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Proscar®: Five-Year Experience

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Abstract

We assessed the long-term safety and efficacy of finasteride, an orally active 5α-reductase inhibitor, in 2 previously reported groups of patients with symptomatic benign prostatic hyperplasia (BPH). Prostate volume was measured by magnetic resonance imaging, and the maximum urinary flow rate was assessed noninvasively. Symptoms were scored utilizing a patient self-administered symptom score questionnaire. Total symptom scores ranged from 0 (or asymptomatic) to 35 (severely symptomatic). After an initial double-blind period, the patients in study 1 were treated with 10 mg finasteride for 1 year and then switched to 5 mg finasteride for an additional 4 years, whereas patients in study 2 were treated with 5 mg finasteride for the entire 5 years. A total of 190 patients were randomized in the double-blind studies, 156 entered year 1 of the open extension and 70 patients completed 5 years of finasteride therapy. In both studies prostate volume was reduced from baseline by 30%, dihydrotestosterone was reduced by 72%, and the maximum urinary flow rate improved by approximately 1.5 ml/s. Prostate-specific antigen was decreased by approximately 50%. Finasteride was well tolerated; approximately 10% of patients reported sexual adverse experiences during the 5-year study period, which were considered drug related by the investigators. The incidence in reporting sexual adverse experiences did not increase with the increased duration of treatment: findings consistent with previous reports. In summary, treatment of BPH with finasteride for 5 years inhibits the progression of the disease with an excellent safety profile and represents a low-risk medical option for the treatment of symptomatic BPH.

Key Words
Finasteride
Benign prostatic hyperplasia
Prostate volume
Prostate-specific antigen
Uroflow
Dihydrotestosterone

Introduction

Benign prostatic hyperplasia (BPH) is an enlargement of the prostate gland, a common disease in men over 55 years of age. Approximately 50% of men have histologic evidence of BPH by age 60 and by age 80 there is histological evidence in almost all men [1].

Finasteride (Proscar®) is an orally active, specific inhibitor of the type-2 5α-reductase isoenzyme. In individuals who are genetically deficient in 5α-reductase 2, the prostate gland is underdeveloped and BPH has not been reported to occur [2, 3]. Previous studies have shown that pharmacologic inhibition of this enzyme with finasteride results in a significant decrease in the conversion of tes-

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tosterone to dihydrotestosterone (DHT) in the serum and prostate gland [2, 3]. The effect of finasteride in patients with BPH in two large placebo-controlled, double-blind, phase-III studies of 12-month duration has previously been summarized [4, 5]. The results of the double-blind and the 1-year open extension for the studies reported here have previously been reported, and demonstrated that the effects of finasteride in lowering DHT levels, reducing prostate size, and improving urinary flow and symptoms were maintained for this period of time [3]. This article summarizes the data on symptomatic BPH patients treated with finasteride for 5 years (in the open extension phase of these studies) and represents the longest follow-up data to date.

Table 1. Summary of efficacy variables

	Baseline	Year 1 (n = 54)	Year 5 (n = 54)
Median prostate volume, cm^3	79.9	53.5	48.5
Median DHT, ng/dl	47.0	9.9	9.5
Median PSA, ng/dl	2.1	1.4	1.0
Maximum urinary flow[a], cm^3/s	10.8	12.9	12.3
Total mean symptom score[b]	–[c]	7.3	6.3

[a] Urinary flow machine changed from month 7 to 18.
[b] Range = 0 (absence of symptoms) to 35 (worst response to all symptoms).
[c] The baseline symptom score questionnaire was different in the two studies.

Patients and Methods

Patients who completed the two double-blind studies (study 1 and study 2) [2] were allowed to continue finasteride therapy in an open-label study for an additional 5 years. Patients on placebo in the double-blind phase of this study were switched to finasteride for the remaining 5 years. Patients were evaluated by the investigator at the end of each year for response to drug prior to continuing in the study. Patients completing study 1 were treated with 10 mg finasteride for the 1st year [4] and then switched to 5 mg for the remainng 4 years. Patients who completed study 2 were treated with the same 5 mg finasteride for 5 years. A total of 156 patients entered the open-extension phase from both studies and 85 continued into the 5th year. Seventy of the men who completed 5 years of finasteride treatment and had efficacy data available are the subjects of this report. The data for the remaining 15 patients were unavailable at the time of this report.

