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REVIEW



Treatment review for male pattern hair-loss

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ABSTRACT

Introduction: Androgenetic alopecia is a common hair loss disorder affecting up to 80% of males by the age of 80. It is characterized by androgen related progressive thinning of hair in a defined pattern. It results in diminished self-esteem, reduced confidence and distress in affected men, irrespective of age or stage of baldness. An effective treatment for hair baldness is needed.

Areas covered: In androgenetic alopecia, hair follicles undergo progressive miniaturization. Genetic factors and androgens are key role-players in disease pathogenesis. Herein the authors review the pharmacologic treatment of androgenetic alopecia, which involves 5 alpha reductase inhibitors, minoxidil and prostaglandins. Non-pharmacologic approaches are also explored.

Expert opinion: Androgenetic alopecia progresses over time and although the current available medical treatments like finasteride and minoxidil are effective in arresting the progression of the disease, they allow only partial regrowth of hair at its best. Early treatment achieves a more optimal outcome. Non-pharmacologic treatments like PRP can be considered in patients refractory to medical treatment.

Abbreviations: MPHL: male pattern hair loss; AGA: androgenetic alopecia; DHT: dihydrotestosterone; 5AR: 5-alpha-reductase; VEGF: vascular endothelial growth factor; PG's: prostaglandins (PG's); PGD2R: prostaglandin D2 receptor; VPA: valproic acid; SR: Serenoa Repens; PRP: platelet-rich plasma; PDGF: platelet derived growth factor; TGF: transforming growth factor; ERK: extracellular signal-regulated kinase; PKB: protein kinase B; LLLT: low-level laser therapy; ROS: reactive oxygen species; RCT: randomized control trial; SFRP1: secreted frizzled related protein 1; DP: dermal papilla; PDE5: phosphodiesterase 5

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1. Introduction

Male pattern hair loss (MPHL) is a progressive patterned hair thinning condition occurring in genetically susceptible men. The cardinal feature of follicular miniaturization represents conversion of terminal follicles to vellus follicles. MPHL affects 50% of men by the age of 50 and is most prevalent in Caucasian men [1–3]. The rate of progression differs from individual to individual and clinical heterogeneity is also observed in affected family members. Racial variations with respect to prevalence and clinical presentations of AGA are recognized. Preservation of the frontal hairline and Ludwig pattern is observed in Asian men whilst the classical Norwood Hamilton pattern is prevalent amongst Caucasian men [1,4,5]. As an androgen dependent condition, MPHL can present soon after puberty. Early onset can be of significant psychological distress [6,7]. Currently, topical minoxidil and oral finasteride are the only FDA approved treatment for androgenetic alopecia (AGA) in men. Given the progressive nature of the condition, nearly all treatments require lifelong compliance for continued ongoing improvement.

In this article we review existing treatments for MPHL, and explore new and emerging therapies.

1.1. Treatment rationale

The overall goal of treatment in AGA is to arrest miniaturization and improve hair density. Therapeutic targets reduce dihydrotestosterone (DHT) production, have vasodilatory effects, trigger anagen, prolong anagen, and subdue inflammation. A variety of pharmacotherapeutic agents and procedural modalities aim to achieve this (Figure 1).

2. Pharmacological therapies

2.1. Finasteride

Finasteride 1mg daily is FDA approved for the treatment of MPHL. It is effective in preventing androgen dependent miniaturization of hair follicles by competitively inhibiting 5-alpha-reductase (5AR) type 2 enzyme, in turn preventing conversion of testosterone to DHT. 1mg of finasteride can lower serum and scalp DHT levels by 60% and results of 10-year follow-up studies confirm significant durable increases in hair growth at this dosage. [8–10] The clinical response to finasteride varies. While finasteride arrests hair loss in over 95% of men, only 66% achieve moderate hair regrowth and 5% marked hair regrowth[11].

