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Medical Treatment of Alopecia

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Abstract

Alopecia means partial or complete loss of hair from a part of the body where it exists naturally. It affects both men and women, and its treatment depends upon its cause, age of onset, and clinical presentation. It is divided into scarring and non-scarring alopecia. Scarring alopecia includes pseudopelade of Brocq, central centrifugal cicatricial alopecia, folliculitis decalvans, acne keloidalis nuchae, lichen planopilaris, frontal fibrosing alopecia and discoid lupus erythematosus, traumatic i.e., injury, radiation and post-operative scarring alopecia and certain neoplasms. Common causes of non-scarring alopecia are androgenic alopecia, alopecia areata, telogen effluvium, anagen effluvium, trichotillomania, traction alopecia, pressure-induced alopecia, alopecia due to iron deficiency, thyroid disease, and polycystic ovary syndrome. Topical remedies available are minoxidil 2 and 5%, topical & intralesional steroids, topical sensitization, anthralin, retinoids, tacrolimus, garlic, ketoconazole and prostaglandin analogs. Among systemic treatments, finasteride, steroids, immunosuppressant like azathioprine, methotrexate, sulfasalazine, zinc sulfate and iron are widely accepted. The phototherapies, photo-chemotherapies, platelet rich plasma (PRP) therapy, pharmacogenetics and hair transplant are new remedies for alopecia. It is concluded that minoxidil, finasteride, PRP, and hair transplant are the most widely being used modalities for alopecia.

Keywords: alopecia, scarring, non-scarring, minoxidil, finasteride, steroids, PRP

1. Introduction

Alopecia means partial or complete loss of hair from a part of the body where it exists naturally. It affects both men and women. According to cause it can be androgenic, autoimmune, traumatic, genetic, metabolic, and neoplastic. Clinically, it is divided mainly into two categories i.e., scarring and non-scarring alopecia. Proper history taking, the onset of disease, family history both paternal and maternal, past medical and surgical history, allergies to

medicine, Physical examination, hair count, pull test, pluck test (trichogram), histological, serological and immunofluorescent data will lead us to proper diagnosis of the cause and its treatment plan. Biopsies provide diagnosis, the degree of hair shedding, type of hair, anagen to telogen ratio and provide information regarding the potential for hair regrowth. Many treatment modalities are available for treating alopecia i.e., medical and surgical. Medical treatments include minoxidil 2% and 5%, topical & intralesional steroids, topical sensitization/immunotherapy, anthralin, retinoids, tacrolimus, garlic, ketoconazole and prostaglandin analogs. Among systemic treatments, finasteride, dutasteride, spironolactone, flutamide, cyproterone acetate, sulfasalazine, corticosteroids, immunosuppressant like azathioprine & cyclosporine, methotrexate, biological agents, photochemotherapy, low-level light therapy, zinc, vitamins & supplements are widely being used. Platelet-rich plasma (PRP) therapy and hair transplant are very popular treatments now a days.

2. Topical treatment

Most common topical treatments are minoxidil, topical & intralesional steroids, topical sensitization/immunotherapy, anthralin, topical retinoids, tacrolimus, garlic, ketoconazole and prostaglandin analogs.

2.1. Minoxidil

Chemically, minoxidil is 2,4-diamino-6-piperidinopyrimidine 3-oxide and it is being used as a topical agent for the treatment of androgenic alopecia since 1987. Mechanism of action is not exactly known, but it shortens telogen phase, extends anagen phase and is a hair growth stimulator. Scalp sulfotransferase converts minoxidil into minoxidil sulfate which is the active form of the molecule [1]. There are certainly proposed mechanisms of minoxidil actions are vasodilation, potassium channel opening, antiandrogen, angiogenesis, the release of growth factors, stimulation of dermal papilla, and immunosuppression [2, 3]. Topical minoxidil is available in spray and foam forms in two strengths i.e., 2 and 5%. Its half-life is 4.2 h and effects occur after 8 weeks and maximum after 4 months. It should be applied twice a day for at least 4 h to get good results. Micro-needling can be associated to enhance its efficiency. It will give good results if the age of alopecia is less than 5 years and hair follicles are not deeply miniaturized. Currently, Topical minoxidil is being used in patients with AGA, AA, hair transplant, scarring alopecia, hereditary alopecia/hypotrichosis, chemotherapy-induced alopecia, and monilethrix.

Adverse effects include allergic contact dermatitis; minoxidil induced telogen effluvium, skin irritation, and scaly changes in the scalp, isolated itching, localized or generalized hypertrichosis and hypotension. It is not advised in pregnant or breastfeeding mother.

2.2. Platelet rich plasma therapy

Platelet-rich plasma (PRP) therapy is a new medical technique widely being used in hair restoration especially in cases of androgenic alopecia and alopecia areata. To prepare PRP,

40–60 ml patient's blood is centrifuged for 10–20 min and 2–4 ml platelet rich portion is separated from the poor platelet plasma portion. It is injected locally in the areas of alopecia as multiple points in the dosage of 0.1 ml/cm² with 27–30 gauge needles with 4–6 mm length. It is repeated at 3–4 weeks intervals.

After activation, platelet alpha-granules release multiple growth factors; platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and interleukin-1 [4]. PRP acts on stem cells at bulge area and stimulates the growth of new follicle and neovascularization. No major side effects reported yet.

