Review on A Alopecia: Etiology, Classification, and Therapeutic Advances

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Abstract: Alopecia, sometimes known as hair loss, is a complex disorder that affects millions of people globally and has a major psychological impact. Mostly divided into scarring (cicatricial) and non-scarring (non-cicatricial) kinds, it includes a wide range of illnesses. Telogen effluvium, alopecia areata, and androgenetic alopecia are some of the most common types. Alopecia is caused by a complex interplay of environmental factors, stress, autoimmune dysfunction, hormonal impacts, dietary inadequacies, and genetic susceptibility.Clinical examination, trichoscopy, and occasionally a scalp biopsy or laboratory testing are used to make the diagnosis. The kind and severity of alopecia determine the available treatment choices, which include immunotherapy, laser therapy, pharmaceutical medicines like minoxidil and finasteride, and more sophisticated options like platelet-rich plasma (PRP) and hair transplantation. The outcomes of recent studies on gene-targeted therapies, JAK inhibitors, and stem cell therapy are encouraging. For efficient treatment and better patient results, a multidisciplinary strategy combining dermatological, endocrinological, and psychological viewpoints is essential.

Keywords: Alopecia, hair loss, androgenetic alopecia, alopecia areata, treatment, PRP, JAK inhibitors, hair regeneration

Introduction

Alopecia Areata is a chronic autoimmune disease that affects the retinal pigment epithelium, hair follicles, and occasionally the nails. By attacking anagen hair follicles, it disrupts the hair cycle and causes reversible hair loss. It is a prevalent, non-scarring, inflammatory kind of hair loss that can manifest clinically as anything from distinct patches to total loss of hair on the scalp or body.
Up to 2% of people worldwide are affected; women and people over 50 are more likely to have it (late-onset).

Classification

- Based on extent:
  - Patchy alopecia
  - Alopecia totalis
  - Alopecia universalis
- Based on pattern:
  - Reticular
  - Ophiasis
- New variant (Sisaiapho):
  - Acute and diffuse total alopecia
  - Unusual pattern
  - Perinovoid alopecia
  - Linear

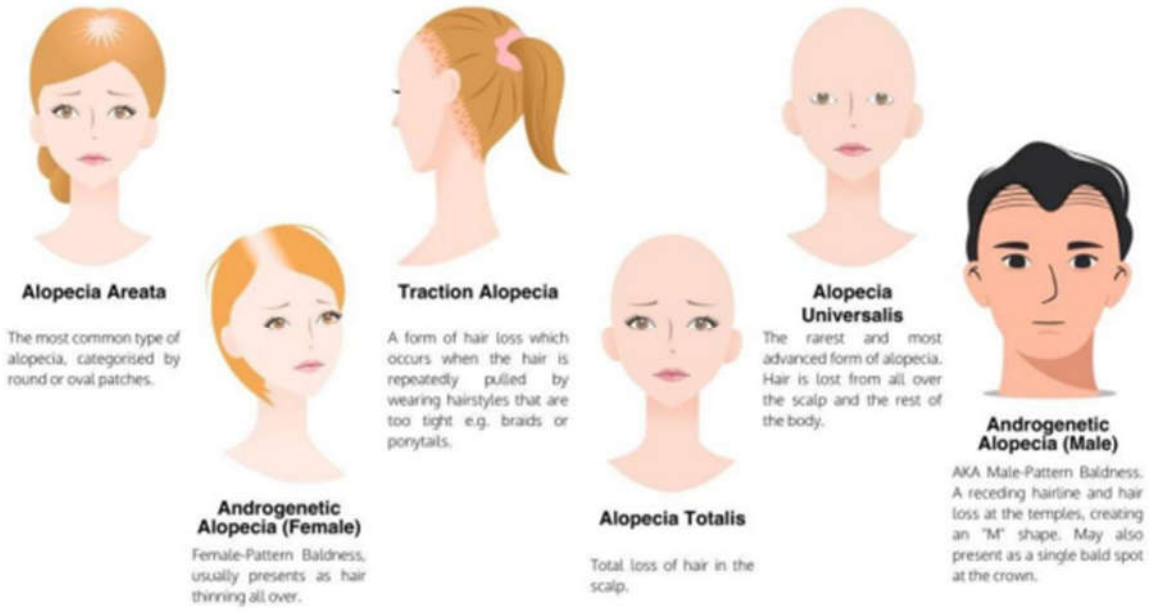
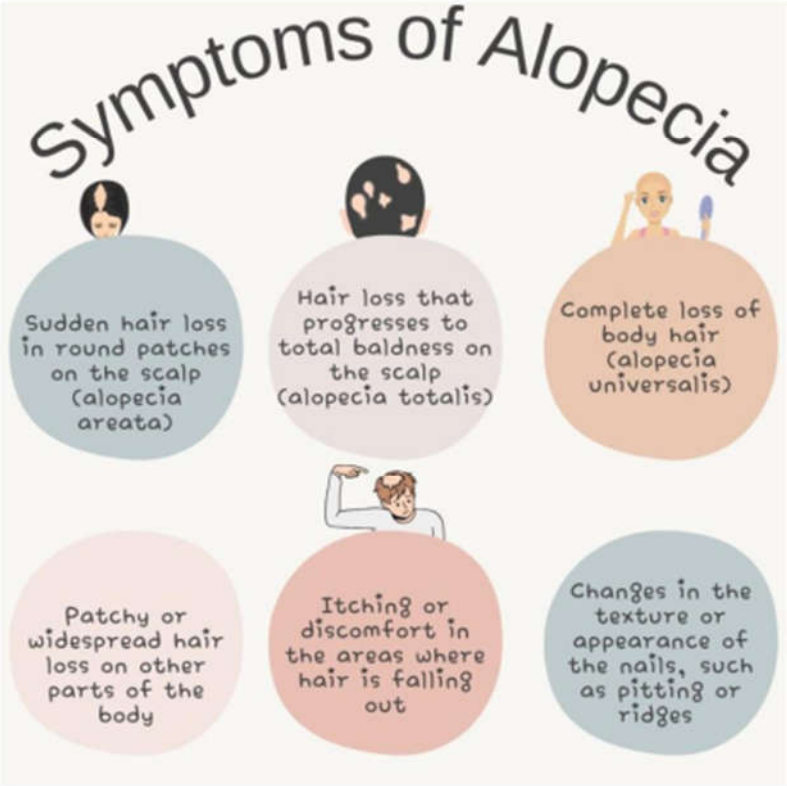


