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Alopecia areata – Current understanding and management

Summary

Alopecia areata (AA) is a chronic, immune-mediated disease characterized by acute or chronic non-scarring hair loss, with a heterogeneity in clinical manifestations ranging from patchy hair loss to complete scalp and body hair loss. An overview of the up-to-date pathophysiology and the underlying signaling pathways involved in AA together with diagnostic and therapeutic recommendations will be provided. Current treatments, including topical, systemic and injectable interventions show varying response and frequent relapses reflecting the unmet clinical need. Thus, the new emerging concepts and therapeutic approaches, including Janus kinase inhibitors are eagerly awaited. Traditional and emerging therapies of AA will be discussed, in order to provide physicians with guidance for AA management. Since the latter is so challenging and often tends to take a chronic course, it can have an enormous psychosocial burden on patients, compromising their quality of life and often causing depression and anxiety. Therefore, the psychosocial aspects of the disease need to be evaluated and addressed, in order to implement appropriate psychological support when needed.

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Introduction

Alopecia areata (AA) is a chronic, immune-mediated disease characterized by acute onset of non-scarring hair loss ranging from small circumscribed patchy areas on the scalp, to complete scalp and body hair loss. Until recently our understanding of the pathophysiology of AA was only scarce, despite being so common, affecting both children and adults. Currently, it is suggested that the collapse of the immune privilege (IP) of the hair follicle (HF), possibly due to genetic and external factors, triggers the onset of the disease [1].

From a therapeutic point of view, there has been a clear unmet need for a treatment able to induce permanent or at least long-lasting remission. The current treatment options, topical and/or systemic, are mostly symptom-based using either unspecific immunosuppressant or immune modulating approaches. Results of genome wide association studies (GWAS) [2], and recent evidence that Janus kinases (JAKs) play a crucial role in the pathogenesis of AA, have helped to recognize the JAK-signal transducer and activator of transcription (STAT) signaling pathway as a possible therapeutic target, opening new avenues in the understanding and management of this disease [3].

Alopecia areata has an unpredictable prognosis, which often includes relapses and remissions, frequently with a chronic course, contributing to the substantial psychosocial burden of AA patients. Therefore, it is of prominent importance to advance our understanding of the disease. The aim of this article is to give an overview of the clinical presentation, diagnostic approach, and traditional and

emerging therapies of AA, in order to provide physicians with guidance on managing this challenging disease.

Historical Background

The term alopecia originates from the word "alōpex" meaning fox and is found in ancient Greek literature describing hairless areas on the scalp, similar to fur loss patches observed in foxes with mange. The word areata is derived from the Latin word area which means "occurring in patches". The French physician Sauvages de Lacroix first used the term alopecia areata in 1763 to describe patchy hair loss caused by various causes [4]. The clinical description of AA is attributed to physician Thomas Bateman in 1817 who named it "porrigo decalvans". A few decades later, the term AA came to be used for the condition as we know it today [4].

Epidemiology

The lifetime incidence of AA is 2 %, affecting both sexes equally and being more prevalent in children than in adults.

Alopecia areata is the second most common cause of hair loss following androgenetic alopecia [5, 6], affecting 2 % of the global population, with an increasing prevalence [7, 8]. Severe AA manifestations or certain clinical subtypes are rarer, with the prevalence of ophiasis type, alopecia totalis (AT), alopecia universalis (AU) being 0.02 %, 0.08 % and 0.03 % respectively. Alopecia areata appears to affect both sexes equally and can occur in all age groups and ethnic backgrounds [6, 8].

In 40 % of patients, the first AA manifestation occurs by age 20 years, and in 83–88 % by age 40 years.

The prevalence of AA is higher in children and adolescents than in adults [8]. Remarkably, 40 % of patients will experience their first AA manifestation by the age of 20 and 83–88 % by the age of 40 years [6]. Furthermore, recent studies report that AA is more common in African or African American populations compared to Asian and Caucasian [8, 9]. Finally, AA is more prevalent in individuals with other autoimmune diseases (see section comorbidities).

Pathophysiology

The hair follicle (HF) is a unique mini-organ which undergoes a continuous, lifelong regenerative cyclic process. The lower part of the healthy anagen HF (bulge and bulb) enjoys relative immune privilege (IP), which protects the hair follicle from inflammatory processes and promotes immune tolerance [10]. These distinct HF compartments are characterized by factors that act as IP guardians to preserve the HF IP [11–14] (Figure 1a).

Collapse of the HF bulb IP plays a critical role in the pathophysiology of AA.

During the normal hair growth cycle, only scattered immune cells can be found around and very occasionally within the bulb of an anagen HF [15]. During the flare-ups of AA, the anagen phase of the hair growth cycle is significantly shortened. Histologically, AA lesions show a characteristic, dense perifollicular and intrafollicular inflammatory cell infiltrate around the bulb area, resembling a swarm of bees, forcing the HF into premature catagen phase, dystrophy and eventually apoptosis [1] (Figure 1b). The infiltrate contains $CD8^+$ T and $CD4^+$ T cells, mast cells, NK cells and dendritic cells. $CD8^+$ T cells are typically the first cells to penetrate into intrafollicular locations, followed by dendritic cells/macrophages, whereas $CD4^+$ T cells are only found later in the disease process when the integrity of the HF is severely disrupted [16].

Even-though the exact etiology of AA is not yet fully elucidated, it is recognized that the HF bulb IP collapse plays a critical role in the pathophysiology of the disease [1]. What exactly causes this IP collapse is not fully understood yet; both genetic

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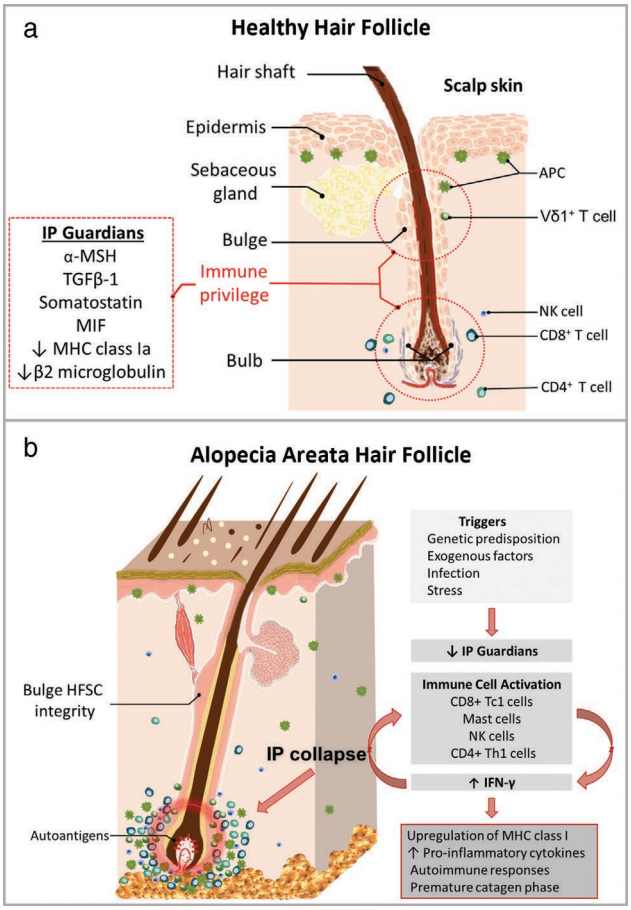

Figure 1 Schematic illustration of the hair follicle in healthy scalp and alopecia areata. Schematic illustration of a healthy hair follicle (HF), illustrating the HF anatomy and the resident immune cells. Antigen presenting cells (APC) like dendritic cells and macrophages are most abundant in the epidermis, whereas immune cells are only sporadically found in the deeper regions of the dermis. The bulb region of the anagen HF is a site of immune privilege (IP), similar to the bulge area. Guardians of IP include the immunosuppressive cytokines, as well as the downregulation of MHC class Ia/β2-microglubin expression (a). The collapse of the bulb immune privilege (IP) of the anagen HF is considered to be a significant driver of AA. What exactly causes the IP collapse is not yet fully understood; however, triggering factors that occur in genetically susceptible individuals such as HF trauma, viral infection, or emotional or physical stress have been reported. These triggering factors suppress IP guardian expression, contribute to the IP collapse and locally activate the innate immune system mostly via NKG2D⁺ cells, leading to subsequent interferon (IFN-γ) production and MHC class I upregulation that further enhance the breakdown of the IP. The inflammatory perifollicular infiltrate, consisting of $CD8^+$ T and $CD4^+$ T cells, mast cells, NK cells and dendritic cells, attacks the bulb region in the form of a "swarm of bees", but the HF stem cell (HFSC) compartment around the bulge area is spared, allowing hair regrowth (b).

and environmental factors have been postulated [17]. Interferon-γ (IFN-γ) and substance P have been proven to be powerful inducers of HF IP collapse [18–21]. In AA the production of substance P and/or IFN-γ causes an increase in pro-inflammatory factors, and significantly decreases IP guardians, contributing to the IP collapse [11].

