Non-scarring alopecia

Diagnosis and treatment

R. Grimalt

Alopecia is a common complaint seen in the dermatologic practice. Androgenetic alopecia (AGA) is seen in about 70% of the population. Another commonly observed type is alopecia areata (AA), which can be localized or generalized. Scarring and other types of alopecia are less frequently encountered but very concerning to patients.

Current research goals

Current research is intended to further elucidate the exact pathophysiology of the different types of alopecia in order to develop drugs that specifically target the disease. Additionally, better models for drug testing have to be developed as well as better, more specific drug delivery systems to decrease the side effect profile.
In this article, we discuss some new drugs (*ie*. dutasteride, jak inhibitors, among others) and new modalities of administration of existing drugs (*ie*. interleukin-2, valproic acid) that look promising for the treatment of alopecia. We also review the role of stem cells and their activation pathways (*ie*. platelet rich plasma, follicular unit extraction) in the treatment of alopecias. The role of vitamins and other nutritional supplements in the management of alopecia will also be discussed.

Scientific rationale

Androgenetic alopecia

Finasteride and dutasteride

Finasteride, a type II 5-alpha-reductase inhibitor is approved for the treatment of AGA in men at the dose of 1 mg per day. Dutasteride, a type I and II 5-alpha-reductase inhibitor, has been shown to be more effective than finasteride. A phase III clinical trial (NCT01231607) showed that dutasteride 0.5 mg, resulted in significantly increased hair growth and restoration in men with AGA after 24 weeks of treatment, compared to finasteride 1mg, dutasteride 0.02mg, 0.1mg and placebo. Dutasteride was overall well tolerated and adverse effects were similar among the different treatment groups with no dose-dependent adverse effects associated to dutasterid. A study by Jung *et al*. demonstrated that a six-month therapy with dutasteride 0.5 mg significantly improved hair density by 10.3% and hair thickness by 18.9% in 24 out of 31 (77.4%) patients who had previously been treated with finasteride 1mg for 6 months with poor results. The main adverse effect encountered was transient sexual dysfunction in six patients (17.1%)

Prostaglandins

In 2008 bimatoprost, a prostaglandin F2 -related analog, was approved by the Food and Drug Administration (FDA) for the treatment of hypotrichosis of the eyelashes. Recently, it was shown that scalp hair follicles also express prostanoid receptors mostly in the dermal papilla and connective tissue sheath surrounding the hair bulb.
Another potential drug target, is prostaglandin-D2 (PGD2), which contrary to PGF2, it inhibits hair growth in mouse and human hair follicles through the G-protein coupled receptor 44(GPCR44). Drugs that block GPCR44 are currently under clinical trials for asthma and may be a possible future treatment of AGA.

Platelet rich plasma (PRP) and platelet rich fibrin matrix (PRFM)

Platelet rich plasma (PRP) is rich in growth factors and other bioactive molecules obtained from the alpha granules of platelet concentrate. PRP has been used since the 1980s in medicine, and now seems promising for the treatment of hair loss, although its mechanism of action for this purpose had not been completely elucidated until recently. A study by Li *et al*. demonstrated that PRP increases the expression of β-catenin (inducing the differentiation of bulge stem cells into hair follicles), FGF-7 (prolonging anagen phase) and Bcl-2 expression (protecting cells from apoptosis) in treated dermal papilla cells [20]. They also demonstrated significant hair growth after PRP injections performed for three weeks in a mouse model. Others, were able to demonstrate an increased number of newly formed follicles as well as accelerated the time of hair formation after grafts treated with PRP in nude mice. Platelet plasma growth factors have been used as an adjunctive therapy in male patients undergoing hair restoration surgery to improve hair density and follicular growth. A similar compound, platelet-rich fibrin matrix (PRFM) was used in a prospective cohort study, where fifteen patients with AGA received three intradermal injections of PRFM on a monthly basis with a significant improvement in the hair density index at six months

Stem cells

The use of hair follicle stem cells (HFSC) located in the bulge area is promising for the treatment of non-scarring alopecia. Contrary to scarring alopecia, the inflammation in