2.3. Topical and intralesional steroids

2.3.1. Topical corticosteroids

Topical corticosteroids are available in many formulations. These are divided into following categories by WHO according to their potencies [5]:

- (I) Ultra high: clobetasol propionate 0.05%, diflorasone diacetate 0.05%.
- (II) High: amcinonide ointment 0.1%, betamethasone dipropionate ointment 0.05%, desoximetasone cream/ointment 0.025%, fluocinonide cream ointment or gel 0.05%, halcinonide cream 0.1%.
- (III) Betamethasone dipropionate 0.05%, betamethasone valerate 0.1%, diflorasone diacetate 0.05%, triamcinolone acetonide 0.1%.
- (IV) Moderate: desoximetasone cream 0.05%, fluocinolone acetonate 0.025%, fludroxycortide ointment 0.05%, hydrocortisone valerate 0.2%, triamcinolone acetonide cream 0.1%.
- (V) Betamethasone dipropionate 0.02%, betamethasone valerate 0.1%, fluocinolone acetonide 0.025%, fludroxycortide 0.05%, hydrocortisone butyrate 0.1%, hydrocortisone valerate 0.2%, triamcinolone acetonide lotion, 0.1%.
- (VI) Low: Betamethasone valerate 0.05%, desonide 0.05%, fluocinolone acetonide 0.01%.
- (VII) Dexamethasone sodium phosphate cream 0.1%, hydrocortisone acetate 1%, methylprednisolone acetate 0.25%.

Topical corticosteroids promote maximum local action and minimum systemic side effects. The main mechanism of action is immunosuppression and reduction of local inflammation around dermal papilla [6]. Corticosteroids suppress the T-cell mediated immune action on the hair follicles.

Topical steroids are indicated in alopecia areata, alopecia areata incognita, lichen planopilaris, discoid lupus erythematosus, central centrifugal cicatricial alopecia, pseudopelade of Brocq, frontal fibrosing alopecia.

Treatment should be continued up to 3 months to see results in case of alopecia areata. Topical steroids are less effective in cases of alopecia totalis and alopecia universalis. A local

telangiectasia and atrophy are seen in cases of high and ultra-high potent steroids and with long-term use of topical steroids.

2.3.2. *Intralesional steroids*

Intralesional steroids in alopecia areata are widely being used since 50 years. They are the first-line treatment therapy if alopecia areata is involved less than 50% of scalp area. Following preparations are used:

- Triamcinolone acetonide: Concentration being used is 3–10 mg/ml and administering dose is 0.1 ml/cm² area.
- Triamcinolone hexacetonide
- Hydrocortisone acetate: Concentration being used is 25 mg/ml and administering dose is 0.1 ml/cm² area.

It is injected into and just beneath the dermis. For an eyebrow and face, lower concentrations 2–3 mg/ml should be used and repeated after every 3–6 weeks. Hair growth is appreciated in 4–6 weeks. Local atrophy is reported with high concentrations of triamcinolone acetonide. Severe cases of alopecia, alopecia totalis, alopecia universalis, rapidly progressing alopecia areata and cases of greater than 2 years' duration of the current episode respond poorly [7].

2.4. **Topical sensitization/immunotherapy**

Sensitizers are the chemicals which can initiate an allergic response and immunity on exposure to the body. An inflammatory response is mounted by the immune system upon further exposure. Happle, in 1980, described the mechanism of this inflammatory response in the treatment of Alopecia areata that topical sensitizers redirect the inflammatory response in AA away from the hair follicles and direct it towards themselves. This theory is unacceptable in all cases as regrowth has been observed at distant sites or even at opposite sides from sensitizer application, called as castling phenomenon.

Topical sensitizers should have following characteristics:

- It should be capable to produce immunomodulation.
- It should not be present in the normal natural environment as this may cause damage to a person in his/her daily life exposures.
- It should not have cross-reactivity with other substances.
- It should be a safe chemical.

Followings are the common sensitizers being used:

- Dinitrochlorobenzene (DNCB)
- Squaric acid dibutylester (SADBE)
- Diphenylpicrylhydrazine (DPPH)

There are a variety of mechanisms of action of topical sensitization/immunotherapy:

- A decrease in CD4 to CD8 lymphocytes count from 4:1 to 1:1 is seen [8].
- The concept of 'Antigenic Competition' was proposed by Happel et al., that an allergic reaction is generated which activates suppressor T cells that non-specifically inhibit the immune reaction against a hair follicle. Topical Immunotherapy reduces the abnormal expression of class I and II MHC molecules [8].
- Delayed-type hypersensitivity reactions to unrelated antigens occurring at remote sites are reduced significantly.
- Topical sensitizers attract a new population of T cells into the treated areas and thus helping in clearance of putative follicular antigen.
- Theory of 'Cytokine Inhibitor' was proposed by Buckley and Vivier that there was a possible interference of contact allergens with the pre-existing pro-inflammatory cytokine, and their continued production by follicular keratinocytes [8].
- The decrease in the raised interferon γ levels and increases in mRNA expression of interleukin 2, 8, 10 and tumor necrosis factor- α in the lesional skin are seen.

Topical sensitizers are usually used in severe cases of Alopecia areata involving more than 50% of total scalp having large patches or alopecia totalis. Overall topical sensitizers are well tolerated. These are usually applied at the scalp. The initial concentration of DPCP is 0.001–0.1% and is applied with a cotton-tipped applicator to an area of at least 10 cm². The patient is advised not to wash the area and avoid sunlight for first 48 h. The application is repeated weekly to induce mild contact eczema and concentration is adjusted according to response. It can take more than 5–7 days to see the significant eczematous response which indicates that sensitization has taken place. Total hair growth rates are 77% with DPCP and 64% with SADBE [9].

Side effects are persistent dermatitis, painful cervical lymphadenopathy, generalized eczema, blistering, contact leukoderma and urticarial reaction. Fever, arthralgia and yellowish discoloration of gray hair are noted with DNCB [10].

