New-Generation Therapies for the Treatment of Hair Loss in Men

Neil Sadick, MD\textsuperscript{a,b,*}

INTRODUCTION

Androgenetic alopecia (AGA), also known as androgenic alopecia or male pattern baldness, is the most common type of progressive hair loss. AGA is less common in Asians, and African Americans are 4 times less likely than whites to develop it. The condition is characterized by the progressive loss of terminal hairs on the scalp in a characteristic distribution with the anterior, mid, temporal, and vertex the typical sites of involvement.\textsuperscript{1–4} Aside from physical appearance, hair loss has great impact on psychological well-being and quality of life, with low-esteem, depression, and social anxiety commonly reported.\textsuperscript{5} In AGA there is progressive miniaturization of the hair follicle leading to vellus transformation of terminal hair resulting from an alteration in hair cycle dynamics: anagen duration gradually decreases and telogen increases. Although androgens are known to be implicated in these changes, the pathophysiology driving hair loss is still largely unknown. Current scientific data support that hair loss is likely a multifactorial disorder caused by interactions among several genes and intrinsic/extrinsic environmental factors.

Genetics play an important role in male AGA. As 1 study showed in 500 monozygotic and 400 dizygotic male twins between the ages of 25 and 36, 80% of the variance in the extent of hair loss was attributed to genetic effects.\textsuperscript{6} Numerous studies have identified genetic susceptibility loci for AGA, including the androgen receptor/EDAR2 locus on the X chromosome.\textsuperscript{7} Exposure to UV light, smoking, pollutants, poor nutrition, and other factors have also been shown to lead to the production of reactive oxygen species and release of proinflammatory cytokines, leading to a state of inflammation and oxidative stress that contributes to hair loss. Evidence of the causative role of inflammation in driving hair loss was highlighted in a study by Sadick and colleagues that included 52 female subjects with AGA, with superficial lymphocytic perifolliculitis involving the superficial isthmic part of the follicle. Treatment of the subjects with anti-inflammatory medications together with minoxidil was more efficacious clinically than monotherapy alone, implying that the...
inflammatory process is key to perpetuating disordered hair physiology. Chronic elevated psychoemotional stress is also increasingly recognized as contributing to hair loss through to the production of stress hormones, like cortisol, which are known to induce catagen.

In terms of current treatment, the 2 therapeutic agents approved by the Food and Drug Administration and European Medicines Agency for treatment of AGA are topical minoxidil and oral finasteride (1 mg/d). Both these agents, however, have had a limited success rate, and, even worse, unfavorable side effects, including sexual dysfunction. More importantly, these therapies fail to address the complex pathophysiology driving hair loss and rely on targeting singular compounds androgens (finasteride) rather than considering a more comprehensive approach that targets stress and inflammation. New therapies, such as PRP, injectable cytokines, low-level laser therapy (LLLT), and nutraceuticals are emerging with promising results, testament to the validity of a paradigm shift in hair loss treatments, one that recognizes and addresses the complexity of hair loss biology.

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) injections have been used for some time in several medical fields, such as in regenerative medicine, sport medicine, and aesthetic dermatology/plastic surgery. In the past couple years, several lines of investigation have reported positive results in the use of PRP for treatment of hair loss. Compared with drugs, PRP injections are safe and cheap, without major side effects, and require only periodic treatment sessions. This is an attractive alternative for patients who have tried finasteride and experienced undesirable side effects or do not want the long-term commitment necessary for minoxidil application. PRP is ideal for mild/moderate hair loss as monotherapy or adjuvant to other procedures, such as hair transplantation.

