Dean&Francis
ISSN 2959-409X

Molecular Mechanisms and Therapeutic Advances in Androgenetic Alopecia

Yukun Zhang

College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing, China
Postal code:215311
Corresponding author:
kkun13646200054@outlook.com

Abstract:

Androgenetic alopecia (AGA), also known as seborrheic alopecia, is the most common type of hair loss in clinical practice, accounting for about 80% of all types of hair loss. In China, the prevalence among men and women is approximately 21.3% and 6%, respectively, affecting a wide population. Although it does not threaten physical health, it seriously impacts patients' mental health and quality of life and has shown a trend toward younger onset in recent years. This article provides a systematic review of the clinical features of AGA, influencing factors, molecular mechanisms, and mainstream drug treatment strategies, with a focus on the core roles of 5α-reductase and androgen receptor (AR) in disease pathogenesis. It explores the mechanisms of action, clinical efficacy, and safety of various drugs such as minoxidil and finasteride, and summarizes research advances in new drug delivery methods and combination therapy strategies. Studies have found that the pathogenesis of AGA is the result of multiple factors, including abnormal androgen metabolism, polygenic inheritance, and microinflammation, with the collaborative regulation of type II 5α-reductase and AR being a key link in disease development. Existing therapeutic drugs still have limitations, while new delivery methods and combination therapies can effectively improve efficacy. Personalized treatment and the exploration of new targets are future research directions. This article reviews recent research findings in the field of AGA, identifies current research shortcomings, and provides references for optimizing clinical diagnosis and treatment as well as for subsequent related studies.

Keywords: Minoxidil; Finasteride tablets; Androgenetic alopecia

ISSN 2959-409X

1. Introduction

Androgenetic alopecia (AGA), often referred to as seborrheic alopecia, is currently the most clinically incident type of hair loss, accounting for about 80% of all types of hair loss cases. With the acceleration of the pace of life in modern society and the continuous increase of mental pressure, AGA has shown a significant trend of rejuvenation in China. Epidemiological data show that the prevalence rate in Chinese men is about 21.3% and that of women is about 6%, and although the physical function of the large population is not directly threatened, the appearance changes caused by hair loss can easily lead to negative emotions such as low self-esteem and anxiety, which seriously interfere with the social, work, and mental health of patients [1].

Therefore, exploring effective treatment strategies for AGA has always been a research hotspot in the field of dermatology. At present, AGA is generally believed to be an androgen-dependent polygenic genetic disease, and its core pathogenesis is closely related to abnormal androgen metabolism and changes in the hair follicle microenvironment. In this pathological process, testosterone (T) is catalyzed into the more active dihydrotestosterone (DHT) by 5α-reductase (mainly type II) within hair papilla cells. After DHT binds to androgen receptor (AR), it induces perifollicular microvascular degeneration and tissue fibrosis by activating downstream signaling pathways, which ultimately leads to hair follicle miniaturization and shortening of anagen phase, leading to progressive hair loss. Based on this mechanism, blocking androgenic action or improving scalp microcirculation has become a key target of treatment.

At present, the mainstream therapeutic drugs approved by the U.S. Food and Drug Administration (FDA) are mainly divided into two categories: one is the vasodilator minoxidil, which promotes local blood circulation and activates hair growth by upregulating vascular endothelial growth factor (VEGF); The other is the 5α-reductase inhibitor finasteride, which inhibits the process of hair loss by reducing DHT levels [2]. However, existing single treatment options still have significant limitations. Topical minoxidil has a slower onset of action, and some patients have contact dermatitis caused by propylene glycol solvents, or poor compliance due to frequent daily medication; Although oral finasteride is effective, there is a potential risk of adverse effects such as decreased libido, and some patients do not respond well to it. In addition, treatment options are particularly scarce for female patients and special populations who cannot tolerate oral medications. In order to break through the above bottlenecks, the focus of research in recent years has shifted to the exploration of new drug delivery methods and combination treatment strategies. In terms of drug development, low-dose oral minoxidil (LDOM) significantly reduces adverse reactions such as hirsutism and edema while ensuring efficacy, showing good application prospects. As a new generation of 5α-reductase inhibitors, dutasteride can inhibit both type I and type II isoenzymes, and may have better efficacy for patients who do not respond to finasteride treatment. In terms of treatment methods, microneedling, platelet-rich plasma (PRP) therapy, and the application of nanocarrier technology aim to improve drug penetration and reduce systemic side effects. However, the pathogenesis of AGA has not been fully elucidated, and existing treatment methods have not been able to achieve complete regeneration and cure of hair follicles.

