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Open Access Review Article

A Review on Finasteride: A 5-Alpha Reductase Inhibitors, its Mechanism, Facts and Benefits

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ABSTRACT

This review gives the information about the Finasteride i.e. 5alpha-reductase inhibitor. Primarily finasteride isused to treat BPH i.e benign prostatic hyperplasia and male androgenetic alopecia. Five-alpha reductase inhibitors (5α-RIs) could stimulate male sexual dysfunction due to their effects on testosterone and DHT i.e. dihydrotestosterone. Some studies account insignificant or acceptable adverse effects, which decrease after a changeable period of time so that they do not require terminating finasteride administration. The 5alpha-reductase inhibitor finasteride blocks the conversion of TT to DHT i.e. testosterone to dihydrotestosterone (DHT), the androgen responsible for androgenetic alopecia i.e. male pattern hair loss. This paper presents a possible explanation of the Finasteride drug.

Keywords: Finasteride, 5alpha-reductase inhibitor, BPH, DHT, alopecia.

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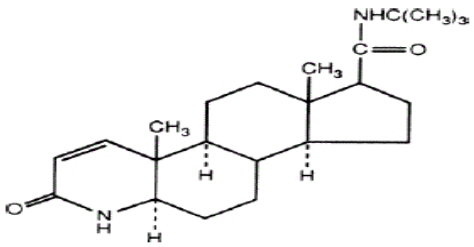
INTRODUCTION:

5a-reductase inhibitors were developed around 20 years ago. Finasteride was the very specific inhibitor of the human type 2 5a-reductase enzyme developed for clinical use.5a-reductase inhibitors (5a-RIs), finasteride and dutasteride, have been approved for treatment of lower urinary tract symptoms, because of benign prostatic hyperplasia, with marked clinical efficacy. Finasteride is also permitted for treatment of hair loss (androgenetic alopecia). Although the adverse side effects of these agents are thought to be nominal, the extent of adverse effects on sexual function, Gynecomastia, depression, and quality of life remains ill-defined. [1]

Finasteride is a competitive inhibitor for 5 alpha-reductase enzyme, being currently used as a pharmacological therapeutic approach of male androgenic alopecia and benign prostatic hyperplasia. Administration of Finasteride is able to induce behavioral changes to animals, while in humans depressive symptoms were relatively frequently reported. For this reason, it was suggested for Finasteride to be carefully administered to patients presenting a history or a high risk to developing depression. [2].

Finasteride (FINA) is chemically N- (1,1-dimethylethyl) –3-oxo-4-aza-5-androst-1-ene- 17- carboxamide. Finasteride (FINA) is an specific inhibitor of steroid 5α-reductase; blocks conversion of testosterone by type II 5α-reductase to 5α dihydrotestosterone (DHT). It is used for the treatment of the symptomatic benign prostatic hyperplasia and male pattern hair loss (androgenetic alopecia) in men. It is official in Indian Pharmacopoeia (IP), BP and USP. [3]

Finasteride Structure



HISTORY OF FINASTERIDE:

Under the code name MK-906 finasteride was developed by Merck. Finasteride (5 mg) was approved by the U.S in 1992. Food and Drug Administration (FDA) for treatment of BPH (Benign Prostatic Hyperplasia), which is marketed under the brand name Proscar by Merk. Merck was successful in obtaining FDA approval for a second indication of finasteride (1 mg) for treatment of male pattern hair loss in 1997, which

was marketed under the brand name Propecia. It was the first 5α-reductase inhibitor to be introduced and was followed by dutasteride in 2001.The first study of finasteride in the treatment of hirsutism in women was published in 1994. [4,5]

BRAND NAME OF FINASTERIDE:

Proscar and Propecia are trade names for the same drug, finasteride. The variation in between these two is in dosage and indication. Proscar is 5 mg of finasteride and is indicated for the treatment of BPH i.e. (Benign Prostate Hyperplasia). Propecia is 1 mg of finasteride and is indicated for the treatment of male pattern baldness. [6]

GENERAL DESCRIPTION:

