LEADING ARTICLE

New and Emerging Therapies for Alopecia Areata

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Abstract

Alopecia areata (AA) is an autoimmune condition that affects up to 2% of the general population. Currently available treatment options for AA are of limited efficacy and can be associated with adverse effects. The advancement in understanding of the genetic and molecular mechanisms of AA has led to the development of novel treatment options, with the Janus kinase (JAK) inhibitor class of drugs at the forefront of ongoing clinical trials. Platelet-rich plasma, fecal transplants, and cytokine-targeted therapy with ustekinumab and dupilumab have also been shown to regrow hair in patients with AA in individual case reports or small studies. Several other novel therapies have preliminary data or are being tested in clinical trials.

Key Points

Alopecia areata (AA) is a chronic autoimmune disease of multifactorial etiology.

The limited utility of traditional treatments for AA is compounded by their negative side effect profiles.

Recent developments in the understanding of the pathophysiology of AA have identified targets for treatment using promising novel therapies including Janus kinase (JAK) inhibitors, dupilumab, and ustekinumab.

1 Introduction

Alopecia areata (AA) is an autoimmune, non-scarring hair loss disorder affecting up to 2% of the general population [1]. AA can present in several patterns, from episodes of well-defined patches on the scalp to more extreme, irreversible, complete scalp and total body hair loss. The chronic relapsing–remitting nature and pathophysiology of AA has made it a notoriously difficult condition to manage and study in clinical trials.

Recent insights into the pathogenesis of AA have led to the development of promising treatments. Traditional systemic therapies such as corticosteroids and other immunomodulators, which have varying responses and unwanted side effect profiles, are being replaced with novel therapies. Janus kinase (JAK) inhibitors have emerged on the forefront of interest as they are expanded beyond the treatment of rheumatoid arthritis (RA) and psoriasis and into the realm of AA. Outside of those pathways, medications such as ustekinumab and dupilumab have been shown to regrow hair in small numbers of patients with AA [2, 3]. Also, non-traditional treatments options for AA, including platelet-rich plasma (PRP) injections and other emerging therapies, are described.

2 Pathophysiology

The concept of loss of immune privilege of the hair follicle is thought to play a major role in AA [4]. The target antigen is not clearly defined, but melanocytes are often targeted by the immune system and are involved during the active pigment production phase of the anagen phase of the hair cycle. Downregulation of major histocompatibility complex (MHC) class I expression in anagen hair bulbs is thought to sequester autoantigens from being presented to CD8 + T cells. Local production of immunosuppressant molecules such as transforming growth factor (TGF)-β1, interleukin (IL)-10,

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and α-melanocyte-stimulating hormone (MSH) are also thought to contribute to this immune privilege [4]. Triggers such as stress or trauma to the skin can cause increased intrafollicular secretion of interferon (IFN)-γ, which induces T helper (Th)1 chemokines CXC motif ligand 10 (CXCL10) MHC class I expression leading to cytotoxic T (Tc)1 and Th1 cells accumulation around hair bulbs. The subsequent loss of hair follicle immune privilege results in the recognition of hair follicle autoantigens by autoreactive CD8 + T cells [5]. The subsequent autoimmune attack of anagen follicles results in prematurely entering catagen phase [6].

Studies in mouse models of AA have shown that cytotoxic CD8 + Natural Killer Group 2D (NKG2D) + T cells produce IFN-γ, which signals via JAK1 and JAK2 to stimulate the production of IL-15 in the hair follicle. IL-15 then binds to the CD8 + T cells, further stimulating production of IFN-γ via JAK1 and JAK3 signaling. Human AA lesion biopsies have shown overexpression of the signaling of IFN-γ, JAK3, and, to a lesser degree, JAK1 and JAK2 [7, 8]. Insight into these and other pathways has led to the investigation of selective immune-modulating drugs targeting various cytokines and immune axes involved in AA.

3 Treatment

The management of AA should focus on both regrowth and maintenance of hair growth. The unpredictable course of remission and relapses creates difficulty when predicting treatment success and prognosis. This also creates a challenge when designing clinical trials to evaluate efficacy of treatments for AA. Given the chronic nature of AA, most therapies lose efficacy after being discontinued.

