Review Article

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Evidence Based Treatments of Alopecia Areata

Ahmed Hamza Al-Shammari[1], Qusay Jassam Shandookh[2]

[1]Department of Pharmacy, Kut University College, Alkut, Wasit, Iraq. Email: ahmedhamzamezaal@gmail.com, ORCID ID: 0000-0001-6215-6551

[2]Department of Pharmacy, Al-Yarmouk University College, Baqubah, Diyala, Iraq.

Email: qusayjassam@gmail.com, ORCID ID: 0009-0001-7122 9625

Abstract

Androgenetic Alopecia (AGA) is considered as major non-cicatricial alopecia which causes progressive hair follicle miniaturization. To a large extent, a person's genetic makeup and hormonal environment determine whether or not their terminal scalp hairs will be transformed into vellus hairs. AGA becomes more common and commoner as people get older. AGA is a progressive disorder characterized by a shortening of the anagen phase and maintenance of the telogen phase. Females with AGA tend to see more diffuse hair loss over the head, while males with AGA tend to experience thinning near the vertex. The gold standard treatments for AGA are minoxidil (used topically) and finasteride (an oral 5α-reductase inhibitor type II inhibitor) and they are the only medications accepted by the Food and Drug Administration (FDA) to date. The success of existing therapy for AGA is frequently questioned, making the discovery of new therapeutics for this illness of critical importance. In an effort to slow the disease's course and boost its outcomes, this article will examine the causes and diagnostic tools used to identify AGA.

Keywords: Androgenetic Alopecia, non-cicatricial alopecia, minoxidil.

Corresponding Author: Dr. Ahmed Hamza Al-Shammari, Department of Pharmacy, Kut University College, Alkut, Wasit, Iraq. Email: ahmedhamzamezaal@gmail.com

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Introduction

Androgenetic alopecia affects both sexes and does not leave scars. Those who are genetically inclined, both men and women, experience a gradual shrinkage of hair follicles distributed in a certain pattern which affects both sexes equally, it is considered as the most common cause of hair loss. AGA typically presents itself gradually and worsens over time. This form of hair loss becomes more common and severe with age. 30% to 50% of males age 50 are affected, and over 80% of Caucasian men over the age of 70 are affected. It often manifests in the third and fourth decades [1]. Female pattern hair loss (FPHL) becomes more common and severe with age, just as it does in males. After analyzing data from 1,006 Caucasian women over thirty years of age, Norwood reports a prevalence of over 30%. Moreover, the prevalence of mid-frontal alopecia escalates with advancing age, as documented by Gan DC, et al. [2]. In fact, 57% of women aged 80 and up experience this condition. Frontal hair loss and overall hair loss are less common among Asians, Native Americans, and many men of African descent than they are in Caucasians because of a reduced prevalence of AGA in these groups [1].

Pathophysiology of AGA

Both genetic predisposition and androgen activity play a role in AGA's etiology. Although there is evidence that AGA has a hereditary tendency, its route of inheritance is poorly understood. Polygenic inheritance, when traits are influenced by both parents' genes, seems highly likely. Concordance values of 80% to 90% in monozygotic twin studies further support the idea that there is a genetic foundation. Early onset and quick progression of the alopecia are more likely in those with a family history of the condition. There is no single cause for it; rather, it has a complex genetic and environmental background. Androgens, in conjunction with predisposed hair follicles, are required for the onset of androgenetic alopecia [1,3,4]. Androgens are recognized to be essential for the onset of balding, although they do not play a role in hair growth on the scalp. As a result, androgens' effects on hair follicles will vary depending on their physical location. In people who are genetically predisposed to the effects, they can cause pubic, axillary, beard, and chest hair to develop. At puberty, testosterone and dihydrotestosterone (DHT) play distinct but complementary roles. Muscle growth, a larger scrotum, a shift in the voice, and appearance of terminal pelvic and axillary hair fibers are all linked to testosterone. This isoenzyme levels are higher in males than in females, and in areas impacted by AGA [3]. This suggests that increased 5-reductase type II activity is essential in the progress of AGA. Dihydrotestosterone (DHT) is linked to hair loss in the temporal region of the scalp, acne development, prostate enlargement, and growth of terminal hairs in the beard, external ear, and limb hairs. Hormone dihydrotestosterone stimulates genes to control a shorter hair growth cycle and a gradual reduction in hair follicle size. Androgens have an effect on these areas of the scalp. Because the anagen phase of the smaller follicles gradually shortens (from terminal to vellus-like follicles), more hairs are in the telogen phase. Hair follicles do not die in AGA, but instead shrink significantly. [5]. In rodent models, DHT has been demonstrated to suppress hair development by impeding the effects of growth hormones such insulin-like growth factor1.[6]

