Noninvasive Hair Rejuvenation

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KEYWORDS

• Androgenetic alopecia • Hair rejuvenation • Medical therapy • Platelet-rich plasma

KEY POINTS

- There are several available noninvasive treatment options for androgenetic alopecia.
- Only 3 treatments are currently approved by Food and Drug Administration: minoxidil, finasteride, and low-light laser therapy.
- Many other treatment options are being used successfully in an off-label fashion, including platelet-rich plasma, microneedling, and topical finasteride.

BACKGROUND

Historically, hair thinning has been associated with the loss of youth, vitality, strength, and sexual attraction. Hair loss can reduce self-esteem, impair the quality of life, and negatively affect other's perceptions of the balding patient.[1] Androgenetic alopecia (AGA) is the most common hair loss disorder in both men and women. In general, AGA can start at a relatively early age, with 30% of men experiencing male pattern hair loss (MPHL) by age 30 years, 50% by age 50 years, and 80% by age 70 years.[2] Women are affected, but to a different degree, and through potentially different pathophysiologic pathways. Female pattern hair loss (FPHL) affects 3% to 12% of Caucasian women by age 30 years and 14% to 28% by age 60 years.[3] AGA can affect all ages, sexes, and ethnicities, but we know that both the incidence and severity of AGA increase with age in all groups and that the incidence of AGA is lower in Chinese, Japanese, and African men when compared with Caucasian men.[4]

HAIR PHYSIOLOGY

The hair cycle involves 4 distinct phases: anagen, catagen, telogen, and exogen (**Fig. 1**). Approximately 50 to 100 hairs enter the exogen phase each day, shed, and then the anagen phase begins again with growth of a new hair follicle. In AGA, the ratio of hair in anagen phase to telogen phase decreases with each successive hair cycle. As a result, more hair is in telogen phase, which delays the cycle resuming the anagen phase. Each phase of the cycle contains specific events that often prepare the hair follicle to enter the subsequent phase (**Table 1**).

MPHL occurs in a predictable pattern, starting at the bitemporal region along the anterior hair line. With time the vertex and then the midfrontal regions of the scalp are involved; however, the occipital region is typically not involved to a significant degree. The classic progression of MPHL from bitemporal and vertex thinning, with a sparing of the temporal and occipital hair, is described in 7-point grading system originated by Norwood, which is used by practitioners all over the world (**Fig. 2**).[5] In contrast, FPHL is considered a different entity, with a different presentation. Typically, FPHL presents with a more diffuse, central thinning over the midfrontal scalp, with preservation of the bitemporal anterior hairline, and vertex regions. This pattern was originally described by Ludwig, and the resulting classification scale is used for FPHL (**Fig. 3**).[6]

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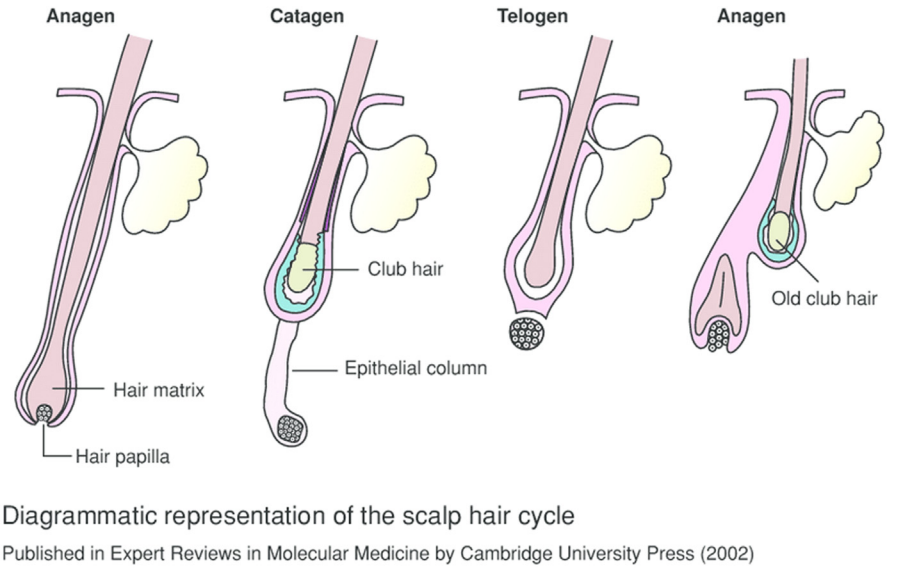

Fig. 1. Stages of the hair cycle. (*Reproduced from* Sinclair R. Male pattern androgenetic alopecia BMJ 1998; 317 :865 doi:10.1136/bmj.317.7162.865. © 1998, with permission from BMJ Publishing Group Ltd.)

