

Long-Term Efficacy of Tamsulosin in the Treatment of Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in Real-Life Practice

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ABSTRACT

BACKGROUND: α_1 -Adrenoceptor antagonists are recommended as the main pharmacological treatment for lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS). Short-term efficacy of tamsulosin has been verified in many randomized controlled trials. However, there is a relative paucity of long-term data on the maintenance of the efficacy of this drug.

OBJECTIVE: To evaluate the long-term efficacy of tamsulosin for patients with BPH/LUTS in real-life clinical practice.

METHODS: A total of 113 males with BPH/LUTS (mean age {SD} = 68.5 {8.8} years; mean prostate volume {SD} = 34.2 {15.7} ml) who were treated with tamsulosin (0.2 mg daily) for more than 3 months were retrospectively evaluated. The International Prostate Symptom Score (I-PSS), quality of life (QOL) score, average and maximum flow rate (Qave and Qmax), and postvoid residual urine volume (PVR) and percentage of residual urine (%PVR) were determined before (baseline) and after the initiation of treatment.

RESULTS: Of these patients, 72 (64%) remained on tamsulosin (12 to 48 months of treatment) and 41 (36%) withdrew after a mean of 17.4 months on average. Reasons for withdrawal were: satisfied with the current condition in 1 patient (1%), lost to follow-up for unknown reasons in 18 (16%), detection of prostate cancer in 5 (4%), insufficient therapeutic response in 16 (14%; 1 patient stopped medication; 6 changed to other drugs; 9 underwent surgery), and adverse effects (headache) in 1 patient (1%). The mean total I-PSS, total I-PSS storage subscore, total I-PSS voiding subscore, post-micturition score, and QOL score were all significantly decreased with P values of < 0.0001 after 1 month and remained stable for up to 48 months of treatment. Qave and Qmax were significantly increased ($P < 0.0001$), and PVR and %PVR were significantly decreased ($P = 0.0051$ and $P = 0.0001$, respectively) after 3-month treatment. The means of these scores did not change significantly, but rather appeared to remain stable for 24 to 48 months.

CONCLUSION: Effects of tamsulosin on BPH/LUTS are immediate (within 1 month) and persist (for over 12 months). Tamsulosin is well tolerated for BPH/LUTS.

KEYWORDS: Alpha-blocker, Benign prostatic hyperplasia, Lower urinary tract symptoms, Tamsulosin, Pharmacotherapy

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INTRODUCTION

α_1 -Adrenoceptor antagonists are recommended as the main pharmacological treatment for lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS) [1-3]. Since Kawabe *et al.* [1] verified the efficacy of tamsulosin in a randomized, placebo-controlled study, this α_1 -adrenoceptor antagonist has been widely used for BPH/LUTS in real-life clinical practice for more than 14 years in Japan. The short-term efficacy of tamsulosin has been verified in many randomized controlled trials (RCTs) [4,5]. Safety of this drug was reported even in patients with BPH/LUTS complicated by diabetes or on antihypertensive agents [6,7]. However, there is a relative paucity of long-term data on maintenance of the efficacy of this drug [8-13]. The aim of the present study is to retrospectively evaluate long-term efficacy of tamsulosin for treatment of BPH/LUTS in real-life clinical practice.

METHODS

We included a total of 113 male BPH/LUTS patients, aged 45–86 (mean = 68.5) years, treated with tamsulosin (0.2 mg daily) for more than 3 months. The inclusion criteria were α_1 -blocker naive patients, I-PSS total score of 8 or greater, maximum flow rate (Q_{max}) of less than 15 ml/sec, and prostate volume of 15 ml or greater (measured by ultrasonography). Exclusion criteria were prostate cancer, urethral stricture, apparent neurogenic bladder, and medications such as anticholinergics or anti-androgen drugs that might affect voiding function. The international prostate symptom score (I-PSS) and quality of life (QOL) score were determined at baseline and evaluated at 1, 3, 6, 12, 24, 36, and 48 months after initiation of therapy. Total I-PSS storage subscore was calculated as the sum of scores for “increased daytime frequency,” “urgency,” and “nocturia.” Total I-PSS voiding subscore was calculated as the sum of scores for “intermittency,” “weak stream,” and “straining.” According to the terminology defined by the International Continence Society in 2002, the symptom of “feeling of incomplete emptying” is a post-micturition symptom, and was classified separately [14]. Postvoid residual urine volume (PVR) and percentage of residual urine (%PVR = PVR/(voided volume + PVR) × 100%) were measured by ultrasonography. Average (Q_{ave}) and maximum (Q_{max}) flow rates and PVR and %PVR were determined at baseline and at 1, 3, 12, 24, 36, and 48

months after initiation of therapy.

