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Systematic Review

A systematic review on the treatment of androgenetic alopecia

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ABSTRACT

Background: Androgenetic Alopecia is predetermined genetic disorder which is also know as Pattern Hair loss occurs due to excessive response to androgens. Hair loss in women often has a greater mental impact because it's less socially acceptable for them and it affects severely women's emotional well-being and quality of life. So this is paper focuses on the treatment procedure and its vast analysis on effectiveness in curing this disorder permanently.

Critical Discussion: This paper has covered the epidemiological aspect along with focused on the early signs and symptoms of Androgenetic Alopecia. It have also stated the causes of this disorder. The objective of this paper was to analyze the treatment of Androgenetic Alopecia along with its effectiveness.

Conclusions and Recommendations: Since there have been very little advancement in the treatment of Androgenetic Alopecia for last 30 years. But with recent investigation of JAK inhibitors, our future could be changed with permanent cure.

Based on our systematic review and evaluation we recommend that physicians should prescribe the pharmacological drugs, which includes Minoxidil, Finasteride and Dutasteride as first line of therapies for the treatment of Androgenetic Alopecia.

1. Introduction

1.1. What is androgenetic alopecia?

In medical literature, Androgenetic alopecia (AGA) is defined as predetermined genetic disorder which occurs due to an excessive response to androgens. In simpler terms, Androgenetic alopecia is a genetically determined disorder which is also known as Pattern hair loss.

Pattern hair loss or Androgenetic alopecia primarily affects the top and front of the scalp.[1] In male this condition is known as Male pattern hair loss (MPHL). In male, it has been witnessed that pattern of hair loss typically presents itself as either a receding front hairline, loss of hair on the vertex of scalp or a combination of both.[2] Overtime, hairline recedes to form a characteristic M shape. In men androgenetic alopecia could lead to partial or complete baldness. In females androgenetic alopecia is known by the name as female pattern hair loss (FPHL) which typically represents as a diffuse thinning of hair across the entire scalp. In women the hairline does not recede and very rarely it leads to total baldness.

This condition of androgenetic alopecia in men has been associated with several medical conditions which commonly includes coronary heart disease and enlargement of prostate, diabetes, obesity and hypertension.

In women androgenetic alopecia is mostly associated with an increased risk of polycystic ovary syndrome (PCOS).[3]

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Pattern hair loss is classified as a form of non- scaring hair loss. According to one study by Harvard, almost every woman eventually develops some degree of female pattern hair loss. Androgenetic alopecia can start after the onset of puberty but it's very noticeable in women more commonly around menopause. This risk usually increases with age and especially for those women with history of hair loss on either side of family. To describe female pattern hair loss, clinicians mostly use Ludwig classification:[4]

Type 1: This stage indicates minimal thinning of hair

Type 2 : This stage is categorized by decreased volume and noticeable widening of the midline part

Type 3: This stage describes diffuse thinning with appearance on the top of the scalp.

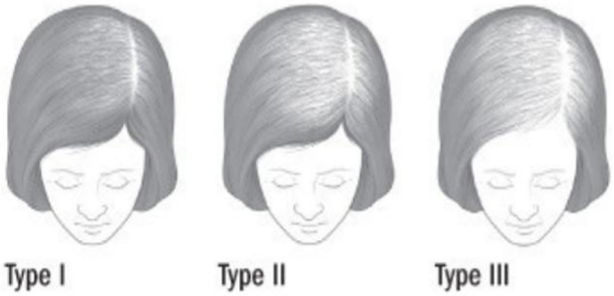

Fig. 1:

Hair loss in women often has a greater mental impact because it's less socially acceptable for them and it affects severely women's emotional well-being and quality of life. topical Minoxidil solution is the only drug available for promoting hair growth in women suffering from Androgenetic alopecia. Other current treatment options include laser therapy, scalp microneedling, and hair transplantation. Food and drugs administration (FDA) have approved two drugs officially as the treatment for pattern baldness:- topical Minoxidil and finasteride.[5]

2. Critical Discussion

2.1. What is the epidemiology of androgenetic alopecia?

According to one cross-sectional study in International Journal of Trichology which states the epidemiology of androgenetic alopecia are mostly affected by Asians, Americans, Africans and Eskimos. In Caucasian males, incidence approximates within 50% affected by 50 years old and up to 80% affected by 70 years old. Whereas in females this disorder is very common and with an increase in incidence after menopause.[6] According to American Academy of Dermatology which reports that around 30 million women are affected in United States annually.

