Original Article: Clinical Investigation

Efficacy and safety of dutasteride in Japanese men with benign prostatic hyperplasia

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Objectives: To assess the efficacy and safety of dutasteride in Japanese men with benign prostatic hyperplasia (BPH).

Methods: This was a randomized, double-blind, placebo-controlled, parallel-group study. A total of 378 subjects with clinical BPH having an International Prostate Symptom Score (IPSS) of 8 points or greater, a prostate volume of 30 mL or greater, and a maximal urinary flow rate (Qmax) of 15 mL/s or less were randomized to receive placebo or dutasteride once daily for 52 weeks. Subjects were stratified according to tamsulosin use at baseline. The numbers of subjects with and without tamsulosin use were 242 and 136, respectively. IPSS, Qmax, prostate volume and drug safety were evaluated.

Results: Continued improvement in IPSS was noted in the dutasteride group, and dutasteride significantly decreased IPSS compared with placebo. At week 52, dutasteride significantly improved Qmax and prostate volume compared with placebo. Drug-related sexual function events in the dutasteride group were infrequent and generally were not treatment limiting.

Conclusions: Dutasteride improves urinary symptoms and flow rate and reduces prostate volume. In Japanese men with BPH, it is effective and generally well tolerated during the one-year treatment period.

Key words: 5-alpha reductase inhibitor, benign prostatic hyperplasia, dutasteride, Japanese, tamsulosin.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases in elderly men. Men with clinical BPH are generally 50 years or older and symptoms of BPH result from obstruction due to prostate enlargement and excessive contraction of the smooth muscle in the prostate and the bladder neck. Currently, two classes of drugs with different mechanisms of action are available for the treatment of BPH. Alpha-blockers are effective at improving symptoms by relieving functional obstructions, but do not reduce prostate volume.[1,2] In contrast, 5-alpha reductase inhibitors (5ARIs) provide relief from mechanical obstructions by reducing prostate size. More than one large-scale randomized clinical trial demonstrates that 5ARIs can reduce prostate volume, alleviate symptoms, improve urinary flow and reduce the risk of complications such as acute urinary retention and the need for BPH-related surgery in patients with BPH.[3–5]

Dutasteride is a dual inhibitor of both type 1 and type 2 5-alpha reductase (5AR) isozymes.[6] Compared with finasteride, a selective inhibitor of type 2 5AR, which reduces circulating dihydrotestosterone (DHT) levels by approximately 70%,[7] dutasteride reduces DHT levels almost completely.[8] Although clinical trials over the last decade have demonstrated that dutasteride is an effective treatment for BPH,[4,9,10] few reports have described the efficacy and safety of dutasteride in Asian populations, including Japanese men. Previously, we reported that dutasteride 0.5 mg suppressed DHT almost completely in Japanese as well as Caucasians and that doses of 0.5 mg and 2.5 mg were associated with similar reductions in prostate volume.[11] We concluded that 0.5 mg of dutasteride should be the recommended dose for Japanese men with BPH.

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Dutasteride in combination with tamsulosin has also been shown to be beneficial compared with each monotherapy in a recent CombAT study.[12] This previous study focused on combination therapy in the form of the simultaneous use of the two drugs, rather than as an add-on therapy. In Japan, patients with BPH are generally treated with alpha-blockers such as tamsulosin because the use of 5ARIs has not been approved. Once dutasteride is approved in Japan, however, its use as an add-on therapy to alpha-blockers will likely be perceived as a treatment option. Therefore, prospective assessment on the effect of dutasteride with or without alpha-blockers at baseline will provide beneficial information in clinical practice.

The aim of the present study was to investigate the efficacy and safety of dutasteride in Japanese men with BPH. We report the results of International Prostate Symptom Score (IPSS), maximal urinary flow rate (Qmax) and prostate volume as well as safety outcomes. Additionally, we focus on the results of subgroup analyses of tamsulosin use at baseline.

Methods

Study design and population

This study was a randomized, double-blind, placebo-controlled, parallel-group study involving the participation of 26 centers in Japan. The institutional review board at each study center approved the study protocol and the study was conducted in accordance with the Declaration of Helsinki. All subjects provided written consent prior to receiving any screening assessments. The inclusion criteria were an age of 50 years or older, a diagnosis of clinical BPH, an IPSS of 8 points or greater, a prostate volume measured by transrectal ultrasonography (TRUS) of 30 mL or greater, and a Qmax of 15 mL/s or less with a voided volume of 150 mL or greater. Men with a history of prostate cancer or a serum prostate-specific antigen (PSA) value greater than 10 ng/mL were excluded. In subjects with a PSA level of 4 ng/mL or greater, it was the responsibility of investigators to rule out the presence

of prostate cancer. At randomization, subjects were stratified into those who had been treated with tamsulosin for more than 4 weeks and those who had not been treated with tamsulosin. Subjects with a previous use of tamsulosin for less than 4 weeks or of any other BPH medications during the past 4 weeks were excluded from the study.