CD8⁺NKG2D⁺ T cells are recognized as the predominant effector T cell population in AA.

Recent studies have identified CD8⁺NKG2D⁺ T cell as the predominant effector T cell population in AA [22, 23]. Global transcriptional profiling of mouse and human AA skin revealed gene expression signatures indicative of cytotoxic T cell infiltration, an IFN-γ response and upregulation of several γ-chain (γc) cytokines (e.g., IL-2, IL-15) known to promote the activation and survival of these IFN-γ-producing CD8⁺NKG2D⁺ effector T cells [23]. Additionally, Vδ1⁺T cells with a pro-inflammatory phenotype were found to be significantly higher in the suprabulbar and bulbar epithelium of lesional AA HFs [24].

Clinical and experimental findings point towards interleukin-2 (IL-2) and interleukin-15 (IL-15) as being crucial mediators capable of inducing topical immune reactions in AA [23, 25]. Therapeutically, antibody-mediated blockade of IFN-γ, IL-2 or IL-15 receptor β prevented disease development, by reducing the accumulation of CD8⁺NKG2D⁺ T cells in a mouse model of AA [23]. In addition, IFN-γ-driven inflammation in AA is JAK mediated, resulting in a "signal loop" (see section JAK inhibitors) [26].

Large GWAS in AA patients revealed various, significantly associated polymorphisms.

Large GWAS in AA patients revealed significantly associated polymorphisms, containing genes that control the activation and proliferation of regulatory T cells, cytotoxic T lymphocyte-associated antigen 4, IL-2/IL-21, IL-2 receptor A, Eos, as well as the human leukocyte antigen (HLA) region, and a region within the gene cluster which encodes activating ligands of the natural killer cell receptor NKG2D [2]. In an effort to find the genetic basis of AA, a GWAS in 20 AA families, including both affected and unaffected individuals, revealed evidence of at least four susceptibility loci on chromosomes 6, 10, 16 and 18, some of which have been previously implicated in psoriasis and Crohn's disease [27].

Alopecia areata results in non-permanent hair loss, as the hair regeneration depends on the preservation of HF stem cells (HFSCs) [28]. Since the inflammatory infiltrate and HF destruction in AA is mainly around the bulb area, the HFSC niche found in the bulge region of the permanent portion of the HF is spared, allowing the HF to regenerate and regrow new hair shafts when the inflammation

Table 1 Clinical variants of alopecia areata with their characteristic manifestations.

Clinical variants of alopecia areata	Presentation
Patchy alopecia areata	Single or multiple circumscribed, well-demarcated patches of hair loss on the scalp
Alopecia totalis	Complete scalp hair loss
Alopecia universalis	Complete loss of facial, body and scalp hair
Ophiasis alopecia areata	Hair loss on the occipital and temporal scalp site
Inverse-ophiasis (or sisaipho) alopecia areata	Central hair loss, lateral and posterior scalp sites are spared
Diffuse alopecia areata/ Alopecia areata incognita	Diffuse hair loss and reduction of hair density
Alopecia barbae	Discrete circular or patchy hair loss areas in the mustache or beard, often along the jawline, rarely diffuse thinning
Alopecia areata of the nails	Nail pitting, trachyonychia, red lunula, longitudinal ridging, onychomadesis, onycholysis and onychorrhexis

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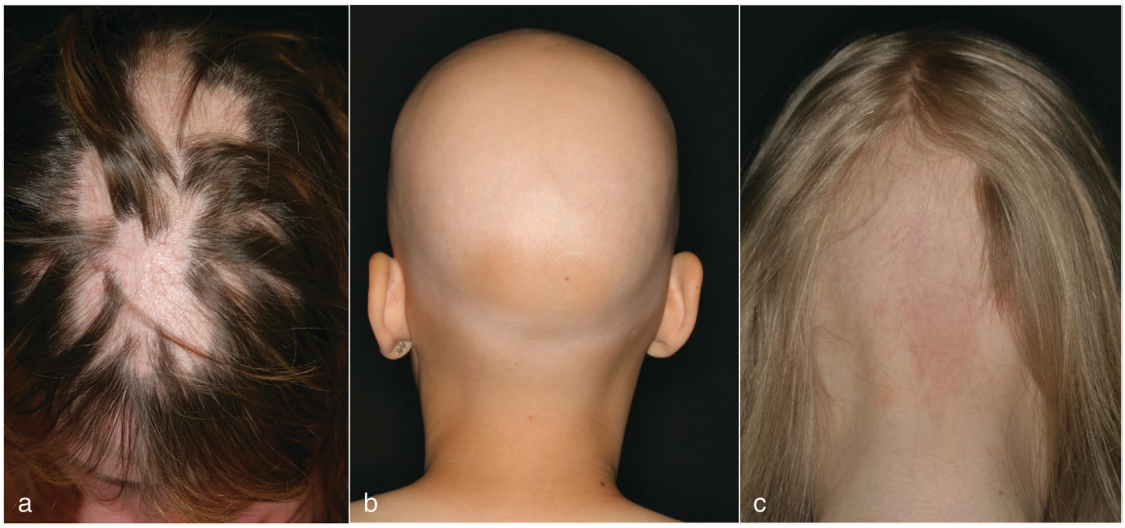

Figure 2 Clinical variants of alopecia areata. Circumscribed, patchy hair loss (a). AA totalis with 100 % scalp hair loss (b). Hair loss of the occipital area as ophiasis type (c).

subsides. Often, the regrown hairs at previous patches of AA are white (i.e., poliosis) [29]. The reason is not yet clear; however, it has been suggested that melanocyte-associated T-cell epitopes can function as autoantigens that could potentially trigger autoimmunity and IP collapse [30, 31].

Clinical presentation

Alopecia areata presents with different clinical manifestations: patchy AA, alopecia totalis, alopecia universalis, ophiasis type, inverse-ophiasis type, alopecia barbae, AA of the nails and diffuse AA.

Alopecia areata has a broad inter- and even intra-individual clinical presentation. Depending on the involved skin areas, the pattern, and the extent of hair loss, the disorder is clinically classified into several variants (Table 1). The most common clinical presentation of AA is patchy AA with the appearance of single or multiple circumscribed patches of scalp hair loss (Figure 2a). These patchy lesions can either be discrete, isolated or can coalesce with other lesions to form a larger area devoid of hair. The skin within the lesions is smooth, healthy-looking, and intact, while sometimes a slight oedema is palpable, but without any erythema or other signs of inflammation. Depending on the activity of the disease, a lesion may be stable in size or increase in diameter, while a spontaneous remission with partial or complete regrowth is also possible. Patchy AA may progress to total scalp hair loss, defined as alopecia totalis (AT) (Figure 2b), or complete loss of all body hair, defined as alopecia universalis (AU).

Alopecia areata of the scalp can also occur in other patterns and can thus be classified into further clinical types. Ophiasis AA is characterized by hair loss on the occipital and temporal scalp, forming a band-like bald area resembling a snake shape ("ophis" meaning snake) (Figure 2c). The opposite condition, called inverse-ophiasis type, or sisaipho, occurs with central hair loss, resembling androgenetic alopecia. Diffuse alopecia areata (DAA) or alopecia areata incognita (AAI) is a rare, non-patchy subtype of AA that is commonly misdiagnosed, or the diagnosis is notably delayed. Diffuse AA is characterized by diffuse hair loss and is more common in women between 20 to 40 years [32, 33]. Some authors suggested DAA and AAI to be two separate entities [34, 35]. Though very rare, other atypical hair regrowth patterns such as concentric or targetoid regrowth have been reported as isolated cases [36].

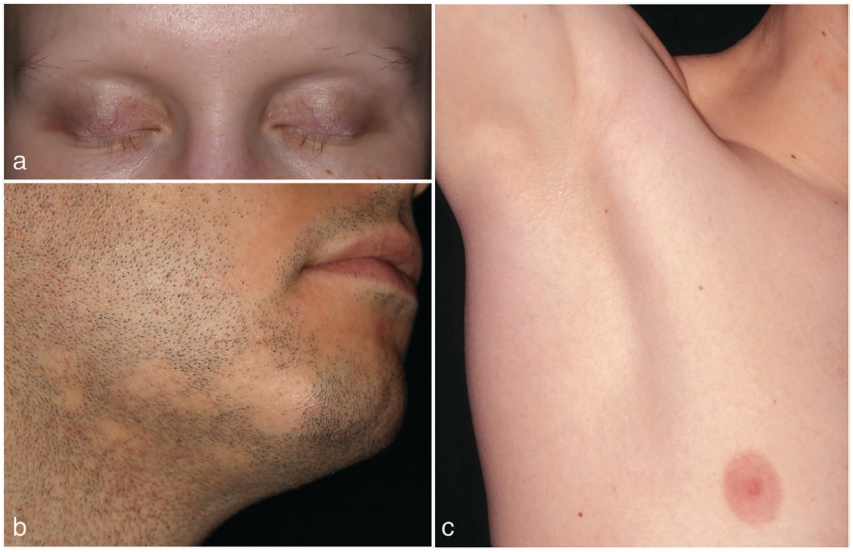

Figure 3 Other presentations of alopecia areata. (a) Partial loss of eyebrows and eyelashes (a). Patchy hair loss of the beard (b). Complete loss of axillary hair (c).

