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Steroidal 5 α -Reductase: A Therapeutic Target for Prostate Disorders

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Abstract

Steroidal 5 α -reductase is a system of NADPH dependent enzyme that catalyzes the irreversible conversion of Δ^4 -3-ketosteroid precursor (testosterone) to its corresponding 5 α -reduced metabolite (dihydrotestosterone). Initial role of DHT was discovered through males pseudohermaphroditism, a genetic disorder with complete or partial 5 α -reductase deficiency accompanied with features at critical juncture of fetal and postnatal development. However, excessive DHT production, has brought a revolution in revealing the etiology of complications like prostate cancer and benign prostatic hyperplasia. Over the last two decades, converging lines of evidences have highlighted the role of 5 α -reductase inhibitors in the treatment of these androgen dependent disorders. Finasteride and Dutasteride, are the two clinically approved inhibitors available in the market, that helps in reducing the prostate volume by blocking the 5 α -reductase enzyme.

Keywords: androgen, isozymes, prostate, genetic disorder, benign prostatic hyperplasia

1. Introduction

The prostate gland located between the bladder and the rectum is an heterogeneous organ, and wraps around the urethra. It is considered to be consisted of central, peripheral or transitional zone and composed of three different types of cells: glandular epithelial cells, smooth muscle cells and stromal cells (**Figure 1**). At the time of birth, prostate is about the size of a pea and undergoes many changes during the course of man's life. It grows only slightly until puberty, then it begins to enlarge rapidly attaining normal adult size and shape [1].

The gland generally remains stable until about the mid 40s, and in most men over the age of 60, the prostate begins to enlarge. The dense capsule surrounding the enlarging prostate prevents it from further expansion outward, which in turn forces the prostate to press against the urethra, and partially block urine flow (**Figure 2**). This apparent increase in number of stromal and epithelial cells results in obstruction of the proximal urethra and condition is called as benign prostatic hyperplasia (BPH). This obstruction, in turn causes bladder irritation and contraction, even for small amount of urine. Eventually the bladder weakens and does not completely empty through urination [2].

Figure 1.
Location and different sections of prostate gland.

Figure 2.
Enlarged prostate gland.

Clinically BPH is manifested as lower urinary tract symptoms (LUTS) and consisting of voiding and storage symptoms such as slow urinary stream, splitting or spraying of urinary stream, recurrent urinary stream, straining to void and terminal dribbling, hesitancy, urgency, increased frequency, and incontinence. Although urge incontinence is an irritative symptom, it may indicate the presence of obstruction [3, 4].

BPH is also described as quality of life disorder, as its affects man’s ability to initiate or terminate urine flow stream (the symptoms interfere with the normal activities) and reduces the feeling of well being. Though the etiology of hyerplastic process of BPH is clearly not known, but many partially overlapping and complementary theories have been proposed for the overgrowth of smooth muscle tissue and glandular epithelial tissue like aging: late activation of cell growth [5], defective cell death and hormonal changes. According to the most widely accepted hypothesis i.e. androgen (dihydrotestosterone hypothesis) BPH occurs due to an age related changes in prostate androgen metabolism that favors the accumulation of DHT and responsible for cell growth in the tissues that lines the prostate gland thus rapid prostate enlargement [6, 7].

2. Treatment options for BPH

During the last two decades, it has become clear that the management of LUTS associated with BPH is much more than just treating symptoms. It is a progressive disease and defined as worsening of symptoms, increase in prostate volume (PV), deterioration of urinary flow rate, inability to void i.e. acute urinary retention (AUR) and the need for surgery either for AUR or deteriorating symptoms [8]. Further, AUR with an annual risk of less than 1% is found to be uncommon, but requires urgent bladder catheterization. Therefore, diagnosis, monitoring, frequency, severity and assessment of the prognosis for disease progression should be assessed before management decisions. EAU guidelines have recommended a series of evaluation as a routine part of the initial assessment of men with LUTS, that includes clinical history, a validated questionnaire to assess symptoms, physical examination, creatinine measurement, urinalysis, flow rates, postvoid residual (PVR) volume and serum prostate-specific antigen (PSA) measurement especially when a diagnosis of prostatic carcinoma is required [9]. A more profound knowledge on the pathogenesis, the natural history and risk of the progression, has enabled more differentiated therapy of elderly men with lower urinary tract symptoms due to benign prostatic hyperplasia as follows (**Figure 3**) [10, 11].

