Dutasteride: A Review of Current Data on a Novel Dual Inhibitor of 5α Reductase

Sibylle Marihart, MD, Mike Harik, MD, Bob Djavan, MD, PhD

Department of Urology, University of Vienna, Vienna, Austria

Dutasteride is used in the treatment of benign prostatic hyperplasia. Like finasteride, it reduces serum prostate-specific antigen levels by approximately 50% at 6 months and total prostate volume by 25% in 2 years. It differs from finasteride in that it inhibits both isoenzymes of 5α reductase and results in near-complete suppression of serum dihydrotestosterone. Randomized placebo-controlled trials over 2 years have shown the efficacy of dutasteride in symptomatic relief, improvements in quality of life and peak urinary flow rate, and reduction of acute urinary retention events and need for surgery. Side effects occurring in therapy with dutasteride are decreased libido, erectile dysfunction, ejaculation disorders, and gynecomastia. However, when dutasteride treatment is compared with placebo, these sexual adverse events are only modestly elevated. Long-term use over 4 years did not increase side effects. An efficient treatment of side effects is the combination of dutasteride and tamsulosin, especially for patients with large prostate volumes. Finally, the anticancer properties of dutasteride have been shown in placebo-controlled trials and are being investigated in the ongoing Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.
[Rev Urol. *2005;7(4):203-210*]

Key words: Benign prostatic hyperplasia • Prostate volume • Efficacy • Sexual adverse events

The prevalence of prostatic diseases is very high in the aging male population. It is estimated that 88% of men aged 80 years or more have the pathologic changes of benign prostatic hyperplasia (BPH), and nearly 50% of men aged 50 years or older have lower urinary tract symptoms characteristic of BPH.[1] At the same time, prostate cancer is rapidly becoming the most common malignancy in the United States and some other Western countries and will affect approximately 1 in 6 American men during their lives.[2]

Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5α reductase. DHT is necessary for normal growth and function, but it also seems to have a great impact on the development of BPH and on the initiation and maintenance of prostate cancer.[3,4] Finasteride, an inhibitor of 5α reductase, has established its role in the management of BPH through a number of well-conducted long-term studies.[5,6] Similarly, the recent Prostate Cancer Prevention Trial showed that the incidence of prostate cancer was decreased with finasteride over a 7-year period.[7]

Dutasteride, a dual inhibitor of 5α reductase that was introduced at the turn of the 21st century, promised better efficacy than its predecessor finasteride. This review discusses its mechanism of action, efficacy, tolerability, drug interactions, and effects on prostate cancer.

Dutasteride: How Does It Work?

DHT synthesis is catalyzed intracellularly by 5α reductase types 1 and 2 enzymes. Dutasteride is the first dual inhibitor of both 5α reductase isoenzymes. This leads to near-complete suppression of serum DHT—more than 90%, compared with the 70% seen with finasteride.[8,9] Type 2 5α reductase is the predominant isoform in normal prostate and in BPH tissues. Type 1 5α reductase is present in BPH tissue in lower quantities, but it predominates in prostate cancer cell lines and seems to be over-expressed in some prostate cancers.[10-12] Theoretically, the greater suppression of DHT arising from the dual 5α-reductase inhibition could result in greater efficacy than is observed in selective type 2 inhibition, and this dual inhibition could prevent type 1–mediated synthesis of DHT.

