Janus Kinase Inhibitors in the Treatment of Alopecia Areata

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Abstract: Alopecia areata is a disease of autoimmune origin which causes non scarring hair loss. The extent of alopecia varies from a small patch to complete scalp and body hair loss, which can have huge psychosocial impact for those affected. Treatment modalities which have been used so far included nonspecific immunosuppressive medications, such as corticosteroids, cyclosporine, and methotrexate, or topical immunomodulators, such as diphencyprone, dithranol, and squaric acid dibutylester. The recognition of the importance of Janus kinase pathway in alopecia areata pathogenesis enabled more specific approaches in treatment. Positive outcomes of Janus kinase inhibitors in several trials granted approval for baricitinib which became the first on-label treatment for alopecia areata. The aim of this review is to summarize the role, efficacy and safety of several Janus kinase inhibitors in alopecia areata.

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Introduction

Alopecia areata is an autoimmune disease which causes reversible hair loss. It affects around 2% of population worldwide regardless of ethnicity and gender (Darwin et al., 2018). Autoantibodies are formed and attack the follicular hair cells of the bulb disturbing the anagen phase and causing hair loss (Darwin et al., 2018). Any hair-bearing region can be attacked, mainly the scalp but also facial and body hair. Hair loss can vary, from a small patch (patchy alopecia) to total scalp hair loss (alopecia totalis) or loss of all body hair (alopecia universalis) (Figure 1) (Villasante Fricke and Miteva, 2015). Even though the loss is described as temporary, only around 65% of patients will demonstrate complete hair regrowth within 5 years and almost all of them will experience one or more relapses within 20 years from the first incident (Trueb et al., 2018). Alopecia areata is associated with atopic diseases, such as atopic dermatitis, rhinitis and asthma, and other autoimmune diseases, namely autoimmune thyroid disorders, vitiligo, pernicious anaemia, and diabetes mellitus 1 (Goh et al., 2006).

Diagnosis is nowadays based on dermoscopic identification of black and yellow dots, exclamation mark hairs, broken hairs, short vellus hairs and tapered hairs (Waśkiel et al., 2018). In doubtful cases, a biopsy taken from the margins of an active lesion typically shows the presence of lymphocytes surrounding and invading hair bulbs (Ohyama, 2018).

Damage to the hair follicle occurs when there is a disruption of the protective shield of growing hair, resulting in formation of autoreactive $CD8^+$ T-cells directed against the follicular cells. In healthy individuals, growing hairs enjoy a state of immune privilege which is a result of several mechanisms (Paus et al., 2003). These include the downregulation of major histocompatibility complex class I (MHC) antigens by the follicular bulb cells, local synthesis of cytokines with potent

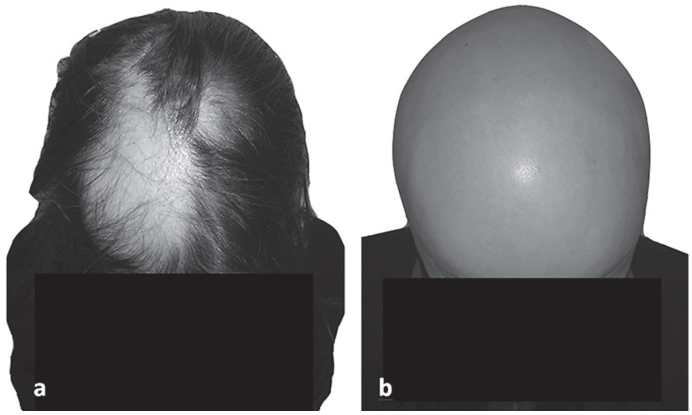

Figure 1 – Clinical manifestation of alopecia areata. a) One large and one smaller patch without hair on the frontoparietal region. b) Alopecia totalis: total loss of scalp hair.

anti-inflammatory activity, such as interleukin 10 (IL-10) and tissue growth factor β1 (TGFβ1), and expression of Fas Ligand (FasL) which causes lysis of autoreactive T-cells (Paus et al., 2003). Genetic mutations in genes encoding MHC antigens as well as environmental factors, such as viral infections, vaccines, low vitamin D blood levels, have been identified as possible triggers for the collapse of follicular protection (Anzai et al., 2019).