THERAPEUTIC OPTIONS

First-Line Treatments

Minoxidil

Minoxidil was incidentally found to work as a powerful vasodilator, which leads to its development as an antihypertensive drug. The favored theory is that the vasodilation action of minoxidil increases blood supply to the scalp (**Fig. 4**B).[7] Initial trials were performed that showed moderate to significant hair growth in ~40% of the patients enrolled.[8] The 2% formulation received approval from Food and Drug Administration (FDA) for treatment of AGA in male and female patients in 1998 and 2001, respectively. The 5% topical foam preparation was FDA approved for men in 2006, and the 5% solution was also FDA approved for men in 2007.[9] Currently, the 5% foam or solution is not FDA approved for use in women, but off-label use is common.[10]

There have been several randomized control trials (RCTs) assessing both 2% versus 5% minoxidil against each other and against placebo. Minoxidil 2% has been shown to be effective in preventing progression of AGA and improving AGA in the frontotemporal and vertex areas in men.[11] Furthermore, 5% minoxidil solution or foam has been shown to be more effective than the 2% solution. One study comparing the 2% and 5% solution of minoxidil found a 60% increase in cosmetic results in the 5% group compared with 40% in the 2% group.[12]

Although men have been more studied than women for alopecia, there are several high-quality studies showing promise in treating FPHL. Minoxidil 2% solution twice daily has been

Table 1
Stages of the hair cycle

	Stage	Length	% of Hair	Processes
Anagen	Active growth	2–6 y	90	Dermal papilla increase size GF's secreted HF grows 1 cm/28 d
Catagen	Transition phase	2–4 wk	1–2	Matrix degenerates HF cut off from blood supply At the end, 1/6 of original length
Telogen	Resting phase	3–5 mo	10	Fully keratinized, "club hair" Once keratinized, shed (50–100/d) Signals begin move to anagen

