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Advances in Alopecia: From Diagnosis to Treatment

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Abstract

Alopecia is the loss or absence of hair in anticipated areas, presenting a diverse spectrum of manifestations, spanning from localised to diffuse and temporary to permanent, affecting individuals of all genders and age brackets. Despite the lack of critical physiological function in scalp hair, its loss has a notable impact on self-confidence, reflected in the substantial annual expenditure of around $US1.5 billion by 60 million individuals in the US on diverse hair regrowth treatments. This prevalent and distressing medical concern reaches most individuals globally by middle age. Recognising the considerable emotional and physical burden associated with alopecia, clinicians must perceive it not merely as a cosmetic issue. Often serving as an indicator of underlying systemic conditions such as autoimmune disease, anaemia, nutritional deficiencies, and chronic infections, alopecia necessitates comprehensive clinical assessment and appropriate treatment. This approach is essential to prevent patient dissatisfaction and facilitate identifying and managing potentially significant medical conditions. Alopecia includes various subtypes, among which the nonscarring type has a higher incidence than the scarring type. Currently, there are very few approved drugs: minoxidil, finasteride and a very few JAK inhibitors for the treatment of various kinds, but most of the drugs are used off-label. This review provides a comprehensive overview of the pharmacotherapy of different alopecia types.

Keywords: Alopecia; JAK inhibitors; Alopecia areata;

Introduction

As per the National Institute of Health's (NIH) definition, alopecia is the absence or loss of hair in expected areas, with manifestations ranging from localised to diffuse, temporary to permanent, affecting

all genders and age groups. This condition, stemming from diverse causes, is broadly categorised as nonscarring (the most prevalent) and scarring (cicatricial). While scalp hair lacks a critical physiological function, its loss can significantly impact self-confidence, which is evident in the annual spending of approximately $US1.5 billion by 60 million people in the US on various hair regrowth treatments.[1]

Alopecia is a widespread and distressing medical issue, affecting a majority of individuals globally by middle age. The psychosocial ramifications of hair loss are considerable, leading to heightened self-consciousness, reduced self-esteem, and an increased risk of psychiatric disorders such as depression and anxiety among those experiencing hair loss compared to the general population. Recognising the substantial emotional and physical burden of alopecia, clinicians must view it beyond as a cosmetic concern. Often indicative of underlying systemic conditions like autoimmune disease, anaemia, nutritional deficiency, and chronic infection, alopecia warrants thorough clinical evaluation and appropriate treatment to prevent patient dissatisfaction and facilitate the identification of medically significant conditions.[2]

Epidemiology

In 2019, a retrospective multi-centre study aimed to examine the prevalence of various types of alopecia among patients seeking consultation at specialised hair clinics and to evaluate global variations. The study encompassed over 3000 alopecia diagnoses, revealing that 73% were nonscarring and 27% were scarring. [3]

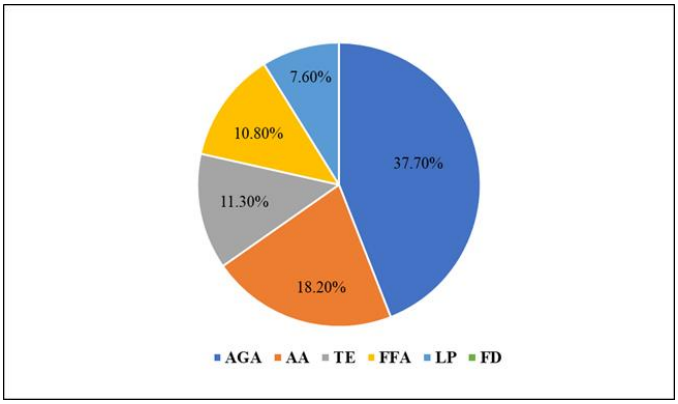


Figure 1: Prevalence of non-scarring and scarring alopecia [3]

Nonscarring alopecia frequency

- Androgenetic alopecia (AGA)
- Alopecia areata (AA)
- Telogen effluvium (TE)

Scarring alopecia frequency

- Frontal fibrosing alopecia (FFA)
- Lichen planopilaris (LP)
- Folliculitis decalvans (FD)

The remaining types of alopecia listed in the study had frequencies below 2%. Furthermore, the article delves into gender-based differences, median age ranges by gender, and continental disparities in the prevalence of hair disorders. [3]

Hair cycle

The pilosebaceous unit, comprised of the hair follicle, erector pili muscle, and sebaceous glands, is responsible for scalp hair dynamics. Throughout life, scalp hair undergoes continuous turnover. Anagen resumes as hair matrix cells divide, and the lower follicle redevelops. The cyclical process involves anagen for growth, catagen for transition, and telogen for resting. Due to this cyclical process, healthy young adults experience a balance between the shedding and regrowth of scalp hair, maintaining typical hair densities ranging from 300 to 350 hairs per cm^2. [1]

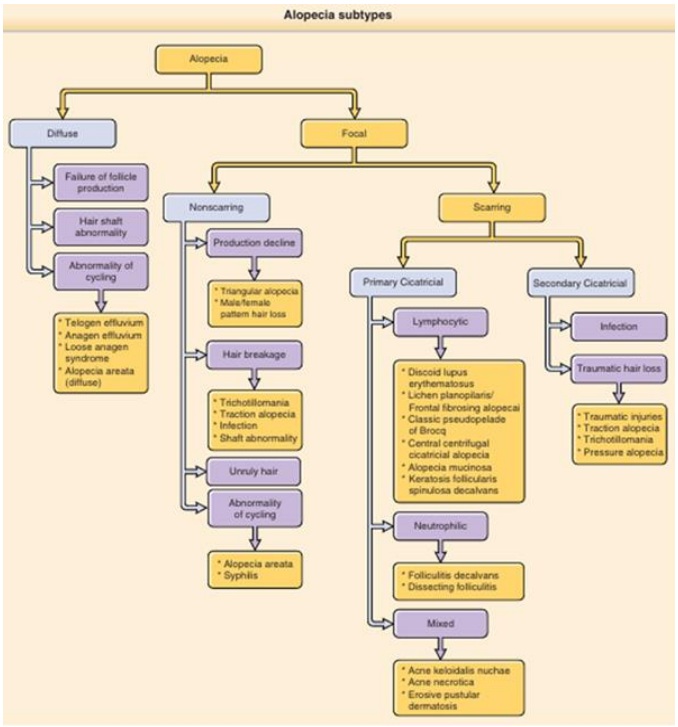
Table 1: Phases of hair cycle

Hair Cycle Phase	Description
Anagen	In the active growth phase, hair matrix cells divide rapidly, forming the hair shaft. Lasts 3 to 8 years on the scalp.
Catagen	Morphological changes, including mitosis cessation, reabsorption, and cell death in the lower follicle segment mark a brief period following anagen.
Telogen	In a 3-month resting phase, the scalp follicle is inactive before hair shedding occurs.

Figure 2: Phases of hair growth cycle [2]

Types of alopecia

Figure 3: Classification of alopecia [2]



Non-scarring alopecia

Non-scarring alopecia, or non-cicatricial alopecia, is a subtype of hair loss that manifests in a localised scalp area. Unlike scarring alopecia, this condition occurs without any scalp scarring, preserving the hair follicles and allowing for the potential of hair regrowth. In contrast to scarring alopecia, where the hair follicles are irreversibly destroyed and replaced by scar tissue, non-scarring alopecia encompasses conditions such as androgenetic alopecia, alopecia areata, telogen effluvium, anagen effluvium, traction alopecia, and trichotillomania. This distinction highlights the preservation of hair follicles in non-scarring alopecia, contributing to the possibility of regaining lost hair. [4]

Androgenetic alopecia (AGA)

Androgenetic alopecia (AGA) stands as the most prevalent form of hair loss, impacting approximately 50% of Caucasians aged 40 and above. It is termed male pattern baldness (MPB) in men and female pattern hair loss (FPHL) in women. This progressive condition can commence as early as late adolescence.[1] AGA is androgen-dependent, displaying a hereditary inheritance pattern. In predisposed individuals, scalp hair undergoes progressive thinning in a specific pattern, commonly at the vertex. Notably, the condition involves non-scarring, progressive miniaturisation of hair follicles and shafts.[5] Despite similar testosterone levels, individuals with AGA exhibit higher levels of unbound or active

testosterone. The inheritance pattern of AGA is complex, likely polygenic and multifactorial, with identified genetic susceptibility loci. [6]

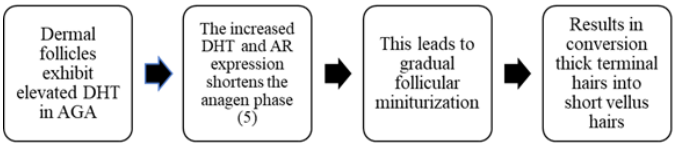
Approximately 73 % of the men over the age of 80 years and 58% of men over the age of 50 years are affected by androgenetic alopecia, leading to reduced self-confidence, helplessness and depression.[7]

The incidence of FPHL rises with age, impacting 50% of women over their lifetime. [8]. FPHL, a prevalent form of non-scarring alopecia in women, is observed in 6% of women under 50 years of age, with the prevalence escalating to 38% in those aged 70 years and older. [9]

Pathophysiology

MPB

The pathogenesis of AGA in men is linked to the purported binding of DHT to androgen receptors (AR) situated at the hair follicle. DHT, produced by converting testosterone through 5-α-reductase type 2, is an enzyme in the follicle dermal papilla. Without intervention, patients experience progressive hair loss. [7]



Sawaya and Price's research revealed a 30% increase in androgen receptor protein concentrations within the outer root sheath and dermal papilla fibroblasts of balding frontal follicles compared to their nonbalding counterparts. This heightened androgen binding at receptor sites has notable effects on follicular physiology. [1]

Additionally, multiple genetic susceptibility loci, including the HDAC9 gene on chromosome 7p21.1, chromosome 3q26, PAX1/FOXA2 locus on chromosome 20p11, and androgen receptor (AR)/EDAR2 locus on the X chromosome, have been identified for AGA. [6]