In summary, although significant progress has been made in the diagnosis and treatment of AGA, facing the growing clinical demand, there is still an urgent need to thoroughly analyze the molecular mechanisms, explore new therapeutic targets, and develop more personalized, safe, and effective diagnostic and treatment guidelines. This article aims to systematically review the pathogenesis of AGA and the research progress in drug therapy, providing a reference for optimizing clinical treatment plans and subsequent related research. In recent years, the exploration of the pathogenesis of AGA and clinical treatment strategies has become a research hotspot, and many important advances have been made in the relevant fields.

2. The Manifestation of AGA and Influencing Factors

The onset of AGA is influenced by multiple factors, among which age is an important one. Adolescence is the onset period, and hair loss may occur around the age of 20, with the incidence increasing as age increases. According to statistics, in Caucasian populations, the incidence increases by about 10% for every additional 10 years from ages 20 to 50 [3]. The incidence of AGA also varies among different races. Caucasians have the highest incidence, with more than half of Caucasian men affected by AGA before the age of 50. According to statistics, compared with Caucasians, the incidence in Asian populations is about 35% lower [4]. AGA shows a significant genetic tendency. Related family genetic studies show that 62.7% of AGA patients have a family history, and the risk for first-degree relatives (65%) is significantly higher than that for second-degree relatives (14%), suggesting that the closer the blood relation, the higher the probability of developing AGA. The genetic susceptibility of this disease is influenced by genes from both parents, but the degree of

influence varies; in AGA individuals with a family history, paternal inheritance accounts for up to 85% [5].

3. Pathogenesis of AGA

The occurrence and progression of AGA are closely related to androgen expression, metabolic levels, and the secretion of downstream cytokines, which is directly reflected in aspects such as disease incidence and severity. The currently recognized mechanism is: testosterone (T) in the patient's body is catalyzed by 5α-reductase to convert into DHT, which has a higher affinity for AR. After forming a complex, it can promote dermal papilla cells to secrete TGF-β and DKK-1 in a paracrine manner. Studies have confirmed that TGF-β can induce apoptosis of microvascular endothelial cells in hair follicles, causing local microvascular degeneration and ultimately leading to hair follicle miniaturization; DKK-1 interferes with the normal hair follicle growth cycle by inhibiting the Wnt signaling pathway. In addition, microinflammatory responses and tissue fibrosis also participate in the pathological process of AGA.

3.1 5-alpha Reductase

Before T combines with AR and exerts its biological effects, it must first be converted into DHT with higher receptor affinity in the cytoplasm catalyzed by 5α-reductase. 5α-reductase includes two isoenzymes, 5α-I and 5α-II, encoded by the SRD5A1 gene on chromosome 5 and the SRD5A2 gene on chromosome 2, respectively; the optimal pH for 5α-I is 6–9, while that for 5α-II is 5.5 [6].

Studies have shown that in dermal papilla cells of the beard area, 5α-reductase activity reaches its peak at pH 5.5; at the mRNA expression level, the expression of 5α-II in the hair papilla (DP) cells of AGA-affected areas and the beard is significantly higher than that in occipital scalp DP cells, while the expression of 5α-I does not differ significantly across scalp regions. These results suggest that 5α-II is highly expressed in the DP cells of androgen-sensitive regions such as AGA-affected scalp and beard [6] [7]. Individuals with congenital 5α-II deficiency who have pseudohermaphroditism do not exhibit typical clinical manifestations of AGA, providing key evidence for the central role of 5α-II in the pathogenesis of this condition. The clinically approved drug for AGA treatment, finasteride, works by specifically inhibiting type 5α-II reductase [8]. Taken together, these pieces of evidence confirm that the occurrence and progression of AGA mainly depend on the activity of 5α-II, with little relation to 5α-I.

3.2 AR

In addition to 5α-reductase, the sensitivity of hair follicles to androgens is also jointly regulated by AR and its co-activators. DHT, produced through the catalysis of 5α-reductase, binds to AR to form a complex that is then transferred into the cell nucleus. There, it binds to the antioxidant response elements (ARE) in the promoter regions of androgen-regulated genes, initiating the gene transcription process, which is regulated by various co-regulatory factors. Among them, the co-activator Hic-5/ARA55 is considered a key molecular regulator of androgen sensitivity in human hair follicles. It is highly expressed in DP cells in androgen-sensitive areas such as beards and AGA-affected scalp, and can significantly enhance AR transcriptional activity. This characteristic suggests that it can further increase the sensitivity of hair follicles to androgens.

