The long-term safety and tolerability of drugs used for treating LUTS due to BPH continues to be important to clinical urologists. The large trial using dutasteride was a 4-year study, and the authors showed that the drug is well tolerated in these patients.

Minimally invasive therapy for BPH has had a mixed press, but the holmium laser is beginning to be seen as a possible addition to the treatment options of such patients. Further evidence is presented here, by authors from the USA, that the holmium laser can be used to enucleate large prostates with safety. Another study on smaller prostates from India had a similar outcome.

Long-term therapy with the dual 5α-reductase inhibitor dutasteride is well tolerated in men with symptomatic benign prostatic hyperplasia

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OBJECTIVE

To examine the long-term (4-year) safety and tolerability of dutasteride in the treatment of symptomatic benign prostatic hyperplasia (BPH).

PATIENTS AND METHODS

Patients who completed the double-blind phase of three dutasteride Phase III studies were eligible to enter a 2-year open-label extension, during which all patients received dutasteride 0.5 mg. Safety was assessed, including adverse-event reporting, clinical laboratory assessments, yearly physical examinations, and vital sign assessments.

RESULTS

In all, 2340 patients entered the open-label phase, 1188 of whom previously received dutasteride during the double-blind phase of the study. The most common drug-related adverse events (occurring in ≥1%) were effects on sexual function, which decreased with a longer duration of therapy. Gynaecomastia was reported in a small percentage of men throughout the 4-year study period. The incidence of individual sexual functional adverse events that led to withdrawal was ≤1% (0.3–1.0%) during the 4-year study period. Dutasteride had no relevant effects on vital signs or clinical laboratory variables.

CONCLUSION

These data show that dutasteride is well tolerated during long-term use for the treatment of symptomatic BPH.

KEYWORDS

BPH, dutasteride, 5α-reductase inhibitor, tolerability, long-term

INTRODUCTION

Dutasteride, a selective dual 5α-reductase inhibitor (5ARI), inhibits the enzyme 5α-reductase that catalyses the conversion of testosterone to dihydrotestosterone (DHT), one of the major contributors to both normal and hyperplastic prostate tissue growth [1]. Dutasteride significantly reduces prostate volume, improves urinary symptoms and flow, and reduces the long-term risks of acute urinary retention and the need for BPH-

related surgery in men with symptomatic BPH [2]. It is well tolerated, with a profile similar to that of placebo, except for a modestly higher incidence of impotence, decreased libido, ejaculation disorders, and gynaecomastia [2,3].

Dutasteride inhibits both Type 1 and Type 2 5α-reductase, whereas finasteride is a mono-inhibitor of Type 2 5α-reductase at therapeutic doses [4,5]. The more comprehensive inhibition of the 5α-reductase isoenzymes achieved with dutasteride results in near-complete and consistent suppression of serum DHT. In a 24-week study, 0.5 mg dutasteride suppressed serum DHT by a mean of 94.7% at 24 weeks, compared with 70.8% suppression for 5 mg finasteride at 24 weeks [6]. This degree of DHT suppression with dutasteride is maintained during long-term (4-year) treatment [7].

Long-term (4-year) safety and tolerability data are available for finasteride, showing that the most common adverse events (occurring in ≥1% of patients) reported were sexual dysfunction, breast enlargement or tenderness, and rashes [8,9]. In the present study we report additional 4-year safety analyses of the dutasteride Phase III studies, which were designed to assess the safety and tolerability of dutasteride for treating BPH in a 2-year double-blind study with 2-year open-label extension [7].

PATIENTS AND METHODS

ARIA3001, ARIA3002 and ARIB3003 were randomized, double-blind, placebo-controlled studies of the efficacy and safety of dutasteride 0.5 mg once daily in the treatment of men with symptomatic BPH. The principal inclusion and exclusion criteria for the studies are shown in Table 1. The design of these studies was reported previously [2]. Briefly, before starting the double-blind phase, patients underwent a 1-month, single-blind placebo run-in period, and were then randomized to treatment with dutasteride 0.5 mg or placebo once daily for 2 years. Patients who completed the double-blind phase were eligible to participate in an additional 2-year open-label phase, in which all patients received daily dutasteride 0.5 mg. Patients receiving dutasteride in the double-blind and open-label phases (a total of 4 years of dutasteride treatment) were classified as the D/D group, while those initially receiving placebo switched to open-label dutasteride (2 years of dutasteride treatment) were classified as the P/D group.

