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Examination Project Work

Androgenetic alopecia and the effectiveness of the combinations of the available treatments and monotherapy with 5α-reductase inhibitors

Naser Awde
Pharmacy
Basic level
2FA01E
Supervisor: Ran Friedman

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Naser Awde

Examination project work in pharmacy
Degree of Bachelor of Science
Pharmacist program 180hp
Linnaeus university, Kalmar

Supervisor:
Ran Friedman
Professor
Department of Chemistry and Biomedical sciences
Linnaeus University
SE-391 82 Kalmar

Examiner:
Marlene Norrby
Department of Chemistry and Biomedical sciences
Linnaeus University
SE-391 82 Kalmar

Abstract

Androgenetic alopecia, also known as male pattern baldness, affects the majority of men at some point during their life. This can significantly damage the mental health of the individuals suffering, especially at a young age. The pathophysiology is not fully understood, but according to the scientific literature, it is mediated by androgen signaling in the scalp. A lack of androgen signaling completely eliminates the possibility of developing the condition. This is the primary reason behind the effectiveness of 5α-reductase inhibitors, which effectively reduce androgen signaling by lowering dihydrotestosterone (DHT) concentrations by 98%. These medications are associated with adverse effects such as sexual dysfunction and anxiety. Use of topical forms of 5α-reductase inhibitors and minoxidil is therefore on the rise. The purpose of this work was to examine the effectiveness of the combinations of the available treatments and the most effective monotherapy option. The results indicate that dutasteride is the most effective option as monotherapy and that a combination of a 5α-reductase inhibitor and minoxidil is more effective than either on their own. It was also shown that microneedling is a valid adjuvant therapy to minoxidil.

Keywords: AGA, finasteride, dutasteride, minoxidil, microneedling, androgens

Sammanfattning

Bakgrund
Androgen alopeci, även kallat ärftligt håravfall, är ett tillstånd där individen tappar hår. Detta kan dramatiskt drabba den psykiska hälsan, speciellt om det sker i en tidig ålder. Enligt den vetenskapliga litteraturen utvecklas sjukdomen av androgen signalering i skalpen. DHT binder till androgena receptorer i hårfollikeln och detta leder gradvis till konversionen av terminalhår till vellushår. Hämmare av enzymet 5α-reduktas fungerar genom att sänka den androgena signaleringen. Användning av 5α-reduktashämmare leder till en sänkning av dihydrotestosteron (DHT) koncentrationer med upp till 98%. Behandling med dessa mediciner är kopplat till biverkningar som sexuell dysfunktion och ångest. På grund av risken för biverkningar har användning av topikala beredningsformer av 5α-reduktashämmare och minoxidil ökat.

Syfte: Syftet med detta arbete var att undersöka effektiviteten av kombinationerna av de tillgängliga behandlingarna, samt att undersöka vilket det mest effektiva alternativet är för monoterapi.

Metod: Alla studier som användes i arbetet var hämtade från databasen pubmed. Ord som söktes efter var "androgenetic alopecia treatment", "finasteride and minoxidil", "microneedling" och "dutasteride", med filtrering efter meta analyser och randomiserade kliniska prövningar.

Resultat: Resultaten visade att dutasterid har med störst sannolikhet den bästa effektiviteten som monoterapi. Det visades också att en kombination av 5α-reduktashämmare och minoxidil är mer effektivt än monoterapi med någon av dessa kategorier. Det visade sig inte vara en stor skillnad i effektiviteten av topikal eller oral finasterid. Utöver detta visades det också att microneedling är en effektiv tilläggsbehandling till minoxidil.

Slutsats: Dutasterid är det mest effektiva alternativet för att stoppa utvecklingen av androgen alopeci. Kombinationsterapi med 5α-reduktashämmare och minoxidil är mer effektivt än monoterapi. Microneedling och minoxidil är mer effektivt än monoterapi med minoxidil. Den sammanlagda slutsatsen av dessa studier indikerar att dutasterid, minoxidil och microneedling tillsammans hade varit den mest effektiva behandlingen av AGA.

Abbreviations

HF - Hair Follicle

DHT - Dihydrotestosterone

DP - Dermal Papilla

Androgenetic Alopecia - AGA

DPCs - Dermal Papilla cells

AR - Androgen Receptor

BMPs - Bone morphogenetic proteins

FMX - Finasteride + minoxidil

MX - Minoxidil

RCT - Randomized Clinical Trial

TAHC - Target area hair count

TEA - Treatment emergent adverse effect

MD - Mean difference

NMA - Network meta-analysis

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1. Introduction

Androgenetic alopecia (AGA), also known as male pattern baldness and as female pattern baldness in women, occurs in roughly 70% of men. This type of hair loss is mediated by androgens and the loss of hair happens in a predictable pattern, hence the name. The advanced stage of this condition results in pigmented terminal hair being replaced by barely visible vellus hair. The pathophysiology of the condition has not been fully elucidated. However, as the name implies, androgens seem to play a vital role in the development of the condition (1). Despite the advances made in medicine and technology over the past decades, a cure for AGA is yet to be discovered. Hair transplant is one of the five most popular surgeries for men and it is the most frequent cosmetic surgery that men undergo. Currently there are only a few promising treatments for the condition. The treatments primarily work by slowing down the process, rather than completely stopping or reversing it (1).

1.1 Human hair growth and signaling pathways

Hair grows in most parts of the body with some exceptions being the bottom of the feet, lips, inside the mouth, the palms, behind the ears, the navel and scar tissue (2). The hair follicle (HF) is an organ that is made up of dermal papilla cells (DPCs) and epithelial cells. Hair growth is tightly regulated by different hormones, peptides and immune cells that will be discussed below (2). DPCs interact with epithelial cells through multiple mechanisms in order for the hair to be able to grow and for stem cells within the HF to activate (2). The mechanisms are beyond the purpose of this work, however, some signaling pathways critical for hair growth will be discussed. Humans have three types of hair: lanugo, vellus and terminal. Lanugo hair is very thin and unpigmented, it is often found on fetuses and it is the first type of hair that grows from hair follicles (3). Vellus hair is characterized by being short, thin, lightly pigmented and replaces lanugo hair during childhood (3). Terminal hair is thick and long and it is this type of hair that grows on the scalp, face, pubic area and under the arms (3). The conversion of vellus

hair to terminal hair in the pubic region, face and under the arms is driven by androgens, the same androgens that are responsible for the conversion of terminal hair back to vellus hair on the scalp (4).

Each individual hair strand grows at its own stage and once the full cycle is complete, the hair sheds and restarts the cycle (5). Scalp hair grows at a rate of roughly 1cm/month and this varies from different individuals based on genetics, age, ethnicity and other factors (5). Hair grows in a specific pattern and follows three stages: anagen, catagen and telogen (5).

The anagen phase, also known as the proliferation phase, is when the hair gets physically longer over time (6). During anagen, the DP contributes to the growth of hair follicles via activation of stem cells, interactions with epithelial cells, supply of oxygen and nutrition, resulting in growth of the follicles (6). This phase varies in length and usually lasts anywhere from three to seven years in people not affected by AGA and as one could imagine, the longer this phase lasts for a given hair follicle, the longer the hair grows. During this phase, not only does the hair shaft lengthen, but other parts of the hair follicle also undergo rapid proliferation (6). The hair shaft is also pigmented during this stage. It is shown that roughly 90% of the hair on the scalp is in this phase. The anagen phase is maintained by a number of growth factors such as insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) (6).