Diagnosis of AGA

Trichoscopy and the hair-pull test are two examples of noninvasive procedures that can aid in making an accurate diagnosis. Further in-depth diagnostic procedures, including a scalp biopsy, may be required in rare instances. In some individuals, especially women, a laboratory evaluation may be very helpful in determining the presence and severity of any related disorders [7].

Classification of AGA

In MPHL, the Hamilton-Norwood Classification stands out as the most common [8]. The frontotemporal region undergoes change throughout the course of seven ages, and so does the pattern of hair loss from the crown to the temples. Some men have a female-like pattern of absent frontal hairline and diffuse crown thinning with retained frontal hairline, as described by the Ludwig Classification.

The most frequent types of female pattern hair loss are:

1. Ludwig's Classification divides the degree of hair loss into three categories, from mild to severe, depending on the density of remaining hair.
2. A five-stage framework for categorizing FAGA is provided by Ebling's Classification. There are two phases that are equivalent to those in the Ludwig system. Diffuse hair loss and frontotemporal hair line regression are included in Type III; frontotemporal recession is also present in Type IV; and in Type V, the top of the head is completely bald, mimicking the appearance of male pattern baldness.
3. Olsen proposed a three-tiered classification system, which he called the Olsen's Classification. The triangular frontal emphasis that characterizes the "christmas tree" distribution is the defining feature of this grouping. Savin Scale: a contemporary 8-level classification scale that uses a computer analysis based in "the density of hair by unit of area", very like to Hamilton-categorization Norwood's with frontal and side sights of the hair loss forms [1].

AGA treatment

Minoxidil

Oral minoxidil was first used to treat hypertension. The increased hair growth was an adverse effect of the medication. Since then, minoxidil used topically has been the standard treatment for alopecia. It wasn't until 1998 and 2001, respectively, that the US-FDA gave their approval for the use of topical minoxidil (at a concentration of 2%) to treat AGA in men and women. In 2007, the FDA approved minoxidil 5% for the treatment of androgenic alopecia in males (AGA), and in 2006, minoxidil 5% foam was agreed for the treatment of AGA in males. Although the FDA has neither approved the 5% solution or the 5% foam for use in women, they are frequently used for this purpose anyhow. Minoxidil is an inactive pyrimidine derivate until it is metabolized into the active sulphate form, minoxidil sulphate. Research suggests that minoxidil's ability to activate ATP-potassium channels is responsible for its ability to stimulate hair renewal. Minoxidil has anti-inflammatory, proliferative, and vasodilatory properties, while its precise mechanism of action is still poorly known [9,10]. Minoxidil's ability to stimulate hair growth could occur via several distinct methods. The growth factor VEGF (also known as vascular endothelial growth factor) is known to stimulate angiogenesis, which in turn increases the rate of hair development, the size of hair follicles, and the number of hairs produced [11]. Applying minoxidil directly to the hair follicle has been shown to raise VEGF mRNA presentation in DP cells [12]. Combinations of minoxidil and other drugs like tretinoin are sometimes recommended by doctors [13].