Chemically finasteride is 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one.It is white in colour and in crystalline powder form as well as amorphous nature. The molecular weight of finasteride is 372.6g/ml and molecular formula of this finasteride is C23H36N2O2. finasteride is competitive inhibitor of enzyme 5α- reductase which converts testosterone responsible for androgen action in tissues together with prostate gland and hair follicles. Finasteride is anti-androgenic drug and also found successfully in male baldness. It is effective orally, metabolized in liver and excreted in urine faeces. [7]

Finasteride is used in benign prostatic hyperplasia (BPH) in small doses and in prostate cancer in large doses. In addition, it is registered in several countries for male pattern-baldness. The therapeutic significance of finasteride has necessitated the development of analytical methods for its determination in dosage forms in compliance with good manufacturing standards. [8]

FINASTERIDE'S MECHANISM OF ACTION:

Finasteride is a competitive 5 alpha-reductase inhibitor for type II and III isoenzymes that preventing the conversion of testosterone to dihydrotestosterone. As a result, the serum level of dihydrotestosterone decreases after Finasteride administration with about 65–70%. Finasteride doesn't inhibit the type I of 5 alpha-reductase isoenzyme due to this fact the partial inhibition of dihydrotestosterone synthesis is occur. Finasteride contributes to reduction of GABAA activity (dihydrotestosterone helps activation of GABAA receptors) by decreasing the level of dihydrotestosterone, which has been involved in depression, anxiety and sexual dysfunctions. Yet, Finasteride decreases androgen activity in the scalp and prostate. [2]

Mechanism of action of finasteride which leads to reduced levels of DHT when the drug is administered orally, which shows a balanced approach to the treatment of men with AGA. Since it is a systemic medication, finasteride is delivered to the intact scalp, including the affected areas. The clinical studies established awareness to finasteride treatment across a broad range of men with AGA, those with mild to moderate degrees of hair loss in the vertex and anterior mid-scalp areas. No major clinical or laboratory adverse effects have been observed with finasteride administration that prohibit its long-term use by men. Moreover, finasteride is not a new drug, and worldwide experience with a higher dose of finasteride over many years in the treatment of men with BPH confirms the long-term safety of the compound. The value of Finasteride in the treatment of men with androgen-dependent disorders, including AGA, has prompted the development of other inhibitors of 5a-reductase, as well as increasing research in modulators of androgen action, for potential use in treating men with these disorders.[9]

The mechanism of action of finasteride in humans is based on its preferential inhibition of the Type II isozyme. In vitro binding studies that examined finasteride's ability to inhibit either isozyme of 5á-reductase documented a 100-fold selectivity for the human Type II over the Type I isozyme. Based on the tissue-specific expression of Type II 5á-reductase in humans, currently approved clinical uses for finasteride target the diminution of DHT levels and the concomitant decrease in activity of DHT at the androgen receptor in the prostate and the scalp of men. In contrast to the selective inhibition of the Type II isozyme by finasteride in humans, both isozymes of the 5á-reductase enzyme in the rodent demonstrate comparable inhibition following finasteride exposure.[10]

PHARMACODYNAMICS AND PHARMACOKINETICS:

In humans, primarily Type I 5á-reductase is found in the sebaceous glands of most regions of skin including scalp, and in liver, muscle, and brain with low levels also present in prostate that may boost in prostate cancer. Approximately one-third of circulating DHT is due to the type I 5á-reductase. The Type II 5á-reductase isozyme is found in prostate, seminal vesicle, epididymis, and hair follicles as well as in liver and is responsible for the remaining two-thirds of circulating DHT. Because of this profile of tissue specific expression and the specificity of finasteride inhibition in humans, few adverse reactions are observed in other organ systems. Finasteride has no affinity for the androgen receptor and exhibits no known androgenic, anti-androgenic, estrogenic, anti-estrogenic, or progesterone-like activity .

