SAFETY AND EFFICACY OF DUTASTERIDE FOR MALE ANDROGENETIC ALOPECIA

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Safety and Efficacy of Dutasteride for Male Androgenetic Alopecia" submitted by Student - S.M. Zahidul Islam (18346042) of Summer 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of pharmacy on November, 2022.

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Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

Background: One of the primary causes of male pattern baldness is thought to be the conversion of testosterone to dihydrotestosterone. Dutasteride, a dual 5-alpha-reductase inhibitor, can prevent this conversion from proceeding in the body.

Objectives: To summarize treatment patterns, baseline characteristics, and the effectiveness and long-term safety and mesotherapy of dutasteride.

Methods: Systemic or structured search.

Efficacy: Dutasteride demonstrated considerably greater efficacy than placebo (Eun et al., 2010). Dutasteride was more successful than finasteride for treating AGA in male patients. Erectile dysfunction (P = 0.07), safety, changed libido (P = 0.54), and ejaculatory difficulties (P = 0.58) did not differ significantly between dutasteride and finasteride (Zhou et al., 2019).

Conclusions: This study unequivocally established that dutasteride increased hair growth while being generally well tolerated in general for the treatment of MPHL.

Keywords: androgenetic alopecia; dutasteride; male pattern hair loss; mesotherapy; hair loss; finasteride.

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List of Acronyms

AGA- Androgenic alopecia

MPHL- Male pattern hair loss

5AR- 5-alpha reductase

5ARI- 5-alpha reductase inhibitor

AR- Androgen receptor

Css- Steady-state concentration

DHT- Dihydrotestosterone

PSA- Prostate-specific antigen

Chapter 1

1.1 Introduction

Androgenic alopecia, also referred to as AGA, is a disorder that causes progressive hair loss triggered by androgens and has a hereditary predisposition. Up to seventy percent of men may be affected by this condition. Male AGA in is characterized by receding temporal hairlines and whorl and/or vertex hair thinning (Choi et al., 2022). Over 80% of Caucasian mens who are 70 years old or older show some MPHL (Male Pattern Hair Loss) symptoms. With age, MPHL becomes more prevalent and more severe (Eun et al., 2010). Androgenetic alopecia, which causes hair loss in both genders, is a common disorder (Vastarella et al., 2020). This condition is also known as male-pattern baldness in men, where the hair thins near the crown area of the head. This might result in bald areas or total baldness. AGA, worsen quality of life, causes self-image issues and it is viewed as an unwelcome, traumatic event that adversely affects their quality of life and body image. Self-image satisfaction, potentially harmful psychosocial issues, and a detrimental influence on patients' lives are all present in AGA patients. Numerous psychological side effects of alopecia are well-known, which includes sadness, low self-esteem, altered self-image, and infrequent social interaction. As a result, it has been suggested that doctors should take these psychosocial and quality-of-life concerns into account when treating alopecia patients (Han et al., 2012). Transplanting hair from one area of the body to another is a costly option. It is invasive, and multiple treatment sessions are required to achieve the desired hair density. It does not always produce satisfactory results for patients.

AGA patients suffer from severe self-image and complacency issues, as well as potentially harmful psychosocial variables and a negative impact on their quality of life. Numerous psychological side effects of alopecia are well-known, including sadness, low self-esteem, changed self-image, and less social interaction. Therefore, professionals treating alopecia patients are urged to pay special attention to their patients' mental health and overall well-being (Han et al., 2012).

A histological analysis found shorter hair growth phases, thinner hair shafts, and smaller terminal hair follicles in areas of the scalp that are genetically susceptible. In men and women, the Norwood-Hamilton type of hair loss is characterized by receding temporal hairlines, diffuse midline thinning on the top of the scalp, and hair loss in the region of the thyrl in the back of the head (Ludwig type). Androgenetic alopecia in men is hypothesized to be brought on by genetic polymorphisms of the receptor called androgen. It is crucial to have dihydrotestosterone (DHT), which is created from testosterone by the enzyme 5-reductase. Male-pattern baldness is a condition not related to the level of blood androgen. Rapid daily hair loss and "hairlessness" are both referred to as "effluvium." Male-pattern baldness does not correlate with blood androgen levels; rather, it is referred as a disease. "Effluvium" and "alopecia" are terms used to describe increasing daily hair loss. It appears that several genes are implicated. There is an X chromosomal location for the androgen receptor gene, allowing for the possibility of maternal inheritance of a man's susceptibility to acquire androgenetic alopecia in old age. There is a clear genetic tendency for androgenetic alopecia in women, notwithstanding the paucity of research on this subject. A 2011 European consensus declaration on the proper diagnostic assessment of androgenetic alopecia included a diagnostic algorithm and the following key findings: Men with a typical balding pattern require further laboratory testing. The diagnosis might be made solely based on clinical evidence.

The usual values are >80% and 20%, respectively, for the percentage of hairs that are actively growing (anagen) and resting (telagen), according to a trichogram (Wolff et al., 2016).

The most prevalent kind of alopecia, male androgenetic alopecia (AGA), is an inherited loss of hair that has a serious negative effect on a patient's mental health. The hair eventually falls off the top of the head as a result of hair loss, which primarily begins at the hairline on both sides of the forehead. Dutasteride, is classified as a dual 5ARI, which is known to be utilized clinically as a treatment for AGA. Thus, demonstrating a unique mechanism as well as exhibits a potent therapeutic effect. After finasteride's diminished effectiveness, dutasteride can be used as an alternative course of treatment for males with AGA. The merits and shortcomings of the two medications cannot currently be determined by the available evidence. Researchers conducted a meta-analysis with the aim of investigating the safety and efficacy of dutasteride in the treatment of AGA through a 24 weeks treatment period (Zhou et al., 2019).

AGA is treated with 5-alpha reductase inhibitors because 5-alpha reductase is the enzyme which converts testosterone to dihydrotestosterone (DHT). Dihydrotestosterone (DHT) is associated with the pathogenesis of androgenetic alopecia (AGA). The human hair follicles, epidermis, sebaceous glands all contain an enzyme system called 5-alpha reductase. This enzyme is responsible for synthesis of dihydrotestosterone (DHT) from testosterone. One of the major androgen which is responsible male pattern hair loss (MPHL) is DHT. In contrast to type II 5AR, which is found in hair follicles and the prostate, there is a widespread expression of type I 5AR, particularly in the skin, including the scalp (Eun et al., 2010).

Hair follicles, sebaceous glands, and skin generally include 5-alpha reductase (5AR) enzyme systems. It is necessary for testosterone to be converted into dihydrotestosterone (DHT), which

primary androgen is responsible for the MPHL. Type I (5AR) isoenzyme 5-alpha reductase is abundantly expressed in skin, along with the scalp. However, type II (5AR) isoenzyme 5alpha reductase is found in hair follicles as well as prostate. Dutasteride (Avodart) was very well tolerated at regular doses of 0.5 mg for four years. Additionally, dutasteride can inhibit both type I and type II 5AR, leading to an improvement in symptomatic benign prostatic hyperplasia.