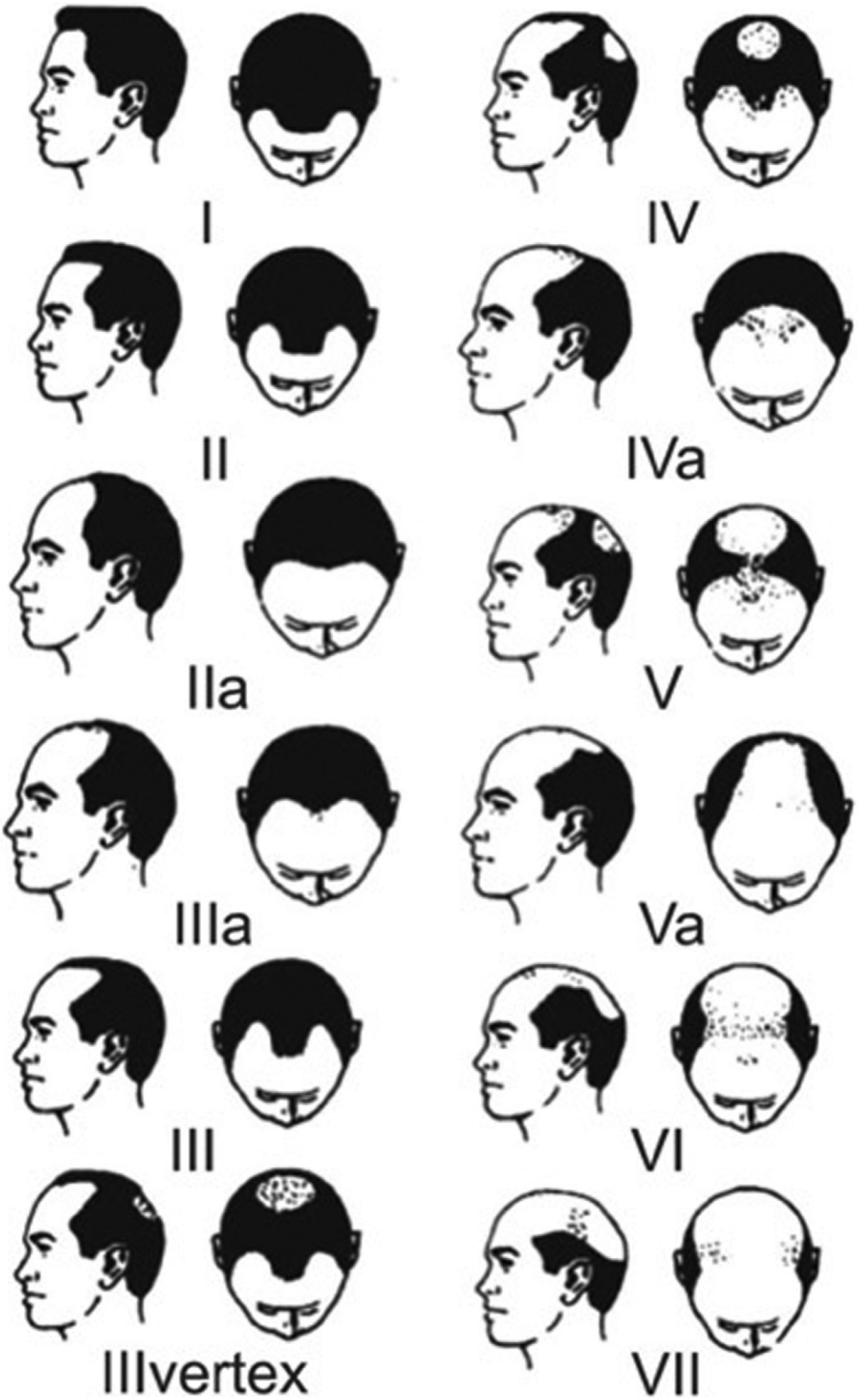

Fig. 2. Norwood-Hamilton staging for MPHL. (Francisco Jimenez, Majid Alam, James E. Vogel, Marc Avram, Hair transplantation: Basic overview, Journal of the American Academy of Dermatology, 85(4), 2021, 803-814, https://doi.org/10.1016/j.jaad.2021.03.124.)

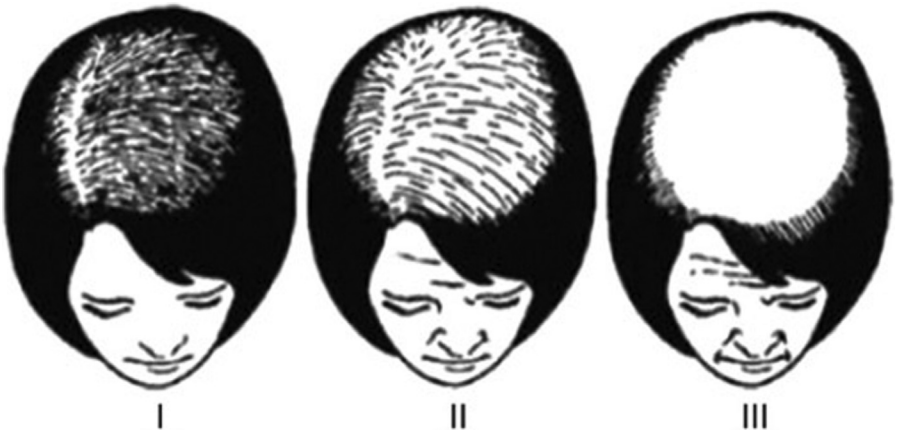

Fig. 3. Ludwig staging for FPHL. (LUDWIG, E. (1977), Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. British Journal of Dermatology, 97: 247-254. https://doi.org/10.1111/j.1365-2133.1977.tb15179.x.)

shown to prevent progression and improve AGA in female patients. The efficacy of 5% minoxidil solution or foam applied once daily was no different when compared with the 2% minoxidil applied twice daily.[13]

Minoxidil treatment should be used for 6 months before assessing the final results. Patients should be warned that there could be a transient period of hair shedding at the 2-month mark. The minoxidil should be spread onto the scalp and left in place for approximately 4 hours. Patients should also be advised that drug interruption will cause acute hair shedding after 3 to 4 months but that hair shedding involves only the hairs that were going to be lost before treatment.[14]

