Review Article

5AR Inhibitors and Related Disease Conditions

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ABSTRACT

This review article discusses the theoretical background of 5a-reductase inhibitors (5ARI) and disease conditions related to it in men and women. The disease like being prostatic hyperplasia and alopecia are discussed in this article with their symptoms, pathogenesis and how5a-reductase inhibitors are act is also discussed. The 5ARIs drugs like Finasteride and Dutasteride, which specifically inhibit the production of dihydrotestosterone by acting as competitive inhibitors of 5a-reductase. 5α-reductases (5AR) are the enzymes responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of benign prostatic hyperplasia (BPH).

Keywords: Benign prostatic hyperplasia, 5AR inhibitors, Finasteride, Dutasteride, dihydrotestosterone, alopecia.

1. INTRODUCTION

5α-reductases (5AR) are the enzymes responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of benign prostatic hyperplasia (BPH). BPH is a common and progressive condition that could impair one's quality of life and affects men in an age-dependent manner; more than 50% of men over the age of 50 and close to 90% of men over 80 years old are affected.[1]It is characterized by various lower urinary tract symptoms, including decreased urinary stream, incomplete voiding, urinary frequency and hesitancy [2]. By blocking the enzyme, 5AR inhibitors decrease the serum concentration of DHT, inhibiting prostatic growth and decreasing disease progression.[3] Goal for development of 5α-reductase inhibitors (5α-RI) was to bind to 5α-R with little or no affinity for the androgen or other steroid receptors. The first inhibitors were steroids that mimicked T and, in many cases, were substrates themselves (i.e., not true inhibitors). The inhibitors can be broadly classified into two categories: steroidal and nonsteroidal. The steroidal class has more inhibitors thus far. The mechanism of 5α-RI is complex but involves the binding of NADPH to the enzyme followed by the substrate. The $\Delta^{4,5}$ bond is broken and a hydride anion is transferred from NADPH directly to the C-5 carbon on the α face followed by a proton attacking the C-4 carbon on the β face leading to the formation of the product that subsequently leaves the enzyme-$NADP^+$ complex. $NADP^+$ departs last and the enzyme becomes free for further catalysis cycles. Based on this, the mechanism of inhibition of 5α-R isozymes is divided into three types[4]

- Competitive with the co-factor (NADPH) and substrate (bi-substrate inhibitors): the inhibitor binds the free enzyme.
- Competitive with the substrate: the inhibitor binds the enzyme-NADPH complex.
- uncompetitive with the enzyme-$NADP^+$ complex: the inhibitor binds the enzyme-$NADP^+$ complex after the product leaves.[5]

1.1 Medical Use

- Benign prostatic hyperplasia
- Prostate cancer
- Androgenic alopecia in both men and women
- lower urinary tract symptoms
- 5-aris are also sometimes employed as supplementary antiandrogens in hormone replacement therapy for trans women.[6]

1.2 Pharmacology of 5α-reductase inhibiter:

The pharmacology of 5α-reductase inhibition is complex, but involves the binding of NADPH to the enzyme followed by the substrate. Specific

substrates include testosterone, progesterone, androstenedione, epitestosteron e, cortisol, aldosterone,and deoxycorticosteron e.The entire physiologic effect of their reduction is unknown, but likely related to their excretion or is itself physiologic.[7] Beyond being a catalyst in the rate-limiting step in testosterone reduction, 5α-reductase isoforms I and II reduce progesterone to 5α-dihydroprogesterone (5α-DHP) and deoxycorticosterone to dihydrodeoxycorticosterone (DHDOC). In vitro and animal models suggest subsequent 3α-reduction of DHT, 5α-DHP and DHDOC lead to neurosteroid metabolites with effect on cerebral function. These neurosteroids, which include all opregnanolone, tetrahydrodeoxycorticosterone (THDOC), and 5α-androstanediol, act as potent positive allosteric modulators of $GABA_A$ receptors, and have anticonvulsant, antidepressant, anxiolytic , prosexual, and anticonvulsant effects.[8] 5α-dihydrocortisol is present in the aqueous humor of the eye, is synthesized in the lens, and might help make the aqueous humor itself.[9] 5α-dihydroaldosterone is a potent antinatriuretic agent, although different from aldosterone. Its formation in the kidney is enhanced by restriction of dietary salt, suggesting it may help retain sodium as follows[10]

$$\textit{Substrate} + \textit{NADPH} + H^+ \rightarrow \textit{5α-substrate} + \textit{NADP}^+$$