Universitat Internacional de Catalunya UIC-Barcelona

non-scarring alopecia does not affect the bulge area of hair follicles. The bulge area is an immune privileged zone mostly because of down-regulation of major histocompatibility complex class I (MHC I) molecules and up-regulation of immunosuppressant molecules, protecting HFSCs from aggressive autoimmune attacks. HFSCs can differentiate into cells of a hair follicle, sebaceous gland or interfollicular epidermis, depending on the surrounding chemical environment. Moreover, the hair cycle can be affected by alterations of the pathways involved in the activation and suppression of HFSCs. One of the main pathways currently being studied is the wnt/β-catenin pathway. The activation of this pathway induces the differentiation of bulge stem cells into hair follicles. Lee *et al*. demonstrated that topical application of valproic acid, which inhibits GSK3β, promotes hair formation in a mice model and on human hair follicle *in vitro* by increasing β-catenin. Recently, in a randomized, double blind, placebo controlled trial, men with moderate AGA were treated with a spray containing 8.3% valproic acid or placebo for 24 weeks resulting in significant increase in total hair count in the experimental group.
Adipose-derived stem cells have also been studied, however, their survival and regeneration potential is induced by hypoxia, and alternative methods of induction have been looked for. Therefore, preconditioning adipose stem cells with ultraviolet B (UVB) to stimulate the hair growth promoting effects was studied . It was found that only low dose UVB (< 20 mJ/cm^2) was able to increase cell survival, migration, angiogenic differentiation, and paracrine effects. By performing this technique prior to cell transplantation, it was observed that mice had increased hair follicle formation and hair weight. UVB preconditioning promotes these effects by generating reactive oxygen species (ROS) and up-regulating Nox4.

Hair transplant
Several studies have demonstrated successful, functional, bioengineered hair follicle transplantation *in vivo*. Given the increasing interest in stem cell therapies, Kumar *et al*. performed a preliminary pilot study to compare the average stem cell yield obtained with follicular unit extraction (FUE) with follicular plucking. They found that with FUE a greater number of stem cells were obtained. FUE being the better option for hair transplants, adjustments to the surgical process have been described to optimize overall results and robotic devices have been added to fasten the process. Older robotic devices were able to successfully decrease the harvest time and transection rate. Newer devices (ARTAS Robotic System, Restoration Robotics, Inc., San Jose, California) include a microscope, a follicular unit identification system and a high precision rate two-step punch harvest device.

Micropigmentation
When available treatments have failed or are not possible to pursue, hair micropigmentation is an alternative to camouflage hair loss in AGA or scars in the scalp. Varying pigments, depending on the hair and scalp skin colors, can be used to tattoo the scalp in the areas where thinner hair, or scars, is present. The procedure should be carefully performed to introduce the pigment at the correct depth (1-2 mm) and at the appropriate distance in the scalp. Possible side effects include infection, tattoo allergy, color fading over time, and the fact that future removal may be difficult and lead to scarring.

Trichotillomania
N-acetylcysteine (NAC)
Recently, N-acetylcysteine (NAC) was investigated as a potential drug given that it increases glutamate extracellular concentration in the nucleus accumbens. It was proven to successfully diminish compulsive behavior of hair pulling in a randomized placebo-controlled trial without adverse effects. After this study, several case reports have further supported its efficacy.

Olanzapine
Olanzapine has also been tested and proved effective for treating trichotillomania but with greater side effects, although its mechanism of action has not been completely elucidated.

Naltrexone
The use of naltrexone has also been studied as it may modulate the mesolimbic dopaminergic circuit, diminishing the urges to incur in the behavior. However, controlled studies have had conflicting results.

Summary
Alopecia is a common concern encountered in the medical practice. Treatment approach varies according to the type and severity of alopecia. However, available treatment options have limited efficacy and several adverse effects. Presently, there are different treatment options being studied to overcome these limitations. Additionally, cellular pathways involved in the pathophysiology of alopecia are further being clarified to potentially target pathogenic molecules.

We searched the literature for recently published articles discussing new treatment options as well as mechanisms involved in alopecia. We discuss the use of stem cells, growth factors, cellular pathways, robotic hair transplant, amongst other emerging therapies used for alopecia. Future looks very promising and new effective treatments such as janus kinase inhibitors could possibly be available for alopecia areata .The stem cell technology is advancing and companies involved in hair follicle neogenesis are starting clinical trials on patients with androgenetic alopecia.

Keywords
abatacept – alopecia areata – androgenetic alopecia – bimatoprost – chemotherapy induced alopecia – dutasteride – excimer laser

Correspondence
Ramon Grimalt
Email: rgrimalt@uic.es