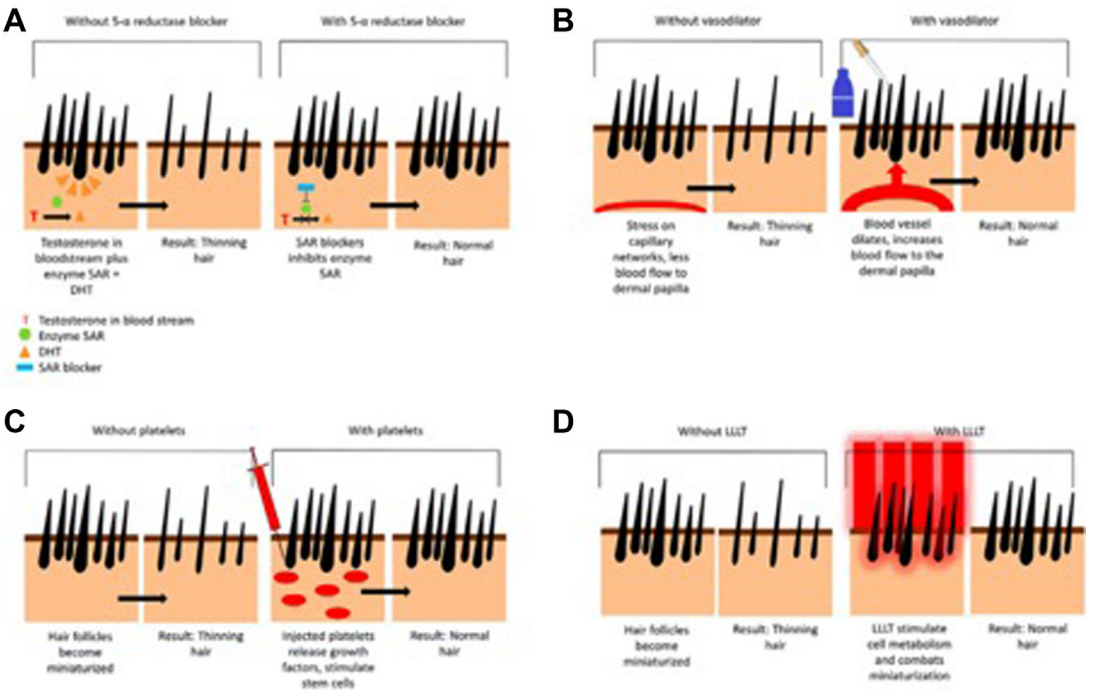

Fig. 4. (*A*) Working hypothesis of antiandrogens in AGA. (*B*) Working hypothesis of vasodilator in AGA. (*C*) Working hypothesis of PRP in AGA. (*D*) Working hypothesis of LLLT in AGA. (*From* Gupta AK, Mays RR, Dotzert MS, Versteeg SG, Shear NH, Piguet V. Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis. J Eur Acad Dermatol Venereol. 2018 Dec;32(12):2112-2125; with permission.)

Finasteride

Finasteride is an oral medication that has been FDA approved at a dose of 1 mg daily for use in men with AGA since 1997. The mechanism of action is through the selectively inhibition of type II 5-alpha reductase (AR), found in hair follicles and the prostate, which produces dihydrotestosterone (DHT) from testosterone (**Fig. 4**A); this results in a reduced level of DHT in both the serum and scalp, but increases the level of testosterone in the scalp.[15] Through the blocking of DHT, finasteride restores the proper length of the anagen phase, which results in an increased growth rate and hair width.[16]

Finasteride at a dose of 1 mg daily has been shown to increase the hair count, physician-assessed hair coverage, and hair mass compared with placebo.[17,18] A systematic review of the efficacy of finasteride in men with male pattern hair loss found that 5.6 patients need to be treated short term, and 3.4 patients need to be treated long term, for one patient to perceive an improvement. There was a 20% absolute increase in patient-perceived improvement in the short term and a 30% absolute increase in the long term. Longer treatment with finasteride promotes greater therapeutic success.[19] Similar to minoxidil, response to finasteride varies, and hair regrowth can be lost after the medication is discontinued.

In contrast, finasteride is not FDA approved for the treatment of FPHL. A study looking at a small population of Asian women showed improvements in hair density, width, and scalp appearance after 1 year of finasteride use.[20] A double-blind, placebo-controlled, randomized multicenter trial found finasteride, 1 mg, to be ineffective in postmenopausal women with female pattern hair loss at 12 months.[21,22] The results of finasteride overall show similar promise in FPHL, but they are on a small population and inconsistent. Further studies will be required to assess ideal dosage and efficacy of finasteride for FPHL.