Efficacy

Two-Year, Placebo-Controlled Trials

In 2002, the first clinical study reported the efficacy of dutasteride at a dose of 0.5 mg/d.[13] This study compared 4325 patients from three randomized, placebo-controlled trials (ARIA 3001 [United States], ARIA 3002 [United States], and ARIA 3003 [19 countries]), covering 400 sites in total, which had identical inclusion and exclusion criteria to allow preplanned pooling of data. A total of 2167 men received dutasteride, and 2158 men received placebo. The median duration of exposure was 604 days for the study medicine and 598 days for placebo. Completing the 2-year study were 66% and 70% of patients in the placebo and dutasteride groups, respectively. The primary endpoints were changes in the American Urological Association Symptom Index (AUA-SI) and the risk of acute urinary retention (AUR). The secondary endpoints described changes in serum prostate-specific antigen (PSA), testosterone, and DHT concentrations, total prostate volume, peak urinary flow rate (Q_{max}), and surgical interventions. At 24 months, serum DHT was reduced from baseline by a mean of 90.2%, and the total prostate and transition zone volumes were reduced 25.7% and 20.4%, respectively. Serum PSA decreased 52.4% in the dutasteride group, compared with an increased serum PSA level from baseline of 15.8% in the placebo group. The symptom score started to improve at 3 months, with pooled significance from 6 months onward and a reduction of 4.5 points (21.4%) at 24 months. The risk reduction of AUR was 57% at 24 months, and the risk of BPH-related surgical interventions was 48% compared with placebo. Q_{max} started to improve significantly at 1 month, with an increase of 2.2 mL/s reported at 24 months. This study provides early evidence of the efficacy of dutasteride in terms of symptoms, Q_{max} improvements, and reduction in prostate volume. Table 1 summarizes the mean change from baseline for primary and secondary outcome parameters in the placebo and dutasteride groups.

Theoretically, the greater suppression of DHT arising from dual 5α-reductase inhibition could result in greater efficacy than is observed in selective type 2 inhibition.

Quality of Life

In the same cohort of patients (n = 4325), O'Leary and colleagues[14] assessed the improvements in quality of life with dutasteride compared with placebo. The BPH Impact Index (BII) consists of 4 questions that measure the impact of urinary problems in terms of physical discomfort, worry about health because of urinary problems, bothersomeness of urinary symptoms, and limitations of activities of daily living because of urinary problems. Dutasteride, but not placebo, showed clinically and statistically significant improvements in mean BII score from 6 months. Treatment with dutasteride improved the scores by an average of 2.41 in patients with a baseline BII score of 5 or more (greatest symptomatic burden), whereas the scores in placebo-treated patients improved by only an average of 1.64. Initially, placebo-treated patients had improvements in BII scores from baseline, but BII scores had deteriorated by 18 to 24 months, showing progressive BPH symptoms and worsening quality of life. In contrast, dutasteride treatment was associated with consistent improvements from 6 months to 2 years.

Table 1
Month 24 Data and Change from Baseline at Month 24 Data for Primary and Secondary Endpoints in the Placebo-Controlled Trials and Values at Month 48 for the Open-Label Extension

Parameter	Time	Placebo (n = 2158)	Dutasteride (n = 2167)	Between-Group Comparison	Open-Label Extension Month 48	
					P/D (n = 1152)	D/D (n = 1188)
Serum testosterone (pg/mL)	Month 24	4002 ± 1481	4817 ± 1780	<.001	4718 ± 1688	4904 ± 2186
	Change	36 ± 1226	749 ± 1475			
	P	NS	<.001			
Serum DHT (pg/mL)	Month 24	426 ± 197	40 ± 77	<.001	29.7 ± 63.0	31.1 ± 60.7
	Change	16 ± 150	−389 ± 228			
	P	<.001	<.001			
Serum PSA (ng/mL)	Month 24	4.3 ± 2.8	1.8 ± 1.8	<.001	2.0 ± 1.8	1.7 ± 1.8
	Change	0.5 ± 2.1	−2.2 ± 2.0			
	P	<.001	<.001			
Total prostate volume (cm^3)	Month 24	54.1 ± 25.2	41.2 ± 20.6	<.001	42.2 ± 20.2	41.3 ± 23.1
	Change	0.8 ± 14.3	−14.6 ± 13.5			
	P	.040	.04			
Transition zone volume (cm^3)	Month 24	28.4 ± 19.1	21.1 ± 13.9	<.001	22.8 ± 18.8	22.4 ± 16.0
	Change	1.9 ± 11.2	−7.1 ± 9.7			
	P	<.001	<.001			
AUA-SI Score	Month 24	14.7 ± 7.2	12.2 ± 6.6	<.001	11.3 ± 6.4	10.2 ± 6.1
	Change	−2.3 ± 6.8	−4.5 ± 6.6			
	P	<.001	<.001			
Q_{max} (mL/s)	Month 24	11.2 ± 4.8	12.5 ± 5.6	<.001	12.6 ± 5.1	12.8 ± 5.5
	Change	0.6 ± 4.7	2.2 ± 5.2			
	P	<.001	<.001			