The anagen phase is followed by the catagen phase, also known as the transitional phase. This phase is characterized by the discontinuation of blood supply to the hair follicle, apoptosis in most of the follicular keratinocytes resulting in slower growth and eventually complete cessation of growth and production of pigment (6). This phase lasts for 10-14 days. This phase in the hair cycle occurs when the expression of the aforementioned growth factors decrease significantly and this transitions the hair from anagen to catagen. This is followed by an increased concentration of pro-apoptotic cytokines such as transforming growth factor beta (TGF-β), interleukin 1-alpha (IL-1α) and tumor necrosis factor-alpha (TNF-α) (6).

The telogen phase, also known as the shedding phase, is the last phase of the hair growth cycle and usually lasts for three months (6). The hair remains dormant on the hair follicle, melanin production has ceased and the hair is not growing due to the lack

of blood flow that was the result of the follicle entering the previous phase (6). After roughly three months, this hair sheds due to being pushed from the growth of a new anagen hair in that same hair follicle. It is during this phase, if the hair is pulled out, one will observe a white bulb at the root of the hair strand. Approximately 10% of the hair on the scalp is in this phase at all times. This number is higher in individuals suffering from AGA (6). The lengths of these different phases give an explanation as to why medications used to treat AGA take time to work and do not work immediately. Normal hair density for a male not suffering from AGA is 124-200 hairs/cm^2, depending on genetics and ethnicity. The hair is said to be noticeably thinning when this number reaches lower than 60 hairs/cm^2 (6).

The hair cycle is regulated by several signaling pathways and two very important signaling pathways implicated in hair growth and cessation of hair growth respectively are the Wnt/β-catenin pathway and the Bone morphogenetic protein (BMP)-signaling pathway (6). Figure 1 illustrates the downstream signaling that is a result from the binding of wnt ligand. Wnt proteins are glycoproteins that allow cells to communicate, regulate differentiation of cells and the growth of cells (6). BMPs are proteins belonging to the TGF-β-superfamily and are correlated with premature termination of anagen and entry into catagen (6). In order for bmp-proteins to have any effect, they have to bind to the bone morphogenetic receptor type 1a (BMPR1a-receptor). In gene expression studies, entry to anagen and activation of stem cells within the hair follicle has been correlated with increased activity of the Wnt/β-catenin pathway aswell as inhibition of bmp-proteins by antagonists of the BMPR1a receptor (6). It was also shown that mice lacking the gene coding for the BMPR1a receptor, experience significant activation of hair follicle stem cells as well as proliferation and premature entry of HFs into the anagen phase (7).

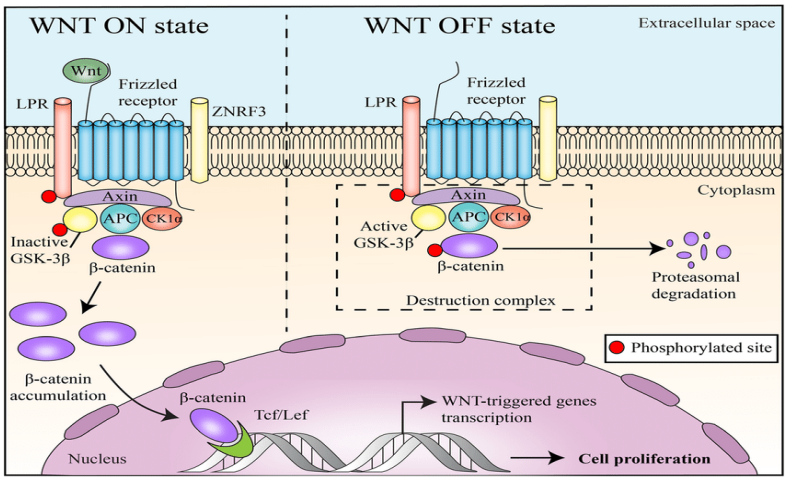

Figure 1: Representation the Wnt/β-catenin pathway. ai, S.G., Carneiro, B.A., Mota, J.M. *et al.* Wnt/beta-catenin pathway: modulating anticancer immune response. Figure from *J Hematol Oncol* 10, 101 (2017) (CC-license)

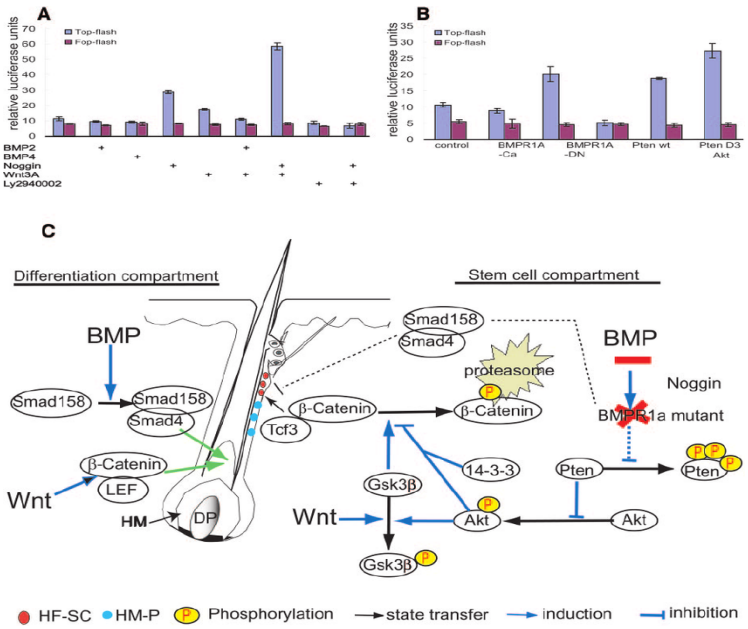

Figure 2: Representation of the BMP-signaling pathway. Jiwang Zhang et al. Bone morphogenetic protein signaling inhibits hair follicle anagen induction by restricting epithelial stem/progenitor cell activation and expansion. Figure from Stem Cells 24 (12) (2006). (CC-license)

1.2 Androgens and the pathophysiology of androgenetic alopecia on a molecular level

Androgenetic alopecia is characterized by the continuous miniaturization of the hair follicles caused by disturbances in the dynamics of the hair cycle (8). This disruption results in shortened duration of the anagen phase with each successive hair cycle and eventually the hair is transformed from a pigmented terminal hair into a vellus hair (8). The catagen phase has been shown to occur due to a decrease in the expression of the anagen maintaining growth factors IGF-1 and VEGF and simultaneously an increase in the expression of the pro-apoptotic cytokines TGF-β, IL-1α and TNF-α (2,6,7). The binding of androgens to the AR located in the DP seems to mediate the premature termination of anagen and entry into catagen (7).

Androgens are steroid hormones that maintain and regulate male sexual characteristics, including development in the embryo (8). This is a result of downstream signaling accomplished by the binding of androgens to the AR. The major androgen in men is testosterone, which gets converted to the more potent dihydrotestosterone (DHT) by the enzyme 5α-re

ductase. DHT is involved in the pathogenesis of many disorders, including AGA as it has a higher affinity for the AR and binds with a 2-10 time greater potency than that of testosterone (8).