There has been a clear identification of a dose association between dutasteride and hair growth from phase II studies in MPHL. The reduction of DHT levels in the scalp was linked to this dose response. After 12 and 24 weeks of therapy, the count of hair in the treatment area increased more with dutasteride than with the placebo at doses of 0.5 mg or higher. Patients who were given a daily dose of 2.5 mg dutasteride were seen to have higher incidences of libido-related adverse events compared to those who were given a dose of 0.5 mg dutasteride daily (Eun et al., 2010).

Taiwan, Japan and South Korea have approved the use of dutasteride 0.5 mg per day for the treatment of AGA, whereas, it has not been approved by the FDA for the U.S. Dutasteride efficacy and safety data are primarily based on brief clinical trials and post-marketing surveillance (Choi et al., 2022).

This article discusses the efficacy, safety, mechanism of action, pharmacokinetics, mesotherapy of dutasteride. Since hair follicles gradually diminish as a result of androgenetic alopecia (AGA), it is undetermined which of these causes has the greatest impact on the onset of hair loss (Shanshanwal & Dhurat, 2017).

1.2 Search strategy and method

On September 7, 2022, a systemic search is conducted on Google PubMed and Google Scholar using a number of MeSH and keyword terms related to male AGA, efficacy, safety, mechanism of action, pharmacokinetics, and mesotherapy with dutasteride. The search found a large number of items. Preliminary screening and deduplication revealed some full-text articles. In addition, the bibliographies of specific publications were also manually reviewed to find relevant literature. The article describes the clinical trials examining the efficacy and safety of dutasteride for male AGA. Other kinds of alopecia like alopecia areata, as well as female AGA and other medicines, such as minoxidil and finasteride were overlooked. Also omitted are clinical trials that do not measure total hair count, terminal hair count, or hair density.

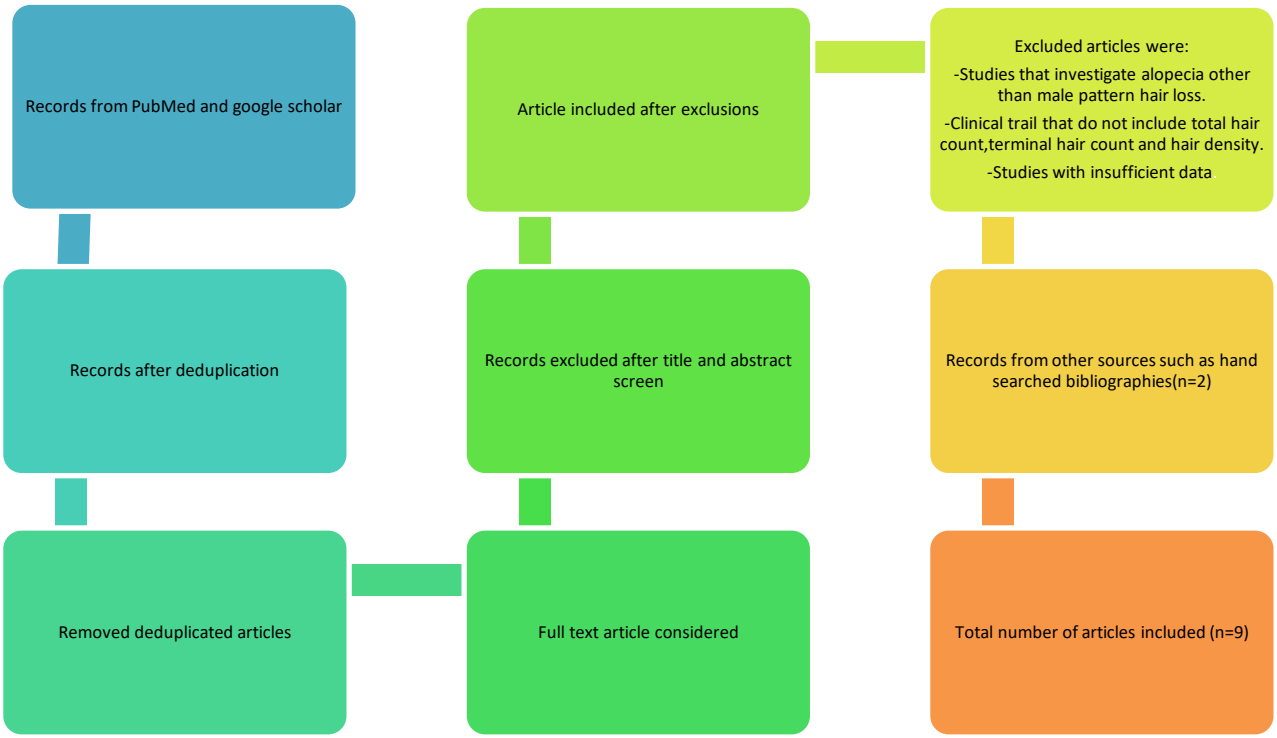

Figure 1: *Sources, search strategy, and the articles' exclusion criteria.*

Chapter 2

2.1Background

Intracrine mechanisms transform testosterone (T) into dihydrotestosterone (DHT), the most potent androgen receptor (AR) ligand, which is used as a prohormone by androgen target cells. DHT production is restricted to tissues that respond to androgens thanks to the enzyme steroid 5 alpha reductase. The 5-alpha reductase isozymes 1 and 2 have been extensively studied, and 5 alpha reductase inhibitors can lower DHT levels in target organs. However, 5 alpha reductase-2 inhibitions have a poor response to male pattern baldness, which is thought to impact 70% of men by the age of 80 (finasteride) (Nickel, 2004).Lower urinary tract symptoms are experienced by 50% of men over the age of 50 due to benign prostate enlargement, and 20% of those who take finasteride (5ARI type 2 inhibitor) or dutasteride (5ARI type 1 and 2) require surgery within 4 years (Godoy et al., 2011).

Dutasteride is an oral synthetic-4-azasteroide. Figure 3, shows the chemical structure of dutasteride. This is one-of-a-kind dual 5ARI which effectively and selectively inhibits both 5-alpha reductase enzyme isoforms. Dihydrotestosterone (DHT) is the primary hormonal mediator involved in the expansion and maturation of the prostate gland, and it is produced by the action of the type I and type II 5- alpha reductase enzymes on testosterone. In 2001, the FDA approved Dutasteridefor the treatment of benign prostatic hyperplasia in symptomatic men. Therefore, it can be used alone or in conjunction with the beta-adrenergic antagonist tamsulosin to achieve a treatment efficacy similar to that achieved by the specific type II 5-alpha reductase inhibitor finasteride (Miller & Tarter, 2009). And despite its efficacy in several randomized, placebo-

controlled and double-blind trials for androgenetic alopecia, dutasteride are not yet recommended for the treatment of androgenic alopecia (Premanand et al., 2020).

When compared with finasteride, dutasteride is almost three times more effective in inhibiting type II 5AR and one hundred times more potent as a type I 5AR inhibitor. Initially, benign prostatic hyperplasia was treated using dutasteride. In addition to this, it lowers the levels of dihydrotestosterone (DHT) in the blood as well as on the scalp, and it raises the levels of testosterone that are produced by the body (Zhou et al., 2019).It has been recommended for the treatment of androgenic alopecia in Japan, Korea, and Mexico by the Pharmaceuticals and Medical Devices Agency (PMDA). Comparative analysis revealed that dutasteride was significantly more effective than finasteride at stimulating new hair growth and reversing the process of miniaturization. In addition, dutasteride has fewer drawbacks comparable to those of finasteride. Results from placebo-controlled studies have shown that duatasteride has side effects, such as sexual dysfunction, a mild to moderate drop in libido, erectile dysfunction, and ejaculatory disorder (Shanshanwal, 2017).