Inhibitors of α-Reductase

The 5'-reductase inhibitors regulate the conversion of testosterone to DHT in DP cells of follicular units [9]. Finasteride and dutasteride are the most common 5α-reductase inhibitors. Taking finasteride in a dose 1 mg per day cause a reduction in DHT levels in both scalp and serum by 64 percent and 68 percent, respectively in contrast to more effective 5α-reductase inhibitors dutasteride that can reduce DHT level by 90%. Finasteride, taken orally, is a competitive and selective inhibitor of type 2 5α-reductase inhibitors. Reduced hair follicles and elevated levels of DHT are found in the balding scalp of males with androgenetic alopecia (AGA). According to Dallob and coworkers, finasteride reduces DHT in the scalp and serum and raises testosterone in the scalp in men with pattern baldness. Finasteride is one of the most effective medications for AGA in males, according to a number of studies. Dutasteride uses showed to be safe and effective in the AGA treatment [15], despite the fact that only a small number of trials have been published too yet. Tsunemi et al., authors of a newly published clinical trial, discovered that patients who received dutasteride 0.5 mg orally once a day for fifty two weeks experienced improvements in hair regrowth at both 26 and 52 weeks [16].

Antiandrogens

Treatment options for FPHL include antiandrogen oral treatment with drugs such cyproterone acetate, spironolactone, or flutamide; however, there is a lack of conclusive evidence supporting the effectiveness of these drugs [9]. Because of their feminizing effect, oral antiandrogens are only recommended for female patients. Ciproterone Acetate (CA) blocks androgen receptors and acts as a strong progestin. Although it has been used for the treatment of hirsutism for over 40 years, there is little evidence that it is effective in FPHL based on the available controlled trial data. Since it blocks androgen receptors, CA reduces testosterone by preventing the production of LH and FSH. Females who are hyperandrogenic may benefit more from CA treatment [17].

New emerging AGA treatments

Topical finasteride

The use of topical finasteride, which has fewer side effects than oral finasteride, is actuality studied as a potential novel management for AGA. Application of finasteride 0.25% solution daily (doses of 100 and 200 L) inhibits scalp DHT, as reported by Caserini et al., which may lessen the

unpleasant sexual side effects connected to systemic DHT reduction. Tanglertsampan C conducted a study comparing the efficacy and safety of 3% minoxidil solution (MNX) with minoxidil 3% plus finasteride solution (MFX) 0.1% in the management of male pattern baldness (AGA). At 24 weeks, both groups had increased their hair count from their initial measurements, although there was no significant difference between them. Topical finasteride is rarely used alone; more often, it is combined with other medications. Insufficient evidence exists at this time to recommend the use of topical finasteride [9]. Unless more research is done with just topical finasteride, its efficacy cannot be determined [1].

Injectable dutasteride

Dutasteride injection shows promise as a therapy for androgenetic alopecia (AGA). Using a mixture containing dutasteride (0.5 mg of dutasteride, 500 mg of D-panthenol 20 mg of biotin and 200 mg of pyridoxin), Moftah et al. assessed the efficacy and safety of mesotherapy in women with hair loss. The study's authors decided the preparation was safe, well-tolerated, and produced the best results in female patients with less advanced disease. More research into injectable dutasteride's effectiveness is required [18].

Treatment using low-intensity laser light

Laser therapy has been found to be beneficial for various medical conditions such as pain and inflammation. This therapy involves the utilisation of light from a low-level laser (LLL) or laser-emitting diodes (LED) that emit light within the spectral range of 600 to 1000 nm [19]. In recent times, it has been utilised as a means of promoting hair growth. Hair loss devices that are available in the market are typically designed to operate at a specific wavelength of 655 nm. In 2007 and 2011, the Hairmax Lasercomb® was granted approval by the US-FDA as a secure therapeutic option for the management of male and female androgenetic alopecia (AGA) [20]. Another evaluation of the literature found LLLT devices are safe and effective for treating FPHL and MPHL. There was a non-significant reduction in the total number of vellus hairs, rise in the total number of terminal hairs, and widening of the hair shafts in research conducted by Avram MR, et al. [21]. The density of the hair did not increase. Although a small number of individuals have shown that LLLT can stimulate hair regrowth, the results are not conclusive. Therefore, research is needed to establish the ideal values for dose, wavelength, coherence, and dosimetric parameters [19].