Findings from a network meta-analysis of finasteride 1mg and dutasteride 0.5mg for AGA, confirmed both agents as being

Article highlights

- MPHL is an androgen dependent progressive patterned hair thinning occurring in genetically susceptible men
- The goal of treatment is to arrest miniaturisation and improve hair density.
- Historically, 5 alpha reductase inhibitors and topical minoxidil have been the mainstay of treatment
- A number of pharmacotherapeutic and procedural modalities have since emerged as new treatment options for MPHL.
- Multimodality therapy incorporating systemic pharmacotherapy with procedural modalities may help to achieve sustainable outcomes

significantly more effective at increasing hair counts than placebo. [12,13] Additional findings demonstrated approximate equivalent efficacy of finasteride and dutasteride. Finasteride's influence on hair count is greatest on the vertex scalp whilst to a lesser degree it can improve hair density on the frontal scalp and it is least effective bitemporally[14]. In addition to improved hair counts, increases in hair thickness and length add to the impression of improved scalp coverage following treatment[9].

While a daily dose of 5mg is recommended for the treatment of prostate hypertrophy, a dose of 1 mg daily is recommended for the treatment of AGA. Finasteride should be continued for at least 12 months to assess its full effect.[15]

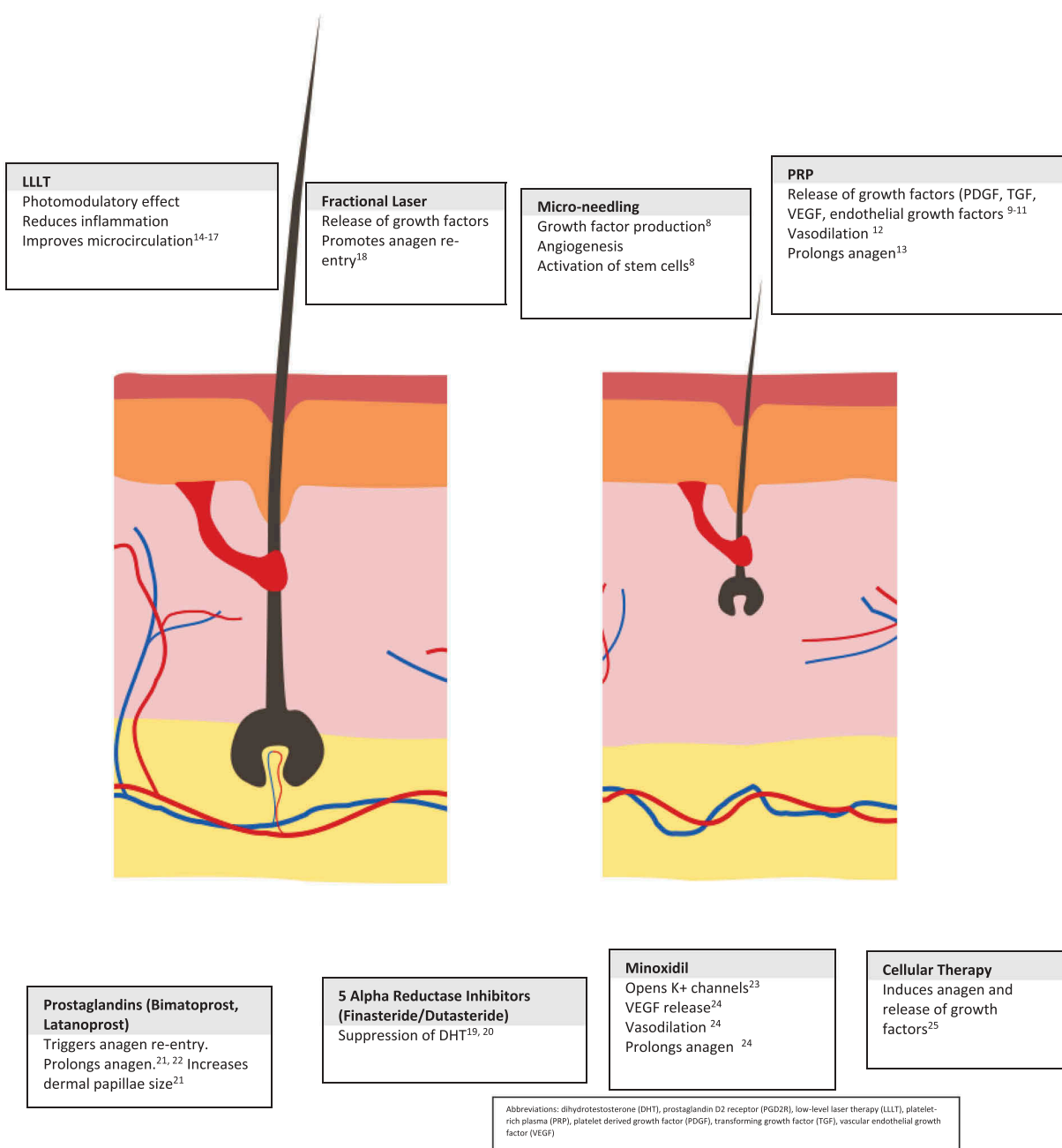


Figure 1. Summary of treatment modalities for male pattern hair loss and proposed mechanism of action.

Long term studies have found that the result after one year may predict its effectiveness going forward. Patients who fail to respond in the first year are likely to be non-responders' long term. Finasteride needs to be continued indefinitely to maintain efficaciousness[15].

Side effects of finasteride include lowered libido, erectile dysfunction, reduced ejaculatory volume, temporary reduction in sperm count, testicular pain, depression and gynecomastia. [16] A 10-year follow-up study reported reduced libido as the most frequent side effect, whilst gynecomastia and depression were not reported at all[17]. A systematic review of nine trials, including 3570 patients, identified sexual dysfunction in 1.5% of men taking finasteride[12]. A more recent network meta-analysis demonstrated no significant difference between active treatment with dutasteride 0.5mg or finasteride 1mg and placebo, for the outcome global sexual disturbance[13]. The lay press has highly publicized persistent sexual side effects associated with finasteride [18–20] but controlled clinical trial data have found a low incidence of sexual side effects that abate on stopping treatment.[21]