FPHL

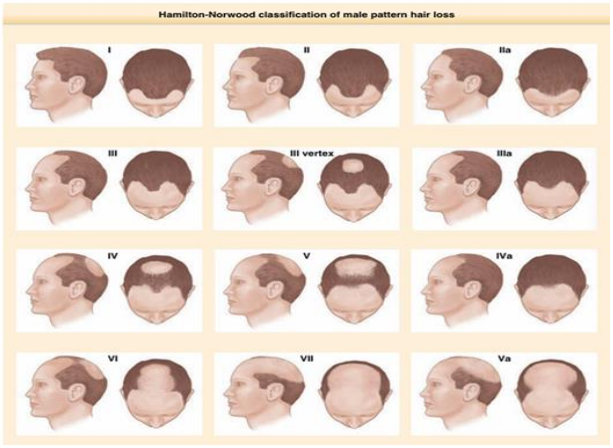
The underlying causes are fundamentally the same as those observed in men. However, it is crucial to rule out the potential for endocrine dysfunction consistently. In females, the conversion of dehydroepiandrosterone (DHEA) into testosterone and the absence of aromatase, a key enzyme facilitating the conversion of androgens into oestrogens, are more commonly observed than in males. Beyond androgens, diminished levels of oestrogens may also play a role in the development of Androgenetic Alopecia (AGA), particularly in situations of hypoestrogenous AGA in post-menopausal women or following ovariectomy. In rare instances, post-menopause or ovariectomy may lead to the receding of the fronto-parietal hairline or the formation of a bald spot, similar to patterns seen in men. [10]

Clinical features

The clinical manifestations of Androgenetic Alopecia (AGA) can range in severity, from a subtle recession of the frontal hairline to extensive hair loss, leaving only the temporal and occipital margins unaffected. In females, the condition typically presents with a milder profile, characterised by diffuse thinning of scalp hair. Onset of clinical symptoms in both men and women commonly occurs by the age of 30 years. [1].

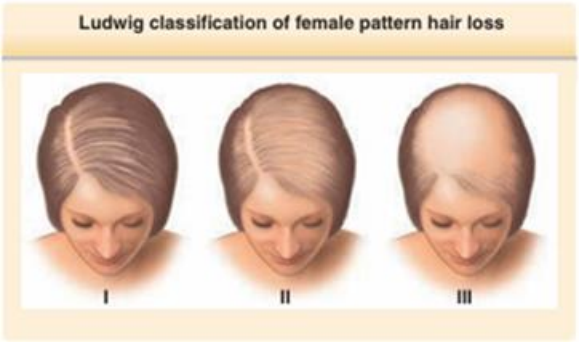
The Hamilton classification system delineates the predominant progression in men, characterised by a receding frontal hairline and bitemporal hair loss merging with vertex thinning.

Figure 4: Hamilton – Norwood classification of MPB [10]



Conversely, the anterior hairline remains intact in women, and thinning predominantly occurs at the crown, following the Ludwig pattern.

Figure 5: Ludwig classification of FPHL [10]



Diagnosis

The severity of hair shedding can be evaluated using the pull test, where 40–60 strands of hair are gently pulled away from the scalp. A negative or routine pull test is indicated when three or fewer hair strands are extracted from a single area, while a positive pull test is characterised by the extraction of six or more strands. Trichoscopy proves helpful in discerning the specific type of hair loss and identifying the presence of perifollicular erythema and/or scale.

The earliest diagnostic feature of Androgenetic Alopecia (AGA) is a hair shaft diameter variation exceeding 20% of the hair shafts, accompanied by an increased proportion of vellus hairs. In severe cases of AGA, yellow dots may be observed, representing hypertrophied sebaceous glands. [6].

Microscopy

Microscopic examination reveals histological features indicative of the initial phase, marked by focal perivascular basophil degeneration of connective tissue surrounding the lower third of the anagen follicle. Subsequently, a perifollicular lymphocyte infiltrate develops. Microscopic analysis also detects a growing prevalence of telogen hairs, with a pronounced increase observed mainly at the frontal and crown regions. Dystrophic hairs, though less frequent, may also be identified. The elevated count of telogen hairs in the peripheral zones of alopecia indicates the progressive nature of the condition. [10].

Treatment

Pharmacological treatment

At present, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved exclusively topical minoxidil (MNX) and oral finasteride (FNS) for the treatment of androgenetic alopecia (AGA) (5). Minoxidil is a topical vasodilator that can prolong the anagen phase and enhance the size of smaller hair follicles. On the other hand, finasteride is an oral medication that acts by inhibiting 5α-reductase type II, preventing the conversion of testosterone to DHT. [11]

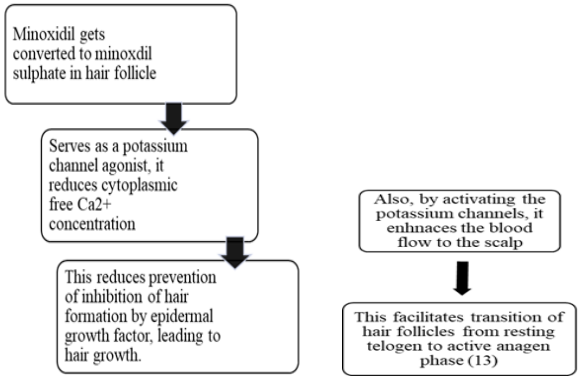
Minoxidil

History: Minoxidil originated in 1970, when it was initially identified as a potent vasodilator and investigated for its oral use in treating severe refractory hypertension [12]. During the early trials, one of the pioneering studies documented the occurrence of hypertrichosis with chronic use of the drug, noting this

effect in five out of eight subjects who had been taking the medication for more than two months. [13].

Following a protracted patent dispute, a significant milestone occurred in 1988 when the first topical minoxidil product, Rogaine®, received approval from the United States (US) Food and Drug Administration (FDA) for the treatment of androgenetic alopecia (AGA). Initially, the original formulation, a 2% solution, was available only by prescription and targeted towards men. Subsequently, the FDA approved topical minoxidil in 1992, which is available as a 2% solution and 5% foam, and it was widely used in women with FPHL. By 1996, both formulations became accessible for purchase without a prescription. [13].

Mechanism of Action: The precise mechanism(s) through which minoxidil facilitates hair growth are not fully comprehended, and multiple pathways are believed to be implicated. [1]



- Alternatively, minoxidil may induce an up-regulation in the expression of vascular endothelial growth factor and its receptors, leading to angiogenesis and anagen stimulation. In a contrasting observation, Philpot and colleagues demonstrated that minoxidil stimulates regrowth in hair follicle cultures even without a blood supply. [1]
- Additionally, other researchers have noted minoxidil's potent activation of prostaglandin endoperoxide synthase-1, an enzyme with cytoprotective properties that stimulates hair growth. It exerts a specific and direct effect on the proliferation and differentiation of follicular keratinocytes, resulting in the prolonged duration of the anagen phase. These alterations contribute to the extension of the anagen phase and the conversion of vellus hairs into terminal hairs [1].

Table 2: Comparison of topical and oral minoxidil

	Topical Minoxidil	Oral Minoxidil
Dosage	• Recommended dosage involves applying a 2% or 5% solution and 5% foam • Dose to apply 1 ml twice daily for individuals> 18 years of age • A 5% solution is preferred in men [6]	• Daily doses range between 10 and 40 mg • Not routinely recommended for AGA due to potential adverse effects. [12]

Formulations	• Available without prescription as a 2% or 5% solution, and 5% foam • These cater to different preferences and provide flexible options for both men and women.	• Available in various formulations, but its use is largely avoided • The specific concentration might be used, based on the patient's unique circumstances.
Efficacy	• Consistent application of minoxidil twice daily for an extended period is necessary. • But the benefits are temporary, and discontinuation may lead to a gradual return of hair loss. [10]	• Generally, it is utilised off-label for various hair conditions such as central cicatricial alopecia and TE.
Adverse Effects	• Transient hair shedding phase typically occurs upon initial application • Facial hypertrichosis, contact dermatitis in the first month of use • Local cutaneous reactions are more prevalent with higher percentage formulations because of high propylene glycol content. [6]	• Sodium and fluid retention, mainly in renal conditions, manifesting as oedema or weight gain, leading to pulmonary congestion • Cardiac implications like pericardial effusion, congestive heart failure.
Contraindications	• In patients with a history of hypersensitivity to the drug.	• Severe renal pathologies

Effectiveness: Most studies focused on male subjects, but adequate data for women using 2% topical minoxidil solution twice daily were available. A meta-analysis of these studies revealed a mean difference of 112.41 hairs/cm2 in the 2% minoxidil group compared to placebo treatment.[7] In male androgenetic alopecia (AGA), Lueangarun et al. investigated the efficacy of a daily 5 mg dose of oral minoxidil over 24 weeks. The study revealed 100% improvement, with 43% of men experiencing "remarkable" improvement, particularly in the vertex and frontal areas, and prolonged treatment showed even more notable results. [14]

Challenges and Compliance with Topical Minoxidil: While topical minoxidil proves effective for hair loss, some patients struggle with compliance due to the requirement for twice-daily application, concerns about hair texture changes, and potential scalp irritation. Patients initiating topical application should be aware of a temporary shedding phase. [6]

Combination Therapies: Combining topical minoxidil with antiandrogens like cyproterone acetate or spironolactone has shown efficacy in reducing hair shedding and improving hair density in female pattern hair loss (FPHL) patients. [15]

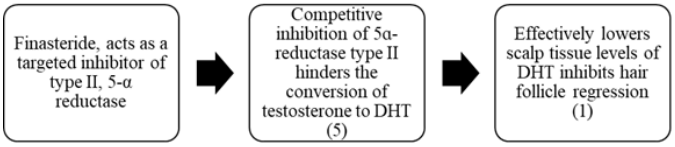
Finasteride

History: The 5-alpha reductase inhibitor (5-ARI) enzyme family (responsible for converting testosterone into DHT), comprising types I, II, and III, plays a pivotal role in regulating the metabolism of three distinct pathways—bile, androgens, and oestrogen. The systemic