2.1 Watchful waiting

Watchful waiting is a well known approach to treat BPH where men are asymptomatic or with mild to moderate symptoms without causing no serious health. It is generally considered as the first tier in the therapeutic cascade and patients are

Figure 3.
Management options.

monitored by his physician without receiving any active intervention. Untreated BPH will progress to AUR and other complications such as renal insufficiency and stones. Thus regular check up along with continual education is recommended to avoid chances of occurrence of serious complications [12, 13]. Further, optimization can be achieved by including certain lifestyle or dietary changes as recommend in EAU guidelines, to prevent the deterioration requiring medical or surgical treatment [9].

2.2 Surgical treatment

Surgical interventions are often endorsed for patients with complications of LUTS such as AUR, renal insufficiency, bladder calculi or recurrent urinary tract infections, persistent gross hematuria secondary to BPH [14]. Further, other candidates for surgery includes the patients refractory to other medical management, or men with unacceptable side-effects following drug therapies and requested for active treatment [15].

Open prostatectomy, transurethral resection of the prostate (TURP), and transurethral incision of the prostate (TUIP) are some of the conventional surgical treatment options for symptomatic BPH. The removal of obstructing tissue was first achieved by open prostatectomy in early 1900s [16] and considered as gold standard for the surgical treatment, but later replaced by TURP. Significant improvement in LUTS were observed with TURP, and it takes only 20–30 min, to resect an average gland weighing 30 g. Though TURP is considered to be as the hallmark by the urologist, the one against which other surgical options are compared, but it carry the complications of excessive bleeding and longer hospital stay [16, 17]. TUIP a comparative less invasive technique than TURP and with similar improvements in symptoms is recommended for prostate gland weighing <25 g of the prostate [18]. An electrosurgical modification of the TURP and TUIP technique i.e. transurethral vaporization (TUVF), is reserved particularly for the patients with a small prostate and bleeding disorders. Its long term efficiency has been found to be comparable with that of TURP, but number of patients reported for irritative symptoms as side effects [19].

Raising the temperature of the cells through the use of low level radiofrequency (microwave) in prostate to 40–45°C (hyperthermia), 46–60°C (thermotherapy) and 61–75°C (transrectal thermal ablation) are found to be more specific techniques for the necrosis of obstructive tissue without affecting normal cells [16]. In comparison to high-energy TUMT with increased morbidity, low range TUMT has been found to well tolerated in patients with reasonable improvement in flow rate and less effect on sexual function [20]. Another simple, safe and relatively inexpensive technique to deliver high frequency radiowaves (temperature range 90–100°C) to produce localized necrotic lesions in hyperplastic tissue is Transurethral needle ablation (TUNA). Its a method of choice over TURP in younger men and with small sized gland, wishing to preserve sexual function, as it poses a low or no risk for incontinence and impotence [21, 22].

Laser vaporization or prostatectomy, has been found to be another safe, effective and widely used form of MIT technique with significant improvement in urinary flow rates and symptoms. Light at different wavelength is being generated using four types of lasers, namely potassium titanyl phosphate (KTP) diode laser; neodymium: yttrium-aluminum-garnet (Nd: YAG) laser, and holmium YAG laser (Ho:YAG), that cause irreversible cellular damage, followed by their coagulation necrosis and ultimately vaporization of tissues. Further, evolution in holium laser prostatectomy i.e. Holmium laser enucleation of the prostate (HoLEP) is being used for prostate of all sizes at considerable faster rate than TURP and now considered to be as new gold standard for the treatment of BPH. HoLEP relieves the pressure on the urethra tube by anatomically enucleating the majority of excess benign prostate tissue. Short operative time & hospital stay, minimal blood loss and fluid

absorption, and bladder neck contractures are some of the advantages of laser prostatectomy over the TURP and other conventional techniques [23–25].

2.3 Pharmacological treatment

The clinical manifestations of BPH are primarily precipitated by increased resistance to the flow of urine through the bladder neck and/or compressed prostatic urethra. Thereby, the treatment strategies are targeted to decrease the urinary resistance by reducing the prostatic volume. A number of strategies are available but great strides in the development of alpha-adrenergic blockers and anti-androgen (androgen deprivation therapy) have fueled this evolution.

