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JAK INHIBITORS IN THE TREATMENT OF ALOPECIA AREATA - A LITERATURE REVIEW

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ABSTRACT

Introduction

Alopecia areata (AA) is a chronic autoimmune disorder causing non-scarring hair loss, which can range from isolated patches to complete scalp (alopecia totalis, AT) or body hair loss (alopecia universalis, AU). It affects people of all ages, genders, and ethnicities. Around 10-20% of cases have a familial component, indicating a genetic predisposition. Symptoms often begin before age 40, with about half of patients experiencing onset in childhood, and it may coexist with other autoimmune diseases. The disease's course is unpredictable, with spontaneous hair regrowth possible, though relapses are common, reaching a 100% relapse rate after 10-20 years. AA significantly affects quality of life, increasing the risk of anxiety and depression. Research has linked AA to autoimmune processes involving the JAK-STAT pathway, which promotes inflammation around hair follicles. Recent studies highlight the potential of JAK inhibitors as effective treatments.

Material and methods

An electronic literature search was performed using PubMed, Cochrane Library, and Evidence-Based Medicine Reviews. Search terms included 'alopecia areata', 'hair loss' , 'JAK inhibitor', 'JAK-2 inhibitors', ' Janus Kinase Inhibitors', 'tofacitinib', ruxolitinib', 'baricitinib' as keywords. The review focused on articles published in English from their inception until 2025.

Conclusions

Janus kinase (JAK) inhibitors represent a significant advancement in treating alopecia areata by specifically targeting the JAK/STAT pathway, which is linked to hair loss. Oral JAK inhibitors like have shown the most promising results. However, challenges remain, including the risk of relapse after therapy, side effects, and limited efficacy of topical formulations. Ongoing research aims to develop more selective JAK inhibitors and maintenance strategies while addressing high treatment costs.

Keywords: JAK inhibitors, alopecia areata, baricitinib, ruxolitinib, topical JAK inhibitors, JAK/ STAT pathway,

INTRODUCTION

Alopecia areata (AA) is one of the chronic autoimmune diseases leading to non-scarring hair loss that can present in many different types, ranging from single foci to complete hair loss on the scalp (alopecia totalis, AT) or the entire body (alopecia universalis, AU).[1] The condition affects both men and women of all ages, irrespective of ethnicity, and its lifetime prevalence is estimated at 1-2%.[2] A familial occurrence is observed in approximately 10-20% of patients, suggesting a significant genetic component. Although AA often appears before the age of 40, half of the patients develop their first symptoms as early as childhood and they may coexist with other autoimmune diseases such as systemic lupus erythematosus, vertigo, atopic dermatitis or autoimmune thyroid conditions. [3]

The course of the disease is unpredictable - in many cases there is spontaneous regrowth of hair within a few months or years, but relapses are often. Studies indicate that after 10-20 years of follow-up, the relapse rate can be as high as 100%. In patients with more advanced types of AA, approximately 75% stay in the AT stage, and a significant proportion of those with AU experience periods of hair re-growth. [4] The disease has a significant impact on patients' quality of life, leading to an increased risk of psychiatric disorders such as anxiety and depression. In advanced cases, AA can cause significant disfigurement and reduction of health-related quality of life. [5]

The pathogenesis of AA has long been unclear, but modern research points to a key role for autoimmune processes in which autoreactive CD8 T cells, activated by the janus kinase (JAK) and signal transducer and activator of transcription (STAT) signalling pathway, attack hair follicles. Animal models have confirmed that JAK-STAT signalling plays a central role in the initiation of the inflammatory response in AA by inducing the production of interferon gamma (IFN-γ) and interleukin 15 (IL-15), which later enhances the inflammation around the hair follicles.[6] This discovery has opened up new therapeutic perspectives, leading to research into JAK inhibitors (JAKis) as potentially effective drugs for the treatment of AA.