Aside from scalp involvement, AA can occur at any other hair bearing body site, either during the disease progress or as an isolated manifestation. In this context, AA may present as partial or complete loss of eyebrows, eyelashes, beard, pubic

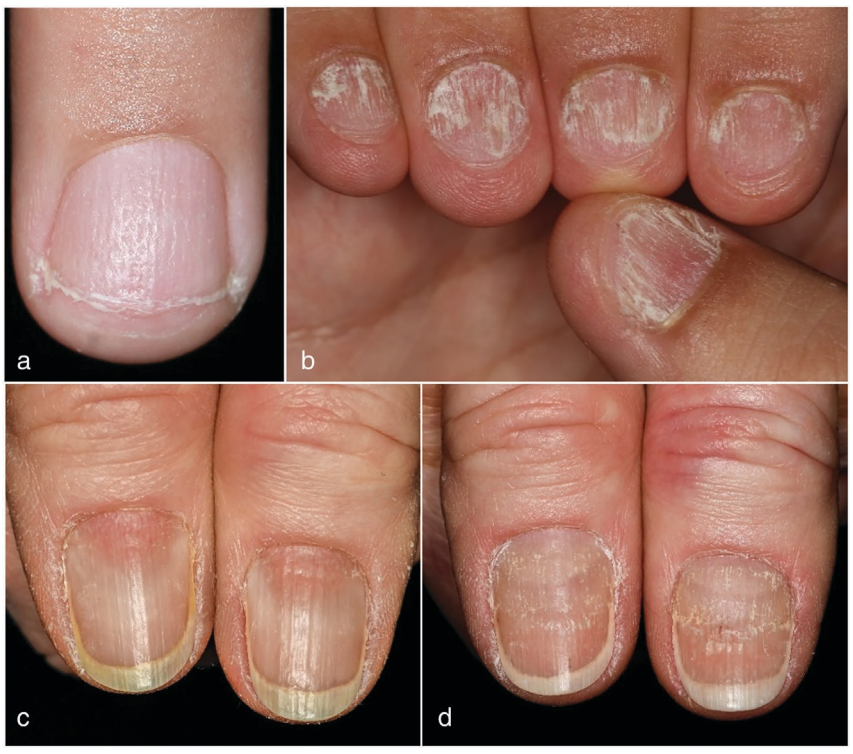

Figure 4 Alopecia areata of the fingernails. Nail pitting (a). Trachyonychia of all nails (b). Red lunula of both thumbs as a sign of the acute inflammatory phase. The patient had patchy, progressive scalp hair loss over the previous four weeks (c). Three months later, transverse grooves and pitting of both thumbs in the same patient. Alopecia universalis developed in the meantime (d).

or axillary hair, or nail changes (Figure 3). Alopecia areata only affecting the beard is referred to as alopecia barbae, and usually affects middle aged males.

Alopecia areata of the nails typically presents with nail pitting, and in severe cases with trachyonychia [37, 38] (Figure 4a, b). Other, less common changes are longitudinal ridging, onychomadesis, onycholysis, onychorrhexis, and the so-called red lunula seen in the acute phase of severe AA [37, 39–41] (Figure 4c, d). Alopecia areata limited to the nails is very rare; nail involvement is usually part of the clinical presentation of other, mostly severe forms. The appearance of nail changes ranges greatly from 7 to 66 %, with an average prevalence of approximately 30 %, and they are more common in children than in adults [37, 38, 40]. Nail changes may precede AA induced hair loss, or can occur months or years after the hair loss, and may even persist after hair regrowth [42].

Ocular findings in the form of retinal pigment epithelium alterations, fundus alterations and punctual lens opacities have been reported in patients with AA [43, 44]. However, those findings do not seem to interfere with visual acuity [44], nor correlate with the severity or activity of the disease [43]. Dry eye disease has also been associated with AA [45].

Diagnosis

The evaluation of an AA patient should include a comprehensive medical and family history, a thorough examination of the scalp, the face and the entire body, including the nails. This should always be complemented by dermatoscopy, and a hair pull test. When clinical findings do not allow a definite diagnosis, additional investigations, such as a scalp biopsy, a fungal culture, or serology for other autoimmune diseases or infectious diseases (such as syphilis) may be necessary.

Medical history

The medical history should include the age of onset (for example, before or after puberty), the disease course, including previous episodes, the duration of the current and passed episodes, and associated symptoms such as paresthesia, itching, etc. Additionally, the history of other autoimmune or inflammatory disorders, including atopy, autoimmune comorbidities (thyroid disorder, vitiligo, inflammatory bowel diseases, etc.), recurrent infections or inflammatory foci, and any recent or current topical or systemic therapies should be evaluated. A positive family history of AA or other autoimmune disorders is also relevant for counselling.

Physical examination

Careful clinical examination should include a macroscopic inspection of scalp and body, especially hair-bearing areas and nails with determination of hair loss pattern and involved areas. Even though patchy hair loss pattern is characteristic for AA, diffuse hair loss is observed in rarer cases (for example, DAA/AAI). Additionally, the appearance of the skin within the lesions should be evaluated for signs of scarring, scaling, erythematous papules, pustules or crusts to exclude other differential diagnoses.

Dermatoscopy

Hair and scalp dermatoscopy, also known as trichoscopy, is an easy, non-invasive diagnostic technique that is very helpful in the diagnosis and follow-up of scalp

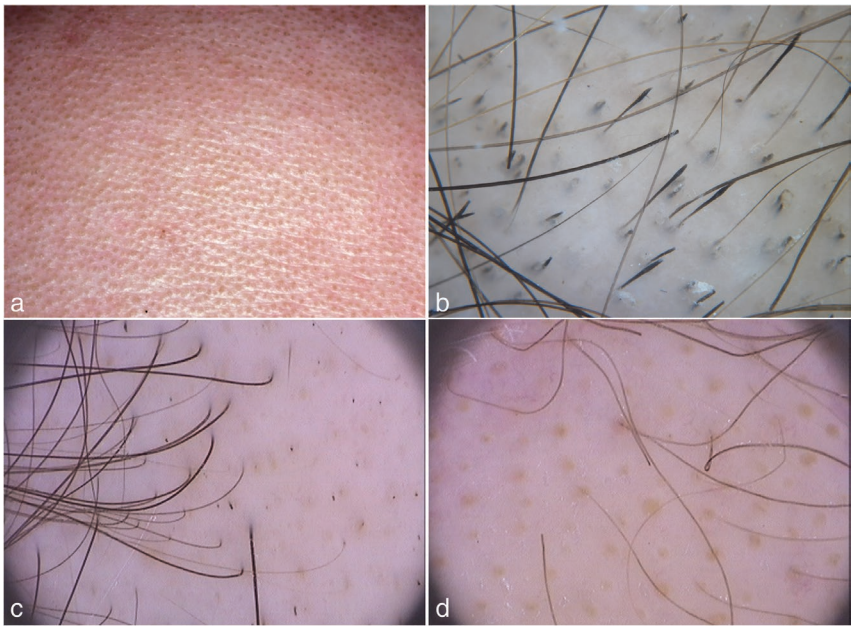

Figure 5 Dermatoscopic findings in alopecia areata. (a) Visible hair follicle openings with no remaining visible hair shafts (a). Exclamation mark and broken off hairs (b). Remaining terminal hairs, black dots and broken hair shafts (c) and characteristic yellow dots in AA (d).

Table 2 Characteristic dermatoscopic findings in alopecia areata.

Dermatoscopic findings of AA	Description
Yellow dots	Round, yellow or pink-yellow circular dots representing the dilated, but intact, hair follicle openings filled with sebum or remnants of follicular keratinocytes.
Black dots	Remnants of hair shafts that were fractured before they could emerge from the scalp, mainly seen in dark-haired patients with a light skin type
Broken hairs	Short, broken-off hair shafts
Exclamation mark hairs	Short, broken hairs which taper towards their proximal end
Vellus hairs	Thin, downy, non-pigmented hairs
Upright hairs	Healthy, regrowing hairs with a straight-up position and a tapered distal end; also found in telogen effluvium, trichotillomania, tinea capitis and temporal triangular alopecia
Tapered hairs	Normal-looking hairs with a tapered proximal end; precursors of exclamation mark hairs and black dots
Pigtail hairs	Short, regrowing, coiled hairs with tapered ends; indicate disease remission
Pohl-Pinkus constrictions	Progressive and irregular narrowing along the hair shaft; indicate disease severity; also found in chemotherapy induced alopecia

diseases [46]. Dermatoscopy is especially crucial for differentiating non-scarring and scarring hair diseases, and for confirming the diagnosis of AA, as well as for evaluating the disease activity. The most common dermatoscopic findings in AA are yellow dots, black dots, broken hairs, exclamation mark hairs, and vellus hairs, whilst other less frequently described findings are upright hairs, tapered hairs, pigtail hairs and Pohl-Pinkus constrictions [47–51] (Figure 5). Detailed descriptions of each finding are summarized in Table 2.

