Chapter

An Updated in the Management of Alopecia Areata

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Abstract

Alopecia areata (AA) is the most frequent type of non-scarring alopecia after androgenetic alopecia. The lifetime risk of developing AA is approximately 1.7–2.1%, and its incidence is increasing over time. Clinically, it is characterized by circumscribed and smooth patches of alopecia with black dots. Several treatments have been used in AA including topical an oral minoxidil and corticosteroids. Although new treatment options are being developed and advances have been made in recent years, there is currently no preventive or curative treatment for AA and classical treatments produce variable results. The design of a treatment strategy for alopecia areata should be based on consensual decision-making with the patient, taking into account his or her preferences and the risk and benefit of each treatment. In this chapter, we review the treatment of AA.

Keywords: alopecia Areata, JAK-inhibitors, minoxidil, non-scarring alopecia, treatment

1. Introduction

Alopecia areata (AA) is the most frequent type of non-scarring alopecia after androgenetic alopecia. The lifetime risk of developing AA is approximately 1.7–2.1%, and its incidence is increasing over time [1, 2]. It is equally prevalent in males and females, but males tend to be diagnosed earlier and have a poorer prognosis [2–5]. AA affects adults and children but usually presents around 25–29 years [6]. AA has a worldwide distribution but regional and ethnic differences have been addressed, being Asians the most heavily affected (Harries). Additionally, AA has been associated with social deprivation and living in urban areas [6].

2. Pathogenesis

The main disorder underlying AA is the premature transition of hair follicles from anagen to catagen and telogen phase. Only anagen hair follicles are targeted by the aberrant immune response. This prompts dystrophy of the affected hair follicles, preventing them from successfully anchoring to the hair canal and leading

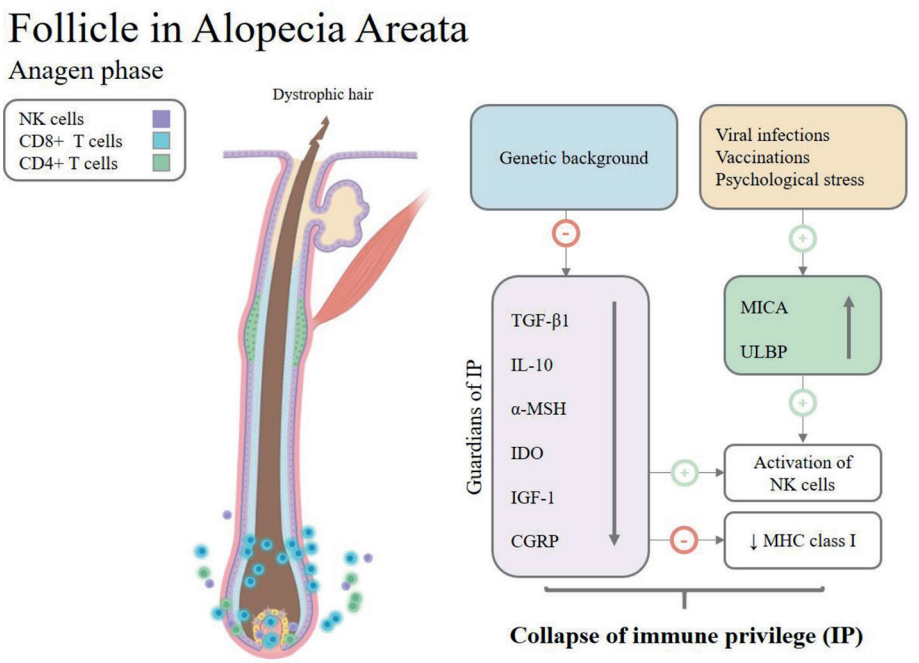

Figure 1.
Simplified pathogenesis of AA. A circled (+) implies the event the arrow is pointing to is encouraged while a (–) implies the opposite. The cornerstone of AA is the collapse of IP. Under normal circumstances, IP is preserved by the action of the IP guardians, which prevent antigen presentation through MHC class I and a down-regulation of NK cells via inhibition of MICA and ULBP. Certain insults combined with genetic predisposition lead to the weakening of these protective mechanisms and the development of AA.IP: Immune privilege; NK: Natural killer; MHC: Major histocompatibility complex; TGF-β1: Transforming growth factor-β1, IL: Interleukin; α-MSH: α-melanocyte stimulating hormone; IDO: Indoleamine-2,3 dioxygenase; IGF-1: Somatostatin, insulin-like growth factor; CGRP: Calcitonin gene-related peptide; MICA: MHC class I polypeptide-related sequence a; ULBP: UL16-binding protein.

to its shedding [7, 8]. Even when alopecia can prolong itself in time, the condition is reversible due to the fact that the bulge region of the hair follicle, that hosts stem cells, is spared from inflammation [9]. This phenomenon is induced by the complex interaction of immune-mediated mechanisms influenced by environmental triggers and genetic background (**Figure 1**).

Environmental triggers. Mental and biological stressors have been linked, albeit sometimes anecdotally to AA. Psychological stress directly affects the neuroendocrine-immune axis via corticotropic-releasing hormone (CRH), substance P and nerve growth factor, contributing to the development of AA [10–13]. Viral infections such as hepatitis B and C, swine flu, Epstein–Barr virus (EBV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been hypothesized to induce AA [14–16]. Vaccination seems to exert a similar effect on the onset of AA [17, 18].

