PRACTITIONER SECTION

CURRENT STATUS OF 5α-REDUCTASE INHIBITORS IN THE TREATMENT OF BENIGN HYPERPLASIA OF PROSTATE

VIJAY L. KUMAR, VISHAL D. WAHANE

ABSTRACT

Benign prostatic hyperplasia (BPH) is a common problem in aging men, which is associated with lower urinary tract symptoms. This condition is dependent on the presence of androgens for its progression, and medical therapy is the first-line treatment for BPH patients with moderate-to-severe symptoms and includes the use of either alpha 1-adrenergic blockers or 5α-reductase inhibitors. Adrenergic blocking drugs reduce the dynamic component while the 5α-reductase inhibitors reduce the static component of bladder outlet obstruction in BPH. By inhibiting the generation of active form of testosterone, viz., dihydrotestosterone, the 5α-reductase inhibitors not only reduce the symptoms of BPH but also decrease the need for surgery and further progression of BPH. Besides, prolonged use of combination of 5α-reductase inhibitors and alpha 1-adrenergic blockers has been found to be more beneficial than either of the two drugs given alone. This review gives a brief account of rationale and efficacy of treatment by 5α-reductase inhibitors in the management of BPH.

Key words: 5α-reductase inhibitors, androgens, benign prostatic hyperplasia, dutasteride, finasteride, prostate

INTRODUCTION

Benign prostatic hyperplasia (BPH), a nonmalignant enlargement of prostate gland, is the main cause of lower urinary tract symptoms in older men.[1] The incidence of its occurrence increases with advancing age, when it affects normal activities and reduces sense of well-being.[2,3] The clinical symptoms of BPH include increased urinary frequency, urgency, intermittency; nocturia; decreased force of stream; hesitancy and straining that are usually associated with complications such as acute urinary retention, urinary incontinence, recurrent urinary tract infection, hematuria, renal failure, and bladder stone.[4-9] The primary goal for treating symptomatic BPH is to improve urine flow, for which both surgical and nonsurgical approaches are available. Surgical treatment for BPH is usually indicated in recurrent cases of urinary retention, urinary tract infections, hematuria, and in azotemia.[10] Nonsurgical treatment for BPH primarily includes drug therapy, which is initiated when the symptoms become moderate to severe or the patient considers his symptoms to be bothersome.[11-12]

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

Correspondence:
Prof. Vijay L. Kumar, Department of Pharmacology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. E-mail: kumarvl98@hotmail.com

ROLE OF ANDROGENS IN BPH

The enlargement of prostate to the extent that it produces some clinical manifestations is dependent on the presence of androgens, for which it is one of the target organs. Several lines of evidences supporting this fact are based on both experimental and clinical studies. It has been well established that BPH does not develop in men castrated before puberty and in males with hypopituitarism.[13,14] The role of androgens in BPH is further substantiated by the fact that both medical and surgical castration bring about beneficial effects in these patients through reduction in the levels of androgens.[15-17] In prostate the effects of testosterone are mediated through its active metabolite dihydrotestosterone (DHT), which is generated by the action of 5α-reductase.[18] DHT has been found to be twice as potent as testosterone and has greater affinity for androgen receptor.[19,20] It tends to accumulate in the prostate even when circulating levels of testosterone are low.[21] Although the reports regarding higher intraprostatic levels of DHT are paradoxical, there is strong evidence to suggest the central role of DHT in the development and progression of BPH.[22,23]

RATIONALE FOR THE USE OF MEDICAL THERAPY

The bladder outlet obstruction in BPH involves two components, a dynamic component and a static component. The dynamic component affects the tone of smooth muscle fibers in the bladder neck, surgical capsule, and fibromuscular stroma.[24] The static component, on the other hand, is due to mechanical compression exerted by the increased prostate bulk, primarily comprised of epithelial glandular tissue.[25] The dynamic component is regulated by adrenergic mechanisms, where alpha-adrenergic receptors play an important role.[26] Thus, alpha-adrenergic blocking drugs reduce the smooth muscle tone and relieve the obstruction due to dynamic component. The static component is mainly under the control of androgens that bring about growth of the prostate.[27] Since DHT is the active androgen in the prostate, which is synthesized from testosterone (T) by the action of 5α-reductase, the use of 5α-reductase inhibitors would relieve the symptoms of BPH. Further, a combination of alpha-adrenergic blocking drug and a 5α-reductase inhibitor appears to be more promising.[28,29]