2.3.1 Alpha adrenergic blockers

Alpha adrenergic blockers relaxes the smooth muscle in and around the prostate and bladder neck without affecting the detrusor muscle of the bladder wall thus relieve the obstruction due to dynamic component of LUTS. The rationale for this approach is based on that noradrenaline (NA) acts at alpha-1 adrenergic receptors (α_1 -AR) in the neck and sphincter of the urinary bladder to promote contraction and urinary retention. NA also acts at alpha-1 adrenergic receptors to control the smooth muscles in the prostate capsule and urethra [26]. Prazosin with a piperazinyl quinazoline nucleus, was the first clinically investigated selective α_1 -adrenergic receptor antagonist for BPH with 1000-fold greater affinity than that for α_2 -receptor. But, because of associated important adverse effects like postural hypotension and retrograde ejaculation, soon it was withdrawn from market [27]. The next advancement in drug therapy was the advent of selective α_1 -drugs, Terazosin and Doxazosin, structurally close analogs of Prazosin [28].

Prazosin

Terazosin

Doxazosin

Tamsulosin

Alfuzosin

Molecular studies have further identified three subtypes α_{1A} , α_{1B} and α_{1D} of the α_1 -AR. The α_{1A} is predominant in prostate, whereas α_{1B} subtype has been found to be predominant in blood vessels [29]. Their relative distribution and concentration in the bladder, prostate, neck, brain and vascular smooth muscle have been exploited to develop uroselective α_1 -adrenergic antagonists with reduced side-effects. Tamsulosin was launched as the first subtype selective α_1 -AR antagonist, but third uroselective α_1 -AR antagonist with ten fold more selectivity for α_{1A} -receptor subtype compared to α_{1B} -receptor subtype. Whereas, Alfuzosin, with comparable clinical efficacy to that of tamsulosin was the fourth uroselective α_1 -AR antagonist with almost similar affinity for all of the α_1 receptor subtypes and [12, 30]. Currently, Tamsulosin and Alfuzosin are the most widely prescribed medications as selective α_1 -AR antagonists for the LUTS associated with BPH.

2.3.2 Androgen deprivation therapy

The biological basis of this therapy lies in the observation that the androgens (dihydrotestosterone). plays a crucial role in the development and maturation of prostate gland. Furthermore, BPH does not develop in the patient who are castrated prior to the puberty [31, 32]. Androgen suppression causes reduction in prostatic volume which is believed to decrease the considerable responsible static component of bladder outlet obstruction resulting from benign prostatic hyperplasia [33].

Progestational agents like medogesterone, and hydroxyprogesterone acetate, acts in reversible manner and are capable of decreasing testosterone level in the serum by inhibiting the release of luteinising hormone (LH) [34]. Further, desensitization and down regulation of pituitary gonadotropin releasing hormone (GnRH) receptors by agonistic GnRH analogues is well established approach in the clinical treatment of BPH [35]. These agents (leuprolide, and Nafarelin acetate) [36], results in the blockage of gonadotropin release from the anterior pituitary gland followed by the suppression of steroidal sex hormones production. Antiandrogens like flutamide, cyproterone acetate, curcumin analogues bicalutamide, 16 substituted/ non-substituted D-homo-pregnane derivatives) compete for androgen receptor with the natural ligand (DHT) binding and are used therapeutically in BPH patients [37–41].

Plethora of the evidences has indicated the role of estrogen along with male androgens in the aging men with BPH condition. Estradiol is the product of the peripheral conversion of testicular and adrenal androgen in man under the influence of enzyme aromatase. Under the estrogenic effect, stromal and epithelial interactions presumably mediate and regulate the proliferative activity of the prostate [42]. Testolactone, atremestone, TZA-2237, and abiraterone are some of the aromatase inhibitors and found application in non-surgical treatment of BPH by blocking this peripheral conversion [43–45].

The importance of androgendeprivation by the use of antiandrogen agents was underscored by the fact that these centrally acting drugs decrease the testosterone level, and cause complications like erectile dysfunction and loss of libido [45, 46]. Therefore, search for the new drugs with more efficacies, selectivity and relative broader therapeutic index was being pursued and continued accrual resulted in the development of 5 α -reductase inhibitors.