Fig : Types of Alopecia

Etiology :

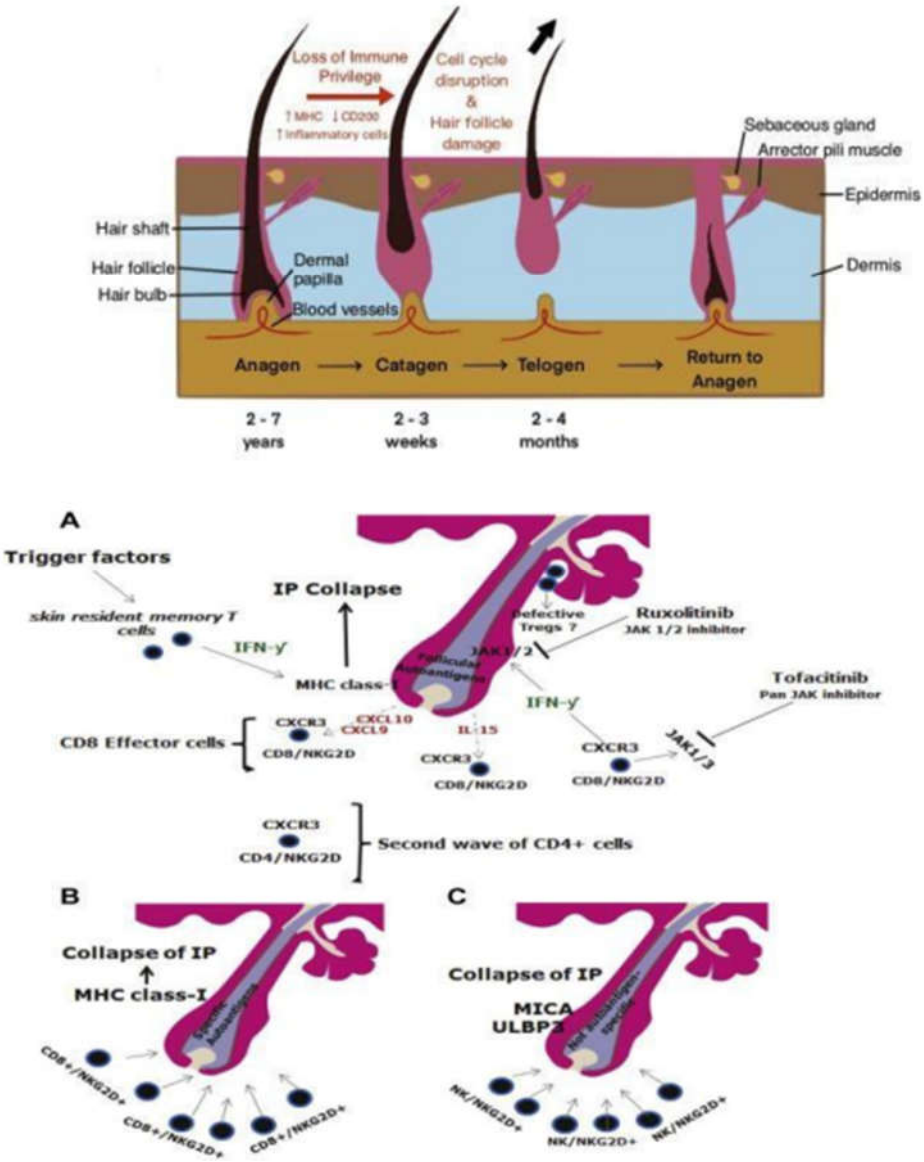
Symptoms:



Pathology:

Pathophysiology of the hair growth cycle. The normal hair development cycle is composed of the following phases: telogen (resting), catagen (controlled apoptosis), anagen (active growth), and return to anagen (also called exogen). The hair follicle can receive nourishment from the blood vessels that travel through the dermal papilla, to which it is attached during the anagen phase. Currently, the hair is actively growing upward from the scalp. Anagen is a phase that lasts for two to seven years and affects between 88 and 90 percent of the hairs on the head at any particular time. During catagen, the hair follicle begins to separate from the dermal papilla due to the controlled death of epithelial cells. Catagen is a condition that lasts for about 2% of hairs at any given moment. About 2% of hairs are in catagen at any given time, and it lasts for two to four weeks. The catagen phase, which lasts for two to four weeks, affects about 2% of hairs at any given moment. During telogen, the follicle splits off from the dermal papilla, which is its food source. The black arrow shows that when the hair is denied its source of nutrients, it dies and falls out of the follicle. At the moment, the follicle is at rest.