The recommended dose of finasteride of 1 mg/d and the result should be assessed at 6 to 12 months. Side effects from finasteride include decreased libido, erectile dysfunction, gynecomastia, and depression. Postfinasteride syndrome is a constellation of sexual, somatic, and psychological disorders that persist after cessation of treatment, independent of age, dosage, or indication.[23] The side effects of finasteride in women have been studied less than in men, but there have been reports of decreased libido, dry skin, mild acne, headache, dizziness, irregular menses, hypertrichosis, and changes in liver enzymes.[24] Because of its antiandrogenic effects, pregnant women are advised against coming into physical contact with finasteride. Doing so may inhibit the proper sexual development of male fetuses or induce genital abnormalities.[25]

Laser- and light-based therapy

Low-level laser therapy (LLLT) is one of the few FDA-cleared devices used for treatment of alopecia. LLLT works by a process called photobiomodulation, where the laser stimulates a specific biological process in the target tissue. LLLT wavelengths typically fall between 500 and 1100 nm with a power density between 5 and 500 mW. The precise mechanism of action is not known, but there are several postulations. LLLT generates oxygen radicals and antioxidants, which increase keratinocyte and fibroblast mitosis. Another theory involves the generation of adenosine triphosphate through inhibiting nitric oxide, which can increase metabolism and abate apoptosis, which causes new hair growth.[26] A final thought is that the LLLT decreases inflammation through decreased prostaglandin E-2, and increasing antiinflammatory cytokines, thereby activating hair growth. These effects are thought to prolong the anagen phase of the hair cycle, stimulate hair follicles that are into the telogen phase to reenter the anagen phase, and inhibit the early entry into the catagen phase (**Fig. 4**D).[27]

A 2020 literature review by Egger and colleagues found 10 RCTs with similar treatment settings, duration, and objective endpoints. Eight of the studies compared LLLT technology with sham devices, and all 8 found a statistically significant increase in hair diameter or density. Five of the studies analyzed included patient satisfaction metrics; in most cases, the treatment group showed a more favorable assessment than the control group. They concluded that these devices work well in men and women with AGA, with minimal adverse effects reported.[28] Recently, Gentile performed a systematic review of LLLT for both MPHL and FPHL. All 7 RCTs analyzed showed an improvement in hair count and density, in both men and women, in mild to moderate AGA.[29]

When looking at the totality of clinical trials, reported adverse effects are minimal. In a 2018 review, out of 13 studies, 5 showed adverse side effects including acne, mild paresthesia, urticaria, headache/scalp tenderness, and pruritis in a small fraction of patients. No adverse effects required disruption or discontinuation of treatment, and most resolved within 2 weeks.[30] Overall, LLLT is clearly an important treatment modality, as there are several FDA-cleared devices including the HairMax Lasercomb, iGrow, Theradome, and the Capillus laser cap, all using low-level laser

technology in an effort to treat patients with hair loss (**Fig. 5**).

Second-Line Treatments

Microneedling

Microneedling (MN) is a minimally invasive procedure that uses fine needles to puncture the outer surface of the skin, the stratum corneum. Previous to its use in alopecia, it has been used in skin rejuvenation, scar treatments, acne treatment, burns, melasma, and keloids.[31] Typically, MN is performed by using a roller or a needle pen over the scalp that contain needles with various depths of penetration between 0.8 and 2.5 mm. The mechanism of action is thought to be partially due to the local trauma from the needles that stimulate the tissue's own growth factors.[32]

Dhurat and colleagues randomized 100 patients comparing weekly MN treatment plus twice-daily minoxidil 5% with minoxidil alone. The MN group had a significantly greater hair count at 12 weeks.[33] Generally, MN is thought to be tolerated well by patients with the adverse effects including bleeding, pain, redness, and scalp irritation. From the literature, it seems that MN is being combined with other first-line treatments including minoxidil and platelet-rich plasma (PRP).[34] MN is thought to increase the penetration of topical therapies, allowing a greater absorption of large molecules[32]; this is a well-tolerated procedure with only mild side effects such as itching, redness, and folliculitis reported.[35]

Platelet-rich plasma

PRP is a relatively new treatment that has been used in several surgical fields including cardiac surgery, dentistry, ophthalmology, orthopedics, and plastic surgery. Within plastic surgery, PRP is used to improve healing, augment tissue, promote stem cell growth, and as an off-label treatment of AGA (**Fig. 4**C). PRP is an autogenously harvested serum that is processed to concentrate various growth factors and platelets.[36] The growth factors contained in PRP include platelet-derived growth factor, transforming growth factor β, vascular endothelial growth factor, epidermal growth factor, and insulinlike growth factor. These factors are known to be mitogenic to several cell types including monocytes, fibroblasts, stem cells, endothelial cells, and keratinocytes. They have also been shown to increase angiogenesis, increase collagen production, and allow increased cellular permeability (see **Table 1**).[37]