2.5. Anthralin

Anthralin (1,8-dihydroxy-9-anthrone), also called as dithranol, is a natural anthraquinone derivative obtained from the Araroba tree in Brazil as an old antipsoriatic agent but later on found effective in alopecia areata too. It inhibits the proliferation of keratinocytes, prevents the action of T-cells, and improves cell differentiation through blocking DNA synthesis and mitochondrial dysfunction [11]. Anthralin suppresses the release of IL-6 and TNF- α from monocytes. A cosmetic response was seen in 25% of patients with severe alopecia areata treated using 0.5–1% anthralin cream in an open study [12]. In another study, only 11% cosmetically acceptable response observed in 51 patients of alopecia areata treated with a combination of 5% minoxidil and 0.5% anthralin [13]. Anthralin should be used with high enough concentration and in daily repeated applications to get a mild irritant reaction to get

effective results. Severe irritation and staining of clothes and skin are most common side effects.

2.6. Topical retinoids

Retinoids are a group of medicines derived from vitamin A. Common topical retinoids are tretinoin, isotretinoin, adapalene, alitretinoin, tazarotene, and bexarotene. Initially, retinoids were used for the treatment of acne but now a day due to their role in the induction of T-cell apoptosis, they are being used in autoimmune alopecia like alopecia areata as we know perifollicular and intrafollicular monocyte infiltrates contain primarily activated CD4+ and CD8+ T-cells.

Hanson and colleagues note that topical bexarotene yielded significant hair regrowth when used to treat patients with follicular mucinosis of folliculotropic Mycosis Fungoides [14]. Retinoids regulate transcription signaling through the Retinoic Acid Receptor (RAR)- γ , RAR-B and RAR- α thus inhibiting proliferation and normalizing differentiation [15]. Topical retinol also increases blood flow to hair follicles and encourage new blood vessel formation [16]. A 55% response in alopecia areata is seen with 0.05% topical tretinoin as compare to 75% with topical betamethasone dipropionate and 35% with 0.25% dithranol paste [17].

Yoo et al. investigated the combined effects of minoxidil and retinol on human hair growth in vitro and on cultured human dermal papilla cells (DPCs) and epidermal keratinocytes (HaCaT) and this combination promoted hair growth, hair shaft elongation than minoxidil alone [18].

Common side effects are irritation, dryness, stinging sensations, redness, swelling, peeling, blistering and sunburn in the treated area and can aggravate eczema. Retinoids are contraindicated in pregnancy and breastfeeding as negative animal studies are not always predictive of human response.

2.7. Tacrolimus

Tacrolimus is a calcineurin inhibitor, and is being used for an immunosuppression since its discovery in 1987 from a Japanese soil bacterium, *Streptomyces tsukubaensis* [19]. It is also known as Fujimycin or FK506. The name tacrolimus is derived from "Tsukuba Macrolide Immunosuppressant".

Topical tacrolimus is mainly used in scarring alopecias like lichen planopilaris (LPP), central centrifugal cicatricial alopecia, discoid lupus erythematosus (DLE), frontal fibrosing alopecia, pseudopelade of Brocq.

Calcineurin, a serine–threonine phosphatase is activated via calmodulin by intracellular calcium which is increased by activation of the T-cell receptor in T-cell. Calcineurin then dephosphorylates the nuclear factor of activated T-cells (NF-AT), which moves to the nucleus of T-cell and increases the activity of genes coding for IL-2 and related cytokines [20].

Tacrolimus by binding itself with an intracytoplasmic protein, FK506, blocks the dephosphorylation of the nuclear factor of an activated T-cell thus preventing entry of nuclear factor into the nucleus and limits lymphocyte proliferation, which is the predominant feature of scarring alopecias [21].

Topical tacrolimus is available in different potencies i.e., 0.1, 0.03 and 0.3%. Regrowth of terminal hair was noted in the outer region of a DLE patient with a monotherapy of topical 0.1% tacrolimus for 2 months [22]. Mild to moderate lichen planopilaris (LPP) involving less than 10% of the scalp is best treated with tacrolimus [23].

The adverse effects of topical tacrolimus are uncommon but some reported are peeling and burning at the area of application. Systemic absorption is undetectable even after topical use of months [24].

2.8. Garlic

Garlic (*Allium sativum*) is a natural product species belonging to genus onion. The raw garlic is composed of 59% water, 33% carbohydrates, 6% protein, 2% dietary fiber and less than 1% fat [25, 26]. It is also rich in calcium, vitamin C, phosphorus, sulfur, zinc, and selenium. Besides its use in alopecia areata (AA), androgenic alopecia (AGA), and scarring alopecias, it is also used for the treatment of cardiovascular disorders, cancers, and the common cold.

Topical garlic is very effective for alopecia areata in children [27]. The combination of topical garlic gel and betamethasone valerate cream was found more effective than betamethasone valerate cream monotherapy in the treatment of localized alopecia areata [28].

Garlic, as well as being good for our body, can be really good for our scalp and hair. Followings are the possible proposed mechanisms of action:

- It provides nourishment to hair follicles especially if the nourishment is blocked by dihydro-testosterone (DHT) or bad diet.
- Garlic can stimulate the flow of blood to the scalp, thereby nourishing the hair, and thus encouraging hair to grow and strengthen. Garlic is also good at adding body to hair, as well as giving hair a nice gloss.
- It contains antiseptic properties and was used as antiseptic in World War II [29].
- It has antifungal properties and anti-inflammatory properties.
- Garlic reduces platelet aggregation [30].
- Hair, nail, and skin have high levels of sulfur and garlic is a rich source of sulfur.

Apply garlic gel/crushed garlic clove and rub it into the area of hair loss 60 min before you go to sleep and wash the area in the next morning. Common side effects include irritation at the site and with systemic absorption, bad smell from mouth and breath may occur.

2.9. Ketoconazole

Ketoconazole is an imidazole antifungal being used mainly in seborrheic dermatitis and lichen planopilaris and has anti-inflammatory properties too. Some hypothesize that ketoconazole plays a role in the local disruption of the DHT pathway. These anti-androgen effects may explain the side effect of gynecomastia in male patients taking oral ketoconazole. Combinations with minoxidil and oral finasteride have shown comparable hair regrowth in both groups than patients without ketoconazole shampoo.

