

Dutasteride: Its Use in the Treatment of Patients with Benign Prostatic Hyperplasia

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BHP contributes to urinary tract symptoms in ageing men.

Lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) are a common complaint seen by primary care physicians and urologists. Dutasteride is a 5-alpha-reductase inhibitor that inhibits the intracellular conversion of testosterone to dihydrotestosterone, thereby decreasing prostate volume. It significantly improves current symptoms and reduces the risk of long-term complications of BPH.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a pathological process that contributes to lower urinary tract symptoms (LUTS) in ageing men. It is a non-malignant enlargement of the prostate gland, causing symptoms such as urinary frequency, urgency, hesitancy, intermittency, decreased urinary stream, straining and nocturia. In the evaluation of men with LUTS, other conditions such as bladder dysfunction from neurological causes or diabetes mellitus, prostate cancer, lower urinary tract infection and urinary calculus

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disease need to be ruled out. A thorough history taking and physical examination are important in the initial evaluation of these men: the International Prostate Symptom Score (IPSS) and Quality of Life scoring should also be obtained, together with adjunct tests such as bedside ultrasound of the prostate and kidneys, uroflowmetry and residual urine measurement, urine for microscopy, an abdominal radiograph and serum prostate specific antigen (PSA) measurement.¹

BPH is histologically evident in 50% of 50-year-old and 90% of 80-year-old men.² BPH leads to bladder outlet obstruction, thereby increasing urethral resistance and causing LUTS. The progressive nature of the disease in many men may lead to complications such as acute urinary retention (AUR), urinary tract infections, bladder stone formation, recurrent macroscopic hematuria and obstructive uropathy.

There are several postulations as to the aetiology of BPH.³ Androgens, primarily via the actions of DHT, are required for normal cell proliferation and differentiation in the prostate. Androgens also actively inhibit cell death, thereby causing prostatic growth and enlargement. In the prostate, testosterone is converted to the active form DHT by 5-alpha reductase (5-AR). Two isoenzymes of 5-AR have been discovered; type 1 and type 2. Of these,



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type 2 is the predominant form found in the prostate, and is critical to the normal development of the prostate and to hyperplastic growth later in life. Other theories in the pathophysiology of BPH include stromal-epithelial interaction and stimulation by growth factors and inflammatory cytokines.

In the management of patients with BPH, there are several strategies commonly employed by the urologist.¹ In patients with mild symptoms (IPSS < 8) or no bothersome symptoms, watchful waiting and behavioural modification are recommended. The treatment options for patients with moderate to severe symptoms (IPSS ≥ 8) include medical therapy or surgery. Part of the obstruction to the bladder outlet is believed to be due to increased prostatic smooth muscle tone mediated

by alpha-adrenergic receptors. Alpha-adrenergic blockers have been shown to be effective in improving symptoms and urinary flow rate in patients with BPH. However, alpha-adrenergic blockers do not decrease the prostate volume nor alter the natural history of BPH. Use of the 5-AR inhibitors finasteride and dutasteride — either alone or in combination with an alpha-adrenergic blocker — has revolutionized the medical treatment of BPH. Finally, surgery is indicated in patients with complications of BPH or in whom medical therapy has failed.

Pharmacology

Dutasteride is a synthetic 4-azasteroid compound. As previously mentioned, there are two types of 5-AR enzymes

in the human body, of which type 2 is the predominant form in the prostate. Type 1, meanwhile, is primarily active in the skin and liver. Finasteride is an inhibitor of type 2 5-AR, whereas dutasteride inhibits both type 1 and type 2 5-AR. Although the actions of DHT in the prostate are mediated mainly via type 2 5-AR, it has been shown that dutasteride reduces circulating DHT by more than 90% compared to 70% by finasteride. However, the clinical benefit of increased suppression of DHT by dutasteride compared to finasteride is unknown. Dutasteride is approved to be taken as a once-daily dose of 0.5 mg. At this dosage, serum DHT is reduced maximally within 2 weeks, and the effect is maintained even after 4 years of continuous therapy.⁴ The efficacy of dutasteride in patients with BPH is believed to be mediated by a reduction in prostate volume. To achieve maximal therapeutic benefit, treatment must be maintained for at least 6 months.

Pharmacokinetics

Data on the pharmacokinetics of dutasteride are mainly from healthy volunteers and are available in the manufacturer's prescribing information.⁵

In the evaluation of lower urinary tract symptoms conditions such as bladder dysfunction from neurological causes or diabetes mellitus must be ruled out.