2.2. What are the early signs and symptoms of androgenetic alopecia?

The common signs of androgenetic alopecia includes mostly:-

1. Gradual onset and increase in shedding off hair
2. Transition in the involved areas from large, thick, pigmented terminal here's to thinnest, shorter hair finally to short wispy nonpigmented hair.
3. End result can be an area of total denudation, this area will gradually very from patient to patient and most commonly occurs at vertex of the scalp.

The common symptoms such as widening part, hairline receding, hair getting loose and bald patches along with itching are associated with pattern hair loss.

2.3. What causes androgenetic alopecia?

Androgenetic Alopecia is caused by a combination of several factors which includes one's own genetics and the effect of male sex organ hormones call androgens.

As the name suggests, androgenetic alopecia involves the action of the hormones called androgens, which are essential for normal male sexual development and have other important functions in both sexes, including sex drive and regulation of hair growth. The condition may be inherited and involve several different genes. It can also result from an underlying endocrine condition, such as overproduction of androgen or an androgen-secreting tumor on the ovary, pituitary, or adrenal gland. In either case, the alopecia is likely related to increased androgen activity. But unlike androgenetic alopecia in men, in women the precise role of androgens is harder to determine. On the chance that an androgen-secreting tumor is involved, it's important to measure androgen levels in women with clear female pattern hair loss.

Researchers aren't precisely aware of why some men are prone to androgenetic alopecia as compared to others. However much research have shown the fact that men with hair loss tends to have higher levels of DHT then their peers, as well as a greater number of androgen receptors in their scalp. Researchers have confirmed a variation in a gene which might contribute to the possibility of causing pattern hair loss. Contrary to majority of popular belief, although researches shows that AGA tends to cluster in families, there is no particular evidence which could relate fully with the inheritance of pattern hair loss.[7]

2.4. What is the history of androgenetic alopecia?

The term alopecia originated from Greek word for fox "alopex" and was so named due to fur loss seen in fox mange. This dated back to the time of Hippocrates.

Famous Polish physician John Jonston first used the phrase alopecia area in his book "Medicina practica" written

in 1664. Towards the end of 19th century there were huge debates on the source of this disease. Some of the physicians supported the theory of parasitic cause while other believed it to be neurotrophic disorder by a connection with emotional stress and experiment showing alopecia after nerve damage in cats. Many physicians have also pointed to sudden hair loss and spontaneous recovery as signs of transient causative toxin or nutritional deficiencies in blood. Dental disease and eye strain were also implicated as causative.

So etiology and treatment have always puzzled physicians for generations after generations.[8]

2.5. What are the various treatments of Androgenetic Alopecia?

2.5.1. Review on FDA approved drug for androgenetic alopecia.

Over the last three decades, there have been very little advancement in the procedure for the permanent treatment of Androgenetic Alopecia. Food and Drug administration (FDA) have approved only two drugs indicated for the treatment of androgenetic alopecia. The drugs which are approved for pattern baldness are:-

1. Topical Minoxidil.
2. Finasteride.

These drugs also require at least four to six months trial before showing any significant improvements and must be used indefinitely to maintain a response. The initiation of this drug might cause initially shredding phase and also they work better together.[9]

2.5.1.1. Minoxidil. Tropical Minoxidil was the first drug which was approved by FDA as the treatment of Androgenetic alopecia. This drug is available in 2% and 5%. Solution and also as 5% foam it is also observed that 5% solution have been more effective than 2% solution.[10] Minoxidil was initially prescribed as a treatment for high blood pressure, but to a surprise people notice that they were growing here in places where they had lost it. There are several mechanisms by which Minoxidil may promote hair growth but the exact mechanism of the action is still unclear.[11] Minoxidil is a potassium channel blocker which widens the blood vessels hypothetically allows more oxygen, blood and nutrients two follicles and promote the anagen phase. It has been shown that both in vivo and in vitro to have a direct mitogenic effect on the epidermal cells and in vitro it prolongs the survival time of keratinocytes. With the application of topical minoxidil it have been observed that in 50% of men hair loss is stopped and a small percentage of men also have experienced hair regrowth.[12] This drug have to be continued indefinitely or hair growth might subside.