2.2 Benign prostatic hyperplasia to Androgenetic alopecia

A steroidal hormone named dihydrotestosterone generated from testosterone by 5-α reductase, is testosterone's primary active metabolite (Wilson, 1996). During the development of the male fetal organs and during puberty, it is essential for the maturation of the external genitalia into a masculine form and for the formation of the prostate gland. DHT is linked to the advancement of benign prostatic hyperplasia, also known as BPH, as well as androgenic alopecia generally in persons who are older. Type 1 and 2 of the both enzyme of 5-alpha reductase are found throughout

the body. It has been noted that Type 1 is primarily present in the epidermis, in sebaceous glands and hair follicles. Also, they are located in the liver, kidney and prostate (Jenkins et al., 1992). Researchers discovered mRNA and enzyme activity of type 1 in the prostate. The prostate and male genitalia contain type 2 cancer (Clark, 2004).

When a defect of the type 2 5AR isoenzyme was identified in conjunction with a clinical illness characterized by male AGA, the involvement of DHT in male fetal development was recognized. These individuals, who are born with an underdeveloped prostate and inadequate masculinization of the external genitalia, develop BPH or prostate cancer as they grow. This deficiency in BPH prompted the creation of a 5-alpha reductase inhibitor, which is now used to treat this all-too-common condition. Finasteride is the first specific inhibitor of type 2, 5-alpha reductase and other indications indicates enlarged prostates. A number of studies have shown its therapeutic efficacy in reducing the size of enlarged prostates, easing the symptoms of BPH, and decreasing the likelihood of complications. Recent studies have shown that inhibiting 5-alpha reductase effectively treats androgenetic alopecia (Kaufman et al., 1998). 70% of serum DHT suppression is observed (Gormley et al., 1990).

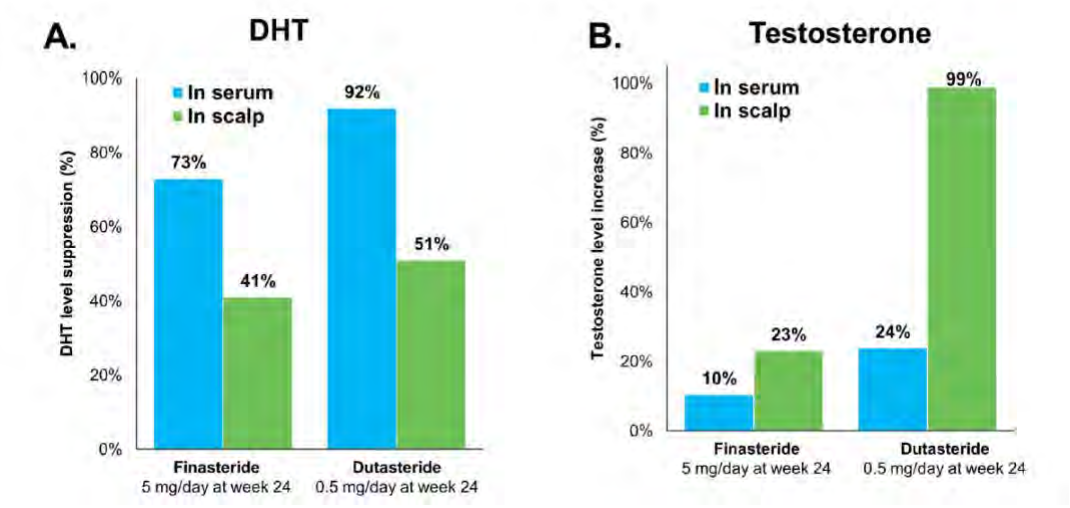

Figure 2: *DHT level suppression (A) and testosterone level increase (B) in serum and scalp due to intake of finasteride 5 mg/d and dutasteride 0.5 mg/d for 24 weeks (Gupta et al., 2022).*

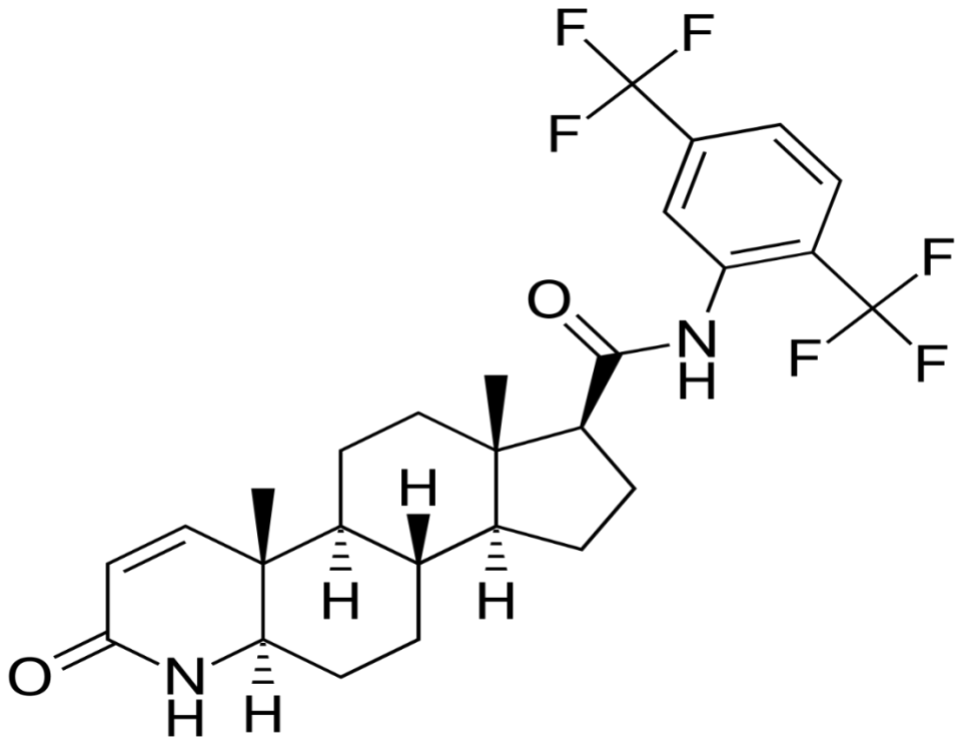

Figure 3: *Structure of Dutasteride(Miller & Tarter, 2009).*

Chapter 3

The dutasteride pharmacology and pharmacokinetics

Dutasteride belongs to the class of medications called 17-substituted 4-aza-steroids with the molecular formula (5, 17)-N. The compound is bis(trifluoromethyl) phenyl-3-oxo-4-azaandrost 1-ene17-carboxamide. It is an inhibitor of both type I and type II, 5AR isoenzymes competitively. It produces a stable, slow-growing compound, dissociation and does not interact with the androgen receptor. The dutasteride's bioavailability is approximately 60% and after two to three hours, the peak serum concentration is attained. At 0.5 milligrams per day for three months, approximately one year is required to reach steady-state and the time for the steady state is dose-dependent. Over 99.5% of plasma proteins bind dutasteride in circulation, and it possesses a distribution volume of 300L to 500L. Clearance is a term used to describe the absence of obstructions. The half-life can be up to 5 weeks at a linear rate of 0.58 L/hour. Pharmacokinetic data summaries are provided below. Serum dutasteride concentrations (>0.1 ng/mL) are observed 4–24 hours after dosing and persist for at least 6 months after therapy discontinuation. The drug is predominantly excreted in the feces after being extensively metabolized in the liver by cytochrome-P3A4. Urine only excretes trace amounts of substances. Following steady-state dosage, the serum detects five main metabolites. The main metabolite, 6-hydroxydutasteride, possesses pharmacological activity comparable to dutasteride. It is prudent to use caution while delivering the medicine in patients with hepatic impairment as well as patients taking cytochrome-P3A4 inhibitors (verapamil, diltiazem, etc.) due to their pharmacokinetics and potential for adverse effects (Premanand et al., 2020).