Data presented as mean ± standard deviation. D/D, subjects initially treated with dutasteride continuing with dutasteride; P/D, subjects initially given placebo then switched to dutasteride; NS, not significant; DHT, dihydrotestosterone; PSA, prostate-specific antigen; AUA-SI, American Urological Association Symptom Index; Q_{max}, peak urinary flow.
Data from Roehrborn et al[13] and Debruyne et al.[15]

In the analysis of risk factors for bothersomeness at the end of the study, regression analysis showed that men with a combination of a baseline BII score of 3 and a high symptom score (AUA-SI score ≥ 20) were more likely to be bothered. Thus, dutasteride not only improves urinary symptoms and flow rate, but it is also associated with significant improvements in BII score, reflecting improvements in quality of life for men with BPH.

Long-Term Studies

All of the studies mentioned above (ARIA 3001, ARIA 3002, ARIA 3003) had an optional 2-year open-label extension period in which patients initially receiving dutasteride in the double-blind phase were maintained on dutasteride, and those initially receiving placebo were switched to open-label dutasteride.[15] In the open-label phase, 2340 patients (54% participation from the original study population) were included, 1188 of whom previously received dutasteride (D/D group) and 1152 of whom previously received placebo (P/D group). At 48 months, the D/D group was checked for improvements in total prostate volume (−25.9%), AUA-SI score (−6.5 points), and Q_{max} (+2.5 mL/s). Changes for the P/D group included prostate volume (−23.1%), AUA-SI score (−5.7 points), and Q_{max} (+0.8 mL/s) (Table 1). In both study groups, there were significant improvements in AUA-SI score and peak urinary flow rates from months 24 to 48. It is important to note that patients in the D/D group had significantly greater improvements in AUA-SI score and Q_{max} and greater reductions in prostate volume than those in the P/D group at the end of 48 months. During the open-label phase, AUR occurred in a small percentage of men in the P/D

group (2.1%), at rates consistent with those seen in the D/D group between months 0 and 24 (1.9%) and between months 24 and 48 (1.2%). Similarly, BPH-related surgery occurred in a small percentage of men in both the P/D (1.1%) and D/D (0.9%) groups. Overall, the cumulative incidences for AUR and BPH-related surgery were significantly lower in the D/D group than in the P/D group (2.4% vs 5.1% and 2.6% vs 4.5%, respectively). Long-term treatment with the dual 5α-reductase inhibitor seems to result in continuing improvements in urinary symptoms and flow rate and, furthermore, seems to lead to a reduction in prostate volumes in men with symptomatic BPH. Moreover, the reduction in risk for AUR and BPH-related surgery seems to be durable over the 4-year term of the studies.