TABLE 1 Principal inclusion and exclusion criteria for the three Phase IIIa studies

Inclusion criteria	Exclusion criteria
Men eligible aged ≥50 years	Postvoid residual volume >250 mL
Diagnosis of BPH by history and physical examination	History of prostate cancer
	Previous prostate surgery
Prostate volume measured by TRUS of ≥30 cm^3	Previous history of acute urinary retention within 3 months of screening
AUA-SI score ≥12 (moderate-to-severe symptoms)	Use of an α_1-blocker within 2 weeks or any previous use of a 5ARI
Q_{max} ≤15 mL/s	
Serum PSA level ≥1.5 ng/mL	Serum PSA level ≥10 ng/mL

During the open-label phase, patients were scheduled to return for assessments at 27, 30, 33, 36, 39, 42, 45 and 48 months. The objectives of the 2-year open-label phase were to assess the safety and tolerability of long-term dutasteride therapy, and efficacy endpoints. The efficacy outcomes were reported elsewhere [7].

Safety was assessed through prompted and spontaneous adverse-event reporting (inclusive of sexual dysfunction) at each visit, clinical laboratory assessments and yearly physical examinations, which included focused gynaecomastia evaluations, a DRE, and yearly vital signs. Prostate cancer was ascribed from either 'for cause' biopsies or review of resected tissue. Liver function was tested at screening and at yearly intervals. Samples for serum testosterone (and DHT) were obtained at baseline and at yearly intervals. Additional clinical chemistry tests (serum glucose, sodium, potassium, albumin, total protein creatinine) and haematology tests (total white blood cell count, platelet count, haemoglobin, and mean red blood cell volume) were also conducted. Adverse events were also examined according to age (<75 vs ≥75 years) and concurrent medical conditions.

Analyses were conducted on pooled data from the three studies. Most analyses were conducted on the open-label intent-to-treat (ITT) population, who received at least one dose of study treatment during the open-label phase. Adverse events reported for this population are those where the onset date was on or after the patients' open-label treatment start date. These data were compared with data from the double-blind ITT population, who received at least one dose of study treatment during the double-blind phase. The mean (SD) percentage change from baseline was calculated for serum DHT and testosterone.

RESULTS

In all, 4325 patients were randomized into the double-blind phase of the studies, 2158 to placebo and 2167 to dutasteride. Of these, 2340 patients enrolled into the open-label phase, 1152 who had previously received placebo (P/D group) and 1188 who had previously received dutasteride (D/D group). Of the 363 study centres that participated in the double-blind phase, 265 participated in the open-label phase, with 16 of the initial 19 countries represented. Of the P/D group, 1022 patients were aged <75 and 130 were aged ≥75 years; in the D/D group, 1015 patients were aged <75 and 173 were aged ≥75 years. In all, 803 patients in the P/D and 864 patients in the D/D group completed the 4 years of study.

At the start of the double-blind phase there were no significant differences in baseline variables between patients in the D/D and P/D group from the open-label ITT population, except for higher mean maximum urinary flow rate (Q_{max}) in the P/D group. Patients from the D/D group who completed the double-blind phase and elected to participate in the open-label phase had a mean AUA-Symptom Index (SI), Q_{max} and prostate volume not significantly different from those who did not elect to enter the open-label phase.

The rates of adverse events, withdrawals and abnormal clinical laboratory values among patients who did and did not enrol in the

TABLE 2 Adverse events, withdrawals and clinical laboratory abnormalities during the double-blind phase for patients who did and did not enrol in the open-label phase (double-blind ITT population)

	Enrolled, %		Did not enrol, %	
Group	P/D	D/D	P/D	D/D
Adverse events	81	83	68	70
Drug-related adverse events	14	19	14	20
Serious adverse events	11	14	17	17
Withdrawals due to adverse events	<1	<1	19	19
Abnormal laboratory values	48	50	43	44

TABLE 3 Demographic and clinical characteristics at the start of the double-blind phase in patients entering the open-label phase (open-label ITT population)

