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Pharmacological Treatment of Alopecia

Robert Gensure

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Abstract

In this chapter, we will explore non-surgical treatments of alopecia. Unlike many other areas of medicine, pharmacological treatments for alopecia are relatively new. There are only two treatments which are approved by the Food and Drug Administration (FDA); the rest are drugs developed for other indications which have gained popular off-label use to promote hair growth. The reasons for this are many, including the designation of alopecia by the FDA as a cosmetic disease. This designation has restricted alopecia development programs to compounds with virtually no side effects. Unfortunately, it has also led to off-label use of far more dangerous compounds as alopecia treatments, without the benefit of controlled trials. There is a growing recognition that alopecia, particularly alopecia areata and chemotherapy-induced alopecia, are disorders which significantly alter the quality of life, similar to acne vulgaris and psoriasis, and merit treatment accordingly. There have also been several recent advances in our understanding of the hair cycle, revealing new targets for developing alopecia therapies. As a result, there is a more robust slate of programs for developing new pharmacological treatments for alopecia. In this chapter, we will review current pharmacological treatments for alopecia and selected treatments under development (i.e., those with significant preclinical or clinical data which have appeared in the published literature).

Keywords: alopecia, pharmacology, minoxidil, finasteride, glucocorticoid, diphenylcyclopropenone, DPCP, tofacitinib, ruxolitinib, bimatoprost

1. Introduction

While alopecia is a common problem, the lack of any direct health effects from hair loss has limited development of pharmacological solutions, mostly due to perceptions by regulatory authorities that there is no benefit to treatment and therefore there should be no side effects as well. Current therapies consist of repurposed drugs which were incidentally noted to have

positive effects on hair regrowth and some therapies designed specifically to regrow hair. Most are applied topically to reduce the risk of systemic side effects, but this can be an inconvenient method of application if the hair loss is minimal, and often reduces the efficacy of the treatment. Insurers rarely provide coverage for such therapies. The resulting "benign but minimal efficacy" therapies have made little impact into the global problem of alopecia, and patients will often opt for surgical options with greater costs and risks, but promises of markedly improved results. In this chapter, we review current pharmacological treatments for alopecia and a selection of those under development (in late preclinical or clinical stage of development), including indications, mechanism of action, efficacy, and side effects.

2. Current pharmacological therapies for alopecia

Currently, there are only two Food and Drug Administration (FDA)-approved therapies for alopecia, minoxidil and finasteride. There are several other therapies commonly used in an off-label fashion as alopecia therapies.

2.1. Spironolactone

Spironolactone is a diuretic, which acts as an antagonist to aldosterone. Given the structural similarity of steroid hormones, spironolactone has also some limited androgen-blocking activity. While spironolactone is not specifically approved for use for hair loss, this weak androgen-blocking effect has led to the off-label use of spironolactone to minimize hair loss from polycystic ovarian syndrome (PCOS), usually in conjunction with oral contraceptive therapy [1]. As it is a weak androgen antagonist, it has not been found to be effective in treating androgenetic alopecia in males. Spironolactone is an oral medication taken twice per day.
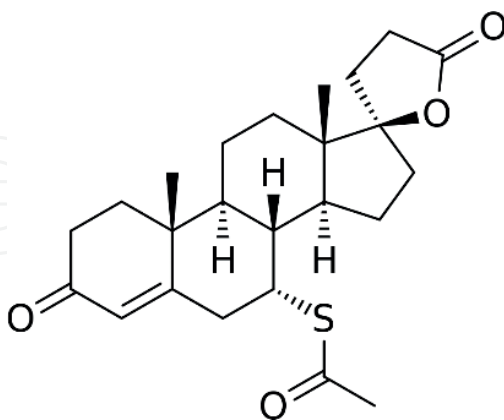
Mechanism of action: spironolactone reduces hair loss by acting as a competitive antagonist at the androgen receptor. While technically, this could serve to block all forms of androgen-induced hair loss, the blockade is not potent enough to provide visible effects in androgenetic alopecia in males. There are observed effects in hair growth patterns, however, in females with

polycystic ovarian syndrome. Spironolactone can improve growth of scalp hair in this condition. Spironolactone can also reduce terminal differentiation and hair growth in androgen-dependent regions of the body (face, arms, back, and abdomen) and thus serve as an effective treatment for hirsutism.