In 2006, Uebel and colleagues were the first to show the potentially positive effects of PRP after hair follicles used for hair transplantation were treated with PRP and showed increased growth and density.[38] In 2016, Alves and colleagues published an RCT looking at 25 patients injected with PRP in one-half of the scalp and saline in the other. At 3- and 6-month intervals, there was an increase in mean anagen hairs, telogen hairs, hair density, and terminal hair density compared with baseline. They also found that mean total hair density, male sex, age less than 40 years, beginning of hair loss at an age greater than 25 years, positive family history, and greater than 10 years of AGA could predict a potential better outcome (**Fig. 6**).[39]

When looking at the effect in women, Puig published an RCT where 26 women were injected with either PRP or saline one time. At 26 weeks, there was no statistical difference in hair count or hair mass, but more subjects in the PRP-treated group reported improvement in hair loss, rate of hair loss, an increase in thickness, and heavier/coarser hair.[40] Gentile performed a systematic review in 2020 looking at 12 trials showing that 84% showed a positive effect of PRP on AGA, 50% of the studies showed a statistically significant improvement of objective measures, and 34% reported an improvement in hair thickness and density. Only 9% (1 study) of the studies reported that PRP was not effective in treating AGA.[41]

One drawback of PRP is the lack of consensus on the exact concentration, the utility of activators, dosing parameters, depth of injection, or frequency of sessions. In general, the studies that showed that PRP had a positive effect on AGA had at least 3 treatments, spaced 1 month apart, and further maintenance treatments yearly. Typically, the PRP is injected at the dermal/subdermal junction, one inch apart, and evenly distributed around the areas of hair loss.[42] Transient pain and erythema are the most common side effects of PRP injections, with no major adverse effects reported in the literature.[43]

Dutasteride

Dutasteride, a potent type I and type II 5-AR inhibitor, is used to treat benign prostatic hyperplasia but is also prescribed as an off-label treatment of pattern hair loss, more specifically, in patients who have not responded to finasteride. One RCT in 416 men with male pattern hair loss demonstrated that dutasteride, 2.5 mg, was superior to finasteride, 5 mg, in terms of increasing hair count over 24 weeks.[44] Zhou and colleagues performed a meta-analysis looking at the safety and efficacy of dutasteride against finasteride in treating AGA over a 24-week cycle. The metanalysis contained 3 RCTs and showed that dutasteride showed an improvement in total hair count, physician assessment of global photographs, and subject assessment. In addition, there was no significant

Fig. 5. Examples of various LLLT devices (Left to Right: Capillus Laser Cap, Theradome, HairMax Laser Band 82, iGrow Laser Helmet, and HairMax Laser Comb).

difference in patient safety, with similar rates of altered libido, erectile dysfunction, and ejaculation disorders.[45]

Jung and colleagues took 31 patients with no clinical response to finasteride and placed them on dutasteride; 77.4% of these patients showed an improvement on dutasteride.[46] Finally, Shanshanwal and Dhurat performed a comparative, randomized, evaluator-blinded study in 90 male patients, which showed an increase in total hair count by 5-fold in the dutasteride group over finasteride. Interestingly, they also noted an increase in thin hair count, where they used a surrogate for reversal of hair follicle miniaturization. The finasteride group showed no increase in thin hair count.[47] There is no significant difference in adverse effects between dutasteride, 0.5 mg daily, and finasteride, 1 mg daily.[44] Similar to finasteride, caution should be given to starting women of child-bearing age on dutasteride.