PRP is an autologous product that is manufactured by centrifugation from patients’ own venous blood, limiting the potential risk of disease transmission. Its utility in the treatment of androgenic alopecia is rooted in the presence of growth factors in plasma factors that are important for cell proliferation and differentiation and has anti-inflammatory properties. The main growth factors are platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β1 and TGF-β2, vascular endothelial growth factor (VEGF), basic fibroblastic growth factor, epidermal growth factor, insulin-like growth factors (IGF-1, IGF-2, and IGF-3), and hepatocyte growth factor (HGF). The mechanism via which PRP is proposed to stimulate hair growth is through the promotion of vascularization and angiogenesis as well as the entry and extension of the duration of the anagen phase of the hair cycle. This is achieved by growth factor–mediated increased activation of wingless (Wnt)/β-catenin, extracellular signal–regulated kinase (ERK), and protein kinase B (Akt) signaling pathways, which lead to cellular proliferation and differentiation in the hair follicle. Although there is a need for larger, more controlled clinical trials with longer follow-up periods and standardized protocols and dose regimes, a recent meta-analysis summarizing PRP studies thus far has shown the treatment overall results in quantitatively beneficial outcomes. In 177 patients treated with PRP, significantly locally increased hair numbers per square centimeter were observed after PRP injections versus control along with a significantly increased hair thickness cross-section per 10^4 square millimeters favoring the PRP group.

INJECTABLE CYTOKINES

Another hair treatment modality currently in development and similar to PRP in terms of its lack of side effects and dosing but not autologous is injectable cytokines, offered by Histogen (San Diego, California) and marketed as Hair Stimulating Complex (HSC). HSC is a soluble injectable formulation based on cell conditioned media (CCM) produced by neonatal cells grown in suspension under simulated embryonic conditions of hypoxia (3%–5% oxygen). Under these conditions, cells become multipotent and secrete key growth factors including keratinocyte growth factor (KGF), VEGF, and follistatin, which have been linked to hair follicle stem cell proliferation. Two proof-of-concept clinical trials of an earlier prototype of CCM were completed outside the United States, reveal promising efficacy results. In 1 trial, 84.6% of patients receiving just 1 treatment showed a significant increase in terminal hair count and hair thickness at 12 weeks and results were sustained at the 12-month follow-up. In the second clinical trial, in which patients received 2 treatments 6 weeks apart, the increase in total hair count was 46.5% above that seen after a single treatment. Significant improvements were observed in total hair count, terminal hairs, and hair thickness at 12 weeks and 1 year. After these initial studies, Histogen plans to conduct a phase 1 clinical study in the United States using HSC, which is purified to enrich for KGF, VEGF, follistatin, and additional growth factors known to be
necessary for hair growth: placental growth factor, angiogenin, and HGF.

LOW-LEVEL LASER THERAPY

LLLT, also called red light therapy, bio-stimulation, and photobiomodulation, is a safe form of light/heat treatment evaluated for a variety of medical conditions, including acne, skin rejuvenation, fat reduction, and more recently hair loss. LLLT is thought to promote tissue repair and regeneration by stimulating cellular activity when penetrating through the scalp. The most commonly used wavelengths are in the range of 500 nm to 1100 nm and deliver fluences of 1 J/cm² to 10 J/cm² with a power density of 3 mW/cm² to 90 mW/cm². LLLT devices are available either as in-office hoods or overhead panels bonnet or at-home head caps/helmets/combs. Treatment protocols vary but according to the author’s experience, in-office treatment protocols that are efficacious involve 1 weekly 30-minute treatment for 8 weeks and 1 bimonthly treatment for another 8 weeks, followed by 1 treatment twice a year and quarterly treatments for maintenance. At-home hair growth devices are also useful when used devices for 20 minutes, 2 times to 3 times a week.

Although the exact LLLT mechanism of action is unclear, evidence suggests that LLLT, by stimulating the mitochondrial cell metabolism, releases nitric oxide from cytochrome c oxidase, leading to increased ATP production, decreased oxidative stress, and thus reduced free reactive oxygen species levels and induction of cell proliferation signaling, such as nuclear factor κB. These events result in improved circulation; decreased inflammation; stimulation of hair follicle growth due to the presence of growth factors, such as HGF, VEGF, and IGF-1; and decreased levels of catagen-inducing dihydrotestosterone (DHT). Several cellular pathways at once. Although the mechanism of action of these formulations is not known, it is hypothesized that cumulating ingredients with antioxidant, anti-inflammatory, and cell proliferative ingredients has synergistic effects in promoting hair growth and reducing cellular damage at the level of the hair follicle.