3.1 Traditional Drugs Treatments

The great need for novel therapies for AA is due to the limited efficacy provided by most currently available treatments, especially in cases of extensive hair loss (see Table 1 for traditional treatment modalities used for AA). The first-line treatment for most patients with patchy AA is a local corticosteroid, primarily via intralesional injections. Intralesional triamcinolone acetonide 5–10 mg/mL injected locally every 2–6 weeks results in localized hair growth in about 60% of treated sites [9]. Adverse effects include localized atrophy and hypopigmentation and relapses often occur [10]. Topical corticosteroids have limited benefit in patchy AA and can be associated with folliculitis [11]. Systemic corticosteroids are also sometimes used to regrow hair in extensive cases [12].

Table 1 Traditional treatment modalities used for alopecia areata

Treatment	Common adverse effects and limitations
Topical corticosteroids [11]	Folliculitis, atrophy, telangiectasia
	Ineffective for AT and AU
Intralesional corticosteroid [10]	Local cutaneous atrophy
	Requires multiple treatments
	Potential Cushingoid features
	Painful
Systemic corticosteroids [12, 30]	Limited efficacy in AT and AU
	Weight gain, Cushing's disease, hypertension, osteoporosis
Contact immunotherapy [13, 30, 31]	Limited efficacy in AT and AU
	Requires prolonged treatment
	Associated with significant dermatitis, edema, urticaria, influenza-like symptoms
	Other adverse effects include hypopigmentation, hyperpigmentation, and symptomatic lymphadenopathy
	Can cause sensitization in healthcare providers
Anthralin [30]	Regional lymphadenopathy, contact dermatitis, folliculitis, local pyoderma
Topical minoxidil [17, 30]	Local irritation
	Less effective in patients with extensive AA
Cyclosporine [30]	Abnormal liver function tests, nephrotoxicity, immunosuppression, abnormal lipid tests
Methotrexate [30]	Nausea, transient hepatic enzyme elevation, leukopenia
PUVA [30]	Nausea, irritation, burning, increased risk of skin cancer
UVB therapy [27]	Erythema, hyperpigmentation, pain and mild itching

AA alopecia areata, *AT* alopecia totalis, *AU* alopecia universalis, *PUVA* Psoralen and ultraviolet A, *UVB* ultraviolet B

Contact immunotherapy using squaric acid dibutylester (DBE) or diphenylcyclopropenone (DPCP) can be effective in cases of patchy AA and alopecia totalis [13]. These therapies induce a contact dermatitis in affected areas and are thought to modulate T cell activity, with variable treatment outcomes [13]. A retrospective data analysis of 50 patients with AA treated with DPCP showed ≥ 50% terminal hair regrowth in 66% of cases [14]. In addition to causing a significant dermatitis in the patient, sensitization can also occur in healthcare providers administering the treatment [13]. Anthralin is another topical immunotherapeutic agent found to adequately treat AA, especially in conjunction with concomitant DPCP [15]. Inhibition of the expression of tumor necrosis factor (TNF)-α and TNF-β was shown in mouse models with AA effectively treated with anthralin [16].

Topical minoxidil therapy is usually an adjunct therapy for AA and tends to work better in less extensive cases [17]. Minoxidil is a vasodilating drug used to treat hypertension and has been associated with hair growth, although the mechanisms of hair growth both in AA and the general population are not well-known [18].

Older immunomodulatory therapies have also demonstrated limited efficacy in the treatment of AA. Methotrexate has been reported to be about 60–70% effective in treating AA, with better response rates occurring when used in conjunction with corticosteroids [19]. Small clinical trials and case reports have shown oral cyclosporine to help regrow hair in some patients with AA through a proposed mechanism of Th cell inhibition [20, 21]. However, a small double-blind, randomized, placebo-controlled clinical trial did not show a difference between cyclosporine and placebo in the treatment of AA [22]. There are variable data on the efficacy of hydroxychloroquine in treating AA [23, 24].