Investigational Therapies

Pathobiology research has led to the creation of several animal models that can be used for testing and developing new medicines. The C3H/HeJ mouse strain is the most widely used animal to study AGA since it spontaneously develops the disease [22].

IL-2

In AGA and other autoimmune disorders, interleukin-2 Treg cells are compromised. As a result of being stimulated to multiply by low dosages of IL-2, the immunological response to the hair follicle is dampened. After 6 months of treatment, patients with AGA universalis showed improvement on a low dose of IL-2 with little side effects. There was a reduction in CD8+ infiltration and an increase in Treg cells in lesional biopsies. Diphenycyclopropene used topically can also boost IL-2 levels; this mechanism needs more research. High dosages of IL-2, on the other hand, have been shown to stimulate T cell proliferation and NK cell activity, both of which can either trigger or exacerbate AGA [23].

IL-17

There is evidence that IL-17-activated Th17 cells contribute to the development of AGA [24]. Furthermore, IL17R Polymorphisms were related with the development or onset of AGA in a case-control association study [25]. All immune cells have the IL-17R, and when this receptor is activated, inflammatory cytokines such IL-, TNF, and IL-6 are produced. Hence, decreasing the number of Th17 cells or blocking the effects of IL-17 may enhance AGA prognosis. ADTA, which reacts well to therapy and has a good result, revealed lower concentration of IL-17 cells, lending credence to this theory [24].

Table1: Alopecia areata clinical trials currently enrolling patients[26]

Drug	Trial number	Phase	Description
Interleukin-2 (aldesleukin, Proleukin ®)	NCT01840046	1/2	• Will evaluate the efficacy and tolerability of recombinant IL-2 in severe or resistant AA.
Abatacept	NCT02018042	2	• Will measure the proportion of subjects obtaining at least a 50% hair re-growth from baseline using SALT score after 24 weeks of therapy.
Ruxolitinib	NCT01950780	2	• Will evaluate the safety and efficacy of ruxolitinib for 3 months.
Stem cell educator	NCT01673789	1/2	• Will explore the therapeutic effectiveness of a stem cell educator, following patients for 54 weeks.
Methotrexate (MTX)	NCT02037191	3	• Will evaluate MTX efficacy in severe AA. • Experimental group will receive MTX alone or in combination with prednisone for 6 months.
PUVA	NCT01559584		• Will evaluate the efficacy of phototoxic PUVA in AA • Control group was treated with monthly injections of potent corticosteroids.
Excimer laser	NCT01802177		• Split lesion, single blinded randomized trial to evaluate the safety and efficacy of Excimer laser.
	NCT01736007		• Will assess the safety and response of Excimer laser in patchy AA in children.

Abatacept

Activation flaws in T cells due to CTL4 gene dysregulation have been linked to AGA. T cell activation necessitates the expression of a co-stimulatory ligand encoded by this gene, which attach CD80 and CD86 on antigen presenting cells. Abatacept, an immunosuppressive medication, can inhibit this activation signal by binding preferentially to CD80 and CD86 on antigen-presenting cells. In this way, abatacept also inhibits the synthesis of inflammatory cytokines. The medicine increases the risk of infection, however, due to its immunosuppressive properties [26].