Currently a growing number of studies suggest that JAK inhibitors may be an effective therapeutic option for the treatment of AA, and their effect has been analysed in the context of several drugs, such as ruxolitinib, tofacitinib and baricitinib. In June, 2022, the U.S. Food and

Drug Administration published the statement as the Baricitinib to be the first officially accepted treatment methode.[7] Therefore, the aim of this review is to comprehensively analyse the available evidence on the role, efficacy and outcomes of JAK inhibitor therapy in the treatment of AA. This review will focus on assessing the efficacy of both oral and topical therapies, analysing potential adverse effects, the durability of therapeutic effects and the future prospects of treating AA with the Janus kinase inhibitors.

PATHOPHYSIOLOGY OF ALOPECIA AREATA

Hair follicles are complex structures that remain immunologically privileged under normal conditions. This means that they are able to evade attack from the immune system due to low expression of major tissue compatibility complex (MHC) class I and II molecules, low presence of anti-inflammatory cytokines such as TGF-β, IL-10 and α-MSH, and a limited number of immune cells in their surroundings.[8] Such a protective mechanism is particularly important during the anagen phase, when the follicles intensively synthesise proteins and tissue-specific antigens. However, in alopecia areata (AA), this immune privilege is disrupted, leading to the immune system attacking and damaging the hair follicles.

The hair growth cycle comprises three main phases: anagen (active growth period), catagen (transitional phase) and telogen (resting phase). Under healthy conditions, hair follicles pass through these phases in an orderly manner, ensuring normal hair growth and replacement. However, in AA there is a rapid change in the microenvironment of the hair follicle, resulting in a loss of its protective immune status. The pathologically altered follicles show increased expression of MHC class I and II, increased levels of pro-inflammatory cytokines such as interferon gamma (IFN-γ), interleukins IL-2, IL-7, IL-15 and IL-21, and the presence of activated CD8+ and CD4+ T lymphocytes.[9] Of particular importance are the cytotoxic CD8+ NKG2D+ T cells, which recognise overexpressed stress ligands such as ULBP3 and MICA, leading to their activation and direct attack on hair follicles.[10] This process results in inhibition of hair growth, accelerated transition of the follicle to the catagen phase and gradual atrophy.

An important risk factor for the development of AA is genetic predisposition, which determines susceptibility to an autoimmune reaction against the hair follicles. It was shown that monozygotic twins who developed AA after mumps infection showed almost identical

patterns of hair loss, suggesting a strong influence of the hereditary component.[11] Genome-wide association studies (GWAS) identified numerous AA-associated single nucleotide polymorphisms (SNPs) involving regions encoding factors that regulate the immune response. Prominent among these were loci on chromosome 6p21.32 containing HLA class II genes, which play a key role in antigen presentation to CD4+ T lymphocytes. It has been shown that specific alleles, such as HLA-DRB*1104 (HLA-DR11) and HLA-DQB*0301 (HLA-DQ7), may be associated with more severe forms of the disease, including total hair loss on the scalp (alopecia totalis, AT) and throughout the body (alopecia universalis, AU).[12]

Although alopecia areata mainly manifests itself as hair loss on the scalp, its biochemical features may also involve other areas of the skin and immune system. Even when hair begins to grow back, the pattern of gene expression in previously affected follicles remains disrupted, increasing the risk of recurrence. Studies have shown that overexpression of the ITGAE gene, encoding CD103 - a marker of resident memory T cells - persists in these regions, suggesting that these cells may be responsible for the chronicity of the disease.[13] Although the exact mechanisms of AA initiation are still unclear, it is speculated that environmental factors such as stress, viral infections or other immune factors may play a role in triggering a pathological immune response against hair follicles.[14]

THE ROLE OF JAK- STAT SIGNALING PATHWAY

The JAK-STAT pathway plays a key role in the maintenance of innate and adaptive immunity, acting as an intracellular signalling mechanism for many pro-inflammatory molecules such as interleukins, interferons, growth factors and hormone-like cytokines. It is composed of a receptor, a janus kinase (JAK) and a signal transducer and activator of transcription (STAT).[6] The JAK kinases, which belong to the cytoplasmic tyrosine kinase family, are involved in the regulation of inflammation and haematopoiesis.