2.10. Prostaglandin analogs

Prostaglandin analogs are synthetic drugs which bind to specific prostaglandin receptor sites on cells to initiate the certain type of cellular activities. Most common are bimatoprost, latanoprost, travoprost, and tafluprost. Initially, they were used to treating glaucoma and eyelashes hypertrichosis and pigmentation notices in lashes and periocular area. They are being used for the treatments of androgenic alopecia, alopecia areata, chemotherapy-induced alopecia, vitiligo and hypopigmented scarring [31]. The extension of the duration of anagen phase and the induction of telogen follicles into anagen phase are supposed mechanisms of action of prostaglandin analogs [32]. The bimatoprost 0.03% lotion used in a mice study and demonstrated a significant proportion of hair regrowth in 14 days [33]. Increased follicular growth rate, number of anagen follicles, and the total number of hair were seen in a study of bimatoprost on cultured scalp cells in patients with androgenic alopecia [34]. Blume-Peytavi et al. demonstrated a significant increase in hair density with 24 weeks use of latanoprost 0.1% at frontotemporal androgenic alopecia [35].

Bimatoprost and latanoprost were used by Ross et al. and Rosoborough et al. respectively in cases of alopecia areata but did not display encouraging results even after use of 4 months. Ochoa et al. suggested some benefit in less extensive cases of alopecia areata [36]. Besides local erythematous reaction, no adverse events are reported yet.

3. Systemic treatment

As we know, there are many varieties of alopecia ranging from non-scarring alopecia like AGA, AA, alopecia associated with iron deficiency, chemotherapy and thyroid diseases to scarring alopecia like pseudopelade of Brocq, central centrifugal cicatricial alopecia, folliculitis decalvans, acne keloidalis nuchae, lichen planopilaris, frontal fibrosing alopecia, discoid lupus erythematosus (DLE), traumatic (injury, radiation and post-operative scarring alopecia) and certain neoplasms so, in many cases only topical treatments are not so much fruitful thus systemic remedies reserve their place in the treatment of alopecia. Available systemic treatments include anti-androgens (finasteride, dutasteride, spironolactone, cyproterone acetate, flutamide), systemic steroids, sulfasalazine, immunosuppressants (azathioprine & cyclosporine), methotrexate, biological agents, photochemotherapy, low-level light therapy, excimer laser & excimer light, vitamins & supplements, pharmacogenetics, wigs, hairpieces, and camouflages.

3.1. Finasteride

Finasteride, 17B – (N-tert-butylcarbonyl)-4-aza-5 α -androst-1-en-3-one, is a synthetic androstane steroid and is analog of androgen steroid hormones like testosterone and DHT. It is a selective and competitive inhibitor of the two isozymes of 5 α -reductase, type II and III, present in certain tissues like prostate, seminal vesicles, epididymis, skin, and hair follicles and responsible for the conversion of testosterone into DHT [37, 38]. The type II 5 α -reductase isozyme is also responsible for two-thirds of circulating DHT. Its half-life is 5–6 h in an adult, metabolized in liver, and metabolites are eliminated 57% in the feces and 40% in urine [39].

Finasteride has been shown to increase the ratio of anagen to telogen hairs. It is effective in increasing more hair weight than hair count [40]. Five-year results with 1 mg oral finasteride per day in men with balding vertex showed significant greater hair count than placebo after 1 year, hair growth peaked at 2 years and still stayed above baseline for 90% of patients after that [41]. A randomized placebo-controlled trial with finasteride 1 mg/day in men showed increased hair growth in men with modified Norwood-Hamilton grades II, II vertex, III or III vertex throughout the second year of the study [42].

Approximately 2% of men reported one or more sexual side effects like decreased libido, erectile dysfunction and ejaculation disorder. It is found that rate of these side effects became indistinguishable from a placebo after 2–4 years and usually got better with time. Gynecomastia and mastalgia are reported in 0.4% of patients. Some cases of depression anxiety and suicidal thoughts are also reported with finasteride.

3.2. Dutasteride

Dutasteride is a 5 α reductase which inhibits all three forms of 5 α reductase i.e., type I, II and III in certain parts of the body like prostate and scalp leading to 98% reduction in DHT levels [43]. It is being used for the treatment of androgenic scalp hair loss in South Korea since 2009 and in Japan since 2015 but in the USA it is often used off-label. In addition to inhibition of 5- α -reductase, it also inhibits neurosteroidogenesis from testosterone which contains antidepressant, anxiolytic and pro-sexual effects thus sexual dysfunction and depression have been seen with 5- α -reductase inhibitors like dutasteride [44]. It is three times more potent than finasteride in preventing 5 α -reductase type II and more than 100 times in type I [45]. Its approved daily dose is 0.5 mg/day, half-life 4–5 weeks, metabolized in the liver and excreted mainly in feces. It is contraindicated in pregnant women. Side effects include decreased sperm count, decreased semen volume and reduction in sperm motility, gynecomastia, menstrual changes, and acne.

3.3. Spironolactone

Spironolactone is a synthetic steroid being used in the treatment of hypertension and different cardiovascular disorders since long time and found having antiandrogen properties. Spironolactone does not affect 5- α -reductase but acts by competitively blocking androgen receptors in prostate and scalp. It also weakly inhibits testosterone synthesis. It is used in

patterned hair loss and the women treated for 1 year with spironolactone 50–300 mg/day showed less hair loss than the untreated group [46]. Side effects are dose-dependent and mainly include menstrual irregularities, postmenopausal bleeding, breast tenderness or enlargement and fatigue. The combination with oral contraceptives reduces its hormonal side effects. No evidence of increased incidence of breast cancer found in women treated with spironolactone [47].

