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Promising Therapies for Treating and/or Preventing Androgenic Alopecia

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ABSTRACT

Androgenetic alopecia (AGA) may affect up to 70% of men and 40% of women at some point in their lifetime. While men typically present with a distinctive alopecia pattern involving hairline recession and vertex balding, women normally exhibit a diffuse hair thinning over the top of their scalps. The treatment standard in dermatology clinics continues to be minoxidil and finasteride with hair transplantation as a surgical option. Here we briefly review current therapeutic options and treatments under active investigation. Dutasteride and ketoconazole are also employed for AGA, while prostaglandin analogues latanoprost and bimatoprost are being investigated for their hair growth promoting potential. Laser treatment products available for home use and from cosmetic clinics are becoming popular. In the future, new cell mediated treatment approaches may be available for AGA. While there are a number of potential treatment options, good clinical trial data proving hair growth efficacy is limited.

Key Words: AGA, androgenetic alopecia, male pattern baldness, female pattern hair loss

Hair Loss

Hair loss comes in many forms and it is an increasingly common complaint of dermatology clinic patients. While there are many potential diagnoses, the most frequently encountered are androgenetic alopecia (male pattern baldness [MPB]; female pattern hair loss [FPHL]), telogen effluvium, or alopecia areata. Several

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forms of scarring alopecia also seem to be becoming more common in dermatology clinics. However by far, the near universal hair loss complaint is androgenetic alopecia (AGA) in men and women. The population frequency of AGA varies with ethnicity, but as a rough generalization up to 70% of men and 40% of women will experience some degree of AGA in their lifetime. While the condition is a widespread experience, negative image perceptions¹ mean affected individuals can be highly motivated to seek diagnosis and treatment.

Androgenetic Alopecia

Clinical Presentation

In most men, AGA develops with a distinctive "patterned" hair line recession. In women, the presentation may be less clear; typically women will develop a diffuse thinning over the top of the scalp yielding a "Christmas tree" pattern with more thinning towards the front, though the frontal hairline is maintained.² Occasionally men may develop a female presentation of hair loss and women, primarily those experiencing excess androgen activity, may develop a more male-like hair loss pattern. Also of note, frontal fibrosing alopecia in women, a scarring alopecia with hairline recession, has been frequently misdiagnosed as AGA.³ Diffuse AGA may be difficult to distinguish from telogen effluvium. Indeed, telogen effluvium may spur AGA onset and the increased shedding of telogen effluvium can be an early phase characteristic of AGA. Where diagnosis is in doubt, a biopsy may clarify.⁴

Biochemistry

Research on subjects with androgen insensitivity syndromes, or 5 α reductase deficiency, implies that AGA is induced via activation of androgen receptors in hair follicles by dihydrotestosterone (DHT). DHT binds to androgen receptors with five times the tenacity of testosterone and consequently has greater downstream activation potency.⁵ Two distinct forms of 5 α reductase (types 1 and 2) differ in their tissue distribution; type 2 is most active in hair follicles, but both likely contribute to AGA. The primary precursor of DHT in men is testosterone, but dehydroepiandrosterone (DHEA) and other weaker androgens, are the precursors for DHT in women. The intracellular signaling cascade after androgen receptor binding is poorly understood, but receptor binding leads to increased production of cytokines, such as TGFbeta1 and 2, which promote telogen and dermal papilla cell senescence.^{6,7} The density of androgen receptors in hair follicles varies with location. Occipital hair follicles, with a low number of androgen receptors, have little or no response to DHT. Consequently, hair loss is mostly restricted to the scalp vertex and fronto-temporal areas.