Table 1. Month 24 and change from baseline at month 24 data for primary and secondary outcome parameters

Parameter	Time	Placebo (n=2158)	Dutasteride (0.5 mg/day; n=2167)	Between Group Comparison
Serum DHT (pg/mL)	Month 24 Change Significance from BL	426 ± 197 16 ± 150 <0.001	40 ± 77 -389 ± 228 <0.001	<0.001
Serum testosterone (pg/mL)	Month 24 Change Significance from BL	4002 ± 1481 36 ± 1226 NS	4817 ± 1780 749 ± 1475 <0.001	<0.001
Total prostate volume (cm ³)	Month 24 Change Significance from BL	54.1 ± 25.2 0.8 ± 14.3 0.040	41.2 ± 20.6 -14.6 ± 13.5 <0.001	<0.001
Transition zone volume (cm ³)	Month 24 Change Significance from BL	28.4 ± 19.1 1.8 ± 11.2 <0.001	21.1 ± 13.9 -7.1 ± 9.7 <0.001	<0.001
AUA-SI	Month 24 Change Significance from BL	14.7 ± 7.2 -2.3 ± 6.8 <0.001	12.2 ± 6.6 -4.5 ± 6.6 <0.001	<0.001
Qmax (mL/s)	Month 24 Change Significance from BL	11.2 ± 4.8 0.6 ± 4.7 <0.001	12.5 ± 5.6 2.2 ± 5.2 <0.001	<0.001
Serum PSA (ng/mL)	Month 24 Change Significance from BL	4.3 ± 2.8 0.5 ± 2.1 <0.001	1.9 ± 1.8 -2.2 ± 2.0 <0.001	<0.001

KEY: DHT = dihydrotestosterone; BL = baseline; NS = not significant; AUA-SI = American Urological Association-Symptom Index; Qmax = maximal flow rate; PSA = prostate-specific antigen.
Data presented as the mean ± SD.

The oral bioavailability of dutasteride in healthy subjects is about 60%. The presence of food reduces the maximum drug concentration, but this is not believed to be clinically significant. Peak concentration after a single dose of 0.5 mg is reached in around 2 to 3 hours. Ninety-nine percent of dutasteride is bound to plasma albumin and it has a large volume of distribution of 300 to 500 L. The drug undergoes extensive metabolism, primarily by the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, and is excreted mainly in the faeces. Dutasteride has a long terminal half-life of 5 weeks; therefore the steady-state concentration is only achieved after 3 to 4 months of therapy. Due to the long half-life of dutasteride, serum concentrations remain detectable for up to 4 to 6 months after discontinuation of treatment.

Less than 0.1% of dutasteride is excreted in the urine. No dosage adjustment is anticipated with regards to its use in patients with renal impairment. Since dutasteride is extensively metabolized by the liver, its use in patients with hepatic impairment is cautioned.

Drug-to-Drug Interaction

Clinical drug interaction studies have not shown any pharmacokinetic or pharmacodynamic interactions between dutasteride, tamsulosin, terazosin, warfarin, digoxin or cholestyramine.

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1,000 ng/mL (25

Table 2. Drug-related adverse events

Study Period	Sexual Adverse Event	Placebo (n=2158)	Dutasteride (0.5 mg/day; n=2167)	Between-Group Comparison
Entire study	Impotence	86 (4.0)	158 (7.3)	<0.001
	Decreased libido	46 (2.1)	91 (4.2)	<0.001
	Gynecomastia	16 (0.7)	50 (2.3)	<0.001
0-1 yr	Ejaculation disorder	17 (0.8)	48 (2.2)	<0.001
	Impotence	n = 2158 65 (3.0)	n = 2167 130 (6.0)	<0.001
	Decreased libido	41 (1.9)	80 (3.7)	<0.001
1-2 yr	Gynecomastia	11 (0.5)	28 (1.3)	0.009
	Ejaculation disorder	15 (0.7)	40 (1.8)	<0.001
	Impotence	n = 1736 21 (1.2)	n = 1744 29 (1.7)	NS
	Decreased libido	6 (0.3)	11 (0.6)	NS
	Gynecomastia	5 (0.3)	23 (1.3)	<0.001
	Ejaculation disorder	2 (0.1)	9 (0.5)	NS

KEY: NS = not significant.

Data presented as the number of patients, with the percentage in parentheses.

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times greater than steady-state serum concentrations in humans). In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam or phenytoin from plasma protein binding sites, nor do these model compounds displace dutasteride. Based on the in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4/5 such as ritonavir, keto-

conazole, verapamil, diltiazem, cimetidine, troleandomycin and ciprofloxacin. Concomitant use with strong CYP3A4/5 inhibitors may require dose reduction of dutasteride.⁵