The mean age of the patients at the initiation of the double-blind studies was 67 years. The study was approved by the institutional review board at each center, and all men gave written informed consent.

Patients were evaluated every 4 months for efficacy and safety. Prostate size was evaluated every 6 months by magnetic resonance imaging from year 1 through year 3 and then annually during years 4 and 5. Safety was assessed throughout the study by clinical and laboratory tests and by monitoring all clinical and laboratory adverse experiences.

Serum testosterone and DHT concentrations were measured by radioimmunoassay after chromatographic separation at Endocrine Sciences (Calabasas, Calif.). The normal range of serum testosterone in men was 344–1,029 ng/dl (12–36 nmol/l), and of serum DHT 30–88 ng/dl (1.0–2.9 nmol/l). The sensitivity of the assay was 5 ng/dl (0.17 nmol/l) for testosterone and 2 ng/dl (0.07 nmol/l) for DHT, and the interassay variation was 9.6 and 11.7%, respectively.

Serum prostate-specific antigen (PSA) was measured every 4 months by Medical Research Laboratories (Cincinnati, Ohio) with a solid-phase, two-site immunoradiometric assay (Hybritech, La Jolla, Calif.). The sensitivity of the assay was 0.2 µg/l and the interassay variation was 3.8%.

Urinary flow rate measurements were determined on a Lifetech recorder at baseline (of the double-blind study) through year 1 of the open extension in study 1 and study 2. The measurements were made on a Dantec uroflow machine for both studies after year 1 of the open extension due to its increased accuracy and reproducibility. A prototype symptom questionnaire modified from that of Boyarsky et al. [6] was self-administered and was used at each visit to assess the effects of the study drug on the symptoms of urinary obstruction. This symptom score was also refined and the modified version was implemented at the beginning of the open extension of study 1 and was used throughout study 2. The total symptom score was the sum of the irritative and obstructive symptoms.

Results

Although safety data are presented for 70 patients, efficacy data are presented only for those 54 patients who had complete efficacy data available at the year 5 time point. The characteristics for these patients at the original baseline, year 1 and year 5 are shown in table 1.

In the original double-blind study, there was a mean reduction in prostate volume of approximately 23% at 24 weeks in the 5-mg group with a mean decrease of approximately 4% observed in the placebo group [2]. The effect of 5 mg finasteride on prostate size after 5 years of continuous treatment showed a mean reduction of 30% from baseline (fig. 1). The mean prostate volume at baseline of these patients was 97 cm^3.

The median PSA at baseline was 2.1 ng/dl and after 5 years of finasteride therapy the median PSA value declined to 1.0 ng/dl. The median percent change from baseline in PSA was 53.7% at year 5 (fig. 2).

Since the machines for measuring maximum flow rate and the parameter for evaluating symptom severity changed at the initiation of the open extensions, the base-

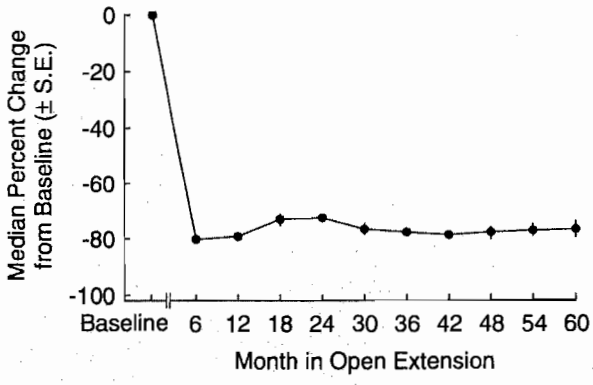

Fig. 1. Median percent change in prostate volume for patients who completed 5 years of therapy (n = 49 at each time point).

