Early symptom improvement of benign prostatic hyperplasia (BPH) treated with once daily alfuzosin

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Introduction and objectives: *A novel slow release formulation of alfuzosin should improve compliance by reducing dosing to one 10 mg tablet per day. The current study examined efficacy, at 9 days and 3 months, and safety of this formulation of alfuzosin in BPH patients.*
Methods: *ALF-X was a 3-month, non-comparative, observational study of 353 BPH patients from 39 Canadian Urology centres.*
Results: *At baseline (BL), mean age was 63.1±9.01 years, 92.6% of patients were Caucasian, 3.4% had a history of acute urinary retention, mean duration of the micturition disorder was 48.6±54.15 months, and mean PSA was 3.3±6.65 ng/mL. Mean total International Prostate Symptom Score (I-PSS) decreased from 17.5 at BL to 10.4 at M3 - an improvement of 7.1±6.82 points (40.6%, p<0.001), mostly occurring (27.0%, p<0.001)) during the first 9 days. Mean Quality of Life Assessment Index improved by 0.7±1.39 points between BL and D9 (17.5%, p<0.001), and by 1.5±1.52 points between BL and M3 (37.5%, p<0.001). The proportion of 'mild' I-PSS patients increased from 11.8% (BL) to 29.7% (D9) to 39.0% (M3); those with 'severe' I-PSS decreased from 37.8% (BL) to 14.5% (D9) to 9.4% (M3). Of 144 patients with nocturia (>2 nightly voidings) at D1, 51.4% improved to ≤2 nightly voidings at D9, and 60.4% at M3. Adverse events related to alfuzosin occurred in 7.8% of patients; 2.0% experienced serious adverse events. There were no vasodilatory events related to alfuzosin or deaths.*
Conclusions: *In routine clinical practice, slow-release alfuzosin is associated with a significant improvement in LUTS, and frequency of nocturia, and an excellent safety profile.*

Key Words: BPH, alpha$_1$-blocker, phase IV trial

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Introduction

Benign prostatic hyperplasia (BPH) is an androgen-dependent condition characterized by a histological prostatic tissue hyperplasia which can lead to prostatic enlargement causing lower urinary tract symptoms (LUTS).[1] The condition affects men of all races and cultures[2,3] and has an incidence as high as 50% in men aged 60 years, rising to 88% in men aged 80 years.[4] It is estimated that nearly half of these patients will develop either moderate LUTS with an International

Prostate Symptom Score (I-PSS) between 8 and 19 or severe LUTS (I-PSS> 20).[5] These urinary symptoms strongly interfere with normal activities of patients and reduce their quality of life.[6-9]

Alpha$_1$ adrenoreceoptor-blocking agents (α_1-blockers) have been recommended in clinical guidelines for the treatment of BPH.[10,11] Selective α_1-blockers (receptor selective or functional selective) are functioning as specific post-synaptic α_1-blockers. They demonstrated a preferential tropism for the smooth muscle of the lower urinary tract (trigone, urethra, prostate) compared with their affinity for vessel smooth muscle.[12-14] Alfuzosin, a uroselective α_1-blocker, has an improved cardiovascular tolerability and can be prescribed with no initial dose titration.[15-18]

Alfuzosin is chemically a quinazoline derivative and has been marketed specifically for the treatment of LUTS and clinical BPH.[16] Immediate-release (2.5 mg TID) and sustained-release (5 mg BID) formulations have confirmed the efficacy of alfuzosin in alleviating symptoms and the improvement of maximum flow rate in well designed controlled and open studies.[19-28] In addition, alfuzosin acts from the first dose, maintains symptom relief for up to 3 years and has a good safety profile on cardiovascular function and sexual function.[16,19,20,27,29]

A new prolonged-release formulation for once daily administration (alfuzosin 10 mg OD) has been developed recently to add convenience and to provide an optimal coverage of the dosing interval with no major plasma concentration fluctuations.[30] This formulation is bioequivalent to both the immediate- and sustained-release formulations.