Dutasteride functions by decreasing DHT levels in the bloodstream and has also been demonstrated to increase urine flow, shrink the shape of the prostate gland, and alleviate the symptoms of benign prostatic hyperplasia when used alone and also in conjunction with tamsulosin. The most significant reduction in DHT levels from dutasteride was seen one to two weeks following the first dose. After 1 and 2 weeks of taking 0.25 mg of dutasteride every day, the average amount of DHT in the blood was cut by 85% and 90%, respectively. After one year of oral administration of 0.5 mg dutasteride per day. In 85% of patients, serum DHT concentrations decreased by greater than 90%. Clinical research has shown that dutasteride may also lower the amount of PSA in the blood of men with prostate cancer (Miller & Tarter, 2009).

3.1 Absorption

Peak plasma concentrations of a single dose containing 0.5 mg dutasteride were reached within 2 to 3 hours after an oral dose. Six months after beginning a daily oral dose of 0.5 mg dutasteride, the steady-state concentration (Css) of 40ng/mL is anticipated to be reached. Absolute bioavailability in healthy persons was 40%-94%, on average 60%. According to reports, food intake has no influence on the bioavailability of the medicine, despite the fact that food intake reduces maximum serum concentrations by 10 to 15% (Gisleskog et al., 1999; K. M. Hwang et al., 2022). In five healthy people, It was shown that dutasteride 0.5 mg soft gelatin capsules had a bioavailability of 60% (the range was 40%–94%).2–3 hours are the T_{max} of dutasteride. The effect of food on dutasteride's C_{max} was 10–15% but clinically negligible (Gupta et al, 2022).

3.2 Distribution

Dutasteride is extensively bounded to protein, about 96% is bound to acid glycoprotein and 99% is bound to albumin. Dutasteride has a volume of distribution in the range of 300 to 500 liters (Gupta et al., 2022). Dutasteride can cross the blood-brain barrier. In a 12-month study involving 26 healthy volunteers who received 0.5 mg of dutasteride daily, the concentration of dutasteride in sperm ranged from 0.4 to 14ng/mL, with a mean of 3.4ng/mL. Similar to serum, the steady-state concentration (Css) of sperm was attained after six months. At 12 months, the dutasteride content in these men's serum was roughly 11.5% (Evans & Goa, 2003; K. M. Hwang et al., 2022).

3.3 Metabolism

The enzymes CYP3A4 and CYP3A5 play an important role in the liver's metabolism of dutasteride. Metabolites are generated at 15-hydroxydutasteride, 4′-hydroxydutasteride, 6, 4′-dihydroxydutasteride, 1, 2-dihydrodutasteride, and 6-hydroxydutasteride. In addition, the presence of the minor metabolites such as 6, 4′-dihydroxydutasteride and 15-hydroxydutasteride has been confirmed. In vitro tests demonstrated that 4′-hydroxydutasteride and 1, 2-dihydrodutasteride inhibited both isoforms of 5-reductase, but to a lesser extent than the parent drug. 6-hydroxydutasteride possesses equivalent action to dutasteride (K.-M. Hwang et al., 2022).

3.4 Excretion

Dutasteride has a clearance for therapeutic doses ranging from 5.83 to 9.67 mL/min. The steady-state terminal half-life of the drug is around 5 weeks. After a year of 0.5 mg/d dutasteride therapy,

the average steady-state concentration of dutasteride in the serum is 40ng/mL. After one month, 65 percent of the total steady-state concentration is obtained and 90% after three months. Dutasteride having a prolonged half-life, remains detectable in the serum (>0.1ng/mL) for 4-6 months after the medication has been discontinued (Gupta et al., 2022).

Through feces, dutasteride as well as its metabolites are excreted. 5% (range: 1–5%) of the orally administered of dutasteride is excreted unchanged in the feces, while 40% (range: 2–90%) is broken down into metabolites. A tiny amount (1%) of unaltered dutasteride is present in the urine. 55% (ranging from 5% to 97%) of the provided dutasteride is unaccounted (K. M. Hwang et al., 2022).

Table 1: *Pharmacokinetics table of dutasteride(Miller & Tarter, 2009)*

Bioavailability	60%
Steady state	3 months
Peak serum concentration	2–3 hours
Volume of distribution	511 L
Elimination half-life	5 weeks

Chapter 4

Pharmacodynamics of Dutasteride

The intracellular steroid enzyme 5-alpha reductase is predominantly localized into prostatic stromal cells where it is attached to the nucleus. This enzyme is responsible for the formation of 5-alpha dihydrotestosterone (DHT) which is a more potent metabolite of testosterone. Therefore, DHT is known as the primary androgen since it plays a major role in the development and growth of the prostate gland (K.-M. Hwang et al., 2022). As it accumulates in the prostate gland, it acts as a hormonal mediator in hyperplasia. DHT has a higher binding affinity on prostate gland androgen receptors than testosterone, and by acting on these receptors, DHT controls genes involved in cell proliferation. Approximately one-third of circulating DHT is produced by type I 5-alpha reductase, which can be found in the liver, scalp and sebaceous glands of most skin regions. Two-thirds of the circulating DHT is produced by the type II 5-alpha reductase isozyme, which is prominent in hair follicles, epididymis, prostate, seminal vesicles, and the liver. Due to its simultaneous inhibition of both isoenzymes of 5-reductase, dutasteride virtually completely inhibits DHT (Miller & Tarter, 2009).

Compared to finasteride, which lowers the amount of DHT in the blood by 70%, dutasteride lowers the amount of DHT in the blood by more than 90% (Zhou et al., 2019).

The phenomenon through which testosterone turns into DHT occurs after 5AR has metabolized the hormone. Three isoenzymes of 5AR exist, which are Type I, Type II, and Type III. Whereas, type I 5AR has been mostly expressed into liver, dermal papilla, epidermis, sebaceous glands, and to a lower level, the prostate. Contrarily, Type II has been mostly located inside the prostate as

well as in the hair follicles (Figure 2). Although there is conflicting information on the type III isoenzyme's location, basal prostate epithelial cells may express it (Gupta et al., 2022).

