LONG-TERM SAFETY AND EFFICACY OF TAMSULOSIN FOR THE TREATMENT OF LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Purpose: We evaluated the long-term (up to 6 years) safety and efficacy of the selective α1A-adrenoceptor antagonist tamsulosin in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia.

Materials and Methods: A total of 609 patients were enrolled in a 4-year multicenter open label extension study. Subjects entered the study after completion of a 1-year open label trial that included patients who previously completed up to 57 weeks of double-blind, placebo controlled studies. Maintenance doses (0.4 or 2 × 0.4 mg daily) established in the 1-year study were continued. Efficacy and safety were assessed every 3 months. Primary efficacy evaluations were changes from baseline maximum urine flow rate and total American Urological Association symptom index, and the responder rates for those 2 end points. Secondary end points were changes in American Urological Association subset scores, Boyarsky symptom scores, average urine flow rate, post-void residual urine volume, quality of life index and investigator global assessment.

Results: Of the 609 patients who entered the 4-year extension study 159 had a 2-year or greater prior experience with tamsulosin, yielding a potential 6-year experience on the medication. Of this 159 patient subset 109 completed the whole 6 years. Initial rapid improvements from baseline in primary and secondary end points were maintained each year throughout the duration of the study. Tamsulosin was well tolerated, confirming the safety profile demonstrated in earlier studies. Orthostatic hypotension was observed in 1.3% of the patients.

Conclusions: This study demonstrates the sustained efficacy, safety and excellent long-term tolerability of tamsulosin for up to 6 years in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia.

Key Words: prostate, prostatic hyperplasia, urination disorders, adrenergic alpha-antagonists

Pathological signs of benign prostatic hyperplasia (BPH) occur in 8% of men in the fourth decade of life with the prevalence steadily increasing to greater than 70% of men in the seventh decade of life.1 As the United States population ages, the number of men with BPH increases, creating a greater demand for effective and safe treatments. Current treatment options include surgical and pharmacological interventions. Tamsulosin, which has been available in the United States since 1997, has proved to be effective for treating lower urinary tract symptoms (LUTS) due to BPH.2–4 The relative lack of cardiovascular side effects and lack of interactions with antihypertensives associated with tamsulosin therapy is probably due to its subtype selectivity for α1A and α1D-adrenergic receptors.5, 6 It is the first drug targeted specifically to treat only LUTS associated with BPH.

Published pivotal double-blind studies have demonstrated the efficacy and tolerability of tamsulosin for up to 1 year.2–4 An extension study showed similar results for up to 2 years.7 We describe a long-term 4-year extension study that enabled patients to continue tamsulosin treatment for up to 6 years (fig. 1).

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MATERIALS AND METHODS

Patients. Eligible patients included in this study (527.2) were men 45 years or older who had completed a previous 1-year open label extension trial of tamsulosin (US93-04).7 This trial recruited patients from 3 shorter double-blind studies, namely US92-03A (17 weeks),5 US92-03B (40-week extension of US92-03A)6 and US93-01 (17 weeks).2 Study US93-04 included patients from active and placebo groups from the previous studies, a number of patients enrolled but not randomized and a few who had had experience with tamsulosin in other trials.7 Patients agreed to continue established treatment maintenance doses (0.4 or 0.8 mg daily), make required clinic visits 3 months ± 7 days apart throughout the 4-year extension and provide informed consent.

Inclusion/exclusion criteria. Exclusion criteria were biopsy evidence of prostate cancer following a prostate specific antigen (PSA) measurement of greater than 4.0 ng/ml or positive digital rectal examination or evidence of cancer on transrectal ultrasound. Other reasons for exclusion included acute urinary retention (AUR) or urinary tract infection, renal dysfunction, abnormal hemoglobin, leukocytes or liver enzymes, postural symptoms, diastolic blood pressure below 60 mm Hg or tachycardia to greater than 120 beats per minute, poorly controlled diabetes and poor compliance during the previous study. α-Adrenergic agents and anticholinergics were prohibited.