The AR plays a critical role in the progression of AGA (1,6,9,10). This was evidently shown when observing individuals suffering from androgen insensitivity syndrome (9). The condition is characterized by a dysfunctional AR, resulting in complete resistance to the effects of androgens (9). Individuals suffering from this condition exhibit no signs of any form of hair loss on the scalp during any period of their life (9). This highlights how vital the effects of androgens are to the progression of AGA. The AR is a nuclear receptor and thus after the binding of an androgen, the receptor-androgen complex translocates into the nucleus and starts the downstream signaling cascades that result in expression of genes that downregulate the activity of the wnt/B-catenin pathway. (9,6). It has also been found that individuals suffering from AGA have a higher expression of the AR on the scalp (10). How sensitive the hair follicle is to androgens seems to be determined purely by the AR and its polymorphism (11). All of these findings clearly demonstrate that the AR and its prevalence on the scalp and polymorphism is the main predictor of AGA (11).

Every single healthy male and female produces androgens, males produce larger amounts. How these are produced is not relevant and is beyond the scope of this paper, however, there are some important differences between the two genders. Both genders have enzymes called 5α-reductases and these enzymes are the target of two of the most successful drugs used to combat AGA (13). The main function of 5α -reductase is to convert testosterone to the more potent DHT (12). There are three isoforms of the enzyme and isoform two is the isoform that catalyzes the conversion of testosterone to DHT to the most significant extent. The function of DHT in the body is to promote prostate growth, body and facial hair growth and sebaceous gland activity amongst other things (13). An unwanted effect in males and females is that DHT also binds to hair follicles in sensitive individuals and causes the subsequent miniaturization of the follicles until the thick terminal hair is transformed into a barely visible vellus hair (11,9,7,1). Females do not produce testosterone in large amounts and therefore the levels of DHT in their body is significantly lower than that of males, however, this condition is also very common in women, especially in the later parts of life. The signaling cascade starts when DHT and potentially other androgens bind to the androgen receptor located on the dermal papilla. (11,9,7,1).

As mentioned above, the development of AGA is linked to the androgen receptor gene (11). This gene has numerous polymorphisms, but no specific gene has been identified as highly correlated with AGA (11). The different polymorphs of the gene dictate the sensitivity of hair follicles to androgens which is crucial for the pathogenesis of AGA (11). The lower the sensitivity, the less DHT and potentially other androgens can bind to the AR and start the downstream signaling that ultimately results in miniaturization of the hair follicle (11). The X chromosome seems to be most critical in inheriting the gene, meaning that most people inherit AGA from their mothers. The role that the Y-chromosome plays has not been studied (11). In addition to this, a large study done in the UK showed that variations in autosomal chromosomes are very highly correlated with different severities of AGA. The study also showed that variations in autosomal chromosomes have been linked to late or early onset of the condition (12).

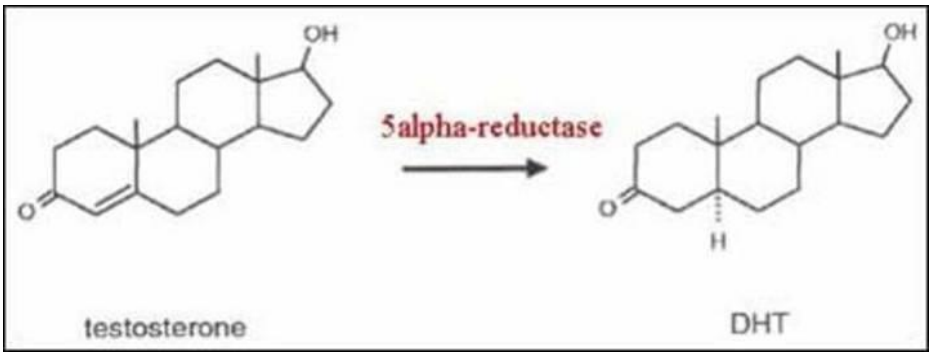

Figure 2: Conversion of testosterone to DHT. Figure from Perera, Marlon. (2016). Benign Prostate Disorders. (cc license)

1.3 Drugs and methods used in the treatment of hair loss

There are numerous drugs that are used to treat hair loss, both over the counter and prescription drugs. The most widely used medicines developed to this day are inhibitors of the enzyme 5α-reductase. Finasteride and dutasteride are the only 5α-reductase inhibitors on the market for hair loss, however, dutasteride can only be used for this indication in Japan since it is yet to be approved by the Food And Drug administration or European Medicines Agency for the treatment of AGA. Despite this, it is often prescribed in the US as "off label" for hair loss. This is likely due to the more favorable effects in treating the condition over finasteride. Finasteride inhibits two isoforms of the enzyme and thereby effectively reducing serum DHT concentrations by roughly 70% (14,15). Dutasteride competitively inhibits all three isoforms of the enzyme and reduces DHT concentrations by upwards of 95-98% (15). Predictably, lowering the concentrations of the chief male sex hormone does not come without side effects in some people. The main issue with using these drugs in the long term are the adverse effects that might follow. The adverse effects are rare, but they include decreased libido, erectile dysfunction, gynecomastia and ejaculation disorders such as watery semen (16). Recently, the use of topical solutions of finasteride has been on the rise. This approach is used to minimize the systemic exposure to the drug, in an attempt to decrease the risk

of experiencing any of the adverse effects that were just discussed. Treatment with these medications is referred to as “blocker therapy” and they are used mostly for their potential to stop the further miniaturization of the hair follicles, rather than stimulate new hair growth. Despite this, new hair growth is often observed when using these drugs. This can be explained by less DHT binding to the hair follicle, resulting in increased amounts of growth factors and less inflammation (1,4,7,9). Oral finasteride is prescribed in 1 mg doses to treat hair loss, the topical form comes in 0.1-0.3% formulations. Dutasteride is primarily used at 0.5 mg doses to treat benign prostatic hyperplasia, but increased off label use for AGA the past decade has been observed (16).

The absorption of finasteride is not influenced by food, and it has a mean oral bioavailability of 65%. Mean peak concentrations are reached within 2 hours of administration and it is metabolized by CYP3A, followed by aldehyde dehydrogenase. The metabolites are not very chemically active. The absorption of dutasteride is not influenced by food and mean plasma levels are reached within 3 hours of administration. The drug is metabolized primarily by CYP3A4 and one of the metabolites has a similar activity level to dutasteride.
Synthesis of neurosteroids is mediated by 5α-reductase, which insinuates that these drugs also inhibit formation of neurosteroids. A low concentration of neurosteroids is implicated in sexual dysfunction, depression and anxiety. Inhibition of neurosteroidogenesis is one of the mechanisms behind the adverse effects of 5α-reductase inhibitors.