3. 5 α -reductase inhibitors

5 α -reductase (5AR) is a nuclear membrane bound enzyme that converts testicular endogenous testosterone T to dihydrotestosterone DHT in the presence of

Figure 4.
 5 α -reductase enzymatic action.

cofactor NADPH. Thus 5AR dictates the cellular availability of DHT to prostatic epithelial cells and consequently modulate its growth as shown in **Figure 4** [47].

Thus, inhibition of androgen action by 5 α -reductase represents a logical treatment of 5 α -reductase activity disorder i.e. BPH. 5ARI decreases the dihydrotestosterone concentration by blocking the enzyme and, provide relief from the symptoms related to the static mechanical obstruction caused by BPH by shrinking the size of prostate [48]. Further, the rationale for use of 5ARI is rooted in the observation that these agents are more specific to DHT action without affecting/ lowering T level, thus capable of decreasing long term side effect of castration associated with loss of testosterone, without compromising the efficacy of hormonal therapy [49, 50].

3.1 Physiology of androgens release

Figure 5 indicating the control of testicular androgen production by hypothalamus and the pituitary gland. Neurons in preoptic area of the hypothalamus secrete the decapeptide lutenizing hormone releasing hormone (LHTH), in a pulsatile fashion, which in turn stimulates the release of lutenizing hormone (LH) from the pituitary. After reaches to the testies, LH binds to the high affinity receptor present on the surface of leydig cells and stimulate them to produce testosterone. Released T travels in the blood either in the free state or after binding with protein [43]. Circulating testosterone levels in a negative feed back mechanism regulates the secretion of hypothalamus and pituitary.

Major androgen in the adult male is Testosterone (T) and 98% of all T in the prostate is of testicular origin, whereas only 5–10% being produced by adrenal gland [51]. The unbound T diffuses into the prostate cell (target organ), where most of it gets converted to dihydrotestosterone (DHT) by the membrane bound NADPH dependent enzyme 5 α -reductase. Within prostate, DHT binds to cytosol androgen receptor protein (AR) followed by entry of DHT-AR complex into the nucleus, where it stimulates the RNA synthesis after interacting with DNA binding sites (**Figure 6**) [52].

T and DHT differ in their physiological action and T also binds to androgen receptor but with lesser affinity to that of DHT [53]. According to Burckovsky and Wilson postulation T acts as a prohormone and DHT is found to be the main active hormone in androgen sensitive tissue [47]. With in embryo, T is responsible for the transformation of Wollffian ducts in epididymis, seminal vesicle & differential ducts & and responsible for production of DHT after activating the expression of 5AR. On the other hand, DHT in embryo is found to be crucial for the sexual differentiation of male foetus organ, formation of external genitalia, like urethera and prostate. After puberty, it's the T that determines the modification of external

Figure 5.
Physiology of androgen release.

Figure 6.
Interaction of androgen within prostate cell.

genitalia, deepening of voice, increase of muscle mass, spermatogenesis, and male sexual behavior. In contrary to that DHT formation in male puberty is related with the increase of facial & body hair, and the enlargement of prostate [32, 37, 54, 55].

Further crucial role of DHT was discovered through male pseudohermaphroditism, a genetic disorder with complete or partial 5α-reductase deficiency. Decreased 5AR activity not only resulted in low level of DHT [56, 57], but also accompanied by several distinguished features at the critical juncture of foetal and postnatal development [58]. Male with such condition showed ambiguous external genitalia

at-birth [59], often raised as girls, little facial hairs as adults, no temporal receding hairline, small prostate no acne and normal libido. Whereas, female with 5AR deficiency did not show any clinical symptoms.

Excessive production of DHT is associated with development of several endocrine diseases such as acne, alopecia in men, male pattern baldness, hirsutism in women, prostatic carcinoma and benign prostatic hyperplasia [7]. In BPH, concentration of DHT is found to 2.5 fold higher than in normal prostate.