After a run-in phase of up to 4 weeks, the subjects were randomized to receive dutasteride (0.5 mg) or placebo once daily orally for 52 weeks, followed by 16 weeks of post-dosing assessments. During the run-in and treatment periods, other BPH therapies were prohibited. In addition, subjects who had been taking tamsulosin were not allowed to change their tamsulosin regimen.

Study endpoint

The primary endpoint was the change from baseline in IPSS. The secondary endpoints included Qmax and the total prostate volume. IPSS and Qmax were evaluated at screening, baseline, and at weeks 12, 24, 36 and 52. Prostate volume was measured by TRUS at screening, week 24 and week 52. Blood samples for PSA measurements were collected at screening and at weeks 12, 24, 36 and 52. To ensure that the investigators were unaware of the study treatment, the PSA values in the dutasteride arm were doubled and adjusted by an independent third party. Safety was assessed based on adverse events, laboratory values, and vital signs.

Statistical analysis

Based on the results in a previous Japanese phase II study,[11] it was estimated that a total of 300 subjects would be sufficient to demonstrate the efficacy of dutasteride for the mean change from baseline in IPSS. The primary efficacy analysis was carried out using the full analysis set, consisting of all randomized subjects but excluding those who did not receive the study treatment or for whom the baseline or post-baseline IPSS data were missing. The population used for the safety analysis consisted of all of the subjects who received at least one dose of the study treatment.

For IPSS and Qmax, the change from baseline at each scheduled post-baseline assessment was compared between the dutasteride and placebo groups using a general linear model with effects for treatment, baseline value, baseline tamsulosin use (Yes, No), and cluster at the 0.05 level of significance. For prostate volume, the percent change from baseline was similarly analyzed, except that log-transformed data were used for comparison. The proportion of subjects with IPSS improvements (≥2 points, ≥3 points, ≥25%) and Qmax improvements (≥3 mL/s, ≥30%) was compared between the treatment groups using the Mantel-Haenszel test controlling for tamsulosin use (Yes, No) at alpha = 0.05. Subgroup analyses by tamsulosin use at baseline were also carried out for the changes from baseline in IPSS and Qmax and the percent change from baseline in prostate volume. All analyses were carried out using a last-observation-carried-forward approach.

Results

Subject demographics and disposition

A total of 378 subjects were randomized to either the placebo ($n = 185$) or the dutasteride ($n = 193$) group. The numbers of subjects with and without tamsulosin at baseline were 242 and 136, respectively. Of these, 327 subjects completed the 52-week treatment period (Fig. 1). The baseline characteristics are shown in Table 1.

Efficacy

A continued improvement in IPSS was noted at week 36 ($P = 0.014$) and at week 52 ($P = 0.003$) in the dutasteride group, compared with the placebo group (Fig. 2a). At week 52, the adjusted mean change from baseline in IPSS was −3.7 points in the placebo group and −5.3 points in the dutasteride group (mean difference, −1.6 points). When the subjects were examined by baseline tamsulosin use, the treatment difference was −1.7 points for both the tamsulosin-treated and untreated subgroups (Fig. 3a). Compared with the placebo group, the proportion of subjects with IPSS improvements (≥2 points, ≥3 points, ≥25%) at week 52 was significantly greater in the dutasteride group ($P \leq 0.009$, Fig. 4a).

The Qmax (adjusted mean change from baseline) increased by 0.7 mL/s in the placebo group and by 2.2 mL/s in the dutasteride group at week 52 (Fig. 2b). The treatment difference was statistically significant at week 36 ($P = 0.005$) and at week 52 ($P < 0.001$). At week 52, the treatment differences in subjects with and without tamsulosin were 1.7 mL/s and 1.2 mL/s, respectively (Fig. 3b). The proportion of subjects with Qmax improvements (≥3 mL/s, ≥30%) at week 52 was significantly greater in the dutasteride group than in the placebo group ($P \leq 0.015$, Fig. 4b).