Side effects: spironolactone's primary clinical use is as a diuretic, and thus patients taking spironolactone for alopecia will experience an increased urine output. As spironolactone antagonizes the effects of aldosterone, potassium levels may become elevated and should be monitored while on therapy.

Clinical application: spironolactone's relatively weak effects at the androgen receptor make the treatment unsuitable as a therapy for androgenetic alopecia. Androgen levels are much lower in females with polycystic ovarian syndrome, and spironolactone therapy does result in some noticeable hair growth in some patients with this disorder. However, the overwhelmingly most prevalent indication for spironolactone therapy is not hair growth, but rather to prevent regrowth of hair in other androgen-dependent regions of the body as a therapy for hirsutism. Spironolactone is effective in reducing regrowth of hair in these regions, and, over time, can reverse terminal differentiation. However, as it does not induce shedding of existing hair, it can require up to 6 months for full effect and thus is often used as an adjuvant therapy to more traditional hair-removal techniques (shaving, depilating creams, laser therapy).

2.2. Minoxidil

Minoxidil (Rogaine) was originally marketed by Upjohn as a therapy for hypertension. It was noted during clinical trials that some male patients with androgenetic alopecia experienced regrowth of hair during the course of treatment. This led to an effort to repurpose the drug as a topical treatment for androgenetic alopecia, which was ultimately approved by the FDA for this indication under the branded name Rogaine. Minoxidil has been found to regrow hair in 40% of patients with androgenetic hair loss after 3–6 months of treatment [2]. Maintenance of this hair regrowth requires continued therapy. The treatment is most effective in younger patients with minimal hair loss. It is least effective if there is a broad region of hair loss.

Mechanism of action: minoxidil has no direct effects on the hair cycle; rather, it stimulates the vascular bed around the hair follicles and provides a more favorable environment for hair growth [3]. Specifically, the transition of hair follicles from a resting telogen phase to an active anagen phase, and maintenance of that anagen phase, depends on interactions between the bulb of the hair follicle and the vascular bed below. Minoxidil enhances these interactions by stimulating the proliferation of this vascular bed. Minoxidil does not directly stimulate hair follicles to transition to anagen phase, nor does it maintain hair follicles in this state. Minoxidil does not cause hair follicles to transition into terminal, or visibly pigmented hair.
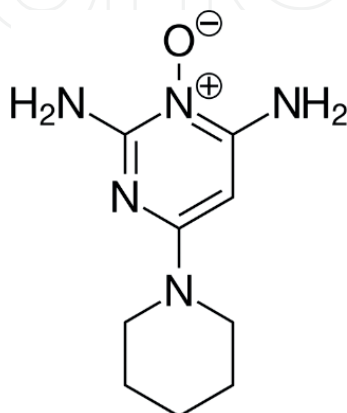
Given this mechanism of action, it is not surprising that minoxidil has minimal effects in the setting of severe hair loss and has maximal effects when there are still ample normal cycling terminal hair follicles to support. As the treatment does not directly stimulate hair follicles to transition to the anagen phase or maintain them in this state, there are also reports that the resulting hair is thin, hypopigmented, and shorter than normal hair. The responses are not sustained, and without continued use, the hair is quickly shed.

Side effects: minoxidil was originally developed as an antihypertensive, and oral use could lower blood pressure and produce symptoms of dizziness, tachycardia, swelling, headache, and fainting. Topical application minimizes the risk of these systemic side effects. Other potential side effects include itchiness, rash, and allergic reactions.