Benefit of Combining α_1 Blockers and Dutasteride

The aim of a combination study by Barkin and colleagues[16] of men with symptomatic BPH was to provide rapid onset of symptom relief, especially for patients with severe symptoms of bladder outlet obstruction. The investigators conducted a prospective study of 327 BPH patients who were randomized to a combination of dutasteride (0.5 mg) and tamsulosin (0.4 mg) for 36 weeks (DT36) or dutasteride (0.5 mg) and tamsulosin (0.4 mg) for 24 weeks, followed by dutasteride and tamsulosin-matched placebo for the remaining 12 weeks (DT24+D12). Of the DT24+D12 patients, 77% felt better or the same at week 30 compared with week 24 (changes in International Prostate Symptom Scores [IPSS] were consistent with this finding). Of the patients with an IPSS of less than 20 who changed to dutasteride monotherapy at week 24, 84% switched without noticeable deterioration in their symptoms. In the 27% of men with severe baseline symptoms (IPSS ≥ 20) who had withdrawal of tamsulosin therapy at week 24, 42.5% reported a worsening of their symptoms, compared with 14% in the DT36 group. The investigators concluded that combination therapy of dutasteride and tamsulosin for 24 weeks provides a rapid onset of symptom relief for patients at risk for underlying disease progression and that this symptomatic relief is maintained in the majority of patients when tamsulosin is removed from the combination. However, a subset of patients with severe symptoms of bladder outlet obstruction might benefit from longer-term therapy. These recommendations were concordant with those of Baldwin and coworkers,[17] who suggested that men with severe BPH would require 9 or more months of combination therapy.

The investigators concluded that combination therapy of dutasteride and tamsulosin for 24 weeks provides a rapid onset of symptom relief for patients at risk for underlying disease progression.

Safety and Tolerability

At 24 Months

In the 3 placebo-controlled studies (ARIA 3001, ARIA 3002, ARIA 3003),[13] most adverse events were mild to moderate and self-limiting. The only adverse events that investigators considered to be at least possibly drug-related and that occurred in at least 1% of patients treated with dutasteride or placebo over a 2-year period were impotence, ejaculation disorders, decreased libido, and gynecomastia. The incidence of side effects was only slightly higher among dutasteride-treated patients than among placebo-treated patients. Table 2 shows the incidence of the adverse events; the majority occurred in the first year of treatment. The incidence of abnormalities in clinical laboratory tests, including liver function tests, was less than 1% in both the dutasteride and placebo groups. Of all drug-related adverse events, impotence was the most common reason for discontinuation of patients in the dutasteride group.

In summary, dutasteride has a tolerability profile comparable to that of placebo when used daily for up to 2 years, with the exception of gynecomastia, impotence, and decreased libido, which occurred at modestly elevated incidences compared with the placebo group.

At 48 Months

Interestingly, the incidence of most drug-related sexual adverse events decreased among patients who received dutasteride throughout the 48-month study period[15] (Table 2). The incidence of such drug-related adverse events that led to withdrawal was less than 1% in the open-label phase. In general, there are no increased adverse events in long-term treatment with dutasteride, and patient compliance is satisfactory.

Is There Any Difference in Side Effects Between Dutasteride and Finasteride?

GlaxoSmithKline protocol ARI40001 compared dutasteride (0.5 mg/d) with finasteride (5 mg/d) for 1 year.[18] There were no significant differences in the incidence of the most common drug-related adverse events between the dutasteride and finasteride groups (Table 3). The only adverse events that the investigators considered to be drug-related that occurred at an incidence of

Table 2
Percentage of Patients Reporting the Most Common Drug-Related Side Effects in the Placebo-Controlled Trials and Open-Label Extension

	Months					
	0-6	7-12	13-18	19-24	24-36	36-48
Patients, n						
Dutasteride	2167	1901	1725	1605	2340	1041
Placebo	2158	1922	1714	1555	No patients	No patients
Decreased libido						
Dutasteride	3.0%*	0.7%	0.3%	0.3%	0.4%	0.1%
Placebo	1.4%	0.6%	0.2%	0.0%	-	-
Gynecomastia						
Dutasteride	0.5%*	0.8%*	1.1%*	0.6%*	0.9%	0.7%
Placebo	0.2%	0.3%	0.3%	0.1%	-	-
Impotence						
Dutasteride	4.7%*	1.4%	1.0%	0.8%	1.4%	0.4%
Placebo	1.7%	1.5%	0.5%	0.9%	-	-
Ejaculation disorder						
Dutasteride	1.4%*	0.5%	0.5%	0.1%	0.3%	0.1%
Placebo	0.5%	0.3%	0.1%	0.0%	-	-

*$P < .05$, dutasteride vs placebo.
Data from Roehrborn et al[13] and Andriole et al.[18]

more than 2% were impotence and decreased libido. In addition, the incidence of clinical laboratory abnormalities was less than 1% in either treatment group for any parameter.