Phototherapy modalities have also been used to treat AA. The effectiveness of Psoralen and ultraviolet A (PUVA) in AA is thought to be due to local immunologic attack through depletion of Langerhans cells. Burns, skin cancer, and a high relapse rate after discontinuation make this therapy less than ideal [25, 26]. Narrow-band ultraviolet B (UVB) and 308 nm UVB excimer laser may also be effective for the treatment of AA [27]. Adverse events include erythema, hyperpigmentation, pain, and mild itching [27]. UVB laser therapy is thought to affect AA through immunomodulation as a result of T cell apoptosis as well as mitochondrial activation-induced oxidative phosphorylation [28, 29].

3.2 Emerging Therapies

Novel therapies for AA are becoming increasingly available as the molecular mechanisms underlying the pathophysiology of AA are elucidated. Many drugs are still undergoing preliminary clinical trials; however, recent treatments that are gaining popularity due to their efficacy and limited side effect profiles are discussed in Sects. 3.2.1–3.2.6.

3.2.1 Janus kinase (JAK) Inhibitors

Involvement of the JAK–signal transducer and activator of transcription (JAK-STAT) pathway in AA as well as the reversal of AA with JAK inhibitors was first demonstrated in mice in 2014 [32]. JAK inhibitors work on the JAK-STAT pathway. There are four JAKs, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), which are expressed in hematopoietic cells [33]. There are seven STATs that bind the phosphorylated cytokine–receptor complex and subsequently undergo phosphorylation by a JAK. The STATs are then translocated to the nucleus where they bind DNA and activate target gene transcription [33]. The JAK-STAT pathway plays a significant role in the maintenance of innate and adaptive immunity and defects can lead to immune-related and hematologic disorders as seen with atopy (STAT6), Behçet's disease (JAK2, STAT3), and systemic lupus erythematosus (TYK2, STAT4) [33].

JAK inhibitors are oral drugs, with convenient dosing regimens that have been demonstrated to be effective and safe in large-scale studies for the treatment of diseases such as RA and psoriatic arthritis [34]. Table 2 lists the JAK inhibitors available on the market and their respective indications. JAK inhibitors are selective but not specific for a single JAK and thus can affect various immunologic pathways [34].

The basis for JAK inhibitor use in AA stems from the understanding of JAK protein kinase pathways implicated in AA, which work as downstream effectors of the IFN-γ and γ_c cytokine receptors [38]. In AA, JAK-STAT inhibition interferes with the positive feedback loop between the follicular cell and the cytotoxic CD8 + NKG2D + T cells in AA [38]. Key genes in the JAK-STAT pathway related to hair growth include *STAT5A/B*, *STAT3*, *JAK1*, *JAK3*, and *Socs2/3*, highly expressed in catagen and telogen phases but suppressed in the early anagen phase [39]. In mice, inhibition of the JAK-STAT pathway promotes hair growth by

Table 2 Janus kinase inhibitors and their respective US Food and Drug Administration-approved indications

JAK inhibitor	Inhibits	FDA-approved indication
Baricitinib [35]	JAK1, JAK2	Rheumatoid arthritis
Tofacitinib [36]	JAK1, JAK3	Rheumatoid arthritis
		Psoriatic arthritis
		Ulcerative colitis
Ruxolitinib [37]	JAK1, JAK2	Myelofibrosis
		Polycythemia vera
		Graft-versus-host disease

FDA US Food and Drug Administration, *JAK* Janus kinase

stimulation of hair follicle stem cells and an antiquiescence signal during the telogen phase, accelerating reentry into the anagen phase [39]. Overexpression of mouse keratinocyte IL-6, which signals via the JAK-STAT pathway, has been found to result in hair growth retardation [40]. IL-6 is also found to be more prominent in balding dermal papilla in mice and inhibits hair shaft elongation human cells in vitro [41, 42]. JAK inhibitors also prevent the production of inflammatory Th17 cells and Th1 and Th2 differentiation [43].

