ELSEVIER

FIRST DOSE EFFICACY OF ALFUZOSIN ONCE DAILY IN MEN WITH SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Objectives. To evaluate the onset of action of alfuzosin once daily (OD) as determined by uroflowmetry early after initial dosing. Alfuzosin OD is an extended-release formulation of a uroselective, alpha$_1$-adrenoreceptor-blocking agent (alpha-blocker) used in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia.

Methods. This was a randomized, placebo-controlled, two-way Latin square crossover study. Forty-nine patients were selected for this study on the basis of their symptomatic improvement during previous treatment with alpha-blockers and significant decreases in urinary flow rate when that treatment was withdrawn.

Results. Our analysis showed that significant increases in the maximal urinary flow rate (Qmax) in 34 assessable patients occurred as soon as 8 hours after the initial dose of medication and persisted for at least 4 days. The ΔQmax for alfuzosin 10 mg OD was 3.2 mL/s and for placebo it was 1.1 mL/s. The difference of means for the assessable population was 2.1 (95% confidence interval 0.8 to 3.4, $P = 0.002$). The overall incidence of adverse events was low. Only dizziness, experienced by 3 patients treated with alfuzosin compared with 1 patient treated with placebo, appeared to be related to the study drug.

Conclusions. Together, our findings suggest that alfuzosin OD exhibits a urodynamically measurable effect on bladder outlet obstruction due to benign prostatic hyperplasia in men with lower urinary tract symptoms within hours of the first administration.

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Alpha$_1$ adrenoreceptor-blocking agents (alpha-blockers) are known to act rapidly after oral administration, but few specifics about their safety and efficacy during the first hours or days after initial dosing are available. Such information may be important for several reasons. Alpha-blockers have become the most commonly prescribed drugs for men with symptomatic benign prostatic hyperplasia (BPH).[1,2] Initial dosing typically occurs in the home, away from medical monitoring. Side effects from alpha-blockers are known barriers to compliance in many men.[3] Knowledge of the efficacy in an individual patient would be highly desirable.

Alfuzosin, a quinazoline derivative, is a uroselective alpha-blocker. The efficacy and safety of a new once-daily (OD), extended-release, formulation of alfuzosin (alfuzosin OD) have been demonstrated in two pivotal double-blind Phase III studies,[4,5] and summarized in a pooled analysis of three studies.[6] Studies of the immediate release formulation had previously demonstrated significant effects on the Qmax as early as 1.5 hours after the initial dose.[7] In this study, we evaluated the early effects of alfuzosin OD in men with symptomatic BPH using a recently reported study model designed for this purpose.[8]

MATERIAL AND METHODS

This was a multicenter study of men with lower urinary tract symptoms due to BPH conducted to assess the early effects of alfuzosin 10 mg OD on noninvasive urodynamic pa-

The ALFIRST Trial was sponsored by Sanofi-Synthelabo. The members of the ALFIRST Study Group are given in the Appendix.

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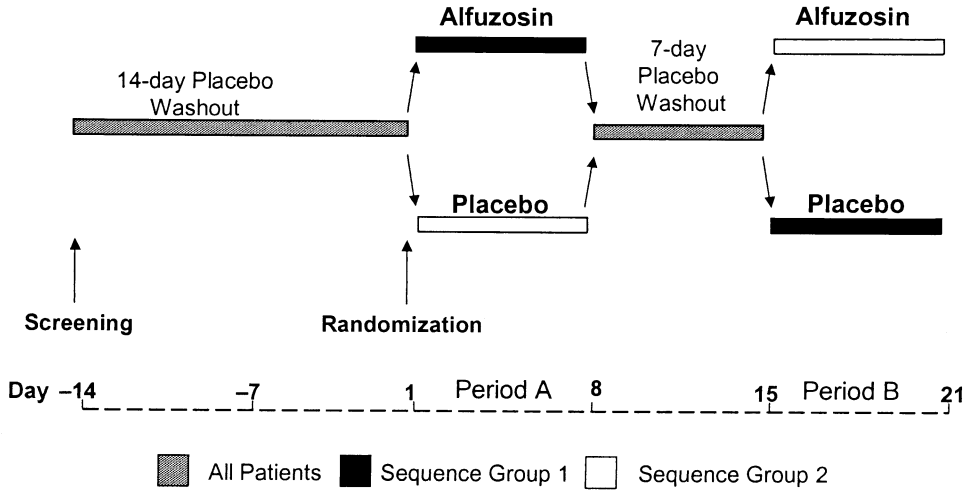