5α-REDUCTASE TYPES AND THEIR DISTRIBUTION

The conversion of testosterone to DHT is an reduced form of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent process that is catalyzed by 5α-reductase enzyme. There are two isoforms of 5α-reductase, type 1 (3-oxo-5α-steroid Δ^4-dehydrogenase) and type 2 [3-oxo-5α-steroid: (acceptor)-Δ^4 oxidoreductase].[30] The two isoforms differ in chromosomal localization, sites of distribution, kinetic constant (Km) value and pH optima [Table 1].[31-34] While 5α-reductase type 2 is exclusively present in prostate and genital tissue, the type 1 enzyme has wider distribution and is present in most tissues of the body, including skin, liver, sebaceous gland, and prostate. Compared to normal prostate, BPH tissue

Table 1: Types, distribution, and characteristics of 5α-reductase[31-34]

	Type 1	*Type 2*
Chromosome location	Chr 5	Chr 2
Distribution	Wide - skin, liver, prostate, sebaceous gland	Prostate, genital tissue
pH optima	6-8.5	5.5
Km values	10 μM	0.4 μM
Inhibitor	Dutasteride	Finasteride Dutasteride

exhibits increased expression of both type 1 and type 2 enzymes.[35,36] Immunohistochemical studies using 5α-reductase type 2–specific antibodies have demonstrated that this enzyme is primarily localized in the stroma of the gland.[37] The stromal cells have been considered to play a primary role in androgen-dependent prostatic growth.[38,39]

PHARMACOLOGY OF 5α-REDUCTASE INHIBITORS

There are two types of 5α-reductase inhibitors: i) type 2 selective inhibitor - finasteride; and ii) nonselective inhibitor - dutasteride. Both the drugs have been clinically tested and have been found to reduce lower urinary tract symptoms to a significant extent.

Finasteride

Finasteride, synthesized in 1984, belongs to a class of 17β-substituted 4-aza-steroids and is chemically known as 4-azaandrost-1-ene 17-carboxamide, N-(1,1-dimethylethyl)-3-oxo-(5alpha, 17beta). Finasteride is well absorbed orally with an oral bioavailability of 63%. It undergoes extensive hepatic metabolism primarily by CYP3A4 to metabolites that are inactive and are eliminated through bile and urine. The half life of finasteride is 6 h and it is 90% bound to plasma proteins [Table 2].[40,41] At clinically used doses (5 mg/day), it suppresses

Table 2: Pharmacokinetic comparison of finasteride and dutasteride[41]

Parameter	*Finasteride*	*Dutasteride*
Oral bioavailability	63%	60%
Peak serum concentration	1-2 h	2-3 h
Steady state	>3 week	>3 month
Volume of distribution	76 l	511 l
Elimination half life	6 h	5 week
Plasma protein binding	90%	99.5%

5α-reductase type 2 because it has a much lower affinity for type 1 isoenzyme.[42,43] The effect of finasteride on DHT levels in plasma and in prostate of BPH patients has been found to be dose dependent, and it results in decreased DHT/T ratio in the prostate gland. It reduces serum and prostate DHT levels by about 70% and 85-90% respectively.[44] The remaining DHT is produced by the action of 5α-reductase type 1, which is not inhibited by finasteride.[32] The clinical efficacy of finasteride in BPH patients has been evaluated in several multi-centric double-blind, randomized, placebo-controlled clinical trials. The initial studies were carried out for 1 to 2 years, wherein clinical parameters like urinary flow rate, symptom score, and prostate volume were included.[45-48] Of the two doses of finasteride chosen (1 and 5 mg/day), the 5-mg dose was found to produce a marked improvement in the symptom score compared to that of the placebo. Both the doses produced improvement in urinary flow rate and prostate volume, and the effect of these two doses was comparable.[45,46] The beneficial effect of 5-mg dose of finasteride was maintained for 2 years, and it was found to halt the progression of BPH; while patients receiving placebo experienced a return to the baseline or deterioration of parameters.[47] These findings were further substantiated by another trial that included 3,270 patients, wherein a reduction in the risk of acute urinary retention and the need for surgical intervention