Baricitinib (chemical structure C16H17N7O2S) selectively inhibits JAK1 and JAK2 and, to a lesser extent, JAK3 [44]. Baricitinib has also been shown to inhibit IL-6- and IL-23-induced JAK signaling [45]. Anti-inflammatory effects of baricitinib have also been demonstrated in a mouse model with reduced CD8 + T cell infiltration and reduced MHC class I and class II expression [46]. Ruxolitinib (chemical structure C17H18N6) selectively inhibits JAK1 and JAK2 and, to some extent, TYK2 [44, 47]. Ruxolitinib has also been shown to have anti-inflammatory properties, thought to be due to a reduction in levels of circulating inflammatory cytokines TNF-α and IL-6, interruption of the IL-17 signaling pathway, and cytokine-induced phosphorylation of STAT3 [47, 48]. Tofacitinib (chemical formula C16H20N6O) selectively inhibits JAK1- and JAK3-dependent STAT activation over JAK2, with minimal effects on TYK2 [44, 49]. Tofacitinib blocks STAT phosphorylation induced by IFN-γ, IL-2, IL4, IL-7, IL-15, and IL-21, affecting the signaling pathway downstream of JAK1- and JAK3-dependent γc receptors in mice and humans [50]. Messenger RNA and protein expression of vascular endothelial growth factor (VEGF), an anagen-maintaining growth factor, has been found to be expressed in mice treated with topical tofacitinib, suggesting an anti-inflammatory role of tofacitinib [51]. In addition to clinical hair growth, topical tofacitinib has also been shown to extend the anagen phase [51].

Several cohort studies (Table 3) and case reports demonstrating the efficacy of oral and topical JAK inhibitors for AA have been published [52]. Of these studies, six were clinical trials, most of which were open-label trials testing the effects of either oral or topical tofacitinib and ruxolitinib. Most patients in these studies achieved clinically significant hair regrowth. AA severity is commonly evaluated by the Severity of Alopecia Tool (SALT), a global severity score that calculates percentage hair loss [53].

A meta-analysis of much of the evidence to date for the efficacy of JAK inhibitors in treating AA has shown oral JAK inhibitors to be associated with better treatment response than topical therapy, regardless of the agent used [52].

Additionally, age, sex, duration of AA, and previous systemic therapy failure response did not influence the response to therapy. Time to initial hair growth was 2.2 months, with relapse occurring after stopping therapy at 2.7 months, indicating the need for maintenance therapy. It is important to note that this meta-analysis was limited by low-quality evidence as most of the analysis was based on case reports; nevertheless, it did corroborate much of the current evidence that supports the use of JAK inhibitors for treating AA [52]. However, a phase II randomized, double-blinded, parallel-group, vehicle-controlled trial, evaluating ATI-502, an investigational topical JAK1/3 inhibitor, found no statistical superiority in the mean percentage change from baseline in the SALT score, Alopecia Density and Extent (ALODEX) score, and multiple investigator- and patient-reported outcomes when compared with the vehicle after 24 weeks of treatment [54].

Improvements in the molecular profile of AA, such as upregulation of hair keratins and downregulation of Th1/IFN-γ, have also been demonstrated in patients being treated with JAK inhibitors [38, 46].

Randomized, double-blind, placebo-controlled trials (ClinicalTrials.gov identifier NCT03899259: phase III for baricitinib; NCT03732807: phase IIb/III for PF-06651600, an investigational JAK3 inhibitor) and open-label studies (NCT03800979: phase IV for tofacitinib; NCT03898479: phase II for CTP 543, an investigational JAK1/2 inhibitor) testing the effects of oral JAK inhibitors on AA are ongoing.

JAK inhibitors are generally well-tolerated. Upper respiratory tract infections were the most commonly reported complications in the studies of JAK inhibitors for AA [52]. Reversible adverse effects reported in patients with AA being treated with tofacitinib include grade 1 and 2 infections (urinary tract infections, upper respiratory tract infections, and herpes zoster), as well as transient elevation of cholesterol and liver transaminases [55, 59, 63]. Grade 1 or 2 infections associated with clinical studies investigating the role of ruxolitinib in AA patients have also been reported [56].