- Immune factors. Current evidence agrees that the main events leading to AA are the loss of immune privilege (IP) and a subsequent exacerbated inflammatory response revolving around the hair follicle. IP is an evolutionary adaptation in which certain key organs or structures are protected from harmful inflammatory immune response. Affected organs comprise the eyes, placenta, testes, central nervous system, and the proximal epithelium of the hair follicle [19]. In the case

of the hair follicle, IP is provided via physical and immune mechanisms. Physical mechanisms include a lack of lymphatic drainage and abundant extracellular matrix which hinder the invasion of immune cells [3, 13, 19]. Immune mechanisms consist of the protection of sequestered antigens from being presented and prevent the subsequent activation of natural killer (NK) cells. Antigens are secured from immune recognition by the downregulation of major histocompatibility complex (MHC) class I of IP guardians. These are transforming growth factor-β1 (TGF-β1), interleukin-10 (IL-10), α-melanocyte stimulating hormone (α-MSH), indole-amine-2,3 dioxygenase (IDO), somatostatin, insulin-like growth factor (IGF-1) and calcitonin gene-related peptide (CGRP) among others [20–23]. Even when preventing MHC class I antigen presentation contributes to IP, this also activates NK cells ("missing self") [24]. Within the hair follicle, NK are thus held back by inhibiting its activating factors such as MHC class I polypeptide-related sequence A (MICA) and UL16-binding protein (ULBP). Under normal conditions, MICA and ULBP are downregulated in the hair follicle environment [3, 11, 25].

Failure of the security mechanisms outlined above leads to the collapse of IP. Oxidative stress and pro-inflammatory signals such as interferon-γ (IFN-γ), interleukin 15 (IL-15), and substance P can result in the attack of anagen hair follicles in predisposed individuals. In fact, both IL-15 and IFN-γ pathways operate through Janus kinase (JAK) signaling which explain the novel success of JAK inhibitors in the treatment of AA and that will be further reviewed in this chapter [26–28].

- Genetic predisposition. Like other immune-mediated conditions, a genetic component is present even when no monogenic cause has been identified [29]. First-degree relatives of patients have a risk of 5.7–7.8% of developing AA, while for monozygotic twins is of 42–55% [14, 30]. Observational association studies and genome-wide association studies have shown multiple genes related to AA including immune-related, human leukocyte antigen, and hair follicle-related genes [29, 31–34]. Treatment strategies reviewed in following sections will address the aforementioned targets involved in the pathogenesis of AA.

3. Diagnosis

3.1 Clinical features

AA presents as circumscribed and smooth patches of non-scarring alopecia. AA can affect any hair-bearing region, including not only the scalp but also eyebrows (**Figure 2a**), eyelashes, beard (**Figure 2b**), and any hair-bearing location. Even when patients are usually asymptomatic, some report a tingling or itchy sensation within the alopecia patches. Course of the disease is unpredictable, but spontaneous hair regrowth is observed in approximately 50% of patients with patchy AA within a year. In these cases, regrowth phase hair lacks pigmentation or is hypopigmented. Nevertheless, recurrence rate is high [3, 35–37]. In case pruritus, redness, scales, or scarring is present, it is primal to exclude tinea capitis.

The main AA subtypes are as follows:

- Patchy AA. Presence of single of multiple patches of alopecia affecting the scalp. Disease duration and treatment response need to be closely monitored, since

Figure 2.
Clinical manifestation of alopecia areata.

patients with persisting disease (beyond 1 year) can transition to AA totalis and universalis in a 30 and 15%, respectively [38] (**Figure 2c**).

- Ophiasis subtype. Alopecia patches converge along the occipital hairline toward the temples (**Figure 2d**). Sisaipho (ophiasis spelled backward) is another subtype in which alopecia follows an opposite pattern to the ophiasis subtype, sparing the periphery of the scalp and affecting the central scalp region.

- **AA totalis**. Complete scalp hair loss.

- **AA universalis**. Complete body hair loss.

AA incognito and diffuse AA. Both subtypes that have been recently described are not yet academically standardized [39]. They present as widespread hair loss without clear alopecic patches that can develop in a few weeks in AA incognito or over a more prolonged period of time, such as in diffuse AA. Even when trichoscopy can hint at the correct diagnosis, scalp biopsy is usually required to distinguish these conditions from telogen effluvium [28, 40].

Nails can also be affected, especially in the most severe forms of AA, such as AA universalis and AA totalis. Nail changes can present as pitting, trachyonychia, onychorrhexis, or non-specific nail dystrophy that may cause pain and cosmetic disfiguration. Findings can precede or be concurrent to the onset of AA.

Pull test, which consists on gently traction of hair at periphery of the alopecia patch, will be positive when disease is active, revealing dystrophic anagen and telogen hairs [41, 42].

The diagnosis of AA is clinical and can be made taking into consideration the aforementioned clinical features. Nevertheless, the role of trichoscopy has proven to be valuable when assessing AA, its activity state and to identify rare forms of AA [43]. Active patches of AA display yellow dots, exclamation mark hairs, and broken hairs as well as Pohl-Pinkus constrictions (**Figure 3**). Conversely, inactive patches can be identified by the presence of yellow dots and vellus hairs. Pigtail hairs and upright regrowing hairs can be spotted during remission [44–48].

3.2 Disease severity

Clinical classification of AA in subtypes provides the clinician with some insight of the severity of AA. Nevertheless, this classification system is insufficient for