In addition, the AR gene is closely related to the genetic susceptibility of AGA, accounting for up to 40% of the genetic risk, making it a high genetic risk factor for AGA. Genome-wide association studies of AGA have confirmed that the AR gene located on the X chromosome shows strong AGA-related signals, clarifying the association between AR and AGA onset while also highlighting the importance of maternal inheritance in the process of AGA development.

To clarify the specific localization and expression characteristics of AR in the hair follicles of AGA patients, a study examined healthy scalp and AGA scalp samples using immunostaining and staining techniques. The results showed that no significant AR activity, or only weak activity, was detected in the epithelial tissue of hair follicles in both groups; whereas in the DP cells of bald AGA scalp, the nuclear localization level of AR was significantly increased. This result indicates that the target of androgen action in hair follicles is the DP cells, not the epithelial cells [9].

4. Molecular Mechanisms and Clinical Effects of Different Drugs in the Treatment of AGA

The only drugs approved by the FDA for the treatment of AGA are topical minoxidil and oral finasteride. However, multiple clinical studies have shown that these two treatment methods are unsatisfactory in terms of both efficacy and safety. In recent years, researchers have focused more on the use of oral minoxidil, dutasteride, topical application of finasteride, PRP, and other treatment methods, either alone or in combination, in order to provide safer and more effective treatment for patients with AGA.

ISSN 2959-409X

4.1 Vasodilator

Minoxidil, as a potassium channel opener, is the first drug approved by the FDA for the treatment of AGA. Its mechanism of action mainly involves increasing the expression level of VEGF, promoting local angiogenesis, dilating blood vessels, and improving blood circulation in the scalp hair regions, thereby promoting hair growth. At the same time, minoxidil has also been shown to upregulate the expression of the key hair growth protein Wnt/β-catenin. Currently, in clinical practice, minoxidil is commonly used topically at concentrations of 2% or 5% for AGA treatment, usually requiring continuous use for several months to show therapeutic effects. However, according to relevant reports, because minoxidil has vasodilatory effects, its treatment of AGA may be accompanied by adverse reactions such as headaches, dizziness, local skin redness and swelling, and edema; additionally, the microinflammatory response present during the onset of AGA also somewhat affects the therapeutic effect of minoxidil, preventing it from achieving the ideal expectation. Therefore, researchers continue to explore the combined use of minoxidil with other treatments to enhance efficacy and reduce adverse reactions. Shah et al. used minoxidil in combination with microneedling and PRP for the treatment of AGA, and after 6 months of treatment, it was found that the hair improvement effect in the combination therapy group was more significant compared to patients using 5% minoxidil alone [10]. Although topical minoxidil is an effective treatment option for AGA, many patients have poor treatment compliance due to the need for twice-daily application, deterioration of hair texture after use, and contact dermatitis caused by the main solvent propylene glycol in the topical preparation [11]. In recent years, the use of oral minoxidil alone or in combination with other therapies has become a research hotspot in the field of AGA treatment, aiming to achieve more effective therapeutic results.

Panchaprateep and others reported a clinical trial involving 24 male patients with an average age of 59, who received LDOM treatment for 24 weeks. The results showed that after 12 weeks of treatment, the total hair count had significantly increased compared to baseline, and after 24 weeks, the average hair count per square centimeter had increased by 35.1 hairs; 43% of patients experienced significant improvement in hair loss symptoms [12]. In this trial, the most common adverse reactions were hypertrichosis (incidence rate 93%) and foot edema (incidence rate 10%). Researchers believe that LDOM is an effective treatment for AGA, but it should be used with caution in male patients with severe hypertension or high risk of cardiovascular events.

Sanabria and others investigated the safety of LDOM by monitoring heart rate and blood pressure for 24 hours after taking oral 5mg minoxidil in multiple male AGA patients. The results showed that only one patient experienced an increased heart rate, and the study concluded that continuous use of LDOM for 24 weeks is safe [13]. However, this study only focused on male patients and did not evaluate the safety of LDOM in female patients, elderly patients, or AGA patients with cardiovascular disease.

Multiple studies have also confirmed the effectiveness and safety of LDOM in female AGA patients. The results show that higher doses of LDOM may provide better therapeutic effects, but they also increase the incidence and severity of hypertrichosis and edema. When the LDOM dose is controlled below 1.5 mg/day, satisfactory efficacy and acceptable adverse reactions (mainly mild hypertrichosis and edema) can be achieved.

