Laser-assisted drug delivery for the treatment of androgenetic alopecia: ablative laser fractional photothermolysis to enhance cutaneous topical delivery of platelet-rich plasma — with or without concurrent bimatoprost and/or minoxidil

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Abstract

Platelet-rich plasma, which contains numerous growth factors that promote hair growth, is a nonsurgical treatment available for patients with androgenetic alopecia. However, neither the quantity nor the location and depth of platelet-rich plasma placement in the scalp is uniform; in addition, multiple painful injections are required. Vertical uniform channels from the skin surface into the dermis, created by ablative laser fractional photothermolysis, can be used to enhance the cutaneous delivery of medications. This technique — referred to as laser assisted drug delivery — may provide an efficacious means for the administration of platelet-rich plasma to the scalp. It would not only enable the uniform placement of platelet-rich plasma in the dermis (instead of inadvertently in the subcutaneous fat) of androgenetic alopecia patients' scalps, but also eliminate the injection-associated pain. In addition, the topical application of either bimatoprost or minoxidil or both could also be enhanced with laser assisted drug delivery. In conclusion, to potentially maximize the stimulation of hair growth, laser assisted drug delivery of platelet-rich plasma — with or without bimatoprost and/or minoxidil — should be considered in patients with androgenetic alopecia in order to effectively deliver the agents to the dermis where the bulge area of the hair follicles is located.

Keywords: ablative, alopecia, androgenetic, bimatoprost, cutaneous, delivery, fractional, fractionated, laser, minoxidil, plasma, platelet, resurfacing, rich, topical

Introduction

The management of androgenetic alopecia includes nonsurgical and surgical treatments. Ablative fractional lasers can be used to enhance delivery of topical agents. The potential application of laser assisted delivery of platelet-rich plasma (with or without bimatoprost or minoxidil or both) for the treatment of androgenetic alopecia is discussed.

Discussion

Androgenetic alopecia

Background

Androgenetic alopecia, the most common type of progressive hair loss, is also known as pattern baldness or pattern hair loss. It has a polygenic mode of inheritance with a high prevalence and a broad range of phenotypic expression. Clinically and microscopically, androgenetic alopecia is characterized by miniaturization of the hair follicles; the thick terminal hairs become thinner and shorter and less pigmented until they are replaced by vellus hairs [1, 2].

In men, androgenetic alopecia is considered an androgen-dependent condition; the Hamilton, Norwood-Hamilton, and adapted Norwood-Hamilton are commonly used classifications to describe the distribution and extent of hair loss [3, 4]. However, in women the androgen signaling may not play as significant a role in the pathogenesis of the condition. Female pattern hair loss is usually

described using the Ludwig classification but other classifications — such as Sinclair or Olsen — also exist [5, 6]. Recently, the basic and specific classification has been proposed as a universal manner to classify androgenetic alopecia in both men and women [3, 5].

Treatment

The management of androgenetic alopecia includes several nonsurgical interventions such as topical minoxidil, oral finasteride, exposure to low-level laser therapy, and injection of platelet-rich plasma [7, 8]. In addition, novel and investigational treatments — including stem cell-based therapies — are being evaluated [6, 9]. Surgical intervention for androgenetic alopecia currently includes hair transplantation [7, 8].

Minoxidil

Minoxidil was developed as an oral agent for the treatment of severe and refractory hypertension. It is a direct arteriolar vasodilator. It lowers blood pressure by opening potassium channels; however, minoxidil's mechanism of action on hair growth remains to be established [10].

An adverse side effect of oral minoxidil therapy, occurring in 24% to 100% of patients, was hypertrichosis. This prompted its use as a topical agent to treat alopecia. The response to topical therapy can be slow and three to six months of treatment may be necessary before objective clinical improvement is observed. Also, in some cases, once the use of minoxidil is stopped not only does the hair growth cease, but a telogen effluvium of the minoxidil-dependent hair also occurs within four to six months [11, 12].

Minoxidil is available not only in 2% and 5% solutions, but also as a 5% foam. Both concentrations are currently approved by the Food and Drug Administration to treat androgenetic alopecia in men and women. The 2% solution is intended to be used twice daily; however, similar improvement with the 5% foam once daily has recently been demonstrated [11-14].

Finasteride

Finasteride is a selective, type 2, 5-alpha reductase inhibitor. It blocks the conversion of testosterone to dihydrotesterone. The daily oral one mg dosage is approved by the Food and Drug Administration for the treatment of androgenetic alopecia in men. Indeed, long term finasteride treatment has demonstrated noticeable improvement in hair growth in about 30% of patients [8, 15].

