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Baricitinib for the treatment of Alopecia Areata

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Abstract

Alopecia areata (AA) is a chronic, tissue-specific autoimmune disorder, characterized by non-scaring hair loss, with a global prevalence of approximately 2%. Typically, it affects a young population, with initial onset frequently occurring before age of 30 years. Even though the exact pathogenesis of AA remains unclear, the predominant hypothesis is the breakdown of the immune privilege (IP) of the hair follicle, resulting in increased self-antigen and MHC expression in the follicular epithelium. The relapsing nature of the disease negatively impacts patients' quality of life and makes them susceptible to develop psychiatric comorbidities. Although many treatment modalities have been proposed, there are no currently available treatments able to induce and sustain disease remission. Traditional treatment modalities despite being widely used present limited results and high risk of adverse effects. Therefore, there is an unmet need for more effective and safer treatments. The recent insights into the pathophysiology of AA and its association with the JAK/STAT pathways, have led to the development of the JAK inhibitors, small molecular agents that block this intracellular signaling pathway. Baricitinib an orally administered, selective JAK1 and JAK 2 inhibitor is a promising alternative to the available treatments, already approved for the treatment of alopecia areata.

Key-words: alopecia areata, baricitinib, treatment, pathophysiology, JAK/STAT, JAK inhibitors.

Resumo

A alopecia areata (AA) é uma doença crónica, órgão-específica, auto-imune, caracterizada por perda capilar não-cicatricial, com uma prevalência global de aproximadamente 2 %. Tipicamente afeta uma população jovem, já que o seu aparecimento dá-se frequentemente em idades inferiores aos 30 anos. Apesar de permanecer indefinida a fisiopatologia exata da AA, a hipótese mais aceite prende-se com a colapso do privilégio imunológico do folículo capilar, o que resulta num aumento da expressão de auto-antigénios e MHC no epitélio folicular. A natureza recidivante da doença tem um impacto negativo na qualidade de vida dos doentes, tornando-os mais suscetíveis ao desenvolvimento de comorbilidades psiquiátricas. Inúmeras modalidades terapêuticas têm sido propostas, contudo, atualmente, não existem tratamentos disponíveis que sejam capazes de induzir e suster a remissão da doença. As modalidades terapêuticas tradicionais apesar de largamente utilizadas apresentam resultados limitados e efeitos adversos consideráveis. Assim, existe uma forte necessidade de tratamentos mais eficazes e seguros. Os conhecimentos mais recentes sobre a patogénese da AA e a sua associação à via JAK/STAT levaram ao desenvolvimento dos inibidores da Janus quinase (JAK), pequenos agentes moleculares que bloqueiam esta via de sinalização intracelular. O baricitinib é um inibidor seletivo da JAK 1 e JAK2, administrado oralmente, sendo uma alternativa promissora às terapêuticas disponíveis, estando já aprovado para o tratamento da alopecia areata.

Palavras-chave: alopecia areata, baricitinib, treatment, pathophysiology, JAK/STAT, JAK inhibitors.

List of abbreviations

AA: alopecia areata
AT: alopecia totalis
AU: alopecia universalis
α-MSH: α-Melanocyte-stimulating hormone
ClinRO: clinician-reported outcome
CTLA4: Cytotoxic T lymphocyte–associated antigen 4
CXCL: Chemokine ligand
EMA: European Medicines Agency
FDA: Food and Drug Administration
GWAS: Genome-wide association studies
HF: Hair follicle
HLA: Human leukocyte antigen
IDO: indoleamine-2,3-dioxygenase
IFN: Interferon
IL: Interleukin
IP: Immune privileged
IR: incidence rate
JAK: Janus kinase
MHC: Major histocompatibility complex
MICA: MHC class I–related chain A
MIF: macrophage migration inhibitory factor
NK: Natural killer
OAT3: Organic anion transporter 3
PRO: patient-reported outcome
SALT: severity of alopecia tool
STAT: Signal transducer and activator of transcription
TGF: transforming growth factor
Th: T helper
Tregs: T-regulatory cells
TYK2: Tyrosine kinase 2
ULBP: UL16-binding protein
VIP: Vasoactive intestinal peptide

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Introduction

Alopecia Areata is an autoimmune disease that causes non-scarring hair loss on the scalp or any hair-bearing surface. Typically, this condition has different clinical hair loss patterns.[1] The most common pattern is one or multiple well-defined patches of bald lesions (patchy alopecia areata) that may proceed to comprise all scalp hairs (alopecia totalis [AT]), or all scalp and body hairs (alopecia universalis [AU]).[2]

Patients with AA often exhibit concomitant autoimmune disorders such as systemic lupus erythematosus, vitiligo, autoimmune haemolytic anaemia, and thyroid diseases.[3] Nail lesions including trachyonychia and nail pitting can be present, as well as eye pathology consisting of focal retinal hypopigmentation, opacities of the lens and cataract.[3,4]

The diagnosis is mostly clinical and is based on visual inspection and dermoscopy; however, histopathology can be utilized when clinical presentation is unclear.[1] AA has a dynamic course, with intermittent flares and remissions. Relapse rates range from 85% to nearly 100% for those who have had the diagnosis for more than 20 years, indicating progression over time.[5]