At any given time, 8–10% of hair is in telogen, which lasts for two to four months. Once the cycle returns to the anagen phase and the dermal papilla rejoins the hair follicle, the hair matrix begins to produce a new hair. In AA, the normal hair growth cycle was disrupted (red writing). Immune privilege is lost during the anagen phase as a result of increased MHC I activity, decreased CD200 immunoregulatory abundance, and CD200 immunoregulatory presence. The catagen phase causes more damage and irritation to the hair follicle, and the telogen phase begins earlier. created with Procreate.



The pathogenesis of alopecia areata (AA) Involves the concept that any form of microtrauma can trigger the release of IFN-g by resident T cells in the skin. Due to an individual's genetic predisposition, IFN-g stimulates the expression of MHC class I and II in the lower regions of the follicular epithelium. This increase in MHC class I expression results in the collapse of hair follicle immune privilege (HF IP) and the buildup of cytotoxic CD8 effector T cells that express the NKG2D marker, which relies on the survival cytokine IL-15. The rise in MHC class II expression prompts a secondary influx of CD4 T cells.

In addition to producing IL-15 and the chemokines CXCL9 and CXCL10, elevated IFN-g levels also stimulate the follicular epithelium to attract T cells that express CXCR3, so escalating the inflammatory response. JAK inhibitors primarily target CD8/NKG2D T cells and interfere with vital cytokines like IFN-g and IL-15 that offer survival signals. Both nxolitinib, a JAK1/2 inhibitor, and tofacitinib, a pan-JAK inhibitor, work well to treat AA patients by focusing on the particular CD8/NKG2D pathway. B, Hair follicles (HFs) engage autoreactive CD81NKG2D1 cells when they identify particular autoantigens that are shown by MHC class I molecules. C, NKG2D1 cells can identify aberrant MICA expression on lesional hair follicles, which could result in non-specific cytotoxic action.
, The engagement of autoreactive CD81NKG2D1 cells by hair follicles (HFs) is triggered when they recognize specific autoantigens presented by MHC class I molecules. C, The abnormal expression of MICA on lesional hair follicles can be recognized by NKG2D1 cells, which may lead to the cytotoxic activity of non-specific NK cells.

1 Corticosteroid

corticosteroids, followed by adverse effects. Due to their anti-inflammatory properties, corticosteroids have been the cornerstone of AA treatment. They have been administered parenterally, topically, and orally. The effectiveness of various topical steroid formulations varies. 0.05% betamethasone dipropionate lotion, 0.1% halcinonide, 0.1% betamethasone valerate foam, 0.2% fluocinoloneacetonide cream, and 0.05% clobetasol ointment/foam have all been used with success rates ranging from 28.5% to 61%. One centimeter outside the affected area is advised. Despite continuing treatment, 37.5% of the respondents experienced relapses. Topical steroids are the first-choice treatment for AA despite their varied efficacy due to their ease of use, particularly in ung patients.

Children frequently use midpotent topical steroids. Atrophy, telangiectasia, and foliculitis may manifest. To stop atrophy, they can be used five days a week or every other day.Topical corticosteroids become more potent when applied under occlusion, which also enhances their negative effects.

Several JAK inhibitors with different characteristics that selectively target JAK isoforms are presently being developed AA . JAK inhibitors work by cytosuppressingkinesignaling in the JAK/STAT system Riticcitinib, the only JAK3 selective inhibitor that is licensed or being studied for the treatment of AA, will be covered separately because of its mechanism of action, which targets TEC family kinases. Recently approved to treat people with severe AA, baricitinib is an oral, selective, reversible noncovalent inhibitor of JAK1 and JAK. . Baricitinib has been approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe active rheumatoid arthritis in adults , the European Medicines Agency (currently undergoing FDA review) for the treatment of

moderate to severe atopic dermatitis in adults, and the US Food and Drug Administration (FDA) for adults hospitalized with COVID-19 . In preclinical research, baricitinib decreased MHC class I and class II expression in C3H/HcJ AA mice as well as CD8+ NKG2D+ cell infiltration as compared to control treatment .Baricitinib quickly normalized the expressing signature of both type I and type II IFN in this mouse model, according to gene expression profiling . Crucially, mice that had disease resolution and those that did not following baricitinib treatment may be distinguished by the Alopecia Areata Disease Activity Index (ALADIN) (36)'s total IFN and cytotoxic T lymphocyte components . In two phase 3 trials, BRAVE-AA1 (NCT03570749) and Brave AA2 (NCT03899259), baricitinib's safety and effectiveness were examined in adult patients who had lost at least 50% of their scalp hair . The percentage of patients with a Severity of Alopecia Tool (SALT) score of \(\leq\)20 (\(\leq\)20% hairless scalp) at week 36 was the main outcome of both investigations. The efficacy results in BRAVE-AA1 were similar, with 38.8% of patients receiving baricitinib 4 mg and 22.8% of patients receiving baricitinib 2 mg having a SALT score of \(\leq\)20 at week 36, compared to 6.2% of patients receiving a placebo; in BRAVEAA2, the corresponding SALT scores were 35.9%, 19.4%, and 3.3% of patients receiving baricitinib 4 mg, baricitinib 2 mg, and placebo, respectively. Acne, urinary tract infections, and increased creatine kinase levels were adverse events (AEs) that were more prevalent in patients on baricitinib than in those on placebo. Major adverse cardiovascular events (MACE), serious infections, herpes zoster infections, and cancers were rare, and the overall benefits risk profile backed AA's approval. Baicitinib's effectiveness persisted for weeks of treatment, and the safety profile was comparable to that observed for 36 weeks.