Randomized trials have found finasteride decreases prostate cancer risk[22]. Although it was found to increase the Gleason score among detected prostate cancers this has been found to be an artifact of tissue sampling and not a true indicator of aggressive tumor biology[23]. Finasteride decreases prostate specific antigen levels which impacts on prostate cancer screening in men[24].

2.2. Dutasteride

Dutasteride inhibits both type 1 and type 2 5AR. Dutasteride is three fold more efficacious at inhibiting type 1 5AR and a hundred fold more efficacious at inhibiting type 2 5AR than finasteride[25]. Dutasteride 0.5mg can decrease serum DHT levels by 90% [25], and thus provides greater suppression of DHT than finasteride. A multicentre prospective study of 110 male patients with AGA on dutasteride 0.5mg for 52 weeks found it to be safe, tolerable and effective.[26]

A randomized controlled study comparing dutasteride to finasteride and placebo in men with AGA, found dutasteride significantly increased hair counts and hair growth compared to finasteride and placebo[27]. However a subsequent network meta-analysis and benefit risk assessment of finasteride and dutasteride demonstrated approximate equivalence of these treatments[13]. Although not FDA approved for AGA, Dutasteride is an alternative treatment option for patients with AGA who do not clinically respond to finasteride in six months[28].

2.3. Topical finasteride

Topical finasteride is not an FDA approved for treatment of AGA; therefore, current use is 'off label'. A recent systematic review on the use of topical finasteride in AGA in men and women found its use to be associated with significant decreases in rate of hair loss, increased total and terminal hair counts and improved hair growth assessments. Topical finasteride also resulted in a decrease in scalp and plasma DHT but no changes in serum testosterone[29]. The preliminary results on the use of topical finasteride are limited but thus

far appear safe and hold promise. A randomized double blind controlled study of 40 men with AGA found at 24 weeks topical finasteride 0.25% admixed with 3% minoxidil was significantly superior to 3% minoxidil solution alone.[30]