ALF-X is a single-arm, observational, 3-month study. It was designed to assess, under routine daily clinical practice conditions, the safety profile and the efficacy of alfuzosin 10 mg OD and to determine the occurrence of AUR and prostatic surgery in this unselected population suffering from lower urinary tract symptoms of BPH. A validated quality of life scale and a sexual function questionnaire were included in order to more accurately determine the benefit for the patient of this new formulation.

Patients and methods

The ALF-X study is a 3-month open, non-comparative, multicentre, observational study conducted among urologists in Canada. There is an ongoing, optional 9-month extension of the study. Patients were enrolled from 39 urology centres in Canada. Written informed consent was obtained from all patients, and the study protocol was approved by either a central IRB service or the ethics committees of each participating centre and/or institution.

Selection of patients

Ambulatory, male patients with a minimum age of 40 years were included if they experienced bothersome lower urinary tract symptoms suggestive of BPH. In addition, a digital rectal examination had to be compatible with BPH. Men with the following conditions were not allowed to participate: BPH surgery scheduled within the next 12 months, no previous improvement with α_1-blocker therapy, known hypersensitivity to alfuzosin, history of postural hypotension or syncope, commencement of finasteride therapy within the preceding 12 months, use of α_1-blocker therapy within the preceding 30 days, urethral stricture, prostate cancer, prior transurethral resection of the prostate or of the bladder neck, known history of hepatic insufficiency, unstable angina pectoris, severe concomitant life-threatening condition, and urethral manipulation within last 30 days (including catheterization/cystoscopy).

Methods

Patients received 10 mg alfuzosin (Xatral®) once daily at the end of the evening meal. The tablets were to be swallowed whole without being chewed or crushed. Patients were assessed at Baseline (BL), study Day 9 (D9) and Month 3 (M3).

Change in urinary symptoms was assessed at each visit using the International Prostate Symptom Score (I-PSS) containing seven questions about urinary symptoms.[31] A score between 0 and 5 was assigned to each response. The total score ranged from 0 (no symptoms) to 35 (highly symptomatic). Disease severity was categorized into mild (I-PSS <8), moderate (I-PSS between 8 and 19, inclusive) and severe (I-PSS > 19). In addition, a single question to assess quality of life was added to the I-PSS questionnaire (Quality of Life Assessment Score). Patients were divided into the categories mild (0-1 points), moderate (2-4 points) and severe (5-6 points) according to their Quality of Life Assessment Score.

Sexual function was assessed using the Sexual Function Questionnaire (DAN-PSS). This questionnaire corresponded to the last three questions of the original DAN-PSS questionnaire validated in 1995 by B. J. Hansen.[32] It assessed the following points: erectile capacity, ejaculation and discomfort during ejaculation. Each question was divided in two parts: part A assessed the severity of symptoms (rated 0 to 3) and part B assessed the bothersomeness of symptoms (rated 0 to 3).

Patients kept a voiding diary to document the number of times they had voided during the day and night. One voiding diary was completed for each day of the initial 9-day period, while a second voiding diary was completed during each day of the last 7 days before the M3 visit.

Any adverse events, infections or serious adverse events spontaneously reported by the patient or observed by the investigator during clinical examination were recorded. No blood and chemistry tests were performed as part of this study.

Statistical analysis

The primary efficacy variable consisted of the change in I-PSS from BL to M3. The study tested the two-side null hypotheses that the mean change in the Total I-PSS was zero with a paired t-test at the alpha = 0.05 level. Secondary efficacy parameters consisted in the change in I-PSS from BL to D9, change in Quality of Life Index from BL to D9 and from BL to M3, cross-sectional distribution of subjects according to Symptom Severity Category at BL, D9 and M3, change in Symptom Severity Category from BL to Day 9 and from BL to M3, change in I-PSS storage, voiding and nocturia subscores from BL to D9 and from BL to M3, cross-sectional summary of frequency counts of voiding (obtained from voiding diaries) for the first 9 study days as well as the last 7 study days before M3 (both am+pm and pm only), cross-sectional summary of DAN-PSS symptomatic subscore (questions 1A + 2A + 3A) at BL and M3 and cross-sectional summary of DAN-PSS bother subscore (questions 1B + 2B + 3B) at BL and M3. Change in continuous outcome measures were evaluated as Change = Endpoint – Baseline or as Relative Change = (Endpoint – Baseline)/Baseline * 100%.