Data are expressed as mean {SD}. Changes from baseline values were analyzed using the paired *t* test or the Wilcoxon’s signed-rank test. A *P* value of less than 0.05 was regarded as statistically significant.

RESULTS

In this series, 72 (64%) patients were still on tamsulosin for 12 to 48 months, including 3 patients followed up in other institutions. Of these patients, 41 (36%) withdrew after a mean of 17.4 (range = 4–45) months of treatment. Reasons for withdrawal were: satisfied with the current condition in 1 patient (1%), lost to follow-up for unknown reasons in 18 (16%), detection of prostate cancer in 5 (4%), insufficient therapeutic response in 16 (14%; 1 patient stopped medication; 6 changed to other drugs; 9 underwent surgery), and adverse effects (headache) in 1 patient (1%). Prostate volume measured by ultrasonography was significantly increased from 35.6 {17.9} ml at baseline to 41.8 {21.4} ml after 1 year in 23 patients studied both before and after 1-year therapy (*P* < 0.028).

Table 1. Baseline characteristics of patients (mean {SD})

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Age (years old) (range)	68.6 {8.8} (45–86)
Treatment period (months)	27.2 {19.0}
I-PSS	
Feeling of incomplete emptying (= post-micturition symptoms)	2.3 {1.8}
Increased daytime frequency	2.3 {1.8}
Intermittency	2.3 {1.8}
Urgency	1.8 {1.7}
Weak stream	3.5 {1.6}
Straining	1.7 {1.7}
Nocturia	0.7 {1.4}
Total storage symptoms	6.8 {3.6}
Total voiding symptoms	7.5 {3.8}
Total I-PSS	16.5 {6.6}
QOL score	4.5 {1.3}
Total prostate volume (ml) (range)	34.2 {15.7} (15–96)

Baseline total I-PSS, total I-PSS storage subscores, total I-PSS voiding subscores, post-micturition score, QOL score, Qave and total prostatic volume are summarized in Table 1. Changes in I-PSS and QOL score were determined at 1 month after initiation of treatment in 82 patients, at 3 months in 81 patients, at 6 months in 59, at 12 months in 70, at 24 months in 38, at 36 months in 28, and at 48 months in 18 (Figure 1 and Table 2). Mean total I-PSS, total I-PSS storage subscores, total I-PSS voiding subscores, post-micturition score, and QOL score all decreased significantly with P values of < 0.0001 after 1 month of treatment and remained stable up to 48 months. Specific individual symptom scores (scores for feeling of incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining, and nocturia) each decreased significantly after 1-month treatment ($P < 0.001$) and remained stable up to 48 months (data not shown).

Changes in Qave, Qmax, PVR, and %PVR were determined after 3 months of treatment in 94 patients, after 12 months in 73 patients, after 24 months in 28, after 36 months in 18, and after 48 months in 15. At present, 18 patients have been treated for 48 months, however urinary flow parameters for 3 patients declined. Mean {SD} of Qave, Qmax, PVR, and PVR at baseline and after 3, 12, 24, 36, and 48 months of treatment are summarized in Table 3. Both Qave and Qmax increased

significantly ($P = 0.0051$ and $P = 0.0001$, respectively) after 3 months of therapy. Mean for these scores did not change significantly but appeared to remain stable for 24 to 48 months, probably because the number of patients was small and the standard deviation was large.

In 9 patients who eventually underwent invasive surgery, mean baseline total I-PSS was 20.8 {7.0} (range = 14–33), mean baseline QOL score was 4.5 {1.3} (range = 2–6), mean baseline total voiding subscores were 11.0 {4.2} (range = 3–15), and mean baseline total storage subscores were 6.63 {4.7} (range = 0–13). Mean baseline Qmax was 6.9 {4.3} ml/sec (range = 3.7–10.7), and PVR was 42.9 {36.0} ml (range = 0–117).