The rodent 5á-reductase isozymes also differ in the mechanism by which finasteride inhibits their enzymatic activity. Finasteride acts as a classical competitive inhibitor of the rat Type I enzyme and time-dependently dissociates from this isozyme, whereas it binds and irreversibly modifies rat Type II 5á-reductase following the formation of a high affinity complex. This mechanistic difference in finasteride binding between rat isozymes results in a 10-fold difference in Ki values Little is known regarding the recovery of the 5á-reductase enzymes and the subsequent restoration of 5á-reduced steroid metabolite levels following the cessation of finasteride treatment in rodents. Based on the competitive vs. irreversible inhibition of the two 5á-reductase enzymes, it is feasible that the rat Type I enzyme would recover more quickly than the Type II enzyme. This difference may have important implications in the rodent, given that Type I is predominantly localized in the CNS and Type II 5á-reductase is largely in the periphery. [10]

PHARMACOKINETICS:

The mean oral bioavailability of finasteride is approximately 65%.The absorption of finasteride is not affected by food. With 1 mg/day finasteride at steady-state mean peak concentrations of finasteride were 9.2 ng/mL (25 nmol/L).. The volume of distribution of finasteride is 76 L/kg. Its plasma protein binding is 90%.The drug has been found to cross the blood–brain barrier, whereas levels in semen were found to be untraceable. Finasteride is widely metabolized in the liver, It has two major metabolites, which are the *tert*-butyl side chain mono-hydroxylated and mono-carboxylic acid metabolites. These metabolites show approximately 20% of the inhibitory activity of finasteride on 5α-reductase.Hence, the metabolites of finasteride are not principally active. The drug has a terminal half-life of 5-6 hours in adult men (18–60 years of age) and a terminal half-life of 8 hours or more in elderly men (more than 70 years of age).It is eliminated as its metabolites 57% in the feces and 40% in the urine.[11,12]

PHARMACOLOGICAL PROFILE OF FINASTERIDE:

Finasteride is a partial inhibitor (only type II) of 5α-reductase enzyme, which converts intracellular testosterone to dihydrotestosterone. Finasteride absorption is not affected by food, presenting a bioavailability around 65%. The maximum plasmatic concentration is reached about 1 to 2 hours after administration, ranging between 4.9 - 13.7 ng/mL for 1 mg/day, and between 27 - 49 ng/mL for 5 mg/day. After successive doses, there is a slow accumulation phase for Finasteride, with 90% of the circulating drug bound to plasma proteins.

Finasteride crosses the blood-brain barrier, a property that explains many Finasteride side effects such as mental and sexual impairments. It is extensively metabolized by the liver, especially through cytochrome P450 3A4 enzyme subfamily. The corresponding metabolites possess no more than 20% inhibitory activity for 5α-reductase comparable to Finasteride action. Oral administration of Finasteride leads to its excretion in urine as metabolites (about 39%) and through feces (57%, in part unmetabolized). The mean terminal half-life of finasteride in men between 45 - 60 years is approximately 6 hours, though longer in men over 70 years (about 8 hours). [13]

FINASTERIDE: USE IN MALE PATTERN HAIR LOSS

The 5alpha-reductase inhibitor finasteride blocks the conversion of TT to DHT i.e. testosterone to dihydrotestosterone (DHT), the androgen accountable for male pattern hair loss (androgenetic alopecia) in genetically predisposed men. In 1879 the results of phase III clinical studies in men have shown that oral finasteride 1 mg/day prevents further hair loss promotes hair growth and in a significant proportion of men with male pattern hair loss. Data suggests that the improvement in hair count reported after 1 year is maintained during 2 years' treatment. In men with vertex hair loss, global photographs showed enhancement in hair growth in 48% of finasteride recipients at 1 year and in 66% at 2 years compared with 7% of placebo recipients at each time point. Furthermore, hair counts in these men showed that 83% of finasteride versus 28% of placebo recipients had no further hair loss compared with baseline after 2 years. The clinical efficiency of oral finasteride has not yet been compared with that of topical minoxidil, the only other drug used clinically in patients with male pattern hair loss. Well tolerated Therapeutic dosages of finasteride. In phase III studies,7.7% of patients getting finasteride 1 mg/day compared with 7.0% of those getting placebo reported treatment-related adverse events. The overall frequency of sexual function disorders, comprising decreased libido, ejaculation disorder and erectile dysfunction, was extensively greater in finasteride than placebo recipients. All sexual adverse actions were reversed on discontinuation of the therapy and many resolved in patients who continued therapy. No other drug-related events were reported with an occurrence > or =1% in patients receiving finasteride. Most events were of placid to moderate severity. Oral finasteride is contraindicated in pregnant women because of the risk of hypospadias in male fetuses. [14]