2.4. Topical minoxidil

Minoxidil is a prodrug, converted in the hair follicle outer root sheath to minoxidil sulfate by the enzyme sulfotransferase. [31] Minoxidil sulfate is an adenosine triphosphate sensitive potassium channel opener.[32] The exact mechanism by which it is effective in AGA is not yet fully understood but its vasodilatory and angiogenesis facilitating effects and its ability to stimulate vascular endothelial growth factor (VEGF) are possible mechanisms of action.[33] Minoxidil promotes hair growth by prolonging anagen duration, shortening telogen, and enlarging miniaturized follicles[34]. Regrowth with both topical and systemic minoxidil is proportional to sulfotransferase activity.[31] Medications that increase sulfotransferase, such as tretinoin enhance the regrowth effect of topical minoxidil while agents that reduce it, such as aspirin reduce minoxidil efficacy [35,36]. Topical minoxidil is available as a 2% and 5% solution, and 5% foam. The 5% formulation is more effective than 2%[37]. No randomized trials have directly compared the efficacy of minoxidil 5% foam to the 5% solution. Only 40% of patients experience cosmetically significant improvement and thus the sulfotransferase enzyme to rule out non responders may have clinical utility [38]. A better response to minoxidil can be expected in patients with larger numbers of non-vellus miniaturized hairs, shorter disease duration and smaller bald areas.[39] Paradoxical hair shedding can occur at the beginning of treatment due to stimulation of exogen as telogen follicles reenter anagen.[15] 1ml of the 5% solution or half a capful of the 5% foam should be applied twice daily to involved areas of a dry scalp. Hair growth is seen within four to eight months and stabilizes at 12 to 18 months; thus a year of treatment is advised before assessing efficacy[40]. Common side effects include: contact irritant dermatitis and facial hypertrichosis [41]. The 5% solution reportedly causes more pruritus and irritation than the 2% formulation. The 5% foam however is free of propylene glycol, which correlates with a lower risk for skin irritation[42].

Two studies examining the efficacy of finasteride 1mg/day versus twice daily application of minoxidil 2% solution found finasteride superior at 12 months [43,44]. In another two studies aiming to compare finasteride 1mg per day to 5% minoxidil solution applied twice a day, contradictory results were reported [45,46].

Combination therapy with 1mg of finasteride and 5% topical minoxidil solution appears to lead to superior improvement than monotherapy with either agent.[45]

2.5. Oral minoxidil

Oral minoxidil, an antihypertensive drug, was first identified to improve hair loss in male androgenic alopecia in 1980[47]. A recent study evaluated the safety and efficacy of low dose oral minoxidil (2.5-5mg daily). Improvement occurred in 37 of

41 patients (90.2%) with 11 (26.8%) showing marked improvement. Adverse effects included hypertrichosis in 10 patients (24%), lower limb edema in 2 patients (4.8%) and shedding in one patient (2.4%). All were mild and well tolerated[48]. A earlier study recorded improvement in 30 men (100%) with AGA given 5mg of oral minoxidil daily[49]. This study did however have a higher rate of adverse effects than the study by Jimenez-Cauhe et al with 93% of patients showing hypertrichosis, 10% pedal edema and 10% ECG alterations.

2.6. Topical prostaglandins

Prostaglandins (PGs) play an important role in regulation of the hair cycle[50]. PGD2 inhibits hair growth whilst PGE2 and PGF2a stimulate hair growth[51]. Increased levels of PGD2 and reduced levels of PGE2 are seen in AGA affected scalp[52]. Bimatoprost is a synthetic PGE2 analogue. [53,54] Studies have found topical bimatoprost 0.03% lotion applied daily for 12 and 16 weeks results in a significant increase in vellus hair diameter and vellus hair count respectively[55]. Studies with longer follow up times and larger sample sizes should be conducted in the future to confirm these findings.

Latanoprost is a PGF2a analogue. A 24 week placebo controlled randomized trial including 16 male patients with AGA who applied latanoprost 0.1% daily, found significant increases in hair density compared with baseline and placebo-treated areas[56].

Cetirizine has been found to decrease PGD2 production.[57] A pilot study of 85 patients with AGA evaluated the efficacy of topical 1% cetirizine applied daily for 6 months versus placebo. A significant increase in both total and terminal hair density was seen. Further studies are needed to explore the efficacy of topical cetirizine in the treatment of AGA.[58]

2.7. Oral prostaglandins

Setipiprant is a selective prostaglandin D2 receptor (PGD2R) antagonist. A multicentre, double blind, randomized phase 2a clinical trial compared setipiprant 500mg twice a day against finasteride 1mg and placebo in males with androgenetic alopecia[59]. Although the hair count per square cm was highest for the setipiprant group, the standard deviations within this group were also the highest, suggesting the participants in this group had very different results from each other. Ultimately the results were not statistically significant. In the future, further research ideally using better-matched participants, will be needed to properly establish its potential.