Currently, a phase 3 trial is needed to examine the pharmacokinetics, safety, and effectiveness of baricitinib in pediatric patients aged 6 to less than 18 years (BRAVA-AA-PEDS; NCT05723198). The percentage of patients with a SALT score of less than 20 at week 36 is the main end measure. A deuterated derivative of ruxolitinib, deuruxolitinib (formerly CTP-543) is a selective inhibitor of JAK1 and JAK2 that is taken orally. Small-molecule medications' pharmacological characteristics can be altered by deuteration, though the effects of this change have varied. Regarding the pharmacokinetics or pharmacokinetic consequences of deuteratingruxolitinib, no research has been found in the literature.

However, while taking into account the mechanism of action of deuruxolitinib, research on ruxolitinib continues to be instructive. According to preclinical research, ruxolitinib stimulates anagen re-entry-related molecules in cultured human dermal papilla cells via the Wnt/β-catenin pathway and downregulates MHC class II expression in cultured murine hair bulbs and surrounding HFs following IFN-γ treatment. By upregulating the expression of PD-1 and the transcription factors thymocyte selection-associated HMG box and eomesodermin, ruxolitinib was also found to encourage T cell exhaustion. Twelve patients with moderate to severe AA receiving ruxolitinib 20 mg twice daily participated in an open-label clinical study. Gene expression changes were noted between baseline and week 12 patients, and the ALADIN IFN and cytotoxic T-lymphocyte components were able to distinguish between baseline non-responders and eventual responders.

To date, deuruxolitinib has been the subject of three phase 2 trials in AA patients (NCT03941548, NCT03811912, and NCT03137381). In a double-blind, placebo-controlled, phase 2 dose-ranging study (NCT03137381), 149 adult patients with AA and ≥50% scalp hair loss were randomly assigned to receive deuruxolitinib 4 mg, 8 mg, or 12 mg twice daily.

With 47% and 58% (P<0.001 vs placebo) of patients showing ≥50% change from baseline SALT score at week 24, respectively, the 8- and 12-mg dosages achieved the primary goal. Deuruxolitinib was generally well tolerated; headache, nasopharyngitis, upper respiratory infection, and acne were the most frequent treatment-emergent adverse events.

Although they have been completed, two randomized double-blind, placebo-controlled, phase 3 trials (THRIVE-AA1 [NCT04518995] and THRIVE-AA2 [NCT04797650]) assessing the safety and effectiveness of oral deuruxolitinib in adult patients with AA and ≥50% scalp hair loss have not yet been published. The purpose of both trials is to assess scalp hair growth following a 24-week course of treatment with 8 or 12 mg twice daily of deuruxolitinib. The percentage of patients with a SALT score of ≤20 at week 24 is the primary outcome of every experiment. The primary effectiveness endpoint was satisfied, according to THRIVE-AA1 topline data.

According to reports, jaktinib, a deuterated counterpart of the JAK inhibitor momelotinib, is a more potent inhibitor of JAK2 and TYK2 than JAK1. Jaktinibinhibitsactivin receptor-like kinase 1 (ACVR1) and receptor bone morphogenic proteins, similar to its parent compound momelotinib. Momelotinib has an approved use, and it has been proposed that ACVR1 inhibition improves anemia in myelofibrosis. According to preclinical evidence, this improvement in anemia may be related to a shift in hepcidin liver expression, which in turn may impact iron metabolism.

No preclinical or translational data for either jaktinib or momelotinib in AA could be found during a literature search. Although a study of the effects of ACVR1 inhibition in the setting of AA would be beneficial, a mechanism of action akin to those of other JAK inhibitors may be anticipated. Jaktinib's stable pharmacokinetic characteristics were demonstrated in a phase 1 investigation, but no comparison with the non-deuterated parent molecule allowed for any inference about the possible advantages of this chemical alteration. Adults with AA are presently undergoing a dose escalation/dose extension (phase 1/2) randomized clinical trial using jaktinib as a topical cream (jaktinib hydrochloride) (NCT04445363). The percentage of patients whose SALT scores improved by 90% by week 24 is the trial's primary outcome. A recent phase 2 trial (NCT04034134) assessed the 24-week safety and effectiveness of jaktinib, an oral tablet, in treating persons with ≥50% scalp hair loss caused by AA. A phase 3 trial with a primary endpoint of a SALT score ≤20 response at week 24 is presently enrolling participants to assess the safety and effectiveness of oral jaktinib in about 420 persons with AA and ≥50% scalp hair loss (NCT05051761).