5α-reductase inhibitor finasteride (FNS), classified as a 4-aza-3-oxosteroid compound, has undergone extensive research and is clinically utilized for treating benign prostate hyperplasia (BPH) and androgenetic alopecia (AGA). In the latter part of 1997, the US Food and Drug Administration (FDA) granted approval for oral finasteride at a daily dosage of 1 mg for the management of AGA in men. However, the authorization does not extend to women due to potential teratogenic effects on a male foetus, hence it is used off-label for female pattern hair loss (FPHL). [16]

Mechanism of action

MPB



FPHL

A study conducted in mice proposed that dihydrotestosterone (DHT) might diminish the expression of insulin-like growth factor-1 (IGF-1) by inhibiting the release of calcitonin gene-related peptide, which interacts with androgen receptors, thereby hindering hair growth. These findings suggested a potential association between finasteride and increased IGF-1 production in the dermal papillae through the reduction of DHT levels. Rushton et al observed that finasteride administration led to a notable rise in mean hair density without significant changes in vellus hair counts. The observed regrowth of hair in female pattern hair loss (FPHL) may be attributed to the reactivation of telogen follicles into anagen follicles, rather than a transformation from vellus to terminal hair. [8]

PK

Oral Formulation: The mean terminal half-life of finasteride is approximately five to six hours in men aged 18–60 years and eight hours in men over 70 years of age. Steady-state is achieved within three days. The bioavailability of oral finasteride is 80%, unaffected by food intake. Metabolism occurs exclusively via cytochrome P450 3A4 in the liver. Approximately 57% of the dose is excreted in faeces, and around 39% is excreted in urine within 7 days of administration. DHT returns to pretreatment levels approximately 14 days after discontinuation. [8]

Topical Formulation: The pharmacokinetics of topical finasteride involve considerations for skin penetration and systemic absorption. The ideal formulation emphasizes high skin penetration and low systemic absorption. [8]

Table 3: Comparison of topical and oral finasteride

	Topical Finasteride	Oral Finasteride
Dosage	• Administered in doses of 100 µL (0.2275 mg) and 200 µL (0.455 mg) of a 0.25% solution applied daily. • Once-daily application is more effective than twice-daily application in decreasing scalp DHT level both men and women. [5]	• Administered at a daily dose of 1 mg • Low-to-medium doses has demonstrated efficacy in reducing serum DHT levels without complications in both men and postmenopausal women. [8]

Formulations	• Delivery methods include nanoparticle formulations, liposomes, micro-plated films, and the use of absorption enhancers such as ethanol and propylene glycol. • Finasteride liposomal gel systems containing 2% methylcellulose and gel systems containing poloxamer P407, have exhibited high skin penetration at the application site. [5]	• Available in tablet form for daily administration • Oral formulation has been associated with systemic side effects thus favouring topical formulation to minimize those effects
Efficacy	• More effective in regrowing hair at the vertex scalp compared with the frontal/ centroparietal scalp. [6] • Combining topical finasteride with minoxidil (MNX) and/or dutasteride has demonstrated greater efficacy at hair regrowth than topical MNX alone	• More effective in treating the vertex type than the frontal type of androgenetic alopecia • The efficacy does not diminish over time, providing consistent results. • It is effective in with a reduction in serum levels of dihydrotestosterone (DHT) and androstanediol glucuronide.[10]
Adverse Effects	• Scalp irritation, erythema, contact dermatitis, as well as increased liver enzymes, bed-wetting, testicular pain, headaches, presyncope, and oropharyngeal pain. [17] • May offer a safe alternative for females, particularly in AGA, where systemic use is not approved during pregnancy and childbearing women due to potential risk of genital defects in male foetus (Category X drug)	• The most concerning side effects include sexual dysfunction, mood disorders, gynecomastia, breast tenderness, malignant neoplasms, decreased ejaculate volume, testicular pain and an increased risk of high-grade prostate cancer in men[17] • Women also reported various side effects such as sexual dysfunction, dizziness, allergic reactions, elevated liver enzymes, and depression[9]

Effectiveness: A retrospective study using 5% topical minoxidil fortified with 0.1% finasteride, following initial use of a combination of 5% topical minoxidil and 1 mg oral finasteride, indicated that topical combination therapy could sustain favorable hair density even after discontinuing oral finasteride. The research included patients who paused treatment for 8-12 months, with 80% showing significant improvement upon resuming the combination of topical minoxidil and finasteride in both male and female pattern baldness[18]

Similar results were seen in a randomized double blind control study for efficacy and safety of topical solution of 0.25 % finasteride administered with 3% minoxidil vs 3% minoxidil alone showed significant difference in hair

density and hair diameter from baseline to week 24 with better tolerance. [9]

Dutasteride

Mechanism of Action: Dutasteride is a second-generation 5-ARI that inhibits both type I and II 5α-reductase isoenzymes. It is notably three times more potent at inhibiting the type I enzyme and an impressive 100 times more potent at inhibiting the type II enzyme than finasteride. This dual blockade distinguishes dutasteride from finasteride, which only inhibits 5-alpha reductase type 2. By inhibiting both isoenzymes, dutasteride is recognized as a dual blocker, offering superiority in treating male androgenetic alopecia (AGA)[16] .

Dosage & formulation: The formulation of dutasteride involves its oral administration at the approved dosage of 0.5 mg. The dual inhibition of the type 1 receptor, responsible for converting 20% of dihydrotestosterone (DHT) from testosterone, contributes to dutasteride's efficacy in treating male AGA. [16]

Efficacy: Dutasteride, as a dual reductase inhibitor, exhibits effectiveness in treating AGA and has shown the ability to reverse miniaturization, a characteristic not shared with finasteride. Comparative studies suggest that dutasteride surpasses finasteride in addressing male AGA. [16]

A recent meta-analysis by with 0.5 mg dutasteride once daily treatment showed significant efficacy in increasing hair count at 24 weeks compared to 1mg finasteride once daily and 0.25 mg once daily. [19]

Adverse Effects: Adverse effects associated with dutasteride, similar to finasteride, include sexual dysfunction, altered libido, erectile dysfunction, ejaculatory dysfunction, and gynecomastia. These are effects were well-tolerated across different treatment groups, and no dose-dependent adverse effects were linked to dutasteride [6].

Prostaglandins

In 2008, the FDA approved bimatoprost, an analogue related to prostaglandin F2α, specifically for the treatment of eyelash hypotrichosis. This marked a significant milestone in the use of prostaglandins for hair-related conditions. [17]

Mechanism of action: Recent studies have revealed that scalp hair follicles also express prostanoid receptors, primarily situated in the dermal papilla and the connective tissue sheath surrounding the hair bulb. Prostaglandin F2 (PGF2) and PGE2 have been identified as contributors to hair growth, promoting the prolongation of the anagen phase. [6]

In a randomized double blinded cross over study in AGA patients over a period of 16 weeks with bimatoprost 0.03% solution showed increased total hair count in target areas. [20]

Oral spironolactone

Spironolactone, recognized as a potassium-sparing diuretic and antiandrogen, has established itself as a significant therapeutic option. Initially developed for its diuretic properties, it has evolved into a treatment for Female Pattern Hair Loss (FPHL) marks a notable historical progression. [6]

Mechanism of Action: Structurally a steroid, spironolactone operates by inhibiting 17-alpha hydroxylase and 17, 20 lyase, leading to a reduction in testosterone production. This dual action positions it as an effective antiandrogen, particularly beneficial in treating FPHL. However, it is contraindicated in male Androgenetic Alopecia (AGA). [6]

Dosage & formulations: The standard dosage for FPHL ranges from 12.5 to 200 mg daily [6]. Available in tablet

form, spironolactone comes in 25 and 100 mg variants. Its off-label use is widely accepted in FPHL, even though it's not FDA approved [15].

Efficacy: Spironolactone has demonstrated remarkable efficacy in the treatment of FPHL, with over 90% of women experiencing a halt in progression. Approximately 30% of women have shown improvement in standardized scalp photographic assessments, underscoring its effectiveness in promoting positive outcomes. [15]

In an open interventional study by Sinclair et al., performed a before after treatment of spironolactone 200 mg in 80 women with FPHL for 12 months showed 44% improvement in hair growth. [15]

Adverse Effects: Notable side effects associated with spironolactone use include postural hypotension, electrolyte imbalances, breast tenderness, and irregular menstrual cycles [6].

Oral flutamide and bicalutamide

Flutamide

Flutamide, renowned for its robust antiandrogenic properties targeting androgen receptors, has exhibited effectiveness in women with Female Pattern Hair Loss (FPHL) characterized by hyperandrogenism. Administered at a daily dose of 250 mg, flutamide has demonstrated positive outcomes.[6]

In a large prospective study with 101 women diagnosed with FPHL received varying doses of flutamide for a period of 4 years showed significant reduction in alopecia scores compared to baseline[21] Despite its efficacy, flutamide carries a recognized risk of inducing elevated liver enzymes, particularly at higher doses. This emphasizes the importance of vigilant monitoring and risk assessment when considering this antiandrogen for FPHL treatment [21]

Bicalutamide

As a nonsteroidal selective antiandrogen, Bicalutamide emerges as a novel medication with distinct advantages over flutamide, it's superior safety and tolerability profile position it as a promising alternative with minimizing adverse effects. [6]

Oral cyproterone acetate

Cyproterone functions as an antiandrogen by inhibiting gonadotropin-releasing hormones and the androgen receptor. In a randomized controlled trial comparing 2% topical minoxidil and cyproterone acetate in FPHL treatment for a period of 12 months showed more efficacy of cyproterone in women with hyperandrogenism compared to minoxidil. [22]

Topical Clascoterone

Clascoterone is an innovative topical inhibitor of the androgen receptor, exhibiting favourable outcomes in individuals with acne vulgaris. The antiandrogenic characteristics of clascoterone are believed to hold potential for the treatment of androgenetic alopecia (AGA). [6]

Topical Pyrilutamide

Pyrilutamide represents another innovative topical androgen receptor inhibitor. In a phase 2 clinical trial by Kintor Pharma, pyrilutamide was found to be effective with better safety profile in patients with MPHL

Injection Botulinum Toxin

The utilization of injectable botulinum A toxin has become popular as a remedy for androgenetic alopecia (AGA) due to its capacity to disrupt the suppressive impact of DHT on the hair follicle. A Randomized controlled trial found combination of botulinum toxin injection with oral finasteride / minoxidil proved better efficacy than treatment with finasteride / minoxidil alone. [23]

