



Commentary

The new regenerative and innovative strategies in hair loss

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The number of clinical trials evaluating new regenerative and innovative strategies in male and female pattern hair loss have exponentially increased during the last five years.

Regarding the innovative strategies, the efficacy of a specific compound obtained from botanical extracts, vitamins, and minerals, called "ALRV5XR", has been tested by Feldman et al. [1] with interesting results in a randomized, double-blinded, placebo-controlled clinical trial in female affected by androgenetic alopecia (AGA) and/or Telogen Effluvium [1]. ALRV5XR aimed to prolong anagen of hair follicle (HFs) and induce neogen in involuted HFs acting also via activation of the Wnt/ β -Catenin cascade in HF stem cells and dermal papilla cells [1]. This kind of biomolecular pathway has been analyzed also during alternative regenerative strategies.

A scientific-clinical need exists for the development of biotechnologies to improve the hair re-growth (HR-G) especially in AGA the most common hair loss disease.

AGA is a dynamic and chronic hair loss disorder, affecting 80% of white men, identified as Male-AGA and 40% of women, identified as Female-AGA, before age 70, in which lymphocytes and mast cells have been seen around the miniaturizing follicle detailed in the stem cell-rich lump zone [2–4]. Miniaturization of the follicles is characterized by a diminishment of anagen phase, with an improvement in the amount of resting hair follicles, telogen, containing microscopic hairs in a hairless scalp [5–7].

In hair loss scalp, HFs stem cell numbers stay unaltered, though the number of more actively proliferating progenitor cells particularly diminishes [8].

The number of investigations evaluating the efficacy of autologous platelet-rich plasma (PRP) and Adult Stem Cell-based therapy (A-SC-BT) in Male- and Female- AGA, commonly considered regenerative

strategies procedures have exponentially increased during the last decade (2010–2020).

Female-AGA is gradually increasing among young women and may bring serious psychological impacts. Women may present with a reduction in hair density, hair thinning, and widening of the area especially on the center of the scalp, which may lead to a serious psychological impact on one's self-esteem, interpersonal relationships, and social status.

Although surgical as hair transplant and multiple non-surgical therapeutic methods like topical Minoxidil[®], oral Finasteride[®], and low-level laser/led therapy (LLLT) had been introduced to the treatment of Female-AGA, further randomized controlled trial treatments must be performed [2,9].

In this field, the aim of regenerative strategies must be the development of new autologous-biotechnologies to involve HR-G by *ex vivo* and *in vitro* culture or by *in vivo* regeneration and bio-stimulation.

The use of autologous platelets derived growth factors, contained in PRP, represented by basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, epidermal growth factor, transforming growth factor- β , and insulin-like growth factor-1 [2–4,9], may represent a valid regenerative strategies for their capacity to promote cell proliferation, differentiation and neo-angiogenesis, favoring, *in vivo*, the wound healing process [3]. *In vitro*, anti-apoptotic effects of PRP have been identified as one of the major contributing factors stimulating hair growth (HG) via the Bcl-2 protein's activation (antiapoptotic regulator) and Akt signaling, prolonging the survival of dermal papilla cells during the hair cycle. In particular, the up-regulation of fibroblast growth factor-7 (FGF-7)/ β -catenin signaling pathways with PRP treatment is suggested to stimulate HG by inducing HF-MSCs differentiation as well as prolonging the anagen phase of the HG cycle [2–4,9].

Comparing with traditional therapies as Minoxidil[®] and Finasteride[®] and hair transplantation, PRP and A-SC-BT appears as novels and promising regenerative treatments both in Female-AGA and Male-AGA, with lower cost and fewer adverse effects [2].

Autologous A-SC-BT have been of great interest for application in HR-G. Some early efforts in the field focused on isolating primary cells from a biopsy of the tissue of interest and growing the cells *ex vivo* for subsequent introduction back into the patient.

In the recent years, the preliminary outcomes related to the use of a new regenerative technique to provide autologous micro-grafts (MCGs) containing human follicle mesenchymal stem cells (HF-MSCs) to be used in patients affected by AGA, have been reported

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[8,10]. The MCGs were obtained by multiple procedures of fragmentation, centrifugation, and filtration of a 2 mm punch biopsy of the scalp [8,10]. However, a major limitation encountered in this area has been the difficulty in expanding cells to sufficient numbers for human use, the necessity to perform this expansion in Good Manufacturing Practices laboratories, and the viability of the expanded cells [8,10]. For this reason, the clinical use of HF-MSCs and A-SC-BT to improve HR-G has not been adequately considered.

Several evidence-based medicine level 1 studies, including systematic review and randomized controlled trials must be performed aiming to confirm the standardized use of regenerative and innovative strategies in hair loss treatment.

Declaration of Competing Interest

None.

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