A selective oral JAK1 inhibitor called ivarmacitinib (previously SHR0302) is being researched to treat a number of immunoinflammatory conditions, including AA. To assess the safety and effectiveness of SHR0302 in adult AA patients, a double-blind, randomized, placebo-controlled, dose-ranging experiment was conducted as part of the phase 2 CRYSTAL2 (NCT04346316) investigation. The primary objective was the percentage change from baseline in the SALT score at week 24 for 94 patients who were randomized to receive ivarmacitinib at doses of 2, 4, or 8 mg or a placebo. Compared to patients receiving a placebo, those receiving any dose of ivarmacitinib had a higher least squares mean change from baseline in their SALT score (2 mg, -30.5%; 4 mg, -56.1%; 8 mg, -51.0%; placebo: -19.9%). One case of COVID-19 pneumonia and one case of follicular lymphoma were among the serious adverse events (SAEs) reported. A phase 1b trial assessing the safety,

tolerability, and pharmacokinetics of a topical version of ivarmacitinib for patients with AA is presently underway, according to a public statement from the investigating company. There are no documented preclinical or translational trials of ivarmacitinib that are pertinent to AA.

For AA, the oral JAK1/2 inhibitor KL130008 is presently being studied. Leukocytes derived from healthy Chinese patients in a phase 1 trial showed dose-dependent suppression of IL-6-induced STAT3 phosphorylation when KL130008 was given in single or multiple ascending doses for seven days. Grade 1 or 2 reductions in neutrophil percentage, decreases in neutrophil count, and increases in lymphocyte percentage were among the treatment-emergent adverse events (AEs) that occurred with KL130008 and not with placebo. A safety and efficacy phase 2 study is currently planned for persons with AA who have alopecia totalis or alopecia universalis and ≥50% scalp hair loss (NCT05496426). At week 24, the SALT score ≤20 response will be the primary outcome. There are currently no published preclinical or translational trials of KL130008 that are pertinent to AA.

The JAK family kinase TYK2, which mediates the type I IFN response including signaling by IFN-α and IL-12/23, is allosterically inhibited by deucravacitinib. For the treatment of moderate to severe psoriasis, deucravacitinib has FDA approval and is presently being considered by the European Medicines Agency. There are currently no published preclinical or translational trials examining deucravacitinib's mode of action in AA, particularly regarding TYK2/JAK2-mediated suppression of IL-12 and IL-23 signaling. Both IL-12 and IL-23 are essential for Th1 and Th17 development, respectively, and myeloid dendritic cells can generate both cytokines after being activated by IFN-α released by plasmacytoid dendritic cells (pDCs). Although AA has been associated with each of these immune cell types, more research is necessary to determine the precise role of IL-12 and IL-23. The safety and effectiveness of a 24-week course of deucravacitinib treatment in adults with AA are being assessed in a double-blind, randomized, placebo-controlled, phase 2 trial that is currently enrolling participants (NCT05556265). It is anticipated that 90 patients with AA who have ≥50% scalp hair loss at baseline will be included. Change from baseline SALT score at week 24 will be the primary outcome.

3 Anthralin

Topical immunotherapeutic medication (dithranol) has been shown to effectively treat AA, particularly when used in combination with concurrent diphenylcyclopropenone (DPCP). Although the precise mechanism of action is uncertain, it is thought to work through the production of free radicals and immunosuppressive/anti-inflammatory effects. In animal models with AA, anthralin substantially inhibited the expression of tumor necrosis factor (TNF)-α and TNF-β.

For 20 to 30 minutes, it is applied at concentrations between 0.5% and 1%. To prevent excessive irritation, the scalp should then be cleaned with shampoo. Initially applied every other day, the applications are subsequently administered daily. Potential side effects include pruritus, erythema, scaling, folliculitis, discoloration of the treated skin and clothing, and regional lymphadenopathy. According to a study by Wong et al., anthralin produced a good response (50-90% regrowth) in 39.5% of patients and a complete response (>90% regrowth) in 25% of patients.

4) PUVA.

The idea behind the use of PUVA (psoralen plus UVA) is that the Langerhans cells and mononuclear cells that encircle the afflicted hair follicles may be directly harmful, and that PUVA therapy can eliminate this inflammatory cell infiltration. Whitmontrecently conducted a study using 8-methoxypsoralen (8-MOP) (oral dose: 0.5 mg/kg) in conjunction with UVA radiation at 1 J per square cm (J/cm2), and they found that patients with AA totalis (53%) and AA universalis (55%) experienced complete hair regrowth, with a low relapse rate among these patients (21%) over a long follow-up period (means 5.2 years). Cooper and Whitmont (2003). Mohamed et al. conducted a comprehensive study in 2005 that included 25 individuals with AA totalis or universalis and 124 patients with AA. They discovered that 14 patients in the AA U group experienced 50% hair regrowth, and 85% of patients in the AA group responded well or very well to topical 8-MOP plus UVA radiancy at higher doses (8–42 J/cm2). After PUVA exposure, patients who did not shield their scalp from sunlight experienced intense burning and mild erythema as side effects. After ten months to two years of treatment,recurrence of hair loss was observed in eight patients. The comparatively straightforward process of PUVASOL therapy (both local and systemic) is better suited in the tropics due to its abundant solar radiation, minimal side effects, promising outcomes, lack of numerous alternative procedures, and frequent treatment failures with these treatment regimens. (Sharma and others, 1990)

5) Minoxidil

3% minoxidil under occlusion with petrolatum caused hair regrowth in 63.6% of participants in a double- blind, placebo-controlled experiment on widespread AA, while the placebo group experienced hair regrowth in 35.7% of participants. Just 27.3% of minoxidil users saw hair growth that was aesthetically pleasing. A research comparing topical minoxidil at 1 and 5% showed dose-response efficacy in treating patients with widespread AA. With topical minoxidil at 1 and 5%, the response rates were 38 and 81%, respectively. As an adjunct to traditional AA therapy (which mostly consists of topical or intralesional corticosteroids), minoxidil 5% solution is administered twice daily. Hypertrichosis and contact dermatitis are the most frequent adverse effects. Minoxidil foam, which doesn't contain propylene glycol, can help reduce contact dermatitis.