While minoxidil is approved for use in androgenetic alopecia, only a small fraction of those with this disorder actually use minoxidil. The public is very aware of this treatment, likely the result of heavy marketing at the time of its release in 1988. The low-market penetrance appears to be the result of continuing costs in the setting of minimal efficacy for those who start therapy, or perception of minimal effects of treatment for those who do not.

2.3. Finasteride

Finasteride (Propecia) was developed by Merck as a therapy for androgenetic alopecia. The drug was developed as an oral antiandrogen, which acts by inhibiting the conversion of testosterone to its more potent form, dihydrotestosterone. The treatment has been shown to be effective in both androgenetic alopecia males; the treatment of alopecia for polycystic

ovarian syndrome females appears to be less effective. Finasteride was approved for treatment of hair loss in the USA in 1997.
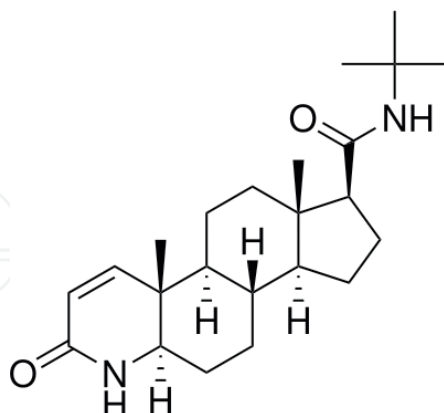
Mechanism of action: finasteride acts as an inhibitor of the enzyme 5-alpha reductase, which converts testosterone to the more potent form dihydrotestosterone. It is extremely effective and can lower levels by dihydrotestosterone by up to 70% in the bloodstream [4]. However, it does not inhibit or reduce testosterone levels, and some androgen effects on hair follicles remain with treatment. Androgens bind to testosterone receptors in stem cells in the bulge of the hair follicle. The complex binds and depletes intracellular beta-catenin. This inhibits the transition of the hair follicle from the telogen to anagen phase. By reducing levels of dihydrotestosterone, the most potent androgen, finasteride, can reverse these changes, allowing hair follicles to resume normal cycling with effects of visual hair growth. In regions of androgen-dependent hair growth (face, arms, abdomen, back), finasteride can reduce hair growth.

Side effects: as finasteride reduces androgen potency, it can lead to sexual dysfunction in males. These effects include a decreased sexual desire and impotency. These effects may be temporary as tolerance develops to the medication.

Finasteride is effective in reducing hair loss in males with androgenetic alopecia, resulting in approximately 30% increases in hair growth [5]. The effects are sustained as long as treatment is continued, and the hair loss resumes if treatment is stopped. As testosterone is still available to activate androgen receptors, the response is not complete. In women with polycystic ovarian syndrome, the effects on stimulating hair growth are more modest. The more pronounced effect on women with this disorder decreases in hirsutism. Similar to minoxidil, the only other FDA-approved therapy for androgenetic alopecia, finasteride, is used by only a small fraction of individuals for whom it is potentially indicated. The limited use appears to be related to limited overall effects on hair growth, requirement for continued therapy to sustain these gains, and the side effects of sexual dysfunction.

2.4. Oral contraceptives

Oral contraceptives are used in women with polycystic ovarian syndrome primarily as a means to regulate normal cycles. The treatments can sometimes complicate scalp hair loss and hirsutism further, as the progestins may have androgenic side effects. The use of oral contraceptives with reduced androgenic, and even some anti-androgen effects, together with the suppression of ovarian androgen production, can result in net improvements in scalp hair growth. Oral contraceptives are designed for use with polycystic ovarian syndrome, including Yasmin, Yaz, and Ocella (drospirenone/ethinyl estradiol).