THE EFFECT OF FINASTERIDE IN MEN WITH BENIGN PROSTATIC HYPERPLASIA

BPH i.e. Benign prostatic hyperplasia is a advanced, androgen-dependent disease resulting in enlargement of the prostate gland and urinary obstruction. The treatment of BPH i.e. benign prostatic hyperplasia with 5mg of finasteride per day that results in a significant decrease in symptoms of obstruction and enhance in the urinary flow and decrease in prostatic level but with slightly increased risk of sexual dysfunction. [15] A 5-mg dose of finasteride is permitted for treatment of symptomatic BPH (Benign prostatic hyperplasia), which reduces prostate level by 19–27% . Finasteride has been shown to be most efficient in men with enlarged prostates and the most rigorous symptoms. Finasteride is also permitted for the treatment of male-pattern hair loss (androgenetic alopecia) and vertex baldness, and is generally given at a lower dose of 1 mg. [9]

FINASTERIDE-ANDROGEN-DEPENDENT HAIR DISORDERS:

Finasteride is widely used for the treatment of androgen-dependent hair disorders such as androgenetic alopecia. Finasteride is a selective 5 alpha reductase inhibitor and is administered orally in a dose of 1 mg once daily for androgenetic alopecia. The oral bioavailability is 65%. It is not related to food intake. The average peak plasma concentration is found to be 9.2 ng/ml. The terminal half-life of finasteride is approximately five to six hours in men between 18 and 60 years of age and eight hours in men older than 70 years of age. It is broadly metabolized in the liver by cytochrome-P450; 3A4 enzyme subfamily and excreted in urine and feces. Finasteride has been tried in several doses ranging from 0.2 mg to 5 mg but 1 mg per day is the optimal dose for the treatment of men with male pattern hair loss. There is no difference in efficacy between doses of 1 mg and 5 mg. Long-term daily finasteride is advocated and leads to sustained improvement. [16]

HAIRLOSS:

Hair loss not only constitutes one of the most commonly encountered problems for dermatologists, it inflicts a reflective negative impact on one's quality of life. Advanced patterned hair loss (PHL), particularly at an early age is frequently a source of depression in young individuals. Androgenetic alopecia (AGA) affects both genders in a distinctive pattern of hair loss from the scalp (MPHL i.e. male pattern hair loss for male PHL and FPHL i.e. Female pattern hair loss for or female PHL). Mid-frontal hair loss affects closely two thirds of women and three quarters of men over the age of 80 years. Loss of hair from the vertex is typical of MPHL(male pattern hair loss), encountered in number of affected men. The trademark of the condition is advanced and gradual shrinking of hair follicles (HFs), accompanied by progressive decrease in the duration of anagen and reduction of anagen to telogen ratio. Additionally in AGA (Androgenetic alopecia) , there is a time lag between the end of the telogen phase and the beginning of the new anagen phase and a resting phase called kenogen during which the hair follicle remains bare. The follicular miniaturization in AGA is an asynchronous phenomenon even within a follicular unit (FU); with affection of secondary follicles occurring in the initial phase and the primary follicles in the last. In contrast, the miniaturization activity is synchronous in alopecia areata (AA).Finasteride (FIN), the only United States Federal Drug Administration (FDA) approved oral agent for MPHL is a specific inhibitor of 5AR, type II isoform. Minoxidil (MNX), the other FDA approved topical agent (for MPHL as well as FPHL) apparently acts by increasing follicular vascularity (as a potassium channel opener), prolonging anagen and shortening telogen, and also by converting partially miniaturized (intermediate) hair follicles to terminal hair. Hair transplantation, of course remains one of the best and sometimes the only therapeutic option in advanced AGA. [17]

USE IN FEMALE ALOPECIA:

Currently minoxidil is considered the first-line therapy for female pattern alopecia; however, finasteride and dutasteride are becoming more frequently used. The most significant adverse effect of 5ARIs in women who are or may become pregnant is the risk of birth defects in the male fetus. 5ARI exposure to pregnant women has been shown to increase the risk of abnormal male external genital development including hypospadias. Due to this risk, 5ARIs are considered contraindicated in pregnancy with some authors advocating testing to rule out pregnancy before starting 5ARIs and concomitant reliable contraception use in nonpregnant women with childbearing potential.5-alpha reductase inhibitors, such as finasteride and dutasteride, are becoming more commonly prescribed for women with hair loss. The limited number of studies indicates that 5ARIs are well-tolerated initially with no increased risk of malignancy or severe side effects. However, headache, gastrointestinal discomfort, and decreased libido are the most common side effects reported. Future long-term studies would be helpful to fully. assess adverse events with chronic use.[18]The mechanisms by which finasteride may arrest or reverse hair loss in women remain unknown. The largest controlled trial to date did not demonstrate significant stabilization or improvement in hair loss. There is little evidence to support any agent as second-line treatment for female hair loss; however, data from uncontrolled studies and case reports suggest that finasteride may be effective in an as-yet unidentified subgroup of patients with FPHL(Female pattern hair loss). Finasteride should therefore be reserved for treatment of FPHL not responding to a 12-month trial of topical minoxidil. The MPHL finasteride regimen of 1 mg orally daily is suggested for treatment of FPHL, although some success has been noted with doses of 2.5 and 5 mg daily. Due to its known teratogenicity, finasteride treatment should be restricted to nonpregnant women who adhere to reliable contraception if they are of childbearing potential.[19]

ROLE OF ANDROGENS IN PATTERN HAIRLOSS AND SEXUAL FUNCTION:

Pattern hair loss i.e. PHL in male is androgenic in aetiology. Antiandrogens like finasteride are therefore usable in the management of the condition. Androgens, particularly testosterone increases the libido. Any drug which hinders with the action of androgens is therefore assumed, by the lay person, to induce impotence. However, the precise role of androgen in penile erection needs to be fully elucidated. Even an individual with low testosterone levels can achieve erection. In addition to androgens, visible, olfactory, tactile, auditive, and imaginative stimuli causation the libido. The penile erection is mainly under the control of parasympathetic nervous system. Ejaculation and detumescence require an intact sympathetic system. The androgens testosterone and dihydrotestosterone (DHT) have somewhat different actions. The enzyme, 5α-reductase converts testosterone to DHT. It exists in two isoenzyme forms. While type I is predominant in liver, type II is predominant in prostate, seminal vesicles, epididymis, hair follicles, and liver.Within the hair follicle too, the two types have a different distribution. Type I 5AR, is generally present in the sebaceous gland, while type II 5AR is present on the outer root sheath of the hair follicles and dermal papillae. At all these sites, the testosterone is converted to DHT. Although the type II 5AR enzyme has a more significant role in pattern hairloss (and therefore mechanism of action of finasteride), the predominant enzyme in scalp skin is type I ,largely because of localization to the sebaceous glands, which are large and plenty in scalp. We know that the finasteride is a specific and competitive inhibitor of Type II 5-AR, and has therefore a selective action on hair follicles. Scalp skin DHT levels fall by more than 60% after administration of finasteride, thereby suggesting that a significant amount of DHT found in scalp skin is derived from both local DHT production and circulating DHT. Thus, the effect of finasteride on scalp DHT is likely because of its effect on both local follicular DHT levels as well as serum DHT levels. This explains why relatively small dose of finasteride may be adequate therapeutically.[20,21]

SEXUAL ADVERSE EFECTS:

Sexual side effects in men who have taken fInasteride (1mg, 5mg) and dutasteride (0.5mg) are well documented and include decreased libido, erectile dysfunction, and ejaculatory dysfunction.