Dutasteride prevents the production of 5-dihydrotestosterone (DHT), the androgen predominantly responsible for such growth and prostatic gland development, by the development of a stable complex with type I as well as type II 5-alpha reductase. Reducing serum DHT levels decreases the size of the prostate and encourages the death of epithelial cells. This supports the idea that DHT is the main androgen that controls the growth of the prostate in its later stages, along with the growth of the prostate gland and the androgenic hormones of the other genitalia.Dutasteride has been shown to be competing and selective receptor antagonist of both type I as well as type II 5-alpha reductase enzymes, which has been reported that the drug's dissociation from the drug-enzyme complex is unusually sluggish both in vitro and in vivo. Dutasteride is unable to bind to human cells' androgen receptor (Clark et al., 2004).

Therefore, dutasteride as well as finasteride significantly reduce DHT level (Figure 3). DHT level is thought to be the cause of hair loss as well as baldness. Therefore, inhibiting DHT synthesis restores hair growth.

Table 2: *Mechanism of Action of dutasteride (K.-M. Hwang et al., 2022).*

TARGET	ACTIONS	ORGANISM
A 3-OXO-5-ALPHA-STEROID 4-DEHYDROGENASE 1	inhibitor	Humans
A 3-OXO-5-ALPHA-STEROID 4-DEHYDROGENASE 2	inhibitor	Humans

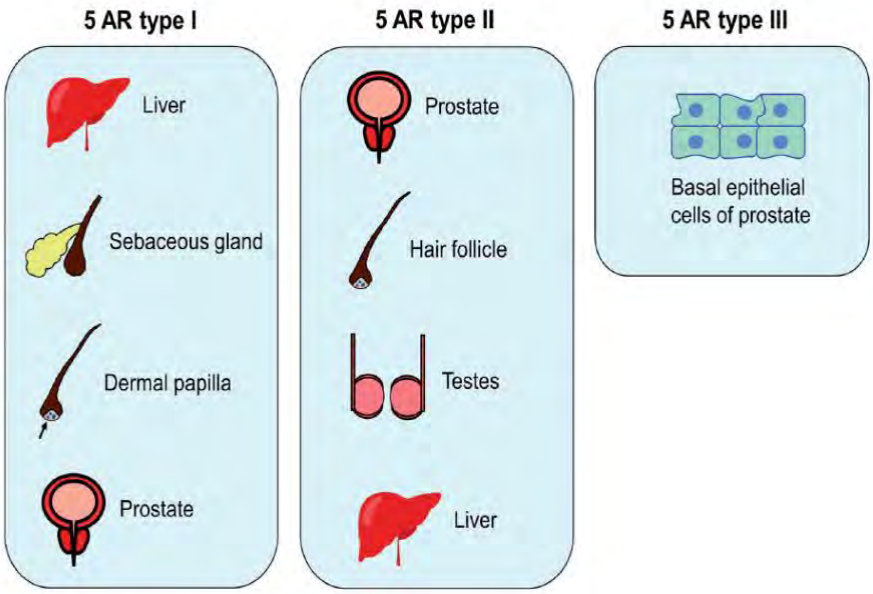

Figure 4: *Differential expression of 5a-reductase type I, type II, and type III isoenzymes in humans (Gupta et al., 2022).*

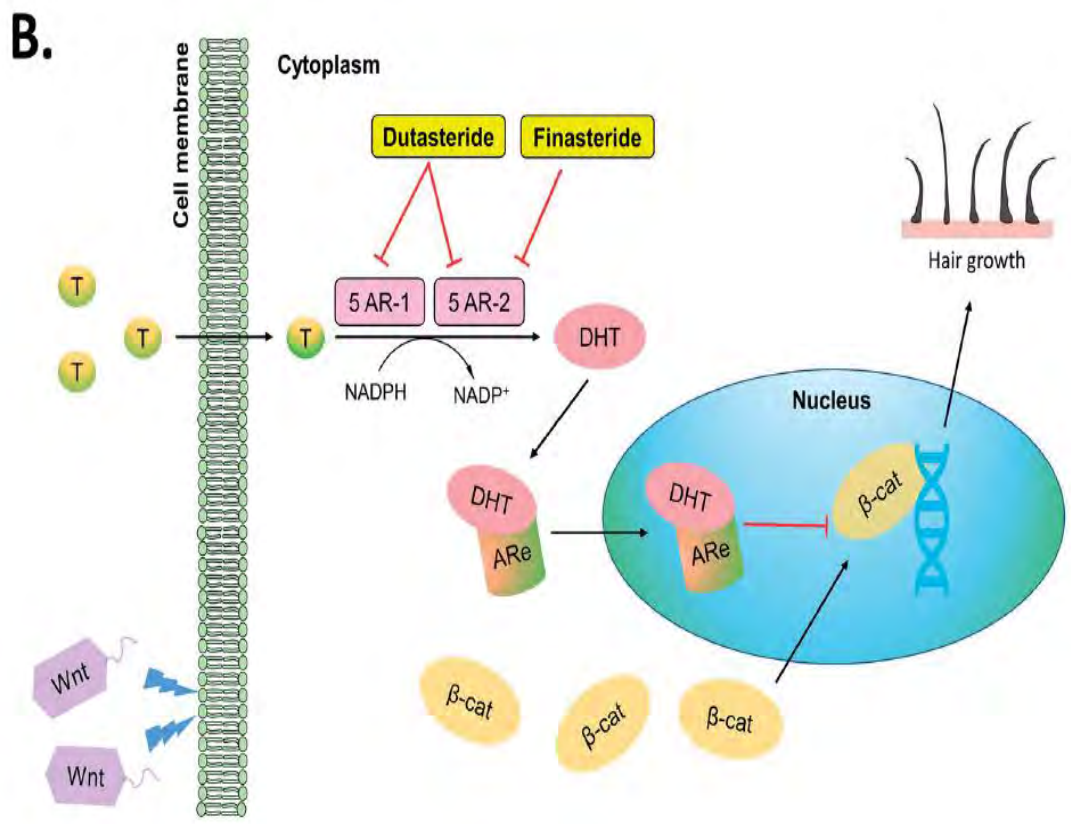

Figure 5: *Finasteride mainly inhibits 5a-reductase type I isozyme, whereas dutasteride blocks both type I and II. The inhibition of 5a-reductase prevents testosterone (Gupta et al., 2022).*

Chapter 5

Mesotherapy using Dutasteride

Mesotherapy is the intradermal administration of minute doses of pharmaceuticals or combined therapies to treat conditions such as hair loss, cellulite, face rejuvenation, and some gastrointestinal diseases or sport injuries (Abdallah et al., 2009).