Yellow dots are primarily present in long-standing patches and in more severe AA forms, AT and AU. Even though they are a sensitive marker for AA, they are also present in other hair diseases such as androgenetic alopecia or trichotillomania [46]. Black dots and short, broken hairs are typical findings at the periphery of active AA patches, but both can also be found in trichotillomania. Exclamation mark hairs are pathognomonic for AA, typically seen in the periphery of active lesions. Vellus hairs are associated with remission or long-standing disease [50].

Hair pull test

A hair pull test is helpful for differential diagnosis, and in determining the activity of the disease. A bundle of 50–60 hairs is grasped firmly close to the scalp and pulled with moderate force in the direction of growth, performed at the border of patchy lesions and at the contralateral clinically non-affected side [52]. Hairs should not have been washed for at least one day. A positive hair pull test with epilation of ≥ 10 % of grasped hairs indicates active disease, whereas a negative test a stable or resolving AA. A positive pull test on the clinically non-affected area may indicate progressive disease with diffuse progression.

Trichogram

Trichograms are not helpful in confirming a suspected AA diagnosis [53]. However, it could differentiate DAA from telogen effluvium, as DAA is characterized by the presence of dystrophic anagen hairs [54].

Biopsy

A scalp biopsy is especially indicated when scarring alopecia cannot be clinically excluded, a single lesion is resistant to treatment, or in the differential diagnosis of DAA. In the context of AA, a single biopsy is usually sufficient to set the diagnosis. The biopsy should be performed at the edge of the lesion, and a location susceptible to androgenetic alopecia should be avoided [53].

Histopathologic findings in AA depend on the disease's activity at the time of the biopsy (Figure 6). At the early (acute) stage, the main characteristic is a peribulbar and intrabulbar lymphocytic infiltrate surrounding the anagen or catagen follicles, described as "swarm of bees". The infiltrate consists mainly of $CD4^+$ and $CD8^+$ T cells; however, eosinophilic cells, mast cells and plasmatic cells may also be detected. A transition to catagen or telogen phase is additionally observed. In long-standing (chronic) AA, the infiltration's intensity may vary; most HFs are in the catagen/telogen phase, while miniaturized HF are also present. An increased number of empty HF may also be observed, corresponding to the total hair loss of the patient, as well as keratin plugs in empty follicular ostia indicating longstanding AA with no regrowth [55, 56].

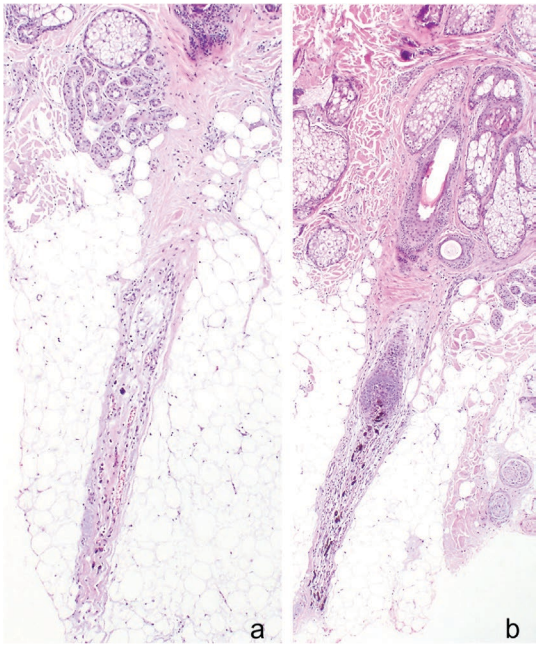

Figure 6 Histopathologic features of alopecia areata. At all stages of alopecia areata, non-sclerosing fibrous tracts as residues of collapsed fibrous hair root sheaths can be observed. Typically, they contain small vessels, deposits of melanin, melanophages and a varying degree of lymphohistiocytic inflammatory infiltrate (a). Depending on the clinical manifestation of localization of biopsy taken, an increased number of telogen hair follicles can be found, diminished anagen hair follicles along the fibrous tracts with their bulbi arranged upward along the former, strong terminal hair follicles (b).

Differential diagnosis

The differential diagnosis of AA mainly includes other diseases presenting with non-scarring, circumscribed and diffuse hair loss, and may differ between the different age groups (Table 3). Trichotillomania, tinea capitis and temporal triangular alopecia, are the main conditions that should be considered in differentiating patchy hair loss, while telogen effluvium, female pattern hair loss and drug induced alopecia should be mainly considered in diffuse forms of AA. The full spectrum of differential diagnosis of AA is summarized in Table 3.

Table 3 Differential diagnosis of patchy and diffuse alopecia areata grouped by children/adolescents and adults.

	DD Patchy alopecia areata	DD Diffuse alopecia areata
Children/adolescents	Tinea capitis	Loose anagen hair syndrome
	Trichotillomania	Telogen effluvium
	Temporal triangular alopecia (N. Breuer)	Congenital hypotrichosis
Adolescents/adults	Mucinosis follicularis	Telogen effluvium
	Alopecia syphilitica	Female pattern hair loss
	Scarring alopecia, such as CDLE, lichen planopilaris	Drug induced alopecia (antiproliferative, etc.)

Classification tools

Assessing the severity of AA is of great importance for patient management, as it guides the physician in the therapeutic decision-making, and helps estimate the therapeutic response and predict the disease's prognosis. To facilitate and standardize the evaluation of the extent and course of AA in clinical trials, a simple but reliable and reproducible disease severity score has been developed; the *Severity of Alopecia Tool* or SALT score [57]. In addition, the SALT is considered a sufficient measure for estimating the extent of patchy AA of the scalp in clinical practice [53].

According to this tool, the scalp area is divided into four quadrants, each representing a percentage (%) of the total scalp area: left side (18 %), right side (18 %), top (40 %) and back (24 %). The percentage of hair loss in each quadrant is visually estimated, and then added together to determine the SALT score, which can have a value of up to 100 %. According to the estimated SALT score, five subgroups of hair involvement can be identified: S_0 = no hair loss, S_1 = < 25 % hair loss, S_2 = 25–49 % hair loss, S_3 = 50–74 % hair loss, S_4 = 75–99 % hair loss, S_5 = 100 % hair loss [57, 58].

SALT score calculation and identification of all involved anatomical sites, including the nails, are essential elements in assessing disease severity.

However, an inherent limitation of the SALT score is that it does not take into consideration the possible involvement of other anatomical areas, a finding related to disease severity and prognosis (see section prognosis). Researchers have introduced newer scores, which add on the SALT, to try to accommodate this limitation. For example Lee et al. recently introduced a new method for describing AA to improve patient characterization, which also factors in the extra-scalp manifestations, including eyebrow, eyelash, mustache, beard, axillary, pubic, and other involvement [59]. This method takes into account the extent of scalp involvement (SALT), the pattern of scalp AA, the number of other anatomical sites involved, and the extent of their involvement. Similarly, Jang et al. developed the *Alopecia Areata Progression Index* (AAPI) for the evaluation of the overall hair loss activity in AA patients with pigmented hair, by adding on clinical findings associated with hair loss (that is, pull test and dermatoscopy findings) [60].

In conclusion, in the everyday clinical practice, the calculation of the SALT score, the identification of other involved anatomical sites, and the inspection of the nails for AA-related lesions, are essential elements in assessing disease severity.

Comorbidities and associated autoimmune diseases

Evidence shows an association of AA with various diseases, summarized in Table 4. Multiple autoimmune diseases have been associated with AA including autoimmune thyroid disease, vitiligo, lupus erythematosus, psoriasis and rheumatoid arthritis. Their association has been supported by various retrospective studies, systematic reviews and genetic research which altogether point out to the possibility of shared molecular pathways among some of these diseases [61, 62]. Alopecia areata patients have a higher risk of autoimmune thyroid disease, positive thyroid autoantibodies, abnormal findings on thyroid function tests and thyroid dysfunction. Interestingly, it appears to be a stronger association between AA and positive thyroid antibodies (TPO-Ab, TG-Ab) than between AA and a clinical or laboratory thyroid abnormality [63].

Alopecia areata is associated with other autoimmune diseases (for example, thyroid disease, vitiligo, LE), atopy, and psychiatric disorders (for example, anxiety, depression).

Furthermore, an increased atopic diathesis has been observed among AA patients, with atopic dermatitis, allergic rhinitis, allergic conjunctivitis and asthma being more prevalent in AA patients [64–66]. The association of AA with diabetes mellitus has been investigated but results are still controversial [67–69]. Other morbidities that seem to be more prevalent in patients with AA include vitamin D deficiency, iron deficiency anemia, metabolic syndrome, infection with

Table 4 Comorbidities reported to be associated with alopecia areata.