Baseline characteristic	P/D	D/D
N	1152	1188
Mean (SD):		
Age, years	66.0 (6.97)	66.2 (7.42)
Duration of BPH symptoms, years	5.2 (4.81)	5.1 (4.67)
Time since BPH diagnosis, years	3.6 (4.28)	3.6 (4.39)
Prostate volume, mL	53.9 (20.85)	56.1 (24.16)
Patients taking α-blockers, n (%)	313 (27)	348 (29)
Time since last taken, months	9.8 (28.10)	7.5 (15.32)
n/N (%) or n (%):		
Sexual function at screening:		
Sexually active	819 (71)	797 (67)
Impotence in previous 3 months	464/1099 (42)	454/1122 (40)
Lack of libido in previous 3 months	346/1098 (32)	349/1122 (31)
Any medical condition	1033 (90)	1053 (89)
Any concurrent medication	1105 (96)	1138 (96)

open-label phase are summarized in Table 2. The overall rate of adverse events was lower in those who chose not to enrol than in those who did. However, the rate of adverse events classified as drug-related was similar in both groups. As would be expected, serious adverse events and withdrawals due to adverse events were more common in those who did not enrol than in those who did. Clinical laboratory abnormalities were no more frequent in those who did not enrol than those who did.

At the start of the double-blind phase, the baseline characteristics of patients who entered the open-label phase that are pertinent to the safety and tolerability analyses are presented in Table 3. Patients who entered the open-label phase had a similar mean age and duration of BPH symptoms/diagnosis at baseline, and reported similar levels of α-blocker use between treatment groups. Comorbidity and concomitant medication use were highly prevalent in both treatment groups, as would be expected of men in this age group. The incidence of current medical conditions was comparable between the treatment groups, with the most frequently reported conditions associated with the cardiovascular, musculoskeletal, and endocrine and metabolic systems. Although most men were sexually active, impotence and lack of libido were common in both treatment groups at baseline.

In the D/D group the mean exposure to dutasteride over the 4-year duration of the two study phases was 3.8 years, with 71% of patients having >3.9 years exposure. The mean extent of exposure to dutasteride in the open-label phase was comparable between the P/D and D/D groups (1.7 vs 1.8 years).

The overall pattern of adverse events and withdrawals due to adverse events in the double-bind and open-label phases are summarized in Table 4. During the open-label phase, the incidence of all adverse events was similar in the P/D and D/D groups, as was the proportion of patients who withdrew due to adverse events. The incidence of adverse events for dutasteride-treated patients decreased between 0–24 and 24–48 months.

The overall incidence of adverse events in the open-label ITT population was higher in elderly P/D-treated patients (81% in those aged ≥75 years; 72% in those <75 years) but comparable for D/D-treated patients in both age groups (69% ≥75 years; 72% <75 years). Adverse events were more frequent in patients with than without concurrent cardiovascular, endocrine or metabolic medical conditions, but similar between the P/D and D/D groups (75% vs 69% for D/D and 76% vs 70%, for P/D with or without concurrent cardiovascular conditions, respectively; 76% vs 70% for D/D and 78% vs 70%, for P/D with or without concurrent endocrine or metabolic conditions, respectively).

During the open-label phase, the proportion of patients with drug-related adverse events was higher in the P/D group, who had been switched from placebo to dutasteride, than in the D/D group, who received continuous dutasteride (Fig. 1). In both treatment groups the proportion of patients with drug-related adverse events diminished with time; this pattern was similar to that in D/D-treated patients during the double-blind phase.

Over the 4-year duration of the double-blind and open-label phases, the incidence of drug-related adverse events continued to decrease in patients from the D/D group (Fig. 1). The proportion of men who withdrew due to drug-related adverse events during the open-label phase was low in both groups (2%). Serious drug-related adverse events were very rare in both treatment groups and decreased during the 4-year duration of the study. The numbers of deaths were similar in both treatment groups; only one death (due to myocardial infarction) in the D/D group was considered possibly related to study medication by the investigators.