Dutasteride Mesotherapy

The popularity of injectable dutasteride has increased in recent years, attributed to its minimal systemic absorption and consequent reduction in side effects. A multi-centre retrospective study with dutasteride mesotherapy in 541 patients for every 3 months with at least 6 months follow up showed better response to therapy in 16% of patient at the end of 1 year. [24]

Fig 6: Treatment algorithm of male AGA [17]

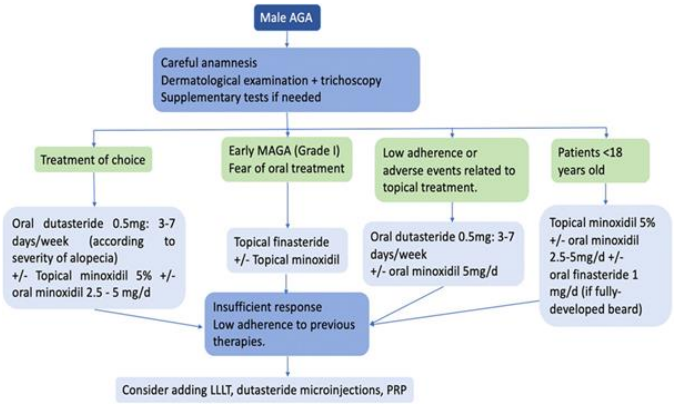
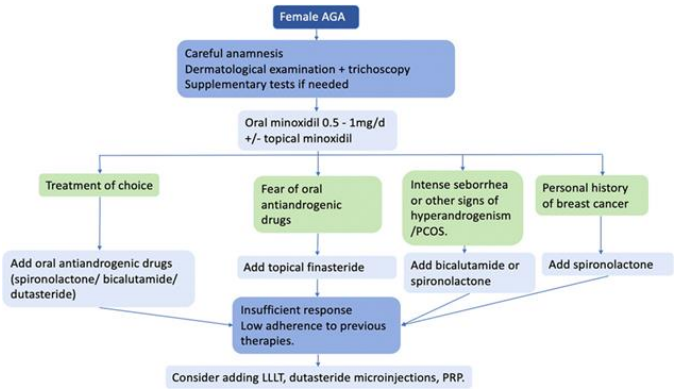


Fig 7: Treatment algorithm of female AGA [17]



Non pharmacological treatment[6]

Platelet-Rich Plasma (PRP): Platelet-rich plasma (PRP) is a recent and popular treatment for androgenetic alopecia (AGA), known for its effectiveness, autologous nature, and minimal side effects. It is prepared from the patient's blood, rich in platelets, growth factors, and cytokines, supporting the body's ability to regenerate and regrow hair. While commonly used in early-stage AGA, PRP requires ongoing long-term treatment for sustained growth,

Low-Level Light Therapy (LLLT): Low-level light therapy (LLLT) utilizes low-energy lasers to stimulate hair regrowth. By oxidizing cytochrome C oxidase, it activates the electron transport chain, increasing ATP production. Devices like the HairMax LaserComb have shown positive results in clinical studies, demonstrating improved hair density and diameter. LLLT is generally well-tolerated, with reported side effects including scalp tenderness and mild urticaria.

Exosomes: Mesenchymal stem cell (MSC)-derived exosomes are emerging as a treatment for AGA, exploiting the regenerative capacity of MSCs and their communication through exosomes. While it is promising in animal models and laboratory studies, the use of exosomes in AGA lacks clear efficacy and safety data and require further research.

Microneedling: Microneedling induces small wounds with needles, promoting platelet-derived growth factor release and angiogenesis. It has shown efficacy when used with growth factor solutions, minoxidil, or PRP in improving hair parameters. While generally these are well-tolerated, microneedling may cause pain, bruising, and folliculitis. Its cost varies, making it an adjunct treatment with varying dosage frequencies.

Vitamins/Minerals: Micronutrient deficiencies have long been linked to increased hair loss. Studies have explored vitamin D, iron, biotin, vitamin B12, folate, and selenium in relation to hair aging and loss. While vitamin D supplementation has shown efficacy in deficiency-related hair loss, specific guidelines for micronutrient supplementation in AGA are still evolving.

Nutraceuticals: Oral and topical nutraceuticals, such as Nutrafol, have gained popularity for promoting hair wellness. Nutrafol, containing a Synergen Complex of 21 phytocompounds, has demonstrated increased hair growth and thickness in clinical trials, with self-assessment parameters improving over time.

Caffeine: Topical caffeine, a phosphodiesterase inhibitor, which increases cAMP and cell metabolism has been considered for AGA treatment due to its stimulant properties. Studies have shown its efficacy comparable to 5% minoxidil solution in promoting hair growth, with no significant side effects reported. Oral caffeine supplements for alopecia treatment remain unstudied.

Plant-Based Oils: Rosemary oil and pumpkin seed oil have been explored for their potential to reduce inflammation, inhibit 5-alpha-reductase, and promote hair growth. Clinical trials have demonstrated increased hair counts and self-rated improvement with the use of these plant-based oils.

Serenoa Repens (Saw Palmetto): Saw palmetto, known for inhibiting 5-alpha-reductase, has been administered topically and orally. Studies have shown improved outcomes in male AGA patients, but finasteride has demonstrated significantly greater efficacy when directly compared. Few minor side effects, including a cold feeling and burning sensation, have been reported.

Combination Therapy: While topical minoxidil and oral finasteride are FDA-approved, various studies and small RCTs have explored combination treatments for AGA. Combinations like LLLT with minoxidil and microneedling with minoxidil have shown significant increases in hair counts, providing viable options for AGA patients, but further studies are required to confirm their efficacy.

Alopecia areata

Alopecia areata (AA) stands as a prevalent hair loss condition, affecting around 2% of individuals throughout their lifetime. AA is recognized as a chronic tissue-specific autoimmune disease characterized by non-scarring hair loss affecting the scalp or any hair-bearing surface. [25] This condition is marked by the sudden onset of non-scarring hair loss, typically occurring in well-defined areas. The extent of involvement varies, ranging from small patches to more widespread or, less frequently, diffuse patterns. While any region with hair can be affected, the scalp, beard area, and eyebrows are often the most visibly impacted. [26]

Epidemiology

Recent estimates indicate that approximately 2% of the general population grapples with AA, encompassing all ethnicities, genders, and age groups. Although both genders display equal susceptibility to AA, studies suggest that male patients may exhibit a comparatively poorer prognosis than their female counterparts, hinting at a potential gender-related influence on the severity of AA. [25]

The onset of AA typically transpires before the age of 40 in 70–80% of affected individuals. Notably, a significant portion (48%) experiences the onset during their initial and second decades, positioning AA as the most prevalent cause of hair loss in otherwise healthy children. While AA can manifest at any age, a substantial 66% of reported cases involve individuals under 30, with a notable frequency of new onset between 25 and 29 years of age. [27]

Etiopathogenesis

The current understanding posits alopecia areata (AA) as an organ-specific autoimmune disease of the hair follicle with a genetic predisposition. The hair follicle (HF) is

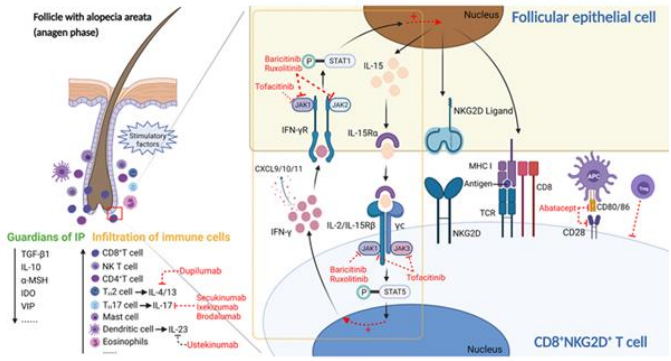
considered an immune-privileged (IP) site, which helps prevent autoimmune responses against autoantigens expressed in the bulge throughout the hair cycle and in the bulb during the anagen phase. This protection is primarily achieved by suppressing the expression of major histocompatibility complex (MHC) class I molecules in anagen hair bulbs, preventing the presentation of autoantigens to CD8 + T cells. Additionally, the secretion of local immunosuppressant molecules, known as "IP guardians," including transforming growth factor-β1 (TGF-β1), interleukin-10 (IL-10), α-melanocyte-stimulating hormone (α-MSH), indoleamine-2,3-dioxygenase (IDO), and vasoactive intestinal peptide (VIP), may contribute to the establishment of a local immunoinhibitory environment, preserving the immune privilege.

Genome-wide association studies (GWAS) and meta-analyses of GWAS have provided further insights into the genetic origins of alopecia areata (AA), identifying about 14 associated genomic regions. (20) A recent examination of copy number variants (CNVs) revealed duplications in melanin-concentrating hormone receptor 2 (MCHR2) and MCHR2 antisense RNA 1 (MCHR2AS1). This suggests a potential role for melanin-concentrating hormone (MCH) signalling in the development of AA.