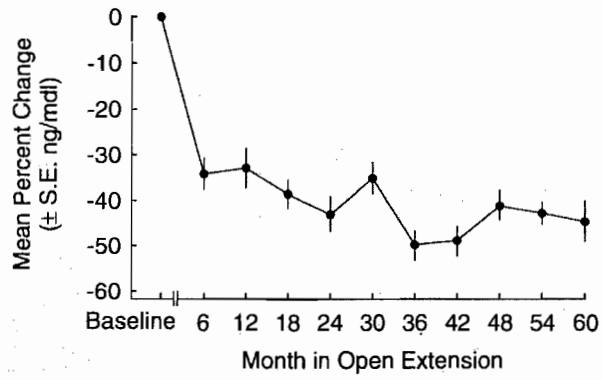

Fig. 3. Maximum flow rate (n = 20 patients with a baseline value of <15 cm^3/s).

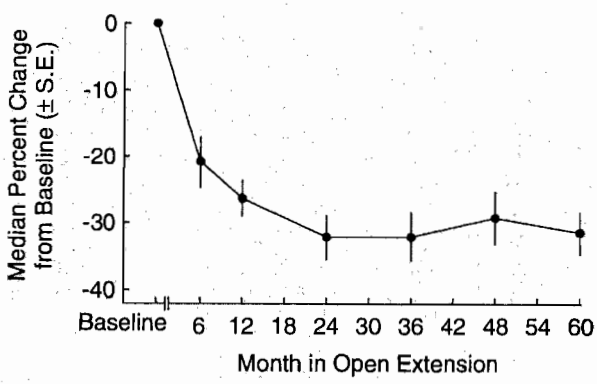

Fig. 2. PSA: mean change from baseline (n = 68 patients).

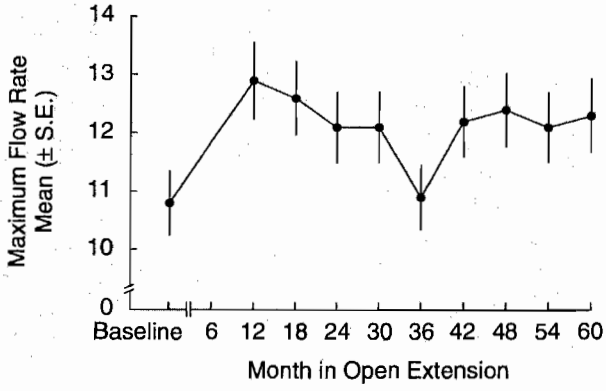

Fig. 4. DHT: median percent change from baseline (n = 37 patients).

line values for these efficacy parameters are taken at year 1 of the open-label studies.

Of 53 patients completing year 5 in whom urinary flow rates had been measured on patients with a voided volume of >150 ml, 20 had a baseline uroflow measurement of <15 cm^3/s. The mean maximum flow rate at year 5 for this group of 20 patients was 12.3 cm^3/s (by Dantec) while the mean at baseline was 10.8 cm^3/s (by Lifetech; fig. 3).

In the original double-blind studies, total and obstructive symptoms improved significantly in the 5-mg treated groups compared to the placebo. The mean symptom score at year 1 of the open-label extension was 7.3 and at year 5 was 6.3, indicating that the decrease in total symptom scores was maintained and improved from year 1 to year 5.

Safety was assessed throughout the open-label studies. Clinical adverse experiences judged by the investigator to be possibly, probably, or definitely drug related and occurring in 1% or more of the patients are presented in table 2. In the extension studies the most frequently reported drug-related adverse experiences were decreased libido and impotence. No serious drug-related adverse events were reported in years 3–5. The reasons patients discontinued participating in the double-blind study and in the open extension from years 1 to 5 are summarized in table 3. The most common reasons were lack of clinical

Table 2. Percent of patients with drug-related clinical adverse experiences occurring in ≥ 1.0% patients