Most common comorbidities in AA
Autoimmune diseases
– Autoimmune thyroid disease
– Vitiligo
– Lupus erythematosus
– Rheumatoid arthritis
– Psoriasis
Atopy
– Atopic dermatitis
– Allergic rhinitis
– Allergic conjunctivitis
– Asthma
Psychiatric disorders
– Depression
– Anxiety
Other
– Vitamin D deficiency
– Iron deficiency anemia
– Metabolic syndrome
– *Helicobacter pylori* infection

Helicobacter pylori and Down syndrome [69–73]. Additionally, psychiatric disorders are remarkably associated with AA, with depression and anxiety disorder being the most prevalent among them [72, 74, 75].

A relationship between co-existing comorbidities and age of onset of AA has also been observed. Atopic dermatitis is a common comorbidity found at ages under ten years, whereas in individuals over 60, atopic dermatitis and thyroid disease seem to be the most prevalent co-existing diseases [76]. Patients with AT/AU are more likely to have at least one associated disease compared those with patchy AA [68].

In clinical practice, routine blood tests and screening for autoimmune diseases are not recommended for all patients at the time of AA diagnosis, but rather, only to those showing related clinical signs or symptoms [53, 77]. In pediatric patients though, routine thyroid function screening should be additionally considered in case of medical history of atopy or Down syndrome or a family history of thyroid disease [77].

Screening for co-morbidities in the absence of related signs or symptoms is not recommended in adults.

Prognosis

Alopecia areata is a chronic disease with an unpredictable and variable course, which over time may include relapses, remissions or the persistence of severe hair loss.

Alopecia areata is a chronic disease with an unpredictable and variable course, which over time may include relapses, remissions or the persistence of severe hair loss. Therapeutic interventions do not seem to affect the long-term course of AA [78]. After the first episode approximately 50 % of the patients will spontaneously recover within one year. However, a relapse rate of up to 85 % has been reported, which reaches 100 % when observed long-term [79]. The primary prognostic factor is disease severity (that is, extent of hair loss) [80, 81]. The clinical presentation of AT, AU, the ophiasis pattern and nail involvement are considered poor prognostic signs, indicating poor hair regrowth rates, treatment resistance, and high relapse rates [37, 82–84]. Nail involvement also indicates increased risk of

developing AT/AU [53]. The reported recovery rate of AT and AU was less than 10 % in previous decades, whereas it has climbed to about 17 % in the diphenylcyclopropenone (DPCP) era [79, 85–87].

The early age of onset is also associated with a more severe disease and poor prognosis [80, 83, 88]. On the other hand, the disease severity and activity, the duration of the current episode and the rate of relapses seem to decrease when the onset age is older [78, 89]. Other poor prognostic factors are therapy resistance, the long intervals between disease onset and therapeutic management, and persistent hair loss [84, 90]. Positive family history of AA, co-existence of autoimmune or atopic disease, and Down's syndrome, have also been associated with more severe disease and poor prognosis [68, 83, 84, 90–92]. Regarding the positive history of atopy, the data are not conclusive [92, 93].

Diffuse AA and AAI have a more favorable prognosis than patchy AA, characterized by lower relapse rates and good treatment response. These patients rarely develop the typical AA patches [34, 94]. Notably, recovery from DAA has been reported within six months, regardless of the treatment method [32, 54]. Although the potential for remission in AA decreases over time [53, 95], the HF regenerative ability in AA is preserved, so that the possibility of hair regeneration, after the inflammation subsides, theoretically remains.

Therapeutic options in Alopecia areata

All current therapies offer poor response and high relapse rates especially in severe disease.

Current therapies for AA aim to immunosuppress or immunomodulate the activity of the disease, with generally unsatisfying responses and high relapse rates, especially in more severe cases. Due to the unpredictable course of the disease and the spontaneous remissions often observed within the first year, therapy efficacy is difficult to estimate. Additionally, the available therapeutic options do not seem to influence the long-term course of the disease, and thus an urgent need remains for novel, more effective therapies. New insights into the pathophysiologic mechanisms in AA are leading researchers to the development of more targeted therapeutic approaches.

There is unmet need for new targeted therapeutic options in AA.

In 2003 the British Association of Dermatologists published the first evidence-based guideline on therapeutic management of AA, revised in 2012 [81]. Only topical and intralesional corticosteroids, and topical immunotherapy (i.e. DPCP) achieved an adequate evidence level. In 2020 an alopecia areata expert consensus study was published summarizing international expert opinion on treatments for alopecia areata [96], and reflecting the currently practiced approaches in AA. From the current therapeutic options used for treatment of AA none is explicitly approved for treating AA. In 2019 the Federal Joint Committee (G-BA) classified betamethasone acetate and triamcinolone as lifestyle-drugs when used for treatment of AA, thus they may no longer be prescribed at the expense of the statutory health insurance system in Germany.

Corticosteroids

Topical Corticosteroids

Topical corticosteroids are a first-line therapy for limited patchy AA, for children < 12 years regardless of disease severity, and as an adjunctive therapy in severe AA.

Topical corticosteroids are widely used in the treatment of limited patchy AA and as a first-line therapy for children, because of their low side-effect profile, when used discerningly. They are also recommended as an adjunctive therapy in more severe forms [96]. A broad spectrum of topical galenic formulations of corticosteroids is nowadays available, such as solutions, shampoos or foam preparations

[52]. Clobetasol propionate foam was reported to be a safe and well-tolerated treatment for AA, with good cosmetic acceptance and compliance, and optimized effects under occlusion [97]. In a recent study of 43 patients receiving 0.05 % clobetasol propionate lotion, 85 % of patients with patchy AA experienced more than 80 % of hair regrowth, whereas ~ 57 % of AT, and 80 % of AU patients had no response [98]. In a study on the efficacy of clobetasol propionate 0.05 % in long-lasting AT and AU, 28.5 % of the patients were treated successfully, and only 18 % maintained hair regrowth [99]. Betamethasone valerate foam is also an effective treatment in mild to moderate AA [100].

In children < 12 years, moderate-strength topical corticosteroids (for example, mometasone furoate, methylprednisolone aceponate) should be preferred due to their good therapeutic index.

Adverse effects include folliculitis and rarely, skin atrophy, which is in most cases reversible.

Intralesional injection of corticosteroids

Intralesional injection of corticosteroids is a first-line recommendation for the therapy of limited patchy AA, alone or combined with topical corticosteroids.

Intralesional injection of corticosteroids is a first-line recommendation for the therapy of limited patchy AA, alone or combined with topical corticosteroids [81, 96]. The preferable corticosteroid is triamcinolone acetonide. Usually, a series of 3 to 5 sessions is performed every 4–6 weeks. If needed, however, more injections may be performed in the absence of adverse effects. During each session, triamcinolone acetonide 10 mg/ml (crystal suspension) is diluted in physiological saline solution or local anesthetic 1 : 1 and intracutaneously injected in little droplets to avoid atrophy. Injections are performed with a thin needle (27 G), preferentially within the border of the lesions to limit progression. The maximum amount of injected triamcinolone acetonide should not exceed 1.5–2 mg per cm^2. Injections in the eyebrows and beard area should only be performed by experienced doctors, while droplet injections should not exceed 1 mg/cm^2. In responders, hair regrowth is expected to start in about 4–8 weeks [101, 102], while in case of no response after 3–4 sessions, therapy should be discontinued.

The efficacy of intralesional steroid injections has been investigated mainly in limited AA, showing a hair regrowth of > 50 %, ranging from 56 % to 97 % [93, 101–103]. However, in a retrospective review of ten patients with extensive AA (SALT > 50 %) the reported treatment response was 60 % [104]. Intralesional injections seem to be more beneficial in patients with active disease [104].

A recent systematic review and meta-analysis on the efficacy of different concentrations of intralesional triamcinolone acetonide in patchy AA reported that at 5 and 10 mg/mL concentrations the hair regrowth rates were comparable, whereas lower rates occurred at concentrations < 5 mg/ml [105]. Information on relapse rates in the literature is limited.

The most common side effect is mild pain during the injection, and development of skin atrophy which is in most cases reversible [101, 103, 104]. When injecting at the eyebrows, there is a risk of elevated intraocular pressure [106].

Systemic corticosteroids

Long-term use of systemic corticosteroids is not advisable because of the potential side-effects; patients should be monitored.

Systemic corticosteroids have been used in the treatment of AA as oral pulse therapy (PT), intravenous (IV) PT, intramuscularly (IM) or continuously (CT). The reported therapeutic schemes vary between studies [107–110]. Thus, results are difficult to compare, with an efficacy varying from 28 to 84 % [111–113], and with ophiasis

type, AT and AU showing rather unsatisfactory response rates. [108, 114] Depending on the follow-up period, relapse rates were reported between 25 and 75 % [113]. In a comparative study, CT was reported to be less effective than PT and IM, with the latter modality being the most effective [115]. A placebo-controlled trial on oral PT found significant response in 40 % of the prednisolone-treated group and 25 % relapse in 3 months [116]. Even-though no serious or long-term side effects of PT have been reported in the literature, also in children [108, 117–119], the well-known side effects of steroids constitute an obstacle for their wider and long-term use in AA.