DISCUSSION

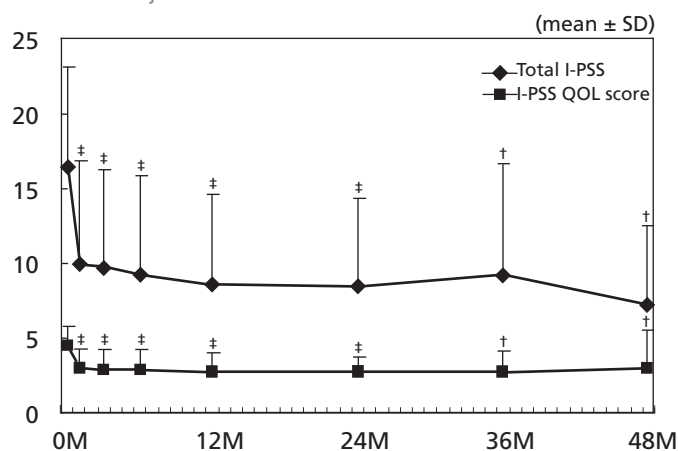
Benign prostatic hyperplasia (BPH) is a common condition caused by enlargement of the prostate gland. This condition may lead to bladder outlet obstruction, lower urinary tract symptoms (LUTS), and reduced QOL. BPH is present in 50% of males over 50 years old [15,16]. Treatments include transurethral resection of the prostate and various minimally invasive therapies for BPH, such as holmium:YAG laser prostatectomy and pharmacological therapy [17]. Of these therapies, pharmacological treatment with α_1 -adrenoceptor antagonists is widely used as a conservative treatment for BPH/LUTS and bladder neck obstruction, [1-12,15,16,18-23]. α_1 -Adrenoceptor antagonists have been reported to relieve bladder outlet obstruction and detrusor overactivity, thus they are effective for both voiding and storage symptoms [2].

Tamsulosin is an α_1 -adrenoceptor antagonist widely used in real-life clinical practice (for more than 14 years in Japan) to treat BPH/LUTS. This drug is considered to be an α_{1A}/α_{1D} AR subtype-selective antagonist [15], with affinity 3.3- and 15.3-fold higher for α_{1A} -adrenoceptors than for α_{1D} - and α_{1B} -adrenoceptors, respectively [24]. Short-term efficacy of tamsulosin in RCTs comparing tamsulosin with placebo [4,5], phytotherapy [2], and other α_1 -adrenoceptor antagonists [19-23] has been reported.

Several long-term studies of tamsulosin have also been reported [8-13]. Most were extensions of previous short-term trials, which differed in patient selection and study protocol. Most patients were asked to visit the hospital according to a strictly defined protocol. In 516 patients enrolled from 2 European open label studies that were extensions of 3 double-blind RCTs, Schulman *et al.* [8] reported significant improvement in Qmax (1.2–2.2 ml/sec increase from baseline) and Boyarsky symptom

Figure 1. Change in total International Prostate Symptom Score (I-PSS) and I-PSS quality of life (QOL) score in BPH patients treated with long-term tamsulosin.

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* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ (Wilcoxon's signed ranks test, compared with the baseline value) significantly ($P < 0.0001$), and both PVR and %PVR decreased

score (decrease by 4.1–4.7 points from baseline), observed while the previous RCTs persisted (i.e., Qmax was maintained at 11.5–12 ml/sec throughout the extension period for up to 4 years in patients that remained on therapy). During the 4-year follow-up, 66% of patients withdrew from the study. The most common reasons for withdrawal were insufficient efficacy and side effects, however only 5% of patients discontinued treatment because of drug-related side effects. In a 1-year open label trial extended to 8 years by Narayan *et al.* [9], the initial rapid improvements were maintained for all 609 patients with BPH, although only 109 (18%) completed the whole 8-year study. The retreatment rate after extension to 5 years of the 3-year follow-up study by De la Rosette *et al.* [10] using tamsulosin, alfuzosin, and terazosin in 316 LUTS patients was 27% for tamsulosin, 37% for alfuzosin, and 49% for terazosin. They concluded that severe LUTS, low Qmax (<10 ml/sec), large prostate (>40 ml), and urodynamically proven bladder outlet obstruction increased the risk of treatment failure. In these extension studies, data up to 12 months seem to be complete, and all reported that the rapid improvement yielded by tamsulosin in the previous short-term study was still present at long-term follow-up. However, the discontinuation rate was high after 3–5 years of treatment (64–79%) [8–10], which is similar to our present study (73% after 3 years).