2.8. Valproic acid

Experiments with topical valproic acid (VPA) have shown some promise in promoting hair regeneration. An experimental study in South Korea showed hair regrowth in male C3H mice treated with topical VPA. The levels of β -catenin in the mice skin were specifically increased by topical application of VPA[60]. In a RCT of 40 patients with AGA treated with VPA or placebo, the mean change in total hair count was significantly higher in the VPA group[61].

2.9. *Serenoa repens*

Serenoa Repens/Saw Palmetto is a type of palm. Extract from its berries results in competitive non selective inhibition of 5AR type I and II and less DHT uptake by the hair follicle. It also has the additional function of estrogen receptor activation which aids anagen maintenance and catagen normalization.[62] It has demonstrated efficacy in BPH[63] but few studies exist to support its efficacy in androgenetic alopecia. In a small randomized double blind placebo controlled pilot study of 10 males with AGA on oral SR, improvement was seen in 60%[62]. An open label study comparing the efficacy of finasteride 1mg to oral SR after 24 months found 38% of patients receiving SR had increased hair growth, whilst 68% of those on finasteride showed improvement.[17] In another small study, SR extract in a lotion and shampoo base were applied for three months by 34 men and 28 women, resulting in a 35% increase in hair density[64].

3. Physical therapies

3.1. Growth factors

Growth factors are signaling molecules secreted by certain cells that stimulate cell proliferation. [65–67] Platelet rich plasma (PRP) is an autologous concentrate of human platelets contained in a small volume of plasma, generated, from centrifugation of patients own venous blood and administered by intradermal injections to the areas of hair loss [66,67]. PRP contains a number of key growth factors secreted by platelets, notably platelet-derived growth factor (PDGF), transforming growth factors (TGF) TGF β -1 and TGF β -2, VEGF, basic fibroblastic growth factor, endothelial growth factor and insulin-like growth factors [66–68]. These cytokines are involved in cell proliferation. In this enriched environment, hair growth is stimulated via the upregulation of fibroblastic growth factor β -catenin expression, extracellular signal-regulated kinase (ERK), protein kinase B (PKB) signaling[69]. Interestingly a recent double blind controlled study did not find an association between platelet counts, certain growth factor levels (PDGF, EGF, VEGF) and clinical improvement in response to PRP, indicating other growth factors or mechanisms may be involved in responses seen[70]. PRP also promotes vascularization[71] and prolongs anagen[69]. A recent meta-analysis of 177 patients from six studies reported increased hair density and hair shaft diameter following PRP injections[67]. The main limitation in interpreting PRP efficacy data is the lack of comparability between studies. However, in spite of this PRP is generally considered a safe option in AGA refractory to medical therapy.

3.2. Micro-needling

Micro-needling is a procedure that uses very short fine needles, to micro puncture the stratum corneum. It has been successfully paired with other hair growth promoting therapies, such as minoxidil and platelet-rich plasma, and shown to stimulate hair growth. The micro-injuries created by the needles increase skin permeability, thereby enhancing delivery of hair growth agents to target areas[72]. In a 12-week randomized, evaluator-blinded controlled study involving 100 male patients with AGA, weekly micro-

needling in conjunction with 5% topical minoxidil twice daily was compared to minoxidil therapy alone. A higher hair count was observed in the micro-needling cohort (91.4 hairs per cm²) than the control group (22.2 hairs per cm²) [73]. Whilst micro-needling may be beneficial when used in conjunction with other hair growth stimulants, data on its role as monotherapy is limited. The ease of administration and availability of devices make it an attractive option, additional studies are required to define and validate optimal treatment protocols.