Antiandrogens

Antiandrogen therapy with spironolactone, cyproterone acetate (CA), or flutamide are used for treatment of FPHL, despite limited evidence.[9] CA blocks androgen receptors and decreases luteinizing hormone/follicle stimulating hormone release, which decreases testosterone. One study found that CA/ethinyl estradiol (2 mg/0.035 mg) taken daily in 35 women resulted in both a cessation of hair loss in 83% of subjects and also hair regrowth in 77%.[48] Treatment with CA has been shown to improve hair growth in patients with FPHL, with both normal and high androgen levels.[49]

Spironolactone is a potassium-sparing diuretic, which reduces testosterone levels and competitively blocks androgen receptors in target tissues.[48] The role of spironolactone has been studied and found to be potentially effective in FPHL, both on its own and combined with minoxidil.[50,51] The starting dose is typically between 50 and 200 mg daily, and response should only be assessed after 6 months. Side effects of antiandrogens can include postural hypotension, electrolyte disturbances (hyperkalemia with spironolactone), menstrual irregularities, fatigue, urticaria, and breast tenderness.[52] Despite some initial promise, neither oral or topical antiandrogens are recommended for hair loss except for cyproterone acetate in hyperandrogenic women.[9] Oral contraception is recommended to prevent pregnancy in premenopausal women, as spironolactone can cause feminization of the male fetus.

Ketoconazole

Ketoconazole is an imidazole antifungal that is predominantly used in shampoo form for seborrheic

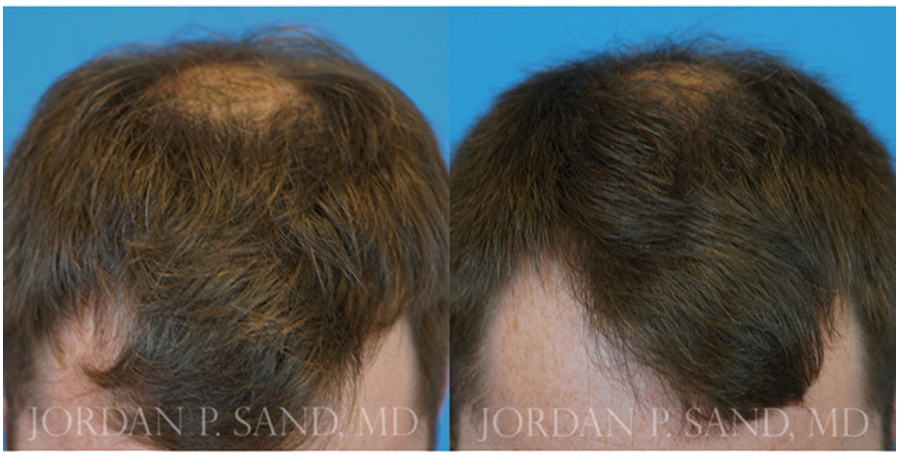

Fig. 6. A 47-year-old man with AGA before (left) and 6 months after 3 monthly PRP (right) treatments.

Table 2
Medical treatment options for androgenetic alopecia

Medication	Intended Population	Method of Administration	Mechanism of Action	Frequency/ Duration	FDA Approval Status	Adverse Effects
Minoxidil[a]	M, F	Topical	Vasodilation, antiandrogenic, antiinflammatory	Daily >6 mo	Approved	• Hypertrichosis • Contact dermatitis
Finasteride[a]	M	Oral	5-α-reductase inhibitor	Daily >6 mo	Approved	• Sexual side effects • Mood disturbances
Dutasteride	M	Oral	5-α-reductase inhibitor	Daily >6 mo	Not approved, approved in other countries	• Sexual side effects • Mood disturbances
Spironolactone	F	Oral	Potassium-sparing diuretic	Daily >6 mo	Not approved for AGA	• Hyperkalemia • Sexual side effects • Feminization • Orthostatic hypotension
Oral minoxidil	M, F	Oral	Vasodilation, antiandrogenic, antiinflammatory	Daily >6 mo	Not approved for AGA	• Hypotension • Lower limb edema • Hypertrichosis
Topical finasteride	M, F	Topical	5-α-reductase inhibitor	Daily >6 mo	Not approved for AGA	• Systematic absorbtion with same sexual and mood problems as oral
Latanoprost	M, F	Topical	Prostaglandin analogue, prolongs anagen phase	Daily >6 mo	Not approved for AGA	• Erythematous reaction
Ketoconazole	M, F	Topical	Imidazole antifungal, antiinflammatory	Daily >6 mo	Not approved for AGA	• Itching, burning • Dry skin

[a] Authors' first-line treatment of AGA.