6) Prostaglandin analogue

When used to treat glaucoma, the prostaglandin analogslatanoprost and bimatoprost, which are available in ocular instillation solutions, have been shown to induce hypertrichosis. 65 This is probably connected to the way they affect prostaglandin receptors that are expressed in the outer root sheath and dermal papilla of eyelash hair follicles. 66 Usinglatanoprost on the eyelids was linked to full eyelash regeneration in 17.5% of 40 participants in prospectivestudies, while 25% of patients showed no change after two years. 67 After 16 weeks, monotherapy was lesssuccessful on the scalp thanbetamethasone diproprionate in 50 adults with scalp AA. 68 In a trial of 30 patients with scalp AA, itstreatment in conjunction with clobetasol was linked to significantly higher hair density (37.2 +/- 26.1 vs.. 14.6+/- 18.6) and regrowth (58.3 +/- 39.3 vs.. 21.6 +/- 24.1) after 12 weeks when compared to clobetasol alone. 69Similarly, after just two weeks, arandomized controlled trial of 108 patients showed that adding latanoprost tobetamethasone was linked to superior SALT score decreases. 70 Iridial pigmentation that cannot be reversedis a common

side effect of latanoprost, affecting 6.3% of patients at one month, 15.7% at three months,37.8% at six months, and 56.5% at twelve months. 71 Bimatoprost has shown little effectiveness in treatingAA patients. " The AA subgroup did not show any treatment advantage in a prospective analysis of 71pediatric patients with eyelash loss caused by chemotherapy or AA. 72While there was no growth of neweyelashes, a different prospective research of persons with AA (n = 17) found that eyelashes had grownlonger and thicker at 4 months. 73. According to a retrospective analysis of 41 AU patients, 24% of themexperienced full regrowth after a year, with atypical recovery period of 4–8 months. 74. In a trial of 30 persons with S1 patchy disease, use twice daily onscalp patches was linked to regrowth and a better response at a faster rate than mometasone .citation Anupdated evaluation of -alopecia Areata

7) Antioxidant.

In addition to pointing to oxidative stress as a potential pathophysiological factor for alopecia areata, theaforementioned research also suggests that antioxidants may be employed as an adjuvant therapy for thecondition, particularly in patients with mild to moderate cases. At the moment, glucocorticoids, contactimmunotherapy, minoxidil, immunosuppressants, and other medications are the principal treatments foralopeciaareata . Patients who take glucocorticoids for an extended period of time may be more susceptible toadverse effects include infections, ulcers, osteoporosis, and high blood sugar.The long-term use of beta-carotene may raise the incidence of lung cancer insmokers , while vitamined controlled lof bleeding in patients taking oral anticoagulants and evenlessen the lipid-lowering effect of statins . These are just a few examples of the potential drawbacks andlimitations of single antioxidant therapy. Thus,more research is warranted to determine the safety and effectiveness of long-term supplemental oral antioxidants. However, using antioxidants in conjunction with steroids as a treatment for alopeciaareata may help lower steroid use. One product of vitamin D is calcipotriol. According to Narang et al. alopecia patients who received 0.005% calcitriol lotion for three months had a notable reduction in the severity of their condition. According to Narang et al. alopecia areata patients who received 0.005% calcitriol lotion for three months had a notable reduction in the severity of their condition. Alam et al. also discovered that external application of 0.1% monetasone cream in conjunction with 0.005% calcipotriol ointment was more effective than external application of monetasone alone in treating alopecia areata. Nevertheless, more research is required to confirm the effectiveness of vitamin D analogs in conjunction with other conventional treatments for alopecia areata patients, including double-blind clinical trials with bigger sample sizes.

In a case-control study carried out in 2020, Abbas discovered that oral ginger powder, a potent antioxidant, was useful in treating alopecia areata. Patients with alopecia areata showed a significant improvement in the antioxidant/oxidative balance of their red blood cells and lymphocytes when compared to healthy subjects. Furthermore, ginger powder has the ability to raise serum zinc levels, even to the level of the healthy control group.