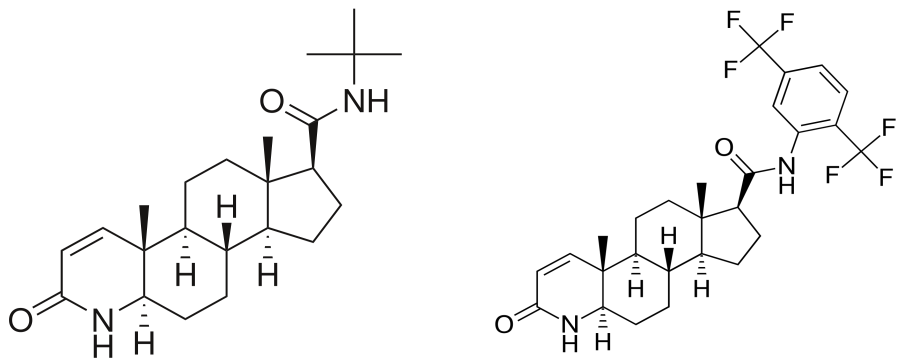

Figure 3: Structure of finasteride (left) and dutasteride (right). Cc license: wikipedia

Speaking of new hair growth, minoxidil is an antihypertensive vasodilator initially used to treat ulcers, this failed and the drug was discovered to be a potent vasodilator (16). When studies were being conducted on the substance, researchers noted unexpected hair growth and the idea that minoxidil could be used for hair loss came to fruition (17). More studies were conducted and minoxidil was approved for the treatment of hair loss on February 12, 1996. The mechanism of action is not fully elucidated, however, the drug acts on K^+-channels. This causes hyperpolarization of cell membranes and therefore widens blood vessels, resulting in increased blood flow everywhere in the body, including hair follicles (17). There is one aspect to this drug that is often overlooked and that is that minoxidil is a prodrug and gets converted to its active form, minoxidil sulfate, by sulfotransferase enzymes located in the outer root sheath of hair follicles. The activity of these enzymes vary in individuals and some respond better to the drug due to having highly active sulfotransferases, meanwhile others are non-responders due to low sulfotransferase activity (17). This was investigated in a study where male participants with AGA responded better to minoxidil when given with a sulfotransferase enzyme booster (18). Treatment with minoxidil is referred to as "stimulation therapy" as this does not address the underlying cause of the condition, which is androgens. Oral minoxidil is extensively metabolized in the liver and the metabolites have a much lower effect than minoxidil itself. It has a half life of around four hours (16).

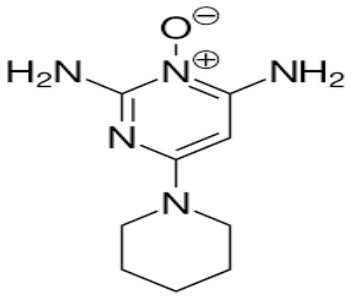

Figure 4: Structure of minoxidil (wikimedia commons cc license)

Another practice used to treat hair loss that has been on the rise recently is microneedling. This is not a drug, it is a cosmetic procedure where the skin is punctured with sterilized needles in order to trigger the wound-healing cascade (19). When it comes to AGA, this is seen as an adjunct therapy to be used in combination with the other drugs discussed, especially minoxidil (19). After microneedling, the affected areas release platelet derived growth factors and VEGF (19). This results in improved vascularization of the area, which is very important in order for the hair to grow in a suboptimal environment where levels of VEGF and other growth factors are low (19). This method also seems to upregulate the activity of the Wnt/β-catenin pathway (19).

1.4 The Hamilton Norwood scale

The Hamilton Norwood scale is a scale developed in 1951 by James Hamilton. The scale was further improved upon by O'tar Norwood in 1975. This scale is used to classify the different stages of AGA and assesses how advanced an individual's hair loss is on a scale of 1-7 (19). This is very useful in a practical sense because it allows practitioners to choose whether the patient would benefit more from treatment with medicine or possibly a hair transplant in combination with stabilizer treatments such as finasteride or dutasteride. Stage I is classified as no hairline recession by some, and by some only slight recession. This depends on the individual, some ethnic groups, particularly middle eastern men are often born with hair very low on their forehead (21). It is in stage II where real noticeable signs of AGA start to manifest. There will often be symmetrical recession of the hairline along with the temples (21). Stage III can be divided into III and IIIv. Stage III is just an advanced form of the previous stage, however, stage IIIv means that the hairs on the crown are also being fewer (19). It is worth mentioning that it is at this level of hair loss that a hair transplant is usually recommended. The reasoning behind this is that practitioners need to identify the pattern of hair loss since this is different for every individual and at stage III or IIIv, the pattern has become apparent. The rest of the stages are just advancements of their predecessors and at stage VII, the individual no longer has visible hair on the top of his head (21).

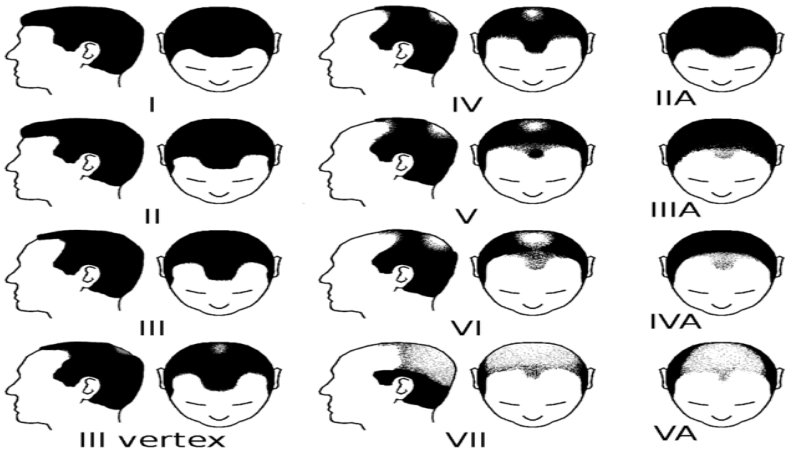

Figure 5: Representation of AGA with the Norwood scale. (CC license: wikipedia)

1.5 Network meta-analysis

A network meta-analysis is a way of analyzing multiple treatment options at once, a more complicated version of a standard meta-analysis (19). This type of study is presented below and requires explanation. It works by putting together direct and indirect evidence. Direct evidence is evidence that is gathered from RCTs, for example, a trial comparing drug A and drug B, direct evidence would be the effect of A compared to the effect of B. If A and B had never been compared, but A had been compared to C and B had also been compared to C, A and B can be indirectly compared (19). This is referred to as indirect evidence. For a network meta-analysis to be accurate, transitivity has to be there, this means that there should exist no differences between the comparisons, only the treatment (19).

2. Purpose

The purpose of this work is to identify the most effective combinations of the available treatment options for androgenetic alopecia, aswell as monotherapy with 5a-reductase inhibitors. This is based on the knowledge of the current scientific literature (May 2022).

3. Materials and methods

A literature search was done to collect information on the most effective combinations of the available treatments for androgenetic alopecia, as well as monotherapy with 5a-reductase inhibitors. Words used were “androgenetic alopecia treatment”, “finasteride and minoxidil”, “microneedling” and “dutasteride”, only searching for meta analysis and RCTs. The PubMed search for androgenetic alopecia treatment yielded a total of 1121 results. Studies were chosen if they studied the outcome of combination therapy with any 5α-reductase inhibitor and minoxidil and minoxidil in conjunction with microneedling. 19 articles were left remaining. Five studies were chosen, four controlled trials and one meta analysis. Studies were excluded if they focused primarily on side effects or female pattern hair loss. The literature obtained was from PubMed and there were no limitations based on when these studies were conducted. The participants in the studies were at least ranked as stage I or above on the Norwood scale and were in fact diagnosed with AGA.