Finasteride is a teratogen and can cause ambiguous genitalia in the male fetus. Therefore, finasteride is contraindicated in pregnancy. In addition, to prevent a pregnant woman receiving this medication during a blood transfusion, men taking finasteride should not donate blood [7, 15].

Sexual and nonsexual adverse effects have been observed in younger men who have been treated with finasteride. The sexual side effects include decreased ejaculate volume, ejaculatory dysfunction, erectile dysfunction, and low libido. Depression and decreased alcohol consumption are the nonsexual side effects. Unfortunately, there are patients in whom the sexual side effects (decreased libido, ejaculation disorder, and impotence), or depression, or both, persist after the finasteride has been discontinued [15-18].

Low level laser therapy

Low level laser therapy (which is also referred to as low level light therapy) is a noninvasive treatment that can provide stimulation of hair growth in men and women with androgenetic alopecia. Use of low level laser therapy for this purpose was prompted by the paradoxical hypertrichosis that was occasionally observed during laser hair removal. Anecdotal evidence suggests that the most effective parameters for treating androgenetic alopecia are wavelengths between 650nm–900nm with a power density of 5mW/cm^2. The number of treatments and the duration of each session is variable. For example, these parameters have ranged from 15 minutes three times weekly to 20 minutes twice weekly [19-21].

The mechanism of action of low level laser therapy for promoting hair growth in androgenetic alopecia patients remains to be determined. It has been postulated that low level laser therapy increased the number and thickness of hair follicles by increasing adenosine triphosphate (ATP) production (and

thereby cellular energy), reducing local inflammation, and improving blood flow to the treated area. As a result, resting telogen hair follicles are transformed into proliferative, longer-lasting, anagen hair follicles [19-22].

Low level laser therapy, a therapeutic modality that has been approved by the Food and Drug Administration, can be safely administered by patients in their home. It is effective as monotherapy — particularly in androgenetic alopecia patients who do not want drug or surgical treatments. In addition, low level laser therapy can also be used as an adjuvant treatment, with either minoxidil or finasteride, to enhance hair growth in patients with androgenetic alopecia [19-22].

Platelet-rich plasma

Platelet-rich plasma is the portion of the plasma fraction of autologous blood with platelet concentrations higher than the basal levels before centrifugation. Platelet-rich plasma is being used for multiple purposes in many fields of medicine. In dermatology, platelet-rich plasma has been shown to be beneficial in several areas ranging from skin rejuvenation and acne scarring to hair loss [23-26].

The preparation of platelet-rich plasma begins with drawing the patient's blood. Centrifugation of the anticoagulated blood is used to separate the plasma containing the platelets from the red blood cells. Exogenous activating factors (such as calcium chloride) are added to activate the platelets. The platelet-rich plasma is then injected into the target tissue — the scalp in patients with androgenetic alopecia [23-26].

Platelet-rich plasma contains numerous growth factors such as epidermal growth factor, fibroblast growth factor, insulin-like growth factor, platelet derived growth factor, transforming growth factor, and vascular endothelial growth factor; in addition, other factors include fibrin, fibronectin, hepatocyte growth factor, interferon-alpha, interleukins (4, 5, 13 and 17), thrombin, tumor necrosis factor, and vitronectin. The growth factors stimulate hair growth by several potential mechanisms. These include apoptosis prevention, an anagen hair growth phase that is not only increased but also prolonged, delay of the progression from anagen to catagen hair growth phase, and increased viability and survival of the hair follicles [23-26].

Platelet-rich plasma is successfully being used to treat men and women with androgenetic alopecia. However, there is variability in the treatment protocols. Typically, patients initially receive three monthly injections. However, treatment can range from two injections within a period of three months to one weekly injection for four weeks. Follow up treatments may occur at three-month to six-month intervals [23-26].

The total volume of platelet-rich plasma injected into the scalp of androgenetic alopecia patients ranges between six to nine milliliters. A small amount of platelet-rich plasma is injected into many sites. However, neither the quantity of platelet-rich plasma nor the distance between injection sites is uniform [23-26].

Injecting platelet-rich plasma into the scalp is also painful. A skin cooling system (such as the epidermal cooling devices that minimize pain during laser and intense pulse light treatments) is frequently used to provide symptomatic relief when androgenetic alopecia patients receive platelet-rich plasma injections. Laser assisted delivery could provide a method for platelet-rich plasma to enter the dermis without injection-associated pain [23-26].

Platelet-rich plasma may influence hair growth in androgenetic alopecia patients by stimulating the proliferation and differentiation of hair follicle bulge area dermal papilla stem cells. The bulge area of the hair follicle is usually located within the dermis whereas the hair bulbs may be located in both the dermis and the subcutaneous fat. Hence, it would be most effective for the platelet-rich plasma to be placed into the dermis [23-26].

