mechanisms involved in AA pathogenesis. Carroll et al. [21]

induced AA in normal-haired C3H/HeJ mice by transfer of skin grafts from mice with spontaneous AA. They found that upregulation and downregulation of 42 genes during the onset of mouse AA was consistent with an inflammatory cell-mediated disease pathogenesis involving antigen presentation, costimulation and a Th1 lymphocyte response [21]. Although their data suggested an autoimmune etiology for both human and mouse AA, a primary disease activating target was not found [21].

Xing et al. [22] demonstrated that cytotoxic CD8+ NKG2D+ T-cells play an integral role in the development of AA. This subset of T-cells infiltrate the epithelial layers of the hair follicle in mice with AA causing an interferon- γ (IFN- γ) response and upregulation of several γ -chain cytokines known to promote the activation and survival of CD8+ NKG2D+ T-cells [22]. Antibody-mediated blockade of IFN- γ , IL-2 or IL-15R β prevented disease development, reducing the accumulation of CD8+ NKG2D+ T-cells in the skin [22]. Administration of systemic inhibitors of JAK tyrosine kinases, downstream effectors of IFN- γ and γ -chain cytokine receptors, eliminated the IFN signature and prevented development of AA [22].

Petukhova et al. [23] performed a genome-wide association study which identified associations between AA and several genes controlling the activation and proliferation of regulatory T-cells, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), interleukin (IL)-2/IL-21, IL-2 receptor A (IL-2RA) and the human leukocyte antigen (HLA) region in AA. There was also a strong association with ULBP (cytomegalovirus UL16-binding protein) [23]. The expression of ULBP in lesional scalp samples was markedly upregulated during active disease [23].

Li et al. [18] analyzed skin biopsies of patients with AA and healthy controls using polymerase chain reaction (PCR). They found that active AA bulbs displayed increased expression of multiple chemokines and chemokine receptors compared with normal hair follicles [18]. In regrown AA bulbs, the transcription pattern remained abnormal, implying that despite recovery of hair growth, these changes persisted in hair follicles previously affected by AA [18]. The ITGAE gene which encodes for CD103, a marker for resident memory T cells, was persistently over-expressed in areas of hair regrowth, although absent in biopsies taken during a first episode of AA, suggesting that these memory T cells develop and lodge in AA bulbs [18].

The role of environmental factors in triggering disease remains speculative [20]. Zhang et al. [24] used a murine model to demonstrate a marked increase in hypothalamic-pituitary-adrenal (HPA) tone and activity in mice with AA. Controlled clinical studies in humans have not found any correlation between stress hormone levels and AA [24].

4. Janus kinase inhibitors

The JAK family is a group of four intracellular enzymes: JAK1, JAK2, JAK3 and TYK2 [25]. JAKs have an important role in host defense, immune responses and hematopoiesis [26]. JAKs phosphorylate sites on a variety of inflammatory cytokine receptors which then act on downstream targets via the signal transducer and activator transcription (STAT) pathway [27]. The JAK-STAT pathway has effects on IFN- γ , IL-2 receptor common γ -chain interleukins (IL-2, IL-4, IL-7, IL-19, IL-15 and

IL-21), IL-5, IL-12, IL-13, IL-23, tumor necrosis factor (TNF)- α , IL-1 and IL-17 [28]. Overexpression of these cytokines is implicated in the pathogenesis of many inflammatory and immune-mediated diseases, although not all may be required for the development of AA [29,30].

Pharmacologic inhibition of the JAK enzyme family has been used to treat immune-mediated diseases. Much of our knowledge of JAK inhibitors stems from rheumatology, hematology and oncology, and various myeloproliferative diseases are associated with increased JAK activity [25,27]. Murine models have demonstrated that systemic administration of JAK inhibitors may prevent the development of AA by modulating IFN- γ gene expression signatures [22].