Studies using mouse models of alopecia areata (AA) reveal that CD8+ NKG2D+ T cells generate IFN-γ through JAK1 and JAK2 pathways, triggering IL-15 production in follicular epithelial cells. This leads to a positive feedback loop, with IL-15 binding to CD8+ NKG2D+ T cells, further enhancing IFN-γ production through JAK1 and JAK3 pathways. The efficacy of Janus kinase (JAK) inhibitors, which block IFN-γ signalling, has been validated in both mouse models of AA and AA patients. [22]

The breakdown of the immune-privileged (IP) status of the hair follicle (HF) is widely acknowledged as a key factor in alopecia areata (AA) development. Factors such as increased IFN-γ secretion, upregulation of NKG2D ligands, MHC molecules, and certain chemokines, along with reduced local "IP guardians," may expose anagen HF-associated autoantigens, leading to HF-IP loss. Inflammation-induced transitions in HF phases can result in AA, but the sparing of HF's epithelial stem cells in the bulge suggests potential reversibility, emphasizing the importance of reestablishing HF-IP for spontaneous or long-term remission. [11]

Fig 8: Overview of etiopathogenesis of Alopecia areata [20]



Clinical features

Clinical manifestations range from small well-defined patches to diffuse involvement of the scalp or the entire body. Typically, AA presents as sudden, patchy hair loss without signs of inflammation or scarring. While some patients may experience mild itching or tingling, most are asymptomatic. Scalp involvement is common (>90%), and other body areas like eyebrows, eyelashes, beard, armpit, and pubic hair may also be affected. Notably, smaller exclamation mark hairs, characterized by thickness at the distal end and thinness at the

proximal end and black dots may be observed at the periphery of active hair loss areas.[25]

Nail involvement, reported in 2-44% of AA patients, is more frequent in children and may persist after alopecia resolution, presenting as twenty-nail dystrophy. [26]

Various AA subtypes include:

1. Patchy alopecia: Single or multiple patches, possibly interconnected.
2. Alopecia total is (AT): Total loss of scalp hairs.
3. Alopecia universal is (AU): Total loss of all scalp and body hairs.
4. Ophiasis: Symmetric band-like hair loss along the hairline.
5. Sisaipho: Extensive hair loss in the central scalp.
6. Acute diffuse and total alopecia (ADTA): Rapid diffuse hair loss, often recovering spontaneously.
7. Marie Antoinette and Thomas More syndrome: Sudden whitening of hair.
8. Alopecia areata incognita (AAI): Diffuse hair thinning without distinct patches.

Several comorbidities are associated with AA, including atopic dermatitis, thyroid disease, lupus erythematosus, vitiligo, psoriasis, inflammatory bowel disease, and rheumatoid arthritis. [20]

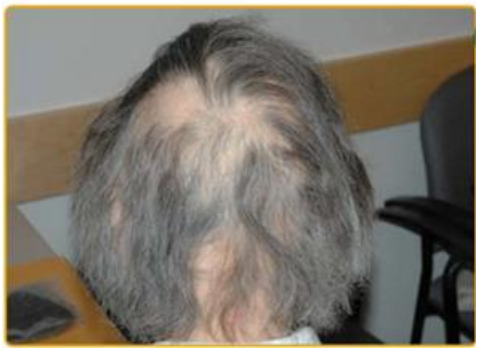


Fig 9: Patchy AA [26]

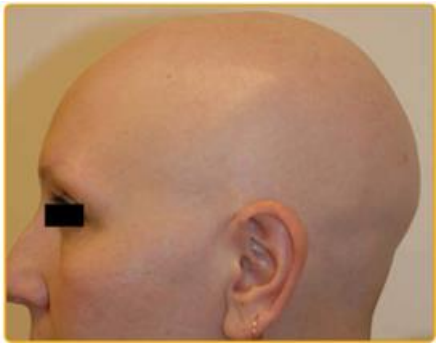


Fig 10: Alopecia total is [26]

Diagnosis

Trichoscopy, a non-invasive technique for diagnosing and monitoring hair loss, reveals specific features associated with alopecia areata (AA). Common trichoscopic findings in AA include yellow dots (62%), short vellus hairs (61%), black dots (53%), tapered hairs (51%), broken hairs (49%), exclamation mark hairs (39%), upright regrowing hairs (23%), and pigtail hairs (21%). Notably, exclamation mark hairs are considered a distinctive indicator of AA. [20]

A gentle hair pull test, particularly during the acute phase, often identifies dystrophic anagen hair roots in AA. Trichoscopy proves valuable in confirming AA while excluding other potential diagnoses. Trichoscopy and histopathology have emerged as clinically significant tools for assessing patients with AA.[27]

Disease course and prognosis

The initial bald patches may either enlarge or multiply, or they can spontaneously resolve with hair regrowth within a few months. Spontaneous recovery occurs in up to 34–50% of patients within a year, but a significant portion may encounter multiple relapses. Approximately 14–25% of patients may advance to either Alopecia Totalis (AT) or Alopecia Universalis (AU), highlighting that complete recovery is infrequent, observed in less than 10% of patients. [20]

Microscopy

The histopathological characteristics of patients with Alopecia Areata (AA) are dynamic and vary across different stages of the disease. During the acute stage, a commonly noted histopathological feature is a peribulbar lymphocytic infiltrate often described as a "swarm of bees." In the chronic stage, a majority of follicles are either in the telogen phase or miniaturized with anagen morphology. This results in a non-inflammatory alopecia appearance with the preservation of sebaceous glands. [20]

Treatment

Current treatments for Alopecia Areata (AA), including corticosteroids, immunomodulators, minoxidil, and contact immunotherapy which exhibit limited efficacy, posing a high risk of adverse effects and frequent recurrence, particularly for patients with severe AA. Advances in understanding the pathogenesis of AA have spurred the development of novel treatment approaches, such as Janus kinase (JAK) inhibitors, biologics, and various small molecular agents. Additionally, contemporary AA therapies, including antihistamines, platelet-rich plasma (PRP) injection, and other innovative methods are still under exploration. [20]

Traditional treatments

Corticosteroids

Corticosteroids are known for its immunosuppressive effect. The pathogenesis of AA includes breakdown of immune privilege in hair follicles. So, the proposed mechanism is suppression of destructive immune reaction targeting hair follicles.

Table 4: Comparison of intralesional, topical & systemic corticosteroids

	Intralesional corticosteroids (ICs)	Topical corticosteroids (TCs)	Systemic corticosteroids (SCs)
Indication	➢ Used in adult patients dealing with one or two small patches of Alopecia Areata (AA). ➢ Applied to larger areas (less than 50% scalp involvement) (20)	➢ Primary therapeutic choice for addressing limited patches in both adult and paediatric patients dealing with alopecia areata (AA).	➢ Predominant treatment avenue for extensive alopecia, particularly in its acute progressive stage (20)
Dosage	➢ Commonly used as intradermal injection with dilutions, doses ranging from 2.5 to 10 mg/ml. ➢ Repeated every 4-6 weeks, and discontinued if no response within 3-6 months. (26)	➢ Clobetasol propionate 0.05% is often the preferred drug, administered at a daily dosage of ointment or foam not exceeding 2.5 grams (21) ➢ 0.25% desoximetasone twice daily is also preferred. (22)	Potential Treatment Options: 1. Methylprednisolone i.v. 500 mg/day for 3 days a month (10 mg/kg in children) 2. Oral prednisolone 300 mg/month (5 mg/kg in children) 3. Oral dexamethasone 0.1 mg/kg/day for 2 consecutive days every week (not tested

			in children) (1)
Efficacy	➢ A recent meta-analysis in 543 patients with focal AA treated with dilute concentrations of TA of <5, 5 and 10 mg/ml showed 62.3%, 80.9% and 76% rate of hair growth respectively.(28)	➢ Studies indicate that the administration of 0.25% desoximetasone twice daily exhibits a higher complete regrowth rate compared to a placebo (57.7% versus 39.9%).	➢ A meta-analysis of 41 studies with 1078 patients with pulse corticosteroid therapy once a week to once a month showed more than 75% of hair re-growth in 43% of total patients.(29)
Adverse Events (AE)	➢ Generally safe, but potential AE like skin atrophy, pain, and telangiectasia, may occur ➢ Slightly increased risk for intraocular pressure, glaucoma, osteoporosis and cataracts should be considered (27)	➢ Transient folliculitis and skin atrophy. (20)	➢ Compared to conventional systemic corticosteroid therapy, pulse therapy is considered relatively safe. ➢ Insomnia, muscular pain, fatigue, and headache, acne, hypertension, cataracts, diabetes mellitus, and bodyweight gain may be seen (1)

In Systemic corticosteroids,

Oral Daily Therapy: Oral daily therapy is started with initial daily dosage, ranging from 40 to 60mg, is gradually reduced by 5mg per week, tapered over 6–12 weeks, is a frequently employed strategy. Its mode of action encompasses immunomodulation, with potential direct stimulation of hair follicles. Oral prednisolone finds applicability in rapidly progressing or extensive alopecia areata affecting over 50% of the scalp. [1]

High Dose Steroid Therapy: High dose steroid therapy, commonly delivered as pulse therapy, proves effective in acute forms of alopecia areata (AA). Corticosteroid pulse therapy, involving a single 3-day intravenous administration of 500 mg/day methylprednisolone, is preferentially adopted for acute and progressive adult AA affecting more than 25% of the scalp within 6 months. Notably, post-treatment hair regrowth becomes observable after a couple of months when new anagen entry starts. Relapses are prevalent, typically starting around 8 weeks post-treatment discontinuation.[27]

Minoxidil

Mechanism of action: Topical minoxidil is applied off-label in conditions like alopecia totalis and alopecia Universalis. Its impact on DNA synthesis and leukocyte inhibitory factor in lymphocytes, without compromising viability or migration behaviour, suggests a local immunosuppressive effect. [17]

Dosage: 5% minoxidil solution with twice daily application is recommended, with an initial positive growth response typically observed after 3 months, reaching its maximum effect around 1 year. In cases with 25 to 99% scalp baldness, cosmetically acceptable regrowth is achieved in 20 to 45% of individuals. [1]

In a year-long double-blind randomized controlled trial involving 21 individuals with severe alopecia areata, alopecia total is, and alopecia universal is, 3% minoxidil showed some sparse vellus regrowth, but no significant difference in cumulative androgenetic hair regrowth (CAHR) was observed compared to the control group. This study, notable for its extended duration, concentrated on the most severe forms of alopecia areata [30]

Combination Therapies: The combination of topical minoxidil 5% with topical betamethasone dipropionate 0.05% demonstrates synergistic effects in treating severe alopecia. After 4 months of therapy, a fair to good response is noted in 56% of individuals receiving both minoxidil and the corticosteroid, as opposed to 27% with minoxidil alone, 22% with corticosteroids alone, and 13% with placebo. [1]

Dithranol

Dithranol cream therapy is predominantly employed in paediatric cases or for individuals grappling with severe alopecia areata. It's effect on AA can be immunomodulatory, but not well understood. Applied at concentrations of 0.5% or 1%, to the affected scalp lasting for a brief period of 20 to 60 minutes. Subsequently, the medication is carefully washed off using an appropriate shampoo. Achieving a cosmetically acceptable response requires a minimum of 6 months of consistent application. [1]

Adverse Effects: Adverse effects may include pruritus, erythema, scaling, and folliculitis. It is imperative to prioritize sun protection for the treated skin and ensure that dithranol does not come into contact with the eyes.