Side Effects of Combination Therapy with Dutasteride and Tamsulosin

In the combination trial,[16] sexual adverse events were the most commonly reported class of drug-related side effects. The only adverse events considered to be at least possibly drug-related and that occurred in at least 5% of patients in either treatment group throughout the 36-week treatment period were ejaculation disorders. The majority of these disorders were related to sperm volume (9% DT36 group; 8% DT24+D12 group), decreased libido (5% DT36 group; 6% DT24+D12 group), impotence (5% DT36 group; 4% DT24+D12 group), and malaise and fatigue (5% DT36 group; 1% DT24+D12 group). The drug-related adverse event profiles for combination therapy were comparable to those expected for the individual drugs, and there was no evidence of synergistic interaction. These data suggest that dutasteride and tamsulosin combination treatment is well tolerated over a 36-week period.

Does Dutasteride Have Any Effects on Bone Density and Lipid Profiles?

GlaxoSmithKline protocol ARIA 1009, a randomized, double-blind study that included a finasteride arm, was conducted to investigate the effects of dutasteride on bone density, bone metabolism markers, and lipid profiles.[18] Subjects were randomized to receive dutasteride (0.5 mg), finasteride (5.0 mg), or placebo for 52 weeks and were followed up for a further 24 weeks after the cessation of study medication. Bone density screening by X-ray absorptiometry was conducted between weeks 48 and 52 and again after 20 to 24 weeks of follow-up. Markers for bone resorption and bone formation, such as serum osteocalcin, serum bone alkaline phosphatase, and urinary n-telopeptide, were measured at baseline, at study weeks 8, 16, 24, and 52, and at

Table 3
Most Common Drug-Related Adverse Events in a Controlled Comparator Trial of Dutasteride and Finasteride for Benign Prostatic Hyperplasia

Adverse Event	Finasteride (n = 817)	Dutasteride (n = 813)
Impotence	69 (8)	55 (7)
Decreased libido	46 (6)	39 (5)
Ejaculation disorders	12 (1)	10 (1)
Gynecomastia	9 (1)	9 (1)
Headache	9 (1)	11 (1)
Dizziness	11 (1)	6 (<1)
Malaise/fatigue	12 (1)	12 (1)

Data are presented as n (%). Adverse events reported in ≥ 1% of patients in either group are listed. There were no statistically significant differences between dutasteride- and finasteride-treated patients.
Reproduced with permission from Andriole et al.[18]

follow-up weeks 8, 12, and 24. Lipid levels were recorded at baseline, at study weeks 8, 24, and 52, and at follow-up weeks 4, 8, 12, and 24. There were no clinically significant changes in bone density or bone metabolism markers from baseline, or significant differences between treatment groups at weeks 48 to 52 or follow-up weeks 20 to 24. In addition, there were no significant differences between treatment groups in the lipid profiles. These findings show that the change in serum androgen levels induced by dutasteride does not affect the bone mineral density and lipid profile.

Drug Interactions

Dutasteride is metabolized by the human cytochrome P-450 isoenzyme CYP3A4. According to in vitro data, blood concentrations of dutasteride might increase in the presence of CYP3A4 inhibitors such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin.[18] However, the incidence of adverse events among patients receiving concomitant agents that inhibit CYP3A4, including cimetidine, ciprofloxacin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, and verapamil, was similar in both the dutasteride and placebo groups in the 3 placebo-controlled trials (ARIA 3001, ARIA 3002, ARIA 3003).[13] Nevertheless, care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors, such as ritonavir.

Care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors, such as ritonavir.