In order to suppress the immune reaction and initiate hair growth in patients with alopecia areata, topical or intralesional corticosteroids are prescribed with varying degrees of success. Alternatively, topical immune modulators, namely difencyprolone or anthralin, and topical minoxidil can be applied. In resistant cases, systemic immunosuppressants, such as cyclosporine and methotrexate or oral corticosteroids, are used but are not very effective and may cause several serious side-effects (Alkhalifah et al., 2010).

Until June, 2022, no treatment was officially approved worldwide for the treatment of alopecia areata. On the 13th of June, 2022, the U.S. Food and Drug Administration (FDA) approved Olumiant (baricitinib), a Janus kinase (JAK) inhibitor, for the treatment of adult patients with severe alopecia areata. The aim of this article is to examine the mechanism of action of JAK inhibitors and the current evidence on the safety and efficacy of currently existing drugs of this class in the treatment of alopecia areata.

JAK/STAT pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a key role in maintaining the innate and adaptive immunity. It is an intracellular signalling pathway which controls and affects several hormones and cytokines, including interleukins (IL), interferons (IFNs), growth factors, and colony-stimulating factors (Fragoulis et al., 2019).

The JAK/STAT signalling pathway consists of three components: the receptor, the JAK, which is connected to the intracellular side of the receptor, and the STAT (Fragoulis et al., 2019). JAKs belong to the Janus family of tyrosine kinases (Rochman et al., 2009). There are four members of this group, TYK2, JAK1, JAK2 and JAK3 with each one being expressed in varying concentrations in cells of hemato/lymphopoietic system. STATs are transcription factors with seven members: STAT 1, STAT 2, STAT 3, STAT 4, STAT 5A, STAT 5B and STAT 6 (Rochman et al., 2009).

Binding of a ligand, for example interleukin, to the receptor causes its dimerization, resulting in activation of JAK proteins by transphosphorylation. JAKs phosphorylate tyrosine molecules on the intracellular domain of the receptor which allows STATs to bind. JAK phosphorylate STATs causing their dissociation and translocation to the nucleus in order to regulate expression of genes via DNA transcription. Each receptor is associated with a particular JAK or combination of JAKs which activate a specific STAT leading to transcription of the respective genes. Suppressors of

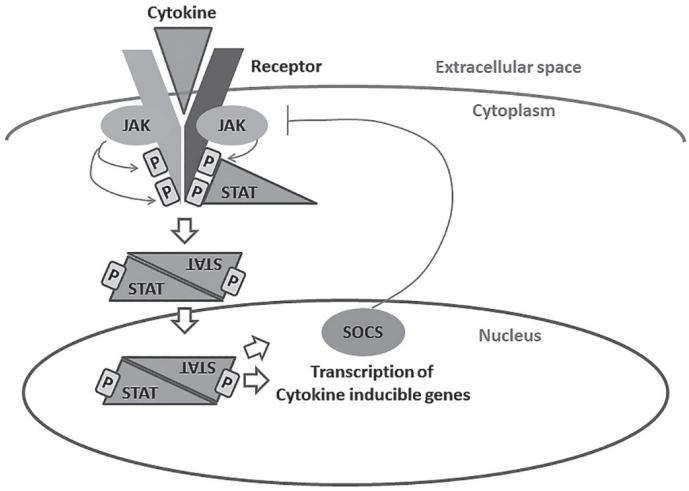

Figure 2 – The JAK/STAT pathway: there are three major components: cell-surface receptors, JAKs and STATs. When a molecule, such as cytokine binds to receptor, JAK prosphorylates the receptor (P molecules). This enables two STATs to bind to the receptor (here only one is shown) which are subsequently prosphorylated by JAK and form a STAT-STAT dimer. The activated dimer enters the nucleus and activates the transcription of target genes, such as cytokine-inducible genes. Suppressors of cytokine signalling (SOCS) are also produced and act as negative feedback.

cytokine signalling (SOCS) act as negative feedback and are responsible for the termination of the cascade. The key components of the pathway are presented in Figure 2.

The types of cytokines produced via the JAK/STAT pathways depend on the ligand and the different combinations of JAKs linked to the receptor. For example, interleukin 15 (IL-15) signals through JAK1 and JAK3 whereas interferon γ (IFNγ) through JAK1 and JAK2. In alopecia areata autoreactive $CD8^+$ effector T-cells produce IFNγ which binds to the IFNγ receptors on follicular epithelial cells and via JAK1/2-STAT pathway induces the production of IL-15. IL-15 binds to receptors on $CD8^+$ T-cells and via JAK1/3-STAT pathway signals the production of more IFNγ. This positive feedback loop potentiates the inflammatory response and leads to disruption of anagen phase with consequent hair loss (Zhou et al., 2021).