Giving the unpredictable and relapsing course of the disease, patients have their quality of life reduced, and are often affected by psychiatric comorbidities, mostly anxiety and depression.[6,7] One in every 1000 people is affected by AA, the majority of whom are less than 30 years of age. Global prevalence is approximately 2%, impacting people of all genders, ages, and ethnicities.[8,9]

AA currently has no preventive or curative treatment.[10] The traditional standard therapies include topical or locally-injected agents or systemic immunosuppressive drugs, however these agents have been found to have problematic safety profiles and inconsistent or poor efficacy particularly for extensive disease.[11]

As the molecular mechanisms underlying the pathophysiology of AA are clarified, novel treatment strategies are becoming more available, such as Janus kinase (JAK) inhibitors, biologics, several small molecular agents and platelet-rich plasma (PRP) injections.[12] Among these agents, JAK inhibitors have collected the most evidence, being the most supported by clinical trials and literature so far.[13] Several cytokines involved in the pathogenesis of AA, including gamma chain (γc) cytokines and IFN-γ, depend on JAK signaling, making this class of small-molecule agents a very attractive therapeutic target.[14] By suppressing the effects of

these cytokines, JAK inhibitors were demonstrated to not only prevent the onset of hair loss but also to reverse alopecia once established.[15] Recently, an important milestone on the treatment of AA was achieved. Baricitinib, an oral, selective, reversible JAK inhibitor was approved for the treatment of AA, making it the first and the only existing on-label drug for adults with AA.[16,17]

In this review, we summarize the efficacy, safety, and mechanism of action of baricitinib for the treatment of AA, while exploring the pathophysiological pathways leading to this disorder.

Objectives

This review aims to highlight the current data regarding baricitinib efficacy and safety in the treatment of alopecia areata.

Methods

This bibliographic review was carried out using Google Scholar and PubMed as databases. The following keywords were utilized, alone or in combination: “alopecia areata”, “baricitinib” “treatment”, “pathophysiology”, “JAK/STAT”, “JAK inhibitors”. A review on the clinical evidence of the efficacy and safety of baricitinib in the treatment AA as conducted, in addition to a search on the pathophysiology of AA.

This review included original and review articles from 2006 to 2023. Only articles written in English were included. The articles were selected based on the relevancy of the abstract, the defined objectives and ultimately the full text analysis. The bibliographic references from the chosen articles were also included when relevant to this review.

Discussion

Alopecia areata pathophysiology

The hair growth cycle is separated into three stages: anagen (growth phase), catagen (controlled apoptosis phase) and telogen (resting phase).[18] In the anagen phase the hair undergoes a period of active growth, during which pigmentation and hair shaft development take place. The catagen phase is distinguished by a time when melanogenesis and hair growth cease. In telogen phase hair sheds and goes back to anagen.[18,19]

The hair follicle (HF) is a site of immune privilege (IP), meaning that the expression of molecules associated with effective immunity, is downregulated.[20] Even though the pathophysiology of AA is not fully understood, it is known that loss of IP in anagen hair plays a significant role.[21] This collapse promotes an effector T-cell response against the HF cells, and a premature shift from anagen to the nonproliferative catagen and telogen stages.[18,20] Interestingly, the HF´s epithelial stem cells are generally not affected, preserving the follicle's capacity to develop new hair in the future, whether through natural remission or effective treatment.[22]

AA is a multifactorial disease, with genetic and environmental factors contributing to its pathogenesis.[1] The application of genome-wide association studies (GWAS) has identified polymorphisms in genes related to immune system, structural proteins, and antioxidant enzymes, that increase susceptibility to this disorder.[23] These studies focused on the Human Leukocyte Antigen (HLA) class II loci, UL16-binding proteins 3/6 loci, cytotoxic T lymphocyte-associated protein 5 (CTLA-4), IL-2/IL-21 locus, IL-2RA locus, and Eos locus.[24] These genes are essentially involved in T cell activation and/or survival and facilitate the autoreactive cells to bypass peripheral tolerance mechanisms.[25]

The IP in healthy hair follicles is accomplished by downregulation of major histocompatibility complex (MHC) in anagen hair bulbs, which prevents autoautoantigen recognition by CD8+ T cells. In addition, there is a local secretion of immunosuppressive agents, such as transforming growth factor-β1 (TGF-β1), interleukin-10 (IL-10), α-melanocytestimulating hormone (α-MSH), indoleamine-2,3-dioxygenase (IDO), and vasoactive intestinal peptide (VIP).[26] Keeping this evasive status may be especially crucial during the anagen stage, where a lot of tissue-specific peptides and antigens are being produced.[27] Melanocyte and keratinocyte epitopes are thought to be the HF autoantigens involved in AA.[28] Although lack of MHCs helps to maintain the IP it can, paradoxically, increase natural killer (NK)

cell attack.[29] To avoid this, there is downregulation of NK cell receptor ligands, along with production of immunosuppressive factors, such as macrophage migration inhibitory factor (MIF).[3,29,30]