A randomized clinical trial was conducted to compare 5% topical minoxidil with 2% topical minoxidil and placebo in the treatment of men with AGA.A total of 393 men (18-49 years old) with AGA applied 5% topical minoxidil solution (n = 157), 2% topical minoxidil solution (n = 158), or placebo (vehicle for 5% solution; n = 78) twice daily. Efficacy was evaluated by scalp target area hair counts and patient and investigator assessments of change in scalp coverage and benefit of treatment. After 48 weeks of therapy, 5% topical minoxidil was significantly superior to 2% topical minoxidil and placebo in terms of changes. The purpose of this 48-week, double-blind, placebo-controlled, randomized, multicenter trial was to compare 5% topical minoxidil with 2% topical Minoxidil and placebo in the treatment of men with AGA. In men with AGA, 5% topical minoxidil was clearly superior to 2% topical minoxidil and placebo in increasing hair regrowth, and the magnitude of its effect was marked (45% more hair regrowth than 2% topical minoxidil at week 48). Men who used 5% topical minoxidil also had an earlier response to treatment than those who used 2% topical minoxidil. Psychosocial perceptions of hair loss in men with AGA were also improved. Topical minoxidil (5% and 2%) was well tolerated by the men in this trial without evidence of systemic effects 22.

Research studies have also confirmed that Minoxidil applied directly to scalp could stimulate hair growth in women. As a result of this studies, FDA have originally approved the over the counter 2% Minoxidil to treat hair loss in women.

2.5.1.2. Side effects associated with minoxidil. Minoxidil is very safe but it could have some unpleasant adverse effects such as:-

1. Hypertrichosis (excessive hair growth in wrong places such as cheeks or foreheads)
2. New hair differs in color and texture from surrounding here
3. Application on site redness
4. Burning
5. Fluid retention or edema
6. Allergic contact dermatitis
7. Irritation
8. Eczema

2.5.1.3. Finasteride. Finasteride is a 5 alpha reductase type 2 inhibitor which is approved by foods and Drug Administration FDA for Androgenetic alopecia treatment. This drug works by inhibiting the conversion of testosterone to DHT by blocking type 2 SAR. It is prescribed at 1MG daily and is more effective at increasing hair regrowth at the vertex region than the frontal areas of scalp. Finasteride drug have been shown to diminish the progression of Androgenetic alopecia in males who are treated and also in many patients it have been reported to stimulate new regrowth. Finasteride affects Vertex balding more than

frontal hair loss, this medication have shown to increase the regrowth on the frontal area as well. Efficiency of finasteride in women is controversial. Finasteride is not indicated for use in women with hair loss (female pattern hair loss) but is occasionally used (off-label) post menopause. Finasteride is contraindicated in women when they are or may potentially be pregnant, because it may cause abnormalities of the external genitalia of a male fetus. Due to unsatisfactory side effects with oral finasteride studies have been conducted comparing finasteride. 25% and.5%. Topical solution with oral finasteride 1MG. These studies have clearly indicated that similar improvements were observed in hair growth with very few side effects compared to topical therapy groups.

A randomised, double blind, placebo controlled study, was planned at All India Institute of Medical Sciences (AIIMS) was conducted at the Department of Dermatology and Venereology, AIIMS, New Delhi, India to study the effect of finasteride on hair growth in male patients of androgenetic alopecia .