3.3. Laser therapy

Low level laser therapy (LLLT) emits monochromatic coherent collimated light [74]. The coherence keeps the energy focussed and the beam narrow so it can penetrate deep into the scalp to the depth of the hair follicles. Although the precise mechanism of action is not clear, there is evidence indicating that LLLT acts on mitochondria, resulting in a rise in reactive oxygen species (ROS) levels, adenosine triphosphate production, and induction of transcription factors, which in turn results in gene activation and the production of proteins useful to the cell [75–78]. In 2007, LLLT mediated by a laser comb was approved by the FDA as a safe treatment for AGA. [74] LED'S emit light in a range of wavelengths, with the beam that is incoherent and not collimated. They operate at a significantly lower power than most lasers. These factors result in it not penetrating as deeply into the scalp. [79] A metanalysis on the effect of photobiomodulation for AGA found it to be an effective modality for the treatment of AGA. LLLT was significantly more effective than a combination of laser/LED treatment. The style of the device (comb/hat/helmet) did not make a significant difference to treatment response. [80]

The non-ablative fractional 1550nm Er:glass laser, ablative fractional 2940 nm Er:YAG laser, and ablative fractional 10600 nm CO₂ laser have been studied in alopecia areata and AGA [81]. Fractional lasers create multiple small columns of thermal injury. This results in the accumulation of various cytokines for wound healing including insulin like growth factor 1 (IGF1) and the upregulation of Wingless-related integration site (WNT) 10A, both of which promote anagen. [82]

Improvements in hair density and growth rates were observed in a pilot study of 20 patients with MPHL treated with the 1550 nm fractional Er:glass laser [83]. A randomized investigator blinded controlled split scalp study on the efficacy of fractional 1550nm erbium-glass laser used in combination with 5% topical minoxidil versus 5% minoxidil alone was recently performed. Combination therapy provided significantly superior results in terms of hair density, diameter and global photographic assessment. The creation of an array of microscopic channels by the laser facilitates transdermal delivery of topical minoxidil [84].

4. Emerging therapies

Emerging therapies may bring new hope to patients with AGA. Hawshaw et al used the hypertrichosis-inducing immunosuppressant, ciclosporin, to identify a new hair growth-promoting target. They showed that the Wnt inhibitor, secreted frizzled related protein 1 (SFRP1), was downregulated in the dermal papilla (DP) of ciclosporin-treated human scalp

HFs ex vivo. An SFRP1 antagonist, WAY-316606, was shown to enhance hair growth ex vivo. [85] Furthermore, a recent study showed a high expression of phosphodiesterase 5 (PDE5) in human DP and hair follicle cells. Sildenafil, a PDE5 inhibitor, enhanced proliferation of human DP cells and upregulated the expression of VEGF and PDGF, which are responsible for hair growth. The researchers also showed that sildenafil upregulated levels of phosphorylated ERK and accelerated induction of the anagen phase by promoting perifollicular angiogenesis after topical application in mice. This study suggested a therapeutic potential of sildenafil in the treatment of hair loss. [86] Table 1 provides a summary of the latest trials for the treatment of AGA.

5. Conclusion

Patients with MPHL can have a varied response to treatment. Oral finasteride and topical minoxidil are both FDA approved for the treatment of MPHL and been the mainstay of treatment to date. However, significant developments in hair research have resulted in a number of new pharmacotherapeutic and procedural treatments for hair growth promotion. Actively recruiting clinical trials aim to explore novel treatments in AGA. Single agent treatment may not be sufficient to produce the desired outcome long-term. Overall, combination therapy incorporating systemic pharmacotherapy with procedural modalities may be the way to produce sustainable results.

6. Expert opinion

AGA occurs universally in all adult men and severity progresses with age. Twin studies have confirmed that the age of onset, severity, rate of progression and pattern of hair loss are all influenced by inherited factors. Heredity is thought to contribute more than 80% to the AGA phenotype, while environmental factors account for less than 20% [87]. AGA is inherited as a complex polygenic trait. Genome wide association studies have identified over 190 genes that are thought to be involved in AGA, however the first gene associated with AGA, the androgen receptor gene, is thought to account for over 60% of the heredity of AGA. [88,89]

The pathogenesis of male AGA involves hair follicle miniaturization, progressive shortening of anagen duration and prolongation of kenogen. Kenogen is a sub-phase within telogen and may lead to empty follicles. Shortening of anagen duration means that hair fails to grow long. Miniaturization initially affects secondary hairs within follicular units and occurs in a characteristic pattern over the scalp. Miniaturization leads initially to a reduction in hair density and subsequently to the emergence of areas of bald scalp. The basis of site specificity is unknown, however epigenetic factors, and in particular methylation of the androgen receptor gene in occipital follicles has been postulated as a mechanism leading to the relative resistance of occipital hair to AGA [90].

