

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

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## KEYWORDS

• PRP • Nutraceuticals • LLLT • Small molecule inhibitors

## KEY POINTS

- Selection of hair transplantation methodology depends on patients' goals, type of hair loss, and quality of hair.
- Robotic hair transplantation is the latest frontier in hair restoration.
- Platelet-rich plasma, low-level laser therapy, and stem cells can be used together with hair transplantation to enhance graft survival.

## 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.<sup>1-4</sup> 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.<sup>5</sup> 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. A 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.<sup>6</sup> Numerous studies have identified genetic susceptibility loci for AGA, including the androgen receptor/EDAR2 locus on the X chromosome.<sup>7</sup> 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

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inflammatory process is key to perpetuating disordered hair physiology.<sup>8</sup> Chronically 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.<sup>9</sup>

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).<sup>10</sup> 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 (LLLTL), 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.<sup>11</sup> 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.<sup>12</sup> 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)- $\beta$ 1 and TGF- $\beta$ 2, vascular endothelial growth factor (VEGF), basic fibroblastic growth factor, epidemic growth factor, insulinlike growth factors (IGF-1, IGF-2,

and IGF-3), and hepatocyte growth factor (HGF).<sup>13,14</sup> 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.<sup>15</sup> This is achieved by growth factor-mediated increased activation of wingless (Wnt)/ $\beta$ -catenin, extracellular signal-regulated kinase (ERK), and protein kinase B (Akt) signaling pathways, which lead to cellular proliferation and differentiation in the hair follicle.<sup>16</sup>

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.<sup>17</sup> 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<sup>4</sup> 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.<sup>18</sup> 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

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