AA hair follicles present an upregulation of NKG2D activating ligands (e.g, MICA and ULBP), increased expression of MHC Class I and MHC Class II, enhanced levels of proinflammatory cytokines (e.g., IL-15, IL-2, and CXCLs), as well as a vast inflammatory cell infiltrate (e.g., CD8+T cells, CD4+T cells, DCs, NK T cells, mast cells, and eosinophils).[21,31] CD8+ T cells found near the HF normally express an activating receptor related to the NK cell lineage, the NKG2D receptor.[29] This subset of CD8+ NKG2D+ T cells were found to be sufficient for development of AA.[15] When activated they produce IFN-γ, via JAK1 and JAK3 pathways, which stimulates the secretion of IL-15, via JAK1 and JAK2 signaling, by follicular epithelial cells. This cytokine then binds to CD8+NKG2D+T cells, causing them to produce even more IFN-γ, generating a positive feedback loop.[32] Through the JAK-STAT pathway as well, IL-15 stimulates CD8+ T cell production of perforin and cytotoxic granzymes.[25]

IFN-γ is the main inducer of IP collapse, as it leads to an increase in pro-inflammatory factors (e.g., MHC I/II, MICA, ULBP, CXCLs) and a decrease in immunosuppressive mediators (e.g., TGF-β1, IL-10, α-MSH, VIP).[21] This changes in the HF microenvironment, results in a wider exposure of anagen autoantigens to effector CD8+ cells. This effector T-cells induce HF dystrophy and premature catagen phase, ultimately causing AA.[21] Although CD4+ T cells might not directly cause hair loss, when activated they are able to release inflammatory cytokines that induce hair follicle cells to secret more cytokines with consequent recruitment of more T cells and NK cells.[25] Moreover, it is recognized that CD4+ T cells produce IL-2, which may stimulate CD8+ T cell activity, and there is a subtype of this cells, T helper type 1 (Th1) cells that when activated release IFN-γ which contributes to the inflammatory environment of the AA.[27] Another factor contributing to AA pathogenesis is the decreased number of T-regulatory cells (Tregs) which makes the HF more vulnerable to autoimmune attack.[33]

JAK/STAT signaling

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway is one of the key communication hubs for cellular activity, being involved in haematopoiesis, inflammation and immune function.[34,35] Various interleukins (ILs), interferons (IFNs), and growth factors use this pathway to transmit signals from the cell membrane to the

nucleus.[36] Three essential elements compose the JAK-STAT pathway: the receptor, the Janus kinase (JAK), and the signal transducer and activator of transcription (STAT).[37]

Tyrosine kinases, such JAKs, transfer phosphate from ATP to tyrosine residues on other proteins, ranging from cytokine receptors, JAKs themselves, and downstream signaling molecules.[38] JAKs bind directly to the intracellular domains of the type I/II cytokine receptors.[38] There are four members of the JAK family: JAK1, JAK2, JAK3, and TYK2, each member is composed by seven homology domains (JH).[35] The STATs have a core DNA-binding domain that enables them to recognize and bind to target genes. This family of proteins consists of seven distinct members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6.[39]

Signalling starts when cytokines bind to their specific receptor on cell membrane. This causes dimerization of the receptor subunits and juxtapositioning of JAKs to their docking sites.[27] This closeness enables JAK to phosphorylate its own tyrosine component with consequent activation of its kinase function.[37] The activated JAKs then phosphorylate STAT proteins, which dimerize and translocate into the nucleus to regulate gene expression.[35] The end result is inflammatory gene transcription with production of inflammatory cytokines.[38,39]

It is well establish that Gamma chain (γc) cytokines such as IL-2, IL-7, IL-15 and IFN-γ rely on JAK-STAT signalling pathway to enhance proliferation and activation of autoreactive T cells in AA.[40,41]

Starting with IFN-γ, its receptor (IFN-γR) is constituted by two chains, each of them has a binding site for JAK1 or for JAK2. When IFN-γ binds to its receptor there is an activation of the JAKS, resulting in the recruitment of two STAT1 monomers, which translocate into the nucleus and drive target gene transcription.[42] As mentioned above, IFN-γ is thought to cause IP collapse and this is supported by experiments where C3H/HeJ mice developed AA-like hair loss after receiving an intravenous injection of IFN-γ.[43] Whereas IFN-γ deficient mice were resistant to AA.[44]

IL-2 can signal via a trimeric or a dimeric receptor. The IL-2Rβ subunit binds to JAK1, while the γc subunit binds to JAK3. Once JAK1/3 is activated, STAT5/5 or STAT3/5 dimers are created and move to the nucleus to regulate gene transcription that enable cellular growth, survival, and maintenance.[27] STAT5 induces the transcription factor T-bet which is essential for differentiation into Th1 cells, which in turn release IFN-γ.[45] In addition, STAT5 plays an important role in Treg differentiation, giving that it stabilizes Foxp3 expression.[46] Structure-wise, IL-15 and IL-2 are very similar.[47]

IL-15 first binds with its chaperone IL-15Rα to then associate with IL-15R complex (IL-2Rβ and γc) causing signaling via JAK1 and JAK3 to drive production of granzymes, IFN-γ, and tumor necrosis factor α as well as to promote CD8+ memory T cell survival.[48] Lastly, IL-7 also signals via activation of JAK1/JAK3 which leads to recruitment of STAT5 dimer, that in turn activates genes that promote cell-cycle progression and differentiation.[49] It is suggested there is a feedback loop between IL-7 and IFN-γ that perpetuates the inflammatory insult to the HF.[27] IFN-γ, produced by CD8+T cells, induces keratinocytes to produce IL-7, which may stimulate the survival of IL-7–dependent lymphocytes.[50]

Treatment paradigm of AA

The chronic relapsing nature of AA makes it an extremely challenging disorder to treat, currently with no curative therapies.[12] When selecting therapies, it is important to consider the patients' age, the extent and impact of hair loss.[51]