Emergence and progression of androgenetic alopecia requires androgens. Progression of hair loss is inhibited and baldness partially reversed by finasteride, a type 2, 5AR inhibitor that prevents conversion of testosterone to its 5 times more potent metabolite DHT. The effect of finasteride on treating

Table 1. Summary of latest trials for the treatment of AGA.

Study ID	Sponsors	Study type	Aim	Subjects	Recruitment Status	Estimated date of completion
NCT01701271 ^[94]	Mexis George.	Open label interventional trial	To determine whether Mexis, MPAF, M6S patent is effective in the treatment of AGA	10 male & female patients with AGA	Completed June 2001	Not applicable
NCT02503137 ^[95]	Samumed LLC	Multicentre randomized double-blind study Phase 2	To determine the safety, tolerability and efficacy of SMO4554 at a concentration of 0.15% and 0.25% in AGA	49 males with AGA	Completed April 2016	Not applicable
NCT02198261 ^[96]	Applied Biology incorporated	Observational case control study	To evaluate the clinical validity of the minoxidil response invitro diagnostic kit	300 males with AGA	Completed October 2014	Not applicable
NCT01286649 ^[97]	TrichoScience Innovations inc	Randomized single center double blind placebo-controlled trial	To assess the safety of performing injections of human autologous hair follicle cells and to study the impact on hair growth	19 women and men with AGA	Completed February 2017	Not applicable
NCT03495817 ^[98]	Aclaris Therapeutics Inc	Phase I/IIa Open label study	To evaluate safety, tolerability, and efficacy of ATI 50002 topical solution	31 male and females with AGA	Active not recruiting	October 2019
NCT037531132 ^[99]	Farid Masoud	A double-blind randomized trial	To compare efficacy and safety of topical herbal solution and minoxidil 5%	35 males with AGA	Active not recruiting	May 2019
NCT03467412 ^[100]	Follicum AB	A multicentre randomized double-blind placebo-controlled phase 2 trial	To investigate the efficacy of FOL-005 on scalp hair growth	60 males with AGA	Active not recruiting	August 2018
NCT03742518 ^[101]	Samumed LLC	Multicentre randomized double-blind placebo-controlled study	To assess the efficacy and safety of topical SMO4554 solution	Males with AGA (Norwood Hamilton stage 3 or 4)	Recruiting	June 2020
NCT02591355 ^[102]	Regen Lab SA	A double blind randomized active and placebo split scalp study	To evaluate clinical effectiveness of PRP in treatment of AGA	Males with AGA (Norwood Hamilton stage 3–5) Females with AGA (Ludwig stage 1–2)	Recruiting	April 2019
NCT03388840 ^[103]	Assiut university	Open label randomized trial	To compare the effect of adipose derived stem cells combined with platelet rich plasma versus PRP alone on follicular unit extraction hair transplantation	Males with AGA	Recruiting	March 2021
NCT03852992 ^[104]	University of Minnesota, clinical and translational science institute	A randomized cohort study	To compare the safety and efficacy of fractional ablative 10,600nm CO2 laser assisted treatments of MPHL: stand-alone laser treatment, laser assisted drug delivery of minoxidil 2% solution and self-application of minoxidil 5% by the patient	Males with AGA (21–65 years)	Recruiting	July 2021
NCT 03938948 ^[105]	Awareable technologies	An open label study	To assess the efficacy of visible red light for promoting growth of scalp hair	Males and females with AGA (18–60 years)	Recruiting	December 2020
NCT 03723369 ^[106]	Shin Kong Wu Ho-Su memorial hospital	An open label study	The effects of micro needling with low energy laser	Males with AGA (20–60 years)	Recruiting	December 2020

hair loss is proportional to the percentage reduction in follicular DHT. Follicular response to testosterone is site specific. Vertex follicles miniaturize. Beard, trunk and limb follicles enlarge, while eyebrow and eyelash follicles are relatively insensitive to androgens. Site specificity of follicles is preserved after follicular unit transplantation and this is known as the principal of donor dominance that underpins the therapeutic use of hair transplantation surgery to treat baldness.[91]