The JAK family comprises four enzymes: JAK1, JAK2, JAK3 and TYK2 (tyrosine kinese 2). JAK1 mediates signalling across a broad spectrum of inflammatory conditions, JAK2 is responsible for regulating cytokines associated with haematopoiesis, while JAK3 is important for lymphocyte function and its mutations can lead to severe immunodeficiency.[15] STAT includes seven members (STAT1-STAT6) that transmit signals from JAK to the cell nucleus, activating gene expression.

Cytokine receptor types I and II cooperate with JAK kinases and STAT factors in the transmission of cellular signals. JAK kinases, attached to the cytoplasmic domains of the receptors, activate upon cytokine binding, leading to STAT phosphorylation. STAT dimers migrate to the cell nucleus, where they bind to promoter sequences of target genes and initiate their transcription.[16] They influence cell proliferation, differentiation and apoptosis and regulate the activity of T cells, such as Th1, Th2, Th17 and Treg, involved in autoimmune processes.

The JAK-STAT pathway is important in the pathogenesis of alopecia areata (AA). IFN-γ activates IL-15 production in hair follicles through JAK1/2 signalling, while IL-15 stimulates IFN-γ production by T cells, enhancing inflammation.[17] JAK inhibitors represent a possible therapeutic approach for the cure of AA, as they reduce this inflammatory cascade.

In addition, studies have shown that hair growth after JAK inhibitors can occur independently of the influence of T-lymphocytes, suggesting an intrinsic regulatory mechanism of the hair follicle. The expression of key genes of the JAK-STAT pathway, including Stat5A/B, Stat3, Jak1, Jak3 and Socs2/3, is high during catagen and telogen phases, but decreases in early anagen. JAK-STAT signalling can therefore inhibit re-entry into anagen, and JAK blockade removes this inhibition, allowing the hair cycle to continue properly.[18] JAK blockade may also facilitate the transition to anagen by upregulating the production of factors such as TGF-β2, FGF7/10, LEF1 and NOTCH family members, which promotes hair regrowth.[19]

ORAL JANUS KINASE INHIBITORS USED IN TREATMENT OF AA

1. TOFACITINIB

Tofacitinib belongs to the Janus kinase (JAK) inhibitor group and is used to treat autoimmune conditions such as rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and ankylosing spondylitis. Studies indicated its potential use in the treatment of various forms of alopecia areata (AA), including more advanced forms such as alopecia totalis (AT) and alopecia universalis (AU).

The retrospective analysis by Liu and colleagues included 90 patients who received oral tofacitinib at doses of 5-10 mg, sometimes in combination with prednisone. Assessing the

effects of therapy using the SALT scale (severity of alopecia tool), they found that 77% of patients improved by more than 50%. Of these, 20% achieved almost complete hair regrowth and 56.9% reported moderate or partial improvement. No significant treatment effects were observed in 23.1% of patients.[20] More favourable treatment results were obtained in patients with a milder form of the disease and a shorter duration (less than 10 years for AT and AU).

Data on tofacitinib monotherapy and combination therapy with steroids suggest that the use of the JAK inhibitor alone has similar effects to its combination with glucocorticosteroids. A retrospective analysis of 61 patients with moderate to severe AA, treated for at least three months with tofacitinib, steroids or a combination, showed no significant differences in efficacy between these treatments.[21]

Despite promising clinical results, the use of tofacitinib is associated with the risk of severe complications. These include infections (tuberculosis, fungal infections such as cryptococcosis or pneumocystosis, as well as viral such as shingles), malignancies (lymphomas, solid tumours), cardiovascular incidents (heart attack, stroke, sudden cardiac death) and thrombosis.[19] For this reason, the US Food and Drug Administration (FDA) has issued a warning regarding the increased risk of these complications, which may inhibit the development of research into the use of this drug for the treatment of alopecia areata.