Adverse events which occurred up until the Month 3 visit date were included in this analysis. Adverse events and serious adverse events were summarized according to MedDRA System Organ Class (SOC) and Preferred Term.

Results

Study population

Out of the 353 patients enrolled, a total of 347 patients were eligible to participate in this study and constituted the safety (SAF) population. Of those, n=323 patients fulfilled the criteria to be included into the intent-to-treat (ITT) population. Patients in the ITT population had to suffer from BPH, receive at least one dose of the studied treatment and perform a second visit. All of the 24 patients who were excluded from the ITT analysis did not fulfill the minimum requirement by failing to provide one I-PSS questionnaire at Baseline and at least one more at either Day 9 or Month 3. A total of 313 out of 323 were able to complete the study without any major protocol violation and constituted the per-protocol (PP) population. Of the ten patients who had to be excluded from the PP population, five had received α_1-blockers in the last 30 days before study commencement, one patient had started finasteride treatment in the last 12 months before study initiation, two patients had received forbidden therapy during the course of the study, one patient did not take alfuzosin on a regular basis, and one additional patient showed poor compliance.

Patient characteristics are shown in Table 1. The mean age of the population was 63.1±9.01 years, and most patients were Caucasian (92.6%). On average, patients had suffered from micturition disorder for

TABLE 1. **Patient characteristics**

Demographics	**Patients (n=323)**
Age (years, mean ± standard deviation)	63.1 ± 9.01
Race, n (%)	
Caucasian	299 (92.6%)
Black	7 (2.2%)
Asian	10 (3.1%)
Other	7 (2.2%)
Duration of micturition disorder (months, mean ± standard deviation)	48.56 ± 54.152
PSA value (ng/ml, mean ± standard deviation)	3.29 ± 6.648
Digital rectal examination, n (%)	
Mildly enlarged	156 (48.3%)
Moderately enlarged	135 (41.8%)
Grossly enlarged	25 (7.7%)
History of acute urinary retention, n (%)	
No	312 (96.6%)
Yes	11 (3.4%)
Cardiovascular disease at baseline, n (%)	
Hypertension	113 (35.0%)
Ischemic heart disease	39 (12.1%)
Heart failure	12 (3.7%)
Neurological disease at baseline, n (%)	
Essential tremors	1 (0.3%)
Parkinson's	1 (0.3%)
Seizure-last one 5 yrs ago on prophylactic dilantin	1 (0.3%)
Seizures	1 (0.3%)

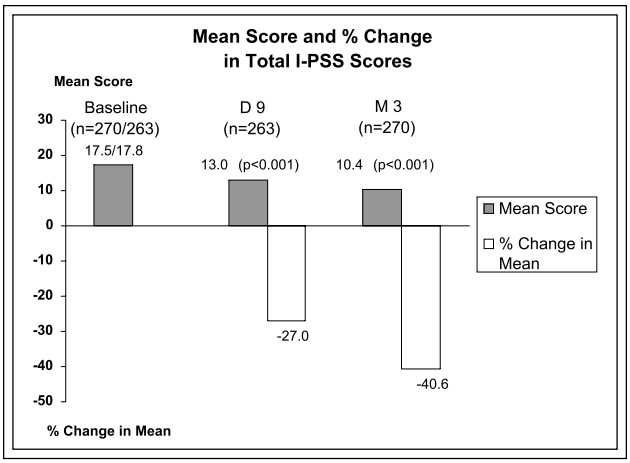

Figure 1a. Mean score and % change in total I-PSS scores.