Kawabe *et al.* [11] retrospectively followed up 300 Japanese BPH patients for 3.3 ± 3.3 years to determine whether disease severity was associated with time to implementation of invasive therapy. Eventually, 83 patients (27.7%) underwent invasive therapy. They found that lower baseline QOL score and Qmax reduced the time to invasive therapy and concluded that overall baseline severity in accordance with the “Severity Criteria for BPH” was a good indicator of prognosis for patients

with BPH treated with tamsulosin. In our present study, only 9 patients (9%) underwent invasive therapy. The reason for the difference may be that our study excluded patients that withdrew after less than 3 months of treatment. Ichioka *et al.* [12] followed up 123 BPH patients treated with tamsulosin for longer than 12 months before enrollment, and reported that significant improvements in all clinical variables except Qmax were maintained for an average of 43 months; 24.4% of patients withdrew because of surgical interventions; and a baseline total I-PSS ≥ 15, lowest total I-PSS of ≥ 13, lowest QOL score of ≥ 3, and lowest BPH impact index score of ≥ 14 during the first 12 months were predictive of failure of tamsulosin therapy. However, neither Qmax nor PVR were significant risk factors. Patient enrollment in their study and our study may be similar in that only patients that remained on therapy after 12 months were included in their study and patients had to remain on therapy for 3 months for our study. The reason we limited enrollment to such patients was that most patients that visit real-life practice withdraw within 3 months, and concerns about short-term (within 3 months) efficacy and safety differ from those for long-term efficacy and safety.

Recently, the 2-year effects of dutasteride, tamsulosin, and combination therapy on BPH/LUTS and prostatic enlargement (CombAT study) have been reported [13]. This study included 4844 patients with moderate to severe LUTS (I-PSS of 12 points or greater) and prostate volume 30 ml or greater, total serum prostate specific antigen 1.5 ng/ml or greater to less than 10 ng/ml, and peak urinary flow greater than 5 to less than 15 ml per second, with a minimum voided volume of 125 ml. Thus, the inclusion criteria in this study were strict and follow-up was better organized than for our real-life practice. In that study, tamsulosin reduced total I-PSS from 16.4 points at baseline

Table 2. Changes in I-PSS (mean {SD})

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	0 M (n = 113)	1 M (n = 82)	3 M (n = 81)	6 M (n = 59)	12 M (n = 70)	24 M (n = 38)	36 M (n = 28)	48 M (n = 18)
Total storage	6.8 {3.6}	4.5 {3.3}‡	4.5 {3.4}‡	4.6 {3.3}‡	4.3 {3.0}‡	3.8 {3.0}‡	4.5 {3.4}*	3.6 {2.8}†
Total voiding	7.5 {3.8}	4.4 {3.8}‡	4.2 {3.6}‡	3.7 {3.4}‡	3.5 {3.1}‡	3.6 {3.3}‡	3.6 {3.6}†	2.7 {3.5}†
Post-micturition	2.3 {1.8}	1.0 {1.5}‡	1.0 {1.4}‡	0.9 {1.3}‡	0.9 {1.3}‡	0.8 {1.1}†	1.1 {1.4}†	0.9 {1.3}†

*P<0.05, †P<0.01, ‡P<0.001 (Wilcoxon’s signed ranks test, compared with the baseline value)

by -4.5 points at 3 months, -4.5 at 12 months, and -4.3 at 24 months. These results appear similar to our study, in which total I-PSS was reduced from 16.5 points by -6.8 at 3 months, -7.8 at 12 months, and -8 points at 24 months after treatment with tamsulosin.