Most of the safety data for JAK inhibitors comes from studies investigating their effects on other diseases. Dose-dependent hyperlipidemia, anemia, and leukopenia have been described [66, 67]. Cutaneous adverse events include herpes zoster as well as drug eruptions reported in patients being treated with tofacitinib for psoriasis and RA [66]. Reactivation of tuberculosis has been reported with baricitinib and tofacitinib use in patients with RA [68, 69]. Gastrointestinal perforations have also been reported in patients taking JAK inhibitors [68, 70]. A study of 3492 patients who received baricitinib for RA for 6637 total patient-years of exposure reported three patients who experienced gastrointestinal perforation while concomitantly taking methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs) [68]. Another study of 6194 patients on tofacitinib for a total 19,406 patient-years' exposure for the treatment of RA reported 22 patients with gastrointestinal perforation while

Table 3 Clinical studies for Janus kinase inhibitors in the treatment of alopecia areata

Study (year)	Study type	JAK inhibitor type	Number of patients	Response
Kennedy Crispin et al. [55] (2016)	Open-label, single-arm	Oral tofacitinib	66	>50% regrowth in 32% of patients
Mackay-Wiggan et al. [56] (2016)	Open-label, single-arm	Oral ruxolitinib	12	≥50% regrowth in 75% of patients
Craiglow et al. [57] (2017)	Retrospective	Oral tofacitinib	13	Median percent change in SALT score of 93% (mean 61%; range 1–100%)
Liu et al. [58] (2017)	Retrospective	Oral tofacitinib	90	>50% regrowth in 58% of patients
Ibrahim et al. [59] (2017)	Retrospective	Oral tofacitinib	13	≥50% regrowth in 54% of patients
Park et al. [60] (2017)	Retrospective	Oral tofacitinib	32	≥50% regrowth in 56% of patients
Liu et al. [61] (2018)	Open-label, single-arm	Topical tofacitinib	10	3 of 10 subjects experienced hair regrowth with a mean SALT score decrease of 34.6% (SD 23.2%)
Lee et al. [62] (2018)	Retrospective	Oral tofacitinib	33	60.5% in overall scalp hair regrowth
Jabbari et al. [63] (2018)	Open-label, single-arm	Oral tofacitinib	12	≥50% hair regrowth in 67% of patients
Bokhari and Sinclair [64] (2018)	Double blind, placebo, and active controlled study	Topical tofacitinib and topical ruxolitinib	16	Partial regrowth noted in 6 patients with tofacitinib and 5 patients with ruxolitinib based on qualitative assessment by investigator global assessment
Almutairi et al. [65] (2019)	Open-label comparative study	Oral tofacitinib Oral ruxolitinib	75	Mean ± SD change in SALT score of 93.8 ± 3.25 in the ruxolitinib group and 95.2 ± 2.69 in the tofacitinib group. No statistically significant difference between the groups
Aclaris Therapeutics (2019) [54]	Phase II randomized, double-blinded, parallel-group, vehicle-controlled trial (ClinicalTrials.gov identifier NCT03759340)	ATI-502, an investigational topical JAK1/3 inhibitor	129	No significant difference in the mean percent change from baseline in the SALT score, ALODEX score, and multiple investigator- and patient-reported outcomes when compared with the vehicle after 24 weeks of treatment

ALODEX Alopecia Density and Extent, *JAK* Janus kinase, *SALT* Severity of Alopecia Tool, *SD* standard deviation

taking concomitant NSAIDs or corticosteroids [70]. A theoretical risk of malignancy is possible given JAK inhibitors' effect on type I and type II IFNs and natural killer (NK) cells, which are involved in cancer cell regulation [71]. However, in patients with RA treated with tofacitinib, the risk of malignancy, including non-melanoma skin cancer, is low and similar to that of biologic agents [72–74]. A meta-analysis comparing overall malignancies in patients with being treated with tofacitinib versus biologic agents did not show an increased risk for malignancies [72]. Pooled malignancy data for studies involving tofacitinib for the treatment of RA over 12,554 patient-years reported 107 of 5671 patients who developed malignancies. When compared to the Surveillance, Epidemiology and End Results (SEER) database, standardized incidence ratios for all malignancies (excluding non-melanoma skin cancer) and selected malignancies (lung, breast, lymphoma, non-melanoma skin cancer) were within the expected range of patients with moderate-to-severe RA [73].