In 2009, the initial clinical investigation assessing effectiveness and tolerability of intradermic administrations was reported on the benefits of 0.05% liquid dutasteride in men with AGA. Three-fourteen from the twenty-eight patients acquired seven injections of a 2-mL dutasteride solution at least one week apart. In the dutasteride group, 92.9 percent of the total of participants reported an increase in hair density, while only 7.1% of placebo group participants reported the same. There were no significant differences among the groups for side effects. The study examined the efficiency of dutasteride 0.005% individually, 0.9 % homeostatic serum and 0.05% dutasteride together in solution containing dexpanthenol, biotin, or pyridoxine (the control group) on 90 male AGA patients who had nine consecutive injections (Moftah et al., 2013). The group that took the vitamin solution with 0.05% dutasteride saw a dramatic increase in the number of inagen follicles. There is still the possibility that the adjuvants played a role in the observed intergroup differences. In a 2013 clinical trial involving 126 women with female AGA, physiological saline was compared to 2 milliliters of 0.05% dutasteride in pyridoxine solution, dexpanthenol, and biotinin the observed intergroup differences. In a 2013 clinical trial involving 126 women with female AGA, physiological saline was matched with 2 mL of a 0.05% dutasteride solution in pyridoxine, dexpanthenol, and biotin. Over the course of 16 weeks, subjects experienced a total of 12

mesotherapy treatments. Dutasteride improved symptoms in 62.8% of patients, while the placebo group improved in 17.5%. Researchers recently looked at the effectiveness of a new, simpler treatment plan for dutasteride microinjections might help patients stick to their treatment plans (Saceda-Corralo et al., 2017). Six patients with AGA got injections during every session comprising 1 mL of 0.01% dutasteride solution (five men and one woman). After three treatments at 3-month intervals, all patients demonstrated an increase in capillary density; two patients showed a notable improvement; and there were no adverse effects. There were no discernible changes in hormone levels during the before and after periods of the laboratory study. As more studies are conducted, evidence mounts indicating oral dutasteride is superior to oral finasteride. Dutasteride has a 100- and 3-fold increase in efficacy over finasteride in inhibiting 5-alpha reductase (5 AR) and secreted proteins 1 and 2, resulting in a 90% reduction in dihydrotestosterone. The lengthy half-life (about 4–5 weeks) also allows for greater time to pass between therapeutic sessions. Dutasteride microinjections may be an effective and safe treatment for AGA. They will probably be utilized more in the future, either in place of or in addition to oral medication (Reguero-del Cura et al., 2020).

Men's treatment options for androgenetic alopecia include inaction and acceptance of the cosmetic result, medication, hair transplantation, and cosmetic assistance. Without treatment, hair loss is progressive and does not improve or reverse. Dutasteride, which is a 5-alpha reductase inhibitor, works systemically to slow the progression of male pattern baldness and even reverse it in over 65% of men who take it. Dutasteride's efficacy in treating male pattern hair loss (MPHL) is understudied. Dutasteride's potential negative effects on erectile and ejaculatory function (many months) and fertility, as well as its lengthy half-life (4 weeks), create reluctance over its extensive

use in the treatment of MPHL. Local administration of dutasteride would mitigate these systemic negative effects (Abdallah et al., 2009).

Mesotherapy with dutasteride is an effective treatment option for MPHL, resulting in a decrease or cessation of hair loss and stimulation of new hair growth. It is believed that dutasteride works in part by altering the hair cycle and in part by enlarging the hair shafts of existing hair. The impact of injection trauma on the outcome of mesotherapy is minimal. Patients who undergo mesotherapy experience considerable improvements in their mental health as a result of the treatment, as well as their happiness. Systemic absorption of dutasteride after mesotherapy, with its detrimental effect on spermatogenesis, is possible, particularly with unlimited injections. The effect of dutasteridemesotherapy on sexual function is debatable. Dutasteride should not be used by patients who are trying to conceive, have borderline or abnormal spermograms, or have ejaculatory or erectile dysfunction. Additional research is required to determine the precise changes in hair quality and quantity caused by mesotherapy with dutasteride (Sobhy et al., 2013).

Chapter 6

Efficacy of Dutasteride

Based on the information in table 3, each clinical trial demonstrated the effectiveness of dutasteride for the therapy of androgenetic alopecia. The results suggested that the recommended dosage of 0.5 mg dutasteride induced the greatest rise in total hair count at baseline. Finasteride is less effective compared to dutasteride because this prohibits the 5AR isoenzyme's subtypes I and II, while finasteride only inhibitsonly subtype II. DHT, the major androgen implicated in the disease pathogenesis of male AGA, can be produced by 5AR through the conversion of testosterone. As a result, blocking 5AR activity has become a crucial AGA therapy strategy. Dutasteride and finasteride, two distinct types of 5ARI, both have specific therapeutic benefits in clinical settings. According to one study, dutasteride has 100 times the ability to inhibit type 1 5AR and about three times the ability to inhibit type 2 5AR compared to finasteride. After comparing the therapies and also mechanisms of actions, it was shown that dutasteride may be more effective than finasteride in resolving AGA (Zhou et al., 2019).

Hair follicle shrinkage can be caused by scalp DHT's ability to suppress Wnt/-catenin production and reduce scalp DHT levels, which is an essential part of treating AGA, by producing passively feedback in notches signaling. According to an associated clinical trial, finasteride at 5 mg/day can reduce scalp DHT levels by 41%, whereas dutasteride at 0.5 mg/day can reduce them by more than

51%.The findings were published in 2019 in the Journal for Clinical Aging Therapy, and they not only showed the function of pate DHT in the etiology of the AGA, but also validated efficacy observed in prior research (Rejeski & Fanning, 2019).

Dutasteride is not only effective in treating androgenetic alopecia, but it is also more effective than finasteride, according to the information in table 3. The hair growth of the treated group, the placebo group, or the group that received treatment with a different medication than dutasteride is mostly described in this efficacy table. In all studies where patients received dutasteride, significant hair growth was observed. This result indicated that dutasteride shown a substantial rise in the overall hair counting as compared to finasteride by assessing the data from the efficacy table of dutasteride.

Table 3: *Efficacy table of dutasteride.(Abdallah et al., 2009; Choi et al., 2022; Eun et al., 2010; Gupta et al., 2022; Reguero-del Cura et al., 2020; Shanshanwal & Dhurat, 2017; Sobhy et al., 2013)*

Study	**Study type & arms**	**Disease**	**Dosage regimen & comparator**	**Results**			
				Total hair density (hairs/cm^2)	**Terminal hair density (hairs/cm^2)**	**Hair diameter (µm)**	**Comments**
Shanshanwal, 2017	Prospective, parallel, randomized, open-labeled study	Male AGA	0.5 mg/day for 6 months weeks & finasteride 1 mg/day for 24 weeks	**Dutasterid:** Baseline: 222.83 ± 50.68 (n=35)” At 24-week: 245.97 ± 49.86 (n=35)” Variance: 23.14 ± 8.44 (n=35)” **Finasteride:** Baseline: 226.78 ± 48.8 (n=37)” At 24-week: 231.08 ± 51.08 (n=37)” Variance:	**Dutasteri:** Baseline: 158.26 ± 49.91 (n=35)” At 24-week: 188.77 ± 46.49 (n=35)” Variance: 30.51 ± 12.86 (n=35)” **Finasterid:** Baseline: 159.46 ± 42.27 (n=37)” At 24-week: 165.03 ± 44.38 (n=37)” Variance:	NR	In comparison to the finasteride group, the dutasteride group appears to have significantly superior hair growth.