3.4. Cyproterone acetate

Cyproterone acetate, a potent progestin, is an androgen receptor blocker which has anti gonadotrophic effects too. Effects of cyproterone acetate are more prominent in women with hyperandrogenism. Commonly dosages being used are 50–100 mg/day for the first 10 days of each menstrual cycle while for postmenopausal women; it can be continuously given with or without estrogens. Side effects include weight gain, breast tenderness, and loss of libido, depression, and nausea. Feminization of male fetus is seen if cyproterone acetate is used during pregnancy or if a woman becomes pregnant while taking it.

3.5. Flutamide

Flutamide, a non-steroidal antiandrogen, inhibits androgen uptake and nuclear binding of androgen within the target tissue. Premenopausal women with female pattern hair loss (FPHL) got good results with flutamide but in postmenopausal women, results were not more than placebo with 1 mg/day dose [48]. Most common side effects are hepatotoxicity and teratogenicity.

3.6. Systemic steroids

Systemic steroids are used in non-scarring alopecia like Alopecia areata and in scarring alopecia like variants of follicular lichen planus i.e., lichen planopilaris, frontal fibrosing alopecia and DLE. With prednisone 0.5–1 mg/kg/day for 1–6 months, more than 25% hair regrowth was seen [49, 50]. There are certain regimens other than daily dosages for systemic steroids like mini pulse and pulse therapy. In a study, patients receiving prednisolone 200 mg once a week (pulse therapy) for 3 months showed better hair regrowth at 6 months than placebo [51]. Mini pulse therapy, tried in many skin diseases like alopecia areata and vitiligo, employs administration of high dose oral corticosteroids on two consecutive days every week with a 5 days' gap between the two pulses.

3.7. Sulfasalazine

Sulfasalazine was approved in the USA in 1950 and was considered a first-line therapy in rheumatoid arthritis, ulcerative colitis, and Crohn's disease and being used in psoriatic arthritis, reactive arthritis, and alopecia areata. Sulfasalazine and its metabolites have immunosuppressive, antibacterial, anti-inflammatory effects and inhibit the cysteine-glutamate

antiporter (a system which imports the amino acid cysteine into cells) [52]. Around 90% of sulfasalazine is metabolized in the colon by bacteria into a sulfapyridine and mesalazine and then most of the sulfapyridine is absorbed and further metabolized and eliminated in urine. The starting dose is 500 mg twice daily and gradually increased up to 1 g three times a day. In one study, 23% of patients of alopecia areata showed a good response with sulfasalazine therapy [53].

3.8. Immunosuppressants (azathioprine & cyclosporine)

Alopecia areata, a common non-scarring alopecia and scarring alopecia like follicular lichen planus are T-cell mediated autoimmune processes; therefore, immunosuppressive therapies are widely used in the treatments of alopecia. Most common immunosuppressants are azathioprine and cyclosporine.

Azathioprine was made in 1957 and was the most effective and safe medicine being used to prevent rejection following organ transplant, autoimmune diseases including rheumatoid arthritis, pemphigus, systemic lupus erythematosus, Behcet's disease, vasculitis, autoimmune hepatitis, atopic dermatitis, myasthenia gravis, reactive lung diseases, alopecia areata, and follicular lichen planus. Azathioprine inhibits purine synthesis, needed to produce DNA and RNA, which are necessary for the production of white blood cells, thus causing immunosuppression. A prospective study of adult patients with recalcitrant alopecia areata universalis (unresponsive to oral corticosteroids) treated with oral 2.5 mg/kg/day for 6 months showed 52.3% mean global hair regrowth [54]. Side effects include nausea, vomiting, skin rash, acute pancreatitis and bone marrow suppression.

Cyclosporine lowers the activity of T-cells by preventing the mitochondrial permeability transition pore from opening and inhibiting calcineurin-phosphatase pathway. A study of adult patients (6 men, 1 woman) of alopecia universalis with oral cyclosporine 6 mg/kg/day for 12 weeks showed cosmetically acceptable hair regrowth in 50% of patients [55]. Side effects of cyclosporine are gum enlargement, increased hair growth, convulsions, peptic ulcer, pancreatitis, increased cholesterol, numbness in lips and high blood pressure.

3.9. Methotrexate

Methotrexate is an anti-metabolite agent being widely used in chemotherapy and immunosuppression. It is mainly used in cases of cancers of breast, head & neck, bladder, blood (leukemia, lymphoma), bones (osteosarcoma) and trophoblastic neoplasms. It is taken by oral or intravenous route in weekly doses and acts by blocking the body's use of folic acid. A study of 31 patients of alopecia areata with 10–25 mg/week methotrexate showed greater than 50% hair regrowth in 67.7% of patients [56]. In another study, Joly reported good results in 22 patients with alopecia areata, with or without systemic corticosteroids [57]. A further study of 31 patients of alopecia areata, with 10–20 mg/week methotrexate with and without 1 mg/kg/day oral prednisone taper, showed overall 71% response rate in 1–3 months and 36% of treated patients got complete hair regrowth in 6–18 months [58].

3.10. Biological agents

Biological agents are thought to act on tumor necrosis factor (TNF)-alpha and inter-cellular adhesion molecules 1 in the treatment of alopecia areata. Common biological agents are etanercept, efalizumab, alefacept, adalimumab, and infliximab. Different clinical trials are done but no promising results gained yet.

3.11. Photochemotherapy

Both systemic and topical photochemotherapy is done by psoralen plus UV-A (PUVA) in the treatment of alopecia areata. In a study, the initial response was 20–73% having relapse rate 50–88%. It interferes with the presentation of antigen to T-lymphocytes by depletion of Langerhans cells. The recommended dose is 0.6 mg/kg and after 2 hours affected area is exposed to UV-A for 20–30 min. In a study of PUVA in alopecia areata, hair regrowth is seen up to 70% [59].