The most common drug-related adverse events in the open-label phase, in common

with the double-blind phase, were impotence, decreased libido, ejaculation disorders and gynaecomastia (including breast/nipple tenderness and/or breast enlargement). When the 4-year duration of the double-blind and open-label phases are examined together, patients in the D/D group most frequently had an onset of new sexual function adverse events within the first 6 months of treatment, with the incidence of new events then decreasing over time (Fig. 2a–d). Gynaecomastia was reported in a small percentage of men and at a relatively constant rate during the study period. Among patients in the P/D group, the incidence of events was comparable with those experienced by D/D-treated patients at the start of therapy, with the incidence declining at 36 to 48 months. The incidence of individual drug-related sexual function adverse events that led to withdrawal was low at ≤1% in the D/D group over 4 years. During the 4-year double-blind and open-label study period, no other drug-related adverse events, except for impotence and decreased libido, were reported in >3% of patients. Neurological drug-related adverse events such as headache and dizziness were reported in <1% of patients in the P/D and D/D groups.

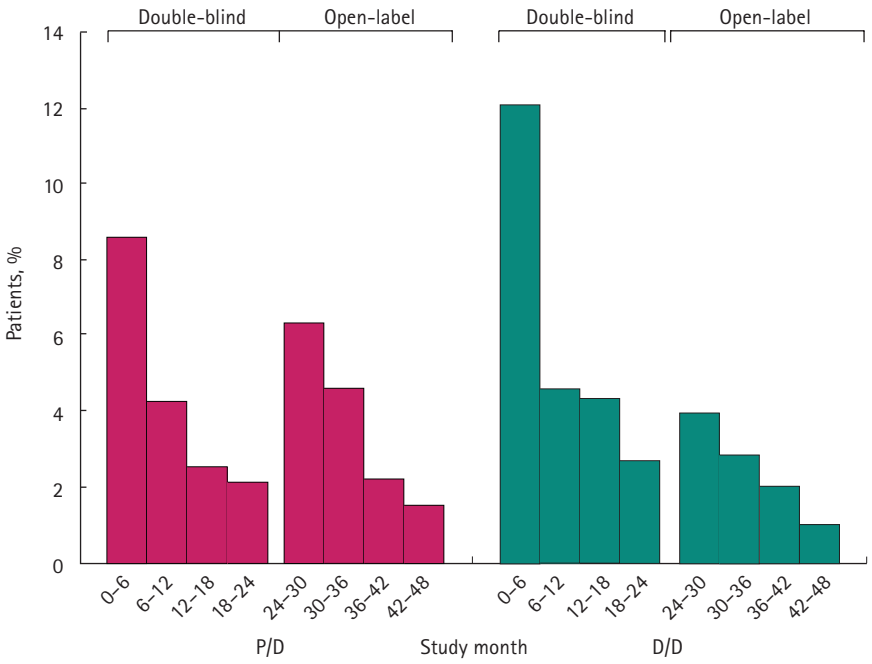
Prostate cancer diagnosed during the studies was recorded as an adverse event. During the open-label phase, 25 prostate cancer diagnoses were made in the P/D group (2.2%) and 20 in the D/D group (1.7%). The effect of dutasteride on the detection of prostate cancer during the double-blind phase of treatment was reported previously [10].

Patients in the D/D group had a median decrease from baseline in serum DHT concentration of 93.7% at 24 months, which was maintained at 48 months (95.3%). Patients in the P/D group had a median 5.9% increase at 24 months, and a subsequent 95.4% decrease at 48 months. As expected, median serum testosterone levels increased among D/D-treated patients by 19.7% at 24 and by 21.9% at 48 months. P/D-treated patients had a median increase in testosterone of 2.2% at 24 and 20.7% at 48 months. A few patients (18 P/D-treated and 35 D/D-treated) had serum testosterone values of ≥10 000 pg/mL during the study. Serum testosterone values returned to within the normal range (3000–10 000 pg/mL) at the end of study for nine P/D and 11 D/D-treated patients.