5α-DHP is a major hormone in circulation of normal cycling and pregnant women.[11] Inhibition of the enzyme can be classified into two categories: steroidal and nonsteroidal. The steroidal class has more inhibitors with examples including finasteride (MK-906), dutasteride (GG745), 4-MA, turosteride, MK-386, MK-434, and MK-963. Several have pursued synthesis of nonsteroidals to inhibit 5α-reductase due to the undesired side effects of steroidals. The most potent and selective inhibitors of 5α-R1 are found in this class, and include benzoquinolones, nonsteroidal aryl acids, butanoid acid derivatives, and more recognizably, polyunsaturated fatty acids (especially gamma-linolenic acid), zinc, and green tea[7]

A. Benign prostatic hyperplasia [12,13]

Commonly referred to as **BPH**, this is the most common issue arising in older men. It basically means that the prostate is getting bigger but that it is not cancerous, i.e. benign. Often times it is accompanied with inflammation, in this case known as prostatitis.

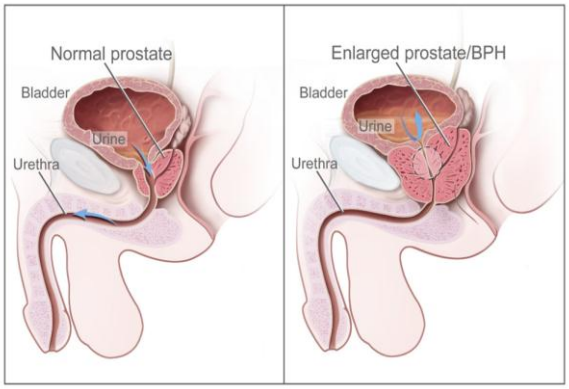

Fig.1: Being prostatic hyperplasia

Benign prostatic hyperplasia is also called BPH is a condition in men in which the prostate gland is enlarged and not cancerous. Benign prostatic hyperplasia is also called benign prostatic hypertrophy or benign prostatic obstruction. The prostate goes through two main growth periods as a man ages. The fist occurs early in puberty, when the prostate doubles in size. The second phase of growth begins around age 25 and continues during most of man's life. Benign prostatic hyperplasia often occurs with the second growth phase. As the prostate enlarges, the gland presses against and pinches the urethra. The bladder wall becomes thicker. Eventually, the bladder may weaken and lose the ability to empty completely, leaving some urine in the bladder. The narrowing of the urethra and urinary retention the inability to empty the bladder completely cause many of the problems associated with benign prostatic hyperplasia.

- **Cause**

The cause of benign prostatic hyperplasia is not well understood; however, it occurs mainly in older men. Benign prostatic hyperplasia does not develop in men whose testicles were removed before puberty. For this reason, some researchers believe factors related to aging and the testicles may cause benign prostatic hyperplasia. Throughout their lives, men produce testosterone, a male hormone, and small amounts of estrogen, a female hormone. As men age, the amount of active testosterone in their blood decreases, which leaves a higher proportion of estrogen. Scientific studies have suggested that benign prostatic hyperplasia may occur because the higher proportion of estrogen within the prostate increases the activity of substances that promote prostate cell growth. Another theory focuses on dihydrotestosterone (DHT), a male hormone that plays a role in prostate

development and growth. Some research has indicated that even with a drop in blood testosterone levels, older men continue to produce and accumulate high levels of DHT in the prostate. This accumulation of DHT may encourage prostate cells to continue to grow. Scientists have noted that men who do not produce DHT do not develop benign prostatic hyperplasia.