JAK inhibitors

JAK inhibitors are small molecules which bind to Janus kinases and disrupt the signalling cascade. Because of their immunomodulatory action, they have been studied and used in the treatment of several myelodysplastic and inflammatory diseases, namely polycythaemia vera, essential thrombocytopenia, rheumatoid arthritis, Crohn's disease, alopecia areata and atopic dermatitis (Kerschbaumer et al., 2020). Ruxolitinib, tofacitinib and baricitinib belong to the first generation of JAK

inhibitors which is not very selective and is able to block more than one type of JAK. With increasing knowledge on the function and importance of each JAK type, more selective JAK blockers have been developed and are tested for their safety and efficacy with various results.

In contrast to biologic therapy which uses large molecules-antibodies administered usually subcutaneously, JAK inhibitors are orally administered, rapidly absorbed and have short half-lives mostly between 4–8 hours. They undergo hepatic metabolism and get excreted in urine and faeces at varying degrees (Ma et al., 2019; Ramírez-Marín and Tosti, 2022).

JAK inhibitors in alopecia areata

As alopecia areata is an autoimmune T-cell mediated disorder, disruption of downstream signalling initiated by pro-inflammatory cytokines, such as IFNγ, could hinder leucocyte recruitment to the hair follicle and block the release of cytotoxic granzymes which are responsible for hair loss. After their approval for other diseases, JAK inhibitors were tried off-license in a small number of patients with alopecia areata with satisfactory outcomes. As a result, several phase 2 and phase 3 clinical trials were designed for patients with this type of autoimmune hair loss.

1) Tofacitinib

This JAK1/3 inhibitor was the first drug of its category to be produced. It is licensed in European Union for the treatment of ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis (European Medicines Agency, 2017). Its effect on alopecia areata was first noted in 2014 in a young male patient with alopecia universalis and psoriasis (Craiglow and King, 2014). Complete regrowth was achieved after 8 months of therapy with tofacitinib. Since then, several studies have been published in patients with moderate-to-severe alopecia with growth rates ranging between 50–90% after 6–12 months of treatment (Kennedy et al., 2016; Liu et al., 2017). Topical tofacitinib has been also formulated and tested but appears to be less effective (Bayart et al., 2017). Side effects after oral administration were limited to grade I and II infections (upper respiratory and urinary tract infections, zoster, folliculitis, conjunctivitis), with rarer occurrences of liver toxicity, thrombocytopenia, neutropenia, hypercholesterolemia and acneiform eruptions (Dillon, 2021). Most side effects were either short-lived or disappeared after drug discontinuation.

However, based on the results of a recent trial that compared the safety and efficacy of tofacitinib with TNF inhibitors in patients with rheumatoid arthritis, the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) concluded that tofacitinib carries an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death (Liu et al., 2022). This could potentially apply for other JAK inhibitors but extensive safety data are lacking.

2) Ruxolitinib

Ruxolitinib is a JAK1/2 inhibitor approved for the treatment of myelofibrosis, polycythaemia vera and graft-versus-host reaction (Triyangkulsri and Suchonwanit, 2018). Several case reports on the use of ruxolitinib in patients with alopecia areata have been published (Dillon, 2021). Notably, in an open label trial, Mackay-Wiggan et al. (2016) administered ruxolitinib 20 mg tablets twice daily to 12 patients with severe alopecia for 6 months. By the end of the trial, more than 50% of them achieved nearly complete hair regrowth. Similar to tofacitinib, side effects were limited to upper respiratory infections. No reports of hospitalisation or malignancy were reported.

3) Baricitinib

Baricitinib is a newer potent JAK1/2 inhibitor but can also block JAK3 (Triyangkulsri and Suchonwanit, 2018). In Europe is licensed for the treatment of severe resistant rheumatoid arthritis and atopic dermatitis (European Medicines Agency, 2017). As of 13th of June, 2022, it is also the first drug which is licensed for the treatment of alopecia areata in the United States and has pending approval in the European Union (U.S. Food and Drug Administration, 2022). The decision was based on the results of two randomized phase 3 clinical trials (BRAVE-AA1 and BRAVE-AA2) involving patients with more than 50% hair loss (U.S. Food and Drug Administration, 2022). Around 40% of patients who received baricitinib 4 mg tablets had at least 80% scalp covered by hair in contrast to only 6% of the placebo group after 36 weeks.