Oral corticosteroids are considered an appropriate first-line treatment for moderate to severe AA in adults (SALT > 30 %), alone, or combined with topical corticosteroids.

Oral corticosteroids are considered an appropriate first-line treatment for moderate to severe AA in adults (SALT > 30 %), alone, or combined with topical corticosteroids [96]. In daily practice, a starting dose of 1 mg oral PT/kg body weight, tapered off over eight days, and followed by a 3-week application of topical corticosteroid was proven to be quite effective; this course should be repeated at least 3–4 times. Oral or IV PT often appears unsuccessful during the acute phase, when the hair cycle is interrupted and hair falls out; however, it can stimulate and shorten the period until regrowth.

Topical Sensitization Therapy

Topical sensitization with DPCP is recommended for long lasting (> 2 years) extensive AA, AT, and AU, with its use being off-label [81]. In this modality, the sensitizer DPCP is applied to induce allergic contact dermatitis that enables hair regrowth through an as yet unknown mechanism of action. It is possible that this occurs due to antigenic competition that leads to topical immunomodulation [120]. Other contact sensitizers, for instance squaric acid dibutylester (SADBE) and dinitrochlorobenzene (DNBC), have been used as alternatives or replacements in cases of no response to DPCP, though the latter remains the most frequently used in specialized hair centers globally.

Topical sensitization with DPCP is recommended for long lasting (> 2 years) extensive AA, AT and AU.

Patients are first sensitized with a 2 % DPCP solution applied to a small area (2 cm^2) of the scalp. Subsequently, slowly ascending DPCP concentrations, starting from 0.001 % solution, are applied weekly, until a mild allergic contact dermatitis lasting 24–48 hours is achieved. The therapy is then continued using the appropriate concentration once weekly. Treatment response, with the beginning of hair regrowth, is to be expected after approximately four months of treatment. Topical DPCP application is then continued until the maximum response is achieved, followed by a maintenance therapy with longer spaced intervals [52]. Cases with relapse after therapy discontinuation or due to prolonged intervals usually respond well to re-initiation of DPCP therapy [81]. In case of no response, therapy should be discontinued after 6 months.

According to a recent systematic review and meta-analysis the DPCP therapy response rate for any hair regrowth was 65.5 % (74.6 % in patchy AA and 54.5 % in AT/AU), ranging widely within studies (4–85 %), whereas the complete hair regrowth rate was only 32.3 %.

Response rates range greatly (4–85 %); relapse rates after discontinuation are high.

Relapse rates were 38.3 % among patients receiving maintenance treatment and 49.0 % among those not receiving one [121]. AT/AU have less favorable therapy responses compared to patchy AA, with AU having the poorest response [122, 123]. In a large trial including 148 patients, only 17.5 % of AT/AU patients experienced hair regrowth, while 62.6 % experienced relapses within three years [123]. DPCP can be also used in children although clinical studies show poor response and high relapse rates [124, 125]. The age limit varies, but most frequently is ≥ 12 years of age.

Adverse effects include occipital or cervical lymphadenopathy, severe dermatitis up to bullous or urticarial reactions, hyperpigmentation, depigmentation, and flu-like symptoms [121, 126]. Erythema multiforme-like reactions, fever and headache are less frequently reported [126].

Topical irritation therapy

Anthralin is an alternative of DPCP in severe AA, especially in children, because of its fewer side effects and the possibility for self-treatment at home.

Anthralin is an alternative of DPCP in extensive AA or in AT, especially in children, because of its fewer side effects, but may also be performed in adults. The topical application of anthralin causes irritant dermatitis that promotes hair regrowth through a yet unknown mechanism of action. The advantage is that it can be used at home, in concentrations ranging from 0.5–1 %, applied nightly in gradually increasing periods, from ten minutes up to overnight. Escalation of dosage or time is performed once the anthralin-induced mild dermatitis has resolved. Response is usually seen after 3–4 months [127, 128]; in that case treatment should continue for longer. There are only a few studies on the efficacy of anthralin as monotherapy; the response rates reported in patchy AA are 75 % [129], and in severe AA and AT range from 18–37 % [127, 130, 131]. Moreover, a study on children with AA reported complete hair regrowth in 33 % of the cases [132].

Adverse effects include severe irritation and discoloration of skin, fair hair, and clothing upon contact. However, many patients appreciate the possibility of self-treatment at home and the fact that the treatment is not associated with specific long-term alterations of the immune system compared to topical sensitization therapies.

Other investigated therapies

Methotrexate

Methotrexate might be considered as an adjunctive treatment for severe AA in adults and in children > 12 years, when standard therapies have failed.

The efficacy of methotrexate (MTX) in severe AA appears to be moderate, with response rates ranging from 38–64 % [133–136], whereas its combination with oral corticosteroids has been reported to be more effective [137–141]. MTX is usually administered over longer periods while relapse rates after discontinuation are high [135, 138, 142, 143]. Most studies reported minimal or no serious adverse events, including those on pediatric patients [142–144]. However, there is still a lack of conclusive evidence on the efficacy and safety of this modality, and its use should be considered only in individual patients with severe disease resistant to standard therapies and accompanied by significant psychological burden. There is consensus that MTX can be administrated to adolescents aged 13 to 18 years [96].

Further systemic treatments

Cyclosporine A monotherapy or combined with oral corticosteroids seems to have moderate effect in severe AA [145]. However, considering its risk profile, it's use in AA should be avoided. The use of azathioprine and sulfasalazine is generally not recommended, while dapsone is unsuccessful in treating AA [96]. Evidence for the efficacy of apremilast and simvastatin/ezetimibe is scarce and does not appear promising [146–149].

Tumor necrosis factor (TNF) inhibitors have failed to demonstrate success in the treatment of AA; reports have even demonstrated a first manifestation of AA in patients during anti-TNF therapy [150–152]. Conflicting are the data regarding dupilumab, which has been shown to induce hair regrowth in patients

with co-existing AA who had been treated for moderate to severe atopic dermatitis [153–155]. However, there are also case reports describing first onset of AA under therapy with dupilumab [156, 157]. Interestingly, the monoclonal antibodies alemtuzumab and ocrelizumab are also suspected to induce AA in patients receiving treatment for multiple sclerosis [158, 159].

Phototherapy

Psoralen plus ultraviolet A (PUVA) therapy has shown a response in some studies [160], but no effect in others [160, 161]. Given the high relapse rates and the fact that prolonged and repeated courses would result in unacceptably high cumulative UVA doses, this modality with limited success rates cannot be recommended.

The effectiveness of excimer laser in treating AA has been investigated in a few studies and was recently reviewed in a systematic review and meta-analysis [162]. Although it appeared to produce a favorable therapeutic response, with 50.2 % of the patients achieving cosmetically acceptable hair regrowth, the evidence base is limited.

Topical calcineurin inhibitors

Topical tacrolimus has demonstrated unsatisfying results in the treatment of AA [163], though off-label application on the eyebrows is frequently used in daily practice to avoid long-term topical use of steroids on facial skin.

Prostaglandin $F_{2\alpha}$ analogues

Topical bimatoprost and latanoprost have shown moderate efficacy in some studies [164, 165], while no response was observed in others [166]. However, they can be tried as an individual treatment approach for eyelash AA [96].

Platelet-rich plasma

The use of platelet-rich plasma (PRP) for the treatment of AA has been suggested in few studies and case reports, however, robust and convincing evidence is lacking [167, 168]. A recent randomized controlled trial on 27 patients showed PRP to have limited efficacy in AA, but may possibly play a role in restoring immune balance in the alopecic patches [169].

Supportive interventions

Topical minoxidil

The use of minoxidil is limited in enhancing hair growth after the inflammation is reversed by other therapies.

In daily practice minoxidil is frequently used for the management of patchy AA [170]. However, it should be kept in mind that topical minoxidil has no anti-inflammatory effect. It is mainly used to enhance hair growth as a co-medication with other treatments which are able to stop or reverse the inflammatory infiltrate [171].

Oral vitamin D and zinc supplementation

The efficacy of oral zinc and vitamin D remains controversial.

The efficacy of oral zinc and vitamin D remains controversial, and the literature mainly consists of small case-control studies and case-reports, with conflicting results on the role of such micronutrients in the treatment of AA. Though zinc deficiency is not common among AA patients [172, 173], lower serum zinc levels

have been observed in AA patients compared to controls, and were significantly lower in patients with resistant AA compared to newly diagnosed AA [174]. The rationale for supplementing zinc orally in AA is mainly based on its immunological effects. Furthermore, serum zinc level correlated inversely with disease duration, severity of AA, and its resistance to therapies. In a double-blinded, cross-over study, researchers evaluated oral zinc sulfate (5 mg/kg/day) for the treatment of AA in 100 patients, resulting in complete hair regrowth in approximately 60 % of patients after 3 months, compared to only 10 % in the placebo group [175]. Therefore, daily oral supplementation of 50–100 mg zinc gluconate, zinc aspartate or zinc sulfate for 2 to 3 months may be safe and beneficial.