Ruxolitinib is a JAK1/JAK2 inhibitor that is approved by the United States Food and Drug Administration (FDA) for the treatment of myelofibrosis, polycythemia vera and refractory graft-versus-host disease [31–33]. Tofacitinib targets JAK1/JAK2/JAK3 and to a lesser extent TYK2 [25]. It is approved by the FDA for use in moderate-to-severely active refractory rheumatoid arthritis, refractory psoriatic arthritis and moderate-to-severely active ulcerative colitis [33,34]. Baricitinib is a JAK1/JAK2 inhibitor which is approved by the FDA for use in moderate-to-severely active refractory rheumatoid arthritis [33,35].

JAK inhibitors are being evaluated for the treatment of a number of other conditions including atopic dermatitis, vitiligo, cutaneous T-cell lymphoma, systemic lupus erythematosus (SLE), renal transplantation, refractory leukemia and solid malignancies [27,28].

5. Adverse effects of JAK inhibitors

JAK inhibitors are associated with an increased risk of a limited number of infections. The most common infections that occur are nasopharyngitis and upper respiratory tract infections [27,36–38]. Urinary tract infections, pneumonia, bronchitis, conjunctivitis, tonsillitis, mononucleosis, bacterial skin infections, herpes zoster, herpes simplex and paronychia have also been reported [27,36,38–40]. Opportunistic infections including tuberculosis, esophageal candidiasis, disseminated or multidermatomal herpes zoster, cytomegalovirus and *Pneumocystis jiroveci* pneumonia have been reported but are uncommon [27].

The incidence of venous thromboembolic events may be increased in people being treated with higher doses of JAK inhibitors [41,42]. The risk of malignancy associated with JAK inhibitors is comparable to what has been reported with disease-modifying anti-rheumatic drugs (DMARDs) and biologic therapies [43]. The most common malignancies include non-melanoma skin cancer (NMSC), followed by lung cancer, breast cancer, lymphoma and gastric cancer [44]. The risk of malignancy is not dose-related except for in the case of NMSC [42,43]. Overall rates and types of malignancies are stable over time with increasing exposure to JAK inhibitors [44].

Smolen et al. [42] evaluated the safety profile of baricitinib in 3492 patients with rheumatoid arthritis. Compared with the placebo group, there were increased rates of infection, deep venous thrombosis (DVT), pulmonary embolism (PE) and laboratory abnormalities (including elevated low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatine

phosphokinase (CPK), alanine aminotransferase (ALT) and creatinine) in the baricitinib group [42]. The rate of NMSC was higher for the group treated with 4mg of baricitinib compared with 2mg [42]. There was no difference in the rates of death, malignancies (excluding NMSC), major cardiovascular events (MACE) or serious infections between the treatment and placebo groups [42].

Other adverse effects which have been reported with JAK inhibitors include gastrointestinal complaints, acneiform eruptions, weight gain, headaches, fatigue, hyper-seborrhea, anemia and neutropenia [28,36–40,45–48]. The use of JAK inhibitors in patients with myelofibrosis is associated with increased rates of aggressive B-cell lymphomas [49].

It is currently recommended that patients who are starting treatment with JAK inhibitors should have a complete blood count, biochemistry profile, fasting lipid panel, hepatitis B (HBV) and C (HCV) serology, human immunodeficiency virus (HIV) testing and tuberculosis screening prior to starting therapy [27,28]. Monitoring investigations are also recommended after 1 month of treatment and then every 3 months [28].

6. Oral tofacitinib

6.1. Case series and open label studies

Case series and open label studies have shown that tofacitinib is efficacious in a proportion of adults and adolescents with AA (Table 1). Liu et al. [36] described a case series of 90 patients, most of whom had AT or AU. They were treated with tofacitinib 5–10mg twice daily with or without prednisone. Twenty percent of patients achieved a complete response with >90% change in Severity of Alopecia Tool (SALT) score from baseline, 38.4% achieved 51–90% change in SALT score, 18.5% achieved 6–50% change in SALT score and 23.1% were non-responders [36]. Patients with AA achieved a greater change in SALT score over 4–18 months of treatment compared with patients with AT or AU [36]. Disease relapse occurred in 12.3% of patients during treatment [36]. Subsequent to relapse, hair regrowth was again achieved in 5 patients with tofacitinib monotherapy (5mg twice daily) and 2 with adjuvant therapy [36]. These results suggest that maintenance therapy may be necessary for continued remission of disease.