Mechanism of action: in normal cycling females, the ovaries produce approximately 50% of androgen, the rest being produced in the adrenal glands. With PCOS, the anovulatory cycles reduce ovarian aromatization of androgens to estrogens, resulting in an increased ovarian androgen production. Oral contraceptives reduce FSH and LH stimulation to the ovaries, effectively reducing ovarian androgen production (but with adrenal androgen production unaffected). These net increases in androgen production, together with increases in serum estrogen levels, can slow or reverse some hyperandrogenic effects in PCOS, including scalp hair loss, hirsutism, and acne. Estrogen itself can improve scalp hair growth as well, having direct effects to make the hair thicker and more plusher. While some progestins, that is, norethindrone, can have some androgenic side effects which limit these effects, oral contraceptives designed for use with polycystic ovarian syndrome contain the progestin drospirenone, which has less androgenic effects. In fact, drospirenone has anti-androgen and anti-mineralocorticoid effects similar to spironolactone and can aid further in inducing regrowth of scalp hair and reduction of hirsutism.

Side effects: side effects of oral contraceptives relate mostly to the dose of estrogen. Estrogen can increase the risk of migraine headaches and deep vein thrombosis. Doses of estrogen in oral contraceptives designed for use in polycystic ovarian syndrome are lower, such that risks of these complications, while increased from pre-treatment levels, should not exceed those of normal cycling females. The progestin drospirenone has an increased risk for deep venous

thrombosis and blood clots beyond that from the estrogen component of the oral contraceptive, which has resulted in warnings to discontinue therapy with surgery [6].

Oral contraceptives are most effective at treating hirsutism and acne from PCOS. Improvements in scalp hair growth can be obtained from a reduced ovarian androgen production, direct effects of estrogen on hair growth, and with some oral contraceptives, the inhibition of remaining androgen effect via competitive blocking of the androgen receptor. Oral contraceptives do not reduce adrenal androgen production, and as such, the effects on scalp hair growth are incomplete. Oral contraceptives provide no benefit for other forms of hair loss.

2.5. Glucocorticoid therapy

Glucocorticoid therapy is used for the treatment of autoimmune alopecia, specifically alopecia areata/totalis/universalis [7]. It has no effect on androgenetic alopecia. Glucocorticoids are injected subcutaneously directly into the sites of hair loss and can require large number (i.e., >80) injections if hair loss is extensive. The response is low, with 30–50% of individuals showing a response in different patient series. This therapy is not approved by the FDA for this indication.

Mechanism of action: glucocorticoids are powerful anti-inflammatory components when given at high doses. Pulsed high-dose oral administration has been shown to be effective [8], but to minimize systemic side effects, the preferred route of administration is direct injection to the affected areas. Topical therapy has been found to be less effective [9]. Glucocorticoids do not directly alter the hair follicles, but the anti-inflammatory effects reduce the autoimmune disruption of anagen hair follicles which is characteristic of alopecia areata. Response rates are higher in milder forms of alopecia areata; it is likely that senescence of hair cycling and the autoimmune response, which is often seen with alopecia totalis and universalis, limits the efficacy of glucocorticoid therapy in the more severe forms.

Side effects: side effects of glucocorticoid injection result from systemic absorption, which is minimized but not eliminated with subcutaneous injection. Glucocorticoid administration can result in increased appetite and weight gain, peripheral muscle wasting, immune suppression, and osteoporosis. Chronic use can result in skin thinning and adrenal suppression, with the resulting risk of adrenal crisis with illness. In children, chronic administration can result in short stature.

Glucocorticoid injections provide a modest hair growth response in alopecia areata with an overall low risk of systemic side effects. Although not approved by the FDA for this indication, it is currently the primary therapy for alopecia areata. While side effects are minimized, the process of receiving multiple scalp injections is difficult, and many patients will decline glucocorticoid therapy for this reason alone.

2.6. Cyclosporin A

Cyclosporin A is an immune-suppressant drug used primarily to prevent the rejection of transplanted organs. As an immune suppressant, it has been used for the treatment of

autoimmune hair loss, specifically in alopecia areata/totalis/universalis. Cyclosporin also has direct effects to promote the cycling of hair follicles, making it more effective and potentially complementary to other immune-suppressant therapies. However, cyclosporine has severe side effects, including an increased risk of serious infections and cancer, hyperglycemia, and diabetes mellitus. As a result, it is not commonly used as an alopecia therapy.