Lower serum zinc levels have been observed in AA, but most frequently daily oral supplementation of 50–100 mg zinc is given due to its beneficial immunological effect.

Considering the high prevalence of vitamin D deficiency in AA patients, screening and supplementing accordingly may be of relevance.

The importance of Vitamin D receptor in hair development is demonstrated in patients with hereditary vitamin D-resistant rickets who develop hair loss [176, 177]. However, the exact role of vitamin D in HF cycling remains unclear [178, 179]. A large prospective study with 12 years of follow-up found no significant association between dietary, supplemental, or total vitamin D intake and incident AA [180]. Considering the high prevalence of vitamin D deficiency in AA patients [172], and even the general population [181], screening patients for Vitamin D deficiency and supplementing accordingly might be of relevance [182]. Interestingly, there are preliminary reports on the safe and effective topical use of calcipotriol in AA [183, 184].

Emerging therapies

JAK Inhibitors

In AA the JAK-mediated IFN-γ and IL-15 production, promotes an inflammatory feedback loop that further contributes to local inflammation.

JAK inhibitors inhibit the JAK enzymes, interfere with the JAK-STAT signaling pathway, and block the downstream signaling of different cytokines.

JAK inhibitors represent an emerging treatment option for AA.

Local inflammation in AA is largely mediated by the JAK-STAT pathway, which is further described in Figure 7 [26, 185, 186]. In AA, we have an overexpression of pro-inflammatory cytokines, which signal through their receptors via the JAK/STAT pathway. This results in JAK-mediated IFN-γ and IL-15 production, which promotes the inflammatory feedback loop that further contributes to local inflammation [187] (Figure 7a). Considering the crucial role of JAK-STAT pathway in mediating the $CD8^+$ $NKG2D^+$ T-cell response, a major component of AA pathogenesis, it is no surprise that JAK inhibitors (JAKis) represent an emerging treatment option for AA [187, 188]. JAK inhibitors are small molecules that inhibit the JAK enzymes, interfere with the JAK-STAT signaling pathway, and thereby block the downstream signaling of different cytokines [189] (Figure 7b).

The efficacy of several JAKis in AA is currently being investigated in clinical trials (Table 5), some of which have already demonstrated promising results. Oral administration of 5 mg tofacitinib showed a response greater than 50 % in 32 % of the patients with severe AA, AT, and AU. Relapse was reported 8.5 weeks after drug cessation [190]. Another study in which higher doses (5–10 mg) were administered showed a response in approximately 67 % of the patients, with relapses being observed from two to six months after the end of therapy [191]. No serious side effects were observed in either study. Oral ruxolitinib also showed good response in moderate to severe AA. 75 % of the patients demonstrated an average hair regrowth of 92 %, and the drug was shown to be safe and well tolerated [192].

A comparative study on the efficacy of oral tofacitinib and ruxolitinib in patients with severe AA, AT and AU, showed that both drugs induced an excellent response (> 75 %) in about 65 % and 68 % of the patients respectively, while the relapse rate at three months was about 70 % in both groups. Interestingly, the mean duration of hair regrowth was shorter in the ruxolitinib treatment group [193].

The efficacy of the topical use of tofacitinib and ruxolitinib has been investigated in a pediatric population. The treatment, which was reported to be safe and well tolerated, yielded hair regrowth in 80 % of cases [194]. Very recently, a yet

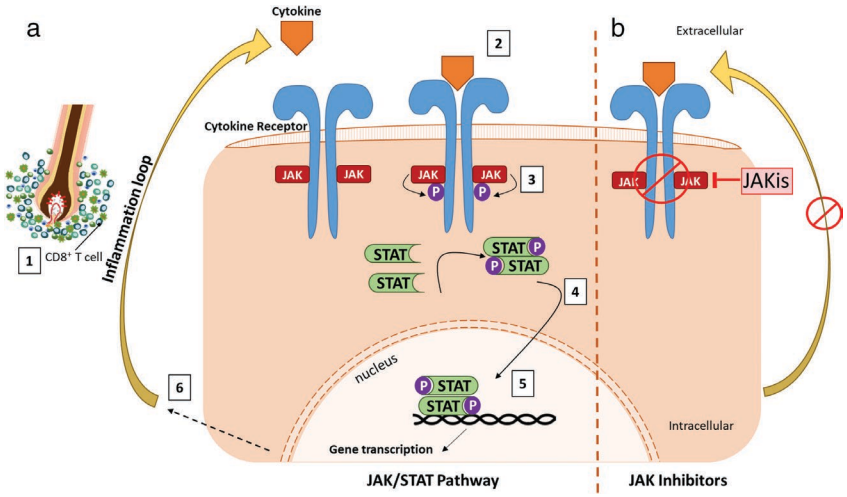

Figure 7 A simplified schematic illustration of the JAK/STAT pathway and the role of JAK inhibitors. In JAK-STAT mediated signal pathways, binding of cytokines to their type I and II receptors, kicks off an inflammatory response. The JAK family contains three JAKs (JAK1–3) and one tyrosine kinase 2 (TYK2), and the STAT family contains seven STATs (STAT1-4, STAT5A, STAT5B, and STAT6). Depending on the ligand and the receptor, different combinations of JAKs and STATs are activated. (1) In alopecia areata, the activated CD8+ NKG2D+T cells release IFN-γ and promote the production of IL-15 through JAK1 and JAK2. Then IL-15 binds to its receptor on $CD8^+$ T cells and induces JAK1- and JAK3-mediated IFN-γ production, which further promotes the inflammatory feedback loop. (2) When the ligand (for example, IFN-γ or IL-15) binds to its receptor, (3) the JAKs are activated through transphosphorylation and phosphorylate the receptor. (4) This attracts STAT proteins, which bind to the receptor and phorphorylate. They then become active and undergo dimerization. (5) The activated STAT dimer then translocates into the nucleus, acting as a transcription regulator, modulating gene expression. (6) These eventually promote the production of (pro-)inflammatory cytokines, which through a positive feedback loop, further enhance the inflammation (a). JAK inhibitors interfere with this pathway by blocking the enzymatic activation of the JAKs, and thus the subsequent STAT activation. As the inflammation loop is then disrupted, the topical inflammation eventually subsides (b).

to be published phase 3 clinical trial on the efficacy and safety of oral baricitinib on AA was reported to have met the primary efficacy endpoint, demonstrating a statistically significant improvement in scalp hair regrowth compared to placebo [195]. Several other phase 2 and 3 trials on CTP-543 (deuterated ruxolitinib), PF-06651600 and jaktinib are currently active.

Although JAKis are not approved for AA, there is an increasing number of approvals for other diseases (Table 5). Therefore, they should at least be included in the therapeutic considerations for AA patients when the associated diseases are also present.

The therapeutic algorithm for AA is summarized in Figure 8.

Emotional burden

Given the high visibility, unpredictable clinical course of the disease, and current lack of curative therapies, AA in the majority of cases creates a significant psychosocial burden for patients. Even though it can be challenging at any age, children and adolescents are especially vulnerable to bullying and social isolation by their peers [196, 197].

Table 5 Investigation of JAK inhibitors in alopecia areata and related studies (clinicaltrials.gov, status 15.10.2021).

Drug name	Inhibits	FDA approved indications	EMA approved indications	Study				
				Administration	Condition	Phase	Study number	Status
Tofacitinib	JAK1, JAK3	RA, PsA, Ulcerative colitis	RA, PsA, Ulcerative colitis, pJIA	Oral	AA	IV	NCT03800979	Completed
					AA, AT, AU	N/A	NCT02312882	Completed
						II	NCT02299297	Completed
						II	NCT02197455	Completed
				Topical		II	NCT02812342	Completed
Ruxolitinib	JAK1, JAK2	Myelofibrosis, Polycythemia vera, aGVHD, cGVHD	Myelofibrosis, Polycythemia vera	Topical	AA, AT, AU	II	NCT02553330	Terminated
				Oral	AA	II	NCT01950780	Completed
Baricitinib	JAK1 JAK2	RA, COVID-19[1]	RA, AD	Oral	AA, AT	III	NCT03899259	Active, not recruiting
						II/III	NCT03570749	Active, not recruiting
CTP-543 (deuterated Ruxolitinib)	JAK1 JAK2	–	–	Oral	AA, AT	III	NCT04797650	Recruiting
						II	NCT03941548	Completed
						II	NCT04784533	Recruiting
						II	NCT03811912	Completed
						III	NCT04518995	Recruiting
						II/III	NCT03898479	Recruiting
						II	NCT03137381	Completed
PF-06651600	JAK3	–	–	Oral	AA, AT, AU	II	NCT04517864	Active, not recruiting

Continued

Table 5 Continued.