Long-term studies assessing safety data for JAK inhibitors in patients with AA are not yet available. Newer JAK inhibitors may also provide similar efficacy and less toxicity in the treatment of AA [34].

3.2.2 Dupilumab

Dupilumab, currently approved for the treatment of atopic dermatitis (AD), is a monoclonal antibody directed against the IL-4 receptor α (IL-4Rα) subunit blocking both IL-4 and IL-13 signaling [75]. Patients with AA have an increased risk of also having AD [76]. Cases have been reported of the reversal of AA in patients with concomitant AD receiving dupilumab treatment [3]. The effect of dupilumab in AA may be related to the inhibition of Th2 pathway activation found in AA scalp lesions [77]. On the other hand, dupilumab has also been reported to be associated with AA both in patients with pre-existing AA and those without prior episodes of AA [78]. Theories for this adverse effect include drug-induced alopecia, de novo AA, and Th1 pathway amplification as a result of dupilumab-induced Th2 downregulation [78, 79]. The most common adverse events reported have been injection-site reactions, conjunctivitis, blepharitis, keratitis, eye pruritus, dry eyes, oral herpes, or other herpes simplex virus infections [80]. A phase II randomized, double-blind, placebo-controlled pilot study (NCT03359356) investigating the treatment of dupilumab in AA patients with and without AD is currently being conducted.

3.2.3 Ustekinumab

The discovery that Th1, Th2, IL-23, and IL-9/Th9, IL-23p19 and IL-23/IL-12p40 cytokine activation can be found in found in AA has led researchers to explore cytokine-targeted therapies [2, 77]. Ustekinumab, in particular, is an IL-12/IL-23p40 monoclonal antibody currently used as an effective treatment for psoriasis and Crohn's disease [81]. Ustekinumab was shown to cause hair regrowth in three patients with moderate to severe AA [2]. Genetic expression of immune and keratin markers was also analyzed in these patients and a higher inflammatory profile and greater suppression of hair keratins at baseline were associated with higher recovery of hair regrowth [2]. Another case series of three pediatric patients with a noted improvement of AA after ustekinumab treatment has also been reported [82]. Common adverse effects include injection-site reactions, headache, and fatigue [81].

3.2.4 Abatacept

Abatacept, currently approved for the treatment of RA and juvenile idiopathic arthritis, is a selective modulator of T cell co-stimulation, comprised of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) with a portion of immunoglobulin (Ig)G1. Abatacept is known to reduce T cell proliferation and inflammatory cytokines such as IFN-γ [83]. It is administered subcutaneously and is currently approved for the treatment of adult RA and polyarticular juvenile idiopathic arthritis [84]. A similar compound was found to prevent induced AA in mouse models [85]. Common adverse effects that have been reported include headache, dizziness, nasopharyngitis, cough, back pain, and hypertension [86]. In clinical trials for RA, a risk of serious infections was noted when abatacept was administered along with biologic disease-modifying antirheumatic drugs (DMARDs), especially anti-TNFα therapies, resulting in the manufacturer recommending that abatacept is only used in combination with non-biologic DMARDs [83, 84]. A phase II open-label clinical trial evaluating the efficacy of abatacept in moderate-to-severe patchy AA in 15 individuals (NCT02018042) has reported adverse effects of injection-site reaction and upper respiratory infections, with results of the study otherwise pending.

3.2.5 Platelet-Rich Plasma Therapies

Injections of PRP have been shown to have varied efficacy in the treatment of AA [87]. The procedure involves an autologous blood product of centrifuged whole blood with subsequent extraction of various proportions of the plasma and platelets or buffy coat [88]. PRP is rich in platelets and growth factors (GFs), such as platelet-derived GF, fibroblastic GF, epithelial GF, insulin-like GF, TGF, and VEGF [89]. These GFs can contribute to wound healing via stimulation of fibroblasts, neocollagenesis, neoangiogenesis, and recruitment of mesenchymal stem cells, which then differentiate at the site of injury [90]. When the alopecic areas are injected