Kennedy Crispin et al. [38] reported on 66 patients with AA, AT or AU who were treated with tofacitinib 5mg twice daily for 3 months. Thirty-two percent of patients achieved an improvement in SALT score of >50% from baseline, 32% had a change in SALT score of 5–50% and 36% were non-responders [38]. Patients with AA and ophiasis subtypes were more responsive than AT and AU [38]. Shorter duration of disease and histological peribulbar inflammation on pre-treatment scalp biopsies were associated with improvement in SALT score [38]. Twenty patients were followed up 3 months after discontinuation of tofacitinib and all of them experienced hair loss [38].

Serdaroğlu et al. [37] reported on 63 patients with AA, AT or AU who were treated with tofacitinib 5mg twice daily for 12 months. Fifty-two patients had >50% change in SALT score, with 25 of these having a complete response (>90% change in

Table 1. Summary of oral tofacitinib reports in AA, AT and AU.

Author, date	Article type	N	Patient demographics	Diagnosis	Duration of disease	Dose	Results*
Anzengruber, 2016 [64]	CR	1	M 51y	AU	2y	5mg BD	-
Castelo-Soccio, 2017 [52]	CS	8	8 adolescents, aged 12–19y	AU	1–12y	5mg BD	++
Cheng, 2018 [45]	CS	11	3M 8F, aged 21–58y	AT, AU	2–11y	5mg daily to 11mg ER BD	-,+,+,+,+,+
Craiglow, 2014 [53]	CR	1	M 25y	AU	23y	5mg BD to 15mg daily	+++
Craiglow, 2017 [47]	CS	13	1M 3F, aged 12–17y	AA, AT, AU	1.5–15y	5mg BD to 15mg daily	-,+,+,+,+,+
Dhayalan, 2016 [67]	CS	3	2M 1F, aged 20s-40s	AU	NR	5mg BD to 15mg daily	-/+
Erduran, 2017 [54]	CR	1	F 23y	AU	9y	5mg BD to 15mg daily	+++
Ferreira, 2016 [55]	CR	1	M 38y	AU	10y	5mg BD	+++
Gordon, 2019 [65]	CR	1	F 44y	AA	5y	5mg BD	-
Gupta, 2016 [62]	CS	2	2M, 42y and NR	AU	1–32y	5mg BD	++
Ibrahim, 2017 [51]	CS	13	1M 12F, aged 20s–60s	AA, AT, AU	5–54y	10–25mg BD	-,+,+,+,+,+
Jabbari, 2018 [39]	OL	12	4M 8F, aged 18–52y	AA, AT, AU	3–34y	5–10mg BD	-,+,+,+,+,+
Jabbari, 2016 [59]	OL	1	F 40y	AA	5y	5mg BD	+++
Kennedy Crispin, 2016 [38]	OL	66	31M 35F, aged 19–65y	AA, AT, AU	0.5–43y	5mg BD	-,+,+,+,+,+
Kim, 2017 [56]	CR	1	F 28y	AU	8y	5mg BD	+++
Liu, 2017 [36]	CS	90	40M 50F, aged 18–70y	AA, AT, AU	2–54y	5–10mg BD ± prednisone	-,+,+,+,+,+
Morris, 2018 [57]	CR	1	M 22y	AU	5y	5mg BD	+++
Mrowietz, 2017 [58]	CR	1	F 20y	AU	2y	10–15mg daily	+++
Park, 2017 [50]	CS	32	16M 16F, aged 18–54y	AA, AT, AU	1–35y	5–20mg BD	-,+,+,+,+,+
Patel, 2018 [46]	CS	2	2M, aged 17–40y	AU	4–16y	5mg daily to 5mg BD	+,+,+,+
Salman, 2017 [66]	CR	1	M 25y	AU	NR	5mg BD	-
Scheinberg, 2017 [61]	CS	4	2M 2F, aged 20–60y	AU	2–10y	5mg BD	+,+,+,+
Serdaroglu, 2019 [37]	CS	63	33M 30F, aged 18–62y	AA, AT, AU	1–40y	7.5–10mg daily	-,+,+,+,+,+
Shivanna, 2018 [63]	OL	6	3M 3F, aged 22–35y	AT, AU	0.5–15y	5–10mg BD	-,+,+,+
Vu, 2017 [60]	CR	1	M 44y	AA	4y	5mg daily	+