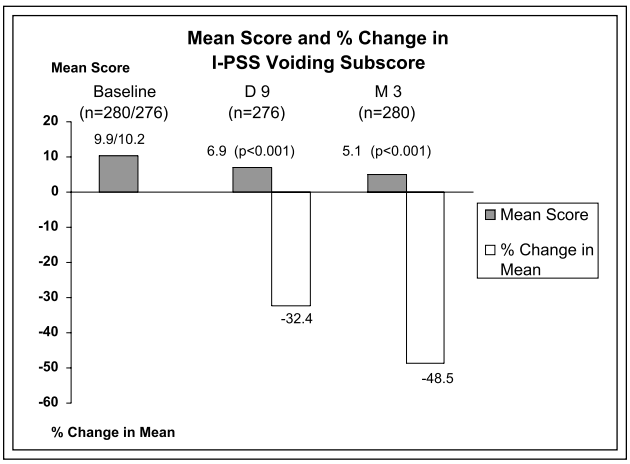

Figure 1b. Mean score and % change in I-PSS voiding subscore.

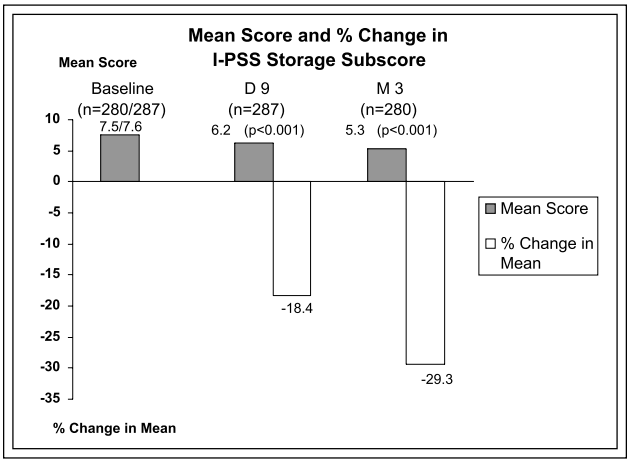

Figure 1c. Mean score and % change in I-PSS storage subscore.

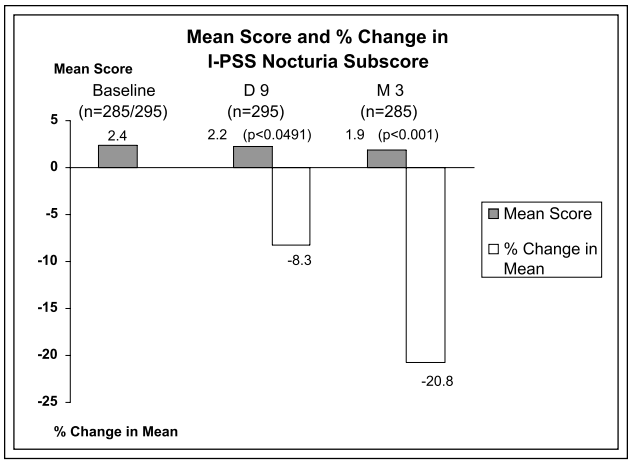

Figure 1d. Mean score and % change in I-PSS nocturia subscore.

more than 4 years, but only few patients (3.4%) had a previous history of acute urinary retention (AUR).

Efficacy

Efficacy results are based on the 3-month analysis of the ITT population (n=323). The primary efficacy variable, consisting of the change in the total International Prostate Symptom Score (I-PSS) from Baseline to Month 3, is presented in Figure 1a. In addition, changes in I-PSS scores were measured during a short-term period of the first 9 days. The frequency of symptoms was assessed by a score ranging from 0 (no symptom at all) to 5 (almost always). Results were compared on a question by question basis using a paired t-test.

During the first 9 study days, the International Prostate Symptom Score (I-PSS) decreased from a mean total score of 17.8 points at BL to 13.0 at day (D) 9, an improvement of 4.8±6.70 points (27.0%, $p<0.001$). Over the full 3-month period, there was a decrease from a mean total score of 17.5 at BL to 10.4 at M3 - an improvement of 7.1±6.82 points (40.6%, $p<0.001$). The total I-PSS score was then divided into voiding, Figure 1b, storage, Figure 1c, and nocturia, Figure 1d, subscores: all subscores showed a statistically significant improvement for both the BL to D9 and the BL to M3 periods (all $p<0.001$). The proportion of patients showing at least a 30% improvement in their total IPSS score was 43.4% between BL and D9, and 63.0% for the between BL and M3.