Janus kinases (JAK) inhibitors

Evidence shows that inhibiting IL-15 signaling via the JAK/STAT pathway able alleviate the inflammation seen in AGA, where levels of this cytokine are elevated. IL-15 and IL-2 use JAK1/3 and STAT3/5 as their primary signaling pathway, whereas IFN signaling stimulates JAK1/2 and, in

turn, STAT1 and blocking theses pathways can allowed for the reduction of future inflammatory consequences. Tofacitinib is a JAK3 inhibitor that has been licensed by the FDA for the treatment of rheumatoid arthritis. Dermal sheath cells are known to be protected against IL-15-induced injury by this compound. After 8 months of treatment with tofacitinib, Full hair growth was reported in a patient with AGA universalis. Additionally, ruxolitinib which is a JAK 1/2 inhibitor that has been licensed by the FDA which cause a reduction in the dermal sheath cells' IL-15 expression and STAT1 activity. When given orally, both JAK inhibitors effectively blocked and reversed AGA in mice. But after 3-5 months of therapy, patients with moderate to severe AGA saw nearly full hair growth [27].

Platelet rich plasma (PRP)

PRP treatment for AGA has yielded mixed outcomes. PRP injections may resulted in considerable hair growth in mice. The authors showed that dermal papilla cells treated with PRP had elevated levels of -catenin (which induces anagen), FGF-7 (which prolongs the anagen phase), and Bcl-2 (which has an anti-apoptotic effect). New hair follicle development and faster hair growth were also shown in a PRP-treated graft experiment with shaved mice. PRP considerably outperformed triamcinolone in a randomized experiment measuring hair growth in patients with chronic AGA. Patients with severe, chronic AGA responded inconsistently to PRP in separate research, and the treatment did not stop the spread of the illness to new areas. The authors postulated that the immunosuppressive effects of TGF- were responsible for the observed effect. Further research into PRP's potential as an AGA treatment is required[28].

Statins

Because of their immunosuppressive effects, statins may be beneficial in the management of AGA. They can reduce IL-17 effects, stop mast cells from degranulating, and stop lymphocytes from migrating, all of which contribute to a shift in the Th1/Th2 ratio. Inflammatory cytokine transcription is generally activated by STAT phosphorylation, which statins can block. The cholesterol-lowering drug atorvastatin, for instance, can also reduce MHC II expression. As a result, the immunological privilege zone is disrupted and fewer T cells are activated. Two months after starting treatment with simvastatin and ezetimibe, a patient with a case of alopecia areata universalis reported that their hair had begun to grow back. Statins, the scientists argued, tipped the scales in favor of Th2, reducing IFN- production. The same treatment was later found to be effective in two further cases of AGA totalis. Simvastatin and ezetimibe are a powerful duo for bringing down CRP levels. In mice, we found that simvastatin prevented the development of AGA caused by HSP (unpublished data). Numbers of both CD4+ and CD8+ T lymphocytes were higher in the untreated group [26].

Phenol

The use of contact irritants, such as phenol, has been demonstrated to be effective in AGA by "deviating" the immunological reaction normally focused against hair follicles. The topical application of 88% phenol to AGA patches was the subject of a prospective research. In fact, after 9 weeks of treatment, 82% of patients reported a good to excellent response, with both hair texture and colour greatly improved. Just 10% of patients experienced a temporary loss of skin pigmentation [29].

Quercetin

As an anti-inflammatory bioflavonoid, quercetin shows promise as a potential treatment for and perhaps a preventative measure against AGA. NF-kB and heat shock protein 70 (HSP70) are both downregulated by quercetin. Extracellular HSP70 can activate NF-kB, leading to the generation of inflammatory cytokines. Subcutaneous quercetin therapy for AGA in mice resulted in hair development after 8 days. Quercetin treatment delayed and diminished AGA development in mice [30]. Hydrovalproic acid Valproic acid has been shown to stimulate hair development in mice by elevating -catenin expression [31].

Tianeptine

It has been demonstrated that the antidepressant and anxiolytic tianeptine is effective in treating animals with AGA-like lesions brought on by ultrasonic wave stress. Around the hair follicle, treatment-induced mast cell degranulation and death, hair cycle recovery, collagen and elastin synthesis, and upregulation of vitamin D receptor expression were all noted. The use of tianeptine as a hair loss treatment did not seem to be more effective than other medications [32].