In the studies that examined the drug-interaction profile of dutasteride,[18] no pharmacodynamic or pharmacokinetic interactions were observed in studies in which healthy male subjects were given 1) 0.4 mg/d tamsulosin or 10 mg/d terazosin with dutasteride (40 mg loading dose followed by 0.5 mg/d); 2) warfarin (international normalized ratio of 1.5 to 2.0) with dutasteride (25 mg loading dose followed by 0.5 mg/d for 21 days); 3) 0.25 mg/d digoxin with dutasteride (25 mg loading dose followed by 0.5 mg/d for 21 days; or 4) cholestyramine (single 12 g dose) 1 hour after administration of 0.5 mg of dutasteride. Taken together, these data suggest that dutasteride is a safe drug with a wide therapeutic window and few known drug interactions.

Effect on the Development of Prostate Cancer

There is abundant evidence that androgens influence the development of prostate cancer. Recently, definitive data have been published on the reduction of prostate cancer risk by 5α-reductase inhibitors.[7] In this Prostate Cancer Prevention Trial, a total of 18,882 men aged 55 years or older with PSA levels below 3.0 ng/mL were randomized to finasteride (5 mg/d) or placebo for 7 years. After the 7 years, it was found that finasteride treatment resulted in a 24.8% reduction in the prevalence of prostate cancer compared with placebo. However, tumors with higher Gleason scores (7-10) were more frequent in the finasteride-treated group (37.0% of tumors vs 22.2%, $P < .01$).

The first article about the effect of dutasteride on prostate cancer was published by Andriole and colleagues.[19] In this study, patients from the 3 placebo-controlled trials (ARIA 3001, ARIA 3002, ARIA 3003) were analyzed for prostate cancer development. The prostate cancer detection rates were determined by non–protocol-mandated biopsies, either during the double-blind phases of the study or during the first 3 months of the open-label extension. The cumulative incidence of prostate cancer as an adverse event was significantly lower in the dutasteride group than in the placebo group at 24 months (1.1% vs 1.9%, $P = .025$) and 27 months (1.2% vs 2.5%, $P = .002$). There were no differences in the diagnosis rates of prostate cancer during the first 15 months, but after that time the prostate cancer detection rate increased in the placebo group and remained low in the dutasteride group. It is important to recognize, however, that the 3 trials were not designed to address prostate cancer prevention and this study was therefore a secondary analysis. Unlike in the Prostate Cancer Prevention Trial, 100% verification of a biopsy-negative status was not achieved, and fewer subjects receiving dutasteride had at least 1 biopsy (7.9% vs 10.1% of placebo subjects).

Andriole and colleagues[20] also performed a study of the effect of dutasteride on markers of tumor regression in prostate cancer. A total of 46 men with localized prostate cancer were randomized to dutasteride (5 mg/d) or placebo for 6 to 10 weeks before radical prostatectomy. Treatment with dutasteride caused a 97% decrease in intraprostatic DHT and was associated with a trend toward increased apoptosis, as evidenced by increased TUNEL and tissue transglutaminase (tTG) staining. In patients receiving dutasteride for 45 days or more, a significant increase in apoptosis and a trend toward decreased microvessel density in prostate cancer tissue were observed. Dutasteride treatment was also associated with an 18% decrease in mean benign epithelial cell width compared with placebo.

Future Trials to Assess the Effect of Dutasteride on Prostate Cancer

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, initiated in 2004,[21] is a 4-year international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of oral, once-daily dutasteride (0.5 mg) for men at increased risk for prostate cancer. A total of 8000 eligible men aged 50 to 75 years with a PSA level of 2.5 to 10 ng/mL (for ages 50 to 60 years) or 3.0 to 10 ng/mL (for ages 60 years and older) and a negative prostate biopsy within 6 months of enrollment will be recruited. The primary endpoint is biopsy-detectable prostate cancer at 2 and 4 years of treatment. Secondary endpoints for prostate cancer include Gleason score at diagnosis, high-grade prostatic intraepithelial neoplasia at biopsy, percentage of cores with prostate cancer at diagnosis, number of cancer-positive cores, treatment alteration score, and incidence of intervention for prostate cancer, as well as overall survival. This trial will increase our understanding of the effects of dutasteride on the natural history of prostate cancer in men at increased risk for this malignancy. It also affords a unique opportunity to examine the biomarkers and genetic linkage for prostate cancer and to assess a range of prostate health outcomes.