An additional question (Quality of Life Assessment Score) assessed the degree to which patients were bothered by their prostate symptoms (0=delighted, 6=unhappy). The Quality of Life Assessment Score improved by a mean of 0.7±1.39 points between

TABLE 2a. **I-PSS symptom shift: BL-D9**

Symptom			**Symptom severity Day 9**		
Severity	Mild	Moderate	Severe	Missing	Overall
Baseline	(n=90)	(n=169)	(n=44)	(n=20)	(n=323)
Mild	18 (47.4%)	15 (39.5%)	2 (5.3%)	3 (7.9%)	38 (100.0%)
Moderate	58 (35.6%)	88 (54.0%)	5 (3.1%)	12 (7.4%)	163 (100.0%)
Severe	14 (11.5%)	66 (54.1%)	37 (30.3%)	5 (4.1%)	122 (100.0%)

TABLE 2b. **I-PSS symptom shift: BL-M3**

Symptom			**Symptom Severity Month 3**		
Severity	Mild	Moderate	Severe	Missing	Overall
Baseline	(n=112)	(n=148)	(n=27)	(n=36)	(n=323)
Mild	20 (52.6%)	12 (31.6%)	0 (0.0%)	6 (15.8%)	38 (100.0%)
Moderate	68 (41.7%)	69 (42.3%)	7 (4.3%)	19 (11.7%)	163 (100.0%)
Severe	24 (19.7%)	67 (54.9%)	20 (16.4%)	11 (9.0%)	122 (100.0%)

TABLE 2c. **Quality of life shift: BL-D9**

Symptom			**Symptom Severity Day 9**		
Severity	Mild	Moderate	Severe	Missing	Overall
Baseline	(n=33)	(n=199)	(n=63)	(n=28)	(n=323)
Mild	1 (25.0%)	3 (75.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)
Moderate	27 (12.5%)	144 (66.7%)	19 (8.8%)	26 (12.0%)	216 (100.0%)
Severe	5 (5.0%)	49 (49.0%)	44 (44.0%)	2 (2.0%)	100 (100.0%)
Missing	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	3 (100.0%)

TABLE 2d. **Quality of life shift: BL-M3**

Symptom			**Symptom Severity Month 3**		
Severity	Mild	Moderate	Severe	Missing	Overall
Baseline	(n=85)	(n=174)	(n=28)	(n=36)	(n=323)
Mild	2 (50.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)
Moderate	65 (30.1%)	120 (55.6%)	5 (2.3%)	26 (12.0%)	216 (100.0%)
Severe	18 (18.0%)	50 (50.0%)	23 (23.0%)	9 (9.0%)	100 (100.0%)
Missing	0 (0.0%)	2 (66.7%)	0 (0.0%)	1 (33.3%)	3 (100.0%)

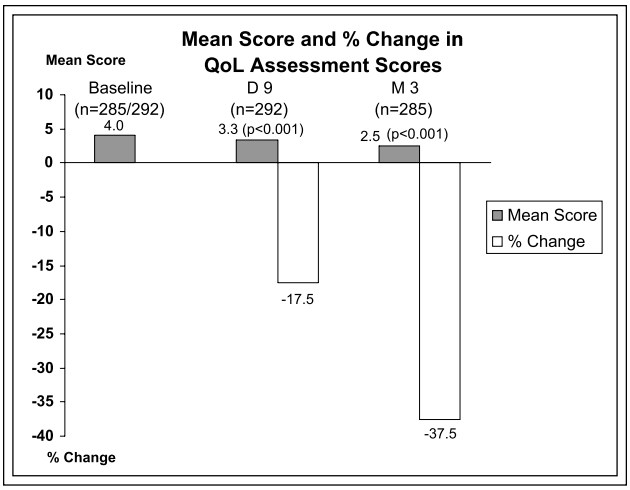

Figure 2. Mean score and % change in quality of life assessment scores.