It is often difficult to inject fluid into the dermis — especially if it is thick or fibrotic. Therefore, a significant quantity of the platelet-rich plasma may be inadvertently injected into the subcutaneous fat where it will only contact the hair bulb instead of the bulge area of the hair follicle. A method that would enable uniform placement of the platelet-rich plasma in the dermis — such as the creation of open

columns from the epidermis into the dermis using ablative laser fractional photothermolysis — could result in the reliable delivery of the platelet-rich plasma to its target site [23-26].

Surgical intervention

The surgical treatment of androgenetic alopecia is hair transplantation. The gold standard is to transplant follicular units. Donor strip and follicular unit extraction are the two alternatives available for harvesting the grafts to be used for follicular unit transplantation. There is a robotic device that has been developed to assist not only in the extraction of follicular units, but also in creating the recipient sites. In addition, recent advances in technology may provide the robotic device with the capability to implant the grafts [27-29].

Laser assisted drug delivery

Lasers have been used as monotherapy to treat alopecia. This includes animal models using nonablative fractional lasers to enhance hair follicle regeneration [30]. It also includes ablative fractional laser treatment in men and women with pattern hair loss [31, 32].

Many drugs have difficulty being absorbed into the skin. Laser assisted drug deliver provides a more efficient delivery of the drug — especially those agents that are larger molecules. Ablative skin resurfacing lasers [such as the erbium: yttrium-aluminum-garnet (Er:YAG) and carbon dioxide (CO_2) lasers] remove the epidermis in a continuous manner. Although this approach provides extensive access of a topically applied drug to the dermis, it also requires substantial time for the treated area to heal. However, lasers that utilize ablative fractional photothermolysis create vertical channels that ablate columns of epidermis and dermis while relatively sparing the surrounding tissue; this not only provides easy access for drugs to enter the dermis, but also minimizes the post-laser healing time [33-36].

Laser assisted drug deliver has been used to enhance the delivery of several drugs including 5-aminolevulinic acid, 5-aminolevulinate, amorolfine, bimatoprost, botulinum toxin, diclofenac, diphencyprone, 5-fluorouracil, hair growth factors, imiquimod, indomethacin, ingenol mebutate, methotrexate, minoxidil, pimecrolimus, platelet-rich plasma, poly-L-lactic acid, stem cells, timolol, tretinoin, triamcinolone acetonide, and vitamin C. This technique has also been used to topically deliver analgesics and vaccines. Hence, this treatment approach has not only been studied, but also used for the management of several conditions such as actinic keratoses, alopecia, arthritis, hemangiomas, hypopigmentation, nonmelanoma skin cancer, onychomycosis, photoaging, post inflammatory hyperpigmentation, psoriasis, and scars [34-36].

Ablative fractional lasers to enhance topical cutaneous delivery of agents for androgenetic alopecia treatment

Hair growth factors

Ablative fractionated photothermolysis, followed by the application of hair growth factors, has been demonstrated to enhance hair growth in men with androgenetic alopecia. Each man received six sessions at two-week intervals. After ablative carbon dioxide laser treatment to half of the scalp, two milliliters of hair growth factor solution (prepared using stem cells derived from the foreskin), which included fibroblast growth factor 2, interleukin-6, interleukin-7, interleukin-8, transforming growth factor-beta 1, transforming growth factor-beta 2, and transforming growth factor-beta 3 was applied to the entire scalp using acoustic-pressure ultrasound. The growth factor solution was also applied topically to the entire scalp once every other day for two weeks. Improvement was observed in 93% of men in the combined (laser and hair growth factor) treated scalp as compared to 67% in the scalp that was only treated with growth factor [37].

Platelet-rich plasma

Platelet-rich plasma has been used following ablative fractional carbon dioxide laser resurfacing of wrinkles of the inner aspects of the arms. Both arms were treated with the laser; platelet-rich plasma was applied to one arm and normal saline was applied to the other control arm. The application of platelet-rich plasma promoted rapid healing and reduced erythema of the treated arm as compared to the control arm that received normal saline. The investigators concluded that topical application of

platelet-rich plasma was an effective method to enhance wound healing and to reduce transient adverse effects after ablative fractional carbon dioxide laser [38].

Laser assisted drug delivery of topically applied platelet-rich plasma after ablative fractional carbon dioxide laser resurfacing would be an ideal approach for the management of androgenetic alopecia in men and women. Indeed, based on the enhanced delivery of the platelet-rich plasma, it is reasonable to postulate that there would be a significant improvement in hair growth as compared to injection of the agent into the scalp. Similar to the current injection schedule of platelet-rich plasma, three or four monthly treatment sessions could be performed with follow up treatment sessions every three to six months.