2. BARICITINIB

Baricitinib is one of the first-generation oral JAK1/JAK2 inhibitors, authorized in 1 mg, 2 mg, and 4 mg doses for treating AA. The initial documented case demonstrating its effectiveness involved a 60-year-old woman, suffering from the AA for 9 months, who achieved a 97% hair regrowth following 8 months of monotherapy with 4 mg of baricitinib, without any reported side effects.[22]

These observations were further validated by research on a mouse model, which showed a decline in disease incidence, a reduction in CD8+ T-cell infiltration, and lower expression of MHC class I and II in the skin.[23] These findings suggest that the drug may help maintain the immune privilege of hair follicles.

Later clinical trials, including a phase 2 double-blind study, reinforced the efficacy of higher doses of baricitinib. After 12 weeks of taking the medication, the 2 mg and 4 mg groups achieved the most favorable Severity of Alopecia Tool (SALT30) scores, leading to the continuation of the trial with these doses. By week 36, 33% of patients on 2 mg and 51.9% on 4 mg reached a SALT score of ≤ 20, compared to just 3.6% in the placebo group.

The promising effects led to phase 3 trials, BRAVE-AA1 and BRAVE-AA2, which enrolled over 1,200 individuals with severe alopecia areata. After 36 weeks, hair regrowth was observed in 35.9–38.8% of patients receiving 4 mg, 19.4–22.8% of those on 2 mg, and only 3.3–6.2% in the placebo group. Additionally, a significant improvement in eyebrow and eyelash regrowth was noted, particularly among patients treated with 4 mg.[24]

On June 13, 2022, the FDA (U.S. Food and Drug Administration) granted approval for baricitinib (Olumiant) as the first systemic therapy for alopecia areata, available in 1 mg, 2 mg, and 4 mg tablets. In Europe, this medication is already indicated for the treatment of severe, treatment-resistant rheumatoid arthritis and atopic dermatitis. The approval of baricitinib represents a significant advancement in managing alopecia areata, offering patients an effective treatment option and new opportunities for addressing this chronic condition.

3. RUXOLITINIB

Ruxolitinib is a selective JAK1/JAK2 inhibitor with some effects on TYK2 that has demonstrated anti-inflammatory properties by interfering with IL-17 signaling. It is available in both oral and topical formulations, primarily used for managing myeloproliferative diseases and graft-versus-host reactions.[6] In a notable open-label trial in 2016 ruxolitinib at 20 mg twice a day was given to 12 patients with moderate to severe alopecia areata in a period of time between three to six months. By week 12, 75% of participants had experienced at least half of hair regrowth, whereas after 6 months , seven of these nine responders had over 95% progress, with a 92% reduction in SALT score.[25]

Additional case studies have examined ruxolitinib's effectiveness in alopecia areata. In 2019, Lui and King documented the progress of eight individuals with severe disease (SALT >50), who were treated with doses ranging from 10 mg to 25 mg daily for a duration of five to 31 months. Five patients showed improvement of 98% in SALT score. Interestingly, four of them

achieved this outcome with just 10 mg taken twice daily—an approach not previously described in medical research.[20]

In terms of safety, ruxolitinib appears to be well tolerated in alopecia areata patients, similar to tofacitinib. Most side effects reported in studies have been mild, including low-grade infections or minor symptoms, with no documented cases of hospitalization or malignancy linked to its use.[7]

4. RITLECITINIB AND BREPOCITINIB

Ritlecitinib is a specific inhibitor of JAK3 and tyrosine kinases belonging to the TEC group, while brepocitinib influences on TYK2 and JAK1. Their efficacy was assessed in the phase 2a ALLEGRO study, which involved 142 patients suffering from advanced alopecia areata, characterised by loss of more than 50% of scalp hair. Participants were randomly divided into three groups: the first received ritlecitinib at an initial dose of 200 mg per day for four weeks, after which the dose was reduced to 50 mg per day for a further 20 weeks; the second group received brepocitinib at a dose of 60 mg per day for the first month and then reduced to 30 mg per day for a further 20 weeks; and the third group was treated with placebo.