TABLE 4 A summary of adverse events, withdrawals and deaths during the 4-year duration of the study. Results from 0–24 months are from the double-blind ITT population, and from 24–48 months from the open-label ITT population

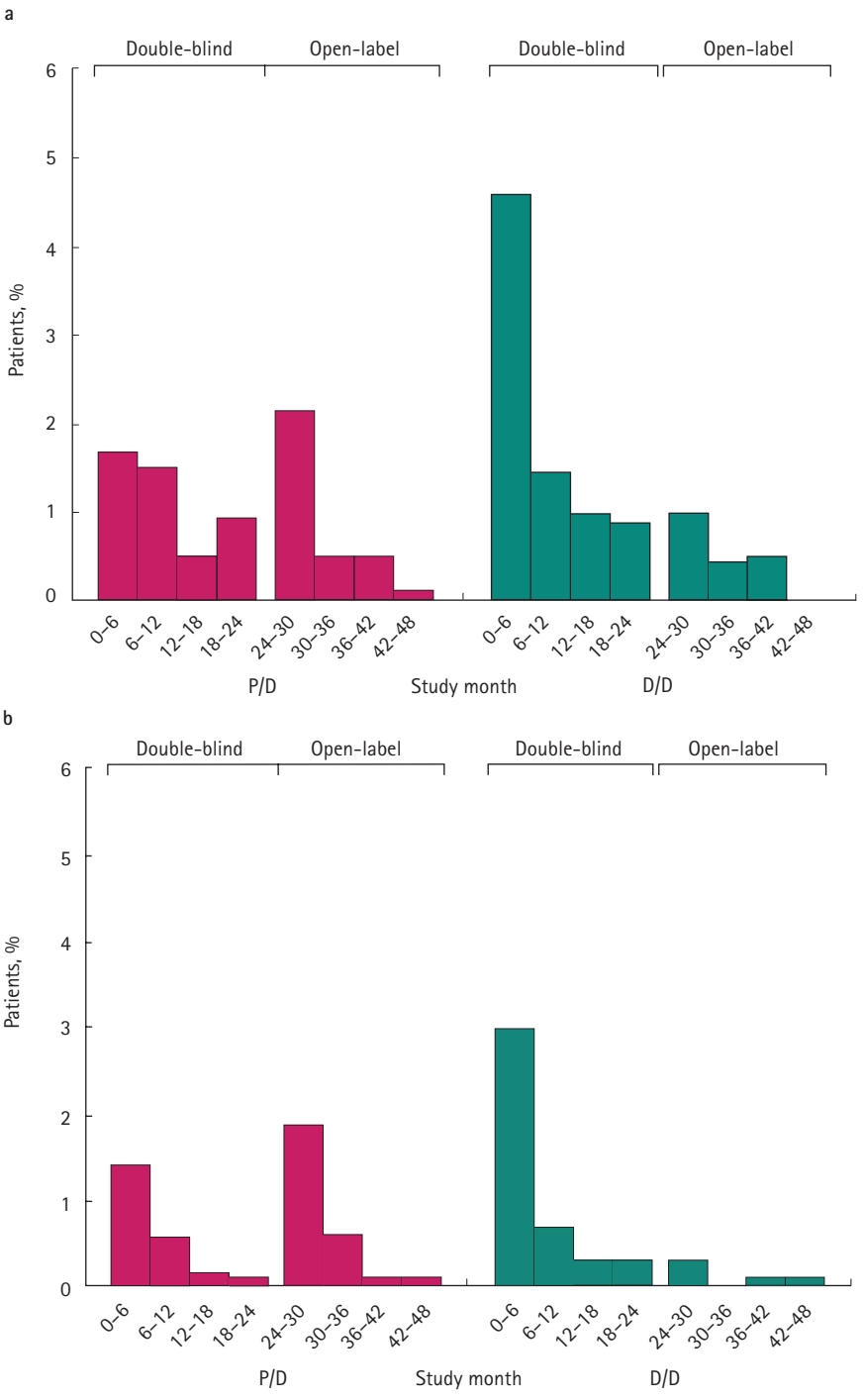
Variable	0–24 months		24–48 months	
	P/D	D/D	P/D	D/D
N	2158	2167	1152	1188
n (%):				
Any adverse event	1612 (75)	1667 (77)	837 (73)	852 (72)
Withdrawal due to adverse event	190 (8)	186 (9)	109 (9)	100 (8)
Drug-related adverse event	303 (14)	412 (19)	139 (12)	98 (8)
Withdrawal due to drug-related adverse event	60 (3)	82 (4)	28 (2)	24 (2)
Serious adverse event	301 (14)	330 (15)	131 (11)	151 (13)
Withdrawal due to serious adverse event	86 (4)	77 (4)	38 (3)	42 (4)
Serious drug-related adverse events	6 (0.3)	3 (0.1)	2 (0.2)	4 (0.3)
Deaths, n	20	26	19	17

FIG. 1. Onset of any double-blind (double-blind ITT population) and open-label (open-label ITT population) adverse events classified as drug-related occurring in ≥1% of patients in either treatment group.