Eighty male patients with AGA, not treated in the previous 6 months were enrolled in this randomized, double blind, placebo controlled trial to assess the safety and efficacy of finasteride, 1mg daily, on hair growth. Patients were randomized into 2 groups: Group 1 received 1 mg of finasteride daily and Group 2 received a placebo for a period of 12 months. Efficacy was assessed by hair counts, photographic records, patient's self-assessment questionnaire and clinical assessment. A total of 39 patients completed the study. Finasteride was rated superior to placebo with respect to all efficacy measures. At the end of study, finasteride treated patients had a mean increase of 20.56±4.73 hairs compared to a decrease of 9.56±5.53 hairs in placebo treated patients. Photographically, 69.56% of finasteride treated patients were rated as improved at 12 months compared to only 6.25% of placebo treated patients. Ten (25%) of finasteride treated patients developed adverse effects (5-decreased libido as well as erectile dysfunction, 4-erectile dysfunction, 1-decreased libido). Finasteride in comparison to placebo was effective in promoting hair growth in male patients of Androgenetic Alopecia 23.

2.5.2. Side effects associated with finasteride

According to Medline Plus common side effects which are associated with these drugs are as followed

1. Depression.
2. Changes in chest area like lumps, pain or nipples discharge.
3. Testicular pain.
4. Erectile dysfunction.
5. Sexual dysfunction.

There is a risk of high grade prostate cancer because PSA is marked and could detected on later stages.

2.5.3. Approved FDA drugs for treatment of androgenetic alopecia.

2.5.4. Review on non

The treatment which are found to be very effective but have not received approval officially from Food and Drugs Administration as treatment protocol for Androgenetic Alopecia are :-

1. Dutasteride
2. Spironolactone
3. Ketoconazole
4. Low level laser therapy
5. Microneedling and Hair Transplantation

2.5.4.1. Dutasteride. This drug is considered to be three times more potent on type 15A reductase enzyme and 100 times more potent on type 1 enzyme. This drug is most often prescribed in patients who have failed finasteride.[13]

A multicenter, randomized, double-blinded, double-dummy, parallel-group study was conducted over 29 weeks in 917 men aged 20 to 50 years with AGA. The men were randomized to dutasteride 0.02, 0.1, or 0.5 mg/day, finasteride 1 mg/day, or matched placebo. The primary endpoint was a change from baseline in hair count within a 2.54-cm–diameter area at the scalp vertex. Dutasteride 0.5 mg was found to be superior to finasteride 1 mg at Weeks 12 and 24 in increasing hair count (both, P = .003). Secondary endpoints included hair growth and hair restoration. Dutasteride 0.5 mg significantly improved hair count and hair width when compared with finasteride at Week 24 (P = .016 and P = .004, respectively).[14]

The tolerability of these agents was similar. This study indicates that dutasteride is an alternative to finasteride in the treatment of AGA, as it appears to offer improved results when compared with finasteride in the short term. Dutasteride is nowadays becoming very popular treatment option for pattern hair loss, due to its excellence response shown by various randomized control study and meta analysis. And in many of the experimental study it was observed that destroyed was found to be better than finasteride with comparable lesser adverse effects.[15]

In our near future, Dutasteride have the full potential to become a treatment of choice for Androgenetic Alopecia.

2.5.5. Spironolactone

Spironolactone or oral anti androgens are often used in women to treat androgenetic alopecia. These drugs are very weak partial agonist to androgen receptor, thus blocking much more potent DHT and free testosterone from interacting with androgen receptor and physiologically behaving like a direct antagonist.