Traditional therapies include corticosteroids (topical, intralesional and systemic), other immunomodulators (methotrexate, cyclosporine, and hydroxychloroquine), topical and oral minoxidil, as well as contact immunotherapy (squaric acid dibutylester and diphencyprone).[31,52]

Intralesional corticosteroids are the first-line treatment for adult patients with limited patches (< 50% hair loss), while topical corticosteroids are the preferred therapy for paediatric patients. Both modalities are associated with skin atrophy and are not suitable for severe AA, AT/AU. Systemic corticosteroids are indicated in extensive AA, especially for acute progressive severe cases. Their undesirable side effects include suppression of the pituitary-adrenal axis, weigh gain, hypertension, diabetes, and osteoporosis.[31]

Topical minoxidil is mainly used in children and adults with patchy AA, frequently with poor response, common side effects include dermatitis and hypertrichosis. Contact immunotherapy in indicated in extensive AA and AT/AU, however, it is not suitable for acute rapidly progressive cases, has a high failure rate, and induces contact dermatitis. Immunomodulators such as methotrexate or cyclosporine, are utilized in extensive and resistant AA and AT/AU, but are associated with several side effects and potentially life-threatening toxicities.[31,53,54]

Unfortunately, these off-label treatments have limited efficacy, a high risk of adverse effects, and a high recurrence rate, particularly in individuals with severe AA.[12,13,31] Hence, there is a strong need for improved clinical management and therapeutic options.[37]

Janus Kinase inhibitors

One of the new treatment options under investigation are the Janus Kinase inhibitors. These immunomodulatory drugs are currently approved for management of autoimmune conditions, including rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, ulcerative colitis and myeloproliferative disorders.[55] JAK inhibitors work by targeting the kinase portion of JAKs. This prevents the phosphorylation of the JAK protein, which in turn interrupts the downstream regulatory signaling cascade involving STAT activation.[56] Inhibiting of JAK-STAT pathway induces reduction of accumulation of autoreactive CD8+ T cells by blocking IFN γ and γc cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 and IL-23) downstream signaling.[15] Other effects include inhibition of CD4+ T helper cell differentiation, and the subsequent Th1, Th2 and Th17 type responses, as well as stimulation of hair follicle stem cells.[11,56]

JAK inhibitors were first found to be efficient in AA in 2014.[15] Since then, there has been a growing interest in this class as well as several clinical trials that demonstrate their efficacy, with remarkable hair regrowth even in patients with a prolonged, therapy-resistant disorder.[57,58,59] Nevertheless, recurrence of hair loss following treatment discontinuation has been described in approximately half of patients treated with JAK inhibitors.[60] Thus, in patients that tolerate and are good responders to JAK inhibitors, it is recommended to maintain a continuous treatment.[61]

First generation JAK inhibitors as tofacitinib, ruxolitinib, baricitinib and oclacitinib are nonselective and inhibit two or more JAKs, which might optimize their therapeutic efficacy [62]. In this category tofacitinib, ruxolitinib and baricitinib, have been widely investigated for AA treatment.[36] There is also a second generation of JAK inhibitors, such as Ritlecitinib, brepocitinib, delgocitinib and deuruxolitinib (CTP-543) that are more selective, by inhibiting a single JAK isoform, which have been showing efficacy in AA in emerging studies.[63,64,65] This mechanism may allow enhanced treatment precision while minimizing adverse effects.[13,64]

Baricitinib

Pharmacodynamics and Pharmacokinetics

Baricitinib has molecular weight of 371.42 g/mol and the following molecular structure: C16H17N7O2S.[66] It is an immunosuppressant that selectively and reversibly inhibits JAK1 and JAK2, at half-maximum inhibitory concentrations (IC50) of 5.9 and 5.7nM, respectively.[67] Furthermore, at higher concentrations, it can also inhibit JAK3 (IC50 > 400 nM) and TYK2 (IC50 = 53 nM).[68] By inhibiting JAK1 and JAK2, baricitinib prevents a wide spectrum of cytokines from signaling, hence its potent anti-inflammatory effects.[69] In AA specifically, baricitinib blocks IFN γ and γc cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 and IL-23) downstream signaling, as well as IL-6 induced STAT3 phosphorylation, crucial for T-cell differentiation and inflammation.[66]

The pharmacokinetic of baricitinib is linear over time. In healthy volunteers, a dose-proportional increase in systemic exposure was observed in the therapeutic dose range, following oral administration. Baricitinib is quickly absorbed after oral administration with maximum plasma concentration being reached in a median time of approximately 1 hour (range 0.5 - 3.0 h) and an absolute bioavailability of about 79%. Administration with meals has no significant clinical effect. After intravenous infusion the mean volume of distribution to tissues is 76L. Nearly 50% of baricitinib is bound to plasma proteins.[67,70]

Less than 10% of a dose of baricitinib undergoes biotransformation, which is mediated by CYP3A4. This drug is primarily eliminated by the kidneys (around 75%) through glomerular filtration and active secretion via OAT3, and the gastrointestinal tract (around 20%), mostly in an unchanged form. Co-administration with potent OAT3 inhibitors such as probenecid results in considerable increased plasmatic baricitinib levels and a decreased renal clearance. As renal impairment was found to enhance baricitinib exposure, the dose should be reduced in patients with creatinine clearance of 30–60 mL/min and avoided in those with creatinine clearance below 30 ml/min. In patients with mild or moderate hepatic impairment, there was no clinically significant influence on baricitinib pharmacokinetics.[67,70]