There was little mean change from baseline for most clinical laboratory analyses, except for platelet count, which increased to a minor degree from baseline at each assessment, although this was not considered clinically relevant. At baseline, 48% of P/D-treated and 49% of D/D-treated patients had one or more abnormal laboratory value, with an abnormal glucose being the most common finding (20% in each treatment group). During the open-label phase, 52% of P/D- and D/D-treated patients had one or more abnormal laboratory value and, as at baseline, abnormal glucose was the most common finding (27% and 28%, respectively). Despite changes in some laboratory values, most remained within the normal range from baseline to the end of open-label treatment. The overall incidence of patients crossing predetermined threshold values for laboratory values was low during the open-label phase (7% in the P/D group and 6% in the D/D group). The glucose threshold (>1.75 times the upper limit of the normal range) was

FIG. 2. Onset of double-blind (double-blind ITT population) and open-label (open-label ITT population) drug-related adverse events in either treatment group: a, impotence; b, decreased libido; c, ejaculation disorders; d, gynaecomastia (includes breast/nipple tenderness and breast enlargement).



exceeded in 4% of patients in each treatment group.

At baseline, 12% of patients in the P/D group and 11% in the D/D group had palpable breast tissue; <1% of patients in both groups had nipple tenderness at baseline. At 48 months the percentages of patients with changes from normal at baseline in palpable breast tissue and nipple tenderness were low and comparable between the treatment groups (4% in the P/D and 5% in the D/D group for palpable breast tissue, and 1% in each group for nipple tenderness).

During the double-blind phase, there were minor decreases in both treatment groups from baseline at 24 months in mean systolic (–0.9 mmHg in the P/D and –1.1 mmHg in the D/D group) and diastolic (–1.1 mmHg in the P/D and –1.0 mmHg in the D/D group) blood pressure, and minor increases from baseline in mean heart rate (0.5 beats/min in the P/D and 0.9 beats/min in the D/D group). These small changes were not considered to be clinically relevant. At 36 and 48 months there was little change in vital signs from baseline for either treatment group, ranging from –0.3 to –1.1 mmHg for systolic blood pressure, –1.6 to –2.2 mmHg for diastolic blood pressure and 0.8–1.1 beats/min for heart rate. During the open-label phase, 9% of patients in each treatment group had at least one vital sign measurement that exceeded predefined threshold levels, with most being a systolic blood pressure >165 mmHg.

The adverse events profile was assessed by concurrent use of cardiovascular drugs (angiotensin-converting enzyme inhibitors, β-blockers, calcium antagonists, and diuretics), endocrine and metabolic drugs (antihyperlipidaemics and corticosteroids), NSAIDs, salicylates, phosphodiesterase Type V inhibitors and 4-quinolones. The overall incidence of adverse events, and associated adverse events (e.g. musculoskeletal pain in NSAID users), was higher in patients using concurrent medication than in nonusers. The incidence of adverse events was broadly comparable between the P/D and D/D groups, except for reproductive system events, which were more frequent in the P/D group regardless of concurrent medication use.