*+++ ≥ 90% regrowth, ++ 50–89% regrowth, + 5–49% regrowth, - <5% regrowth or relapse on discontinuation, -/+ indeterminate
NR = not recorded. BD = twice daily. ER = extended release. CR = case report. CS = case series. OL = open-label study.

SALT score) [37]. Among the complete responders, relapse was observed in two patients when the dose was tapered [37]. Park et al. [50] studied 32 patients with AA, AT or AU, most of whom were refractory to previous treatments. Eighteen patients had >50% hair regrowth, 6 patients had 5–50% hair regrowth and 8 had no response [50].

Ibrahim et al. [51] reported on 13 adults with AA, 7 of whom achieved at least 50% hair regrowth with tofacitinib. In an open-label trial of 12 adults with AA, Jabbari et al. [39] described >50% hair regrowth in 8 of 12 patients after an average length of time of 32 weeks. Cheng et al. [45] reported on 10 patients with AT or AU who had a mean improvement in SALT score of 61% over a mean duration of 14.4 months. Five of these patients experienced complete remission [45].

Castelo-Soccio et al. [52] reported on 8 adolescents with AU who all had >50% scalp, eyebrow, eyelash and body hair regrowth after 4–12 months of treatment with tofacitinib. Two of these patients also had improvement in nail dystrophy associated with AA. Craiglow et al. [47] reported on 13 adolescents with AA, 10 of whom experienced hair regrowth on tofacitinib treatment with a mean change in SALT score of 61%.

6.2. Case reports and small case series

There have been numerous case reports and small case series describing clinical improvement in AA using oral tofacitinib at doses of 10mg to 15mg per day (Table 1) [46,53–63]. The timeframe from starting oral tofacitinib treatment to experiencing significant hair regrowth ranged from 6 weeks to 10 months of therapy. Relapse of AA either during treatment or after discontinuation of oral tofacitinib has been described [64,65].

Improvement in concurrent medical conditions has been reported in patients treated with tofacitinib for AA [53,57,58]. Craiglow et al. [53] and Salman et al. [66] reported improvement in concurrent plaque psoriasis with tofacitinib. Mrowietz et al. [58] described improvement in psoriatic arthritis but no improvement in plaque psoriasis. Morris et al. [57] reported on a patient with AU and concurrent atopic dermatitis (AD) who had improvement in both conditions with oral tofacitinib treatment. Vu et al. [60] described a patient with AA, AD and vitiligo who had significant improvement in their AA and AD, and marginal improvement in vitiligo, after 6 months of tofacitinib treatment. Patel et al. [46] described a patient with AU who had concurrent vitiligo which did not improve on tofacitinib treatment. Dhayalan et al. [67] described improvement in AA-associated nail dystrophy with tofacitinib.

7. Oral ruxolitinib

Table 2 summarizes reports of oral ruxolitinib in the treatment of AA. In an open-label trial, Mackay-Wiggan et al. [40] studied 12 patients with AA treated with ruxolitinib 20mg twice daily for 3–6 months. Nine of 12 patients had significant hair regrowth with an average of 92% change from baseline [40]. Three months after cessation of ruxolitinib, 3 of 9 responders had significant hair shedding and 6 had minor shedding [40]. One patient had concurrent vitiligo which improved with ruxolitinib treatment [40].

Liu et al. [48] reported on 8 patients with AA, AT or AU who were treated with ruxolitinib 10–25mg twice daily. Six of these patients had previously been treated with oral tofacitinib for at least 4 months. Five of 8 achieved complete or near-complete hair regrowth with a mean improvement in SALT score of 98% [48]. Of these patients, 2 were never treated with tofacitinib and 2 had previously achieved significant scalp hair

Table 2. Summary of oral ruxolitinib reports in AA, AT and AU.