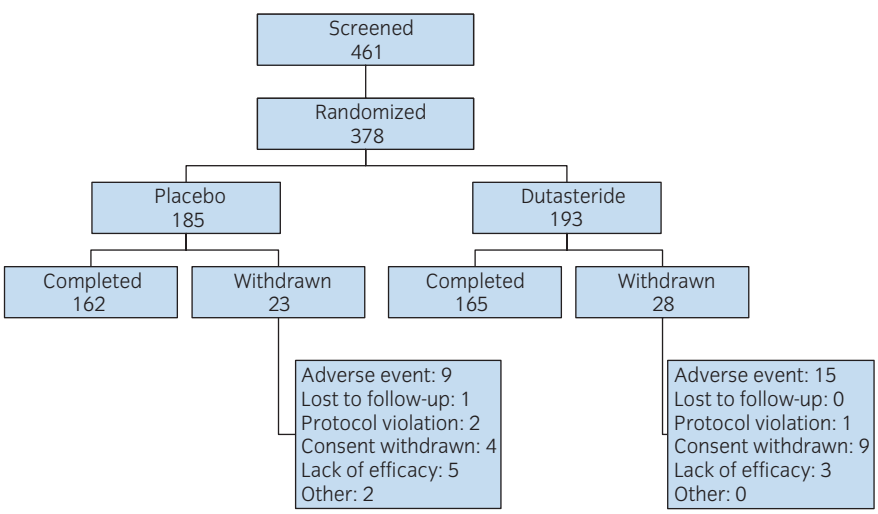

Fig. 1 Subject disposition. Number in the square: the number of subjects. Completed: subjects who completed the 52-week treatment period. Withdrawn: subjects who withdrew from the study due to various reasons.

Table 1 Baseline demographics and patient characteristics in the study of dutasteride vs placebo

	All		With tamsulosin		Without tamsulosin	
	Placebo (n = 181)	Dutasteride (n = 184)	Placebo (n = 116)	Dutasteride (n = 117)	Placebo (n = 65)	Dutasteride (n = 67)
Age (years)	66.9 ± 6.76	68.0 ± 6.07	68.2 ± 6.28	68.1 ± 6.27	64.4 ± 6.96	67.7 ± 5.75
No. Japanese	181	184	116	117	65	67
Height (cm)	165.7 ± 6.33	165.4 ± 5.66	165.3 ± 6.13	164.8 ± 5.75	166.5 ± 6.64	166.5 ± 5.36
Weight (kg)	65.1 ± 7.76	64.2 ± 8.14	64.6 ± 7.66	63.1 ± 7.89	66.2 ± 7.89	66.1 ± 8.29
Time since BPH diagnosis (years)	3.4 ± 3.38	3.5 ± 3.60	4.0 ± 3.69	3.7 ± 3.34	2.2 ± 2.36	3.3 ± 4.01
No. previous alpha-blocker use	150	157	116	117	34	40
IPSS (unit)	16.0 ± 6.01	16.6 ± 6.56	15.7 ± 6.23	16.7 ± 6.60	16.4 ± 5.63	16.4 ± 6.54
Qmax (mL/s)	11.2 ± 4.41	11.2 ± 4.13	10.5 ± 4.49	10.9 ± 4.33	12.3 ± 4.06	11.6 ± 3.75
Prostate volume (mL)	49.4 ± 17.16	50.2 ± 19.79	51.7 ± 18.73	52.6 ± 21.15	45.2 ± 13.05	46.0 ± 16.45

Plus-minus values are means ± standard deviations. BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; Qmax, maximal urinary flow rate.