3.2 Isozyme of 5 α -reductase

The family of 5AR is composed of three known isoenzymes with the types I and II being the most known. Steroidal 5 α -reductase is a system of NADPH dependent enzymes that catalyzes the irreversible conversion of 4-en-3-oxo-steroid to the corresponding 5 α -H-3-oxo-steroid [60–62]. Based on the anatomical location, biochemical properties, and tissue expression pattern three different isozymes of 5AR have been isolated, expressed and characterized (**Table 1**). The type 2 isozyme is predominantly present in the prostate, seminal vesicle, epididymis, genital skin, and liver. It has been found to be essential for differentiation of male external genitalia during foetal life, and its deficiency leads to the condition known as male pseudohermaphroditisms [63, 64]. Whereas, type 1 is not the major species expressed in the prostate and exhibit only micromolar affinities for steroidal natural substrate (T) [65, 66].

Both the isoforms have optimal activity at different pH range as type 1 is active at alkaline pH of 8.5, while type 2 is active at pH 4.7–5.5. Studies have shown that the activity of type I enzyme is several times higher in PC than in BPH. Whereas the 5AR type II (5AR-2) isoenzyme with higher affinity for T at the optimum pH 5.5 predominates in the prostate and other genital tissues and plays a major role in BPH [67, 68].

	5AR-1	5AR-2	5AR-3
Gene	SRD5A1	SRD5A2	SRD5A3
Location	5p15	2p23	4q12
Length (b)	36,173	56,385	25,458
Protein size	259	254	319
Transmembrane helices	5	4	6
Protein weight (Da)	29,459	28,393	36,521
Optimal pH	6–8.5	5–5.5	6.9
Affinity for testosterone	Km = 1.7 μ M	Km = 0.2 μ M	—
In vitro inhibition	K _i $\geq$ 300 nM	K _i = 3–5 nM	—
Localization (in tissues)	Sebaceous glands of skin, sweat glands, dermal papilla cells, fibroblasts from all areas	Prostate, genital skin, epididymis, seminal vesicles	Hormone refractory prostate cancer cells, pancreas, brain, skin, adipose tissue
Selectivity to the inhibitors	Inhibitors with 4-methyl-4-aza functionality are very potent	4-aza, 6-aza and charged 3-substitutents derivatives are highly selective.	—

Table 1.
5AR isozymes and their characteristic features.

A new isoenzyme of 5AR, type III (5AR-3) have been identified recently in castration resistant prostate cancer (CRPC) cells as well as in other tissues such as pancreas, brain, skin and adipose tissues [69, 70]. The length, location and other characteristics of these isoenzymes have been presented in **Table 1** [71].

3.3 Mechanism of 5 α -reductase action

The detailed chemical and kinetic mechanisms of conversion of T into DHT by 5AR have been investigated as follows:

3.3.1 Chemical mechanism

Figure 7 is indicating the proposed mechanism of T reduction to DHT under the influence of 5 α -reductase. It is based on the known regio and stereoselectivity of the reduction that involves the formation of binary complex between the enzyme and NADPH, followed by formation of ternary complex with the substrate [72, 73]. Binary complex formation follows the activation of the enone system by based on its strong interaction with commonly present electrophilic residue (E^+) (proton, +ve charged group, proton donor) in the active site. Enone activation gives the delocalized carbocation which is being reduced selectively at C-5, on the α -face, by a direct hydride transfer from NADPH and lead to the formation of the enolate of DHT [74]. Generated intermediate duly coordinated with $NADP^+$ on the α -face, is further attacked by a proton on the β -face at C-4 and results into the formation of

Figure 7.
Chemical mechanism of action of 5 α -reductase.

ternary complex E-NADP⁺-DHT. Towards the end of reaction, release of DHT gives the binary NADP⁺-enzyme complex, followed by the release of NADP⁺ leaving the enzyme free for further catalytic reactions.

3.3.2 Kinetic mechanism

The kinetic mechanism was studied for the natural substrate T using rat and human prostatic 5 α -reductase and both the models showed similar kinetic mechanism as shown in **Figure 8**. 1,4-reduction of the substrate (T) depends on the initial velocity data from progesterone and 5 α -reductase, wherein NADP⁺ is found to be competitive versus NADPH but non-competitive versus progesterone. Further catalysis occurs with the initial release of DHT followed by NADP⁺.

3.4 Classification of 5 α -reductase inhibitors

The control of the physiological action of major androgen DHT, without significant change in the overall profile of other hormones especially (T), through the inhibition of specific enzyme 5AR involved in its synthesis and metabolism, plays an important role in the design of ARIs, mimicking the electronic and steric properties of the enolate [75].