Study	Study type & arms	Disease	Dosage regimen & comparator	Results			
				Total hair density (hairs/cm^2)	**Terminal hair density (hairs/cm^2)**	**Hair diameter (µm)**	**Comments**
				4.30 ± 12.46 (n=37)"	5.57 ± 12.97 (n=37)"		
Marwa Abdallah, 2008	Treated and controlled type study	Male AGA	dutasteride 5mg, D-panthenol 500mg, biotin 20mg, and pyridoxine 200mg per vial of 10 ml (i.e. 0.05% dutasteride)	**Group I:** 37.107 ± 11.325(n=14) At 12 week: Increased 7.739±1.104 **Group II:** 37.107 ± 11.325(n=14) At 12 week: Decreased 0.173±0.940	NR	Increase in hair thickness which is statistically significant (p = 0.009)	Preparation containing dutasteride Proved to be considerably more efficient (p0.05). Compared to the placebo.

Study	Study type & arms	Disease	Dosage regimen & comparator	Results			
				Total hair density (hairs/cm^2)	Terminal hair density (hairs/cm^2)	Hair diameter (µm)	Comments
GubelinHarcha et al.	Study design: randomized, double-blind, dummy-controlled, parallel-group Dutasteride 0.5 mg/d, 0.1 mg/d, 0.02 mg/d; finasteride 1 mg/d, and placebo make up the five groups being studied.	Male AGA	Finasteride in the following dosages: 0.5 mg/d for 24 weeks, 0.1 mg/d for 24 weeks, 0.02 mg/d for 24 weeks, 1 mg/d for 24 weeks, and placebo	Baseline 151.78 ± 43.08 (n¼218)" At 24 weeks mean change from baseline: 17.71 ± 1.56" Dutasteride 0.1 mg/d: Baseline 142.49 ± 43.48 (n¼220)" At 24 week mean change from baseline 12.45 ± 1.52" Dutasteride 0.02 mg/d Baseline: 152.96 ± 44.66 (n¼226)"At 24 week mean change from baseline: 3.38 ± 1.52" Finasteride 1 mg/d Baseline: 150.99 ± 35.77 (n¼171)" At 24 week mean change from baseline: 11.17 ± 1.6" Placebo	NR	NR	After using dutasteride 0.5 mg/d, males with androgenetic alopecia (AGA) noticed a significant recovery in both overall hair density and hair width.

Study	Study type & arms	Disease	Dosage regimen & comparator	Results			
				Total hair density (hairs/cm^2)	**Terminal hair density (hairs/cm^2)**	**Hair diameter (µm)**	**Comments**
				Baseline: 150.40 ± 44.86 (n¼227)" At 24 weeks mean change from baseline: 0.97 ± 1.57"			
HeeChulEun,2009	Multicenter, randomized, placebo-controlled and double-blind investigation.	Male AGA	Dutasteride 0.5 mg once daily for 6 months	Baseline: 148.1 ± 36.3 (73) At month 6: 162.3 ± 38.5 (70) Increases 12.2 ± 23.6 (70) placebo: Baseline: 144.3 ± 32.3 (75) At month 6: 149.6 ± 34.4 (73)	NR	NR	During six months of treatment, the dutasteride group's hair counts increased continuously.

Study	Study type & arms	Disease	Dosage regimen & comparator	Results			
				Total hair density (hairs/cm^2)	**Terminal hair density (hairs/cm^2)**	**Hair diameter (µm)**	**Comments**
				Increases 4.7 ± 16.8 (73)			
Gwang-Seong Choi, 2022	multicentre, retrospective medical chart review study	Male AGA	0.5 mg of dutasteride	Dutasteride (n=295) Age at index (yr) 41.7±10.6 (42.9) p-value <0.001*	NR	NR	Dutasteride had more efficacy in enhancing BASP classification in the treatment of male AGA and had a comparable or potentially lower incidence of adverse effects overall. Dutasteride

Study	Study type & arms	Disease	Dosage regimen & comparator	Results			
				Total hair density (hairs/cm^2)	Terminal hair density (hairs/cm^2)	Hair diameter (µm)	Comments
							may offer male patients with AGA an effective and safe therapy option.
Olsen et al.	Randomized ,placebo-controlled study Six arms: Dutasteride 2.5 mg/d, 0.5 mg/d, 0.1 mg/d;	Male AGA	2.5 mg/d for 24 weeks, 0.5 mg/d for 24 weeks, 0.1 mg/d for 24 weeks, 0.05 mg/ d for 24 weeks, and 1 mg/d finasteride for 24 weeks, and Placebo	Baseline: 191.99 ± 48.88 (n¼70)" At 24 week mean change from baseline: 21.66 ± 16.35 (n¼62)" Dutasteride 0.5 mg/d Baseline 183.3 ± 43.45 (n¼67)" At 24 weeks mean change from baseline 18.70 ± 14.12 (n¼61)" Dutasteride 0.1 mg/d	NR	NR	Dutasteride increased the hair count in a dose-dependent manner. Dutasteride 2.5 mg/d was superior to

Study	Study type & arms	Disease	Dosage regimen & comparator	Results			
				Total hair density (hairs/cm^2)	Terminal hair density (hairs/cm^2)	Hair diameter (µm)	Comments
	0.05 mg/ d, finasteride 1 mg/d, and placebo			Baseline 179.41 ± 44.32 (n¼72)" At 24 weeks mean change from baseline 15.51 ± 17.39 (n¼58)" Dutasteride 0.05 mg/d Baseline 179.75 ± 59.71 (n¼70)" At 24 weeks mean change from baseline 5.57 ± 14.12 (n ¼ not available)" Finasteride 1 mg/d Baseline 178.28 ± 51.95 (n¼70)" At 24 weeks mean change from baseline 14.94 ± 15.75 (n¼66)" Placebo Baseline 181.82 ± 46.71 (n¼64)"At 24 weeks mean change from baseline 6.38 ± 11.29 (n¼50)"			finasteride 1 mg/d.

Chapter 7

Safety of Dutasteride

A safety evaluation was undertaken using the outcomes of laboratory analysis, physical examinations, and details of erectile purpose and unpleasant events. Using the part of the sexual arousal questionnaire that deals with problem assessment, the sexual quality was looked at the start of therapy, 3, 6, and 10 months later. The sexual function inventory has five scales, and one of them is the difficulty evaluation domain. This consists of three measurements that indicate how troublesome the individual believes the following to be: (1) sexual apathy; (2) the potential to attain and manage erections; and lastly (3) the ejection. An overall score was created by adding together three factors (Choi et al., 2016).

CNS symptoms and sexual dysfunction were the adverse effects that were reported to the FAERS database the most frequently (reporting years: 2004–2022), followed by musculoskeletal side effects (18.37%) and CNS symptoms (18.37%). Sexual dysfunctions (8.61%) and are two of the most frequently reported side events associated with male participants in the dutasteride research. In the FAERS database (reporting years: 2004–2022), sexual dysfunction was the most common side effect (30.61%). This was followed by CNS symptoms (18.37%) and musculoskeletal side effects (18.37%) (Eun et al., 2010).

The therapy of males with prostate glandular cancer with dutasteride potentially lowers the serum PSA levels. Dutasteride might increase the probability of advanced prostate cancer comparable to

finasteride. A 4-year study indicated that men who used dutasteride (0.5 mg/d) had a greater hazard of acquiring higher grade of prostate glandular cancer than those who took a placebo, even though their biopsy findings were negative for malignancy. The dutasteride group (n142447) reported 12 cases of cancer with a Gleason grade of 8–10 throughout years 3 and 4, while placebo group appeared with only one case (Miller & Tarter, 2009).