DISCUSSION

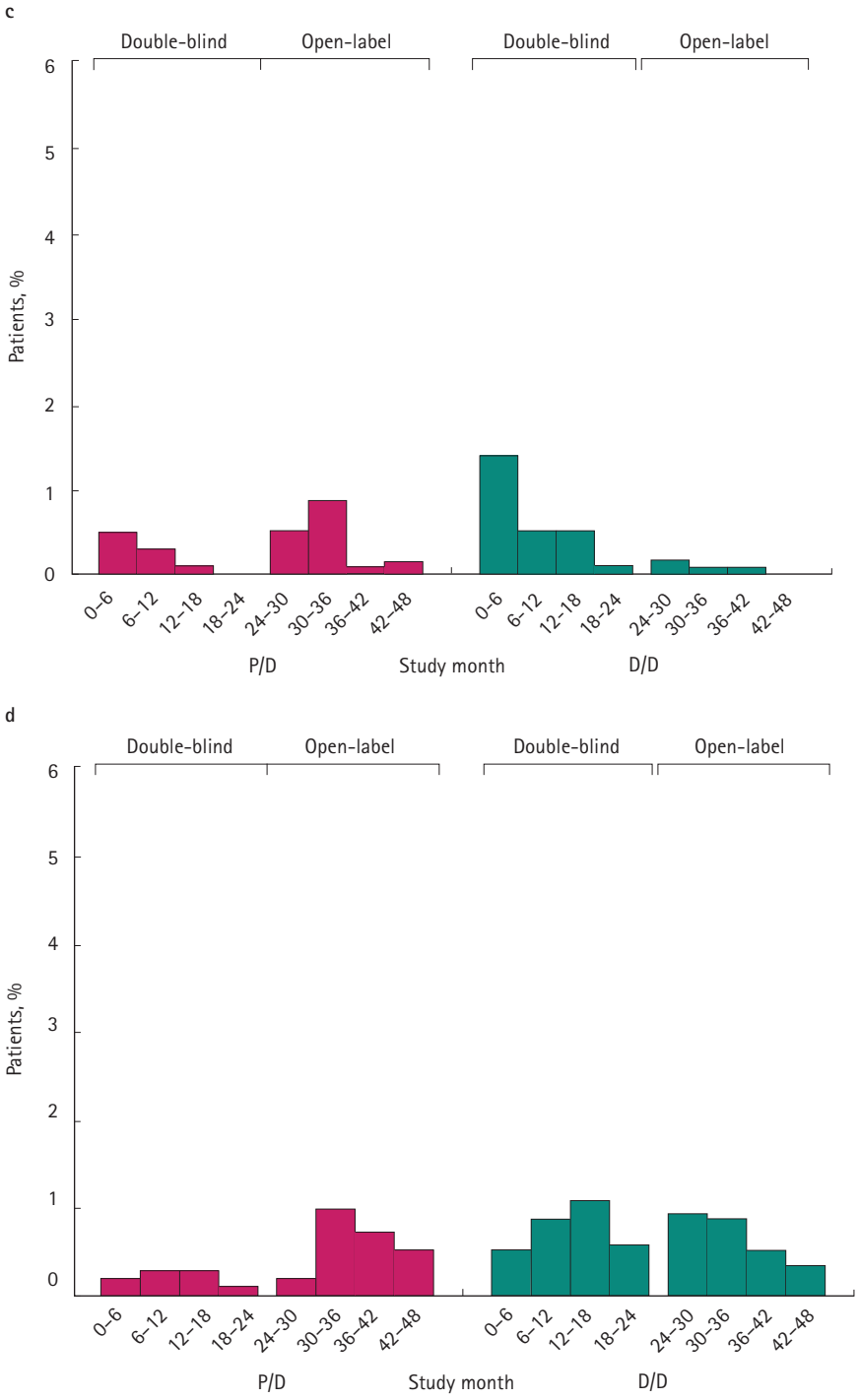
This study shows that dutasteride was well tolerated throughout the 4-year study period in men with symptomatic BPH, with a low rate of drug-related adverse events and few withdrawals associated with these events. There are inherent limitations with assessing drug safety in an open-label study, i.e. there is no placebo control, and by definition the pool of patients entering the open-label phase are those who have not withdrawn during the

double-blind phase. However, the data show that the type and incidence of adverse events reported in the open-label phase were consistent with those reported in the double-blind phase [8,9]. The most common drug-related adverse events were sexual events, i.e. erectile dysfunction, ejaculation disorders, decreased libido and gynaecomastia. Except for gynaecomastia, the incidence of these adverse events diminished over the 4-year course of the studies in men from the D/D group, with the highest rates in the first 6 months from baseline. The incidence of gynaecomastia remained low throughout the 4-year period. For men switched to dutasteride at 24 months, the timing of adverse events followed that of the double-blind phase, with most events in the first year of therapy.