Mechanism of action: cyclosporin is a power anti-inflammatory agent, which acts by blocking the transcription of cytokine genes in activated T-cells [10]. Cyclosporin complexes with cyclophilin and inhibits phosphatase activity of calcineurin, which in turn alters the activation of NFAT transcription factors. Cyclosporin also blocks antigen recognition pathways by preventing the activation of the JNK and p38 pathways.

Cyclosporin also acts directly on hair follicles, promoting transition from telogen to anagen phase and promoting hair growth [11]. This combined mode of therapy makes cyclosporin ideal as a therapy for alopecia areata. Cyclosporin can be used in combination with glucocorticoid therapy to improve responses [12]. The effects of cyclosporine do not persist if the therapy is discontinued.

Side effects: side effects from cyclosporine therapy are severe. The immune suppression is significant and can increase risks of a serious bacterial infection and certain cancers, particularly lymphoma. Monitoring for immune function is recommended on therapy. Cyclosporin also causes hyperglycemia and can cause diabetes mellitus.

While cyclosporine is theoretically an excellent choice for several forms of hair loss, including alopecia areata and androgenetic alopecia, the side-effect profile results in very limited use in clinical settings. As a telling example of this, the patient in the cited case report [12] is now deceased from pneumonitis.

2.7. Janus kinase (JAK) inhibitors (tofacitinib and ruxolitinib)

Janus kinase inhibitors have been developed primarily as an immune-suppressant therapy for rheumatoid arthritis. Primary research into the immune-signaling mechanisms for alopecia areata revealed that janus kinases are integral to these pathways, and janus kinases inhibitors have been shown to promote hair growth in alopecia areata. While there are specific janus kinase inhibitors in development for this indication, there is significant off-label clinical use of janus kinase inhibitors approved for rheumatoid arthritis for the therapy of alopecia areata. These agents have the highest reported response rates in the most severe forms, alopecia totalis and alopecia universalis. An initial report indicated that 75% of patients responded with at least 50% improvement in hair growth by SALT score after 12 months of therapy, although the study employed a small number of subjects [13]. A larger series show a more modest 33% of patients with >50% increase in SALT score at 6 months, which is still superior to other therapies [14]. While JAK inhibitors are effective, they are also expensive, and the hair growth is not maintained once the treatment is discontinued. They do not appear to be effective in other forms of alopecia, even to the point that treatment with a JAK inhibitor revealed unknown androgenetic alopecia in a patient who had alopecia totalis from early in life [14].

Mechanism of action: there are three janus kinases, designated JAK-1, JAK2, and JAK3. Their primary substrates are the various STAT proteins, and they play a critical role in signaling of immune regulatory factors. JAK-2 has additional clinical importance as the primary signaler for growth hormone, through linking with STAT-5b; mutations in this STAT protein have been shown to cause growth hormone resistance and short stature. JAK inhibitors used for applications of hair growth target JAK-1 and JAK-3, which in turn inhibit STAT3. Inhibition of JAK pathways inhibits interferon-gamma signaling and inhibits signaling in CD8 + NKG2D+ T-cells, which have been shown to cause alopecia areata in mouse models [15]. There may also be some direct effect to promote hair cycling [16].

Side effects: JAK inhibitors have been found to cause elevated liver function studies and serious bacterial infections in trials for rheumatoid arthritis and psoriasis [17]. Studies in alopecia areata have not shown these side effects, but the total number of patients in those studies was much lower. Given the similarities in dosing and duration of treatment, it is likely that these same side effects will be observed with larger numbers of patients treated.