One of the first nutraceuticals for hair loss was Viviscal (Lifes2good, Chicago, Illinois), incorporating special marine extracts and a silica compound. An early randomized, double-blind, study comparing the effects of Viviscal with those of a fish extract for the treatment of AGA showed that twice-daily intake of the supplement for 6 months led to a statistically significant increase in nonvelus hair of 38% of patients receiving Viviscal compared with a 2% increase in the fish extract treatment group. Moreover 95% of the Viviscal subjects showed both clinical and histologic cure at the end of treatment whereas none of the subjects treated with fish extract showed any clinical or histologic difference in the same timeframe. A new-generation formulation of Viviscal, containing marine complex, biotin, vitamin C, and apple extract, was also shown in a recent 6-month, randomized, double-blind, placebo-controlled study to promote hair growth in men with AGA.

Another supplement, Forti5 (Q-SkinScience, Miami, FL), containing green tea extract, omega-3 and omega-6 fatty acids, cholecalciferol, melatonin, β-sitosterol, and soy isoflavones, was shown in a proof-of-concept clinical trial to benefit hair growth: after 24 weeks of twice-daily supplements, 80% of subjects had improved hair count, with 40% rating it moderate and 10% rating it great.

Nutrafol is another new nutraceutical supplement on the market that selectively uses patented, bio-optimized botanic ingredients that have clinical data on absorption and efficacy and are standardized to contain consistent fractions of phytoactive components. Key ingredients of Nutrafol are curcumin, ashwagandha, saw palmetto, vitamin E, and 17 more ingredients, including minerals,
resveratrol, horsetail, marine collagen, and hyaluronic acid. The supplement was designed to target the multiple underlying causes of hair loss, particularly on relatively new aspects like inflammation, stress, and oxidative damage, in addition to more well-studied parameters like DHT. Currently 3 randomized, placebo-controlled, double-blind trials are in progress, to evaluate the clinical safety and efficacy of Nutrafol, while several case series and physician reports have demonstrated promising results in treating hair loss either as monotherapy or in combination with other modalities like PRP.

**MICRONEEDLING AND ENERGY-BASED DEVICES**

Scalp microneedling and energy-based devices, such as fractional lasers/radiofrequency, have also been explored in their ability to promote hair growth. These strategies have been documented as effective in several dermatologic conditions, such as acne scars, skin rejuvenation by creating microinjuries and subsequently stimulating a wound-healing response. The proposed mechanism of action of these treatments includes up-regulation of hair-related genes, release of growth factors (PDGF and VEGF), and activation of follicle stem cells.29–31

A 12-week randomized, evaluator-blinded study in 100 patients with mild to moderate AGA comparing weekly microneedling treatment, combined with 5% topical minoxidil twice daily, to only 5% topical minoxidil twice daily showed that the mean hair count was significantly higher in the microneedling group.30 A follow-up case series in 4 men (already taking finasteride and minoxidil) who received 4 weekly microneedling sessions followed by 11 sessions at 2-week intervals, for a total of 24 weeks of treatment, showed high patient satisfaction from all subjects and results were maintained at the 18-month postprocedure follow-up.29

Although microneedling/energy devices seem to be a promising hair treatment, there is a paucity of studies using this modality as monotherapy; thus, more studies are needed to standardize treatment protocols and document their safety and efficacy. In the author’s experience, microneedling and energy-based devices deliver synergistic effects when used in combination with PRP, LLLT, and conventional drugs, and clinical trials are under way to evaluate the optimal combination strategies.

**SUMMARY**

Treatment of AGA is an extremely challenging feat for the medical community, given the complex biology of hair, and the interplay of intrinsic/extrinsic factors that drive the pathophysiology of hair loss. A promising step toward hair loss treatment is the design of therapeutics that do not target 1 aspect of hair loss, such as hormones, but comprehensively address and target all hair loss triggers. Continued evaluation of the new treatments described (PRP, LLLT, and nutraceuticals) in the clinic should be performed to establish their efficacy and safety and optimize therapeutic protocols to ensure successful clinical outcomes.

**REFERENCES**