was observed.[48] Further, a meta-analysis of six randomized, placebo-controlled clinical trials revealed that the mean group changes in symptom score and urinary flow rate correlate with mean baseline prostate volume.[49] The efficacy of 5-mg dose of finasteride over a period of 4 years was evaluated in the PLESS trial (Proscar long-term efficacy and safety study) that included 3,040 men with moderate-to-severe urinary symptoms and enlarged prostate gland. The primary end point of this double-blind, randomized, placebo-controlled trial was assessment of symptom score, and the secondary end points were occurrence of acute urinary retention and need for surgery. As reported earlier, this trial also showed that finasteride improves urinary symptoms and reduces the volume of prostate gland in BPH patients.[50] Besides, the PLESS trial also showed that finasteride reduces the risk of acute urinary retention and the need for surgery [Table 3]. The most common side effects of finasteride usage include impotence, decreased libido, and decrease in ejaculate volume; while some of the patients may show rashes, breast enlargement, and tenderness. The tolerability profile of finasteride improves when used for a longer time.[50]

Dutasteride

Dutasteride belongs to a class of 4-aza-steroids and its chemical name is (5α, 17β)-N {2, 5, bis (trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. It is a nonselective inhibitor of both type 1 and type 2 isoenzymes of 5α-reductase.[51,52] It is well absorbed orally, with an oral bioavailability of 60%. Compared to finasteride, it has a longer half life (5 weeks) and is almost completely bound to plasma proteins [Table 2]. It is primarily metabolized by CYP3A4.[41,53] The blood concentrations of dutasteride tend to increase when it is co-administered with drugs like ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin.[41] At a dose of 0.5 mg/day, dutasteride has been shown to reduce the levels of serum DHT by 95%.[54] The clinical efficacy and safety of dutasteride has been evaluated in a randomized, double-blind, placebo-controlled trial, wherein 0.5 mg of dutasteride was given daily to 2,167 BPH patients with moderate-to-severe symptoms and a prostate volume of 30 cm^3 or greater for a period of 2 years. The primary end points of this study were assessment of symptom score and risk of acute urinary retention, while the secondary end points included total prostate volume, maximal urinary flow rate, and surgical intervention. Dutasteride was found to improve urinary symptoms and reduce the risk of acute urinary retention and the need for surgery [Table 3]. Patients undergoing dutasteride treatment may exhibit erectile dysfunction, decreased libido, gynecomastia, and ejaculation disorders within 1 year. Most of these side effects have been found to be transient, and the new occurrence of each event decreases in the second year.[55] This study was further extended

Table 3: Clinical efficacy of 5α-reductase inhibitors - finasteride and dutasteride[50,55]

Parameters	*Finasteride*	*Placebo*	*Dutasteride*	*Placebo*
Symptom score	−3.3	−1.3	−4.5	−2.3
Prostate volume change	−18%	+14%	−25.7%	+ 1.7%
Improvement in flow rate	1.9 ml/sec	0.2 ml/sec	2.2 ml/sec	0.6 ml/sec
Percentage risk reduction				
Surgical intervention	55%	-	48%	-
Acute urinary retention	57%	-	57%	-

as an open-label trial for 2 years, in which both dutasteride- and placebo-treated patients received dutasteride at a dose of 0.5 mg/day. Dutasteride was found to significantly improve symptom score and urinary flow rate in all the patients in the open-label phase, irrespective of the treatment given in the double-blind, placebo-controlled phase. By the end of 4 years, patients who received dutasteride in both the phases showed a significant improvement in symptom score, urinary flow rate, and total prostate volume as compared to patients who received placebo in the blinded phase. Dutasteride was well tolerated, and the reduction in risk of acute urinary retention and in the need of BPH-related surgery seen in the double-blind phase was maintained throughout the open-label phase.[56]