References

1. Gilhar A, Etzioni A, Paus R. Alopecia areata. New England Journal of Medicine. 2012;366(16):1515–25.

2. Bertolini M, et al. JAK-STAT pathway activation in AA. J Invest Dermatol. 2020;140(1):68–78.

3. Harris JE, et al. A mouse model for AA. J Clin Invest. 2010;120(8):3175–86.

4. Xing L, et al. IFN-γ–dependent inflammatory response in AA. Nature Medicine. 2014;20(9):1043–9.

5. Craiglow BG, King BA. Tofacitinib for severe AA. JAMADermatol. 2014;150(9):976

6. Mackay-Wiggan J, et al. Oral ruxolitinib for AA: pilot trial. JCI Insight. 2016;1(15).

7. Jabbari A, et al. Molecular signature for AA response to JAK inhibitors. Nat Med. 2015;21(9):1015–9.

8. Kennedy Crispin M, et al. T-cell dysregulation in AA. J Invest Dermatol. 2013;133(2):298–306.

9. Ito T, et al. Collapse of immune privilege in AA. J Invest Dermatol. 2008;128(2):345–53.

10. Zöller M, et al. MHC class I antigens in hair follicle epithelium. J Invest Dermatol. 1987;89(4):342–8.

11. Freyschmidt-Paul P, et al. Hair follicle–specific immune privilege. Skin Pharmacol Physiol. 2005;18(3):153–64.

12. Gilhar A, et al. Development of AA model in human scalp grafted to mice. J Invest Dermatol. 2013;133(3):748–53.

13. Hamed FN, et al. IL-15 involvement in AA. J Invest Dermatol. 2015;135(6):1578–84.

14. Wang ECE, et al. CXCL9/10 and CXCR3 in inflammation. Immunology. 2013;140(2):225–36.

15. King BA, et al. JAK inhibitors for AA consensus. J Am AcadDermatol. 2018;78(2):403–14.

16. Kinnunen T, et al. Pediatric AA and treatment outcomes. PediatrDermatol. 2011;28(3):306–11.

17. Kaur M, et al. Treatment responses in AA. Int J Trichology. 2015;7(2):45–50.

18. Zhang X, et al. JAK inhibitors and COVID-19. J Allergy ClinImmunol. 2021;147(1):71–89.

19. Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014;20(9):1043–9. doi:10.1038/nm.3645

20. Pirali T, Serafini M, Cargnin S, Genazzani AA. Applications of deuterium in medicinal chemistry. J Med Chem. 2019;62(11):5276–97. doi:10.1021/acs.jmedchem.8b0180

21. Kim JE, Lee YJ, Park HR, Lee DG, Jeong KH, Kang H. The effect of JAK inhibition on the survival, anagen entry, and hair follicle immune privilege restoration in human dermal papilla cells. Int J Mol Sci. 2020;21(14):5137. doi:10.3390/ijms21145137

22. Dai Z, Sezin T, Chang Y, Lee EY, Wang EHC, Christiano AM. Induction of T cell exhaustion by JAK1/3 inhibition in the treatment of alopecia areata. Front Immunol. 2022;13:955038. doi:10.3389/fimmu.2022.955038

23. Mackay-Wiggan J, Jabbari A, Nguyen N, Cerise JE, Clark C, Ulerio G, et al. Oral Ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight. 2016;1(15):e89790. doi:10.1172/jci.insight.89790

24. King B, Mesinkovska N, Mirmirani P, Bruce S, Kempers S, Guttman-Yassky E, et al. Phase 2 randomized, dose-ranging trial of CTP-543, a selective Janus kinase inhibitor, in moderate-to-severe alopecia areata. J Am AcadDermatol. 2022;87(2):306–13. doi:10.1016/j.jaad.2022.03.045

25. King B. Top-line results from THRIVE-AA1: a clinical trial of CTP-543 (deucravacitinib), an oral JAK inhibitor, in adult patients with moderate to severe alopecia areata. Milan, Italy: 31st EADV Congress; 2022. p.3473

26. Zhang Y, Ma H, Jiang Z, Wu D, Zhuang J, Li W, et al. Safety and efficacy of Jaktinib in the treatment of Janus kinase inhibitor-naïve patients with myelofibrosis: Results of a phase II trial. Am J Hematol. 2022;97(12):1510–9. doi:10.1002/ajh.26709

27. Schöff M, Petzer V, Warr MR, Haschka D, Tymoszuk P, Demetz E, et al. Momelotinib inhibits ACVR1/ALK2, decreases hepcidin production, and ameliorates anemia of chronic disease in rodents. Blood. 2017;129(13):1823–30. doi:10.1182/Blood-2016-09-740092

28. Liu J, Lv B, Yin H, Zhu X, Wei H, Ding Y. A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple ascending dose and food effect study to evaluate the kinetics of jaktinib, a novel selective Janus kinase inhibitor in healthy Chinese volunteers. Front Pharmacol. 2020;11:604314. doi:10.3389/fphar.2020.604314

29. Zhou C, Yang X, Yang B, Yan G, Dong X, Ding Y, et al. A randomized, double-blind, placebo-controlled phase II study to evaluate the efficacy and safety of Ivarmacitinib (SHR0302) in adult patients with moderate to severe alopecia areata. J Am AcadDermatol. 2023. doi:10.1016/j.jaad.2023.02.063

36) Bissonnette R, Luger T, Thaci D, Toth D, Lacombe A, Xia Y, et al. Secukinumab demonstrates high sustained efficacy in subjects with moderate to severe plaque psoriasis through 5 years of treatment: Results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J Am AcadDermatol. 2023;88(1):29–39. doi:10.1016/j.jaad.2022.07.002

36) Bugaut H, Aractingi S. Major role of the IL17/23 axis in psoriasis supports the development of new targeted therapies. Front Immunol. 2021;12:621956. doi:10.3389/fimmu.2021.621956

37) Ito T, Suzuki T, Sakabe JI, Funakoshi A, Fujiyama T, Tokura Y. Plasmacytoid Dendritic cells as a possible key player to initiate alopecia areata in the C3H/HeJ mouse. Allergol Int. 2020;69(1):121–31. doi:10.1016/j.alit.2019.07.009