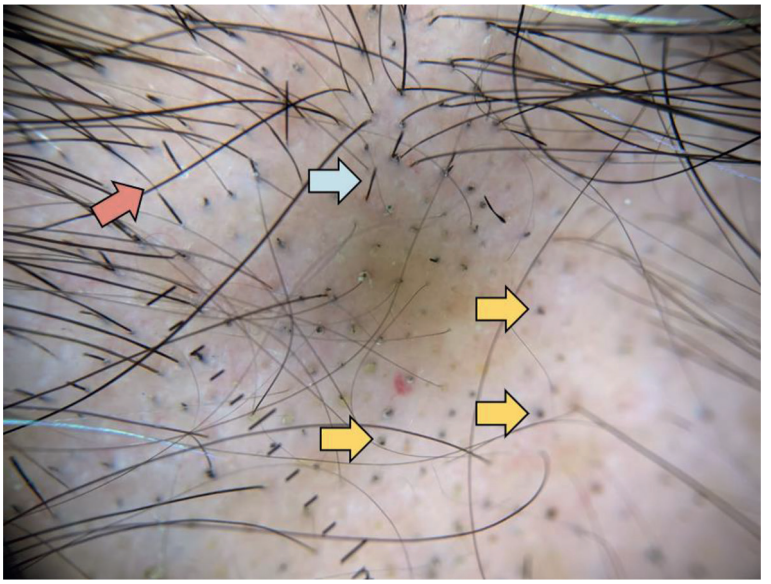

Figure 3.
Trichoscopic image of active AA. Red arrows: Pohl-Pinku constriction; yellow arrows: S black dots; white arrow: Exclamation mark hair. Image courtesy of Dr. Díaz-Calvillo.

describing the extent of the alopecia and does not allow for assessing response to treatment. The Severity Alopecia Tool (SALT) is a visual scoring system in which the scalp surface area is divided in four views and each view (back, sides, and top view) in quadrants. The clinician assesses and adds the areas affected by alopecia, and a final score is rendered. A scoring higher than 50% is considered severe (**Figure 4**) (Olsen). Other validated scoring systems with similar methodology have been conceived for accounting for eyelashes and eyebrows such as the Brigham Eyebrow Tool for Alopecia (BETA) and the Brigham Eyelash Tool for Alopecia (BELA), respectively [49, 50].

3.3 Prognosis

Early onset, family history of AA, severe forms such as AA totalis or universalis, ophiasis, nail disease, and atopic dermatitis are factors associated with a poor prognosis [4, 40, 51–53].

3.4 Histopathology

Scalp biopsies are occasionally required in cases in which diagnosis is uncertain as it remains the gold standard. Usually, a punch biopsy at the activity border of the lesion is taken. Histopathological findings depend on the duration of the AA episode. Overall, the main feature is the presence of peribulbar lymphocytic infiltrate [28, 40]. During episodes of active hair shedding, peribulbar lymphocytic infiltrates mainly composed of lymphocytes, Langerhans cells and to a lesser extent, plasma and mast cells as well as eosinophils. This arrangement receives the name of swarm of bees. In chronic phases, inflammatory infiltrates are still present, although less evident and there is an abundance of follicles in telogen and catagen stages [28, 40]. Syphilitic alopecia does not only resemble AA clinically but also histologically. A lack

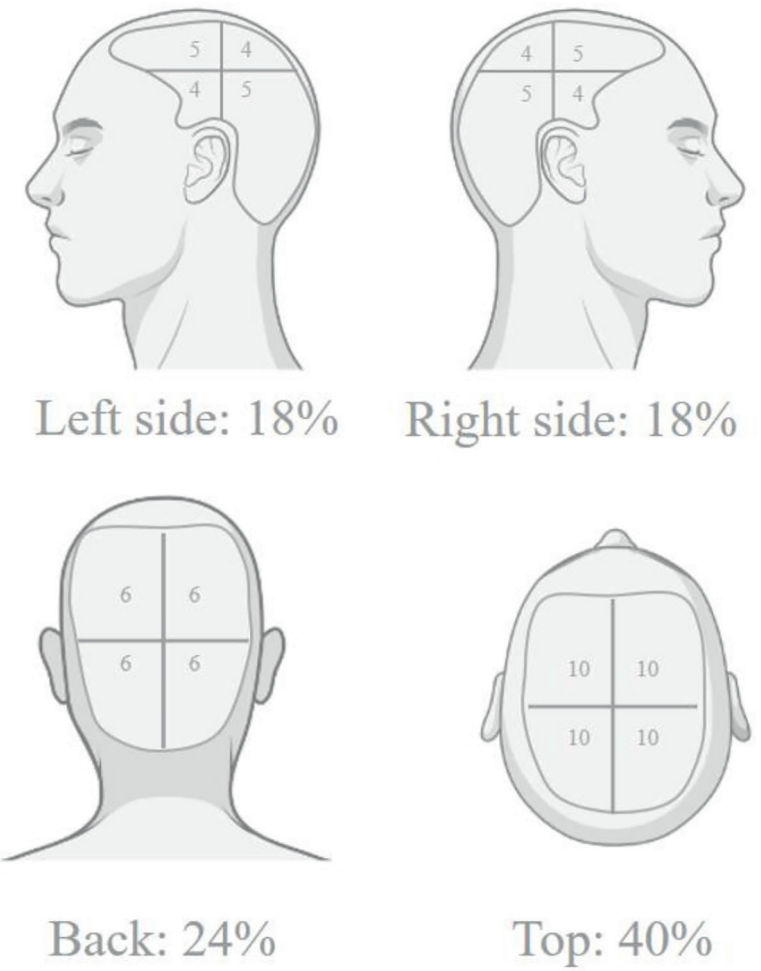

Figure 4.
The severity alopecia tool (SALT) visual aid allows the evaluator to estimate the percentage of alopecia surface via adding the values of the affected quadrants.

of miniaturized follicles and eosinophils and the presence of spirochetes may aid the diagnosis of syphilitic alopecia [54–56].

3.5 High-frequency ultrasonography (HFUS)

Recently, HFUS has gained some attention on the diagnosis and follow-up of hair disorders. HFUS allows to visualize deep structures in the scalp skin such as subcutaneous tissue below hair follicles. Hair follicles present with lower echogenicity than the surrounding tissue in HFUS. A group of Polish researchers characterized the findings found in different stages of AA. Active stage of AA showed presence of distinct, drop-shaped follicular structures, while during inactive stages follicular structures are reduced and undefined [57, 58].