3.1 First study: Placebo‐controlled dose‐effect studies with topical minoxidil 2% or 5% in male‐patterned hair loss treated with oral finasteride employing an analytical and exhaustive study protocol

Purpose: The purpose of this trial was to evaluate the effects of 2% topical minoxidil versus 5% topical minoxidil versus placebo in patients already being treated with oral finasteride.

Background: Oral finasteride has an overwhelming amount of evidence supporting the effectiveness it has in treating AGA, however, finasteride is used mostly to stop the progression of the disease. Minoxidil itself does not address the root cause of the problem, it only stimulates hair to grow. This study assesses the effectiveness and synergy of combining the two FDA approved medications finasteride and minoxidil.

This was a study that used male subjects (n=22) that were suffering from AGA. Exclusion criteria included any abnormalities in the initial screenings, having had a hair transplant, any history of other hair loss treatments during the last 6 months. 8 of the 22 participants were disqualified from entering phase Ia. There were also 33 healthy male controls, these participants used no drugs to treat hair loss and only served to show hair parameters in people not suffering from AGA, using the same imaging as the imaging used for 14 males suffering from AGA (21).

Materials and methods:

This was a placebo-controlled trial and in phase Ia, participants during the first 3 months of oral finasteride usage were given either a 5% minoxidil lotion to apply topically or 5% of a control lotion (placebo). Phase IIa was initiated 3 months after giving the lotions and during this phase, both of the lotions were discontinued, but the participants were still on oral finasteride. Phase IIIa was initiated 3 months after the discontinuation of the topicals, where the participants only received oral finasteride for 6 months before entering phase B. In phases I, II and IIIa, before entering phase B: Participants were on oral finasteride for 12 months and either on minoxidil 5% for 3 months along with finasteride or placebo for 3 months along with finasteride (21).

Phase Ib was the next phase and 12 months into the study. 14 participants randomly received either 2% minoxidil or 5% minoxidil for 3 months. The participants were investigated using images every month during phase Ib. Oral finasteride was still being used and has been throughout the study. After 3 months, the participants stopped receiving any topical minoxidil. This was 15 months into the study and marked the end of phase Ib.

During phase IIb which took place between months 16-18 of the trial, subjects were monitored monthly without receiving any topical minoxidil, but oral finasteride was still maintained. This was done in order to evaluate how oral finasteride alone compares to oral finasteride + 2% or 5% minoxidil.

Hair counts and measurements

Hair growth was studied by following hairs on different widths, hairs with a diameter of <20μm were not considered. Any hair with a diameter of <30μm was considered a vellus hair. Any hair with a diameter of 40-60μm was considered an intermediate hair.

Any hair with a diameter of >60μm was considered a terminal hair. The validity of these hair measurements were repeatedly checked using calibrated images. The technicians responsible for the validity control were blinded in regards to treatment, patient and time of study. Exogen hairs were examined under a microscope at x40 magnification and the measurement used was units/cm^2 (20).

Results:

The study began with 22 male subjects, however, only 14 entered phase A and were able to complete the study. Hair parameters in healthy controls vs participants suffering from AGA does support the claim made in the introduction where it was stated that individuals suffering from AGA have less hairs in the anagen phase and more hairs in the telogen phase on average. See table 1.

The addition of 5% topical minoxidil to oral finasteride showed significant increases in anagen hair counts and decreases in telogen hair counts in hair fibers of almost every thickness. The individuals only receiving oral finasteride and placebo did not experience any significant differences in telogen hairs or anagen hairs of any diameter, they did however not experience any progression of AGA. See table 2.

During phase IIa when the topical minoxidil was discontinued, patients experienced significant changes in hair parameters. Anagen hair counts of all diameters were lowered, combined with an increased amount of telogen hairs. Linear hair growth rate was not affected. Individuals receiving placebo did again not experience any significant differences in hair counts. See table 3.

It was also shown that 2% minoxidil appeared less efficient than 5% minoxidil. Anagen hair counts increased with both 2% and 5% minoxidil, however, the changes were greater with the 5% lotion. The difference between 5% and 2% minoxidil was not statistically significant (21). The tables below only show the results for 5% topical minoxidil versus placebo.

Table 1: Table showing hair parameters of healthy controls (n=33) and the participants suffering from androgenetic alopecia (n=22), as well as the P-values. It becomes clear that individuals suffering from AGA have fewer hairs of all diameters in the anagen phase and more hairs in the telogen and exogen phase. The linear hair growth rate (LHGR) also highlights that hair on average grows slower in people affected by AGA.

Hair stage and diameter	Controls (n=33)	AGA (n=22)	P
Nano hair <20µm	4	30	<0.0005
Anagen >20µm	227	101	<0.0005
Telogen >20µm	37	115	<0.0005
Anagen >30µm	221	84	<0.0005
Telogen >30µm	32	56	<0.0005
Anagen >40µm	206	67	<0.0005
Telogen >40µm	25	26	not significant
Anagen >50µm	189	57	<0.0005
Telogen >50µm	22	11	not significant
Exogen	1	10	<0.0005
LHGR 30-60µm /24h	319	260	<0.0005
LHGR >60µm /24h	380	340	not significant

Table 2: Table showing hair parameters during the last month of phase Ia, 3 months after application of either 5% topical minoxidil along with the base of oral finasteride, or placebo and the base of oral finasteride (n=14).

Hair stage and diameter	Topicals	Baseline	month 3	P
Nano hair <20µm	minox placebo	34.7 23.9	-8.4 +4	not significant
Anagen >20µm	minox placebo	128.8 96.7	+81.2 +5.5	<0.0005
Telogen >20µm	minox placebo	104.5 108.1	-33.2 -5.2	<0.05
Anagen >30µm	minox placebo	108.5 79.8	+68.5 +6.5	<0.005
Telogen >30µm	minox placebo	67.4 41.7	-14.4 +2.4	>0.05
Anagen >40µm	minox placebo	82.4 69.2	+57.7 +1.9	<0.005
Telogen >40µm	minox placebo	34.8 20.4	-5 +4.5	<0.05
Anagen >50µm	minox placebo	68 60.8	+44.2 +1.5	<0.005
Telogen >50µm	minox placebo	21.3 12.8	-5 +4	<0.05
Exogen	minox placebo	10.143 11.53	-0.29 +2.19	not significant
LHGR 30-60µm/ 24h	minox placebo	256.2 267.5	+19.1 +7.6	not significant
LHGR >60µm /24h	minox placebo	369 351.7	-64.5 +14.1	not significant

Table 3: Table showing variations after phase IIa, in this phase participants were not given any topicals.