Drug name	Inhibits	FDA approved indications	EMA approved indications	Study				
				Administration	Condition	Phase	Study number	Status
						III	NCT04006457	Recruiting
						III	NCT03732807	Completed
					AA, AT	II	NCT02974868	Completed
PF-06700841	JAK1 TYK2	–	–	Oral	AA, AT	II	NCT02974868	Completed
Jaktinib Hydrochloride	JAK1 JAK2 JAK3	–	–	Oral	AA, AT	II	NCT04034134	Recruiting
LEO 124249 (Delgocitinib)	PanJAK	–	–	Topical	Eyebrow AA	II	NCT03325296	Terminated
					AA, AT, AU	II	NCT02561585	Completed
ATI-501	JAK1 JAK3	–		Oral	AA, AT, AU	II	NCT03594227	Completed
ATI-502	JAK1 JAK3	–	–	Topical	AA, AT, AU	II	NCT03759340	Terminated
ATI-50002	JAK1 JAK3	–	–	Topical	AA	II	NCT03354637	Terminated
					Eyebrow AA	II	NCT03551821	Completed
					AT, AU	II	NCT03315689	Completed

Abbr.: RA, Rheumatoid arthritis; PsA, Psoriatic arthritis; AA, Alopecia areata; AT, Alopecia totalis; AU, Alopecia universalis; AD, Atopic dermatitis; pJIA, polyarticular juvenile idiopathic arthritis; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; COVID-19, coronavirus disease 2019.
1Emergency Use Authorization (EUA).

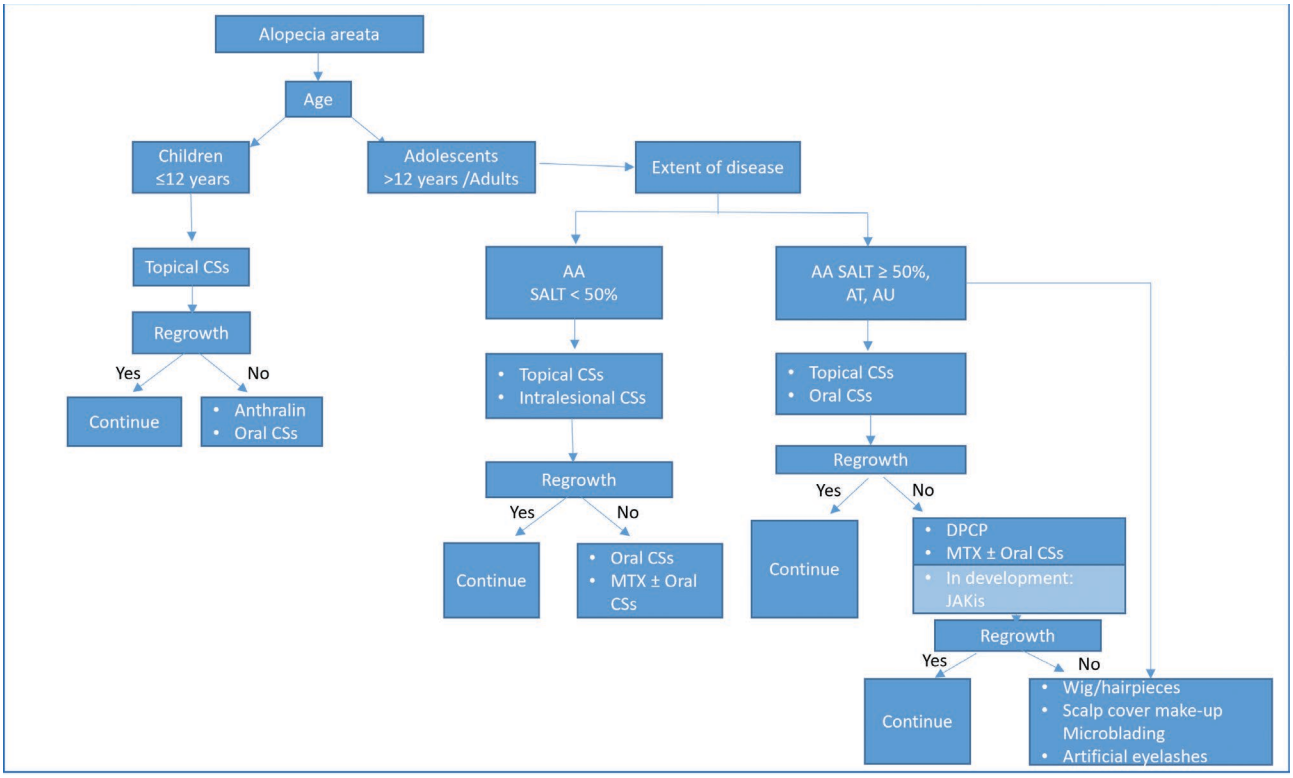

Figure 8 Therapeutic algorithm of alopecia areata.
Abbr.: AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; CS, corticosteroids; MTX, methotrexate; JAKis, janus kinase inhibitors.

AA patients experience a compromised quality of life and have a higher lifetime prevalence of depression and generalized anxiety disorder.

Systematic psychiatric evaluations and professional support might be required, especially in severe AA, and for pediatric patients and their parents.

Patients suffering from AA may experience a compromised quality of life [198], and have a much higher lifetime prevalence of psychiatric disorders such as depression and generalized anxiety disorder [6, 199]. Therefore, the physician has a crucial role in recognizing the psychological impact of alopecia in order to help patients overcome and adapt to this issue in a timely manner and to set realistic long-term expectations [200]. To do so, systematic psychiatric evaluations and professional support from a clinical psychologist or patient support organizations might be required, especially for patients with severe AA and for pediatric patients and their parents [200, 201].

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Conflict of interest

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CME Questions/Lernerfolgskontrolle

1. Which clinical type is the most common in alopecia areata?
a) Patchy alopecia areata
b) Alopecia universalis
c) Alopecia areata of the nails
d) Ophiasis alopecia areata
e) Alopecia totalis

2. What is the most typical histological finding in a scalp biopsy of alopecia areata in the acute phase?
a) Infundibular hypergranulosis
b) Pilosebaceous unit damage and dermal fibrosis
c) Follicular inflammatory cell infiltrate around the bulb area
d) Hyperkeratosis with verrucous papillomatosis
e) basal cell vacuolization and dermo-epidermal junction obstruction by T cells

3. Alopecia areata of the nails most commonly presents with ...
a) Parakeratosis pustulosa
b) Nail pitting
c) Onycholysis
d) Leukonychia
e) Onychogryphosis

4. What are the most typical dermatoscopic findings in alopecia areata patients?
a) Brown peripilar sign, white peripilar sign, yellow dots
b) Focal atrichia and scalp honeycomb pigmentation
c) Perifollicular scaling, loss of follicular ostia, milky-red areas and perifollicular erythema
d) Upright hairs, tapered hairs, pigtail hairs and Pohl-Pinkus constrictions
e) Yellow dots, black dots, broken hairs, exclamation mark hairs, and vellus hairs

5. Which is a favorable prognostic factor for alopecia areata?
a) Disease onset in childhood
b) Alopecia totalis
c) Other coexisting autoimmune diseases
d) Late disease onset
e) Ophiasis alopecia areata

6. What is the first line treatment for patchy alopecia areata in children under twelve years?
a) Topical corticosteroids
b) Pulse therapy with oral corticosteroids
c) Topical immunotherapy with DPCP
d) Oral cyclosporine A
e) Oral methotrexate

7. What is the recommended treatment for limited patchy alopecia areata in adults?
a) Intralesional ± topical corticosteroids
b) Topical immunotherapy with DPCP
c) Oral PT with corticosteroids ± MTX
d) Minoxidil
e) PUVA therapy

8. Which event plays a critical role in the pathophysiology of alopecia areata?
a) Hair follicles are subjected to prolonged or repetitive tension.
b) Immune privilege collapse of the bulge area of the hair follicle
c) Immune privilege collapse of the bulb area of the hair follicle
d) Administered radiation or chemotherapy
e) There are still no insights in the pathophysiology of the disease.

9. How is the mechanism of action of JAK inhibitors in the treatment of alopecia areata?
a) They block the activation of the JAK and STAT proteins, thus they interfere with the JAK-STAT signaling pathway and block the downstream IFN-γ and IL-15 inflammatory signaling.
b) They inhibit AICAR that results in the release of adenosine in the extracellular space, which inhibits white blood cell accumulation and reduces the TNFα and IFN-γ production.
c) They have a systemic immunosuppressive effect, by reducing the activity and the volume of the immune system in the body.
d) JAK inhibitors block the metabolism of cortisol.
e) They are able to preserve the immune privilege of the hair follicle.

10. Which disease is not amongst the most common comorbidities in alopecia areata patients?
a) Depression
b) Autoimmune thyroid disease
c) Diabetes mellitus
d) Atopic dermatitis
e) Vitiligo

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31. März 2022. Die richtige Lösung zum Thema „Morbus Darier und Morbus Hailey-Hailey: Update 2021“ in Heft 10 (Oktober 2022) ist: 1a, 2d, 3c, 4b, 5b, 6b, 7e, 8a, 9a, 10d.

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