Author, date	Article type	N	Patient demographics	Diagnosis	Duration of disease	Dose	Results*
Harris, 2016 [71]	CR	1	M 35y	AA	19y	20mg BD	+
Liu, 2019 [48]	CS	8	4M 4F, aged 14–57	AA, AT, AU	0.5–5y	10–25mg BD	-,+++
Mackay-Wiggan, 2016 [40]	OL	12	5M 7F, mean age 43.7y	AA	NR	20mg BD	-,+++
Pieri, 2015 [68]	CR	1	F 38y	AU	4y	15mg BD	+++
Ramot, 2017 [69]	CR	1	M 33y	AU	11y	20mg BD	++
Vandiver, 2017 [70]	CS	2	2F, aged 45–59y	AT, AU	14mo–10y	10–30mg daily	+++
Xing, 2014 [22]	OL	3	NR	AA	NR	20mg BD	+++

*+++ ≥ 90% regrowth, ++ 50–89% regrowth, + 5–49% regrowth, <5% regrowth or relapse on discontinuation,

-/+ indeterminate

NR = not recorded. BD = twice daily. CR = case report. CS = case series. OL = open-label study.

regrowth with high dose tofacitinib (10mg twice daily) [48]. One patient had not responded to high-dose tofacitinib previously and achieved near-complete remission with ruxolitinib 10mg twice daily [48]. There have been other case reports or small case series demonstrating significant hair growth with ruxolitinib [22,68–70]. Harris et al. [71] reported on a patient with concurrent vitiligo who experienced rapid improvement in vitiligo on ruxolitinib treatment which subsequently relapsed after cessation of the drug.

8. Oral CTP-543 (deuterated ruxolitinib)

A Phase 2 randomized, placebo-controlled, dose-ranging trial reported that the investigational product CTP-543 was efficacious in treating patients with moderate to severe AA [72]. CTP-543, an oral JAK1/2 inhibitor, is a deuterium-modified form of the JAK1/2 inhibitor ruxolitinib [72]. The primary efficacy endpoint of statistically significant differences relative to placebo in the percentage of patients achieving a ≥ 50% relative change in SALT from baseline at week 24 was met in the 12mg twice daily cohort (58% of participants) and 8mg twice daily cohorts (47% of participants) [72].

9. Oral PF-06651600 and PF-06700841

A Phase 2a randomized double-blind placebo-controlled trial reported that two new oral JAK inhibitors, PF-06651600 and PF-06700841, were efficacious and well-tolerated in patients with AA with ≥50% scalp hair loss [73]. PF-06651600 is an oral JAK3 inhibitor and PF-06700841 is an oral TYK2/JAK1 inhibitor [73].

A total of 142 participants were randomized to receive either once daily PF-06651600, PF-06700841 or placebo. Statistically significant changes in SALT score versus placebo were observed for both drugs at weeks 4 and 6. At week 24, the SALT score change from baseline, compared to placebo,

was 42.1 for the PF-06651600 group and 53.4 for the PF-06700841 group in participants with an AA episode duration of less than 3.5 years [73]. The week 24 SALT score change from baseline, compared to placebo, was 22.7 for the PF-06651600 group and 39.1 for the PF-06700841 group in participants with an AA episode duration of 3.5 years or longer [73].

10. Oral baricitinib

Improvement in AA with oral baricitinib treatment has been described in a case report by Jabbari et al. [74]. A 17-year-old man with Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated temperature (CANDLE) syndrome was commenced on oral baricitinib. He also had a 7-year history of AA which had started in patches and progressed to the ophiasis subtype. He experienced complete remission of AA after 9 months of treatment [74].