Diphencyprone

Diphencyprone (DPCP), also known as diphenylcyclopropenone, functions as a contact sensitizer and has demonstrated efficacy in addressing severe cases of alopecia areata that encompass more than 50% of the scalp. [1]

Mechanism of action: The application of diphencyprone frequently induces allergic contact dermatitis. Paradoxically, this allergic reaction is considered a crucial element for stimulating the regrowth of hair in affected areas. The controlled induction of dermatitis is perceived as an integral component of the therapeutic mechanism. [1]

Dosage & efficacy: It involves the application of a diphencyprone solution to one half of the patient's scalp at weekly intervals. Subsequent to a 48-hour period post-application, the solution is meticulously washed off. Price et al., documented that DPCP showed cosmetically acceptable outcomes in severe forms of the disease (50-99% baldness) in 40-60% of the patients.

Adverse Effects: The primary adverse effects associated with diphencyprone treatment include the development of severe eczema, and disseminated contact eczema.

Contact immunotherapy

Contact Immunotherapy (CI) is a therapeutic approach that involves inducing allergic contact dermatitis on areas affected by hair loss, aiming to stimulate the regrowth of hair. This method employs topical sensitizers, including diphenylcyclopropenone (DPCP) and squaric acid dibutyl ester (SADBE), to trigger a controlled inflammatory response.

A meta-analysis with CI in patchy AA and AT/AU showed regrowth rate up to 74.6% and 54.5% respectively. [31]

Mechanism of action: The exact mechanism of CI remains unclear, but it is hypothesized that hair regrowth may result from a shift in inflammatory infiltration around hair follicles towards the induced dermatitis. The

immunomodulatory effects are thought to involve the induction of perifollicular lymphocyte apoptosis or alterations in the distribution patterns of lymphocyte infiltration, resulting in change in the perifollicular CD41/CD81 T-lymphocyte ratio which helps in in promoting hair regrowth. CI is not recommended for acute and rapidly progressive cases. [32]

Sensitization Process: Prior to initiating the treatment, patients undergo sensitization with a sensitizer, typically a 2% solution of SADBE or DPCP. This sensitization involves applying the solution under a closed patch on the alopecic scalp for 48 hours. After a 3-week interval, the treatment commences with a weekly application of SADBE or DPCP, diluted in acetone at a carefully chosen concentration to elicit a mild and tolerable contact dermatitis. [33]

Immunosuppressants

The utilization of a combination therapy involving methotrexate and corticosteroids has demonstrated a more robust complete response compared to the use of methotrexate in isolation in AA variants. This enhanced efficacy was particularly observed in adult patients, showcasing a notable advantage over paediatric patients, but potential systemic adverse effects associated with these agents should be dealt with caution. [20]

Another option is the oral administration of cyclosporine at a dosage of 5-6 mg/kg/day, leveraging its immunosuppressive properties. [27] While effective, it is crucial to weigh the long-term side effects linked to its sustained use. A 3 -month cyclosporine treatment with 4mg/kg/day showed at least 50% reduction in SALT score in 31.3% of moderate to severe patients.

Fumaric acid esters

Fumaric acid is an aliphatic, dicarboxylic acid without double bonds. It function by inhibiting T-suppressor cells and T-helper cells, leading to the suppression of cytokines such as INF-γ, IL-2, IL-12, and TNF-α. (32) Additionally, they block ICAM and keratinocyte proliferation. In an open, non-placebo study, ten patients with alopecia areata (AA) were prospectively treated with fumaric acid esters, resulting in improvement for six patients, with three experiencing almost complete remission. (34)

Photochemotherapy

Psoralen and UV-A Synergy (PUVA): The application of psoralen in conjunction with ultraviolet (UV)-A irradiation, commonly known as PUVA, has emerged as a therapeutic approach for alopecia areata. This method operates through an immunomodulatory mechanism, purportedly influencing T lymphocyte function and potentially mitigating local immunological attacks on hair follicles by depleting Langerhans cells. Typically, photochemotherapy sessions are administered 2 to 3 times weekly. Observable regrowth often becomes apparent after 20 to 40 sessions, with the maximum effect manifesting within a year. [1]

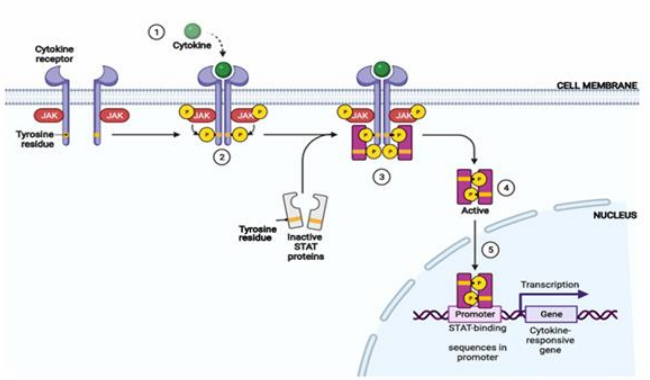
Adverse effects: Despite its efficacy, PUVA treatment is not without potential side effects. Adverse reactions may include nausea, potential scalp burning, pigmentary alterations, photoaging, and the risk of squamous cell carcinoma. Psoralen plus UVA therapy, while less commonly employed, is characterized by insufficient efficacy and the associated risks of photoaging and photo carcinogenesis.[11]

Janus kinase (JAK) inhibitors

Within the human system, the Janus kinase (JAK) family encompasses four distinct members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Each member intricately associates with different cytokine receptors, and their function involves phosphorylating

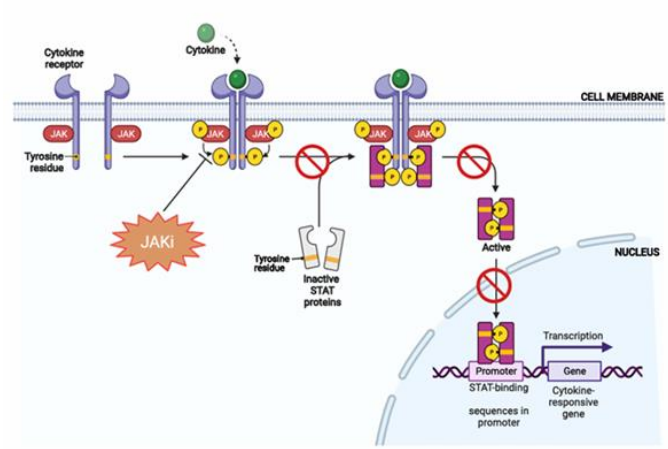
signal transducers and activators of transcription (STATs) when ligands bind to their respective cytokine receptors. The ensuring phosphorylation event leads to the translocation of STATs to the nucleus, where they bind to specific DNA sequences, ultimately regulating gene transcription. This intricate system forms the basis for the promising therapeutic potential of JAK inhibitors (JAKi) [20].

Fig 11: The JAK-STAT signalling pathway [35]



Therapeutic Potential in Alopecia Areata (AA): Research attention shifted towards JAK inhibitors when it became evident that blocking single cytokines such as IFNγ, IL15, and IL2 proved insufficient to halt and reverse AA. The complex interplay involves MHC expression by hair follicle epithelial cells, enabling the activation of CD8+ NKG2D+ T lymphocytes. This activation triggers a cascade involving IFNγ, JAK1/2-STAT1 pathway, IL15, JAK1/3-STAT5 pathway, and perpetuating loop, forming the basis for JAK inhibition as a potent pharmacological strategy. Inhibition of the JAK-STAT pathway interrupts intracellular signalling, effectively blocking T cell-mediated inflammation, blocking downstream effects of major players like IFN-γ and IL-15, thereby addressing the loss of immune privilege in anagen and melanogenic active hair follicles in AA. JAKi emerge as potential therapeutic targets in addressing the characteristic CD8+ NKG2D+ T cell inflammatory infiltrate seen in AA. JAK inhibition is observed to exert a direct effect on mid-telogen hair follicles, promoting re-entry into the anagen phase independent of the T cell infiltrate.[33]

Fig 12: Role of JAK inhibitors in JAK-STAT pathway [35]



Tofacitinib

Tofacitinib citrate, an FDA-approved JAK1/3 inhibitor for rheumatoid arthritis, is currently undergoing clinical trials for psoriasis. As the pioneer among first-generation JAK inhibitors, tofacitinib selectively inhibits JAK 1/3 dependent STAT, with minimal impact on the TYK 2 pathway. It disrupts the downstream signalling pathway of JAK 1/3 dependent γc receptors by blocking STAT phosphorylation induced by γc cytokines, including IL-2, IL-4, IL-7, IL-15, IL-21, and IFN γ, as evidenced in both human and mice models.[35]

Systemic tofacitinib demonstrates positive responses in addressing alopecia areata across diverse age brackets. In adults, doses of 5 to 10 mg bid show favourable outcomes, while adolescents respond positively to a 5 mg bid regimen. Preadolescent children, receiving doses ranging from 5 mg qd to 5 mg bid, also exhibit encouraging results, with no major adverse events noted during the study [20]

Ruxolitinib

Ruxolitinib, an FDA-approved JAK 1/2 inhibitor for myelofibrosis. As a first-generation JAK inhibitor, its use in AA is still under investigation. Ruxolitinib selectively inhibits JAK1/2, with lesser TYK2 impact, and exhibits anti-inflammatory effects by disrupting IL-17 signalling, as evidenced in mice models. Currently, the recommended dosage of ruxolitinib for AA is 20 mg twice a day. [28]

Multiple case reports and a trial by Mackay-Wiggan et al. (2016) support its oral and topical use in alopecia areata (AA). In this trial, 20mg ruxolitinib administered twice daily for 3–6 months resulted in ≥50% regrowth in 75% of patients at 12 weeks, and by the end of 6 months, 7 of these patients had >95% regrowth (all 9 patients had a 92% reduction in SALT). Like tofacitinib, ruxolitinib is well-tolerated in AA patients, with few studies reporting grade I and II infections with mild symptoms.