	Controlled studies 0–6 months		Extension				
	placebo (n = 41)	finasteride (n = 149)	year 1 (n = 156)	year 2 (n = 118)	year 3 (n = 100)	year 4 (n = 88)	year 5 (n = 70)
Abdominal pain	2.4	–	–	–	–	–	–
Alopecia	2.4	1.3	2.6	2.5	–	–	–
Anorexia	2.4	–	0.6	–	–	–	–
Asthenia	2.4	1.3	0.6	–	–	–	–
Blurred vision	2.4	–	0.6	–	–	–	–
Constipation	–	2.0	1.9	–	–	–	–
Dysuria	–	2.0	1.3	–	–	–	–
Ejaculation disorder	–	–	5.8	1.7	1.0	1.1	5.7
Headache	–	2.7	2.6	0.9	–	–	–
Impotence	–	0.7	7.1	3.4	1.0	2.3	4.3
Libido decrease	–	0.7	10.9	4.2	2.0	1.1	4.3
Sweating	2.4	–	0.6	–	–	–	–

Table 3. Percent of patients who discontinued from the double-blind and 5-year open-extension studies

	6-month double-blind		Open extension, 5 mg				
	placebo (n = 41)	finasteride (n = 149)	year 1 (n = 156)	year 2 (n = 118)	year 3 (n = 100)	year 4 (n = 88)	year 5 (n = 70)
Sexual AE	–	–	1.9	0.8	1.0	–	–
Prostate cancer	–	1.3	–	–	2.0	2.3	–
Death	–	–	–	–	1.0	–	–
Other clinical AE[1]	2.4	7.4	7.7	2.5	2.0	–	1.4
Therapeutic failure[2]	–	–	1.3	0.9	1.0	2.3	1.4
Lost to follow-up[3]	9.8	2.7	2.6	10.2	4.0	2.3	2.9
Total	12.2	11.4	13.5	14.4	11.0	6.8	5.7

AE = Adverse events.

[1] The 3 most common AE were cardiovascular malignancies (various non-prostate types), and non-prostate surgery.

[2] Lack of improvement and need for other drug therapy.

[3] The most common reason patients were lost to follow-up was loss of interest in continuing participation.

improvement, sexual adverse experiences and cardiovascular adverse events. From years 2–5, 7 of 118 men who entered the second year open extension had a TURP, 4 were elective. The discontinuation rate for drug-related adverse experiences over 5 years was 2.6%.

Prostate cancer was reported in 7 patients. Two patients were described previously [2]. One additional patient was diagnosed with prostate cancer prior to entering the 1st year open extension and 4 patients were diagnosed in years 2–5 of the open extension (table 4). None of the cases were considered to be drug related by the investigator.

The median percent decrease from baseline in DHT in 37 patients treated for 5 years was 76.6% with a median baseline value of 47.0 ng/dl (fig. 4).

In the double-blind studies, treatment with finasteride resulted in an approximately 10% mean increase in testosterone levels. Although this increase was statistically significant, this value remained within the normal range for adult males. At year 5 the mean testosterone value in

Table 4. Summary of patients with prostate cancer diagnosed from years 2 to 5

Patient No.	Duration of therapy years	Baseline PSA ng/dl	PSA at diagnosis ng/dl	Primary mode of diagnosis
1	3	5.3	2.3	Exacerbation of BPH symptoms
2	3	26.0	11.6	Elevated PSA
3	4	15.0	11.1	Elevated PSA
4	4	3.9	5.7[1]	Palpable nodule

[1] Measurement off drug.

37 patients with measurements through this time period was 481.5 ng/dl as compared to a mean value of 469.2 ng/dl at baseline.

At year 5, the median LH value was 9.2 mIU/ml in 36 patients assayed as compared to 7.2 mIU/ml at baseline for the same patients (both values are within the normal range for adult males).