11. Topical tofacitinib

Reports of topical tofacitinib use in AA have shown some efficacy, although not to the extent of oral tofacitinib. Table 3 summarizes these reports. In a 24-week open-label trial of 10 patients with AA or AU treated with tofacitinib 2% ointment to the scalp, 3 out of 10 patients were considered responders, with a change in SALT score ranging from 18% to 61% [75]. In another study of 16 patients with AU treated with tofacitinib 2% ointment twice daily over a 12-week period, 6 patients had partial hair regrowth in the treated area [76]. Cheng et al. [45] reported on 4 adults with AU treated with tofacitinib 2% cream twice daily for a mean duration of 7 months, with varying efficacy. Craiglow et al. [77] reported on a patient with upper eyelash loss who was treated with topical tofacitinib to the upper eyelid and experienced complete upper

Table 3. Summary of topical tofacitinib reports in AA, AT and AU.

Author, date	Article type	N	Patient demographics	Diagnosis	Duration of disease	Dose	Results*
Bayart, 2017 [79]	CS	5	1M 3F, aged 3–15y	AA, AT, AU	1–11y	Tofacitinib 1–2%	-,+,+++
Bokhari, 2018 [76]	PCT	16	10M 6F, aged 25–59y	AU	NR	Tofacitinib 2%	-,+
Cheng, 2018 [45]	CS	4	3M 1F, aged 28–58y	AU	2–10y	Tofacitinib 2%	-,+++
Craiglow, 2018 [77]	CR	1	F late 20s	AA	11mo	Tofacitinib 2%	+++
Liu, 2018 [75]	OL	10	6M 4F, aged 19–58y	AA, AU	0.2–26y	Tofacitinib 2%	-,+,++
Putterman, 2018 [78]	CS	11	2M 9F, aged 4–16y	AA, AT, AU	2–10y	Tofacitinib 2%	-,+,+,++++

*+++ ≥ 90% regrowth, ++ 50–89% regrowth, + 5–49% regrowth, <5% regrowth or relapse on discontinuation,

-/+ indeterminate

NR = not recorded. CR = case report. CS = case series. OL = open-label study. PCT = placebo-controlled trial.

Table 4. Summary of topical ruxolitinib reports in AA, AT and AU.

Author, date	Article type	N	Patient demographics	Diagnosis	Duration of disease	Dose	Results*
Bayart, 2017 [79]	CS	2	1M 1F, aged 4–17y	AU	1–14y	Ruxolitinib 1–2%	-/+
Bokhari, 2018 [76]	PCT	16	10M 6F, aged 25–59y	AU	NR	Ruxolitinib 1%	-/+
Craiglow, 2016 [80]	CR	1	F late teens	AU	NR	Ruxolitinib 0.6%	+
Deeb, 2017 [81]	CR	1	F 66y	AT	50y	Ruxolitinib 0.6%	-
Gordon, 2019 [65]	CR	1	F 48y	AA	20y	Ruxolitinib 1.5%	-

*+++ ≥ 90% regrowth, ++ 50–89% regrowth, + 5–49% regrowth, <5% regrowth or relapse on discontinuation,

-/+ indeterminate

NR = not recorded. CR = case report. CS = case series. PCT = placebo-controlled trial.

eyelash regrowth after 4 months. Ophthalmologic examination after 2 months of therapy showed no abnormalities [77].

Topical tofacitinib has also been used in children and adolescents. Putterman et al. [78] reported on 11 children and adolescents aged 4–16 years treated with topical tofacitinib 2%. Three patients had almost complete remission, 5 had 5–50% hair regrowth and 3 had no response [78]. Bayart et al. [79] reported on 5 children and adolescents aged 3–15 years treated with topical tofacitinib 1–2%, with varying efficacy. One patient had no response when applying tofacitinib 2% in VeraBase cream to the scalp but had 95% regrowth with a liposomal base formulation [79].

12. Topical ruxolitinib

Topical ruxolitinib has been used in AA with limited efficacy (Table 4). In a 12-week placebo-controlled trial of 16 patients with AU, 5 patients had partial regrowth in the areas treated with ruxolitinib 1% ointment [76]. Bayart et al. [79] reported on 2 patients with AU who applied ruxolitinib 1–2% to the eyebrow regions. One had 75% eyelash regrowth and the other had no response [79]. Craiglow et al. [80] described a case of a patient with AU who achieved 10% scalp regrowth and normal eyebrows after 12 weeks of treatment with ruxolitinib 0.6%. Deeb et al. [81] described lack of improvement in AA with ruxolitinib 0.6% cream. Gordon et al. [65] described a case of improvement in SALT score by 73% with topical ruxolitinib, with subsequent relapse after discontinuation of the drug.