In 9 of our patients that eventually underwent invasive surgery, the most important risk factor for surgery appeared to be a baseline total I-PSS of ≥ 14 . In total, 8 patients had a mean baseline total voiding subscore ≥ 7 (11.0 {4.2}), but only 3 had mean baseline total storage subscore of 10 (6.63 {4.7}). Comparing patients transferred to those not transferred to invasive therapy, there were significant differences in "straining" score (3.75 {1.8} vs. 1.5 {1.6}; $P = 0.0016$) and voiding subscore (11.0 {4.2} vs. 7.2 {3.7}; $P = 0.0128$). Mean baseline Qmax was 6.9 {4.3} (range = 4–10.3) ml/sec. Thus, there was a tendency to transfer patients with lower baseline Qmax to invasive therapy ($P = 0.07242$ vs. noninvasive therapy). The withdrawal rate (36%) in our study was similar to that reported for other studies [8–12]. Dissatisfaction with improvement in LUTS may account for discontinuation of α_1 -adrenoceptor antagonist therapy [10]. To evaluate this phenomenon, analysis of long-term effect of the drug on the rate of secondary interventions is necessary [11]. In the present study, the rate of discontinuation due to insufficient therapeutic response was 15%, similar to that reported by de la Rosette *et al.* (27%) [10]. The rate of discontinuation due to adverse effects was 1% (observed in only 1 patient), which may be lower than

that reported by Schulman *et al.* (5%) [8], but is similar to that reported by Narayan (1.3%) and Ichioka (0%) [9,12]. The low incidence of withdrawal attributable to adverse effects may be because most patients with adverse events experienced them within 3 months and had already been excluded. The percentage of withdrawals due to bothersome side effects has been reported to be similar for both tamsulosin- and placebo-treated patients (about 4–10%) using meta-analysis [25]. Since the incidence of drug-related adverse events in the short-term study was low, long-term tamsulosin therapy was thought to be safe. Insufficient therapeutic response was another reason for withdrawal (9 patients underwent surgery because of urinary retention or severe voiding difficulty).

Tamsulosin may improve LUTS immediately: mean total I-PSS, total storage score, total voiding score, and QOL score decreased significantly ($P < 0.0001$) at 1 month after the initiation of treatment and remained stable up to 48 months. Therefore, tamsulosin therapy may prolong improvement in LUTS.

Prostate volume after 1 year (40.9 {22.0} ml) increased slightly from baseline (34.1 {15.7} ml). During the study, 4 patients (4%) had prostate cancer, which did not markedly differ from that reported by Narayan *et al.* (12 of 609 patients: 2%) [9]. In consideration of the low incidence of prostate cancer, tamsulosin may not affect the risk of prostate cancer.

In conclusion, the withdrawal rate of BPH/LUTS patients treated with tamsulosin for more than 3 months in real-life practice was 36%. Discontinuation due to adverse effects was observed in only 1 patient. Tamsulosin improved LUTS immediately

Table 3. Changes in uroflowmetric parameters and postvoid residual volume (mean {SD})

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	0 M (n = 113)	3 M (n = 94)	12 M (n = 73)	24 M (n = 28)	36 M (n = 18)	48 M (n = 15)
VV [§]	185.6 {111.4}	217.8 {123.4} [†]	213.0 {114.6}	232.3 {113.2}	252.0 {154.6}	267.1 {136.8}
Qave	5.5 {2.6}	6.9 {3.4} [‡]	6.5 {3.4} [†]	6.0 {2.4}	6.4 {2.9}	6.4 {3.4}
Qmax [¶]	9.8 {7.5}	11.4 {5.4} [‡]	11.8 {5.9} [*]	13.0 {6.9}	13.1 {6.7}	12.8 {5.8}
PVR ^{**}	43.6 {58.7}	24.5 {44.6} [†]	29.3 {53.7} [*]	34.1 {41.8}	50.8 {49.8}	56.2 {49.6}
%PVR ^{††}	17.9 {18.6}	10.3 {14.9} [†]	10.7 {16.1} [†]	12.0 {13.3}	19.6 {17.3}	18.9 {17.8}

* $P < 0.05$, [†] $P < 0.01$, [‡] $P < 0.001$ (paired t-test, compared with the baseline value); [§]voided volume (ml), ^{||}average flow rate (ml/s), [¶]maximum flow rate (ml/s), ^{**}postvoid residual urine volume (ml), ^{††}percent of PVR.

(within 1 month of treatment) and this improvement persisted for over 12 months. Tamsulosin is well tolerated for BPH/LUTS.

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