The identification of different isozymes of 5AR, their specific role in physiological and pathological developments of BPH has opened the door for more specific and selective inhibitors of this enzyme [76]. Broadly 5 α -reductase inhibitors have been divided into following major groups a) Transition state analogues b) Mechanism based inhibitors c) Structure based.

3.4.1 Transition state analogues

Based on chemical mechanism of 5AR, two possible transition states (**Figure 9**) have been postulated substrate like and product like. [77, 78]. The 'substrate like' transition state is the one in which the C-5 has not yet changed its sp²-hybridization and the structure of C-3, C-4, and C-5 are similar to those of intermediate carbonation. On other hand in 'product like' TS C-5 has assumed its final sp³ hybridization and structure of C-3, C-4 and C-5 are similar to those of enol form of DHT.

Transition state analogue states that the binding to the enzyme and thus its inhibition could be greater for molecules being mimic of the transition of the enzymatic process [77].

3.4.2 Mechanism based analogues

According to the kinetic mechanism of T reduction to DHT, three different types (Type A, B and C) of inhibitors have been identified [79, 80]:

- a. Type A: Inhibitors compete with substrate testosterone and cofactor NADPH i.e. bisubstrate.

Figure 8.
 Kinetic mechanism.

Figure 9.
Transition states of the enzyme (5AR).

- b. Type B: These are the compounds that got the potential to bind reversibly to NADPH-enzyme complex and competitive with natural substrate T thus competitive inhibitors.
- c. Type C: Such inhibitors fit the enzyme- NADP complex and are uncompetitive versus the substrates.

Number of steroidal and non-steroidal analogs ranging from classical, reversible and irreversible inhibitors, and transition state analogues to mechanism-based analogues have been synthesized and evaluated during last two decades as shown in **Figure 10**.

Biological basis for the steroidal inhibitors lies in the observation that enzyme could be best inhibited by the compounds having structural similarities to natural substrate i.e. T. One of the earlier report in 1970 by Voigt and Hsia, indicate the ability of 23 steroidal hormones to inhibit 5AR in human skin thus the efficacy of steroidal derivatives in BPH [81]. Progesterone, a competitive substrate of T, restrained transformation by upto 93.3% and was converted to 5-pregnane-3, 20-dione. Great affinity of progesterone for 5AR was further indicated by its high value of inhibitory constant ($K_i = 700$ nm). Other potent inhibitors were deoxycortisone, deoxycortisone acetate and dehydroepiandrosterone [82]. In 1973, synthesis and evaluation of series of 5ARI, indicated the key structural requirements for the 5ARI activity i.e. presence of 4-en-3-one function and 17 β -side chain having one or more oxygen functionalities. Molecules possessing these features act as competitive inhibitors of 5AR, therefore, all of them could be regarded as a substrate of the enzyme 4-en-3-one steroids [83]. The clinically approved first inhibitor was

Figure 10.
Chemical classes of 5AR inhibitors.

prepared by modification of the structure of naturally existing substrates. This modification included the substitution of various hetero atom such as nitrogen, by forming the azasteroids by replacing carbon atom of the ring with nitrogen in the steroidal moieties.

Finasteride.

Chemically Finasteride (MK-906) is 17 β -(N-tert-butyl-carbamoyl)-4-aza-5 α -androst-1-en-3-one. It was synthesized in 1984, and got clinical approval in 1992 in the United States as the first 5 α -reductase inhibitor for the treatment of BPH [84]. It is a competitive inhibitor of 5 α -reductase type 2 with 10-fold high affinity than type 1 and forms a stable complex with enzyme. Clinical doses of 5 mg/day has been found to decrease the prostatic DHT level by 70 to 90%, in human beings, thus decreases prostate volume or size followed by improvement in urinary flow rate [85, 86]. It has neither any other hormone (androgenic, antiandrogenic) related properties, nor it interferes with the binding of T or DHT to the androgen receptor [87]. Though significant improvement in term of increased flow rates and decreased prostate-specific antigen level has been observed in finasteride-treated group. But, its long term usage results in common side effects like decreased libido, ejaculatory dysfunction, or impotence, while rashes and breast enlargement have also been observed in some of the patients.

Finasteride

Dutasteride.