Anti-Parathyroid Hormone (PTH)

Several studies on PTH's impact on the hair cycle have yielded contradictory findings. PTH stimulates hair follicles to enter anagen by activating the Wnt signaling pathway in keratinocytes, which increases nuclear -catenin. Treatment with PTH for just one day resulted in hair growth that persisted for two to three weeks, according to the authors. Anagen follicles increased histologically despite a persistent inflammatory response [32].

Vitamin D

Inadequate vitamin D associated with autoimmune illnesses due to its impact on lymphocytes. The lack of vitamin D has been linked to AGA [33]. levels of which were inversely related to illness severity. Seasonal changes in AGA have also been noted, with people who suffer from chronic or frequently relapsing AGA showing lower vitamin D levels. Functional vitamin D receptors in keratinocytes were shown to be necessary for an appropriate hair cycle generation irrespective of vitamin D levels. Another study found that lower levels of vitamin D receptor expression were linked to reduced activity in the wnt/-catenin pathway, which in turn reduced hair follicle proliferation and differentiation [33]. Together, these findings suggested that improving vitamin D levels in AGA patients could have a beneficial effect.

Vitamin A

Alopecia can be caused by either a lack of vitamin A or an

overabundance of it, but in different ways in each case. In turn, AGA may be influenced by vitamin A because it stimulates robust immunological responses. Increased expression of genes involved in retinoid metabolism was shown by Duncan et al. in AGA [34]. Hence, more research into the role of retinoid metabolism regulation in AGA is warranted.

Microneedling

Microneedling has been used to treat scars from acne, rejuvenate the face, and promote hair growth. The microinjury is thought to create growth factors, which in turn activate the dermal papillae and stem cells, increase blood supply to the hair follicles, and cause hair growth. Two patients with refractory AGA saw great outcomes using a combination of microneedling and triamcinolone acetonide, with no recurrence at three months and no side effects. Another study used a scalp roller to apply a solution including triamcinolone acetonide, minoxidil, and growth hormones and amino acids to treat refractory AGA. Each type of AGA improved significantly, but the ophiasis-pattern AGA and the universalis-type AGA exhibited the highest progress [35].

Combination treatments

In 2018, Tanaka and colleagues employed a combination therapy that included 1mg oral finasteride (5α-reductase type II inhibitor) once daily, 2.5mg oral and 5% solution topical minoxidil twice daily, and an injection once monthly for more than six months. Four milliliters (mL) of a solution comprising panthenol, copper tripeptide, aspartic acid, niacin, minoxidil, caffeine, arginine, sodium hyaluronate, lysine, propylen glycol, propanediol, pyridoxine, retinyl palmitate, and ubiquinone were injected into the scalp at each session. Six and 12 months post-op checkups were planned. Digital images of the areas treated by this method indicated a considerable improvement over the pre-treatment states for all patients. Given that this therapy provides safe and effective treatment of AGA among males with minimum problems, the authors also noted that 96% and 80% of patients, respectively, indicated satisfaction with the results of the treatment after 6- and 12-months post-treatment [36].

Lactate dehydrogenase-mediated activation of hair follicle stem cells.

When a new hair cycle begins, the typically quiescent Hair Follicle Stem Cells (HFSCs) rapidly become activated and begin to divide. Many lines of evidence from a recent study show that HFSCs rely on glycolytic metabolism and generate a lot more lactate than other epidermal cells. Deletion of lactate dehydrogenase (Ldha) additionally inhibited HFSC activation, suggesting that lactate production is essential for their activation. Deleting the mitochondrial pyruvate carrier (Mpc1) sped up HFSC activation and the hair cycle by increasing lactate synthesis in these cells genetically. As a further advantage, Flores and colleagues discover small molecules that increase lactate production by stimulating Myc levels or inhibiting Mpc1 carrier activity and can topically induce the hair cycle; these results suggest that HFSCs maintain a metabolic state that allows them to remain dormant but quickly respond to appropriate proliferative stimuli, suggesting a novel approach to the treatment of alopecia [37].

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