38) Jekl-Burnat A, Osinska M, Salinska A, Blicharz L, Goldust M, Olszewska M, et al. The role of serum Th1, Th2, and Th17 cytokines in patients with alopecia areata: Clinical implications. Cells. 2021;10(12):3397. doi:10.3390/cells10123397

39) Renert-Yuval Y, Guttman-Yassky E. The changing landscape of alopecia areata: the therapeutic paradigm. AdvTher. 2017;34(7):1594–609. doi:10.1007/s12325-017-0542-7

40) Abou Rahal J, Kurban M, Kibbi AG, Abbas O. Plasmacytoid dendritic cells in alopecia areata: missing link? J EurAcadDermatolVenereol. 2016;30(1):119–23. doi:10.1111/jdv.12932

41) Nasimi M, Ghani N, Abedini R, Mirshamsi A, Shakoei S, Ehsani AH. Efficacy and safety of anthralin in combination with diphenylcyclopropenone in the treatment of alopecia areata: A retrospective case series. Arch Dermatol Res. 2019;311:607–13. doi:10.1007/s00403-019-01940-x

42) Tang L, Cao L, Sundberg JP, Lui H, Shapiro J. Restoration of hair growth in mice with alopecia areata-like disease using topical anthralin. J Invest Dermatol. 2004;13:5–10. doi:10.1111/j.0906-6705.2004.00998.x

43) Nelson PA, Sluggett LW. Anthralin therapy for alopecia areata. Int J Dermatol. 1985;24:606–7. doi:10.1111/j.1365-4362.1985.tb05863.x

44) Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. Arch Dermatol. 1987;123:1491–3.

45) Wong WK, Shin H, Choi GS. Therapeutic effect of topical anthralin for treatment-resistant extensive alopecia areata. Korean J Dermatol. 2008;46:641–7.

46) Sharma PK, Jain RK, Sharma AK. PUVASOL therapy in alopecia areata. Indian J DermatolVenereolLeprol. 1990;56:301–3.

47) Tosti A, Piraccini BM, Pazzaglia M, et al. (2003) (Text cut off at this point in the image)

36) Buguati H, Aractingi S. Major role of the IL17/23 axis in psoriasis supports the development of new targeted therapies. Front Immunol. 2021;12:621956. doi:10.3389/fimmu.2021.621956

37) Ito T, Suzuki T, Sakabe JI, Funakoshi A, Fujiyama T, Tokura Y. Plasmacytoid Dendritic cells as a possible key player to initiate alopecia areata in the C3H/HeJ mouse. Allergol Int. 2020;69(1):121–31. doi:10.1016/j.alit.2019.07.009

38) Jekl-Burnat A, Osinska M, Salinska A, Blicharz L, Goldust M, Olszewska M, et al. The role of serum Th1, Th2, and Th17 cytokines in patients with alopecia areata: Clinical implications. Cells. 2021;10(12):3397. doi:10.3390/cells10123397

39) Renert-Yuval Y, Guttman-Yassky E. The changing landscape of alopecia areata: the therapeutic paradigm. AdvTher. 2017;34(7):1594–609. doi:10.1007/s12325-017-0542-7

40) Abou Rahal J, Kurban M, Kibbi AG, Abbas O. Plasmacytoid dendritic cells in alopecia areata: Missing link? J EurAcadDermatolVenereol. 2016;30(1):119–23. doi:10.1111/jdv.12932

41) Nasimi M, Ghani N, Abedini R, Mirshamsi A, Shakoei S, Ehsani AH. Efficacy and safety of anthralin in combination with diphenylcyclopropenone in the treatment of alopecia areata: A retrospective case series. Arch Dermatol Res. 2019;311:607–13. doi:10.1007/s00403-019-01940-x

42) Tang L, Cao L, Sundberg JP, Lui H, Shapiro J. Restoration of hair growth in mice with alopecia areata-like disease using topical anthralin. J Invest Dermatol. 2004;13:5–10. doi:10.1111/j.0906-6705.2004.00998.x

43) Nelson PA, Sluggett LW. Anthralin therapy for alopecia areata. Int J Dermatol. 1985;24:606–7. doi:10.1111/j.1365-4362.1985.tb05863.x

44) Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. Arch Dermatol. 1987;123:1491–3.

45) Wong WK, Shin H, Choi GS. Therapeutic effect of topical anthralin for treatment-resistant extensive alopecia areata. Korean J Dermatol. 2008;46:641–7.

46) Sharma PK, Jain RK, Sharma AK. PUVASOL therapy in alopecia areata. Indian J DermatolVenereolLeprol. 1990;56:301–3.

47) Tosti A, Piraccini BM, Pazzaglia M, et al. Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. J Am AcadDermatol. 2003;49:96–8.

48) Coronel-Perez IM, Rodriguez-Rey EM, Camacho-Martinez FM. Latanoprost in the treatment of eyebrow alopecia areata and universalis. J EurAcadDermatolVenereol. 2010;24:481–5.

49) Vila TO, Camacho Martinez FM. Bimatoprost in the treatment of eyelash universalis alopecia areata. Int J Trichol. 2010.

55) Abbas AN. Ginger (Zingiberofficinale (L.) Rosc) improves oxidative stress and trace elements status in patients with alopecia areata. Niger J ClinPract. 2020;23:1555–60. doi:10.4103/njcp.njcp_59_19