Table 4 Other potential treatment options for alopecia areata

Agent	Mechanism of action	Clinical relevance to alopecia areata
Apremilast	PDE4 antagonist	PDE4 is highly expressed in AA and apremilast was shown to suppress AA in humanized mouse models [77]; however, a single-center, randomized, placebo-controlled study did not show treatment response [94]
BMD1141	PTH receptor agonist	Activation of the PTH/PTHrP receptor stimulates β-catenin within the hair follicle, which promotes the transition of hair follicles into an anagen growth phase, as demonstrated in mouse models [95]
BNZ-1	Binds the γc receptor of lymphocytes to selectively block IL-2, IL-15, and IL-9 signaling [96]	IL-2 and IL-15Rβ blockade has been shown to reduce the accumulation of CD8+NKG2D+ T cells and IFN in a mouse model of AA [38]. A phase II placebo-controlled clinical trial (NCT03532958) is in preparation
Crisaborole	PDE4 antagonist	Currently approved for the treatment of mild-to-moderate atopic dermatitis [97]. Potential target for treatment of AA as PDE4 is highly expressed in AA [77, 98]
Fexofenadine	Histamine 1 receptor antagonist	Fexofenadine may cause an indirect effect through improvement of atopic dermatitis in atopic AA patients [99]. IFN-γ production from T cells and ICAM-1 expression on epithelial cells involved in AA may be reduced by fexofenadine [99]. Substance P, which may play a role in AA, is decreased by fexofenadine [99]. A retrospective trial of 121 AA patients with >50% hair loss being treated with topical immunotherapy found that atopic AA patients taking fexofenadine experienced significantly better hair regrowth than those not taking fexofenadine [99]. Cases of AA, AU, and AO responsive to fexofenadine, with or without topical immunotherapy, have also been reported [100, 101]. It has been suggested that both fexofenadine and contact immunotherapy may act synergistically to inhibit IFN-γ [100]
Fractional photothermolysis	Laser technique that produces columns that extend into the reticular dermis stimulating a controlled wound-healing environment [102]	Cases of hair regrowth as a result of this therapy in AA have been reported, with the premise that wound healing milieu could hypothetically cause hair growth [103]. A clinical trial investigating the effect of transepidermal delivery of triamcinolone acetonide or platelet-rich plasma using fractional carbon dioxide laser or microneedling for the treatment of AA (NCT04147845) is currently recruiting patients
Fumaric acid esters	Inhibits cytokines INF-γ, IL-2, IL-12, and TNF-α via inhibition of T-suppressor cells and Th cells	Hair growth has been noted in AA in open-label and retrospective studies [104, 105]. 10 patients with AA resistant to 3 traditional therapies without success were enrolled in an open, non-placebo-controlled pilot study with daily fumaric acid ester application for 6 months. 3 patients had almost complete remission, 1 patient had focal remission, 2 patients had fair to moderate effects with diffuse growth of thin hair, and 4 showed no growth [104]
Statin/vytorin	Antihyperlipidemic agents that are immunomodulatory and work synergistically to decrease CRP [106–108]	Studies show varying efficacy in the treatment of AA [106, 109]. In one study with 29 patients with AA who received simvastatin/ezetimibe 40 mg/10 mg daily for 24 weeks, 14 of the 19 patients who completed 24 weeks of treatment were judged responders as determined by 20% hair regrowth on week 24 using the NAHRS scale [109]. In another study with 14 patients with recalcitrant AA who took simvastatin (40 mg) and ezetimibe (10 mg) daily, 4 patients (28.6%) were judged as responders showing regrowth of 30–80% after 3 months of treatment [106]
Tralokinumab	Anti-IL-13 monoclonal antibody [110]	Blocks Th2 axis [110]. A pilot study testing tralokinumab in subjects with moderate-to-severe AA has been completed, with analysis pending (NCT02684097)
Treg/IL-2	Stimulate Treg and IL-2	Low-dose IL-2 induces immune tolerance and promotes Treg development, thus suppressing immune responses [111]. 5 patients with severe AA resistant to previous systemic treatments received subcutaneous IL-2 over a 9-week period. Median SALT score decreased from 82 (range 63–100) at baseline to 69 (range 28–100) at 6 months. Immunochemical analysis of lesions biopsies showed a notable increase in Treg cell count [112]

Table 4 (continued)