Efficacy

In 2015, Jabbari et al published the first case report describing a case of a 17-year-old man with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated

temperature (CANDLE) syndrome and long-standing AA that progressed to an ophiasis pattern. In the first 3 months of treatment the patient was given oral baricitinib 7 mg daily; 6 months later, the dose was increased to 11 mg daily (7mg in the morning and 4mg in the evening), with gradual reduction of oral corticosteroids to 3 mg/day.[71]

After a total of 9 months of treatment the patient achieved complete hair regrowth, which was sustained by continuous treatment. Studies conducted in the same report using the murine AA model (C3H/HeJ) provided additional support for this clinical data. In alopecic mice systemic administration of baricitinib either before or after the disease onset, as well as topical administration resulted in persistent hair growth, in contrast to vehicle control treated mice showing no clinical evidence of hair regrowth. Baricitinib treated mice exhibited a decline in skin MHC I/ II expression and reduction in CD8+ T cell infiltrates. Additionally, the results of INF gene expression assay revealed a normalization of the IFN gene expression profile following baricitinib treatment, indicating its possible ability to inhibit IP collapse of hair follicle.[71]

In a later case-report a woman in her 60s with progressive AT, despite treatment with intralesional triamcinolone, platelet-rich plasma, and tofacitinib 1% solution, started receiving 2mg/day oral baricitinib in monotherapy. After 4 months of treatment, she remained unresponsive, therefore the dose was increased to 4 mg/day which led to considerable improvements. Upon 8 months of treatment the patient experienced 97% regrowth of scalp hair, as well as regrowth on eyebrows and eyelashes. Regrowth has been sustained after 13 months of treatment, and no side effects were observed.[72]

The efficacy and safety of baricitinib in patients with severe AA (Severity of Alopecia Areata Tool [SALT] score ≥50%: with 0% corresponding to no scalp hair loss and 100% corresponding to total scalp hair loss) was first assessed in a phase 2, randomized, double-blind, placebo-controlled trial, BRAVE-AA1 (NCT03570749). A total of 110 patients were randomized 1:1:1:1 into four experimental groups: placebo (28 patients), 1 mg (28 patients), 2 mg (27 patients), or 4 mg (27 patients) of baricitinib once a day.[73]

Eligible patients were adults between the ages of 18 and 60 for males and between 18 and 70 years for females. Additionally, patients experiencing a current episode of AA that lasted longer than 6 months were included. Patients with episodes lasting more than 8 years were only eligible if there were hair regrowth episodes over the previous 8 years. The exclusion criteria applied to patients who previously exhibited an unsatisfactory response to oral JAK inhibitors. Patients using topical, systemic or intralesion corticosteroids within 1 and 2 weeks, respectively, before randomization, were also excluded. Finasteride (or other 5 alpha

reductase inhibitors), oral or topical minoxidil, and bimatoprost ophthalmic solution for eyelashes, if at a stable dose at trial entrance, were the only simultaneous AA treatments allowed. Throughout treatment groups, the mean SALT scores ranged from 83.4 to 90.0. The average age was 41 years with 74.5% females. In general, there were no significant differences in baseline characteristics across groups, however the 2mg and 4 mg groups had a higher number of female patients.[73]

The first interim analysis aimed to determine which two baricitinib doses would proceed to the study's phase 3. The proportion of patients obtaining ≥ 30% improvement from baseline in SALT score (SALT30) at week 12 and, for those with week 16 data available, the proportion of patients having ≥50% improvement from baseline in SALT score (SALT50) at week 16, served as the basis for the dose selection. After 12 weeks of treatment, the 2 mg and 4 mg groups exhibited the largest percentages of patients obtaining SALT30 scores (29.6% and 33.3%, respectively), compared to 17.9% in 1mg group and 10.7% in placebo group. Among 87 patients that reached week 16 or were discontinued, 31.8% in the 2 mg arm and 38.1% in the 4 mg arm attained SALT50, contrasting with 18.2% in the 1 mg group and 4.5% in the placebo group. Given these results, the 2mg and 4 mg groups were chosen for phase 3. Patients initially given a 1 mg dose were sifted to a 4 mg dose for the remainder of the trial.[73]

For the subsequent interim analysis at week 36, the primary endpoint was the frequency of patients with SALT score ≤ 20. Secondary endpoints included the percent change from baseline in SALT score; absolute SALT score ≤ 10; percentage of patients achieving a Patient-Reported Outcome (PRO) for Scalp Hair Assessment score of 0 or 1 (0 to 20% of scalp missing hair) at week 36 with ≥2 point improvement from baseline; percentage of patients achieving a PRO and a Clinician-Reported Outcome (ClinRO) Measures for Eyebrows and Eyelashes of 0 or 1 (full eyebrow/eyelash coverage or minimal gaps) at week 36 with a ≥2 point improvement from baseline.[73]

In the 2 mg and 4 mg groups, the proportion of patients achieving SALT score ≤ 20, at week 36, was respectively 33% (p =0 .016) and 51.9% (p = 0.001) comparing to 3.6% in placebo group. Regarding the secondary outcomes, the percent change from baseline in SALT score was -58.1 ± 7.8 in the 4-mg arm; -48.2 ±7.9 in 2-mg arm and -11.7 ± 7.8 in placebo arm. When compared to placebo, a higher proportion of subjects in the 4mg group (40.7%, p = .008) and the 2mg group (25.9%) reached SALT score ≤ 10 by week 36. The percentage of patients reaching ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of 0 or 1 was 39.1% / 60.0% for the baricitinib 4 mg arm, 28,6 % / 40.0% for the baricitinib 2 mg and 4.3% / 5.9% for placebo.