FIGURE 1. *Two-way crossover design. Patients were given a placebo to be taken orally OD after the morning meal for 14 days. During period A, either alfuzosin OD or placebo was taken orally OD after the morning meal for 7 days (days 1 to 8). During the washout phase, placebo was taken orally OD after the morning meal for 7 days. During period B, either alfuzosin OD or placebo was taken orally OD after the morning meal for 7 days (days 15 to 21).*

rameters. All participants gave written informed consent, and the institutional review boards of the respective study sites approved the study protocol. The trial was a randomized, placebo-controlled, two-way Latin square crossover study of alfuzosin in men with symptomatic BPH who were proven subjective, historical responders to alpha-blockers, as defined in the study design by Curtis *et al.*[8] (described below). The study design and drug regimen are shown in Figure 1.

Patient Selection

Men aged 50 years or older with BPH who had an enlarged prostate on digital rectal examination and transrectal ultrasonography within the previous 12 months were eligible for enrollment. Only those who demonstrated good compliance during the preinclusion period were accepted. Bladder dysfunction, acute or chronic prostatitis, active urinary tract infection, and carcinoma of the prostate were excluded conditions. Patients with a history of prostate surgery or radiotherapy to the pelvic region were also excluded. In addition, patients with a history of serious cardiovascular disease, malignancy, uncontrolled diabetes, active liver disease, or known hypersensitivity to alpha$_1$-blockers could not be enrolled.

As mentioned above, patients were required to be known responders to alpha$_1$-antagonists (tamsulosin, terazosin, doxazosin, or prazosin). All patients had been treated with a stable therapeutic dose of an alpha$_1$-blocker for at least 1 month at the time of screening. Before receiving their alpha$_1$ blocker, all had a history of micturition disturbances that showed improvement with standard therapy recommended by treatment guidelines for patients with bothersome symptoms.[9] When the alpha$_1$-blocker was withdrawn, patients who had a voided volume of at least 150 mL and demonstrated a greater than 2-mL/s decrease in Qmax on both day −7 and day 1 (predose) compared with day −14 were entered. For each individual patient, Qmax values between 5 and 12 mL/s were required, as was a postvoid residual urine volume of less than 350 mL on day −7.

Methods

After a 14-day placebo washout period, during which patients took placebo orally OD after the morning meal, the patients were randomly allocated to receive either alfuzosin 10 mg OD or placebo OD after the morning meal for 7 days (period A, days 1 to 8). This was followed by a 7-day placebo washout phase with dosing OD after the morning meal. Patients were then crossed over to the alternative therapy, administered orally OD after the morning meal for 7 days (period B, days 15 to 21). Group 1 patients received the treatment sequence of alfuzosin first, crossing over to placebo, and group 2 patients received the reverse treatment sequence, placebo followed by alfuzosin. Dosing and measurements were performed in a clinic setting on the days when the Qmax evaluations were performed (days 1, 4, 8, 15, 18, and 21).

The primary objective of the study was to determine the effect on Qmax of administration of a single dose of alfuzosin 10 mg. The secondary objectives were to determine the effect on the maintenance or improvement of Qmax and the safety of alfuzosin OD during a 7-day multiple-dosing period. Qmax was measured 8 hours after the initial dosing on days 1 and 15, a time that coincides with peak plasma drug levels,[10] and at 8 hours after dosing on days 4, 8, 18, and 21. The responses for each treatment sequence were combined for alfuzosin or placebo (ie, days 1/15, days 4/18, and days 8/21).

Efficacy and Safety

The Qmax, voided volume, and flow time were measured by uroflowmetry (Urodyne, Dantec Medical, Copenhagen, Denmark). The main outcome parameter was the Qmax as determined by manual over-reading of the original flow rate strips by a central reader unaware of the assignment of the patient using the 2-second rule (ie, Qmax is the highest flow rate maintained for at least 2 seconds). Urinary flow rates record the voided volume of urine over time and the Qmax was the maximal observed on the recording.