While JAK inhibitors provide excellent efficacy for hair growth in alopecia areata, the high cost, latency to effect (6–12 months), lack of durable effect, and side-effect profile are all potential concerns and limit current clinical use. In addition, JAK inhibitors do not appear to be effective in other forms of alopecia. Importantly, there are JAK inhibitors under development, including topically applied compounds, which may provide a more favorable side-effect profile and expand the use of these compounds in clinical practice.

2.8. Bimatoprost

Bimatoprost (Latisse) is a prostaglandin analog which was discovered to promote eyelash growth. It has been approved by the FDA for this indication. Its mechanism of action is to promote the entry of hair follicles into the anagen phase, and given this, there was promise that bimatoprost could be used as a more general treatment for various forms of hair loss.

However, clinical trials have been disappointing, and it appears that the effect is restricted to the eyelash region.

Bimatoprost was developed for therapy for open-angle glaucoma, under the trade name Lumigan. However, in clinical trials, it was noted to have a remarkable effect to increase the growth of eyelashes. It was repurposed for this indication and has been approved by the FDA and currently marketed for regrowth of eyelashes [18]. It appears to be effective across a variety of conditions, including chemotherapy, alopecia universalis, and normal individuals desiring thicker eyelashes [19]. It is applied topically to the eyelash region, and growth of eyelashes occurs rapidly.

Mechanism of action: bimatoprost is a prostaglandin F2a analog which inhibits prostamids. There are known links between prostaglandins and hair cycling, including prostaglandin D2 [20], and it appears that bimatoprost grows eyelash hair by transitioning hair follicles into the anagen phase. This results in rapid regrowth of eyelashes.

Side effects: as bimatoprost is applied topically to eyelash area directly, there are minimal reports of systemic side effects. Local side effects include conjunctivitis and blurry vision. There are additional off-target benefits, a decreased intraocular pressure, based on its original development as a therapy for open- angle glaucoma.

While bimatoprost is very effective at promoting the growth of eyelashes, its effects are minimal for promoting hair growth outside the eyelash region, with phase 2 trial showing a similar or only slightly superior efficacy to minoxidil. The reasons for this are not clear, but it does appear that the interaction between prostaglandins and hair cycling differs based on the site and/or type of hair follicle. Eyelashes are very different from scalp hair, producing a thicker shaft that only grows to a specific length; thus, it is not surprising that the regulation of the hair cycle for these follicles might be different as well. Unfortunately, this limits the clinical application of bimatoprost to therapy for eyelash shedding.

2.9. Diphenylcyclopropenone (DPCP)

DPCP is a sensitizing agent which is used in the treatment of alopecia areata. The agent is topically applied weekly and left in place for 6–24 h. Approximately 50% of patients treated with DPCP respond with regrowth of hair after 6 months of treatment [21]. The response is durable, with 60% of responders showing a continued hair growth 12 months after receiving therapy. DPCP is not effective in treating other forms of alopecia.

Mechanism of action: DPCP induces a contact dermatitis, which is thought to redirect the immune reaction from the hair follicles, allowing regrowth of hair. This includes decreasing the CD4/CD8 ratio and decreasing levels of interferon-gamma at the site of application. The patient must first be sensitized to DPCP prior to therapy on the scalp. The response develops slowly, requiring up to 6 months of treatments. However, once the response develops, it persists after treatment is discontinued.

Side effects: DPCP treatments are expected to cause a contact dermatitis, with redness and itching. More severe reactions, including swelling, burning, urticaria, and blistering, can occur.

Other side effects include fever, arthralgia, more widespread eczema, erythema multiforme, hyperpigmentation, and hypopigmentation (vitiligo) [22].

DPCP treatments provide response rates in alopecia areata as high as JAK inhibitors, at a lower cost and with a less severe side-effect profile. However, the contact dermatitis, which is required for a therapeutic response, is irritating to the patients. Hair growth takes months to develop, and dermatitis can prevent patients from wearing wigs during the treatment phase.