Table 3
Adjuvant procedures for androgenetic alopecia

Treatment	Mechanism	Protocol	FDA Approval Status	Adverse Effects
Low-level laser therapy	• Stimulation anagen • Activation dormant follicles • Increase ATP, GFs	• 3x per wk, 15–25 min • Every other day, 25–30 min • >6 mo	Approved	• Photosensitivity
Platelet-rich plasma (PRP)	• Differentiation of stem cells into hair follicles • Prolong anlagen phase • Prevent hair cells from apoptosis	• Monthly for 3 mo, maintenance treatment yearly[a] • 2/3 sessions at 3-mo interval	Not approved	• Pain, irritation at site • Bleeding
Scalp microneedling	• Release of PDGF • Activation of follicular stem cells • Inflammation to puncture site	• May combine with PRP • Alone, 1 session per wk for 12 wk	Not approved	• Pain, irritation at site • Bleeding • Telogen effluvium • Lymph node enlargement
Adipose tissue injections	• Improve vascularity and blood supply to scalp • Delivery of early induced PGDF, FGF, VEGF	• 1 session of injections	Not approved	• Pain, dermatitis • Recurrence of alopecia

Abbreviations: ATP, adenosine; FGF, fibroblast growth factor; GF, growth factors; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.
[a] Authors' preferred PRP protocol.

dermatitis. It acts as an antiinflammatory and an androgen-receptor antagonist. Topical ketoconazole 2% shampoo may also have some efficacy in treatment of AGA; a small trial of 39 men with AGA showed an increase in hair density after 6 months of treatment.[53] Ketoconazole can also work as an adjunct when combined with finasteride to further decrease DHT levels.[54] A 2020 systematic review showed an increase in hair shaft diameter with ketoconazole use, in addition to improvements on clinical photographs and subjective evaluations of AGA.[55]

Prostaglandins

Prostaglandin (PG) levels are unregulated in AGA and could be of importance in discovering an effective treatment modality. Recent studies have shown a role for prostaglandins in hair growth. Latanoprost and bimatoprost, both PG-F2 analogues, have been shown to prolong the anagen phase and stimulate hair growth.[56] One RCT with 16 male patients showed improvement in hair density using topical latanoprost 0.1%.[57] PG-E2 analogues have been shown to protect hair loss in radiated mice.[58] Elevated PG-D2 levels, in contrast, are known to increase miniaturization and inhibit hair growth.[59] Adverse effects tend to only be located at the treatment site and include erythema and folliculitis.[57]

Topical finasteride

Recently, topical finasteride has been studied and shown to have promise in both MPHL and FPHL.[60] Topical finasteride is used at a far lower dose than the oral version, which minimizes potential side effects, and allows use in women of reproductive age. One study looked at 52 men and premenopausal women treated with 0.005% topical finasteride applied twice daily for 16 months. There was a significant reduction in hair loss starting at the sixth month of treatment, which extended to the end of the study.[61] Postmenopausal women were also studied in an RCT looking at 3% minoxidil alone versus 3% minoxidil and 0.25% finasteride. There was an increase in hair diameter at week 24, and clinical improvements were seen in 90% of the study group. The side-effect profile includes itching, irritation, and lowered serum DHT in women.[62]

Oral minoxidil

Oral minoxidil works through a similar mechanism as the topical form. It has been studied at a dose of

0.25 mg alone and in combination with spironolactone in FPHL.[52] The current evidence does show efficacy of 5 mg daily for MPHL and 0.25 mg daily with 25 mg spironolactone for FPHL.[63] At higher doses (5 mg and higher), oral minoxidil may cause pedal edema, postural hypotension, and electrocardiogram abnormalities.[52]

SUMMARY

Hair loss affects both men and women and may start at an early age. Three FDA-approved treatments for AGA exist: minoxidil, finasteride, and LLLT (numerous devices). There are several other potential promising non–FDA-approved treatments including PRP injections ± microneedling, antiandrogens, prostaglandin analogues, and adipose injections (**Tables 2** and **3**). Despite the many options, treatments typically take 6 to 12 months before a clinically objective result may occur, and once the treatment starts, it must continue indefinitely to sustain the results.

CLINICS CARE POINTS

- MPHL and FPHL can cause distress to patients but the pathology may be different, in addition to, the potential side effects of treatment.
- Both minoxidil and finasteride are commonly prescribed and have positive results in the treatment of AGA.
- LLLT also show promising results and can be used as a solo modality and in combination with other treatments for AGA.
- PRP treatments are showing positive results in both MPHL and FPHL, but more rigorous studies need to be performed.
- Aside from hair transplantation, many of the current therapies for AGA must be continued on an ongoing basis; therefore compliance is of utmost importance.

DISCLOSURE

The authors have nothing to disclose.

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