Side effects include upper respiratory and urinary tract infections, acne, increased low-density cholesterol and creatine kinase levels, and herpesvirus infections (European Medicines Agency, 2017).

4) Ritlecitinib

JAK3 is exclusively associated with the common gamma chain receptor; therefore, it is involved in the functions of T-cells, B-cells and natural killer (NK) cells but does not interfere with metabolic and hematopoietic pathways (Ramírez-Marín and Tosti, 2022). Ritlecitinib is a highly selective and irreversible JAK3 inhibitor. It also blocks another family of tyrosine kinases found in hematopoietic cells, called tyrosine kinase expressed in hepatocellular carcinoma (TEC), because they share similar chemical structure with JAK3 (Ramírez-Marín and Tosti, 2022). Inhibition of JAK3 and TEC blocks the function of $CD8^+$ T-cells, $CD4^+$ T-cells, B-cells, Tregs and NK cells which are involved in the pathogenesis of alopecia areata.

Data for the efficacy of ritlecitinib in alopecia areata were extracted from various ALLEGRO trials. A phase 2b/3 randomised, placebo-controlled double-blind trial involved 718 patients older than 12 years from around the world, including Czech Republic (Pfizer, 2021). Scalp hair loss was required to be greater than 50% persisting for more than 6 months but less than 10 years. After 24 weeks, at least 80% of scalp was covered with hair in a "statistically significant" proportion of patients receiving

ritlecitinib in comparison to placebo. ALLEGRO-LT is a global phase 3 trial in patients older than 12 years with more than 50% hair loss which is currently running and expected to finish by 2026 (ClinicalTrials.gov, 2022).

5) Brepocitinib

TYK2 is an important regulator of IFNα, IFNγ, IL12/23, IL-6 and IL-10 signalling pathways (Winnette et al., 2022). These cytokines are crucial in the pathogenesis of several autoimmune diseases, including chronic plague psoriasis and alopecia areata. Brepocitinib, a TYK2/JAK1 inhibitor, was developed and tested against ritlecitinib and placebo in a randomised study involving 142 adults with more than 50% hair loss persisting for at least 6 months (Winnette et al., 2022). At the end of the 24-week period, the proportion of patients who managed to regain at least 70 of their scalp hair was 64% with brebocitinib, 50% with ritlecitinib and only 2% with placebo.

Safety profile of JAK inhibitors

JAK inhibitors have been only recently used for the treatment of alopecia areata. As a result, the majority of safety data are pooled from studies and reports from patients with different background than individuals with alopecia areata. A recent retrospective study analysed almost 127,000 safety reports from the pharmacovigilance database of World Health Organization (WHO) concerning the use of ruxolitinib, tofacitinib and baricitinib in patients with haematological and autoimmune disorders (Hoisnard et al., 2022). The median age of patients with adverse events was 71 years for ruxolitinib and 61 years for baricitinib and tofacitinib. Ruxolitinib was mainly used for the treatment of oncological and haematological disorders, tofacitinib for the treatment of rheumatoid arthritis and psoriasis, and baricitinib for the treatment of psoriasis. Most reports pertained to higher doses of drugs. JAK inhibitors were associated with herpetic infections, upper respiratory tract infections, musculoskeletal and connective tissue disorders, embolism and thrombosis and neoplasms, such as benign and malignant skin tumours and benign soft tissue neoplasms. Tumours were mostly associated with ruxolitinib. Patients receiving high doses of tofacitinib were in increased risk of gastric perforation.

The safety and efficacy of tofacitinib in alopecia areata was documented in several small retrograde studies and case series. After oral administration, the prevailing adverse events were upper respiratory tract infections, urinary tract infections, acne, and headache, followed by nausea, liver enzyme abnormalities and leukopenia (Kennedy et al., 2016; Liu et al., 2017; Jabbari et al., 2018). Side effects were inconsistent amongst studies, mostly mild and transient. No malignancy was noted. When given topically, tofacitinib was associated with scalp irritation and folliculitis according to one open label study (Liu et al., 2018).