Genetics and Diagnostic Tests

AGA susceptibility is largely determined by genetics, though the environment may also play a minor role. Androgen receptor polymorphisms probably make the key determination for androgen responsiveness, but 5 α reductase, aromatase, and sex hormone binding globulin (SHBG) genes may also contribute along with other hormone metabolism associated genes.⁸ While the complete genetic picture is not clear, at least one company claims to have a gene polymorphism based diagnostic test (HairDX™) that will predict the chances of future AGA development.^{9,10} For young patients concerned about hair loss this test may

help to define the value of early treatment initiation. Perhaps of more immediate practical significance, a test that predicts responsiveness to treatment with finasteride is also available.¹¹ In women, serum ferritin levels may also be assessed to determine iron deficiency, thyrotropin levels may be evaluated to rule out thyroid dysfunction, and free testosterone is assessed when androgen excess is suspected. If serum ferritin is low, iron supplementation has been recommended as an enabler of response to other treatments.²

Current and Future Treatments

Drug therapies specifically approved for treating AGA are limited to minoxidil and finasteride. Both can be used in combination.¹² Several other drugs are also used off label (see below) and a plethora of treatments with unsubstantiated hair growth claims can be obtained over the counter. Recently, a review and development of evidence-based guidelines for the treatment of AGA in men and women was published, which may assist with treatment decisions.¹³

Minoxidil

Minoxidil (Rogaine®) was originally an antihypertensive therapy but was subsequently developed as a topical treatment (available in 2% and 5% solutions) for hair loss. Minoxidil use is associated with vasodilation, angiogenesis, and enhanced cell proliferation, probably mediated via potassium channel opening.¹⁴ Side effects include contact dermatitis and a transient shedding during the first ~4 months of use. Use of 5% minoxidil in a commercially available foam vehicle that does not contain propylene glycol (potential irritant), reduces the incidence of pruritus.¹⁵ Several products that include minoxidil, sometimes combined with other active ingredients such as tretinoin, are available from different manufacturers in the US.

Finasteride

Finasteride (Propecia®) is the most common treatment approach for MPB. It is a synthetic type II 5 α reductase inhibitor that reduces the conversion of testosterone to DHT.¹⁶ Improvement in hair count and thickness is possible, with responsiveness improving over 6 months to 1 year with 1 mg daily intake.¹⁷ Adverse sexual events have been reported more frequently with finasteride. Finasteride has significant, adverse consequences for the development of male embryos and, as such, it is not officially approved for use in women. However, in combination with an effective oral contraceptive, finasteride is being prescribed off label. Small scale studies suggest it may be effective in women where androgen activity is involved in FPHL.¹⁸

Dutasteride

Dutasteride (Avodart®), a type I and II 5 α reductase inhibitor, is on hold in Phase III trials for AGA.¹⁹ It is currently approved for treatment of benign prostatic hyperplasia. Phase II studies for AGA demonstrated a dose-dependent increase in hair growth. The efficacy of dutasteride 2.5 mg/day was superior to that of finasteride 5 mg/day.²⁰ Side effects are similar to finasteride.

Prostaglandin Analogues

The prostaglandin F_{2α} analogues latanoprost and bimatoprost are used in treating ocular hypertension and glaucoma. A noted side effect was increased eyelash hair growth, a feature that has been investigated in several small scale studies. Bimatoprost (Latisse®) is now available as a treatment for eyelash growth.²¹ More recently, latanoprost (Xalatan®) has been investigated for its potential to promote scalp hair growth. Latanoprost significantly increased hair density compared with baseline and placebo and may also encourage pigmentation.²²

Ketoconazole

A topical shampoo containing 2% ketoconazole (Nizoral®) is available over the counter while higher concentrations are available by prescription only. As an imidazole anti-fungal agent, ketoconazole is effective for the treatment of dermatitis and dandruff, and its action on scalp microflora may benefit those with AGA associated follicular inflammation.^{23,24} However, ketoconazole is also an anti-androgen and has been suggested to improve hair growth in AGA through androgen dependent pathways.²⁵ Ketoconazole shampoo is typically utilized in conjunction with other AGA treatments.