- **symptoms**
  a) urinary frequency—urination eight or more times a day
  b) urinary urgency—the inability to delay urination
  c) trouble starting a urine stream
  d) a weak or an interrupted urine stream
  e) dribbling at the end of urination
  f) nocturia—frequent urination during periods of sleep
  g) urinary retention
  h) urinary incontinence—the accidental loss of urine
  i) pain after ejaculation or during urination
  j) urine that has an unusual color or smell

- **Pathogenesis** [14]

The exact molecular mechanism(s) that causes prostate enlargement is not known. It is known that advancing age and male hormones play a major role in the gradual and continuous enlargement of the prostate gland which most men experience. Prostatic hyperplasia can be seen microscopically in men in their 30's and 40's but significant prostate enlargement generally begins in the late 40's or older. By the time a man has reached his 70's or 80's, there is approximately a 90% chance that he will have an enlarged prostate (EP).

In addition to aging, male hormones are required for prostate enlargement to occur. Testosterone, produced by the testes, is converted to dihydrotestosterone (DHT) which is the major androgen that causes the prostate to enlarge as men age. It is hypothesized that multiple growth factors and perhaps changes in the characteristics of hormone receptors are involved in prostate enlargement but the precise mechanism of this process remains unclear

As the prostate gland enlarges, it causes partial, and at times complete, obstruction of urinary flow from the bladder. Since the bladder is a muscle, the bladder wall becomes thicker and stronger when it has to squeeze harder to empty through the obstruction of the prostate. The thick wall bladder does not stretch as readily as a thinner softer bladder so the functional urine capacity of the bladder decreases. In addition, in many men the bladder becomes hyper sensory so that a smaller volume of urine and a lower pressure of urine in the bladder feels like a full bladder. The result of this process is a constellation of urinary symptoms which are commonly called lower urinary tract symptoms (LUTS).

LUTS are divided into two broad categories, obstructive and irritative symptoms . The most common symptoms that bother men are irritative symptoms such as nocturia and frequency. These symptoms occur because the functional capacity of the bladder is decreased and it is hyper sensory which makes men have to empty their bladder with lower volume than when they were younger. Urgency (the sudden urge to urinate which is hard to control) occurs because the bladder has an uninhibited muscle contraction as a result of its hyper sensory state. The obstructive symptoms (weak stream, hesitancy, double voiding, intermittent stream, post void dribbling) occur from the same mechanism one would expect from pumping water through a partially plugged pipe: the obstruction diminishes the flow and requires a higher pressure to initiate bladder emptying.

The symptom nocturia deserves special mention. This is probably the most bothersome symptom to the majority of men and certainly the most bothersome symptom to the wives' of those men. It is important to know that nocturia can occur from causes other than EP. Certainly, an enlarged prostate is one of the more common, if not the most common cause of nocturia and in a large percentage of cases, treatment of the enlarged prostate improves nocturia significantly. The nocturia can also be caused by increased fluid intake in the evening, a light sleep pattern where a man awakens for other reasons and gets up to urinate because he has some urine in his bladder, and fluid retention during the day which leads to an increase in urine volume at night.

As people age, it is common for them to retain fluid during the day. This can be manifested as swelling in the feet and ankles in many people. When a person lies down, and the force of gravity comes off the kidneys and they "float", blood flow through the kidneys increases. In patients who are fluid overloaded, there will be an increased volume of urine produced. Since most people do not lie down much during the day, the increased urine output occurs at night while they sleep causing them to have to urinate several times. A patient who has few if any complaints about urinary frequency during

the day but has frequent urination during the night needs to consider the possibility that the problem is not the prostate gland but instead retention of fluid during the day. These problems are generally best treated by a primary care physician instead of by a urologist.