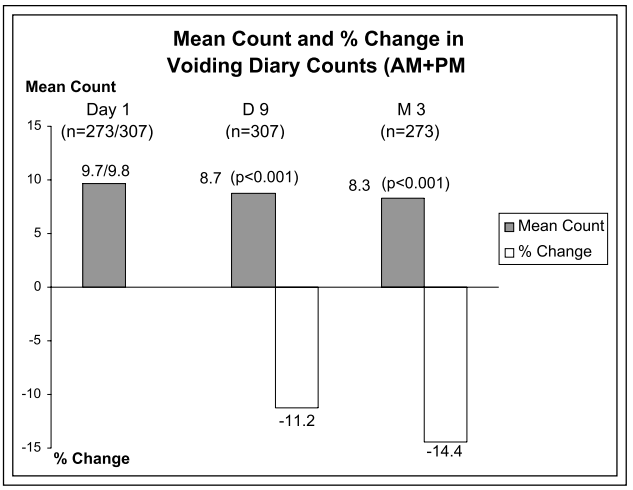

Figure 3. Mean count and % change in voiding diary counts (am+pm).

BL and D9 (17.5%, p<0.001), and by 1.5±1.52 points between BL and M3 (37.5%, p<0.001, Figure 2).

The proportion of patients with mild I-PSS symptom severity increased from 11.8% at BL to 29.7% on D9 and 39.0% at M3, while the proportion of patients with severe I-PSS symptom severity decreased from 37.8% at BL to 14.5% on D9 and 9.4% at M3. In analogy to the above observation, of the 122 patients with severe disease at Baseline, 66 (54.1%) improved to moderate disease up to Day 9, and an additional 14 patients (11.5%) even improved to mild disease, Table 2a. For the 3-month period, a similar effect was observed: 67 out of 122 patients with severe disease (54.9%) shifted to moderate disease and another 24 (19.7%) had mild disease at Month 3, Table 2b. The severity of the Quality of Life Assessment score also improved over the course of the study. Out of those patients with severe disease at Baseline, 49 out of 100 (49.0%) showed improvement in their Quality of Life Assessment score to moderate status on Day 9, and an additional 5 out of 100 (5.0%) improved to mild status, Table 2c. The same effect was observed in the 3-month observation period, when 50 out of 100 patients (50.0%) with a severe score improved to a moderate score, and an additional 18 out of 100 (18.0%) improved to a mild score, Table 2d.

Voiding counts (am+pm) improved by an average of 1.1 voidings (p<0.001) during the first 9 days and an average of 1.5 voidings (p<0.001) between Day 1 and Month 3, Figure 3. In addition, of those 144 patients with nocturia (more than two nightly voidings on Day 1), 74 (51.4%) showed an improvement to two nightly voidings or less on D9, and 87 (60.4%) remained at or below two nightly voidings at M3, Table 3.

Evaluation of sexual function (DAN-PSS questionnaire) showed no statistically significant improvement when questions were analyzed separately. However, when the questionnaire was divided into the symptomatic and the bother subscore, symptoms improved from a mean of 2.1 points to mean of 1.7 points (19%) which was statistically

TABLE 3. **Shift in voidings from baseline**

		Day 1		
		≤ 2 night voidings (n=163)	**> 2 night voidings (n=144)**	**Overall (n=307)**
Day 9	≤ 2 night voidings	136 (83.4%)	74 (51.4%)	210 (68.4%)
	> 2 night voidings	27 (16.6%)	70 (48.6%)	97 (31.6%)
Month 3	< 2 night voidings	144 (88.3%)	87 (60.4%)	231 (75.2%)
	> 2 night voidings	19 (11.7%)	57 (39.6%)	76 (24.8%)
	0 (0.0%)	3 (100.0%)		