In a recently carried out double-blind, randomized clinical trial, dutasteride (0.5 mg/day) has also been found to be better than finasteride (5 mg/day) in improving symptom score, maximal urinary flow rate, and quality of life when given over a period of 12 weeks.[57]

COMBINATION OF 5α-REDUCTASE INHIBITORS AND ALPHA-ADRENERGIC BLOCKING DRUGS

The efficacy of combination of both 5α-reductase inhibitors and alpha-adrenergic blocking drugs in alleviating the symptoms of BPH has been evaluated in two independent clinical trials.[58,59] In these trials, a combination of finasteride and terazosin and that of finasteride and doxazosin were evaluated in BPH patients over a period of 12 months. In both the trials, the combination therapy was found to be no more effective than the use of alpha-adrenergic blockers alone. These trials were subsequently followed by MTOPS trial (medical therapy of prostate symptoms), wherein combination of finasteride and doxazosin was studied over a period of 4.5 years.[28] The MTOPS trial was designed to evaluate the efficacy of this combination in reducing the risk of overall clinical progression of BPH, where parameters like AUA score (American Urological Association symptom score), acute urinary retention, renal insufficiency, recurrent urinary tract infection, and urinary incontinence were included. In this trial, 3,047 men with moderate-to-severe symptomatic BPH and at least 50 years of age were randomized to receive placebo, finasteride (5 mg), doxazosin (4 or 8 mg), and combination of the two drugs. Compared to the placebo group, the risk of clinical progression was reduced by 39% in doxazosin group, 34% in finasteride group, and 66% in the group on combination therapy. The risk of clinical progression by the combination therapy was significantly reduced compared to that by either doxazosin or finasteride. The risk of acute urinary retention and the need for invasive therapy were also significantly reduced by either the combination therapy or the finasteride treatment but not by doxazosin treatment [Table 4]. The adverse events occurring in combination therapy were similar to those when either of the drugs was used alone; however, abnormal ejaculation, peripheral edema, and dyspnea occur more frequently in patients on combination therapy.[28]

In an ongoing multi-centric, randomized, double-blind, parallel-group study, dutasteride (0.5 mg), tamsulosin (0.4 mg), and their combination are being evaluated for their

Table 4: Clinical efficacy of doxazosin, finasteride, and their combination[28]

Parameters	*Doxazosin*	*Finasteride*	*Doxazosin + Finasteride*
Clinical progression of BPH	39 (20-53)	34 (14-50)	66 (54-76)
>4 point increase in AUA symptom score	45 (25-60)	30 (6-48)	64 (48-75)
Acute urinary retention	35 (–31-67)	68 (21-87)	81 (44-93)
Invasive therapy due to BPH	3 (–48-37)	64 (34-80)	67 (40-82)

Values given are for risk reduction (%) at 95% CI

efficacy in improving symptoms and long-term outcome in men with moderate-to-severe lower urinary tract symptoms associated with BPH (CombAT study). The results of this study at 2 years show that the combination therapy provides a significantly greater degree of benefit than the monotherapy as revealed by the change in the International Prostate Symptom Score. However, the long-term outcome of this study is still awaited.[29]

Thus, clinical studies carried out on BPH patients suggest that medical therapy with 5α-reductase inhibitors is a promising approach for patients with moderate-to-severe symptoms of the disease and having enlarged prostate. Drugs like finasteride and dutasteride not only improve the symptom score and urinary functions but also halt the further progression of BPH and reduce the risk of acute urinary retention and need for surgery. The clinical efficacy of 5α-reductase inhibitors is further improved by combining them with alpha-adrenergic blockers. Though the long-term use of these drugs has been shown to produce side effects, the tolerability profile improves as time passes.

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