4.2 Reductase Inhibitor

The main androgen in the blood is testosterone, which can be converted into DHT, a compound with higher affinity for the AR, through the catalysis of 5α-reductase. DHT is the core pathogenic factor that leads to AGA. Based on this mechanism, inhibiting the activity of 5α-reductase can achieve the therapeutic goal for AGA.

Finasteride, approved by the FDA in 1997, is an oral drug used for the treatment of male AGA. Essentially, it is a type II 5α-reductase inhibitor, and its administration can significantly reduce DHT levels in serum, prostate, and scalp tissue, with a reduction of up to 65%. Besides oral administration, researchers have optimized drug formulations to further enhance the therapeutic effect of finasteride and diversify the methods of administration. For example, finasteride has been loaded onto cinnamic acid-coated iron oxide nanoparticles to prepare topical treatment formulations, and its combination with microneedle technology has achieved better therapeutic effects than traditional delivery methods [14,15].

Finasteride, as a 5α-reductase inhibitor, has proven effective in the treatment of AGA, which has prompted researchers to explore the therapeutic potential of other similar inhibitors. Dutasteride is a drug that can inhibit both type I and type II 5α-reductase isoenzymes. Vañó-Galván and colleagues treated 42 AGA patients with oral dutasteride, and the results showed that hair loss symptoms improved in 38 patients, with 10 patients experiencing significant improvement [16]. In addition, dutasteride's inhibitory activity against type II 5α-reductase is three times that of finasteride and has a longer half-life, which suggests it may have superior therapeutic effects and can be used to treat patients who respond poorly

to finasteride [17].

Motofei and colleagues conducted a 6-month dutasteride treatment on 23 AGA patients who did not respond to finasteride, with 9 patients showing improvement in hair loss symptoms [18]. Dhurat and colleagues conducted a randomized controlled study comparing dutasteride and finasteride in treating AGA patients. The results showed similar incidence rates of adverse reactions for both drugs, but the overall therapeutic effect of dutasteride was superior to finasteride. Therefore, researchers believe dutasteride may become a better treatment option for AGA patients [19].

A phase III randomized controlled trial by Piraccini and colleagues showed that compared to placebo, a 24-week treatment with topical finasteride spray significantly increased hair count in the target area compared to baseline (20.2 hairs vs 6.7 hairs, $P<0.001$), and its effect was similar to oral finasteride [20]. Regarding safety, in this trial, topical finasteride caused smaller changes in serum DHT levels, suggesting it has better tolerability.

5. Conclusion

AGA, as an androgen-dependent polygenic hereditary disease, has a core pathogenesis that lies in the synergistic action of type II 5α-reductase and the AR, leading to elevated DHT levels and deterioration of the hair follicle microenvironment. In current clinical treatment, drug intervention remains the main approach. Minoxidil, as a VEGF up-regulator, can effectively promote hair growth but has side effects such as slow onset, contact dermatitis, and hypertrichosis; finasteride reduces DHT levels by specifically inhibiting 5α-reductase, with definite efficacy, but faces adverse reactions such as decreased libido and limited response in some patients. To address these issues, studies have shown that novel treatment strategies have significant potential: LDOM significantly reduces the incidence of adverse reactions while ensuring efficacy; dutasteride, as a dual inhibitor, shows a better therapeutic prospect for patients unresponsive to finasteride; additionally, combination therapies such as microneedle delivery, PRP, and nanocarrier applications effectively improve drug penetration and treatment adherence.

Although current research has made significant progress in elucidating molecular mechanisms and clinical applications, deficiencies remain. Firstly, the genetic heterogeneity of AGA and its microinflammatory mechanisms have not been fully clarified; secondly, existing drugs cannot reverse already fibrotic hair follicles, and long-term safety data still need to be accumulated. Future research should focus on discovering new therapeutic targets, optimizing personalized diagnosis and treatment plans, and deeply exploring hair follicle regeneration techniques in order to achieve a fundamental cure and clinical healing of AGA.

References

[1] HU Z Q, MIAO Y. Guidelines for the diagnosis and treatment of androgenetic alopecia in Chinese population[J]. Chinese Journal of Aesthetic and Plastic Surgery, 2019, 30(1): 8-12.

[2] HUANG F J, ZHOU X, CAO W F. Overview of etiology and treatment research of seborrheic alopecia[J]. Journal of Practical Traditional Chinese Medicine, 2023, 39(5): 1041-1042.