After 24 weeks, the study found that the mean improvement in SALT score was 31% in the ritlecitinib group and 49% in those treated with brepocitinib. 25% of patients taking ritlecitinib and 34% of those taking brepocitinib experienced almost complete hair regrowth, while no such results were observed in the placebo group.

In addition, scalp biopsies were taken from a selected group of participants (46 subjects) at different points in the study: at baseline, after 12 weeks and after 24 weeks. Histological analysis proved a reduction in the number of CD3+, CD8+ and NKG2D+ T lymphocytes in the affected areas. Furthermore, a correlation was observed between clinical improvement and a reduction in inflammatory mediators such as IFN-γ, CCL5 (TH1), CCL17, CCL18, IL-5 (TH2), IL-32 (TH22). The gene expression profile shifted towards that characteristic of healthy skin, implying an inhibition of activation of T-cell-related pathways. The greatest results were observed in the ritlecitinib group.

Another research, ALLEGRO 2b/3, evaluated only ritlecitinib. It included 718 patients aged 12 years and older with scalp hair loss of more than 50%. These subjects were divided into four groups getting: 50 mg, 30 mg, 10 mg ritlecitinib or placebo. After 24 weeks, those taking the 30 mg and 50 mg doses achieved significant symptom reduction, as assessed by the SALT scale (value ≤20). Following the study results, in September 2022, the US FDA approved the drug's application for approval for the treatment of AA in adults and adolescents.[1]

The ALLEGRO-LT study (Phase 3), which includes patients over 12 years of age with severe disease, is currently ongoing. It is scheduled for completion in 2026.

TOPICAL JAK INHIBITORS

Existing reports on the use of topical Janus kinase (JAK) inhibitors for managing alopecia areata in children primarily consist of individual case studies and small case series. Pediatric patients represent the primary target group for topical treatments since the use of oral JAK inhibitors is restricted in this population. One study detailed six children between the ages of three and 17 who underwent theraphy with either 1% or 2% topical ruxolitinib or 2% topical tofacitinib for periods ranging from three to 18 months. Depending on the alopecia subtype, treatment area, and formulation used, most patients experienced partial hair regrowth (only 2 of them did not notice any effect).[26]

The second example might be an adolescent with AU who did not respond to previous interventions (such as corticosteroids, sulfasalazine, and anthralin) but succeeded with nearly complete eyebrow and partial head hair regrowth after 12 weeks of twice day application of 0.6% ruxolitinib cream.[27]

In a randomized research with mature people, individuals with AA applied one of four formulations to their eyebrows and temples: 2% tofacitinib, 1% ruxolitinib, 0.05% clobetasol, or placebo. 3-months period of application brought hair regrowth in 38% of participants using tofacitinib, 31% using ruxolitinib, 62% using clobetasol, while no improvement was noted in the placebo group.[28]

Although some case reports show satisfying outcomes, there are suspicions about potential partiality in the reporting of topical JAK inhibitor efficacy.[29] Among the eight identified

studies on these treatments, four were discontinued without disclosing the results, potentially indicating negative findings. However, the topic of using topical JAK inhibitors in the treatment of alopecia areata remains open and worth exploring.