Safety measurements included blood pressure, heart rate, reported adverse events, findings on physical examination, and abnormal laboratory values. Cardiovascular safety was assessed at each visit. Blood pressure and heart rate values were measured with the patient in the supine position after 10 minutes' rest and after 2 minutes in the standing position using the same arm. Postural hypotension was defined as a 20 mm Hg or greater difference (decrease) in systolic blood pressure between the supine and standing values. All adverse events, regardless of severity and attribution to the study medication, were recorded.

TABLE I. *Patient characteristics*

Characteristic	Treatment Sequence		Total
	Period A (Alfuzosin/Placebo)	Period B (Placebo/Alfuzosin)	
Patients (n)	24	23	47
Race (n)			
White	19	18	37
Black	1	2	3
Asian	1	2	3
Hispanic	2	1	3
Other	1	0	1
Age (yr)			
Mean	64.7 (9.4)	66.6 (7.6)	65.6 (8.6)
Range	45.0–79.0	52.0–79.0	45.0–79.0
Prior alpha-blocker treatment			
Doxazosin/doxazosin mesylate	4	5	9
Prazosin	0	1	1
Tamsulosin hydrochloride	14	12	26
Terazosin hydrochloride	6	5	11
Prostate volume (mm^3)			
Mean	30.3 (18.5)	36.3 (35.9)	33.0 (27.5)
Range	10.9–76.0	6.1–166.8	6.1–166.8
Peak flow rate (mL/s)			
Day −14 (mean)	12.2 (3.2)	13.3 (2.5)	12.8 (2.9)
Day 1 (predose)	8.1 (2.1)	8.4 (2.2)	8.3 (2.1)

Data in parentheses are the standard deviation.

RESULTS

Study Population

The patient characteristics are shown in Table I. A total of 49 patients were randomized to the alfuzosin/placebo sequence (n = 24) or to the placebo/alfuzosin sequence (n = 25). Of these, 45 patients completed the study and constituted the intent-to-treat population. All patients who received at least one dose of alfuzosin OD were included in the safety assessment (47 of 49, 95.9% of the randomized patients). Among the 49 randomized patients, 34 (69.4%) were considered assessable (ie, they were randomized, took at least one dose of study medication in both crossover periods, had a baseline Qmax recording, and at least one 8-hour postdose Qmax recording in each period, and were not associated with a major protocol violation).

Of the 4 patients who discontinued the study, 2 withdrew because of adverse events (1 before randomization because of visual disturbances and 1 after receipt of the study drug on development of a urinary tract infection), and 2 patients in each treatment group withdrew (1 because he no longer met the eligibility criteria [Qmax less than 2 mL/s decrease] and 1 at the patient's request unrelated to the study drug).

Efficacy

The combined efficacy data obtained in periods A and B are summarized in Table II. Before dosing on day 1, the mean Qmax values were similar for the two treatment groups (Table I). Among the assessable patients, the change in Qmax on days 1/15 from baseline was significantly greater after treatment with alfuzosin than after treatment with placebo, with a least squares mean value of 3.2 mL/s and 1.1 mL/s, respectively ($P = 0.002$). Among the intent-to-treat patients, the respective least squares mean values of 2.7 mL/s and 1.3 mL/s were also significantly greater for alfuzosin ($P = 0.015$). Although alfuzosin was statistically superior to placebo, an overall net increase in Qmax was observed after each treatment, with the subanalysis showing a somewhat more pronounced placebo effect in period A than in period B. This was likely a reflection of a unilateral regression to the mean after the restriction of patient enrollment on the basis of an upper level of Qmax during screening.[11]

Figure 2 presents a plot of the pooled mean Qmax values for the assessable patients for periods A and B combined (days 1/15 and days 4/18). The secondary endpoints included the change from baseline in Qmax at approximately 8 hours after dose administration on day 4 during period A and day 18 during period B combined. The change from baseline in Qmax on days 4/18 was significantly greater after treatment with alfuzosin than after treatment with placebo ($P < 0.001$). The least squares mean on days 4/18 for the alfuzosin and placebo treatment groups was 2.7 mL/s and 1.0

TABLE II. *Peak flow rate: change from baseline*

Eight Hours After Dose, Day 1/15	Alfuzosin OD 10 mg	Placebo	Difference of Means (95% CI)	*P* Value*
ITT population† (n = 45)	2.7	1.3	1.4 (0.3–2.5)	0.015
Assessable population‡ (n = 34)	3.2	1.1	2.1 (0.8–3.4)	0.002