[3] ZHANG L. Study on the therapeutic effect of Isatis tinctoria grass on androgenetic alopecia animal models[D]. Lanzhou University, 2016.

[4] FENG J, ZHANG Z Y, XIE J, et al. Investigation of androgenetic alopecia prevalence and influencing factors in Wuhan population[J]. Journal of Wuhan University (Medical Sciences), 2023, 44(1): 65-69.

[5] ZHAO J Y, FENG Y J, QI H J. Analysis of related factors in 201 cases of male pattern hair loss and experience with finasteride treatment[J]. Journal of Clinical and Experimental Medicine, 2008(4): 79,81.

[6] INUI S, ITAMI S. Molecular basis of androgenetic alopecia: from androgen to paracrine mediators through dermal papilla[J]. Journal of Dermatological Science, 2011, 61(1): 1-6.

[7] CERUTI J M, LEIRÓS G J, BALAÑÁ M E. Androgens and androgen receptor action in skin and hair follicles[J]. Molecular and Cellular Endocrinology, 2018, 465: 122-133.

[8] PETERSON R E, IMPERATO-MCGINLEY J, GAUTIER T, et al. Male pseudohermaphroditism due to steroid 5-alpha-reductase deficiency[J]. American Journal of Medicine, 1977, 62(2): 170-191.

[9] DENG Z L, CHEN M T, LIU F F, et al. Androgen receptor-mediated paracrine signaling induces regression of blood vessels in the dermal papilla in androgenetic alopecia[J]. Journal of Investigative Dermatology, 2022, 142(8): 2088-2099.e9.

[10] SHAH K B, SHAH A N, SOLANKI R B, et al. A comparative study of microneedling with PRP plus minoxidil (5%) and minoxidil (5%) alone in androgenetic alopecia[J]. Journal of the American Academy of Dermatology, 2017, 76(6): AB11.

[11] RANDOLPH M, TOSTI A. Oral minoxidil treatment for hair loss: a review of efficacy and safety[J]. Journal of the American Academy of Dermatology, 2021, 84(3): 737-746.

[12] PANCHAPRATEEP R, LUEANGARUN S. Efficacy and safety of oral minoxidil 5 mg once daily in the treatment of male patients with androgenetic alopecia: an open-label and global photographic assessment[J]. Dermatology and Therapy, 2020, 10(6): 1345-1357.

[13] SANABRIA B D, PALMEGIANI E, SERON A F, et al. Prospective cardiovascular evaluation with 24-hour Holter and 24-hour ambulatory blood pressure monitoring in men using 5

ISSN 2959-409X

mg oral minoxidil for androgenetic alopecia[J]. Journal of the American Academy of Dermatology, 2023, 88(2): 436-437.

[14] AFIUNE L A F, USHIROBIRA C Y, BARBOSA D P P, et al. Novel iron oxide nanocarriers loading finasteride or dutasteride: enhanced skin penetration for topical treatment of alopecia[J]. International Journal of Pharmaceutics, 2020, 587: 119709.

[15] KIM S, EUM J, YANG H, et al. Transdermal finasteride delivery via powder-carrying microneedles with a diffusion enhancer to treat androgenetic alopecia[J]. Journal of Controlled Release, 2019, 316: 1-11.

[16] VAÑÓ-GALVÁN S, SACEDA-CORRALO D, MORENO-ARRONES O M, et al. Effectiveness and safety of oral dutasteride for male androgenetic alopecia in real clinical practice: a descriptive monocentric study[J]. Dermatology and Therapy, 2020, 33(1): e13182.

[17] ZHOU Z B, SONG S Q, GAO Z L, et al. The efficacy and safety of dutasteride compared with finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis[J]. Clinical Interventions in Aging, 2019, 14: 399-406.

[18] MOTOFEI I G, ROWLAND D L, GEORGESCU S R, et al. Dutasteride for men with androgenic alopecia unresponsive to finasteride[J]. Journal of Investigative Dermatology, 2016, 136(9): S195.

[19] DHURAT R, SHANSHANWAL S. Randomized controlled evaluator-blinded study of dutasteride versus finasteride in men with androgenetic alopecia[J]. Journal of the American Academy of Dermatology, 2016, 74(5): AB138.

[20] PIRACCINI B M, BLUME-PEYTAVI U, SCARCI F, et al. Efficacy and safety of topical finasteride spray solution for male androgenetic alopecia: a phase III, randomized, controlled clinical trial[J]. Journal of the European Academy of Dermatology and Venereology, 2022, 36(2): 286-294.