4. Associated diseases

Several medical conditions have been linked to AA. Skin disorders such as vitiligo, psoriasis, or atopic dermatitis (as well as atopic triad) were more commonly found in AA patients compared with healthy individuals. Furthermore, the association with thyroid disease and lupus erythematosus has been reported [59, 60]. This association is likely due to shared genetic loci and cytokine profiles [31, 32]. Patients with genetic conditions such as Down syndrome and polyglandular autoimmune syndrome type 1 show increased incidence of AA [61, 62]. Psychiatric comorbidities have also been reported in AA patients, but causality remains obscure since hair loss can increase anxiety and mood disorders [63, 64].

5. Treatment options and management of alopecia areata

Although new treatment options are being developed and advances have been made in recent years, there is currently no preventive or curative treatment for AA and classical treatments produce variable results [65]. The design of a treatment strategy for alopecia areata should be based on consensual decision-making with the patient, taking into account his or her preferences and the risk and benefit of each treatment [66] (**Figure 5**).

5.1 Psychosocial support and cosmetic options

The psychological impact of AA in children and adults may make the patient desire treatment regardless of clinical severity, and, on the other hand, makes psychosocial support by the physician part of the therapeutic arsenal in AA [67].

As a complement to medical treatment, or as the only measure in patients who refuse medical treatment, there is a wide range of cosmetic resources that the physician should be aware of: wigs, eyebrow tattooing, synthetic eyelashes, sprays, or lotions designed to make hair look fuller can be useful in AA [68].

5.2 Local treatment options

5.2.1 Topical and intralesional corticosteroids

5.2.1.1 Topical corticosteroids (Cs)

High-potency (class 3–4) topical Cs applied once daily to the lesion and 1 cm of healthy perilesional skin are the most frequent treatments for limited patches in adult patients who refuse intralesional therapy or in pediatric patients [69, 70]. The relapse rate of topical therapy varies from 37 to 63% [69]. A response evaluation should be performed after 3 months of treatment and discontinued if there has been no response after 6 months [70].

Possible adverse effects are folliculitis, atrophy, stretch marks, telangiectasias, and acneiform eruptions [69]. Medium potency Cs are recommended for use on face and beard areas [70].

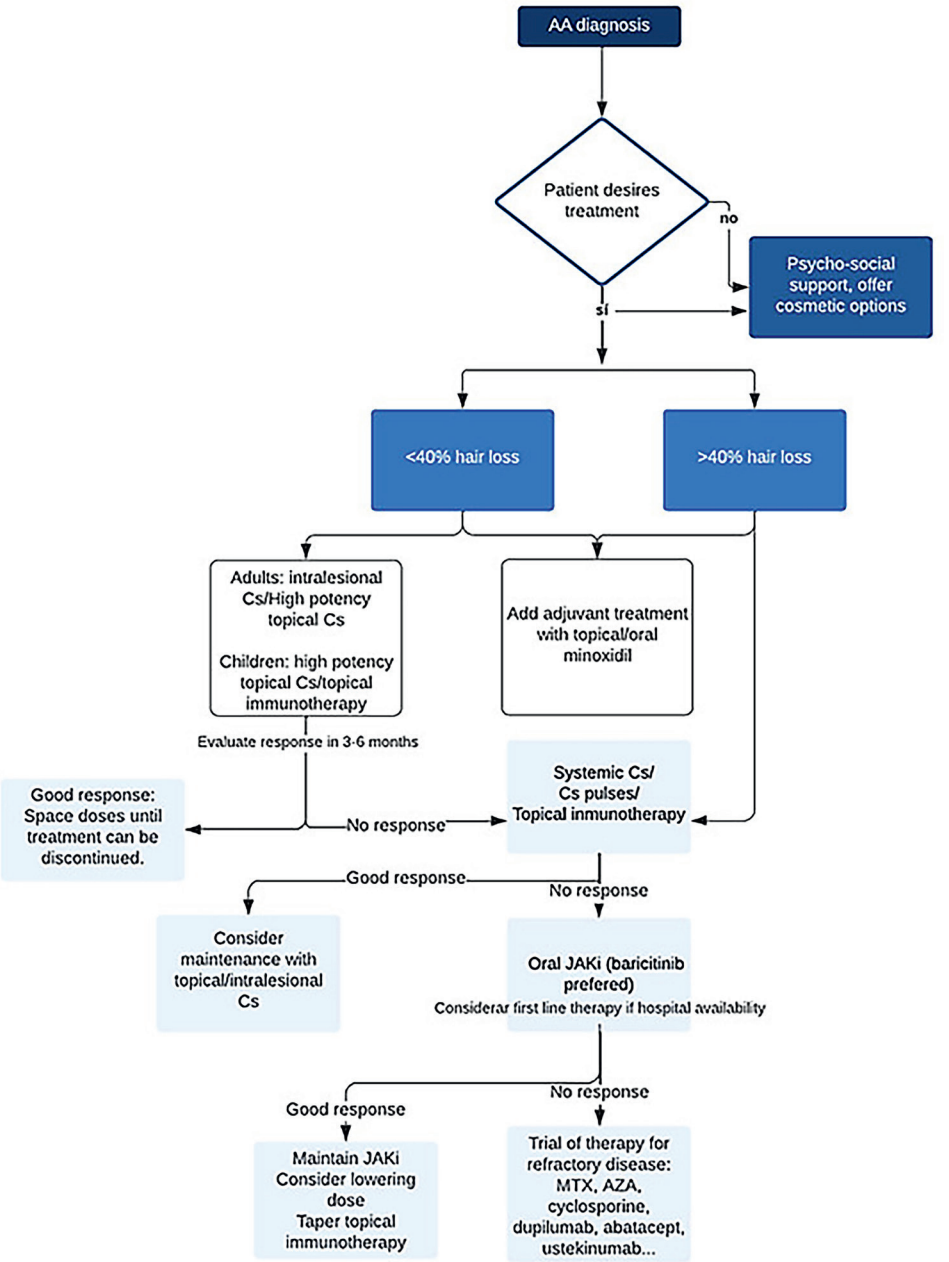

Figure 5.
Treatment strategy for alopecia areata. AA: Alopecia areata. Cs: Corticosteroids. JAKi: JAK inhibitors. MTX: Methotrexate. AZA: Azathioprine.