Hair stage and diameter	Topicals	change from m6 to m0	P	change from m3 to m6	P
Nano hair <20µm	minox placebo	-18.6 +2	<0.05	-10.1 -1.9	not significant
Anagen >20µm	minox placebo	-29.6 -4	>0.05	-110.8 -9.5	<0.0005
Telogen >20µm	minox placebo	+47.7 +7.4	<0.05	+80.9 +2.7	<0.0005
Anagen >30µm	minox placebo	-22.5 -3.8	>0.05	-91 -10.2	<0.0005
Telogen >30µm	minox placebo	+53.1 +9.9	<0.05	+67.5 +7.5	<0.05
Anagen >40µm	minox placebo	-12.6 -2.3	>0.05	-70.3 -4.3	<0.0005
Telogen >40µm	minox placebo	+40.9 +4.4	<0.05	+45.8 0	<0.005
Anagen >50µm	minox placebo	-8.7 -1.9	>0.05	-52.8 -3.4	<0.005
Telogen >50µm	minox placebo	+26.6 +1.4	>0.05	+31.6 -2.6	<0.005
Exogen	minox placebo	+2.29 +1.72	>0.05	+2.57 -0.47	>0.05
LHGR 30-60µm /24h	minox placebo	+2.2 -34.9	>0.05	-16.9 -42.5	>0.05
LHGR >60µm /24h	minox placebo	-50.9 -33.9	>0.05	+13.5 -48.1	>0.05

3.2 Second study: Randomized trial of electrodynamic microneedle combined with 5% minoxidil topical solution for the treatment of Chinese male Androgenetic alopecia

Purpose: The purpose of this study was to investigate the effectiveness of monotherapy with 5% minoxidil, monotherapy with microneedling and a combination of microneedling with 5% minoxidil, with a hypothesis that microneedling increases the absorption of minoxidil and therefore hair growth (22).

Materials and methods: This was a 24 week randomized and blinded study where group 1 (n=18) received topical 5% minoxidil, group 2 (n=18) received only microneedling and group 3 (n=20) received topical 5% minoxidil and also underwent microneedling once every 2 weeks. 2ml 5% minoxidil was given with every microneedling session in the group receiving both minoxidil and undergoing microneedling. The males treated were all classified as being Norwood scale III-IV.

Table 4: Table presenting baseline hair counts/cm^2 for the different groups

Groups →	Group 1	Group 2	Group 3
Total hair count/cm^2	152.5 ±17.1	151.6±23.2	151.3±16.6

Results: After 24 weeks, the group receiving only minoxidil showed the least improvements with an increase of 18.8 hairs/cm^2. The group who only microneedled surprisingly grew more hair after 24 weeks than the minoxidil group, improving by 23.4 hairs/cm^2. The last group that received 5% minoxidil while simultaneously microneedling improved the most. This improvement was more than double that of the minoxidil only group, with an increased hair count of 38.3/cm^2. The results were statistically significant across the board ($P<0.001$). See table 5.

In addition to improvements in hair density, there were also improvements in hair thickness in non vellus hairs, however, the improvement from microneedling alone was not statistically significant. Minoxidil and microneedling together showed the biggest improvement, followed by monotherapy with minoxidil and microneedling. See table 5.

Table 5: Table representing changes in hair density and hair thickness 24 weeks after treatment

Hair count/cm^2	5% minox (n=18)	microneedling (n=18)	5% minox + microneedling (n=20)	P
Non vellus hair count	24.1 ± 7.8	20.5 ±7.3	34.7 ± 13.2	<0.001
Vellus hair count	-5.4 ±3.8	3.4 ± 3.5	4.2 ± 2.1	<0.001
Total hair count	18.8 ± 9.6	23.4 ± 5.1	38.3 ± 11.1	<0.001
Change in non-vellus hair thickness (µm)	10.7 ± 5.5 P<0.001	3.2 ± 6.2 P=0.09	11.8 ± 3.7 P<0.001	

3.3 Third study: A randomized, double-blind controlled study of the efficacy and safety of topical solution of 0.25% finasteride admixed with 3% minoxidil vs. 3% minoxidil solution in the treatment of male androgenetic alopecia

Purpose: The purpose of this trial was to investigate how effective and safe 3% topical minoxidil mixed with 0.25% topical finasteride is compared to monotherapy with 3% topical minoxidil.

Background: The reasoning behind topical use stems from the fact that oral finasteride is correlated with adverse effects and this refrains individuals from committing to the drug. Topical application is a way to reduce the risk of adverse effects due to less systemic exposure to the drug.

Materials and methods

In order to be eligible for the study, men had to be between ages 18-60 and be classified as stage IIIv, IV or V according to the Norwood- Hamilton scale. For this study, every participant was told to keep the same hair style, hair color and length. Exclusion criteria included use of finasteride or dutasteride within the last 18 months, use of other topicals such as minoxidil, RU58841 or breezula. Further exclusion criteria that could impact the results of the study were scalp diseases or allergies to any ingredient in the topical solutions. The primary endpoint of the study was change in hair diameter and hair density within a diameter of 1cm on the vertex of the head. This was assessed at week 8,16 and 24 with trichoscopy, photography and measuring.

This was a randomized, double blinded study with 40 initial participants, but only 37 completed it. The participants were instructed to apply the finasteride+minoxidil (FMX) solution (n=19) or the minoxidil (MX) solution (n=18) twice daily for 24 weeks.

Results:

After 8, 16 and 24 weeks, the group receiving a combination of 0.25% topical finasteride and 3% minoxidil showed a significant improvement in both hair density and hair diameter (P=0.03 and 0.04 respectively). See table 6 and 7. Demographics were similar for both groups and no one reported any sexual adverse effects.

Table 6: Table representing changes in hair density. FMX was significantly better than MX alone at increasing hair density after 16 and 24 weeks.

Timeline	Fin+minox hair/cm^2	minox hair/cm^2	P
week 8	27	19.11	>0.05
week 16	42.84	26.05	=0.02
week 24	61.84	34.88	=0.03

Table 7: Table representing changes in hair diameter (μm) from baseline to 24 weeks after treatment. FMX was significantly better than MX alone in increasing hair diameter after 24 weeks of treatment.

Timeline	Fin+minox hair diameter	Minox hair diameter	P
week 8	6	6	>0.05
week 16	11	9	>0.05
week 24	17	13	=0.034

3.4 Fourth study: Efficacy and safety of topical finasteride spray solution for male androgenetic alopecia: a phase III, randomized, controlled clinical trial

Purpose: The purpose of this study was to assess how effective and safe topical finasteride is and to compare potential benefits over oral finasteride.

Background: As shown repeatedly in the scientific litterature, oral usage of 5α-reductase inhibitors is associated with sexual adverse effects and this stops patients from wanting to use them, even though the risks of developing sexual side effects are

low. This study compares topical finasteride to oral finasteride and placebo in terms of systemic exposure, hair growth and adverse effects.

Materials and methods: This was a 24 week phase III multicentre, randomized, double blinded, double dummy, placebo-controlled study in men suffering from AGA. Participants were between the age of 18-40 and classified as stage IIIv, IV or V. Main exclusion criteria included use of anabolic androgenic steroids, drugs with hair loss as a side effect, antiandrogens within the last 6 months or any scalp conditions. The ITT population (n=250) was established as all patients with acceptable measurements for the primary efficacy endpoint, the per-protocol population was established as all patients in the ITT population that completed the study without any considerable violations. The safety population (n=446) was defined as any randomized patient who received one dose of the study drug. The topical finasteride used was 0.25% formulation, applied with a plastic cone sprayer to prevent the substance from dispersing into the air. One spray corresponded to 0.114mg of finasteride and the participants were instructed to spray 1 to 4 times daily, depending on their degree of hair loss. The oral dosage of finasteride was 1mg/day. The placebo was a pill that looked identical to the finasteride pill, filled with chemically inactive powder. The area of application was the vertex of the head. The primary efficacy endpoint was change in target area hair count (TAHC) on the vertex, measured in hairs/cm^2. Secondary efficacy endpoints that were relevant to this work included changes in hair width. There was also a safety assessment regarding adverse effects done on the safety population.