Influence on Daily Clinical Practice

What have we learned about this new dual 5α-reductase inhibitor, dutasteride? Current data confirm that dutasteride reduces serum DHT levels by more than 90% at 2 weeks and significantly reduces prostate volume by 1 month, producing approximately 25% reduction at 2 years. In addition, dutasteride reduces total serum PSA concentration approximately 40% after 3 months of treatment and approximately 50% after 6, 12, and 24 months of treatment. This result suggests that, for men beginning dutasteride treatment, a new PSA baseline should be established after 6 months to assess potential cancer-related changes in PSA. Thus, in determining whether isolated PSA values lie within normal ranges, PSA values should be doubled for patients who have received dutasteride for at least 6 months.

Moreover, dutasteride was found to improve urinary flow after 1 month of treatment and to produce symptomatic improvement after 3 months of treatment in patients with BPH. For patients with severe bladder outlet obstruction, dutasteride alone might not be sufficient for rapid symptom relief. Because these patients with severe BPH usually have enlarged prostates, combination therapy with a 5α-reductase inhibitor (dutasteride) and an α_1-blocker might solve this problem. Depending on the severity of the symptoms, the α_1-blocker might be withdrawn after 6 to 12 months of treatment.

BPH is known to be a progressive disease, and the development of AUR and the need for BPH surgery are well documented in both longitudinal community studies[22] and clinical studies.[5,23] Dutasteride has been shown to reduce progression in many long-term studies[5,23] and to reduce the incidence of AUR and the need for

Main Points

- Dihydrotestosterone (DHT) is necessary for normal growth and function but also seems to have a great impact on the development of benign prostatic hyperplasia (BPH) and on the initiation and maintenance of prostate cancer; DHT synthesis is catalyzed intracellularly by 5α reductase type 1 and 2 enzymes.
- Dutasteride is the first dual inhibitor of both 5α reductase isoenzymes and produces near-complete (> 90%) suppression of serum DHT.
- In 2002, the first clinical study reported the efficacy of dutasteride at a dose of 0.5 mg/d in 4325 patients enrolled in 3 randomized, placebo-controlled trials; the study provided early evidence of dutasteride's efficacy in terms of symptom and peak urinary flow improvement and reduction in prostate volume.
- An analysis of the same cohort showed that dutasteride was also associated with significant improvements in BPH Impact Index score, reflecting improvements in quality of life for men with BPH.
- Long-term treatment (up to 4 years) with dutasteride seems to result in continuing improvements in urinary symptoms and flow rate and also seems to produce a reduction in prostate volume in men with symptomatic BPH.
- Dutasteride has a tolerability profile comparable to that of placebo when used daily for up to 2 years, with the exception of gynecomastia, impotence, and decreased libido, which occurred at modestly elevated incidences compared with the placebo group.
- Dutasteride might be advantageous in the chemoprevention of prostate cancer, owing to its near-complete suppression of serum DHT.

surgery. Patients with large prostate volume (> 30 mL) and a serum PSA concentration above 1.5 ng/mL are more likely to have progressive disease and develop complications, such as AUR; therefore, dutasteride might be an ideal drug for this group of patients. The safety and tolerability of a drug is an important factor for long-term consumption. Dutasteride seems to be safe in long-term studies, but the importance of proper patient counseling on related sexual adverse events must be considered.

Conclusion

Dutasteride is comparable to finasteride with respect to its efficacy for patients with benign prostatic hyperplasia.