A large subset of men with LUTS does not have particularly enlarged prostates. In these men, the smooth muscle in the bladder neck and prostatic urethra does not relax during urination like it normally does and they end up with a "functional" obstruction. Normally, when a man urinates, the bladder squeezes and the bladder neck and prostatic urethra relax and open and the urine flows out through a good sized opening. If the bladder neck and prostatic urethra do not relax, out flow is impeded. There is smooth muscle in the bladder neck and prostate which normally relaxes. This relaxation is modulated by alpha receptors. As we will learn later in this article, one of the major first line treatments for LUTS is alpha blockers. These medicines help relax the bladder outlet and prostatic urethra.

The large majority of men with prostate enlargement present to their physician with a complaint of urinary symptoms. A subset of these men is at risk for progression to urinary retention (where the bladder can't empty and a catheter is required for drainage) or prostate surgery (discussed below). As we will see, men primarily at risk for urinary symptoms can be treated differently than men who are also at risk for progression to retention or surgery.

An important recent trial on the natural history of prostate enlargement and medical management of BPH was published in the New England Journal of Medicine in December of 2003. The trial was named Medical Therapy of Prostatic Symptoms (MTOPS). This NIH sponsored study provided a wealth of new information on the natural history and medical management of BPH. A few of the more important findings were that in many men, combination medical therapy (alpha blocker plus 5-alpha reductase inhibitor) works better than either medication class alone. In addition, alpha blockers are an excellent medication choice to control bothersome urinary symptoms while 5-alpha reductase inhibitors have the advantage of decreasing the risk of a patient developing urinary retention or the need for prostate surgery. In the long run, 5-alpha reductase inhibitors also provide excellent symptom control for men with enlarged prostates.

- **Correlation of 5-alpha reductase and BPH:[15]**

5-alpha reductases (5AR) are the enzymes responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of benign prostatic hyperplasia (BPH). BPH is a common and progressive condition that could impair one's quality of life and affects men in an age-dependent manner; more than 50% of men over the age of 50 and close to 90% of men over 80 years old are affected.

By blocking the enzyme, 5AR inhibitors decrease the serum concentration of DHT, inhibiting prostatic growth and decreasing disease progression. There are two 5AR inhibitors available: fiasteride and dutasteride. Finasteride is a selective inhibitor of the Type 2 isoenzyme whereas dutasteride inhibits both Type 1 and Type 2 .Thus difference in mechanism results in a significantly greater and more consistent reduction in DHT with dutasteride than fiasteride; however it is unclear whether this leads to a clinically significant difference.

There have been three systematic reviews on the use of dutasteride versus fiasteride for the treatment of BPH but these reviews contain several methodological issues that may affect the reliability of their findings. Bias may have been introduced through inclusion of retrospective cohort studies and inadequate blinding around subjective symptoms. One review only included results from one trial.

B. Alopecia areata:[16,17]

Alopecia areata is "a common condition of undetermined etiology characterized by circumscribed, nonscarring, usually asymmetric areas of baldness on the scalp, eyebrows, and bearded portion of the face."

In the case of alopecia areata, the immune system attacks the hair follicles causing inflammation, which leads to hair loss.

Fig. 2: Alopecia areata

- **Causes**

The condition occurs when white blood cells attack the cells in hair follicles, causing them to shrink and dramatically slow down hair production. It is unknown precisely what causes the body's immune system to target hair follicles in this way.

While scientists are unsure why these changes occur, it seems that genetics are involved as alopecia areata is more likely to occur in a person who has a close family member with the disease. One in five people with the disease has a family member who has also developed alopecia areata.

Other research has found that many people with a family history of alopecia areata also have a personal or family history of other autoimmune disorders, such as atopy (a disorder characterized by a tendency to be "hyperallergic"), thyroiditis, and vitiligo.

Despite what many people think, there is very little scientific evidence to support the view that alopecia areata is caused by stress. Extreme cases of stress could potentially trigger the condition, but most recent research points toward a genetic cause.

- **Symptoms**

The most prominent symptom of alopecia areata is patchy hair loss. Coin-sized patches of hair begin to fall out, mainly from the scalp. Any site of hair growth may be affected, though, including the beard and eyelashes.