5.2.1.2 Intralesional corticosteroids

Considered the first-line treatment for adult patients with one or two small patches, preferred in the active phase of AA, when a positive hair pull test and exclamation mark hairs are present [69, 70]. Small volumes (0.1 ml or less) are

injected into multiple sites 1 cm apart, and new growth is usually visible within 6 to 8 weeks [69, 70]. Treatment with intralesional Cs should be discontinued if there is no response at 6 months [70].

The most common adverse effect, local atrophy, can be minimized by limiting the volume injected, injecting not too superficially and using triamcinolone hexacetonide (class 2 glucocorticosteroid) [69].

5.2.2 Topical immunotherapy

Immunotherapy may be a good treatment option in patients with more than 50% of the scalp affected [71]. It is based on inducing a local allergic contact reaction [69]. The mechanism of action of topical immunotherapy is unknown, but it is believed to have an immunomodulatory effect on the inflammatory infiltrate surrounding the hair follicles [71].

Topical immunotherapy can be performed with diphenylcyclopropenone (DPCP), squaric acid dibutyl ester (SADBE), or dinitrochlorobenzene (DNCB) [71]. DPCP is often preferred over SADBE because it is less expensive, safer, and more stable in solution [69]. In the literature, success rates vary from 9 to 87%, but one systemic review described an average of 53.7% [69, 72].

Longer courses of DPCP therapy are required to consider therapeutic failure (6–12 months) [71]. The main side effects are cervical/occipital lymphadenopathy, disseminated eczema or generalized eczema, and hypo/hyperpigmentation [69]. Treatment is not recommended in pregnant women and patients with a history of atopic eczema [69].

5.2.3 Topical minoxidil

Although a meta-analysis confirmed the efficacy of topical minoxidil 5% in children and adults with patchy AA, topical minoxidil may be insufficient as monotherapy for extensive AA [73]. Controversy exists as to whether the combination of minoxidil with topical Cs is superior to monotherapy with topical Cs [74]. One milliliter of topical minoxidil solution should be applied once or twice daily, with the 5% solution being more effective than the 2% solution [70, 74]. Patients should be aware that therapy should be continued for at least 3 to 4 months to see any effect. Reversible hypertrichosis and allergic contact dermatitis are possible side effects [69].

5.2.4 Ultraviolet light therapy

An immunomodulatory effect is proposed in the mechanism of action of ultraviolet light-based therapies, which could be useful in AA [75, 76].

5.2.4.1 Ultraviolet B (UVB) laser excimer

The excimer laser emits monochromatic ultraviolet B (UVB) light at a wavelength of 308 nm. Its mechanism of action in alopecia areata is believed to involve T-cell apoptosis and the generation of mediators, such as IL-4, IL-10, prostaglandin E2, platelet-activating factor, histamine, and cis-urocanic acid with immunomodulatory effect [75, 76]. In some small studies and case reports, excimer laser treatment was associated with improvement in patchy alopecia areata of the scalp [75, 77]. Patients with limb lesions, alopecia totalis (AT), or alopecia universalis (AU) have not responded to treatment [75].

5.2.4.2 Psoralen plus ultraviolet a (PUVA) therapy

PUVA photochemotherapy involves topical or oral administration of a psoralen, a photosensitizing agent, followed by exposure to ultraviolet A (UVA) light [76]. A meta-analysis of 36 studies evaluating the efficacy of physical therapies in alopecia found that ultraviolet light in the AA group was superior to control, although with a high relapse rate [76]. In general, the efficacy of PUVA as monotherapy in AA is known, but the response is variable and poorly maintained over time [70]. It is not completely clear at what accumulative dose they appear, but the adverse effects reported in PUVA are skin photoaging, actinic keratosis, and non-melanoma skin cancer [76].

5.2.5 Platelet-rich plasma

Platelet-rich plasma (PRP) is an autologous plasma preparation with concentrated platelets containing various growth factors and cytocines useful for cell proliferation and differentiation and with anti-inflammatory properties [78].

In a randomized, double-blind, placebo-controlled trial, 45 participants with AA of at least 2 years duration were randomly assigned to intralesional injections of PRP, intralesional triamcinolone acetonide or placebo, and PRP was superior to triamcinolone acetonide in inducing hair growth and revealed significantly better dermoscopic results than intralesional triamcinolone [79]. In a randomized controlled study, a total of 90 patients with different types of AA were randomly assigned to three groups: the first group was treated with topical minoxidil 5% twice daily. The second was treated with three sessions of PRP treatment every 4 weeks. The third group received placebo. Significant hair growth was obtained in patchy AA (70%) and AU (30%) after three PRP sessions; however, AT did not respond to PRP [80].

Although PRP is relatively safe and potentially effective, further large-scale studies are needed to evaluate the efficacy of PRP as monotherapy or in association with other therapeutic modalities for AA [78].

5.2.6 Topical anthralin

Anthralin is a topical irritant agent, applied as a 0.5–1% cream daily on the affected areas for 20–30 minutes, with progressive increases in exposure time until reaching a mild dermatitis. The available evidence of its use is limited; efficacy has been demonstrated in children undergoing other topical treatment (Cs, minoxidil), although the irritation produced may compromise the adherence [81]. A systematic review found that topical anthralin monotherapy achieved a complete response rate of less than 50% (30–35%) in pediatric patients with AA [82]. The use of anthralin could achieve longer-lasting effects than laser therapy or topical immunotherapy, but less efficacy [82].