Anti-androgens

Several synthetic anti-androgens can be used as inhibitors of 5α reductase activity and can also block androgen receptor binding. The efficacy of topical anti-androgen compounds for AGA has been investigated in some small studies,¹⁸ but this approach is not generally considered.¹³ More commonly, anti-androgens are combined with estrogens for the treatment of FPHL. Treatment approaches using oral anti-androgens are significantly more popular in Europe than North America. Cyproterone acetate, available in Canada but not in the US, has been used for FPHL to some effect. However, spironolactone is typically the preferred oral anti-androgen for hair loss in North America.²⁶

Estrogens

Estrogens are indirect anti-androgens, and are sometimes used for the treatment of androgenetic alopecia in women in the form of a birth control pill. When used systemically, estrogens increase SHBG production, which binds to androgens, including testosterone, reducing their bioavailability. Topical estrogen compounds are also commercially available in Europe.¹³ Hair follicles have estrogen receptors and it is believed that topical compounds may act on the hair follicles as direct hair growth promoters as well as by antagonizing androgen activity. However, large clinical studies demonstrating efficacy are lacking and topical treatment is not generally available in North America.

Laser Treatment

Laser/light treatment for hair loss has become very popular in the last few years; it has also been promoted as a preventative measure against AGA. Several different manufacturers provide lasers and light sources of varying wavelengths and with different suggested modes of use. While some laser machines are designed for use at home on a daily basis, others are only available through clinics for weekly or monthly use. Whilst there is evidence that laser light can stimulate hair growth at some wavelengths,²⁷ the biological mechanism by

which it occurs has not been defined. With one exception,²⁸ clinical data from large scale, placebo controlled trials is lacking. While lasers may be options that patients wish to independently explore, so far they have not become a significant treatment approach in most dermatology clinics.²⁹

Surgical Treatment

The hair follicles on the scalp occiput are relatively androgen resistant. This enables their transplantation to balding areas to provide a permanent treatment for AGA. Significant advances have been made in surgical hair restoration techniques. Follicular unit transplantation (FUT) is widely available from transplant clinics in North America and beyond. More recently, specialized techniques have been developed involving individual hair follicle and unit extraction (FUE) to avoid scarring from strip graft harvesting. Hand held motorized devices are now available for the extraction of grafts and most recently robots capable of automated hair follicle extraction have been developed and are commercially available.³⁰ Hair transplant costs vary from \$5,000 to \$20,000 per session and sometimes more depending on the number of grafts and the surgeon. One or two sessions may be required depending on the extent of hair loss. Surgical treatment is limited by the hair density in the donor region and the reluctance of some patients to undergo what is a fairly invasive procedure.

Cell Mediated Treatment

Several companies and academic research groups are focused on the development of cell mediated treatments for AGA. Two main approaches are under investigation: the direct injection of cultured cells or the use of cell secreted factors as a hair growth promoting product. It has been shown that cells from the hair follicle mesenchymal tissue can be cultured and then used to induce new hair follicle formation from epithelial tissue. The injected cells can also migrate to resident hair follicles to increase their size.³¹ Alternatively, cells are cultured and the culture supernatant is processed to produce a compound rich in hair growth promoting factors, such as Wnt proteins, for use in treatment. These cell mediated treatment approaches are still in Phase I or II trials, but may be available in a few years. Also of note, currently gaining popularity in the marketplace is platelet rich plasma (PRP) isolated from whole blood. Platelets have multiple growth factors associated with them as well as other potentially stimulatory mediators. Some hair transplant surgeons use this product to encourage transplanted graft growth.³⁰ PRP is also available from some clinics as a standalone treatment for AGA, though so far there is only one small published study in support of this approach.³²

Alternative Treatments

Numerous products marketed direct to the consumer contain blends of herbal, vitamin and mineral components, though independent data supporting their claims as hair growth promoters are absent. Some of the more common herbs that patients may take include saw palmetto (*Serenoa repens*), black cohosh (*Actaea racemosa*), dong quai (*Angelica sinensis*), false unicorn (*Chamaelirium luteum*), chaste berry (*Vitex agnuscastus*), and red clover (*Trifolium pratense*) which are claimed to have anti-androgenic or estrogen promoting activity. Other products may contain biotin, caffeine, melatonin, copper complexes, and various proprietary compounds with diverse purported modes of action.^{13,33}

Conclusion

Overall, there are a number of treatment options currently available to people with AGA, though the clinical data supporting their use is often very limited. Finasteride and minoxidil are still the most common therapeutic drugs prescribed for AGA. New treatment approaches are under active investigation.

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