The loss of hair can be sudden, developing in just a few days or over a period of a few weeks. There may be itching or burning in the area prior to hair loss. The hair follicles are not destroyed and so hair can re-grow if the inflammation of the follicles subsides. People who experience just a few patches of hair loss often have a spontaneous, full recovery without any form of treatment.

About 30 percent of individuals who develop alopecia areata find that their condition either becomes more extensive or becomes a continuous cycle of hair loss and regrowth.

About half of patients recover from alopecia areata within 1 year, but many will experience more than one episode. Around 10 percent of people will go on to develop alopecia totalis or alopecia universalis.

- Alopecia areata can also affect the fingernails and toenails, and sometimes these changes are the first sign that the condition is developing. There are a number of small changes that can occur to nails.
- Pinpoint dents appear
- White spots and lines appear
- Nails become rough
- Nails lose their shine
- Nails become thin and split

▪ **Additional clinical signs include:**

a) Exclamation mark hairs - where a few short hairs that get narrower at their bottom and grow in or around the edges of bald spots
b) Cadaver hairs - hairs broken before reaching the skin surface
c) Regrowth of white hair in areas affected by hair loss

- **Pathogenesis**

a) Basic Immunopathology

Examining the skin lesions may best attain the understandings of the immunopathological mechanisms in AA. CD8+ T cells appear to be the first lymphocytes to enter the proximal follicular epithelium even though CD4+ T cells predominate numerically in the perifollicular infiltrates. The increased numbers of NK cells and mast cells in perifollicular infiltrates raises the question of whether these cells are also involved in the pathogenesis of AA. Although no pathogenic evidence, autoantibodies against follicular autoantigens are often found in the serum and skin of patients with AA.

As a matter of fact, in murine models of AA, CD8+ T cells alone can transfer the disease. This is especially after the T cells have been prepared by contact with melanogenesis-related autoantigens. The most effective way instigating the disease in widely used murine model, is to transfer the CD8+ T cells together with CD4+ T cells, whilst the transfer of serum or autoantibodies from patients with AA fails to elicit hair loss. Contrariwise, the depleting CD8+ T cells restore hair growth in a rat model of AA. It is therefore reasonable to consider AA a CD8+ T-cell–dependent, organ-specific autoimmune disease.

b) Genetic Component in Alopecia Areata

Strong genetic component can be associated to the development of AA. For instance, many patients with known family history of AA also have a history of atopy, Down's syndrome, autoimmune polyendocrinopathy- candidiasis-ectodermal dystrophy syndrome, other immune diseases or a combination of these disorders. A poorer prognosis, rapid progression, frequent relapses and greater resistance to therapy often characterize familial cases of AA. Also, relatives of affected family members are at risk of AA. The role of genetic factors in the pathogenesis of AA is further emphasized by ethnic variations in the incidence and relative risk.

Martinez-Mir and friends have identified that AA can coexist with psoriasis in a genomwide

association study of 20 families with AA. In psoriasis, it has been linked with Cytotoxic T-lymphocyte–associated antigen 4 (CTLA4), which is a co-stimulatory molecule that is involved in the negative regulation of T-cell activation. It may also be an exposure gene for AA especially in patients with a severe form of the disorder. The CTLA 4 association is strengthened by another study in which Petukhova and friends have stated the significance of both innate and acquired immunity in the pathogenesis of AA and emphasized the point that this disorder shares routes with other autoimmune diseases. [4] Both Martinez-Mir et al. and Petukhova et al. studies identified susceptibility loci common to AA on chromosomes 6p (HLA), 6q (UL 16 binding protein [ULBP]), 10p (IL2RA), and 18p (PTPN22). Also, Petukhova et al. identified some genes that may be related with AA and other autoimmune diseases, such as the genes for *ULBP,* which encrypt a class of ligands for activating NKG2D.