Efficacy. Primary efficacy evaluations at each visit were changes from baseline in total American Urological Associa-
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RESULTS

A total of 609 patients entered the 4-year extension trial, of whom 5 were excluded due to an incomplete post-baseline safety assessment, so that 604 patients comprised the safety population. Of the 609 men 159 entered with 2 or more years of experience with tamsulosin (potential 6 years of treatment) and of these 609 men 109 completed 6 years. Mean patient age and weight were 58.9 years and 192.7 pounds, respectively. Of the men 94.9% were white, 4.5% were black or severely disabling event, or event requiring or prolonging immediately life threatening clinical experience, permanently or markedly improved). Other criteria included uroflowmetry, post-void residual urine volume (PVR) and a quality of life (QOL) questionnaire consisting of 5 questions, of which 4 were validated (possible score 13). Safety. Safety assessments at each visit were evaluated for treatment emergent (TE) adverse events (AEs), changes in digital rectal examination and other changes on physical examination (body weight and vital signs). Assessments also included chest x-ray, 12 lead electrocardiogram and clinical laboratory tests (blood chemistry, PSA, hematology and urinalysis). Clinically significant orthostatic hypotension was defined by a decrease in systolic blood pressure of 20 mm Hg or greater, or symptoms with a change in posture.

FIG. 1. Tamsulosin long-term study. Asterisk represents double-blind, placebo-controlled trial. Of 208 patients 74 were from placebo treated group of US92-03A/B, 104 from placebo treated group of US92-01, 15 from placebo treated group who completed study US92-03A and did not continue to study US92-03B, and 15 who qualified by exceptional enrollment and were on tamsulosin in previous trials. Of 239 patients, 219 on tamsulosin completed study US93-01 and 20 on tamsulosin completed study US92-03A but did not continue to study US92-03B. Total of 162 patients on tamsulosin completed studies US92-03A and US92-03B, and had potential 6-year experience with tamsulosin.

Patient Age

Patient weight

Age range

Fatality

Other criteria

Orthostatic hypotension

Changes from baseline to the first evaluation (AUA) symptom index score (7 questions scored 0 to 5) and maximum urine flow rate (Qmax). Qmax was measured by uroflowmetry and patients voided at least 125 ml. Other primary efficacy evaluations were the percent of total AUA symptom score responders and the percent of total Qmax responders.

Secondary efficacy evaluations included changes from baseline in AUA subset scores (obstructive 3 questions, irritative 4 questions, AUA bother score 7 questions, scored 0 to 4), Boyarsky symptom scores (9 urinary symptoms scored 0 to 3), changes from baseline for mean urinary flow rate and investigator global assessment (scored 0—worsened to 4—markedly improved). Other criteria included uroflowmetry, post-void residual urine volume (PVR) and a quality of life (QOL) questionnaire consisting of 5 questions, of which 4 were validated (possible score 13). Safety. Safety assessments at each visit were evaluated for treatment emergent (TE) adverse events (AEs), changes in digital rectal examination and other changes on physical examination (body weight and vital signs). Assessments also included chest x-ray, 12 lead electrocardiogram and clinical laboratory tests (blood chemistry, PSA, hematology and urinalysis). Clinically significant orthostatic hypotension was defined by a decrease in systolic blood pressure of 20 mm Hg or greater, or symptoms with a change in posture.

AEs occurring between dose 1 and 28 days after the last dose were classified as TEAEs and categorized by us as probably, possibly or remotely related, or unrelated to the study drug. Serious AEs were classified as any fatal or immediately life threatening clinical experience, permanently or severely disabling event, or event requiring or prolonging hospitalization.

The safety population received at least 1 dose of tamsulosin. Safety data were recorded throughout the 4-year extension. The intent to treat (ITT) population received at least 1 dose with efficacy data collected after visit 1. Baseline values were established during the visit prior to the initial tamsulosin dose in patient respective earlier studies.
related) TEAEs decreased during the 6 years. During the whole study 95 patients (15.7%) discontinued tamsulosin due to TEAEs, which was less than the 18.7% who discontinued for other reasons, including protocol violations, nonstudy drug related reasons, poor compliance and personal reasons. Only 5 patients (0.8%) discontinued due to abnormal ejaculation and only 3 discontinued due to dizziness, postural hypotension and syncope (0.2%, 0.2% and 0.2%, respectively).