Discussion

Although symptoms of BPH are present in the majority of men 60 years of age and older [7], gross measures of total prostate size have not shown a strong statistical correlation with either symptoms or other clinical measures of obstruction [8], despite the fact that the obstruction is a direct biological consequence of the abnormal growth. Because localized periurethral nodules may be the cause of significant obstruction, prostate size may not correlate well to symptoms [8]. The results of the phase-III 3-year data have recently been published [9]. After 36 months of treatment with 5 mg finasteride, prostate volume was reduced from baseline by approximately 27%, uroflow improved by 2.3 ml and symptom scores improved by 3.6 points. This study also shows that there is improvement and a sustained effect of finasteride on symptomatic relief and urinary flow rates for patients with BPH, which is associated with significant shrinkage of the prostate gland, through 5 years of finasteride therapy. As stated previously, at the beginning of the phase-II studies the Merck symptom score questionnaire was validated. The symptomatic improvement reported here is following year 1 of open-label finasteride therapy to year 5. The results of this study supplement the analysis of the phase-III open-extension data [9, 10] and clearly show a maintenance of clinical efficacy. Although the increases in urinary flow rates with medical therapy were smaller than those observed after TURP, studies of the natural history of BPH indicate that the mean decrease in urinary flow observed in the finasteride studies represents a reversal of about 10–15 years in the natural history of the disease. The mean symptom score improvement with medical therapy observed using the identical questionnaire showed about one half of the effect of TURP [11]. The mean urinary flow rate in this study is greater than 12 cm^3/s in this group of men past 70 years of age treated for 5 years.

Safety

The most frequently reported drug-related adverse experiences were sexual adverse events. The three most common non-drug-related adverse events were cardiovascular, various, non-prostate malignancies and non-prostate surgery. At the end of 5 years the percent incidence of reported sexual adverse experiences was less than the percent reported at year 1. Additionally, some sexual adverse experiences resolved with continued treatment. Finasteride continued to have an excellent safety profile and be well tolerated. There is no increase in urinary tract complications with long-term therapy. Few patients required invasive treatment for BPH. The study shows that sexual adverse experiences are reported infrequently with continued use of finasteride. Only 5 patients discontinued due to sexual adverse experiences.

The data indicated that the sustained efficacy of finasteride in lowering DHT and PSA, decreasing prostate volume, increasing maximum uroflow rate and improving symptoms after 1 and 2 years of treatment is maintained over 5 years. There was no particular baseline characteristic that predeveloped greater efficacy in this population of men with an enlarged prostate gland. These findings represent a reversal of the natural progression of BPH and compares favorably with recent long-term natural history studies: demonstrating that in BPH the mean expected decrease in urinary flow is about 0.2 cm^3/s/year and the increase in prostate volume is approximately 0.6 cm^3/year [12]. Thus, this long-term follow-up study extends the findings of the finasteride open extension of the phase-III studies [9], which demonstrated a decrease in prostate volume, a maximum urinary flow rate improvement of approximately 2.3 cm^3/s and a symptom score improvement of 3.6 points from baseline over the 3-year study duration.

Efficacy results of treatment of BPH with finasteride are consistent with the short-term results observed by Pe-

ters and Walsh [13] with an LHRH agonist, nafarelin acetate, which blocks the production of testosterone. After 6 months of therapy, these men showed a 25% decrease in prostate volume and increased uroflow rates as well as symptomatic improvement in obstructive symptoms. All patients experienced impotence and hot flashes. Stone [14] reported the effect of flutamide, a nonsteroidal antiandrogen that effectively competes with DHT for cytosol androgen receptor sites. After 6 months of treatment the patients experienced a 35% improvement in uroflow and a 41% decrease in prostate volume with a majority of men reporting some adverse experience. Finasteride has a tolerability profile superior to both of these drugs.

To further assess the effect of finasteride therapy on the natural history of BPH, we are currently conducting a 4-year, placebo-controlled study in 3,000 men with BPH. The results of this study will provide long-term placebo-controlled data to support the hypothesis that the natural history of BPH is halted in patients treated with finasteride on a long-term basis.

In conclusion, finasteride markedly reduces the DHT levels in the prostate thereby decreasing prostate size. The long-term symptomatic relief and excellent safety profile indicate that daily finasteride is a well-tolerated, effective treatment for symptomatic BPH.

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