- **Correlation of 5-alpha reductase and Alopecia[18]**

Dihydrotestosterone is a tissue metabolite of testosterone.It is formed under the influence of the 5a reductase enzyme, which exists as two isoforms. Type 1 5a-Ris mainly found in the sebaceous glands and the epidermis,but is also present in sweat glands, hair follicles, endothelialcells and Schwann cells in the myelin sheathsof nerves, while type 2 5a-R is mainly located inthe hair follicles (inner layer, infundibulum, sebaceousglands) (15). The conversion of circulating testosterone into DHT is mainly performed by isoenzyme 5α-R type 2. Dihydrotestosterone has the ability to bind to sex hormone binding globulin (SHBG) more than three times higher than testosterone. In men, approximately 70% of DHT is formed from the conversion of testosterone, while in women, the substrate is androstenedione. While elevated concentrations of DHT can be observed in men with androgenetic alopecia or Klinefelter's syndrome, as well as in approximately 40% of women with idiopathic hirsutism and approximately 35% with PCOS, decreased concentrations occur in men with azoospermia and anorchia.Determination of DHT concentration is helpful for antiandrogen therapy in patients with prostate cancer or androgenetic alopecia.

1. Synthetic drugs which act as 5 Alpha-Reductase Inhibitor[8,19,20,21]

2.1 Finasteride

Class: 5 Alpha-Reductase Inhibitor

Available dosage form in the hospital: FINASTERIDE 5MG TAB

Dosage

- Benign prostatic hyperplasia (Proscar®): Oral: 5 mg once daily as a single dose; clinical responses occur within 12 weeks to 6 months of initiation of therapy; long-term administration is recommended for maximal response
- Male pattern baldness: Oral: 1 mg daily
- Female hirsutism: Oral: 5 mg/day

Renal Impairment: No adjustment is necessary.

Hepatic Impairment**:** Use with caution in patients with liver function abnormalities because finasteride is metabolized extensively in the liver

Common side effect:

- Endocrine & metabolic: Impotence, libido decreased
- Neuromuscular & skeletal: Weakness
- Pregnancy Risk Factor: X

2.2 Dutasteride

There are two steroid 5α-reductase enzymes which have been discovered, type 1 and type 2. Type 1 has been reported to be located throughout the body including the liver, prostate, and skin. Type 2 is also found in extra-prostatic tissues but is predominantly located in the male genitalia and prostate. Investigators have demonstrated presence of 5 α-reductase types 1 and 2 mRNA in each zone of the prostate. When compared with normal prostate tissue BPH tissue was found to have a significant increase in expression of 5 α-reductase types 1 and 2 mRNA. They also found in prostate cancer specimens higher expression of 5 α-reductase type 1 but not type 2 mRNA than in normal prostate tissue.

Dutasteride, a synthetic 4-azasteroid, is a selective and competitive inhibitor of both type 1 and type 2 5α-reductase isoenzymes. 5α-reductase is responsible for the intracellular conversion of testosterone to DHT, the primary androgen critical in the initial development and subsequent growth of prostate tissue. In comparison to fiasteride, a specifi inhibitor of type 2 5 α-reductase, dutasteride is more potent with a higher reduction in DHT concentrations at equally potent doses. After treatment with dutasteride 0.5 mg daily for two weeks, DHT serum levels were decreased by 90%.

Dutasteride is administered orally. Upon reaching systemic circulation, dutasteride is highly bound to albumin (99%) and alpha-1 acid glycoprotein (96.6%) and widely distributed throughout the central and peripheral compartments. Dutasteride is extensively metabolized in the liver by the cytochrome P450 (CYP) isoenzymes CYP3A4 and CYP3A5. Dutasteride and its metabolites are mainly excreted in the feces (5% unchanged and 40% as metabolites). Less than 1% of dutasteride was found unchanged in the urine.

Side effect

Sexual side effects including impotence, decreased libido, gynecomastia and ejaculation disorder were most commonly seen in patients treated with dutasteride compared to placebo. In three large, randomized, double-blind placebo controlled clinical trials, sexual side effects occurred in at least one percent of patients who received dutasteride 0.5 mg daily over a two year period. Patients experienced the majority of these sexual side effects during the initial six months of dutasteride therapy. With the exception of gynecomastia, there were no significant sexual side effects seen beyond six months of treatment.

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