Randomized clinical trials have demonstrated increased incidences of these sexual side effects.[22]

In most of the men who improved persistent sexual side effects (near about ≥3 months) despite the discontinuation of finasteride, the sexual dysfunction continued for numerous months or years. Although various rat studies have shown harmful changes to erectile function caused by 5 alpha reductase inhibitors (finasteride), the persistent nature of these changes is an area of active research. Prescribers of finasteride and men contemplating its use should be made aware of the potential adverse medication effects.[23]

MALE BREAST CANCER DURING FINASTERIDE THERAPY:

Male breast cancer is an uncommon disease, with an estimated incidence of one case per 100 000 man-years . Relative estrogen excess or lack of androgen are associated with an increased risk of breast cancer in both women and men .An example of increased rates of male breast cancer associated with increased estrogen-to-testosterone ratios can be seen in men with Klinefelter's syndrome, who are 50 times more likely to develop breast cancer than their normal counter parts. Sometimes, this ratio affected by finasteride (Proscar), which has been widely marketed and used to treat benign prostate hyperplasia (BPH). Proscar shrinks androgen-dependent prostate tissue by inhibiting steroid 5alpha-reductase, an enzyme that converts testosterone to dihydrotestosterone (DHT). However, inhibition of DHT production alters the estrogen-to androgen ratio and may also increase the risk of gynecomastia and male breast cancer. Reports to the U.S. FDA from June 1992 through February 1995 pretending that gynecomastia had been observed in 214 men receiving Proscar therapy.

Two of these men were afterwards found to have invasive ductal breast carcinoma . There was also a higher incidence of gynecomastia in men participating in the Prostate Cancer Prevention Trial. The rate of gynecomastia was 426 (4.5%) of 9423 subjects randomly allotted to the Proscar arm compared with 261 (2.8%) of 9457 subjects randomly allotted to the placebo arm. There was one case of breast cancer in each and every arm of the trial. Evidence of the organization of Proscar with male breast cancer comes from the Medical Therapy of Prostatic Symptoms (MTOPS) study, a National Institutes of Health (NIH)-sponsored study of about 3047 men that compared Proscar, doxazosin, and the combination for the treatment of BPH . Men were randomly assigned to one of four treatment arms: Proscar and doxazosin (n 786), Proscar (n 768), doxazosin (n 756), and placebo (n 737). Four cases of breast cancer were reported. According to a letter from the NIH to the MTOPS principal

investigators, one man in the Proscar/doxazosin group and three in the Proscar-alone group developed male breast cancer. The rate of breast cancer in this trial for men taking Proscar either alone or with doxazosin was therefore 4 in 1554, or nearly 200 times that of the general population. One of us (S. C. Lee) was patient No. 14–214 who participated in the MTOPS trial from 1997 through 2002 and wasrandomly assigned to receive 5 mg of Proscar daily. This patient was a previously healthy 69-year-old man with no family history of cancer who developed lymph node–positive estrogen and progesterone receptor–positive breast cancer (tumor–node–metastasis [TNM] staging T1cN1M0). He was subsequently treated with modified radical mastectomy with axillary lymph node dissection, chemotherapy, and tamoxifen. He was one of the four breast cancer cases mentioned in the letter from the NIH to the MTOPS. As this patient and his physician, we strongly suggested that the FDA require that data about the possible association between male breast cancer and Proscar be clearly stated in the manufacturer's patient information leaflet for prescriptions and in its advertisements. Proscar has been well accepted to improve quality of life in men suffering from BPH i.e. Benign prostate hyperplasia. Patients and their physicians need to be better informed about this potential life-threatening risk. Men who take Proscar need to be aware of any changes in their breasts and report these changes immediately to their physicians.[24]

CONTRAINDICATIONS:

Finasteride may cause birth defects in a male fetus if a pregnant woman takes finasteride or is exposed to finasteride pill fragments. It is classified in the FDA pregnancy category X. Finasteride stimulate equivocal genitalia in male fetuses when granted to pregnant rhesus monkeys, whereas no abnormalities are observed in female fetuses. There is a single case report of accidental finasteride exposure during pregnancy, although in a female infant. [25,26]

CONCLUSIONS

Finasteride is 5alpha reductase inhibitor. Finasteride mainly used in the male pattern hair loss i.e. MPHL as well as in BPH i.e. benign prostate hyperplasia but not approved for prevention of prostate cancer..Mechanism of finasteride is depend on the level of testosterone and DHT i.e. dihydrotestosterone, finasteride blocks the conversion of testosterone to dihydrotestosterone. Overdose of finasteride may causes harm to the patient and finasteride contraindicated in some cases like in pregnancy etc. Finasteride administered during pregnancy causes birth defect. Finasteride have some sexual adverse effect which may lead to severe disorders.

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