Baricitinib

Baricitinib, an oral JAK inhibitor, recently approved for severe alopecia areata in May and June 2022 by the EMA and FDA, respectively. It has 100-fold selectivity for JAK1 and JAK2 over JAK3, its lower affinity for JAK3 holds potential to mitigate the anticipated immunosuppressive effects associated with JAK3 inhibition. It is currently sanctioned for the treatment of moderate to severe RA (2017 FDA), moderate to severe atopic dermatitis (2020, EMA), and, more recently, coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, (2022 FDA). The recommended dosage starts with 7 mg per day for the first 6 months, followed by a regimen of 7 mg in the morning and 4 mg in the evening [36].

Baricitinib is well tolerated compared to other drug of same group and has a bioavailability of 80%, with a half-life of 12 hour, and it is metabolised by CYP3A4. In a randomized, double blinded parallel group, placebo control study conducted for a period of 36 weeks, demonstrated 38-40% increase in SALT20 score in baricitinib 4mg group compared to placebo group.[36]

Ritlecitinib

Ritlecitinib, a kinase inhibitor is a recently approved by FDA in June 2023 for severe alopecia areata. It acts by irreversibly inhibiting Janus kinase 3 (JAK3) and the tyrosine kinase family, effectively blocking the adenosine triphosphate (ATP) binding site. In cellular contexts, it hinders cytokine-induced STAT phosphorylation mediated by JAK3-dependent receptors and also disrupts signalling from immune receptors. [33]

The recommended oral dosage of LITFULO is 50 mg once daily, irrespective of food intake. It boasts a 64% oral bioavailability, achieves peak plasma concentration within an hour, and has a half-life ranging from 1.3 to 2.3 hours. It is contraindicated in patients with documented hypersensitivity and used cautiously in individuals with known blood disorders, severe infections, and malignancies. Ritlecitinib was evaluated in a randomized, double-blind, placebo-controlled trial involving subjects aged 12 and above with alopecia areata, exhibiting ≥50% scalp hair loss, including cases of alopecia total is (AT) and alopecia universal is (AU).

Overall adverse Effects: The predominant adverse effect associated with Janus kinase inhibitors (JAKi) revolves around an elevated susceptibility to infections, encompassing upper respiratory tract infections, urinary tract infections, and herpes zoster. Concurrently, notable adverse effects include heightened liver enzymes, hyperlipidaemia, cytopenia, and an augmented risk of venous thromboembolic events. As a part of ongoing investigations, topical JAKi are being explored for their

potential in mitigating systemic side effects, especially during long-term treatment in patients with alopecia areata (AA). Discontinuation of JAK inhibitors, however, may precipitate the recurrence of alopecia areata at a rate ranging from 17.9% to 31.3%. [22]

Oral Administration vs. Topical Application: When administered orally, all JAK inhibitors are associated with adverse events, with upper respiratory infections, urinary infections, and gastrointestinal complaints emerging as the most frequent non-cutaneous effects. In contrast, topical application of JAK inhibitors has been reported to have minimal adverse effects, primarily limited to skin irritation and folliculitis. Regular monitoring, including complete blood cell count, liver enzymes, bilirubin levels, cholesterol profile, triglycerides, creatinine, hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), tuberculosis is recommended at baseline, after 1 month, and subsequently every 3 months. [33]

Biologics

Given the well-established role of the Th1/IFN-γ axis in the pathogenesis of alopecia areata (AA), there is growing interest in exploring biologics that target Th1 cytokines as potential therapeutic candidates. Extensive studies have highlighted the pronounced Th1 signature, alongside the activation of IL-23, Th2, and Th17 cytokines in AA. [20]

Dupilumab, a humanized monoclonal antibody designed to block the IL-4 receptor α (IL-4Rα), emerges as a noteworthy contender, inhibiting both IL-4 and IL-13 is currently utilized in the treatment of allergic diseases, particularly moderate to severe atopic dermatitis (AD), is known to have efficacy in AA. Penzi et al., reported a case report of a girl with AD treated with subcutaneous injection of Dupilumab 30mg every other week showed significant improvement in AT after 11 months of therapy. [37]

Ustekinumab, originally approved for Crohn's disease and ulcerative colitis treatment, also indicated in psoriasis stands out as an IL-12/IL-23p40 monoclonal antibody. Recent case reports indicate that Ustekinumab could trigger hair regrowth in several AA patients, both with and without concomitant psoriasis. [38] It may cause injection-site reactions, headache, and fatigue. [20]

PDE4 inhibitors

Phosphodiesterase 4 (PDE4) inhibitors, characterized as small-molecule modulators of the innate immune system, play a pivotal role in down regulating inflammatory responses by degrading intracellular cyclic adenosine monophosphate (cAMP). Among these inhibitors, Apremilast stands out as an oral medication approved for addressing conditions such as psoriasis, psoriatic arthritis, and Behçet's disease.[27]

Apremilast, functioning as a PDE4 inhibitor, operates by suppressing pro-inflammatory cytokines, including IFN-γ, through the upregulation of cAMP. This mechanism has generated expectations regarding its utility in managing AA. Its potential efficacy is seen particularly for individuals with mild-to-moderate AA or those exhibiting a notable over-expression of PDE-4. Magdaleno-Tapial et al., reported a case of a women who showed significant scalp hair growth after 15 weeks of treatment with Apremilast. [39]

Abatacept

Abatacept is a fusion protein that selectively modulates T-cell co-stimulation, consisting of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) combined with a segment of IgG1 (CTLA-4Ig) has FDA approval for various conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriatic

arthritis.[32] This innovative modulator functions by binding to CD80/86 on antigen-presenting cells, effectively preventing their interaction with CD28 on T cells. This binding inhibition results in the suppression of T-cell activation, proliferation, and a reduction in the production of inflammatory cytokines such as TNFα, IFNγ, and IL-2.[17]

Groundbreaking insights into the genetic landscape have uncovered a significant genetic susceptibility at the CTLA4 locus in patients with alopecia areata (AA). Genome-wide association studies (GWAS) have illuminated the role of CTLA4 in the pathogenesis of AA, providing a foundation for targeted interventions in AA. An open label clinical trial with moderate to severe patchy AA, AT and AU treated with Abatacept for 24 weeks showed increased hair growth in 15-25% of patients. [40]

Adverse Effects: While demonstrating its efficacy, abatacept comes with a set of common adverse effects, including nasopharyngitis, upper respiratory tract infection, and bronchitis. These effects highlight the need for a nuanced approach in considering the balance between therapeutic benefits and potential side effects associated with this selective immune modulator [20].

Low dose IL-2

The strategic administration of low-dose interleukin-2 (IL-2) holds the promise of selectively enhancing the expansion and functionality of T-regulatory cells (Tregs) which play a vital role in suppressing inflammation and orchestrating immune system activity. In alopecia areata (AA), a condition where immune privilege breakdown (increased presence of CD4- and CD8-positive cells, indicative of compromised T regulatory cell function) is evident, a deficiency in Tregs is implicated in the pathological process. Low-dose IL-2 has demonstrated its ability to activate T regulatory lymphocytes, offering a therapeutic strategy to address this immune dysregulation and thus emerges as a potential avenue for the effective treatment of AA [20].

Castela et al., conducted a prospective pilot study with SC injection of low dose IL-2 in refractory severe AA and demonstrated partial hair re-growth in 4 out of 5 patients. [41]

Adverse events: They are generally mild to moderate, encompassing asthenia, arthralgia, urticaria, and localized reactions at the injection site. [17]

IL-17 inhibitors

IL-17 inhibitors, such as secukinumab, ixekizumab, and brodalumab, are well recognized for the treatment of plaque psoriasis and some other inflammatory diseases. In a male patient with psoriasis and AU, a mild hair regrowth was noticed during treatment with secukinumab. [20]

Statins

In addition to their well-known lipid-lowering capabilities, statins exhibit noteworthy anti-inflammatory and immunomodulatory effects. Among these, simvastatin has been identified as a multifaceted agent with anti-inflammatory properties involved in down regulation of nuclear factor-κB (NF-κB) and type 1 cytokine secretion (IL-2, IL-12, IFN-γ, and TNF-α) via JAK/STAT pathways, diminishing reactive oxygen species (ROS) production, and activating the Wnt/β-catenin pathway which may contribute to the improvement of AA. Moreover, the collaborative effect of simvastatin with ezetimibe has been proposed to enhance its immunomodulatory efficacy. [27]

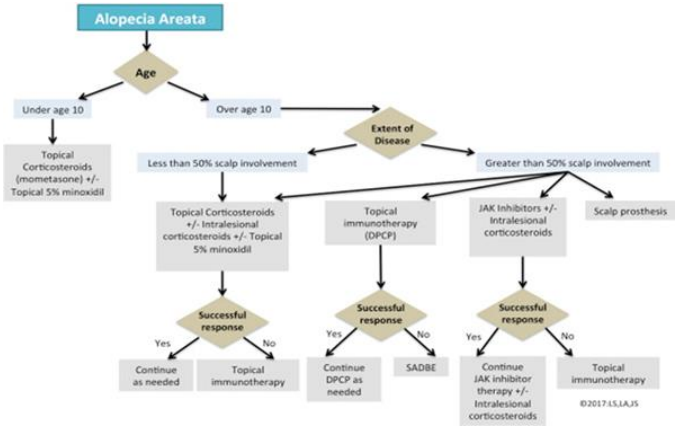
In a pilot study conducted by Lattouf et al., in 12 of 19 AA patients with 40-70% of scalp involvement

demonstrated hair re-growth in 50% of patients without any side effects. [42]

Antihistamines

Reports of hair regrowth following the administration of ebastine have been seen, yet the precise underlying mechanism remains unclear. Ebastine may contribute to reducing the production of Th2-type pro-inflammatory cytokines, while fexofenadine targets IFN-γ and substance P. Moreover, antihistamines have shown promise in inhibiting T-cell proliferation and mitigating infiltration around the hair follicles (HFs). Remarkably, no adverse events necessitating the discontinuation of antihistamines have been reported to date [20]. In a retrospective study patients treated with antihistamines in combination with topical corticosteroids showed better outcomes of hair re-growth with better tolerance. [43]