Efficacy of Dutasteride

Data from several phase III trials have proven the efficacy and safety of dutasteride up to a period of 4 years. In a multicentre, double-blind, randomized, placebo-controlled trial involving 4,325 men, one group received placebo whilst the other received 0.5 mg dutasteride daily for 2 years.⁶ Inclusion criteria were men aged 50 years or older with a diagnosis of BPH, a prostate volume measured by transrectal ultrasound of 30 cm³ or greater, American Urological Association-Symptom Index (AUA-SI) score of 12 or greater, and a maximal urinary flow rate of 15 mL/s or less. In addition, eligible subjects needed

to have a baseline PSA level of 1.5 ng/mL or greater but less than 10 ng/mL for entry. Men with postvoid residual volumes greater than 250 mL, a history of prostate cancer, previous prostate surgery, AUR within 3 months of screening, use of an alpha-blocker within 4 weeks or any previous use of a 5-AR inhibitor were excluded. The investigators reported a significant improvement in symptom score of 4.5 points (p<0.001) and improvement in maximal flow rate of 2.2 mL/s (p<0.001) at 24 months for the dutasteride group. (Table 1) The mean reduction in total prostate volume was found to be 25.7% from baseline (p<0.001). In addition, the risk reduction of AUR was 57% and risk reduction of BPH-related surgery was 48%, compared with placebo.

An open-label extension period of an additional 2 years was initiated to evaluate the long-term efficacy and safety of dutasteride. A total of 569 subjects received dutasteride for 48 months, showing a further improvement of prostate volume of -26.2%, AUA-SI score of -6.1 points and peak urinary flow rate of +1.8 mL/s.⁴ Gittelman in a subanalysis of patients with modest prostatic enlargement (30 to 40 cm³) also reported similar results with respect to symptom score, peak urinary flow rate, rate of AUR and BPH-related surgery.⁷

Adverse Effects of Dutasteride

The most commonly reported drug-related adverse events included effects on sexual function, mostly occurring within the first year of treatment. (Table 2) In the trial mentioned above, 6% of patients in the dutasteride group complained of impotence compared to 3% in the placebo group during the first year of treatment. Decreased libido and ejaculatory disorders were reported in 3.7% and 1.8% in the dutasteride group, compared with 1.9% and

0.7% in the placebo group, respectively. Breast tenderness and enlargement occurred in 1.3% of patients in the dutasteride group, compared with 0.5% in the placebo group. These rates decreased after the first year of treatment. In patients with a total of 4 years of dutasteride treatment, the rates of adverse events remained low and decreased with time.⁴ No new safety issues emerged during the 4-year treatment period.

Application

The efficacy of dutasteride together with an alpha-blocker has also been studied. In the ongoing, multicentre, randomized, double-blind, parallel group CombAT study, the investigators are looking at whether combination therapy with dutasteride and tamsulosin (a selective alpha-1a adrenergic receptor antagonist) is more effective than either monotherapy alone for improving symptoms and long-term outcomes.⁸ Men with moderate to severe lower urinary tract symptoms and prostate volumes of 30 cm³ or greater were randomized to 0.5 mg dutasteride, 0.4 mg tamsulosin or the combination once daily for 4 years. Preplanned analysis at 2 years found that combination therapy resulted in significantly greater improvements in symptoms versus dutasteride from month 3 and tamsulosin from month 9. The improvement in peak urinary flow was also significantly better in the combination therapy group compared to either monotherapy from month 6.

However, the investigators reported significantly higher drug-related adverse events with the combination therapy compared to either monotherapy. Erectile dysfunction, retrograde ejaculation, decreased libido, decreased semen volume, ejaculation failure and nipple pain were more common with

the combination therapy. Less than 5% of men in each treatment group withdrew from the study as a result of these events.

Data for the use of finasteride in men with BPH are more mature, having been in clinical usage earlier than dutasteride. In a randomized, double-blind and placebo-controlled study referred to as the Proscar Long-Term Efficacy and Safety Study (PLESS), McConnell and co-workers reported the safety and efficacy of finasteride in men with symptomatic BPH.⁹ Significant improvements in symptom score, peak flow rate and prostate volume were found in men treated with finasteride for 4 years compared with placebo. Furthermore, a 57% risk reduction in the cumulative incidence of AUR and a 55% reduction in BPH-related surgery was found in the treatment group. Combination therapy with finasteride has also been well studied. Medical Therapy of Prostate Symptoms (MTOPS) was a 5 year randomized, double-blind and placebo-controlled study that examined the effects of doxazosin (a long acting alpha-1 blocker), finasteride or a combination of these agents in men with symptomatic BPH.¹⁰ Results of this trial suggest that men who received the combination of doxazosin and finasteride were significantly less likely to experience BPH progression, AUR, and surgery (67%, 67% and 64% respectively compared with placebo).

Conclusion

Dutasteride improves both objective and subjective disease measures in men with BPH. It alters the natural history of urinary retention in men with LUTS and an enlarged prostate, and reduces the rate of surgical intervention. It acts by inhibiting the conversion of

testosterone to DHT, thereby reducing prostate volume. When combined with an alpha-blocker, a better outcome can be achieved. The incidence of drug-related adverse events is low and related mainly to sexual function.

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