Data on ruxolitinib are also based on case reports and small studies. In one open label study with 12 patients, oral intake of ruxolitinib 20 mg tablets twice daily for

3–6 months resulted in seven patients contracting upper respiratory tract infections, one contracting urinary tract infection, one reporting mild gastrointestinal symptoms and one developing anaemia (Mackay-Wiggan et al., 2016). Adverse events after local administration of ruxolitinib were limited to scalp irritation and folliculitis in a minority of patients (Olsen et al., 2020).

Currently, the only JAK inhibitor registered for the treatment of alopecia areata is baricitinib. Reported side effects from the two phase 3 BRAVE-AA trials, were limited to acne and increased levels of creatine kinase, high-density, and low-density lipoproteins (King et al., 2022). A study on healthy volunteers also reported reduced levels of reticulocytes and neutrophils in some patients (Shi et al., 2014).

Results on the safety of ritlecitinib, a selective JAK3 inhibitor, were reported after 24 weeks of the ALLEGRO phase 2a trial (Ramírez-Marín and Tosti, 2022). Adverse events were reported by almost two thirds of patients. About 20% developed herpes zoster and 10% reported headache, acne, nasopharyngitis and upper respiratory tract infections. Two of the 48 participants were diagnosed with breast cancer and were withdrawn from the study.

The use of JAK inhibitors in pregnant and lactating women is contraindicated (Kerschbaumer et al., 2020). Even though there are no sufficient data in humans, animal studies showed that baricitinib and tofacitinib can be toxic to fetus and are excreted in milk (Jorgensen et al., 2022).

Drug interactions

JAK inhibitors are metabolised in the liver by the cytochrome P450 enzymes (CYP450) but the degree of metabolism as well as the extent or renal excretion varies greatly amongst group members (European Medicines Agency, 2017). More than 99% of ruxolitinib and 70% of tofacitinib undergo first-pass metabolism necessitating dosage adjustment of the drug when strong CYP450 inhibitors or inducers are co-administered (European Medicines Agency, 2017; National Center for Biotechnology Information, 2022).

Studies demonstrated that only 6% of baricitinib is metabolised by C450 enzymes (National Center for Biotechnology Information, 2022). Co-administration of strong CYP450 inhibitors or inducers, such as ketoconazole or rifampin did not affect significantly drug concentrations. However, because baricitinib binds to several transporters, co-administration with strong inhibitors, such as probenecid decreased renal clearance and increased plasma concentrations (European Medicines Agency, 2017). According to labelling, baricitinib dose should be reduced if probenecid is co-prescribed (European Medicines Agency, 2017).

Caution should be also exercised when combining JAK inhibitors with other immunosuppressive agents, such as azathioprine, methotrexate, and cyclosporine, because of the additive immunosuppressive effect.

Relapse after drug withdrawal

Alopecia areata is typified by relapses and remissions. The main concern with the disease management is whether and when will hair falls after drug withdrawal. Several small retrospective and prospective studies involving oral tofacitinib and ruxolitinib reported hair loss in at least 90% of patients three-to-six months after treatment cessation (Ramírez-Marín and Tosti, 2022).

These results demonstrate the importance of continuing the treatment with JAK inhibitors after achieving hair growth at least with some maintenance dose. In BRAVE-AA2 study, patients successfully treated with oral baricitinib 4 mg for a year, were randomized to receive either 4 mg or 2 mg of baricitinib for six months (King et al., 2022). Almost all patients in high dose group and around 75% of patients in low dose group maintain their hair at the end of study.

In a study following the ALLEGRO trial, patients who were successfully treated with oral ritlecitinib for 52 weeks, lost at least 30% of their scalp hair within 4 months after drug withdrawal (Ramírez-Marín and Tosti, 2022). Reintroduction of ritlecitinib for 24 weeks resulted in 70% hair regrowth in only 57% of previously successfully treated patients. This study demonstrated that ritlecitinib loses its efficacy after withdrawal and retreatment.

Conclusion

After the recognition of the importance of JAK/STAT pathway in the pathogenesis of alopecia areata, several JAK inhibitors have been tested in the treatment of this disease with positive outcomes. Baricitinib has become the first representative of its class to obtain registration and is currently the only on-label option for the treatment of alopecia areata. The selective inhibition of JAK3, the key JAK in alopecia areata, appears to provide higher efficacy with more favourable safety profile. Studies to demonstrate the long-term safety of JAK inhibitors are necessary because patients may need to receive maintenance treatment in order to prevent relapse.

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