Chemically dutasteride is 17 β -N-{2, 5-bis (trifluoromethyl) phenyl} -3- oxo- 4-aza- 5 α - androst - 1- ene - 17-carboxamide and belongs 4-aza-steroids [86] It was approved in 2002 by the US FDA for the symptomatic treatment of BPH. Unlike finasteride, dutasteride is a nonselective competitive inhibitor of both isozymes. 5 α -reductase type 1 and type 2.

At clinical dose of 0.5 mg/day, it decreases DHT levels >90%, by forming a stable complex with a slow rate of dissociation constant. Dutasteride has been found to improve urinary flow rate, decrease the risk of AUR and need for surgery by reducing the size of enlarged prostate [88–90]. Dutasteride is found to be 60 times more active than finasteride and efficacy has been improved in terms of symptom score, maximal urinary flow rate, and quality of life [86].

Dutasteride

These two drugs have been found to display competitive blocking effect in short-term kinetic, whereas long-term reaction analysis revealed their irreversible inhibitory effect by forming a stable complex of enzyme-bound intermediates [91]. The binding affinity between 5 α -R isoenzyme and 4-azasteroids can be described in the two step mechanism:

Where K_i is the inhibition constant for the first step equilibrium and K_3 is the rate constant for the time-dependent second step [92]. Mechanistically, finasteride has been proven to be 5 α -R2 inhibitor by acting on alternative substrate for 5 α -R2 which is initially bound to highly stable complex of enzyme-bound NADP-dihydrofinasteride. The resulting adduct is finally processed to form dihydrofinasteride [93]. The bisubstrate complex of NADP-dihydrofinasteride is a potent inhibitor with dissociation constant $k_i 1 \times 10^{-31}$ M that makes it as one of the extremely potent known non-covalently bound complexes.^{180,183} Finasteride is also

	K_3 (s ⁻¹)	K_1 (IC ₅₀ , nM)	K_3/K_1 (M ⁻¹ s ⁻¹)
5 α -R 1			
Finasteride inhibition	1.4×10^{-3}	360	4×10^3
Dutasteride inhibition	1.1×10^{-3}	6	1.8×10^5
5 α -R 2			
Finasteride inhibition	2.2×10^{-2}	69	3.2×10^5
Dutasteride inhibition	4.9×10^{-3}	7	6.8×10^5

Table 2.
Inhibition of 5 α -R isozymes by clinically approved drugs.

known for its inhibitory effect on 5 α -R1. However, the resultant dihydrofinasteride complex has comparatively lower rate constant (**Table 2**).

4. Combination therapy

The scientific rationale for combining 5ARIs and α_1 -AR antagonists is based on their different and complementary modes of action, that help in managing static and dynamic component responsible for of an enlarged prostate gland and symptoms of LUTS. The rationale for this combination was further recommended on account of rapid relief of symptoms by the α_1 -AR antagonists, without targeting the underlying disease process along with mid or more sustained relief of symptoms by the 5ARIs [94]. The efficacy and safety of the treatment with different combinations versus treatment with either agent alone has been investigated by different groups in large multicentral trials [95, 96].

Veterans Affairs Cooperative Study and Prospective European Doxazosin group evaluated the combination of finasteride with terazosin & doxazosin, respectively for one year. Significant improvement in the symptom score and flow rate was observed with α_1 -AR antagonists alone or combination therapy as compared to placebo or finasteride alone, but there was no significant difference observed for combination therapy over α_1 -AR antagonists alone. Short term successful trials were followed by studying the combination of finasteride and doxazosin for a period of 4.5 years as Medical therapy for Prostate Symptoms. Finasteride alone and this particular combination reduced the risk of AUR and need for BPH-related surgery versus placebo, whereas none of these outcomes were reduced significantly in patients consuming doxazosin alone.

Outcomes of another long term study examining the role of combination of dutasteride and tamsulosin (CombAT) over the α_1 -AR antagonists (tamsulosin) alone would be a major step in assessing the combination therapy and treatment decision [97]. Though present observations demonstrated a higher incidence of impotence with combination therapy compared with 5ARIS, in addition to higher incidence of α_1 -AR antagonists-mediated dizziness, hypotension [93]. Cost-effectiveness studies by Nickel suggest that the combination therapy is more suitable for men at high risk for BPH progression, patients with high symptom score, large prostate volume and low $q_{\max}$ value.

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