Additionally, the percentage of participants in the 4 mg, 2 mg, and placebo groups that achieved a PRO Measure for Scalp Hair Assessment score of 0 or 1 was 37.0% (p=.007), 33.3%, and 3.6%, respectively. As for the proportion attaining PRO Measure for Eyebrow/Eyelash score of 0 or 1 was 45.8% / 57.9% in baricitinib 4 mg group, 40.0% / 27.8% in 2mg group and 0% / 0% in placebo group. Ultimately, this trial showed that extended treatment periods with higher baricitinib dosages were well tolerated and efficient at promoting hair regrowth.[73]

As a result of the previous trial's successful results, two double-blind, randomized, placebo-controlled, phase 3 trials, named BRAVE AA-1 (NCT03570749) and BRAVE-AA2 (NCT03899259), were conducted to evaluate the efficacy of 2 mg and 4 mg of oral baricitinib in the treatment of severe AA (SALT score ≥50%). BRAVE-AA1 contained 654 patients while BRAVE-AA2 contained 546 patients. In each trial patients were randomized in a 3:2:2 ratio, receiving placebo, 2mg or 4 mg of baricitinib, once daily. The percentage of patients with a SALT score of ≤ 20, at week 36, was the primary outcome. Key secondary outcomes were similar to the those of the phase 2 portion of BRAVE-AA1, and included the percentage of patients attaining a PRO for Scalp Hair Assessment score of 0 or 1 at week 36 with ≥2 point improvement from baseline; percentage of patients achieving a ClinRO Measures for Eyebrows and Eyelashes of 0 or 1 at week 36 with a ≥2 point improvement from baseline; the percent change from baseline in SALT score and absolute SALT score ≤ 10. The inclusion and exclusion criteria as well as the permitted concomitant AA treatments were the same as in the prior phase 2 trial. The average age of patients in all treatment groups was 37.5 years, with 61% of them being females. In both studies the median SALT score was 96, while the mean duration of AA since onset was 12.2 years. The average duration of the current episode of alopecia was 3.9 years.[59]

In BRAVE-AA1, the proportion of patients achieving the primary outcome was 38.8% in 4 mg group, 22.8% in 2 mg group, and 6.2% in placebo group. The difference between the baricitinib 4 mg arm and placebo was 32.6 % (95% CI, 25.6 to 39.5), while the difference between the baricitinib 2mg arm and placebo was 16.6 % (95% CI, 9.5 to 23.8), both of which were statistically significant (p 0.001 for each dose vs. placebo). As for key secondary outcomes, the proportion of patients achieving PRO Measure for Scalp Hair Assessment score of 0 or 1 was 35.8% (p<0.001), 17.1%, and 5.9%, in 4 mg group, 2mg group and placebo group, respectively. ClinRO Measure for Eyebrow Hair Loss scores of 0 or 1 were achieved by 35.2% (p 0.001) of patients in baricitinib 4 mg arm, 22.0% in 2 mg arm, and 4.4% in placebo arm. As for the percentage achieving ClinRO Measure for Eyelash Hair Loss scores of 0 or 1 was 36.2% (p<0.001) for the 4 mg group, 14.8% for the 2 mg group and 4.4% for placebo group. The SALT

score changed by -47.1±2.7 percent from baseline in the 4-mg arm, −32.7±3.1 percent in the 2-mg arm, and −9.0±3.1 percent in the placebo arm. Moreover, a greater percentage of patients in the 4mg group (27.9%) and the 2mg group (13.0%) had SALT score ≤ 10 by week 36, compared to the placebo group (4.1%).[59]

In BRAVE-AA2 the 4 mg group had 35.9% of patients reaching the primary outcome, the 2mg group had 19.4% and placebo had 3.3% of patients reaching the primary outcome. The difference between the 4 mg/2mg group and placebo was 32.6 % (95% CI, 25.6 to 39.6) and 16.1 % (95% CI, 9.1 to 23.2), respectively, both proved to be statistically significant ($p<0.001$ for each dose vs. placebo). Regarding important secondary outcomes, the percentage of patients in the 4 mg, 2 mg, and placebo groups reaching a PRO Measure for Scalp Hair Evaluation score of 0 or 1 was 37.8% ($p<0.001$), 18.5%, and 5.1%, respectively. ClinRO Measure for Eyebrow Hair Loss scores of 0 or 1 were achieved by 38.9% ($p<0.001$) of patients in the baricitinib 4 mg arm, 13.2% in the baricitinib 2 mg arm, and 5.5% in the placebo arm. The percentage of patients attaining ClinRO Measure for Eyelash Hair Loss scores of 0 or 1 in the 4 mg group was 36.8% ($p<0.001$), 12.3% in the 2 mg group, and 6.9% in the placebo group. Moreover, the percent change in SALT score from baseline was −48.7±2.6 in the 4-mg arm ($p <0.001$), −29.9±2.8 in the 2-mg arm, and −4.3±2.8 in the placebo arm. At week 36, the proportion achieving absolute SALT score ≤ 10, was 25.6% of patients in the baricitinib 4 mg group, 12.0% in the 2 mg group and 1.0% in the placebo group.[59]