KEY: CI = confidence interval; ITT = intent to treat; Qmax = peak urinary flow rate.
Data presented as the mean Qmax in milliliters per second.
** Data from alfuzosin treatment in groups 1 and 2 were pooled, and the least squares mean was calculated; data from placebo administration in groups 1 and 2 were also pooled; P values for differences between means were derived by analysis of covariance.*
† ITT population defined as those patients who were randomized, received at least one dose of study medication in both crossover periods, and had a baseline and at least one 8-hour postdose Qmax recording in each period.
‡ Assessable population defined as those patients who were randomized, took at least one dose of study medication in both crossover periods, had a baseline and at least one 8-hour postdose Qmax recording in each period, and were not associated with a major protocol violation.

mL/s, respectively. By contrast, the change from baseline on days 8/21, when a pronounced placebo effect was found on day 8, was not significantly different between the two treatment groups ($P = 0.66$). The increase in Qmax for both alfuzosin and placebo groups on day 8 was comparable to the values on day −14, before discontinuation of the previous alpha-blocker, demonstrating a regression to the mean.

SAFETY

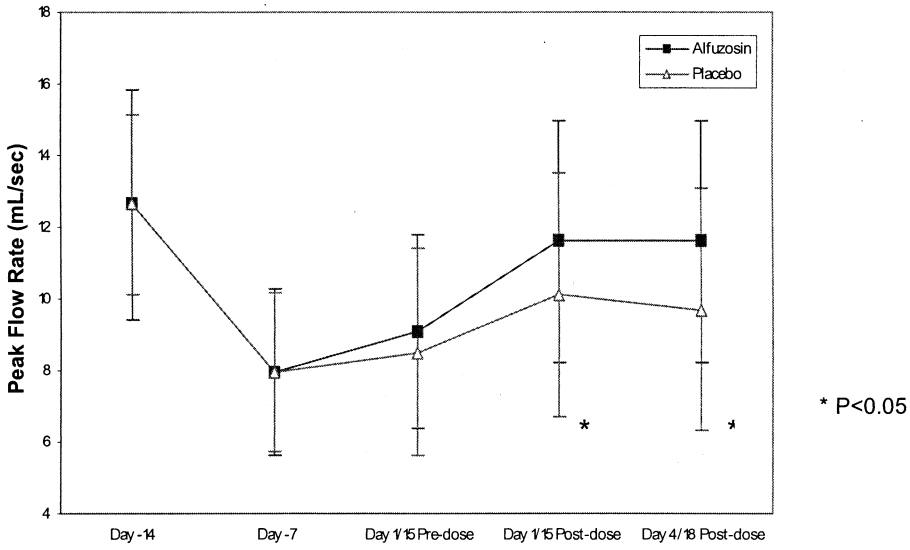
The overall incidence of adverse events was somewhat greater after treatment with alfuzosin (9 of 47 patients; 19.1%) than with placebo (5 of 47 patients; 10.6%; $P = 0.25$). During the initial 2-week placebo washout period, 8 (17.0%) of 47 patients experienced at least one adverse event. The only adverse event reported by more than 1 patient for which a relationship to the study drug could not be excluded was dizziness, experienced by 3 (6.4%) of 47 patients after treatment with alfuzosin and by 1 patient after placebo. However, overall, the incidence of adverse events for which a relationship to alfuzosin could not be excluded was low. No serious adverse events were reported. Changes from baseline in clinical laboratory test results were minor and revealed no clinically meaningful trends. Two patients experienced orthostatic hypotension during the study, defined as a fall in systolic blood pressure of 20 mm Hg or greater after 2 minutes in an upright position after rising from a supine position. One patient, who had no previous cardiovascular history and symptoms, experienced a drop in blood pressure of 20 mm Hg 8 hours after receiving his initial dose of alfuzosin. This patient's blood pressure increased by 14 mm Hg within 20 minutes after rising. The other patient had a history of hypertension and experienced orthostatic hypotension five times during the study (three times after receiving placebo and twice after receiving alfuzosin).

COMMENT

Despite the frequency of alpha-blocker use in men with symptomatic BPH, little is known regarding the initial experiences of patients who are treated with such drugs. This study was undertaken to document the safety and efficacy of first dosing with an OD alpha-blocker, alfuzosin. The effects of alpha-blockers may vary widely from patient to patient. The design of this study, modeled on that of Curtis *et al.*,[8] was intended to permit rapid assessment of the ability of alfuzosin OD to increase urine flow without requiring large numbers of patients.