Dutasteride might be advantageous in the chemoprevention of prostate cancer, owing to its near-complete suppression of serum DHT. The results from the REDUCE trial will provide more information about this issue. However, longer-term placebo-controlled trials are necessary to confirm the durable efficacy of dutasteride. ■

References

1. Napalkov P, Maisonneuve P, Boyle P. Worldwide patterns of prevalence and mortality from benign prostatic hyperplasia. *Urology.* 1995;46: 41-46.
2. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics 2001. *CA Cancer J Clin.* 2001;51:15-37.
3. Petrow V. The dihydrotestosterone (DHT) hypothesis of prostate cancer and its therapeutic implications. *Prostate.* 1986;9:343-347.
4. Bruchovsky N, Rennie PS, Batzold FH, et al. Kinetic parameters of 5 alpha-reductase activity in stroma and epithelium of normal, hyperplastic, and carcinomatous human prostates. *J Clin Endocrinol Metab.* 1988;67:806-811.
5. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy Safety Study Group. *N Engl J Med.* 1998;338:557-563.
6. Marberger MJ. Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. PROWESS Study Group. *Urology.* 1998;51: 677-686.
7. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349: 215-224.
8. Clark RV, Hermann DJ, Gabriel H, et al. Effective suppression of dihydrotestosterone (DHT) by GI198745, a novel dual alpha-reductase inhibitor [abstract 1037]. *J Urol.* 1999;161:268.
9. McConnell JD, Watson JD, George FW, et al. Finasteride, an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. *J Clin Endocrinol Metab.* 1992;74:505-510.
10. Bruchovsky N, Sadar MD, Akakura K, et al. Characterization of 5 alpha-reductase gene expression in stroma and epithelium of human prostate. *J Steroid Biochem Mol Biol.* 1996;59:397-401.
11. Thigpen AE, Silver RI, Guileyardo JM, et al. Tissue distribution and ontogeny of steroid 5 alpha-reductase isoenzyme expression. *J Clin Invest.* 1993;92:903-908.
12. Thomas LN, Douglas RC, Vessey JP, et al. 5 alpha-reductase type 1 immunostaining is enhanced in some prostate cancers compared with benign prostatic hyperplasia epithelium. *J Urol.* 2003;170:2019-2023.
13. Roehrborn CG, Boyle P, Nickel JC, et al. Efficacy and safety of dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology.* 2002;60:434-441.
14. O'Leary MP, Roehrborn CG, Andriole G, et al. Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5-alpha-reductase inhibitor. *BJU Int.* 2003; 92:262-266.
15. Debruyne F, Barkin J, van Erps P, et al. Efficacy and safety of long-term treatment with 5 alpha-reductase inhibitor of dutasteride in men with symptomatic benign prostatic hyperplasia. *Eur Urol.* 2004;46:488-495.
16. Barkin J, Guimaraes M, Jacobi G, et al. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the 5-alpha-reductase inhibitor dutasteride. *Eur Urol.* 2003;44:461-466.
17. Baldwin KC, Ginsberg PC, Harkaway RC. Discontinuation of alpha-blockade after initial treatment with finasteride and doxazosin for bladder outlet obstruction. *Urol Int.* 2001;66:84-88.
18. Andriole GL, Kirby R. Safety and tolerability of the dual 5α-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur Urol.* 2003;44:82-88.
19. Andriole GL, Roehrborn C, Schulman C, et al. Effect of dutasteride on the detection of prostate cancer in men with benign prostatic hyperplasia. *Urology.* 2004;64:537-543.
20. Andriole GL, Humphrey P, Ray P, et al. Effect of the dual 5α-reductase inhibitor dutasteride on markers of tumor regression in prostate cancer. *J Urol.* 2004;172:915-919.
21. Andriole GL, Bostwick D, Brawley O, et al. Chemoprevention of prostate cancer in men at high risk: rationale and design of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. *J Urol.* 2004;172:1314-1317.
22. Sarma AV, Jacobsen SJ, Girman CJ, et al. Concomittant longitudinal changes in frequency of and bother from lower urinary tract symptoms in community dwelling men. *J Urol.* 2002;168: 1446-1452.
23. McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003;349:2387-2398.