3.12. Low-level light therapy

Many products are available in the market utilizing low-energy laser beams but only one device called Hairmax Lasercomb (Lexington International, Boca Raton, FL, USA) has got 510K FDA approval for use in hair loss as a medical device. Significant hair regrowth is seen with a light device in the treatment of male pattern hair loss [60].

3.13. Vitamins & supplements

There are many products available in the market as vitamins and supplements but not promising trials available. Commonly in use products are Saw Palmetto, biotin, zinc, and iron. Saw Palmetto inhibits the 5-alpha-reductase conversion of testosterone to DHT in the prostate [61]. A study of androgenic alopecia patients treated with Saw Palmetto showed increased hair growth [62]. Biotin is used to treat onychoschizia but no clinical trials are available in hair loss. Significant hair regrowth is seen with 30–50 mg/day zinc gluconate in patients of alopecia areata [63].

3.14. Pharmacogenetics

Pharmacogenetics is an emerging medical field which provides information about inherited genetic differences in metabolism, effects and adverse effects of a drug in genetically susceptible individuals. It is found that AGA has polychromosomal as well as polygenic origin associated with increased levels of androgen receptors and 5-alpha-reductase in both men and women. AR-DHT complex interacts with genomic DNA and initiates such cellular mechanisms that lead to AGA. By genetic studies, it is found that variations in the AR genes are present on the long arm of the X chromosome and polymorphisms of the AR gene are associated with hormonal and medical responses [64]. The repeat cytosine-adenine-guanine (CAG) nucleotide sequences in the exon 1 of AR gene are related with androgen sensitivity to the cell in men and women. Short CAG sequences are related with AGA. In pharmacogenetics,

there are two research points: Identification of potential therapeutic targets and individual variability in response to a specific drug. A strong correlation between the number of CAG repeats in AR gene and response to finasteride therapy is found administering finasteride 1 mg/day and variable follow up between 12 and 24 months. In this study, it was discovered that subjects with CAG repeat less than 21 showed greater response with finasteride than subjects having CAG repeats more than 23 [65]. In a study of chemotherapy-induced alopecia, a strong association in genetic variants near genes CACNB4 is found [66].

In the future, pharmacogenetics will help us to decide the treatments of an individual throughout its life about the drugs which can or cannot be used on the basis of metabolism, safety, and its effects. This analyzation of individual's DNA will be done only once and will provide information for the lifetime and as companies and laboratories that perform these testing can do so at low prices, the field of pharmacogenetics will gain great acceptance in the day to day medical treatments.

3.15. Hair transplant

In the hair transplant, follicular units are harvested from the safe zone at occiput and then implanted at bald areas. There are two popular methods i.e., follicular unit transplant (FUT) and follicular unit extraction (FUE). In FUT, a strip is harvested from safe zone and then follicular units are prepared by slivering the strip under a microscope. In FUE, follicular units are extracted one by one with 0.7–1.0 mm wide and 4–6 mm lengthy sharp or blunt punches which may be manual or motorized and then these follicular units are implanted at bald areas.

4. Conclusions

It is concluded that minoxidil, finasteride, and PRP are the best treatments for androgenic alopecia and alopecia areata while steroids, sensitizers, and immunosuppressants are mainly used in autoimmune alopecia. Hair transplant is the best option in cases of androgenic alopecia and stable forms of scarring alopecia. Pharmacogenetics is a newly emerging medical field which can change the future of medical treatments.

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Conflict of interest

I have no conflict of interest.

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References

- [1] Goren A, Shapiro J, Roberts J, McCoy J, Desai N, Zarrab Z, Pietrzak A, Lotti T. Clinical utility and validity of minoxidil response testing in androgenetic alopecia. *Dermatologic Therapy*. 2015;**28**(1):13-16
- [2] Badri T, Dinesh Kumar D; University of Tunis El Manar. Minoxidil. Treasure Island (FL): StatPearls Publishing; 2018 Jan
- [3] Yum S, Jeong S, Kim D, Lee S, Kim W, Yoo JW, Kim JA, Kwon OS, Kim DD, Min DS, Jung Y. Minoxidil induction of VEGF is mediated by inhibition of HIF-propyl hydroxylase. *International Journal of Molecular Sciences*. 2018 Jan;**19**(1):53. DOI: 10.3390/ijms19010053
- [4] Khatu SS, More YE, Gokhale NR, et al. Platelet-rich plasma in androgenic alopecia: Myth or an effective tool. *Journal of Cutaneous and Aesthetic Surgery*. 2014;**7**:107-110
- [5] WHO. Model prescribing information: Drugs used in Skin Diseases. Classification of Topical Steroids. 1997. p. 116-117
- [6] Mandani S, Shapiro J. Alopecia areata update. *Journal of the American Academy of Dermatology*. 2000;**42**:549-566
- [7] Abell E, Munro DD. Intralesional treatment of alopecia areata with triamcinolone acetonide by jet injector. *The British Journal of Dermatology*. 1973;**88**:55-59
- [8] Buckley DA, Du Vivier AW. The therapeutic use of topical sensitizers in benign dermatoses. *The British Journal of Dermatology*. 2001;**145**:385-405
- [9] Contellessa C, Peris K, Caracciolo E, Mordenti C, Chimenti S. The use of topical diphenylcyclopropenone for the treatment of extensive alopecia areata. *Journal of the American Academy of Dermatology*. 2001;**44**:73-77
- [10] Rokhsar CK, Shupack JL, Vafai JJ, Washenik K. Efficacy of topical sensitizers in the treatment of alopecia Areata. *Journal of the American Academy of Dermatology*. 1998;**39**:751-761
- [11] Mrowietz U, Jessat H, Schwarz A, Schwarz T. Anthralin (dithranol) in vitro inhibits human monocytes to secrete IL-6, IL-8, and TNF-alpha, but not IL-1. *The British Journal of Dermatology*. 1997;**136**(4):542-547