Advantages of laser assisted drug delivery of topically applied platelet-rich plasma for the treatment of androgenetic alopecia include being able to get the platelet-rich plasma to the growth center of hair, the bulge of the hair follicle, that is located in mid to deeper dermis. In addition, the platelet-rich plasma would not — unintentionally — be injected into the subcutaneous fat. Also, the topical application of platelet-rich plasma following ablative fractionated photothermolysis would provide a uniform distribution of the agent to the affected areas.

Bimatoprost

Bimatoprost is a synthetic prostamide F2 alpha analog. It is used in the treatment of open-angle glaucoma and ocular hypertension. Ophthalmic use of bimatoprost demonstrated several side effects; some of these included not only iris pigmentation and periorbital hyperpigmentation, but also darkening of the eyelashes in addition to increased length and thickness of the hair [39, 40].

The topical use of bimatoprost 0.03% solution was approved by the Food and Drug Administration in 2008 for the treatment of eyelash hypotrichosis [39]. Subsequently, several investigators have demonstrated once or twice daily topical application of bimatoprost 0.03% solution to be efficacious in hypotrichosis of the eyebrows [39, 40]. In addition, topical bimatoprost has shown improved hair regrowth in patients with alopecia areata and androgenetic alopecia [40].

Local hyperpigmentation was observed around the sites of topical bimatoprost application [39]. This observation prompted researchers to use laser assisted drug delivery of bimatoprost to promote darkening of hypopigmented scars. Nonablative fractional photothermolysis with a 1,550 nanometer laser was used in an attempt to improve the topical absorption of twice daily applied bimatoprost 0.03% solution with concurrent daily application of either tretinoin 0.05% or pimecrolimus 1% cream. There was a mean of 4.5 laser treatment sessions at four to eight week intervals. All 14 patients demonstrated prolonged results after a mean follow up of 20.1 months. Improvement in hypopigmentation was greater than 75% in five of the patients and was greater than 50% in 11 patients [41].

Hence, laser assisted drug delivery of bimatoprost using a nonablative fractional laser resulted in enhanced delivery of bimatoprost and promoted darkening of hypopigmented scars [41]. Therefore, topical application of bimatoprost after ablative fractionated carbon dioxide laser of affected areas of androgenetic alopecia is a logical idea. Bimatoprost could be applied either once or twice daily for a minimum of three to four days, until the columns created by the laser had healed, or until the subsequent laser treatment session.

Minoxidil

Laser assisted drug delivery of minoxidil for the treatment of hair loss has been evaluated in mice. The researchers performed ablative nonfractionated skin resurfacing using an Er:YAG laser; minoxidil skin accumulation was enhanced by twofold to ninefold [42]. Indeed, topical minoxidil may already be incorporated as a component in the management of a patient with androgenetic alopecia. Therefore, continued (or initiation) of twice daily minoxidil 5% solution or foam on the scalp areas that have been treated with ablative fractionated carbon dioxide laser, may enhance delivery of the drug and demonstrate increased hair growth.

Conclusion

Androgenetic alopecia, characterized by miniaturization of hair follicles, is the most common type of progressive hair loss in men and women. Nonsurgical (minoxidil, finasteride, low level laser therapy, and platelet-rich plasma) and surgical (hair transplantation) modalities are potential alternatives for the management of androgenetic alopecia; each of these treatments has advantages and therapy-associated disadvantages. Platelet-rich plasma contains numerous growth factors that stimulate hair growth. However, its delivery to the scalp requires multiple injections that are not only painful, but also of variable quantity (of the agent) and placement (with regard to both the location and the depth). Laser assisted drug delivery — often using ablative fractional photothermolysis to ablate uniform columns of epidermis and dermis thereby creating vertical channels from the skin surface into the dermis — can be used to enhance the cutaneous delivery of medications. This technique would be an excellent alternative to injections for the administration of platelet-rich plasma to the scalp. It would provide a uniform placement of platelet-rich plasma in the dermis of androgenetic alopecia patients without injection-associated pain and inadvertent delivery into the subcutaneous fat. In addition to platelet-rich plasma, laser assisted drug delivery could also be utilized for the topical application of either bimatoprost or minoxidil, or both, so that the drugs can effectively enter the dermis and contact the bulge area of the hair follicles in order to stimulate their growth in patients with androgenetic alopecia.

Potential conflicts of interest

The author declares no conflicts of interests.

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