In both trials, higher percentage of patients in the 4mg baricitinib group were able to reach a SALT ≤ 20 at week 36 compared to placebo, starting at week 8 in BRAVE-AA1 and week 12 in BRAVE-AA2. The baricitinib 4 mg arm also exhibited a consistent response in most of the secondary endpoints. All in all, baricitinib was shown to be superior to placebo in terms of hair regrowth, in patients with severe AA.[59]

Safety

Safety outcomes were divided into treatment-emergent adverse events, adverse events of special interest and abnormal laboratory changes. In the phase 2 portion of BRAVE-AA1 trial, given an observational period of up to 52 weeks, 77.8% (incidence rate, [IR] 244.5) and 70.4% (IR, 224.2) of patients in the baricitinib 4 mg and 2 mg groups, respectively, experienced treatment-emergent adverse events, as opposed to 60.7% (IR, 179.6) of patients in the placebo group. No deaths or serious adverse events were observed in any group,

including major adverse cardiovascular events, thromboembolic events, malignancies, and serious infections.[73]

In baricitinib treatment groups, upper respiratory tract infection, acne, and nausea were the most frequent adverse events. Although some laboratory abnormalities were observed, these were unrelated to adverse events. There was one occurrence of thrombocytopenia in the baricitinib 4-mg group and one case of neutropenia in the placebo group. Whereas elevated creatine phosphokinase levels were reported in one patient in placebo arm and 3 patients 2 mg baricitinib arm.[73]

In the BRAVE-AA1 and BRAVE-AA2 phase III trials, treatment-emergent adverse events were documented in 59.6%, 50.8%, and 51.3% of patients and in 66.1%, 68.4%, 63.0%of patients receiving 4mg baricitinib, 2mg baricitinib and placebo in BRAVE-AA1 and BRAVE-AA2, respectively. The percentages of patients that discontinued treatment due to adverse events were low and consistent across the study groups. In BRAVE-AA1, serious adverse events affected 2.1%, 2.2% and 1.6% of patients receiving 4 mg baricitinib, 2mg baricitinib and placebo. In BRAVE-AA2, serious adverse events occurred in 3.4%, 2.6%, and 1.9% of patients who received 2mg baricitinib, 4 mg baricitinib and placebo, respectively. In BRAVE-AA1, one patient with cardiovascular risk factors, receiving 2mg baricitinib suffered a myocardial infarction. In BRAVE-AA2, one patient in 4 mg group developed B-cell lymphoma, while one patient in placebo group developed prostate cancer. There were no reports of venous thromboembolic events, opportunistic infections, or gastrointestinal perforations in either trial.[59]

The overall adverse effects were in line with the previous study. In both trials, the most common adverse effects included acne, upper respiratory tract infections, headache, urinary tract infection, and elevated creatine kinase levels. Only a modest proportion of patients experienced herpes zoster infection, which was more frequent in those receiving baricitinib compared to those receiving placebo in BRAVE-AA2. In both trials, increased LDL cholesterol levels were observed in 25% of patients in baricitinib groups, while increased HDL cholesterol levels were reported in 40% of patients receiving baricitinib.[59]

Other JAK inhibitors on investigation for AA

Ritlecitinib, brepocitinib, delgocitinib and deuruxolitinib (CTP-543) are second generation JAK inhibitors that have been showing efficacy in AA in emerging studies.[63,64,65,74]

Notably, in randomized control trials, ritlecitinib, a selective inhibitor of JAK 3, and deuruxolitinib, a selective inhibitor of JAK1/JAK2, showed up to 30.6% (38/124) and 41.7% (15/36) of patients achieving treatment success, defined as ≥80% scalp coverage, respectively, after 24 weeks of treatment whit each agent.[63,64] In a double blinded RCT with brepocitinib, a selective inhibitor of TYK2 and JAK1, 53.2% (25/47) of patients achieved a 50% improvement in the SALT (Severity of Alopecia Areata Tool) score.[63]

The vast range of possible adverse effects found across this pharmacological class reflects their nonspecific anti-inflammatory and immunosuppressive actions.[75] The main safety issues with their use include the risk of varicella zoster emergence, pneumonia, tuberculosis, thromboembolism, and malignancy.[5,76,77] Minor adverse effects commonly reported comprise acne, headache, urinary and respiratory tract infections, cytopenia, elevated creatinine levels and LDL levels.[57,78]

Most of this safety data and side effect profiles comes from clinical trials of tofacitinib and baricitinib conducted on rheumatoid arthritis patients.[62] Therefore, these adverse effects should be carefully regarded up till more extensive safety trials tailored to AA are concluded.[27]

Conclusions

AA is a common autoimmune disorder which has a significant negative impact in patients´ quality of life, mental health, and productivity, representing much more than an aesthetic concern. Considering the overall burden on patients' quality of life and the lack of efficient treatments options there is an urgent need for treatment alternatives.