5.3 Systemic treatment options

5.3.1 Systemic corticosteroids

Systemic corticosteroids can be effective in extensive and rapidly progressive AA, often as a temporary measure or as bridge therapy to other therapies, considering that recurrence after discontinuation of therapy and systemic adverse effects in chronic therapy are common [69].

Daily oral therapy with an initial prednisolone dose of 1–0.5 mg/kg and a gradual reduction over 6 to 12 weeks is often used [70]. There is growing interest in the efficacy of intravenous or oral corticosteroid pulses [69, 70], since the toxicity and recurrence rate may be lower than with daily systemic corticosteroids. A systematic review on pulsed corticosteroid therapy included 41 articles, most of them using intravenous corticosteroid pulses, generally a treatment of 1 to 3 days per month. Very few cases of complete response were found, but in responders the risk of relapse was low (17%). Therefore, therapy may be useful in patients with good prognostic factors: multifocal AA, first episode of AA, and new-onset AA (less than 2 years) [83].

An observational study with a prospective cohort of 40 patients evaluated the efficacy and safety of treatment with dexamethasone minipulses in patients with AA, who did not improve with topical therapies. A significant and progressive overall decrease in SALT score was observed during treatment: at 9 months, a SALT-50 response was achieved in 51.8% of patients. Hypothyroidism and early age of onset were identified as factors for lack of response to treatment [84].

A high recurrence rate, following dose reduction or discontinuation, as well as adverse effects (e.g., pituitary–adrenal axis suppression, weight gain, ocular and skeletal changes, and aggravation of hypertension or diabetes) during long-term therapy have restricted the application of systemic corticosteroids as chronic AA therapy [70].

5.3.2 Oral minoxidil

A systemic review including 10 articles (19,218 patients) showed that oral administration of low-dose minoxidil (0.25 to 5 mg) twice daily improved 18 to 82.4% of patients (including severe and refractory AA) [85]. The dose of oral minoxidil ranged from 0.25 to 5 mg daily and twice daily. The most frequent adverse effects were generally mild and well tolerated (facial hypertrichosis and postural hypotension), which, together with the convenience of oral administration, may improve adherence to treatment with respect to topical minoxidil [85].

5.3.3 Classic immunosuppressants

Immunosuppressants used for refractory AA include methotrexate, azathioprine, cyclosporine, and sulfasalazine. The use of these drugs requires monitoring of their toxicity by periodic blood analysis, and there is limited evidence of their efficacy [69, 70].

5.3.3.1 Methotrexate (MTX)

A meta-analysis of 16 observational studies evaluated the efficacy of MTX in severe AA in monotherapy or combined with other therapies, as well as its safety and relapse rate [86]. Patients were generally treated with doses between 7.5 and 25 mg per week. MTX induced hair regrowth of more than 50% in 63.2% of patients with AA. Adults appeared to respond better to methotrexate treatment. MTX taken together with corticosteroids was found to be more effective than in monotherapy. Initial hair regrowth with MTX may be evident after approximately 3 months, and 6 to 12 months of therapy may be required for full regrowth. However, recurrence appears common with gradual tapering of MTX. MTX complication rates were acceptable and similar between adult and pediatric cases [87].

5.3.3.2 Azathioprine (AZA)

Oral AZA may be a therapeutic option for adult patients with severe recalcitrant AA. However, given the frequency of adverse effects, close follow-up with analytical controls is recommended [70]. In a prospective study of 14 adult patients with AU refractory to other treatments, hair regrowth of ≥75% was achieved in six patients with AZA doses of 2.5 mg/kg/day adjusted for thiopurine methyltransferase levels [88]. Responses occurred 4 to 6 months after treatment initiation, and four of the six responders had a maintained response after discontinuing AZA. Adverse effects (diarrhea, hepatitis, pancreatitis, or myelosuppression) occurred in 35.71% of participants [88].

5.3.3.3 Cyclosporine

Cyclosporine may be a therapeutic option at doses up to 6 mg/kg/day for the treatment of AA totalis, AA universalis, or multifocal AA (sterkens). However, cyclosporine therapy is associated with the potential for serious adverse effects, including hypertension and nephrotoxicity, that make its use unsuitable as maintenance therapy [69, 70, 74]. A randomized, double-blind, placebo-controlled trial of 32 patients with moderate to severe AA evaluated the efficacy of cyclosporine at a dose of 4 mg/kg per day for 3 months. The treatment group achieved a ≥ 50% reduction in SALT score compared to the placebo group, but the difference between the two groups was not statistically significant [89]. In a retrospective study of 25 patients with severe AA treated with cyclosporine at 2.5–6 mg/kg/day for 2–12 months, 10 achieved significant hair growth [90]. A better response was obtained in patients with AA of less than 4 years duration, so the duration of the disease could influence the efficacy of cyclosporine [90].

5.3.3.4 Sulfasalazine

It is a prodrug activated by bacteria in the colon to sulfapyridine and 5-aminosalicylic acid with immunosuppressive and immunoregulatory properties [69]. In an open-label, uncontrolled clinical trial, 26 patients with recalcitrant or severe AA on treatment with 3 g/day sulfasalazine for 6 months were followed for 3 years. Six patients showed complete regrowth, nine patients showed partial regrowth, and ten patients experienced complete or partial relapse [91]. In a prospective study of 39 patients with refractory AA, the response to 3 g/day sulfasalazine for 6 months was evaluated. Ten patients experienced 60–100% regrowth, and 17 patients experienced no response [92]. Side effects of sulfasalazine may include gastrointestinal distress, headache, fever, rash and, less commonly, hematologic disorders and hepatotoxicity [91–93]. Starting therapy at a low dose may decrease gastrointestinal symptoms [91–93]. Blood count and liver function should be monitored closely during the first 3 months of therapy and every 3 to 6 months thereafter [93].