SIDE EFFECTS OF JANUS KINASE INHIBITORS IN ALOPECIA AREATA TREATMENT

Janus kinase (JAK) inhibitors represent a novel therapeutic option for the treatment of alopecia areata (AA), showing significant potential in restoring hair loss caused by immune system dysfunction. However, their use is also associated with a significant risk of serious side effects. This is due to the fact that JAKs play a key role in the signalling pathways of many cytokines, growth factors and hormone receptors. Commonly observed, relatively mild side effects in AA patients include skin lesions such as acne, headaches, nausea, urinary and respiratory infections, and haematological disorders including anaemia, thrombocytopenia, neutropenia and elevated blood creatinine levels.[30] Some patients have also been found to have an increase in low-density lipoprotein cholesterol degree, which may increase the chance of cardiovascular disease.

More life threatening side effects associated with the use of JAK inhibitors in alopecia areata include infections such as chickenpox, hemiplegia, pneumonia and tuberculosis. In rare cases, septicaemia and the occurrence of skin tumours (other than melanoma) have also been reported. Safety studies of these drugs, conducted in the context of other autoimmune and inflammatory diseases such as rheumatoid arthritis, atopic dermatitis or psoriatic arthritis, have shown that the most common complications are viral infections (e.g. herpes and influenza), fungal infections, thrombosis and cancer risk.[31]

Studies comparing tofacitinib with TNF-α inhibitors in patients with rheumatoid arthritis found a higher incidence of cancer and cardiovascular events in tofacitinib users. The most frequently diagnosed cancer in this group was lung cancer, whereas breast cancer predominated in the group treated with TNF-α inhibitors. In terms of cardiovascular incidents, for tofacitinib the most common complication was myocardial infarction.[32] Although both therapies proved effective, the risk associated with tofacitinib was clearly higher.

Ruxitinib, as one of the JAK inhibitors, has also found use in the treatment of alopecia areata, although its use remains limited due to its safety profile. Clinical studies indicate the potential for serious infections, such as hemiplegia and respiratory tract infections, as well as thromboembolic events and tumours, mainly of the skin. Adverse effects such as headaches, nausea and gastrointestinal disorders have also been reported.[25] Patients using ruxitinib should be carefully monitored for possible side effects, especially with long-term use.

JAK inhibitors should not be used in pregnant or breastfeeding patients. Although there is limited human information available, animal studies have demonstrated that both baricitinib and tofacitinib may pose a risk of fetal toxicity and can be passed through breast milk.

In conclusion, although JAK inhibitors are beneficial in the treatment of alopecia areata, their use should be preceded by a thorough risk assessment. Patients should be informed of the potential risks and possible side effects so that they can make an informed decision about the use of this therapy.

CONCLUSIONS

Janus kinase (JAK) inhibitors stand for a major breakthrough in the treatment of alopecia areata, offering a more precise therapeutic approach compared to traditional immunosuppressive drugs such as steroids, for example. With the discovery of the key role of the JAK/STAT pathway in the pathogenesis of this disease, it has become possible to develop therapies targeting the inhibition of JAK kinase activity to modulate the inflammatory response responsible for hair loss. Oral inhibitors such as baricitinib, tofacitinib, ruxitinib and rituxitinib have demonstrated efficacy in numerous clinical trials, yielding significant improvements in hair regrowth in many patients. Baricitinib, in particular, is noteworthy as the first drug of this group approved for the treatment of alopecia areata, making it an important therapeutic option. Despite promising results, JAK inhibitor therapy still brings some issues, mainly due to the risk of relapse after treatment and potential side effects, as in the case of tofacitinib used in rheumatoid arthritis. In addition, currently available topical formulations do not show equally high efficacy, limiting treatment options. In response to these challenges, research is underway to develop more selective JAK inhibitors that can provide a better safety profile, and to identify optimal maintenance therapy regimens to prevent relapse after remission has been achieved. At the same time, the cost of therapy

remains problematic and represents a significant barrier to accessing modern treatment. As research into the pathogenesis of alopecia areata evolves, new therapies can be expected to be introduced to address the needs of patients struggling with this chronic and difficult-to-treat condition even more effectively and safely.

AUTHOR'S CONTRIBUTIONS

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