Fig 13: Treatment algorithm of Alopecia areata



Telogen effluvium

Telogen effluvium, a scalp disorder characterized by widespread, non-scarring hair shedding, is distinguished by the excessive shedding of telogen club hair from the scalp. Typically, it initiates 8–12 weeks after a triggering event, such as pregnancy, significant illness, or complex surgery, and spontaneously resolves within 3–6 months. The retrospective diagnosis labels the self-limiting condition as acute telogen effluvium (ATE) if resolved, while if it persists beyond 6 months, it is termed chronic telogen effluvium (CTE).[44]

The majority of telogen effluvium cases are subclinical, showing no racial predilection, affecting both males and females, with a higher incidence in females. It is noteworthy that women tend to seek medical treatment more frequently than men for hair shedding concerns. Elderly women, especially following events like fever, trauma, haemorrhage, or psychological stress, are more susceptible to acute telogen effluvium. Studies report an incidence of around 2.7% of telogen effluvium in children. [45]

Treatment in telogen effluvium focus on induction of anagen in telogen follicles, inhibiting catagen to prolong anagen, and suppressing exogen to reduce hair shedding. [46]

Aetiology

Various factors can disrupt the normal hair cycle and trigger telogen effluvium. These factors include:

Drugs	Telogen hair loss can be caused by numerous medications, typically commencing around 12 weeks after initiating drug therapy. Medications associated with telogen effluvium include oral contraceptive pills, androgens, retinoids, beta-blockers, ACE inhibitors, anticonvulsants, antidepressants, and anticoagulants (heparin).
Physiological Stress	Increased physiological stress, such as surgical trauma, high fever, chronic systemic illness, and haemorrhage, can induce telogen effluvium.

Telogen Gravidarum	A common form of telogen effluvium is telogen gravidarum, occurring post-partum due to elevated levels of circulating placental oestrogen during pregnancy, which prolongs the anagen phase, resulting in a full head of hair during pregnancy. With the withdrawal of these hormones at delivery, anagen hair transitions to the catagen phase simultaneously, leading to increased shedding of telogen hair a few months after delivery.
Emotional Stress:	The relationship between emotional stress and hair loss is complex, as hair loss itself can be a source of emotional stress for the patient.
Medical Conditions	Both hyper and hypothyroidism can lead to this condition, and it is reversible upon achieving a euthyroid state. Chronic systemic disorders, including systemic amyloidosis, hepatic failure, chronic renal failure, inflammatory bowel disease, and lymphoproliferative disorders, can also cause telogen effluvium. Additionally, it is reported in some autoimmune diseases such as dermatomyositis, chronic infections like HIV, and secondary syphilis. Inflammatory disorders such as psoriasis and seborrheic dermatitis can also result in diffuse telogen hair loss.
Dietary Triggers	Severe deficiencies in protein, fatty acids, and zinc, along with chronic starvation and caloric restriction, can lead to telogen effluvium. Essential fatty acid deficiency typically manifests two to four months after insufficient intake. While the relationship with decreased body iron stores is controversial, it can potentially cause telogen effluvium. Deficiency in vitamin D, crucial for cell growth, could also be a possible cause. Biotin deficiency is reported rarely.
Ultraviolet Light	Researchers have observed an increased frequency of telogen effluvium between July and October, hypothesizing an actinic effluvium, a summer effect induced by sunlight and ultraviolet (UV) light, manifesting in autumn. Electron microscopy of hair exposed to sunlight reveals alterations in cellular components and damage to the hair cuticle and cortex. Both mechanisms could contribute to increased shedding of hair in the telogen phase, although scientific confirmation is pending.

Pathophysiology

Headington proposed five distinct functional types of telogen effluvium[38] based on alterations in specific phases of the follicular cycle. The mechanisms by which

hair shedding occurs in telogen effluvium are delineated as follows:

1. **Immediate Anagen Release:** Stemming from an underlying cause, follicles prematurely exit the anagen phase, entering the telogen phase ahead of schedule. This culminates in escalated shedding approximately two to three months later.
2. **Delayed Anagen Release:** Resulting from the prolonged anagen phase, this type leads to substantial telogen shedding.
3. **Short Anagen Syndrome:** Characterized by the idiopathic shortening of the anagen phase, persistent telogen effluvium ensues. The pathogenesis of most chronic telogen effluvium cases is attributed to the short anagen syndrome.
4. **Immediate Telogen Release:** Arising from the abbreviation of the telogen phase, a massive release of club hair occurs.
5. **Delayed Telogen Release:** Stemming from a prolonged telogen phase and a postponed transition to the anagen phase.

Clinical presentation

Table 6: Clinical presentation of TE

Acute Telogen Effluvium (ATE)	Chronic Telogen Effluvium (CTE)
ATE is characterized by hair shedding lasting for less than six months, typically manifesting two to three months after the triggering event. In approximately 33% of cases, the cause remains unidentified. Remission occurs in around 95% of instances of acute telogen effluvium. Examination of resolved cases reveals the presence of shorter, re-growing frontal hair, often observable in abundance through videodermoscopy. [38]	Whiting described CTE as a primary idiopathic disease entity in 1996. Chronic telogen effluvium persists for more than six months, predominantly affecting middle-aged women with a prolonged and fluctuating course. Scalp examination shows hair of normal thickness, with indications of shorter re-growing hair in the frontal and bitemporal regions. Primary CTE typically onset suddenly in females aged 30 to 50 which includes bi-temporal recession of the anterior hairline, a reduction in ponytail diameter, and trichodynia. 37

Diagnosis

Trichodynia: A prominent symptom of telogen effluvium is trichodynia, characterized by complaints of tenderness, pain, burning, itching, stinging, and diffuse alopecia.

Modified Wash Test and Hair Loss Count: The modified wash test, conducted after five days without shampooing, aids in identifying telogen effluvium or androgenetic alopecia, determining disease severity. The procedure involves washing and rinsing hair over gauze, collecting, drying, and placing them in an envelope. Results and possible diagnoses are as follows:

1. Telogen effluvium: More than 100 shed hair, less than 10% vellus.
2. Androgenetic alopecia: Less than 100 shed hair, more than 10% vellus.
3. Association of telogen effluvium and androgenetic alopecia: More than 100 shed hair, more than 10% vellus.
4. Normal or remitting telogen effluvium: Less than 100 shed hair, less than 10% vellus.

Trichogram: Involving the plucking of 40-60 hairs in a defined area, the trichogram reveals a significant reduction in the anagen: telogen ratio in cases of telogen effluvium, with more than 25% of hair in the telogen phase.

Videodermoscopy: In acute telogen effluvium, videodermoscopy reveals numerous short re-growing hairs with consistent density.

Scalp Biopsy: Recommended for telogen loss lasting over six months, multiple biopsies enhance diagnostic accuracy. Acute telogen effluvium biopsies show a normal to supernormal anagen: telogen ratio, lacking follicular miniaturization and peribulbar infiltrate. Chronic telogen effluvium biopsies exhibit increased telogen hair, with an anagen: telogen ratio of 8:1 compared to the normal 14:1 on scalp biopsies. [38]

Treatment

Acute Shedding versus Chronic Shedding: Acute telogen effluvium tends to be self-limited when the triggering factor is identified and removed. Treating causative conditions such as scalp conditions (e.g., psoriasis, seborrheic dermatitis) is crucial. A detailed drug history should be obtained, and medications suspected of causing the condition replaced or discontinued. For longer shedding durations, involving multiple and repetitive triggers like nutritional deficiencies, thyroid disease, systemic illnesses, or infections, the search for triggers becomes more complex, requiring frequent visits.

Patient Education: Educating patients about disease management is vital. Explaining the correlation between the disease and triggers, along with the timing of hair loss, helps address frustrations.

Correcting Deficiencies: If a measurable deficiency is identified, it should be corrected. Maintaining a balanced diet and stable body weight is essential.

Minoxidil and Finasteride: FDA-approved standard drugs, minoxidil and finasteride, lack efficient catagen inhibition or anagen induction. Catagen-inducing drugs (e.g., beta-blockers, retinoids, anticoagulants, antithyroid drugs) should be avoided. Treating catagen-inducing endocrine disorders (e.g., androgen disorders, thyroid disorders, abnormal prolactin levels) is crucial for reversal. [38]

Topical Corticosteroids: Dermatologists use topical corticosteroids in treatment. Improvement in trichodynia after applying topical corticosteroids indicates the therapy's effectiveness.

Systemic Corticosteroids: In chronic telogen effluvium, systemic corticosteroids may be administered, especially if it manifests as an underlying systemic disorder like SLE.

CNPDA: Davis et al., reported a novel treatment of thinning of hair named as CNPDA which combines caffeine, niacinamide, panthenol, dimethicone, and an acrylate polymer. This combination increases the cross-sectional area of individual terminal scalp hair by 10%. [47]

Mesotherapy: A non-surgical treatment, mesotherapy involves multiple injections of plant extracts, pharmaceutical medications, or multivitamins into the intradermal layer. Goals include restoring and increasing local microcirculation, providing nutritional input, slowing down follicular involution, stimulating the hair's environment through needling. [39]

Botulinum Toxin: Recently introduced for hair falling disorders, botulinum toxin (A) relaxes muscles, reducing pressure on musculocutaneous components and

perforating vasculature, potentially increasing blood supply and transcutaneous pO2. This high-oxygen environment washes out accumulated dihydrotestosterone (DHT) and reduces signals for hair follicle miniaturization. Botulinum toxin A involves a single session, offering an advantage over mesotherapy involving multiple sessions. Side effects include pain, bleeding, edema, urticaria, allergic reactions, and muscle weakness. [39]

Conclusion & Future directions

The progression of alopecia poses significant distress, contributing to reduced self-confidence, heightened anxiety, depression, and substantial impacts on mental health. It has transcended being perceived solely as a cosmetic concern and, despite the availability of numerous drugs for treatment, approved therapies addressing its course remain limited. Ongoing clinical trials explore additional treatment options, yet the existing ones are often constrained by efficacy issues or adverse events. Consequently, there persists a critical need for potential drugs that can effectively reverse the progression of the disease.

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