5.3.4 Biological drugs and new molecules under investigation

5.3.4.1 Apremilast

It is a phosphodiesterase 4 (PDE4) inhibitor that reduces the production of proinflammatory cytokines [69, 94]. PDE4 is found to be upregulated in human scalp

lesions of patients with AA [69, 94]. In a double-blind, placebo-controlled study in 30 patients with moderate to severe AA, the efficacy of oral apremilast administered for 24 weeks was evaluated [94]. At 24 weeks, only 1 of 12 apremilast-treated subjects achieved SALT50, and similarly 1 of 8 placebo-treated subjects achieved SALT50. The difference between the mean percentage improvement in SALT score compared to baseline for the two study groups was not statistically significant [94]. Despite having demonstrated efficacy in animal models, results in humans are conflicting, with lack of efficacy of apremilast in some recent studies of severe AA, but also some case reports of positive effects [69, 74, 94].

5.3.4.2 Dupilumab

It is a human monoclonal antibody that acts as a dual inhibitor of IL-4 and IL-13, used in the treatment of atopic dermatitis [65, 95]. There have been case reports of patients with atopic dermatitis and AA on dupilumab treatment who have experienced improvement of AA [65, 95]. It is proposed that the efficacy observed in these cases is due to the pathophysiological characteristics shared between atopic dermatitis and AA, with an involvement of the Th2 immune pathway in the pathogenesis of AA [65, 95]. On the other hand, dupilumab has also been associated with AA in patients with preexisting AA and those without prior episodes of AA [96]. Theories for this adverse effect include the amplification of the Th1 pathway as a result of dupilumab-induced downregulation of Th2, which calls into question the involvement of the Th2 pathway in AA [95].

A Phase II, randomized, double-blind, placebo-controlled, pilot study (NCT03359356) investigating dupilumab (300 mg) treatment in AA patients without atopic dermatitis is currently underway [97]. The dupilumab-treated arm included 40 patients. At week 48, the dupilumab-treated group experienced improvement of SALT30/SALT50/SALT75 in 32.5, 22.5, and 15% of patients, respectively [97]. Moreover, patients with baseline IgE levels ≥200 IU/mL had even higher response rates, making baseline IgE postulated as a predictor of response to dupilumab in patients with AA [97].

The most common adverse events reported are injection site reactions, conjunctivitis, blepharitis, ocular pruritus, xerophthalmia, and symptomatic reactivations of herpes simplex virus [95].

5.3.4.3 Ustekinumab

It is a monoclonal antibody that blocks the p40 subunit of IL-12/IL-23 used for treating psoriasis and Crohn's disease [95]. Ustekinumab caused hair regeneration in three patients with moderate to severe AA [98]. Common adverse effects include injection site reactions, headache, and fatigue [95].

5.3.4.4 Abatacept

It is a selective modulator of T-cell co-stimulation, composed of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) with an immunoglobulin (Ig)G1 moiety. It is currently approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis [95]. An open-label, single-arm phase II clinical trial (NCT02018042) evaluated the efficacy of abatacept (125 mg daily subcutaneously for 24 weeks) in 15 patients with moderate-to-severe patchy-type AA, AA totalis, and AA

universalis [99]. Although most patients had a low or moderate response with abatacept, one patient achieved complete scalp hair growth at week 36. Three subjects did not respond to treatment [99]. Common adverse effects reported include headache, dizziness, nasopharyngitis, cough, back pain, and hypertension [95].

5.3.5 Janus kinase inhibitors (JAKi)

The JAK–STAT pathway is a signal transduction and intracellular transcription regulation pathway in which numerous pro-inflammatory pathways converge [65] (**Figure 6**). The pathway involves the JAK family of four kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]), which are located in the intracellular domains of type I and II cytokine receptors [65, 95]. Their activation when ligand binds to the receptor leads to binding and phosphorylation of the STAT family of proteins, which bind DNA and mediate processes of cell proliferation, differentiation, migration, and apoptosis [65]. Recently, the involvement of several JAK–STAT pathway-dependent cytokines in the pathogenesis of AA (IL-2, IL-7, IL-15, IL-21, and interferon-gamma) has been described [65]. Key genes in the JAK–STAT pathway related to hair growth includeSTAT5A/B, STAT3, JAK1, JAK3, and Socs2/3, highly expressed in the catagen and telogen phases but suppressed in the early anagen phase [95]. In AA, inhibition of JAK–STAT interferes with the positive feedback loop between follicular cell and cytotoxic CD8+ NKG2D+ CD8+ T cells in AA [95]. Given the involvement of this pathway and its dependent cytokines in the pathogenesis of AA, JAK–STAT has become a potential therapeutic target [65, 69, 70, 95].