13. Topical ATI-502

In a Phase 2 randomized, double-blind, vehicle-controlled clinical trial assessing the efficacy of ATI-502, an investigational topical JAK 1/3 inhibitor in patients with AA, statistical superiority was not demonstrated at the primary or secondary endpoints due to high rates of disease resolution in vehicle-treated patients [82].

14. Conclusion

Chronic AA is an unpredictable, relapsing and remitting disease which significantly impacts quality of life and has limited therapeutic options. Although there is a paucity of high-quality evidence to date, inhibition of JAK enzymes has shown promising results in numerous case reports, case series, open-label studies and most recently in two randomized placebo-controlled trials. JAK inhibitors have a favorable safety

profile. The literature suggests that maintenance therapy may be necessary to produce a sustained response. The most significant barrier to treatment with JAK inhibitors at present is the cost. Clinical trials are currently underway to further assess the efficacy and safety of JAK inhibitors in AA.

15. Expert opinion

AA is an autoimmune hair loss disease with an incidence of 0.7% to 4% and prevalence of approximately 0.2% [4]. It is a chronic, relapsing and remitting disease that affects adults and children, males and females, with no significant ethnic differences. Approximately 60% of patients develop acute AA that presents with one or more circular patches of scalp hair loss that recovers within 6 to 12 months without treatment [2]. Relapses of acute AA can occur after many years. Approximately 40% of patients develop chronic persistent or chronic relapsing and remitting AA that fails to resolve spontaneously [2]. Among patients with chronic AA approximately 30% will ultimately experience complete loss of scalp hair (AT), or complete loss of scalp and body hair (AU) [2].

AA has a significant psychological impact, with patients experiencing increased rates of depression and anxiety. Suicide has been reported in adolescents who had been recently diagnosed with AA and who had no preceding psychological disorders [83]. No therapy for AA has been approved by the US FDA. Treatments currently used include topical, intralesional and oral corticosteroids and a variety of non-steroidal anti-inflammatory, steroid-sparing medications. A recent systematic review of systemic therapy for AA failed to identify a therapy supported by robust evidence-based data [84].

AA is mediated by T-cells. In a murine model, upregulation of IL-15 in hair follicles led to recruitment and activation of natural-killer, gene 2D-expressing CD8 + T-cells, which produce IFN- γ , leading to breakdown of hair follicle immune privilege [22]. Cell signaling via IFN- γ and IL-15 occurs through the JAK/STAT signaling pathway.

The JAK family of enzymes, JAK1, JAK2, JAK3, and TYK2 are cytoplasmic tyrosine kinases that interact with Type 1 and Type 2 cytokine receptors to mediate signal transduction, thereby affecting the activation, proliferation, and function of leukocytes and other cell types. Results from open-label clinical trials and case series evaluating the JAK inhibitors tofacitinib and ruxolitinib in patients with AA suggest that JAK inhibitors may be effective at reversing hair loss.

After 40 years of minor and generally inconsequential, incremental advances in the treatment of AA, this

identification of JAK/STAT pathway inhibitors as a treatment for AA represents a major breakthrough as a number of these agents are currently FDA-approved and marketed for myeloproliferative disorders, inflammatory arthritis and are currently under investigation for inflammatory skin diseases including psoriasis, atopic dermatitis and vitiligo.

Phase 3 clinical trials of JAK inhibitors in AA have commenced and there is now a growing sense of optimism among patients with long-standing, treatment-refractory, disfiguring AA. Further work is still required to determine optimal dose, the requirement for loading doses and the optimal target within the JAK family. Over the next few years this information will gradually become available along with ideal treatment duration and whether maintenance therapy is universally required.

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