Table 8: Table representing baseline TAHC for the different groups

Oral fin (n=48)	Topical fin (n=105)	Placebo (n=97)
201.9 ± 72.6	201 ± 67.6	204 ± 67.2

Results: After 24 weeks, topical finasteride induced a much greater improvement in TAHC than placebo ($P<0.001$). The difference between topical and oral finasteride was not statistically significant. The improvement in TAHC started becoming statistically significant over placebo at week 12. See table 9. Hair width decreased slightly in all

groups except for oral finasteride, where it slightly increased. None of these results were deemed statistically significant. See table 10. Plasma serum DHT concentrations decreased by 34% in the topical finasteride group, 0% in the placebo group and 55.6% in the oral finasteride group.

As for the safety population, in the group receiving topical finasteride, 41.4% reported developing TEAEs, followed by 42% in the placebo group and 48% in the oral finasteride group. The group receiving oral finasteride developed the most sexual adverse effects at 4.8%, followed by 3.3% in the placebo group and 2.8% in the topical finasteride group.

Table 9: Table representing changes in TAHC on the vertex of the head, 24 weeks after treatment.

Timeline	Oral fin (n=48)	Topical fin (n=105)	Placebo (n=97)
week 12	22.5	20.4 (P<0.001)	7.6
week 24	21.1	20.2 (P<0.001)	6.7

Table 10: Table representing change in hair thickness (μm)

Week 24	Oral fin (n=48)	Topical fin (n=105)	Placebo (n=97)
	0.72	-0.81	-1.51

3.5 Fifth study: Relative Efficacy of Minoxidil and the 5-α Reductase Inhibitors in Androgenetic Alopecia Treatment of Male Patients

Purpose: The purpose of this network meta analysis was to investigate the relative effectiveness of monotherapy with oral and topical minoxidil, finasteride and dutasteride.

Background: The effectiveness of the three most commonly used medications for AGA has been well established, however, there are still questions regarding the effectiveness of different dosage forms and dosages of these drugs. This study investigated the relative efficacy of orally or topically administered minoxidil, finasteride and dutasteride.

Materials and methods: This study did not involve any interaction with humans, therefore it did not require any approval. There were four outcomes of interest, namely change in total and terminal hair counts, 24 and 48 weeks after treatment. A study was accepted if it explored the clinical outcomes of therapy with monotherapy of minoxidil, dutasteride or finasteride. Dose and dosage form was not a restriction, data used was both from randomized studies and observational studies. Pubmed was searched on March 5, 2021 and after extensive screening and reviewing, 23 studies were eligible for analysis. Each study that was analyzed was also assessed for risk of bias. This included blinding, randomization and other factors. For each endpoint, a surface under the cumulative ranking curve (SUCRA) was created. SUCRA is a numeric presentation of the overall ranking of a drug and is represented by a percentage from 0-100. The closer to 100, the higher the chance that the intervention is the most efficacious. The results of this study was achieved by an extensive combination of indirect and direct evidence. A total of 4 NMAs were created for each outcome. For each NMA, the sucra value of the different drugs were calculated

Results: The results of this study indicate that 0.5mg dutasteride has the highest possibility of being the most effective treatment, followed by 5mg/day finasteride, 5mg/day oral minoxidil, 1mg oral finasteride, 5% topical minoxidil and 2% topical minoxidil. This ranking scale was put together after taking into consideration the sucra values of every intervention in every NMA in this study.

For the first end point, it was found that 0.5mg/day dutasteride produced the highest increase in total hair count after 24 weeks. The second endpoint was the increase in

terminal hair counts after 24 weeks. In regards to this, the highest increase was with 5mg/day of oral minoxidil, which was found to be significantly superior to all interventions compared. The third endpoint was the increase in terminal hair counts after 48 weeks. In regards to this, the highest increase was with 5mg/day of finasteride. The fourth endpoint was the increase in total hair counts after 48 weeks. In regards to this, the highest increase was with 1mg/day of finasteride. See table 10. Sucra values for each intervention are presented in table 11.

Table 10: Table representing the mean change in hair counts versus placebo for all different interventions. This table presents the results gathered from every possible pairwise comparison across 23 different trials. Light green indicates P<0.01, dark green indicates P<0.05. Yellow indicates P>0.05. Evidence quality for these comparisons ranged from very low to high.

Endpoint →	1	2	3	4
0.5mg/d dut	18.7			
5mg/d fin	16.4		21.5	
topical min 5%	15.3	10.7		14.6
0.1mg/d dut	12.5			
1mg/d fin	11.6	30.0	16.4	40.7
0.2mg/d fin	11.1			
1% topical fin	10.8	29.2		
2% topical min	10.2	11.3	0.9	8.7
1% topical min	9.0	6.4		
0.02mg/d dut	4.3			
5mg/d oral min	3.7	40.5		
3% topical min	4.0		-2.6	20.2
placebo	5.3	8.3	-4.1	4.0
0.1% topical min	-2.5	1.2		
0.25mg/d min	-4.9	-3.2		

Table 11: Table representing SUCRA values for all 15 interventions. Some drugs were not able to be compared in all endpoints due to lack of available data. The highest ranked treatment, dutasteride, only had data available for 1 endpoint.

Endpoint →	1	2	3	4
0.5mg/d dut	95.7			
5mg/d fin	87.8		98.3	
topical min 5%	80.4	54.6		55.2
0.1mg/d dut	73.1			
1mg/d fin	65.2	84.4	76.7	99.9
0.2mg/d fin	61.9			
1% topical fin	59.1	78.2		
2% topical min	55.3	56.6	34.6	26.6
1% topical min	51.4	36.1		
0.02mg/d dut	29.7			
5mg/d oral min	29.6	99.9		
3% topical min	28.6		13.3	68.2
placebo	13.5	12.3	27.1	0.2
0.1% topical min	10.5	18.0		
0.25mg/d min	8.4	9.8		

4. Discussion

Hair transplants are on the rise and there are currently a large number of methods and drugs used to treat AGA, some of them with great success such as the ones discussed in this work. The most widely used drug is minoxidil, the attractiveness of the drug mainly stems from the fact that it is not associated with sexual adverse effects, unlike the other succesful FDA approved medication. The problem with minoxidil is that it does not address the root cause of the problem, which clearly is androgens (1,4,7,8,9,10,11,12). Inhibitors of 5α-reductase address this issue by reducing the amount of DHT and

therefore decreasing the androgen load in the body, resulting in a slower progression of AGA (1,4,7,9).