Medical treatment includes inhibition of DHT synthesis via 5AR inhibitors such as finasteride and dutasteride; inhibiting the downstream effects of androgen receptor activation with prostaglandin analogues such as bimatoprost, latanoprost, stemoxycine or setipiprant; or medications that modify hair cycle dynamics such as minoxidil. Minoxidil increases hair linear growth rate, increases fiber diameter, prolongs anagen duration and shortens catagen through anagen initiation.[92]

Finasteride stops hair loss in most men and results in partial regrowth in around 66%.[11] Dutasteride is an alternative therapeutic option for men with AGA who show no clinical response to finasteride[28]. Of the prostanoids, stemoxycine appears to be the most effective agent. Topical minoxidil is also efficient in arresting hair loss progression and stimulating regrowth and can be used in conjunction with finasteride or dutasteride to augment regrowth. It is weakly soluble in solution and so only low concentrations can be formulated. Systemic minoxidil therapy appears to be more effective than topical minoxidil due to the ability to titrate the dose. Regrowth with both topical and systemic minoxidil is proportional to sulfotransferase activity thus agents that increase sulfotransferase, such as tretinoin enhance the regrowth effect of topical Minoxidil while agents that reduce it, such as aspirin reduce minoxidil efficacy. [31,35,36] Minoxidil induces a dose dependant influx of the cysteine, a sulfur- rich amino acid into the supra-bulbar follicle. Cysteine infusion in sheep leads to increase linear hair growth, increased fibers diameter and prolongation of anagen. Cysteine has a similar effect in vitro in organoid hair follicle culture and cysteine infusion may be important in the effect of minoxidil[93].

Scalp micro-needling also induces sulfotransferase, which may explain part of its effect in stimulating hair regrowth. LLLT, LED light therapy, fractionated laser and injections of platelet rich plasma may induce hair follicle neogenesis or convert vellus follicles into terminal follicles. Evidence documenting the efficacy of these modalities is emerging, but placebo-controlled data is only available for LLLT. Non-pharmacologic treatments like PRP can be considered in patients refractory to medical treatment. While progress has been made in the medical management of androgenic alopecia and a number of physical therapies are emerging, hair transplantation remains the best treatment for advanced disease. Men with advanced disease unable or unwilling to have a hair transplant may still benefit from cosmetic camouflage and concealment of their hair loss with a wig. The combination of medical and physical therapies seems more successful than monotherapy.

Several promising emerging pharmacotherapeutic and procedural modalities are now available for AGA however treatments for hair loss tend to be widely adopted before the evidence confirming efficacy is available. A number of treatments commonly used today will ultimately prove ineffective.

New treatments should be viewed skeptically until placebo-controlled trials confirming safety and efficacy are published. In that regard, topical minoxidil and oral finasteride remain the only proven medical therapies for AGA.

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Declaration of interest

R Sinclair is the principal investigator on the photon revian cap study. He is also a director at Samson Clinical and the inventor of patents on the use of oral minoxidil (Australian patent 2018250398 - promoting hair growth and treatment of hair loss and US patent 10,226,462B2 - Detection and treatment of excessive hair shedding). Finally, Dr Sinclair also declares that has served as a consultant for, acted as a paid speaker, or has participated in clinical trials sponsored by Leo Pharma, Amgen Inc, Novartis, Merck & Co., Celgene, Coherus Biosciences, Janssen Pharmaceuticals, Regeneron, MedImmune, GlaxoSmithKline, Cutanea, Samson Clinical, Boehringer Ingelheim, Pfizer Inc, Merck Sharp and Dohme, Oncobiologics, Roche, Eli Lilly and Company and Bayer Healthcare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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