Of the patients 29 (4.8%) experienced a serious AE considered related to tamsulosin treatment, including skin or prostate cancer, syncope, myocardial infarction and chest pain. During the study course there were 9 deaths. Only 1 death (due to heart arrest) was considered remotely related to drug therapy. Four of the 8 episodes of syncope were considered related to treatment. Table 2 lists TEAEs reported by 10% or greater of the patients.

Only 30 patients (5%) had clinically significant PSA elevations from 4.0 or less to greater than 4.0 or greater than 4.0 to greater than 6.0 ng/ml throughout the whole 6-year experience. Of 122 patients 21 had clinically elevated PSA during the 4-year extension, of whom 11 discontinued treatment because PSA increased to 10 ng/ml or greater. Of the 604 patients 12 had prostate cancer during the 4-year extension.

A total of 11 patients (1.8%) had AUR during the 6-year experience. No new cases developed during years 5 and 6. Only 1 patient withdrew from the study because of AUR. Eight patients (1.3%) experienced clinically significant orthostatic hypotension.

**DISCUSSION**

To our knowledge this study represents the longest clinical trial experience of α-blocker therapy in patients with LUTS associated with BPH. Tamsulosin provided sustained relief of symptoms and urine flow for up to 6 years with high levels of safety and tolerability, and no decrease in the drug effect. This study corroborates and extends previous results regarding tamsulosin administration.2–4

Significantly no new safety issues arose during the 4-year extension that had not been apparent in previous clinical trials. Consistent with previous tamsulosin studies,2–4 discontinuation rates due to adverse events were low throughout the 6-year experience with the incidence of drug related TEAEs steadily decreasing. The discontinuation rate in this study due to TEAEs was 15.7%, which compares favorably with rates in other BPH drug trials.
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<th>TABLE 1. Changes from baseline in secondary efficacy parameters, QOL and PVR in 6 years in the ITT population</th>
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<td><strong>Tamsulosin Experience, Yrs</strong></td>
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<td>Baseline</td>
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<td>No. pts</td>
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<td>Mean irritative ± SE (range 0–15)</td>
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<td>Mean QOL score (median)</td>
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<td>Mean ml PVR ± SE (95% CI)</td>
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<th>Secondary efficacy parameters (vs baseline 95% CI p &lt; 0.05)</th>
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* Potential 6-year experience at study entry in 159 patients.
When finasteride was compared with placebo in a 4-year study, 9 discontinuation rates due to TEAEs were high in each arm (34% and 42%, respectively). 9 In a 4-year doxazosin 10 study and a 42-month terazosin 11 study the therapeutic effect of each drug was maintained with time but dizziness led to discontinuation in 3.3% and 6.7% of patients, respectively. In addition, a significantly greater percent of patients who were treated vs those who received placebo (3.9 vs 0%) reported hypotension as an adverse reaction. 10 In contrast, in our study dizziness, postural hypotension and syncope led to discontinuation in only 0.2% of patients each. These low discontinuation rates may reflect tamsulosin selectivity for the α1A-receptor subtype. Abnormal ejaculation led to only 5 discontinuations (0.8% of patients), suggesting that patients did not perceive it to be as important as other events that led to discontinuation. 12

The low incidence of AUR in patients treated with tamsulosin for up to 6 years suggests that this agent may decrease the risk of AUR. The reported increase in PSA in the current study is consistent with observations in other long-term studies of patients with BPH. For example, in a placebo controlled finasteride trial elevated PSA occurred in 34% of the patients on placebo. 13 The low incidence of prostate cancer in our study, comparable to that in a placebo group of a similar population, 13 was achieved, although the tamsulosin population included some patients with high PSA who were at greater risk. Tamsulosin does not affect the risk of prostate carcinoma or detecting prostate cancer using PSA measurements. 14

CONCLUSIONS

Tamsulosin has been shown to provide sustained significant relief of BPH symptoms for up to 6 years without a decrease in the drug effect. No new safety issues were reported during the 4-year extension study that had not been observed in previously published studies of shorter duration. The rate of discontinuation due to AEs was lower than in similar trials. The long-term safety and efficacy profiles of tamsulosin in patients with LUTS associated with BPH, corroboration and expanding results from previous short-term clinical trials, support its usefulness as first line long-term therapy for LUTS associated with BPH.

REFERENCES