Spironolactone also inhibit androgen synthesis and enhances conversion of testosterone to estradiol. Anti-androgens are more effective if there are other signs of viralisation. Most of the clinical data using 15 to 200

Drug	Dosage	Side Effects	Counseling Points
Finasteride oral tablets (Rx only)	1 mg daily	Orthostatic hypotension (9%), dizziness (7%), erectile dysfunction (5%-19%), ejaculatory dysfunction (1%-7%), decreased libido (2%-10%)	May take 3 months or longer to see benefit. Must continue product to maintain results. Side effects may decrease over time. Pregnant females or those of childbearing age should avoid direct contact with crushed or broken tablets
Dutasteride oral tablets (Rx only)	0.5 mg daily	Decreased libido (≤3%), gynecomastia (≤1%), impotence (≤5%)	May take 3 months or longer to see benefit. Must continue product to maintain results. Side effects may decrease over time. Pregnant females or those of childbearing age should avoid direct contact with crushed or broken tablets
Minoxidil topical foam/aerosol 5% (OTC)	One-half capful twice daily	Local erythema (6%), pruritus (6%), hair color or texture may change	Hair color or texture may change. Must continue the product to maintain results. Foam may melt on warm fingers, so run cold water over fingers and dry hands before use
Minoxidil topical 2% or 5% solution (OTC)	1 mL twice daily	Local erythema (6%), pruritus (6%), hair color or texture may change	Hair color or texture may change. Must continue the product to maintain results

Fig. 2:

MG per day of spironolactone have been in women with androgenetic alopecia and the results have been variable.[16]

2.5.6. Ketoconazole

Ketoconazole shampoo has been considered very effective agent in combination therapy with oral finasteride to treat androgenetic alopecia. Ketoconazole basically inhibits the DHT pathway conferring anti- androgenic properties.

2.5.7. Low level laser therapy

Low level laser therapy has also been used for the treatment of androgenetic alopecia which appears that laser can stimulate hair growth at certain wavelengths however this action has not been determined fully. This therapy might be used in conjunction with drug therapy to improve results.

2.5.8. Hair transformation and microneedling

Hair transplantation, a procedure used in the United States since the 1950s to treat androgenic alopecia, involves removing a strip of scalp from the back of the head and using it to fill in a bald patch. Today, 90% of hair-transplant surgeons use a technique called follicular unit transplantation, which was introduced in the mid-1990s.

Microneedling has gained popularity and has been found to be beneficial in stimulating hair regrowth in alopecia. It was previously used for cosmetic purposes and is now used to improve topical drug delivery. Microneedling uses multiple fine needles, generally attached to a roller, to create tiny punctures in the skin that stimulate neovascularization, release growth factors, and promote the expression of Wnt proteins. Hair growth is a result of the release of certain growth factors and activation of the hair bulge, and Wnt proteins have been found to stimulate dermal papillae stem cells, leading to hair growth. Microneedling is generally used in conjunction with topical therapy such as minoxidil and it has been used with PRP. Studies assessing the efficacy of microneedling in conjunction with topical minoxidil are small, but some have reported statistically significant

results.[17–19]

2.6. Researches and Emerging Therapies of future.

Several researches and new therapies are emerging or being studied as treatment options for AGA, including JAKs and PRP injections. JAKs are under investigation as new drugs to treat alopecia; however, there is limited information about their use in AGA. One of these products has been granted Fast Track approval by the FDA for the treatment of moderate-to-severe alopecia areata (autoimmune-related hair loss). The class of drugs was found to proliferate hair regrowth in cases of alopecia universalis (hair loss over the entire body) and, topically, the class promoted hair growth in mice and follicle growth in humans. Injecting autologous PRP into the scalp is a new therapy for the treatment of AGA. The platelets are gathered through a blood draw and then separated, concentrated, and prepared through several methods utilizing commercially available kits. Platelets release growth factors that are involved in the stimulation of endothelial and stem cells.

3. Conclusions and Recommendations

Since then, there have been very little development and advancement in the treatment of alopecia for many decades. However with vast research and investigations of JHK inhibitor, our future may be altered with a permanent solution as a treatment for Androgenetic alopecia. We conclude and recommend that, based on our study, physicians must consider the treatment options with pharmacological products like Finasteride, Minoxidil and Dutasteride which have been analyzed and studied thoroughly and have positive outcomes . These drugs should be considered as the first line therapies for pattern hair loss.

One must consult and discuss options with patients thoroughly and then prescribed treatments based on the actual outcomes in conjunction with patient preference while taking into consideration doing schedules and cost.

4. Conflicts of Interest

None.

5. Source of Funding

None.

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