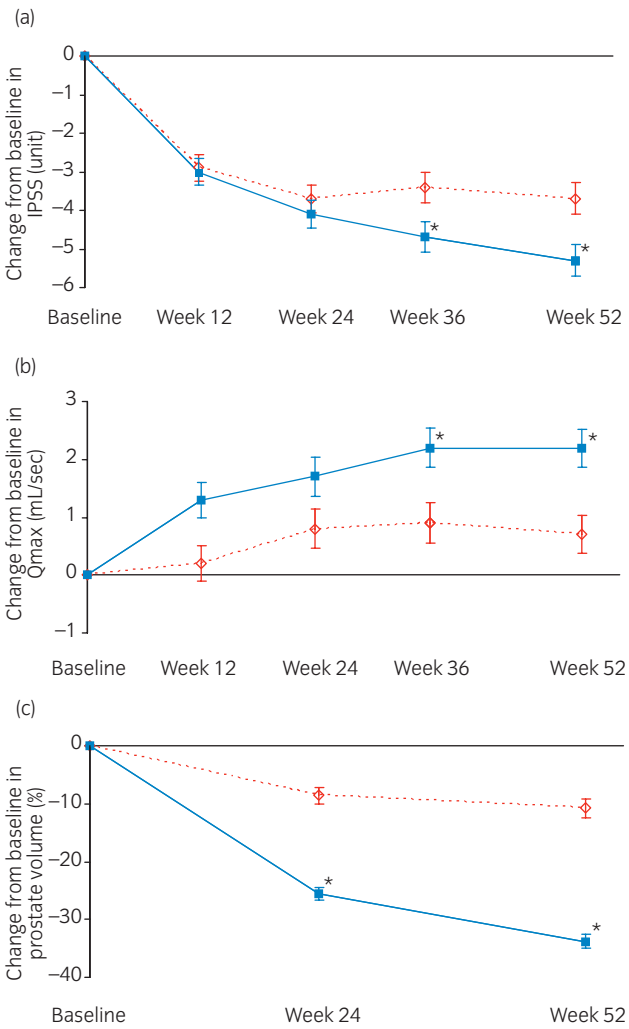

Fig. 2 Adjusted mean change from baseline in (a) International Prostate Symptom Score (IPSS), (b) Qmax and (c) prostate volume during the treatment period. Adjusted mean ± standard error, *$P < 0.05$ vs. placebo, based on t-test from the general linear model. ···◇···, Placebo (n = 181); —■—, Dutasteride (n = 184).

A statistically significant decrease in prostate volume was noted at week 24, and this decrease persisted throughout the study period ($P < 0.001$, Fig. 2c). At week 52, the treatment differences in subjects with and without tamsulosin were −23.7% and −22.0%, respectively (Fig. 3c).

Safety

The mean serum PSA at baseline was 3.5 ng/mL (median, 3.1 ng/mL) in both treatment groups. At week 24, the mean change from baseline in PSA was 12.0% (median, 5.8%) in the placebo group and −42.2% (median, −48.0%) in the dutasteride group. At week 52, the mean change from baseline was 10.1% (median, 6.1%) in the placebo group and −46.1% (median, −54.2%) in the dutasteride group.

Overall, the percentage of subjects who experienced adverse events was 90% in the placebo group and 88% in the dutasteride group. The incidence of each adverse event was generally similar between the two groups. Five cases of acute urinary retention were reported in the placebo-treated subjects, while one case was seen in the dutasteride-treated subjects. There were no reports of prostate cancer in both treatment groups. The percentages of subjects with drug-related adverse events were 5% and 6% in the placebo and dutasteride groups, respectively. The most common drug-related adverse events (≥1% in any treatment group) included erectile dysfunction, stomach discomfort, libido decreased, and dizziness. The incidences of these events are summarized by tamsulosin use in Table 2.

Discussion

Prostate enlargement is known as a predictor of the efficacy of 5ARIs.[13] Men with a prostate volume of 30 mL or greater were therefore enrolled in the present study, as in previous clinical trials conducted in Europe and the United States.[4,9,10] This inclusion criterion for the present clinical study in a Japanese population is supported by recent epidemiological data that about half of Japanese patients with lower urinary tract symptoms have a prostate volume of 30 mL or greater.[14]

In the present study, dutasteride significantly reduced prostate volume and numerically improved IPSS and Qmax compared with placebo at week 24, with further improvements noted at week 52. At