- [12] Fiedler VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. *ARC Journal of Dermatology*. 1987;**123**(11):1491-1493
- [13] Fiedler VC, Wendrow A, Azpunar GJ, Metzler C, DeVillez RL. Treatment-resistant alopecia areata. Response to combination therapy with minoxidil plus anthralin. *ARC Journal of Dermatology*. 1990;**126**(6):756-759
- [14] Hanson M, Hill A, Duvic M. Bexarotene reverses alopecia in cutaneous T-cell lymphoma. *The British Journal of Dermatology*. 2003;**149**:193-196
- [15] Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for a topical therapy of psoriasis: A vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *Journal of the American Academy of Dermatology*. 1997;**37**(1):85-92
- [16] Rogers NE, Avram MR. Medical treatments for male and female pattern hair loss. *Journal of the American Academy of Dermatology*. 2008;**59**(4):547-566. DOI: 10.1016/j.jaad.2008.07.001
- [17] Das S, Ghorami RC, Chatterjee T, Banerjee G. Comparative assessment of topical steroids, topical tretinoin (0.05%) and dithranol paste in alopecia areata. *Indian Journal of Dermatology*. 2010;**55**(2):148-149
- [18] Yoo HG, Chang IY, Pyo HK, Kang YJ, Lee SH, Kwon OS, Cho KH, Eun HC, Kim K. The additive effects of minoxidil and retinol on human hair growth in vitro. *Biological & Pharmaceutical Bulletin*. 2007 Jan;**30**(1):21-26
- [19] Kino T et al. FK-506, a novel immunosuppressant isolated from *Streptomyces*. 1. Fermentation, isolation, and physicochemical and biological characteristics. *The Journal of Antibiotics*. 1987;**40**:1249-1255
- [20] Ganong WF. *Review of Medical Physiology*. 22nd ed. Lange Medical Books. USA: The McGraw-Hill Companies; August 2005. p. 530. ISBN: 0-07-144040-2
- [21] Kirchhof MG, Dutz JP. The immunopathology of cutaneous lupus erythematosus. *Rheumatic Diseases Clinics of North America*. 2014;**40**(3):455-474, viii
- [22] De la Rosa Carrillo D, Christensen OB. Treatment of chronic discoid lupus erythematosus with topical tacrolimus. *Acta Dermato-Venereologica*. 2004;**84**(3):233-234
- [23] Megahed M. Lichen planopilaris, succesful treatment with tacrolimus. *Der Hautarzt*. 2008;**59**(11):874-877
- [24] Lampropoulos CE, Sangle S, Harrison P, Hughes GR, D'Cruz DP. Topical tacrolimus therapy of resistant cutaneous lesions in lupus erythematosus: A possible alternative. *Rheumatology (Oxford, England)*. 2004;**43**(11):1383-1385
- [25] "*Allium sativum* L". Kewscience; Plants of the World Online; Kew, England: Royal Botanic Gardens. Retrieved: 2017-05-26
- [26] Nutrition facts for raw garlic, USDA National Nutrient Database, version SR-21. Conde Nast. 2014. Retrieved: 2 November 2014

- [27] Pope E. Topical garlic concentrate for alopecia in children. ClinicleTrials.gov 2018; NCT02691117
- [28] Hajheydari Z, Jamshidi M, Akbari J, Mohammadpour R. Combination of topical garlic gel and betamethasone valerate cream in the treatment of localized alopecia areata: A double-blind randomized controlled study. *Indian Journal of Dermatology, Venereology and Leprology*. 2007 Jan-Feb;73(1):29-32
- [29] Tattelman E. Health effects of garlic. *American Family Physician*. July 1, 2005. Aafp.org. Retrieved February 28, 2014
- [30] Garlic at a Glance. National Center for Complementary and Integrative Health, US National Institutes of Health. 2014. Retrieved 2 November 2014
- [31] Choi YM, Diehl J, Levins PC. Promising alternative clinical uses of prostaglandin F2a analogs: Beyond the eyelashes. *Journal of the American Academy of Dermatology*. 2015; 72:712-716
- [32] Sasaki S, Hozumi Y, Kondo S. Influence of prostaglandin F2a and its analogs on hair regrowth and follicular melanogenesis in a murine model. *Experimental Dermatology*. 2005;14(5):323-328
- [33] Tauchi M, Fuchs TA, Kellenberger AJ, Woodward DF, Paus R, Lütjen-Drecoll E. Characterization of an in vivo model for the study of eyelash biology and trichomegaly: Mouse eyelash morphology, development, growth cycle, and anagen prolongation by bimatoprost. *The British Journal of Dermatology*. 2010;162(6):1186-1197
- [34] Khidhir KG, Woodward DF, Farjo NP, et al. The prostamide-related glaucoma therapy, bimatoprost, offers a novel approach for treating scalp alopecias. *The FASEB Journal*. 2013;27(2):557-567
- [35] Blume-Peytavi U, Lonnfors S, Hillmann K, Garcia Bartels N. A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia. *Journal of the American Academy of Dermatology*. 2012;66(5):794-800
- [36] Ochoa BE, Sah D, Wang G, Stamper R, Price VH. Instilled bimatoprost ophthalmic solution in patients with eyelash alopecia areata. *Journal of the American Academy of Dermatology*. 2009;61(3):530-532
- [37] Azzouni F, Godoy A, Li Y, Mohler J. The 5 alpha-reductase isozyme family: A review of basic biology and their role in human diseases. *Advances in Urology*. 2012;2012:530121. DOI: 10.1155/2012/530121. PMC 3253436
- [38] Yamana K, Labrie F, Luu-The V. Human type 3 5 α -reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride. *Hormone Molecular Biology and Clinical Investigation*. August 2010;2(3):296
- [39] Foye WO, Lemke TL, Williams DA. *Foye's Principles of Medicinal Chemistry*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 1286. ISBN: 978-0-7817-6879-5