Two of the five studies analyzed in this work investigated the synergy between finasteride and minoxidil (22,24). Study two investigated an approach without decreasing the androgen load, where patients only microneedled and used minoxidil (22). Study four investigated the efficacy of monotherapy with topical or oral finasteride (24). Study five is a meta analysis that investigated the relative efficacy of monotherapy with finasteride, dutasteride, oral minoxidil and topical minoxidil (26). The only study with conflict of interest was study four (24). The findings of these studies indicated that a combination of minoxidil and finasteride is significantly better than monotherapy with either finasteride or minoxidil at stimulating hair growth and halting the progression of AGA. The results also showed that microneedling is a valid adjuvant therapy to minoxidil (23).

In the case of study 1, it becomes apparent from table 2 that a combination of minoxidil and finasteride is significantly stronger than finasteride alone at increasing anagen hairs and decreasing telogen hairs across hair fibers of all diameters. This indicates that a combination of finasteride and minoxidil is more beneficial for hair growth than monotherapy with finasteride. To further support these results, table 3 shows what happened 3 months after the discontinuation of minoxidil. Three months following the withdrawal of minoxidil, anagen hair counts across all hair diameters were hemorrhaged along with a simultaneous significant increase in telogen hairs. The placebo group did not once during the time of this study experience any significant changes. This indicates that finasteride alone can not maintain the benefits of minoxidil (20). Looking at the oral finasteride + placebo group in table 2, there are no significant changes in anagen or telogen hairs, indicating a halt in the progression of AGA by finasteride alone. There were some limitations to this study, the main one being the low study population. Another limitation in this and the majority of studies involving minoxidil is that the researchers do not check the sulfotransferase enzyme activity of the participants. Some individuals are poor responders or non-responders due to low sulfotransferase enzyme activity in the scalp (16,17).

Study 2 investigated the effects of an approach unrelated to androgens. This kind of approach is attractive for individuals seeking to treat their hair loss without

manipulation of their hormone profiles, which ultimately results in no sexual adverse effects. The results of the study showed that minoxidil plus microneedling had more than double the efficacy of minoxidil alone in stimulating hair growth, see table 4. A major limitation of this study is the small sample size. Another limitation is the length of it. Finasteride has overwhelming evidence supporting its efficacy in the long term, however, that is lacking for minoxidil and microneedling (25,26). The only conclusions that can be drawn from this study is the short term efficacy. The issue that arises from only using stimulation therapy such as minoxidil and no blocker therapy such as 5α-reductase inhibitors, is that DHT is still able to bind to sensitive hair follicles in large amounts and the root cause of AGA, the androgens, are not being dealt with. More studies with a longer duration are required to draw further conclusions about the long term efficacy of minoxidil and microneedling.

The third study was also inspired by the fact that individuals suffering from AGA are hesitant to use oral finasteride. This study compared the effectiveness of 0.25% topical finasteride mixed with 3% topical minoxidil versus monotherapy with 3% topical minoxidil. The results showed that the combination of topical finasteride and minoxidil induced a significantly superior improvement than minoxidil alone in regards to both hair diameter and hair width. See table 6 and 7. No sexual adverse effects were reported in any group. The results of this study should be viewed as very positive for individuals looking to use finasteride, but with a lower risk of adverse effects. This study had no conflict of interest, but a low study population. Based on the results of study one and three, it seems that both oral finasteride and topical finasteride are effective, but is there any difference regarding effectiveness?

This perfectly transitions into study four where the researchers compared the efficacy and safety of topical finasteride compared to placebo and to oral finasteride. This was a phase III study where both topical and oral finasteride proved to be significantly better than placebo in regards to stimulating hair growth on the vertex of the scalp at both 12 and 24 weeks. See table 8. What is worth mentioning in this study is that the dosage use of oral finasteride was 1mg/day and the dosage used of topical finasteride was roughly 0.114-0.5mg/day. This was a huge limitation in the study and did not allow for a fair comparison between the two dosage forms. Despite this, the difference between oral and topical finasteride was minimal and not deemed statistically significant in any primary

or secondary efficacy endpoint (23). The only significant difference between oral and topical finasteride was the change in plasma DHT concentrations where it had decreased by 34.6% in the topical finasteride group and 55.6% in the oral finasteride group. Regarding adverse effects, the difference between the groups was not deemed statistically significant, however, two patients in the oral finasteride group dropped out of the study due to sexual adverse effects. Zero patients dropped out due to this reason in the topical finasteride, and surprisingly, one patient dropped out due to sexual adverse effects in the placebo group. This was most likely a nocebo effect. Study four had the most limitations out of all the studies used, the main ones being a non-equal dose of finasteride and high conflict of interest. Almost all of the authors were employed at pharmaceutical companies at the time the study was conducted.

In study 5, the evidence quality for the comparisons ranged from very low to high. With this in mind and the fact that the results from the study are probabilities due to the nature of NMAs, more and longer studies are needed to draw better conclusions. Despite this, the results found do make sense from a theoretical standpoint.

It was found that dutasteride is more effective than 1mg/day of finasteride, but statistically similar and only slightly more effective than 5mg/day of finasteride after 24 weeks. The increased efficacy can be explained by the additional decrease in androgen load that is provided by dutasteride. There are also other studies showing similar results. As mentioned in section 1.3, dutasteride reduces DHT by up to 98% due to inhibition of all isozymes of 5a-reductase. There was no evidence available regarding the efficacy of any dosage form of dutasteride after 48 weeks. It was also found that dutasteride is significantly superior to 5mg/d oral minoxidil, however this result is misleading. Looking at table 9, 5mg/d oral minoxidil and dutasteride were only compared in regards to increase in total hair count after 24 weeks, where oral minoxidil performed surprisingly bad. The evidence of quality for comparisons for these interventions was very low. In addition to this, 0.25mg/d minoxidil did not differ significantly from 5mg/d minoxidil in regards to the first endpoint, however, in the second endpoint, the biggest difference in interventions is between 0.25 and 5mg min/d and the difference is very big. This goes to show that this study and this approach has limitations.

Minoxidil is FDA approved in the 2% and 5% topical solution for the treatment of AGA, however, oral minoxidil prescriptions off label for the condition are on the rise. The results of this study found that 5mg/day oral minoxidil is more effective than both 5% and 2% topical minoxidil. Oral minoxidil has never been directly compared to any intervention before, so this conclusion has been drawn purely by analyzing indirect evidence. From a practical sense it makes sense when it comes to adherence. It is easier to swallow a pill once daily than to topically apply a greasy solution to the scalp.

5. Conclusions

Based on the scientific literature and the controlled trials, the evidence does point toward a combination of minoxidil and finasteride being more effective than monotherapy. Minoxidil in conjunction with microneedling does seem to produce more favorable effects than minoxidil alone. In regards to monotherapy, dutasteride is a better option than finasteride. Grounded on the results of the studies used in this work and the scientific literature, hypothetically, a combination of dutasteride, 5mg/d oral minoxidil and microneedling would be the most effective treatment.. This approach covers both pathways of AGA by stopping the miniaturization of hair follicles by reducing the androgen load in the body, as well as increasing blood flow to the hair follicles.

As mentioned in the introduction, the normal hair density for a male not suffering from AGA is 124-200 hairs/cm^2. This illustrates that these treatments are not sufficient enough to recover all of the lost hair.

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Linnaeus University
Sweden

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