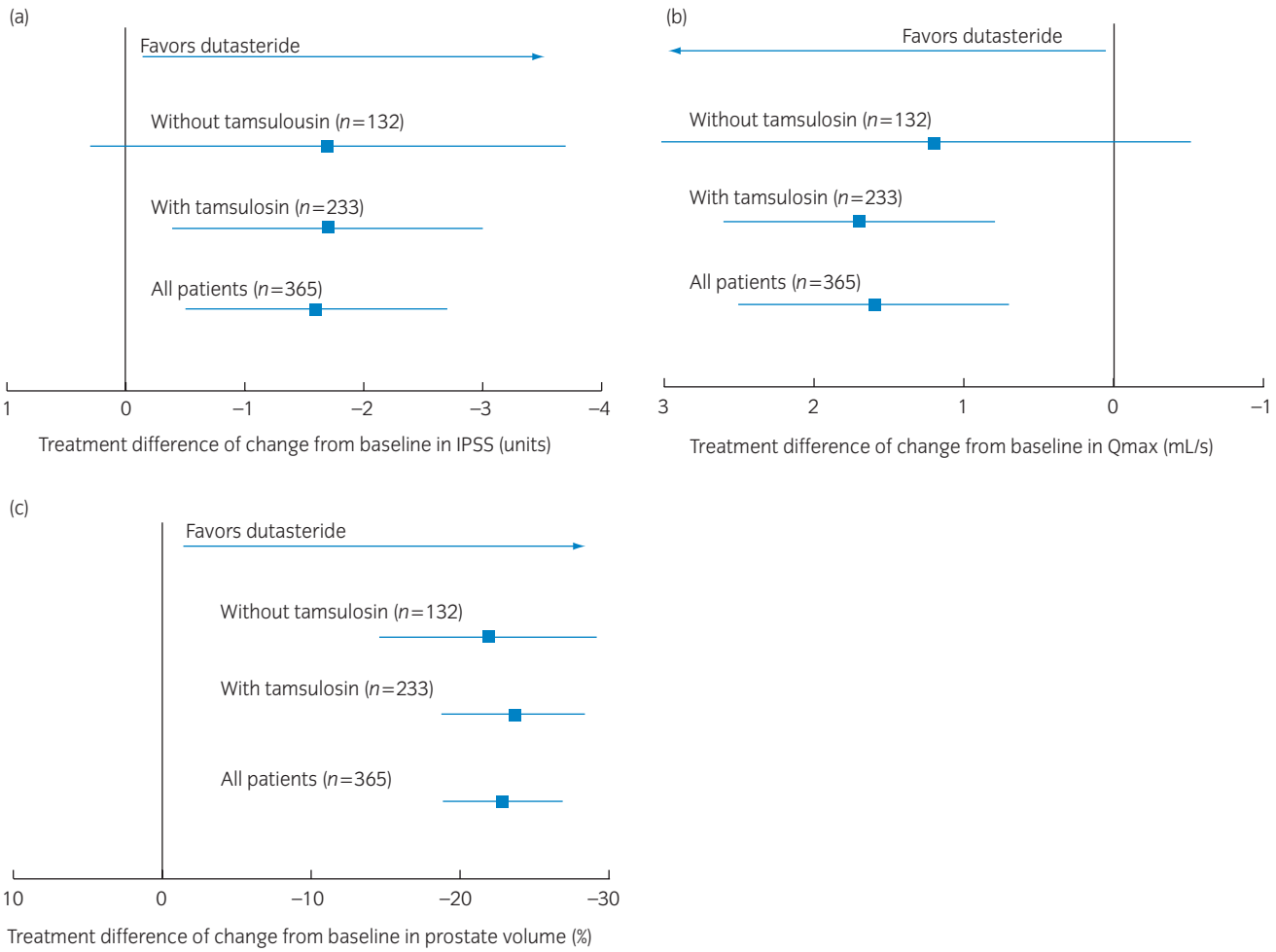

Fig. 3 Treatment difference of change from baseline to week 52 by tamsulosin use in (a) International Prostate Symptom Score (IPSS), (b) Qmax and (c) prostate volume. Adjusted mean ± 95% confidential interval (CI).

Table 2 Most common (≥1% in any treatment group) drug-related adverse events in the study of dutasteride vs placebo

	All		With tamsulosin		Without tamsulosin	
	Placebo (*n* = 184)	Dutasteride (*n* = 193)	Placebo (*n* = 118)	Dutasteride (*n* = 123)	Placebo (*n* = 66)	Dutasteride (*n* = 70)
Any AEs (%)	166 (90)	170 (88)	110 (93)	108 (88)	56 (85)	62 (89)
Any drug-related AEs (%)	9 (5)	12 (6)	6 (5)	6 (5)	3 (5)	6 (9)
Erectile dysfunction	1 (<1)	4 (2)	1 (<1)	1 (<1)	0	3 (4)
Stomach discomfort	3 (2)	0	2 (2)	0	1 (2)	0
Libido decreased	0	2 (1)	0	2 (2)	0	0
Dizziness	0	2 (1)	0	1 (<1)	0	1 (1)

AE, adverse event.

week 52, dutasteride significantly improved IPSS, Qmax and prostate volume compared with placebo. These data suggest that the continued reduction in prostate volume during the 52 weeks of dutasteride treatment resulted in a progressive improvement in urinary symptoms and flow rate.