The data from this placebo-controlled study indicate a pronounced effect on Qmax values for alfuzosin OD at 8 hours after the first dose, a time coincident with known peak plasma levels of the drug.[10] Confirmation of the effect was obtained after 3 days of continuous therapy. In the rigidly controlled subgroup of 34 assessable men, the Qmax after a first dose of alfuzosin OD increased at 8 hours by a net mean of 2.6 mL/s, similar to the effects of the same drug after 3 months of therapy.[4,5] These results are consistent with those of Teillac *et al.*,[7] in which the onset of action for the immediate release formulation coincided with its time of maximal concentration of 1.5 hours.

During the period of drug administration, mild side effects were seen in 9 of 47 men after receiving alfuzosin OD and in 5 of 47 men after receiving placebo (P = nonsignificant). Only one individual who had received the study drug discontinued because of side effects. An examination of the blood pressure results revealed that 2 patients experienced postural hypotension at any point in the study, 1 patient after alfuzosin and 1 patient after placebo in period A and alfuzosin in period B. A few statistically significant differences between the two treatment groups were noted in the changes from baseline in heart rate and blood pressure.



Day	Alfuzosin Q_{max} ± SD (mL/sec)	Placebo Q_{max} ± SD (mL/sec)
-14	12.6 ± 2.9	12.6 ± 2.9
-7	7.9 ± 2.1	7.9 ± 2.1
1/15 Pre-dose	9.1 ± 2.7	8.5 ± 2.9
1/15 Post-dose	11.6 ± 3.4	10.1 ± 3.4
4/18 Post-dose	11.6 ± 3.4	9.7 ± 3.4

FIGURE 2. *Mean Qmax values in the intent-to-treat population. Qmax values were obtained at days −14, −7, 1, 4, 15, and 18 of the study. Data obtained before randomization on days −14 and −7 were pooled and least squares means calculated for the entire group. After randomization, alfuzosin or placebo data from the two different sequence groups 1 and 2 were pooled (days 1/15 and days 4/18) for calculation of the least squares means. Data from each point were plotted, with standard deviations given as error bars.* P *values were generated using the* t *test for comparing mean Qmax values for alfuzosin and placebo.*

However, the changes were at sporadic points and were not likely to be clinically relevant on the basis of their small magnitude. These results are consistent with the lack of significant first postdose orthostatic hypotension observed in pivotal trials.[4,5]

Not clear from this study is whether the observed early effects of alfuzosin OD on Qmax will correlate with long-term symptomatic relief in individual patients. In this small sample, the Qmax values achieved on day 8 did not reach statistical significance because of a pronounced placebo effect, possibly due to regression to the mean and interpatient variation. Nonetheless, the early and long-term effects of alfuzosin OD have already been demonstrated in double-blind placebo-controlled trials in large patient populations.[4,5] These studies established increases in Qmax values starting at 2 weeks,[5] with significant benefits at 3 months.[4,5] These effects extended to up to 1 year in open-label follow-up trials.[12] Significant improvements were also observed for symptomatic relief of lower urinary tract symptoms at 3 months in these double-blind studies,[4,5] and for up to 1 year in the open-label follow-up periods.[12] Furthermore, immediate-release (three-times daily dosing) and sustained-release (twice-daily dosing) formulations of alfuzosin have demonstrated that efficacy in improving lower urinary tract symptoms is maintained for more than 3 years.[13,14] This study demonstrated that alfuzosin OD exhibits a urodynamically measurable effect on bladder outlet obstruction due to BPH in men with lower urinary tract symptoms within hours of the first administration. Therefore, alfuzosin OD has the potential

to offer early benefits to men who report interference with daily routines from BPH symptoms and seek treatment for symptoms that are bothersome.

CONCLUSIONS

Our findings suggest that alfuzosin OD exhibits a urodynamically measurable effect on bladder outlet obstruction due to BPH in men with lower urinary tract symptoms within hours of the first administration.

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APPENDIX

A complete list of the members of the ALFIRST Study Group follows: R. Anderson, Tacoma, Washington; J. Bannow, St. Joseph, Michigan; R. Dmochowski, Fort Worth, Texas; J. Kaufman, Aurora, Colorado; E. Kleer, Ann Arbor, Michigan; and J. Young, Laguna Woods, California.

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