Agent	Mechanism of action	Clinical relevance to alopecia areata
Stem cells	Regenerative properties	Human hematopoietic mesenchymal stem cells stimulate the Wnt/β-catenin pathway and phosphorylation of STAT1 and STAT3 [113]. Human autologous adipose-derived adult cells of stromal vascular fraction increased hair growth in AA [114]. A phase II clinical trial assessing stem cell educator therapy combined with minoxidil for the treatment of AA is in preparation (NCT04011748)
Vitamin D	Contributes to maintenance of immune privilege of the hair follicle by decreasing IFN-γ, downregulation of NKG2D- and CXCR3-activating ligands, JAK/STAT inhibition, attenuation of oxidative stress [115]	AA is associated with vitamin D deficiency [116]. A lack of expression of 1,25-dihydroxyvitamin D_3 receptors (VDR) is associated with reduced growth of hair follicles. The decreased expression of VDR in AA is related to decreased expression of Wnt/β-catenin signals, which inhibits hair follicle proliferation and differentiation [117]. Calcipotriol (topical vitamin D analog) has been shown to promote hair regrowth in AA [118, 119]. In a study with 22 AA patients treated with calcipotriol lotion 0.005% twice daily for 3 months, hair regrowth was observed in 13 patients. SALT50 and SALT100 were observed in 6/13 and 2/13 patients, respectively. Response to treatment was better in patients with lower vitamin D levels [119]

AA alopecia areata, *AO* alopecia ophiasis, *AU* alopecia universalis, *CRP* C-reactive protein, *CXCR3* C-X-C motif chemokine receptor 3, *ICAM-1* intercellular adhesion molecule 1, *IFN* interferon, *IL* interleukin, *IL-15R* interleukin-15 receptor, *JAK* Janus kinase, *NAHRS* North American Hair Research Society, *NKG2D* Natural Killer Group 2D, *PDE4* phosphodiesterase type 4, *PTH* parathyroid hormone, *PTHrP* parathyroid hormone-related protein, *SALT* Severity of Alopecia Tool, *STAT* signal transducer and activator of transcription, *Th* T helper, *TNF* tumor necrosis factor, *Treg* T regulatory, *VDR* vitamin D receptor, *Wnt* Wingless-related integration site

locally, PRP can affect hair growth via induction and maintenance of the anagen phase of the growth cycle [87, 91]. Few randomized controlled studies exist for this intervention in AA; however, the studies performed so far show benefits, especially in limited disease, with the added benefit of little to no adverse effects. In a randomized, double-blind, placebo-controlled study of 45 patients, PRP was found to increase hair regrowth and decreased hair dystrophy in patients with patchy AA when compared with patients who received injections of placebo or triamcinolone acetonide [87]. Another randomized clinical trial demonstrated that patients with AA treated with PRP injections showed significant hair growth, along with another group in the study treated with topical 5% minoxidil, when compared with placebo [92]. PRP injections may have limited benefit in patients with chronic and severe cases of AA, as global treatments are needed and injections can be painful [93]. PRP treatments for AA have been shown to be generally well-tolerated [87]. Long-term randomized controlled studies are still necessary to determine the benefits of PRP therapy for AA.

3.2.6 Future Treatment Directions

Several other novel therapies are either being tested in clinical trials or have been reported in the literature to be effective in the treatment of AA as listed in Table 4. Recent advances in the understanding of the microbiome and its role in autoimmunity is a popular area of study [120]. Microbiome dysbiosis has been noted in patients with AA and two patients with AA experienced hair regrowth after receiving fecal transplant for the treatment of *Clostridium difficile* [121–123]. Adverse effects associated with fecal transplants include transmission of multi-resistant organisms, vomiting, fever, diarrhea, bacteremia, and peritonitis [124, 125].

4 Conclusion

AA poses a challenge to both the patient and clinician given its refractory nature. However, advances in the understanding of the pathophysiology of AA has opened up the doors to several new treatment options, with JAK inhibitors being at the forefront of clinical investigation. As clinical trials come underway for further treatments options, clinicians and patients will have a larger repertoire of treatment options for this challenging disease.

Compliance with Ethical Standards

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