Four to six months after treatment is over, dutasteride is still detectable in the blood; hence, dutasteride-treated males should not donate blood or organs at least for 6 months after their final dose. This guidance is intended to prevent pregnant women from acquiring dutasteride *through* blood transfusion, as this can be harmful to the developing fetus.

However, Dutasteride was found at a maximum concentration of 14ng/mL in men's sperm. Due to the drug's high protein binding (>96%) in human sperm, dutasteride vaginal absorption is likely to be low. The expected blood concentration of dutasteride in a female weighing 50 kg at the highest measured concentration would be estimated 0.0175ng/mL, it is almost 100 times less than the plasma amounts that caused abnormalities in male sex organs in animal research. This is based on the assumption that dutasteride is absorbed completely through the vaginal 5 mL of seminal fluid at the maximum observed concentration, taken from the canal. In general, there are no definitive recommendations about when men should cease using dutasteride prior to becoming fathers. Dutasteride could impact male fertility. Therefore, it is probable that users of dutasteride with a history of infertility would have a more difficult time becoming fathers. In one study, dutasteride 0.5 mg/d was administered to 50 ordinary, healthy participants (n = 427 dutasteride, n = 423 placebo) between the ages of 18 and 52 for a total of 52 weeks, followed by 24 weeks of follow-up after therapy. When compared to the placebo group, the dutasteride group experienced a

reduction of 26, 23, and 18%, respectively, in total semen volume, sperm count and sperm motility after 52 weeks of treatment. Both the concentration and the structure of the sperm were unaltered. After 24 weeks of observation, all of the sperm measures were normal within dutasteride group; however, the overall sperm counting was still 23% less from it had been at the outset of the trial (Gupta et al., 2022).

Table 3: *Dutasteride side effects were reported in the FAERS database when indicated for AGA (Gupta et al., 2022).*

Side effects	**Dutasteride, Male**
CVS symptoms	4/49 (8.16%)
Hypertrichosis	1/49 (2.04%)
CNS symptoms	9/49 (18.37%)
kin-related adverse events	5/49 (10.20%)
Sexual dysfunction	15/49 (30.61%)
Musculoskeletal side effects	9/49 (18.37%)

Chapter 8

Discussion

Follicles become smaller as an outcome of AGA because the anagen period gradually shortens while telogen phase lengthens. Since terminal hairs become vellus hairs, hair density decreases. According to the stage, patterned male hair loss is categorized into seven degrees, first defined by Hamilton in the 1950s and then refined by Norwood (Busanello & Turcatel, 2017).

Alopecia, or hair loss, is a serious dermatological concern around the globe. Alopecia is a widespread term that encompasses numerous curable types of hair loss. In accordance with the cause of hair loss, alopecia is classified as telogen effluvium, androgenic alopecia, anagen effluvium, alopecia areata, alopecia totalis, scarring alopecia and alopecia universal is. Each type of alopecia is distinct and is caused for a variety of reasons. Alopecia areate and androgenetic alopecia are the most common types of baldness. Alopecia areata is a type of patchy hair deprivation that is acquired by the destruction at hair follicles by immune system. Pattern baldness is caused by heredity. It is now widely known that androgens and the enzyme known as Type-II of 5-alpha reductase play important roles in the pathogenesis of MPHL. The active form of testosterone is 5-alpha dihydrotestosterone, which is produced through the transform of testosterone by 5-alpha reductase (DHT) enzyme. In androgen-responsive tissues like hair follicles, the type II isoform of 5-alpha reductase is expressed. On the other hand, the type-I isoform is widely expressed in numerous tissues and hair follicles. In the earliest times, the FDA authorized the use of dutasteride as a treatment for benign prostatic hyperplasia since it is a binate inhibitor of each of the enzyme isoforms. Only a few studies looked at its effectiveness as a

treatment for dutasteride in males. Concerns have been raised over the broad use of dutasteride in the treatment of MPHL as a result of its potential adverse effects on erectile function, ejaculatory function, and reproductive function. Additionally, the drug has a lengthy half-life. These systemic adverse effects could be lessened with the administration of dutasteride at the local level. The treatments that were recommended most frequently for male pattern baldness associated with androgenetic alopecia (MAGA) were minoxidil (98%), oral finasteride (96%), topical finasteride (37%), nutricosmetics (44%), oral dutasteride (33%), low-level laser therapy (8%), and platelet-rich plasma (14%) (Pindado-Ortega et al., 2018).

Similar decreases in hair loss were observed in the dutasteride arm as in previous research. In the finasteride group, hair loss and growth were less pronounced than in prior research. Possible explanation can be variation within the steroid-5-alpha-reductase alpha polypeptide 2 gene. The action of 5-alpha reductase is reduced in living cells when leucine is substituted with valine at codon 89. It has been revealed that the V89L location in the Indian population is highly polymorphic. A post-treatment increase in the quantity of thinning hairs in the finasteride group demonstrates the lack of effectiveness of the medicine. Similar to the previous trial, 15.6% of individuals in the dutasteride group experienced sexual adverse effects in this investigation (Choi et al., 2022).

Results from this study showed that the dutasteride group experienced a similar rate of sexual adverse effects (15.6%) to those described by a study (17.1%).When treatment with dutasteride is maintained for up to 4 years, the occurrence of sexual dysfunction due to the drug decreases. Consistent with prior reports, both dutasteride and finasteride were well tolerated by the majority of the participants, with similar rates of reported adverse effects. Although the controlled clinical

evidence shows a minimal prevalence of sexual adverse effects that subside upon cessation of medication, the lay press has widely reported on the persistence of sexual side effects linked with finasteride. There is no data that 5-alpha reductase inhibitors negatively impact erectile function, according to much immense population-based, long duration, placebo-controlled investigations. Nocebo effects have also been linked to erectile dysfunction (Zhou et al., 2019).

In addition to being more effective than a placebo, the researchers found that 0.5 mg of dutasteride also featured a long - term safety and was well accepted that was comparable to that of the placebo group (Eun et al., 2010). Adverse drug-related and overall incidents were comparable between two researchers, as well as the majority of adverse effects were mild. Regarding sexual function, none of the group was significantly different from the other. This research shows that 0.5 of dutasteride increased hair development, and both the dutasteride and placebo participants experienced the same side effects (Sanchez-Meza et al., 2022).

Chapter 9

Conclusion

However, dutasteride represents the only binary inhibitor of 5-reductase accepted in some countries for use as a medication of AGA in men. Dutasteride for treatment of AGA is not yet established by the Food and Drug Administration. Male AGA is treated using 0.5 mg of oral dutasteride daily has been approved by regulatory authorities in Japan and South Korea. Due to the positive response seen in numerous randomized control studies and meta-analysis, dutasteride is quickly overtaking finasteride as the preferred treatment for AGA. In addition, the majority of these trials showed that dutasteride is preferable to finasteride while having comparable adverse effects. Oral dutasteride may be a positive feature to the therapeutic options for individuals who do not respond well enough to topical minoxidil or even other AGA drugs, or who are unable to take other therapies for various reasons. However, further research and evidence are needed to regulate the safety and efficacy of dutasteride.

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