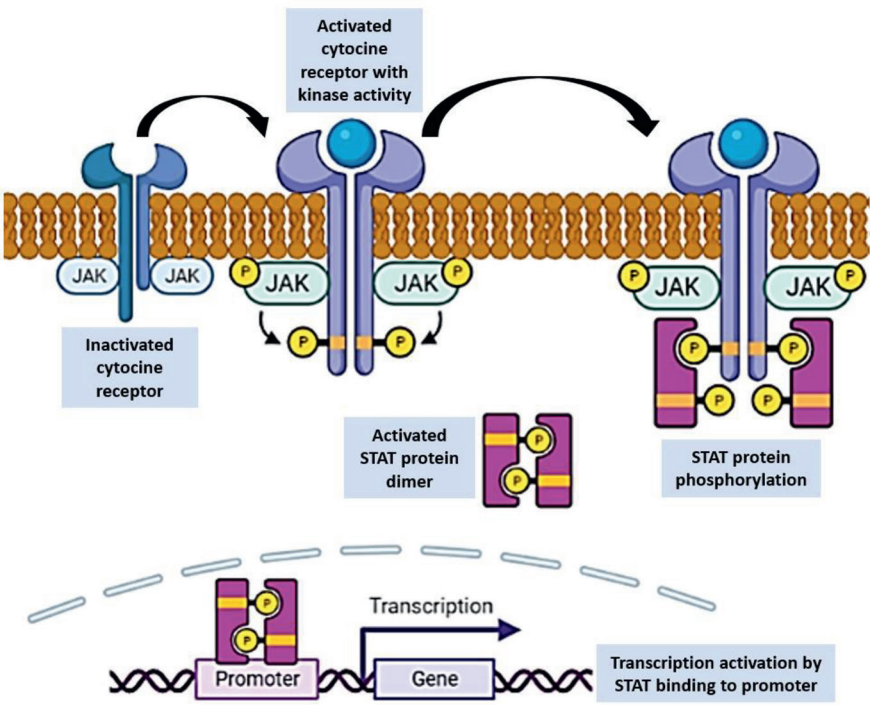

Figure 6.
JAK–STAT pathway. This image was created using Biorender.com.

JAKi are oral drugs that have demonstrated effectiveness and safety for the treatment of diseases such as rheumatoid arthritis and psoriatic arthritis [95, 100]. JAKi are selective, but not specific for a single JAK and, therefore, can affect several immune pathways [95]. The FDA has issued warnings for oral JAKi due to concerns about an increased risk of serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis [69, 70, 95].

5.3.5.1 Baricitinib

It is a selective and reversible JAK1 and JAK2 inhibitor, it has also been shown to indirectly inhibit IL-6, and Il-23 activity, and to a lesser extent inhibit JAK3 [95]. Baricitinib has demonstrated efficacy for severe alopecia areata [95, 100, 101]. In 2022, the FDA approved baricitinib for the treatment of adults with severe alopecia areata [65, 95]. In two randomized, placebo-controlled, phase 3 trials BRAVE-AA1 (n = 654) and BRAVE-AA2 (n = 546), adults with severe alopecia areata (SALT ≥50) were randomized to baricitinib 4 mg per day, baricitinib 2 mg per day, or placebo [101]. At week 36, the proportion of patients in the baricitinib 4 mg, baricitinib 2 mg, and placebo groups who achieved a SALT score of ≤20 in BRAVE-AA1 was 39, 23, and 6%. In BRAVE-AA2, 36, 19, and 3% of patients in the 4 mg, 2 mg, and placebo groups achieved this end point, respectively [101]. The dose of baricitinib is 2 mg once daily with an increase to 4 mg once daily if response is inadequate. Patients with near complete or total scalp hair loss may be treated initially with 4 mg once daily. The dose is reduced to 2 mg once daily upon adequate response [65, 95, 101]. The most common adverse effects encountered with baricitinib are acne, urinary tract infections, and elevated serum creatinine kinase and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [101].

5.3.5.2 Tofacitinib

It selectively inhibits JAK1 and JAK3 and blocks STAT phosphorylation induced by IFN-γ, IL-2, IL4, IL-7, IL-15, and IL-21 [65, 69, 95]. Treatment with oral tofacitinib has been shown to achieve hair regeneration in patients with AA in case series and retrospective studies, and patients are typically treated with 5 mg twice daily [65, 69]. In a retrospective study of 90 adult patients with severe AA (SALT >40), including AA totalis or AA universalis, the efficacy of oral tofacitinib at doses of 5–10 mg/day for at least 4 months was demonstrated (77% clinical response in AA of less than 10 years duration). Duration longer than 10 years and having AA totalis or AA universalis were defined as predictors of low response to tofacitinib. The relapse rate 3 months after discontinuation of oral tofacitinib treatment is high [102]. Treatment with oral tofacitinib increases the risk of infections [102]. Cases of serious infections and malignancies have been reported in patients receiving tofacitinib treatment [69].

5.3.5.3 Ruxolitinib

It selectively inhibits JAK1 and JAK2 and, to some extent, TYK2 [95]. The utility of oral ruxolitinib in the management of AA has been reported in case reports, case series, and an open-label trial [65, 69, 95, 103]. In an open-label clinical trial of 12 patients with moderate to severe AA, the efficacy of oral ruxolitinib, 20 mg twice daily, was evaluated during 3–6 months of treatment, and 9 patients (75%) achieved at least 50% hair growth at the end of treatment [103].

5.3.5.4 Other oral Janus kinase inhibitors under investigation

It is a phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral JAKi drugs ritlecitinib and brepocitinib in patients with severe AA (SALT >50%). The trial includes 47 patients in each study group [104]. Results at week 24 suggest efficacy of riclecitinib and brepocitinib in AA, although two patients experienced a serious adverse event (rhabdomyolysis) in the brepocitinib group [104].

5.3.5.5 Topical Janus kinase inhibitors

The utility of topical JAKi is currently under investigation in patients with AA to minimize the risk of systemic side effects, especially for maintenance treatment [70]. Topical ruxolitinib and baricitinib creams in 1 and 2% formulations have been reported to produce hair regrowth in patients with AA [65, 105]. Topical tofacitinib has also achieved hair growth and prolongation of the anagen phase [65]. However, there are also case reports and clinical trials reporting inconsistent or no induction of hair growth with topical ruxolitinib or tofacitinib cream.

5.3.6 Proposed management strategy for alopecia areata

According to the literature reviewed, we propose this scheme depending on the age and extent of AA. Response to treatment should be re-evaluated every 3–6 months of initiation of new therapy.

Conflict of interest

The authors declare no conflict of interest.

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