An improvement in the symptom score was achieved in more subjects in the dutasteride group than in the placebo group for all of the categories of improvement that were examined (≥2 points, ≥3 points, ≥25%). A previous report suggested that the minimum perceptible difference in IPSS on an individual basis is 3 points, although patients with more severe diseases may require a greater change for a perceptible difference.[15] Thus, the fact that a greater percentage of subjects who were treated with dutasteride perceived a meaningful improvement is important.

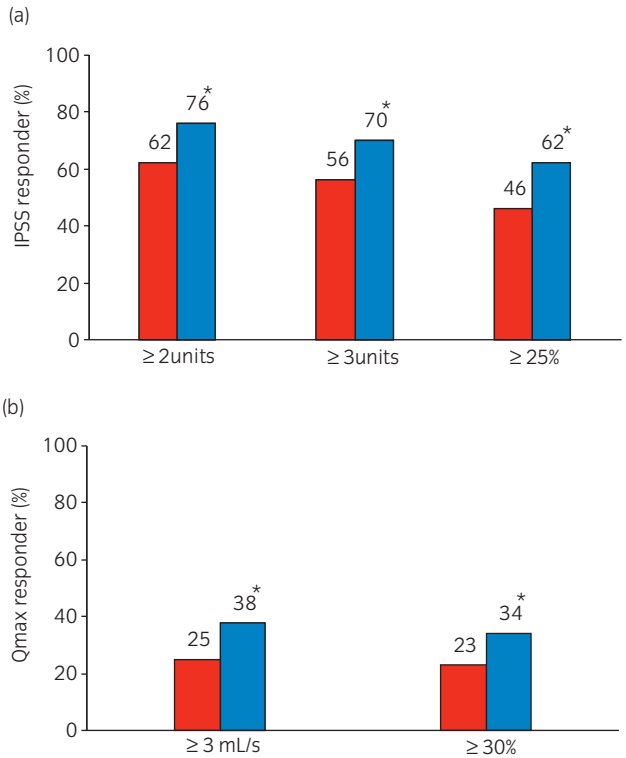

Fig. 4 Proportion of subjects classified as (a) International Prostate Symptom Score (IPSS) responders (≥2 units, ≥3 units, ≥25% improvement) and (b) Qmax responders (≥3 mL/s, ≥30% improvement) at week 52. *$P < 0.05$ vs. placebo, based on the Mantel-Haenszel test controlling for tamsulosin use. ■, Placebo ($n = 181$); ■, Dutasteride ($n = 184$).

Compared with tamsulosin-untreated subjects, tamsulosin-treated subjects had numerically larger prostate volumes, lower Qmax values, and longer durations of BPH at baseline. These differences at baseline may reflect clinical practices, since BPH is a progressive disease. As might be expected, the treatment difference in the percent change from baseline in prostate volume was comparable in the tamsulosin-treated and untreated subgroups. Additionally, the treatment differences in IPSS and Qmax were also generally similar between the subgroups. Although there is a limitation that the present study was not designed to detect treatment difference by subgroup, these consistent findings suggest that dutasteride may be effective in terms of symptoms and urinary flow improvements, whether used with or without tamsulosin. The results of CombAT subgroup analyses that have shown the combination therapy provided greater symptoms improvements than tamsulosin monotherapy regardless of previous BPH treatment status,[16] support our subgroup results by tamsulosin use at baseline.

It is well-known that using the PSA doubling factor is effective for prostate cancer detection in men receiving 5ARIs.[17–19] In the present study, the decrease in the PSA level by 46% in the dutasteride group was consistent with the approximately 50% reduction seen after one-year of treatment in placebo-controlled studies conducted in predominately western men.[20] Because of these consistent PSA reductions in western and Japanese men, the PSA levels should also be multiplied by 2 in Japanese men treated with dutasteride for 6 months or longer to monitor serial PSA measurements, with a biopsy considered in any patient with an increasing PSA level.

Dutasteride was generally well tolerated during the one-year treatment period. Adverse events that were considered as drug-related by the investigator were mainly sexual function events. The incidences of sexual function events were slightly higher in the dutasteride group than in the placebo group. These events were infrequent (≤2%) and generally were not treatment limiting.

In conclusion, symptom improvement with dutasteride was continuous and clinically relevant. Dutasteride significantly improved symptoms, urinary flow and prostate volume compared with placebo. In Japanese men with BPH, dutasteride was effective and generally well tolerated during the one-year treatment period.

Acknowledgment

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