- [40] Rhodes L, Harper J, Uno H, et al. The effects of finasteride (Proscar) on hair growth, hair cycle stage and serum testosterone in adult male and female stump-tail macaques (*Macaca arctoides*). The Journal of Clinical Endocrinology & Metabolism. 1994;**29**:991-996
- [41] Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of Japanese men with androgenic alopecia. Journal of the American Academy of Dermatology. 1998;**39**:578-589
- [42] Ledyn J, Dunlap F, Miller B, et al. Finasteride in the treatment of men with frontal male pattern hair loss. Journal of the American Academy of Dermatology. 1999;**40**(6 pt 1):930-937
- [43] Yamana K, Labrie F, Luu-The V. Human type 3 5 α -reductase is expressed in peripheral tissues at higher levels than types 1 and 2 and its activity is potently inhibited by finasteride and dutasteride. Hormone Molecular Biology and Clinical Investigation. January 2010;**2**(3):296
- [44] Traish AM, Mulgaonkar A, Giordano N. The dark side of 5 α -reductase inhibitors' therapy: Sexual dysfunction, high Gleason grade prostate cancer, and depression. Korean Journal of Urology. 2014;**55**(6):367-379
- [45] Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5-alpha-reductase inhibitor. The Journal of Clinical Endocrinology and Metabolism. 2004;**89**:2179-2184
- [46] Rushton DH, Futterweit W, Kingsley D, Kingsley P, Norris MJ. Quantitative assessment of spironolactone treatment in women with diffuse androgen-dependent alopecia. Journal of the Society of Cosmetic Chemists. 1991;**42**:317-325
- [47] Mackenzie IS, Macdonald TM, Thompson A, Morant S, Wei L. Spironolactone and risk of incident breast cancer in women older than 55 years: A retrospective, matched cohort study. British Medical Journal. 2012;**345**:e4447
- [48] Price VH, Roberts JL, Hordinsky M, et al. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. Journal of the American Academy of Dermatology. 2000;**43**:768-776
- [49] Burton JL, Shuster S. Large doses of glucocorticoids in the treatment of alopecia areata. Acta Dermato-Venereologica. 1975;**55**:493-496
- [50] Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. Archives of Dermatology. 1992;**128**:1467-1473
- [51] Kar BR, Handa S, Dogra S, Kumar B. Placebo-controlled oral pulse prednisolone therapy in alopecia areata. Journal of the American Academy of Dermatology. 2005;**52**:287-290
- [52] "US Sulfasalazine label" (PDF). FDA. February 2014. Archived (PDF) from the original on 2017-02-16
- [53] Ellis CN, Brown MF, Voorhess JJ. Sulfasalazine for alopecia areata. Journal of the American Academy of Dermatology. 2102;**46**:541-544

- [54] Sergio VG, Angela HG, Natalia SN, Laura MG, David SC, Rita RB, Pedro L. Treatment of recalcitrant adult alopecia areata universalis with oral azathioprine. *Journal of the American Academy of Dermatology*. May 2016;**74**(5):1007-1008
- [55] Gupta AK, Ellis CN, Cooper KD, Nickoloff BJ, VC H0, Chan LS, Hamilton TA, Tellner DC, Griffiths CE, Voorhees JJ. Oral cyclosporine for the treatment of alopecia areata. A clinical and immunohistochemical analysis. *Journal of the American Academy of Dermatology*. 1990;**22**(2 Pt 1):242-250
- [56] Mariana H, Fabiane MB. Efficacy and safety of methotrexate in alopecia areata. *Anais Brasileiros de Dermatologia*. 2014;**89**(5):729-734
- [57] Joly P. The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis. *Journal of the American Academy of Dermatology*. 2006 Oct;**55**(4):632-636
- [58] Joseph CE, Silke H. Methotrexate treatment for alopecia areata with greater than 50% involvement. *Hair Therapy & Transplantation*. 2015;**5**:3
- [59] Behrens WSC, Leiter U, Schiener R, et al. The PUVA-turban therapy as a new option of applying a dilute psoralen solution selectively to the scalp of patients with alopecia areata. *Journal of the American Academy of Dermatology*. 2001;**44**:248-252
- [60] Leavitt M, Charles G, Hetman E, Michaels D. Hairmax laser comb laser phototherapy device in the treatment of male androgenetic alopecia: A randomized, double-blind, sham device-controlled, multicenter trial. *Clinical Drug Investigation*. 2009;**29**(5):283-292
- [61] Bent S, Kane C, Shinohara K, et al. Saw Palmetto for benign prostatic hyperplasia. *The New England Journal of Medicine*. 2006;**354**:557-566
- [62] Prager N, Bickett K, French N, Marcivici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. *Journal of Alternative and Complementary Medicine*. 2002;**8**:143-152
- [63] Park H, Kim CW, Kim SS, Park CW. The therapeutic effect and the changed serum zinc level after zinc supplementation in alopecia areata patients who had a low serum zinc level. *Annals of Dermatology*. 2009 May;**21**(2):142-146
- [64] Ellis J, Stebbing M, Harrup S. Polymorphism of the androgen receptor gene is associated with male pattern baldness. *The Journal of Investigative Dermatology*. 2001:452-455
- [65] Yuha YK, Akio S, Koh-ei T. The emerging role of pharmacogenetics in the treatment patterned hair loss. In: Unger, *Hair Transplantation*. Informa Health Care UK. 5th ed. 2011. pp. 97-101
- [66] Suyoun C, Low S-K, Hitoshi Z, Atauahi T, Michiaki K, Mitsunori S, Yukuse N. A genome-wide association study of chemotherapy-induced alopecia in breast cancer patients. *Breast Cancer Research*. 2013;**15**(5):R81