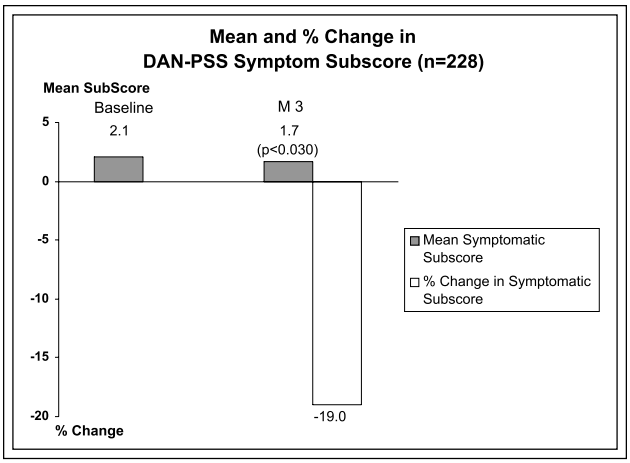

Figure 4a. Mean and % change in DAN-PSS symptom subscore (n=228).

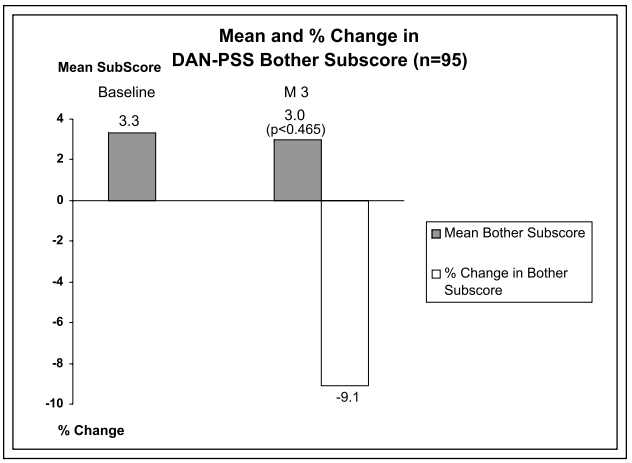

Figure 4b. Mean and % change in DAN-PSS bother subscore (n=95).

significant (p<0.03, Figure 4). Similarly, the bother subscore improved from a mean of 3.3 points to a mean of 3.0 points. This decrease, however, was not statistically significant (p=0.465).

Safety

Safety results are based on the safety (SAF) population (n=347). No patient died while treated with alfuzosin. Out of the 70 adverse events (20.2%) reported, 34 were classified as "mild" (9.8%), 30 as "moderate" (8.6%) and 6 as "severe" (1.7%). The most frequent adverse events reported included nervous system disorders (7.8%) and gastrointestinal disorders (3.7%). Fewer adverse events were reported to be related to the study drug (n=27, 7.8%). They included three patients with hypertension and one patient with angina pectoris. No vasodilatory events related to the study drug were reported. One patient suffered from acute urinary retention and also had to undergo acute prostate surgery. Alfuzosin was tolerated in older patients as well: the overall rate of adverse events in patients 65 years or older was 18.8% and comparable to those

TABLE 4. **Serious adverse events by severity**

	Overall (n=347)							
System Organ Class Preferred Term	**Mild n (%)**		**Moderate n (%)**		**Severe n (%)**		**Overall n (%)**	
Any event	2	(0.6%)	2	(0.6%)	3	(0.9%)	7	(2.0%)
Angina pectoris	0	(0.0%)	0	(0.0%)	1	(0.3%)	1	(0.3%)
Arrhythmia	1	(0.3%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Bradycardia	0	(0.0%)	0	(0.0%)	1	(0.3%)	1	(0.3%)
Palpitations	1	(0.3%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Inflammation	0	(0.0%)	0	(0.0%)	1	(0.3%)	1	(0.3%)
Infection	0	(0.0%)	1	(0.3%)	0	(0.0%)	1	(0.3%)
Pain in extremity	0	(0.0%)	0	(0.0%)	1	(0.3%)	1	(0.3%)
Paraesthesia	1	(0.3%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Urinary retention	0	(0.0%)	1	(0.3%)	0	(0.0%)	1	(0.3%)
Pruritus	1	(0.3%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Rash	1	(0.3%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Cardiac pacemaker insertion	0	(0.0%)	0	(0.0%)	1	(0.3%)	1	(0.3%)

younger than 65 years (21.2%). A total of seven patients experienced serious adverse events (SAEs, 2.0%, Table 4). Amongst the leading causes for SAEs were cardiac disorders, which included episodes of angina pectoris, arrhythmia, bradycardia and palpitation (three patients, 0.9%).