The 4-year Proscar Long-term Efficacy and Safety Study showed similar patterns of drug-related adverse events in finasteride-treated patients. During the first year of the study, sexual dysfunction adverse events (erectile dysfunction, ejaculatory disorders and decreased libido) were typically more frequent in finasteride- than placebo-treated men (15% vs 7%, respectively), with the incidence tending to decrease with time (during years 2–4, the incidence of new sexual adverse events was 7% in each group) [11]. Sexual adverse events were also reported with other treatment options for BPH. The Prospective European Doxazosin and Combination Therapy (PREDICT) trial, an efficacy and safety study of finasteride, the α-blocker doxazosin and combined therapy in men with BPH, showed that the incidence of impotence and decreased libido were similar between the finasteride and doxazosin groups [12]. Similarly, there were no statistically significant differences in the incidence of erectile dysfunction or decreased libido in patients treated with finasteride compared with terazosin in a further study [13]. Several studies reported a higher incidence of retrograde ejaculation in tamsulosin-treated patients (up to 18%, vs 1% for placebo) [11,14–16]. Sexual adverse events are also recognized as potential sequelae of TURP in men with BPH. The AUA guidelines report an incidence of 65% for retrograde or abnormal ejaculation and 10% for erectile dysfunction in patients with BPH treated with TURP [16].

In the present study, drug-related adverse events leading to withdrawal from dutasteride therapy were rare in the open-label phase (2%), and serious drug-related adverse events were very rare (0.2–0.3%). No new safety issues emerged during the 4-year treatment period and there were no clinically relevant trends in gynaecomastia examinations or vital sign measurements. Furthermore, although there was a higher incidence of adverse events in patients receiving concomitant medications, there was no further evidence of drug interactions, beyond the profile recognized in previous studies [3].

FIG. 2. Continued



By inhibiting the conversion of testosterone to DHT, 5ARIs decrease serum DHT levels and increase serum testosterone levels. The near-maximum suppression of serum DHT with dutasteride in the first 24 months of the study was maintained at 48 months, with patients switched to dutasteride therapy at 24 months achieving similar levels of suppression. Testosterone levels increased predictably, but only a very small minority of patients had testosterone levels that exceeded the predefined threshold of 10 000 pg/mL. Although decreases in serum testosterone levels were proposed to decrease bone mineral density and affect lipid levels [17], a study comparing the effects of 52 weeks of dutasteride and finasteride on bone mineral density and bone metabolism showed no clinically significant changes in either variable with dutasteride [3]. The present study and previous data show that the effects of dutasteride on serum testosterone levels have no significant clinical sequelae.

The results of the present 4-year study are consistent with those for finasteride over a 4-year period, as assessed by placebo-controlled finasteride trials [8,9,11]. Therefore, it may be considered that near-maximum DHT suppression with the dual 5ARI dutasteride does not increase the risk of adverse events compared with those in previous studies with the Type 2-specific inhibitor, finasteride.

In conclusion, the present data show that the type and incidence of adverse events reported over 4 years were similar to those reported in the 2-year double-blind phase, showing that dutasteride is safe and well tolerated in long-term use for treating symptomatic BPH.

CONFLICT OF INTEREST

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Abbreviations: **ITT**, intent-to-treat; **5ARI**, 5α-reductase inhibitor; **DHT**, dihydrotestosterone; **SI**, Symptom Index; $\mathbf{Q}_{max}$, maximum urinary flow rate.

EDITORIAL COMMENT

This report of the long-term safety data on dutasteride, although perhaps representing the end of the story contains much valuable data for the practising urologist and primary-care physician. As was previously described for efficacy [1], the durability of the response over a 4-year period is well documented for a

large number of patients. GlaxoSmithKline is to be applauded in conducting a study ensuring a reasonable number of 'completers' allowing some credible clinical assumptions to be made. It is often all to easy to criticise the pharmaceutical industry with respect to post-registration studies as these are generally considered to serve the company's marketing strategy more than patient or physician. In this context it is acknowledged that there are inherent limitations with any open-label study, as there is no placebo control. However, it is important to note that patients from the placebo group and dutasteride group entering into the open-label phase were of a similar number and had similar baseline characteristics (AUA-SI score, peak urinary flow and prostate volume). Overall, therefore, the publication of this data will better enable the physician to make a judgement on the relative merits of dutasteride vs other therapy.

MICHAEL WYLLIE

1 **Roehrborn CG, Lukkarinen O, Mark S, Siami P, Ramsdell J, Zinner N.** Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5α-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int* 2005; **96**: 572–7