3. Pharmacological therapies for alopecia under development

There are many therapies for alopecia in various stages of development. A partial list of the major categories of compounds is subsequently provided, including those with significant clinical data or established mechanism of action.

3.1. JAK inhibitors

Aclaris is developing JAK inhibitors specifically for therapy for alopecia areata. A-201 is an oral product, and A-301 is a topical product. The mechanism of action is likely to be similar to tofacitinib and ruxolitinib, described earlier. Topical application may improve the safety profile by minimizing systemic exposure and may improve efficacy by delivering higher doses to the skin regions where hair growth is desired. Aclaris is also developing its JAK inhibitors as therapy for androgenetic alopecia, although studies with other JAK inhibitors suggest that this will be ineffective.

Concert pharmaceuticals are also developing a JAK inhibitor specifically for therapy for alopecia areata. CTP-543 is a deuterium-modified analog of ruxolitinib and is believed to have a similar mechanism of action. Deuterium may alter the compound's pharmacokinetics. Leo Pharmaceuticals is developing LEO-124249, a topical JAK inhibitor for the treatment of alopecia areata. Incyte Corporation is developing a topical preparation of ruxolitinib for the therapy of alopecia areata.

Tigo GmbH is developing interferon-gamma receptor antagonists as a therapy for alopecia areata. These would act upstream in the same signaling pathway targeted by JAK inhibitors.

3.2. Androgen receptor antagonists

Androscience Corporation is developing an androgen receptor antagonist ASCJ-9 for the treatment of androgenetic alopecia. The compound is also being developed for acne vulgaris and wound healing. It is a small molecule which is topically applied and increases degradation of the androgen receptor. Valeant Pharmaceuticals is developing CB-0301, an androgen receptor antagonist, for the therapy of androgenetic alopecia.

3.3. Vitamin D analogs

Berg L.L.C. is developing BPM 31543, a topically applied analog of 1,25-dihydroxyvitamin D. It is being developed specifically for the therapy of chemotherapy-induced alopecia. Patients

with VDR receptor mutations have total body alopecia. However, it is the unoccupied VDR that is required to activate the hair cycle, apparently by forming complexes with beta-catenin and LEF-1. There is no hair loss observed in patients with 1-alpha-hydroxylase deficiency, who make no 1,25-dihydroxyvitamin D. It is therefore unclear how 1,25-dihydroxyvitamin D analogs would prevent hair loss.

3.4. Parathyroid hormone analogs

Parathyroid hormone antagonists can promote hair growth by preventing hair follicle transition from anagen to catagen phase. ICI Pharmaceuticals was developing parathyroid hormone antagonists as a therapy for chemotherapy-induced alopecia, but the project was discontinued because of lack of efficacy. Parathyroid hormone agonists can promote hair growth by stimulating hair follicles to transition from telogen to anagen phase. BiologicsMD is developing parathyroid hormone agonists as a therapy for several forms of alopecia, including alopecia areata, androgenetic alopecia, and chemotherapy-induced alopecia.

3.5. TGF-beta receptor antagonists

Auxagen is developing a small molecule compound that suppresses TGF-beta, inhibiting the transition of hair follicles from anagen to catagen phase. The compound is topically applied. The company reports that this product is more effective than minoxidil at promoting hair growth.

3.6. Anti-fibrogenic factor

Birch Biomed Inc. is developing a combination therapy for alopecia areata. Fibrostop 2 is a kynurenic acid cream which is administered topically. Fibrostop 2 is being developed as a therapy for psoriasis, alopecia, and scars.

3.7. Neurotrophic activator

BRIM Biotechnology, Inc. is developing a peptide compound that acts to enhance cell proliferation. The compound, BRM-421, also has ophthalmologic applications and is proceeding to clinical trials for these indications.

3.8. Stem cell signalers

Histogen is developing a mixture of biologics called hair stimulating complex. This product includes KGF, VEGF, and follistatin, compounds which signal stem cells in the body and are critical for hair follicle formation and stimulation of existing hair follicles. The compound activates stem cells in the bulge and promotes anagen transition of hair follicles.