Discussion

ALF-X was a 3-month, single-arm, multicentre observational study with an optional 9-month extension period. These findings are based on the first 3 months of this study, and do not include data collected from the 9-month extension. The purpose of this study was to collect data on safety and efficacy of prolonged-release alfuzosin under conditions of routine clinical practice. Patients targeted for inclusion were those with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). Patients received regular dosing of alfuzosin (10 mg once daily), and were monitored for urinary function (I-PSS), frequency of micturition (voiding diary), sexual function (DAN-PSS) as well as safety parameters.

Alfuzosin led to a statistically and clinically significant improvement in the total I-PSS score averaging 7.1 points ($p<0.001$) over a 3-month period. It is important to highlight that these findings need to be seen in the light of an observational study design, which is limited by the absence of both a placebo group and the randomization of data. However, it shows that current usage of alfuzosin by a large number of Canadian urologists under condition of routine clinical practice is leading to outcomes similar to those seen in the more controlled environment of a randomized clinical trial, e.g. the reduction in total I-PSS score is in line with a recent pooled analysis of three parallel, randomized, double-blind, placebo-controlled 3-month studies showing an average improvement of 6.0 points (n=473).[16] Like the current study, this pooled analysis was able to establish statistically significant improvements in all three sub-scores of the I-PSS (voiding, storage and nocturia subscore) as well as the Quality of Life Score.

Unlike previous studies, the current analysis also focused on the immediate 9-day period following the start of therapy. During the first 9 days, the I-PSS total score improved by an average of 4.8 points. This highlights that the effect of alfuzosin is noticeable within days major improvements in urinary flow and retention are achieved in the early period. The same is true for the Quality of Life Score, where almost half of the average improvement was achieved during the first 9 days (mean improvement at D9: 0.7; M3: 1.5). Furthermore, the effects of alfuzosin have a marked and immediate impact on the severity of BPH disease: the majority (65.6%) of all patients with severe disease at BL was able to improve to moderate or mild disease status within the first 9 days, while an additional 9.0% of patients improved later on during the first 3 months. Finally, more than half of all 144 patients with nocturia (51.4%) improved to less than two voidings per night during the initial 9-day period, while an additional 9.0% improved up to M3.

Sexual function as expressed by the symptomatic sub-score of the DAN-PSS improved significantly by 19% ($p<0.03$). However, patients did not show a significant increase in their bother sub-score. In contrast, a larger study (n=3076) conducted recently displayed a significant increase in both sub-scores.[33] Alfuzosin also had no negative impact on sexual function: two mild events (0.58%) of sexual disorder or failure were reported as adverse events, but none showed any evident causal relationship to the study drug. This is comparable to previous findings of Hoefner et al who did not report an ejaculatory disorder in relation to alfuzosin in 536 patients receiving 2.5 mg TID or 407 patients receiving 5 mg BID.[34] In contrast, tamsulosin (another a_1-blocker) treated patients experienced abnormal ejaculation at a rate of up to 18% (13 week observational period, 0.8 mg dosage).[35,36] This might be explained with tamsulosin's affinity to the a_{1A}-receptors of the vas deferens and the seminal vesicle compromising their contraction.[37,38]

The overall safety profile of alfuzosin was very satisfactory: no patient died and there was no vasodilatory event associated with the study drug. One single patient (0.29%) experienced an episode of acute urinary retention leading ultimately to BPH surgery. There were three events of hypertension (two mild and one moderate) as well as one single event of mild hypotension - all characterized as unrelated to the study drug. A total of 4% of all patients withdrew from the study due to adverse events which is lower than the rate of 9.5% found in the recent pooled analysis.[16]

Conclusion

The findings of the current study suggest that alfuzosin 10 mg once-daily provides effective improvements in BPH patients' urinary symptoms and quality of life, while combining an excellent safety profile with the convenience of once-daily administration. It is safe to use in older patients and does not contribute to an increase in ejaculation disorders. □

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