Over the past decade, broad-acting immunosuppressants are being replaced by agents targeting the various pathways implicated in AA pathogenesis, which minimizes side effects as well as off-target downstream effects. The JAK-STAT pathway plays a crucial role in AA maintenance, since the cytokines responsible for the activation and proliferation of autoreactive T cells rely on it. JAK inhibitors are competitive inhibitors of JAK enzymes at their ATP binding sites. They work by inhibiting IFN γ and γc cytokines, which decreases the accumulation of autoreactive CD8+ T cells, and by inhibiting CD4+ T helper cell differentiation.

Currently, the available data points to oral JAK inhibitors, as a promising new class of drugs that can promote significant hair re-growth while having mild to moderate side effects.

Baricitinib, a selective and reversible inhibitor of JAK1 and JAK2, was shown to be effective in phase 2 and phase 3 randomized controlled trials carried out in adult patients with severe AA. It also appeared to be well tolerated, with most events being classified as mild or moderate. There were no reports of venous thromboembolic events, opportunistic infections, or gastrointestinal perforations. To evaluate the long-term efficacy and safety of baricitinib, extension phases of the two phase 3 trials are currently ongoing.

The demonstrated efficacy from large-scale clinical trials led the approval of Baricitinib by EMA and the FDA, for the treatment of AA, in 2022. Nevertheless, longer trials will be necessary to assess the long-term safety of this drug in AA.

Attachments

Table I - Studies on efficacy and safety of baricitinib in AA

AA, Alopecia areata; CPK, Creatine Phosphokinase; ClinRO, clinician-reported outcome; EB, eyebrow; EL, eyelash; PRO, Patient-reported outcome; SALT, Severity of Alopecia Tool.

Study	Design	Outcomes	Efficacy	Safety
BRAVE-AA2 (NCT03899259)[59]	Phase 3, randomized, double-blind, placebo-controlled trial 546 patients adult patients with severe AA. 3 arms (3:2:2, 36 weeks)	Primary outcome: SALT score of ≤ 20, at week 36 - % of patients - Secondary Outcomes: Scalp Hair PRO score of 0 or 1 with ≥2 point improvement from baseline at week 36 - % of patients ClinRO for EB and EL of 0 or 1 with a ≥2 point improvement from baseline at week 36 - % of patients	-Primary endpoint: Placebo arm: 3.3% 2mg arm:19.4 % 4mg arm: 35.9% - Secondary endpoints: *Scalp Hair PRO* Placebo arm:5.1% 2mg arm:18.5 % 4mg arm: 37.8% *ClinRO for EB* Placebo arm:5.5% 2mg arm:13.2 % 4mg arm: 38.9% *ClinRO for EL* Placebo arm:6.9% 2mg arm:12.3 % 4mg arm: 36.8%	-Treatment emergent adverse events: Placebo arm: 63.0% 2mg arm: 68.4% 4mg arm: 66.1% -The most common adverse events: Acne, upper respiratory tract infections, headache, urinary tract infection, and elevated CPK levels.
BRAVE-AA1 (NCT03570749)[59,73]	Phase 3, randomized, double-blind placebo-controlled trial 654 patients adult patients with severe AA. 3 arms (3:2:2, 36 weeks)	-Primary outcome: SALT score of ≤ 20, at week 36 - % of patients -Secondary Outcomes: Scalp Hair PRO score of 0 or 1 with ≥2 point improvement from baseline at week 36 - % of patients ClinRO for EB and EL of 0 or 1 with a ≥2 point improvement from baseline at week 36 - % of patients	-Primary endpoint: Placebo arm: 6.2% 2mg arm:22.8 % 4mg arm: 38.8% -Secondary endpoints: *Scalp Hair PRO* Placebo arm:5.9% 2mg arm:17.1 % 4mg arm: 35.8% *ClinRO for EB* Placebo arm:4.4% 2mg arm:22.0 % 4mg arm: 35.2% *ClinRO for EL* Placebo arm:4.4% 2mg arm:14.8 % 4mg arm: 36.2%	-Treatment emergent adverse events: Placebo arm: 51.3% 2mg arm: 50.8% 4mg arm: 59.6% -The most common adverse events: Acne, upper respiratory tract infections, headache, urinary tract infection, and elevated CPK levels.

	Phase 2, randomized, double-blind, placebo-controlled trial 110 patients adult patients with severe AA 4 arms (1:1:1:1, 36 weeks)	-Primary outcome: SALT score of ≤ 20, at week 36 - % of patients -Secondary Outcomes: Percent change from baseline in SALT score Absolute SALT score ≤ 10, at week 36 - % of patients Scalp Hair PRO score of 0 or 1 with ≥2 point improvement from baseline, at week 36 - % of patients	-Primary endpoint: Placebo arm:3.6% 2mg arm:33 % 4mg arm: 51.9% -Secondary endpoints: *Percent change from baseline in SALT score*: Placebo arm: -11.7 ± 7.8 2mg arm: -48.2±7.9 4mg arm: -58.1± 7.8 *Absolute SALT score ≤ 10*: Placebo arm: 0% 2mg arm: 25.9% 4mg arm: 40.7% *Scalp Hair PRO* Placebo arm:3.6% 2mg arm: 33.3% 4mg arm: 37.0%	-Treatment emergent adverse events: Placebo arm: 60.7% 2mg arm:70.4 % 4mg arm: 77.8% -The most common adverse events: Upper respiratory tract infection, acne, and nausea.

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