Rivertown Therapeutics is developing RT1640 for the treatment of androgenetic alopecia. RT1640 is a mixture of three molecules which is applied topically and stimulates hair growth

—the compounds are minoxidil, cyclosporin A, and a proprietary compound RT1640. The compound is applied topically.

3.9. RNAi

There are several companies, including OliX Pharmaceuticals, Quark Pharmaceuticals, and RXi Pharmaceuticals developing RNAi-based treatments for alopecia. There is little information at this time regarding specific compounds or targets.

3.10. Stem cell therapy

RepliCel Life Sciences is developing a method of autologous cell therapy which utilizes dermal sheath cup cells to treat androgenetic alopecia.

3.11. Histone deacetylases

TetraLogic Pharmaceuticals is developing remetinostat for the therapy of alopecia areata. The compound is suberohydroxamic acid phenyl ester (SHAPE), which acts by inhibiting histone deacetylases. It is topically applied and is also being developed for the therapy of cutaneous T-cell lymphoma and plaque-type psoriasis.

3.12. Interleukin antibodies

AstraZeneca is developing Tralokinumab for the treatment of alopecia areata. Tralokinumab is a human monoclonal antibody that inhibits interleukin 13, which is an important cytokine for developing hair loss in alopecia areata. Novartis is developing secukinumab for the treatment of alopecia areata. Secukinumab is a human monoclonal antibody that inhibits interleukin 17A, which is also an important cytokine for developing hair loss in alopecia areata. Secukinumab is also being developed for severe plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and uveitis.

3.13. Stem cell therapy

Stem cells play a critical role in hair follicle regeneration and in the hair cycle. Stem cells are located in the bulge region of the hair follicle, and under control of Wnt signaling, they proliferate and migrate down the hair follicle shaft to transform the follicle into the anagen phase. Efforts have been made to treat various forms of hair loss, including androgenetic alopecia and alopecia areata, with stem cell injections. There are reports of improvements of hair growth with these techniques [23], and there are some hair growth centers which utilize these techniques.

3.14. Platelet-rich plasma therapy

Rather than infusing stem cells, one can also infuse plasma, which is rich in factors which can stimulate stem cells. Platelet-rich plasma (PRP) is a plasma concentrate which has been used

for regenerative purposes in a variety of settings, including wound healing, cartilage damage, and scarring. Injection with autologous PRP has been shown to increase hair growth in androgenetic alopecia [24], presumably by stimulating stem cells in the bulge region to regenerate hair follicles and induce anagen transition.

3.15. Adipose-derived stromal vascular fraction (SVF)

Adipose-derived stem cells, also referred to as stromal vascular fraction (SVF), are another potential source of stem cells and/or stem cell-stimulatory factors which can be used to promote hair growth. This was discovered incidentally by observing effects after the transplant of autologous fat on hair growth. Early trials of injection of SVF show photographic evidence of hair regrowth and quantifiable (23.3%) increase in hair counts [25] in patients with androgenetic alopecia.

4. Conclusions

While there are only two FDA-approved pharmacological treatments for alopecia, there are a wide variety of compounds used off-label and an even larger number of compounds in various stages of development. This reflects a large and growing interest in developing effective therapies for alopecia. However, most of these compounds in clinical use suffer from the same limitations, which are poor efficacy and lack of durable effect. Several, particularly the immune modulators, are also hampered by being associated with severe side effects. Development programs have been hindered by the designation of alopecia as a cosmetic disease, which restricts programs to compounds with virtually no side effects. Advances in basic science have led to an improved understanding of the hair cycle, revealing new targets for drug development. As a result, there is a robust slate of development programs, which show promise for the development of more effective treatments for alopecia in the future.

Acknowledgements

Conflict of interest

Robert Gensure is a consultant and has an equity stake in BiologicsMD, a biotechnical company which is developing alopecia therapies.

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