Open Access Journal of Urology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Effect of silodosin on specific urinary symptoms associated with benign prostatic hyperplasia: analysis of international prostate symptom scores in 2 phase III clinical studies

This article was published in the following Dove Press journal:
Open Access Journal of Urology
21 December 2010
Number of times this article has been viewed

Marc C Gittelman[1]
Leonard S Marks[2]
Lawrence A Hill[3]
Weining Volinn[3]
Gary Hoel[3]

[1]South Florida Medical Research, Aventura, Florida, USA; [2]University of California at Los Angeles and Urological Sciences Research Foundation, Los Angeles, California, USA; [3]Watson Laboratories, Salt Lake City, Utah, USA

Purpose: Pooled results from 2 randomized, placebo-controlled, US phase III studies (NCT00224107, NCT00224120) showed that silodosin, a uroselective α-blocker, significantly improved International Prostate Symptom Scores (IPSS) in men with symptomatic benign prostatic hyperplasia (BPH). This analysis evaluated the effect of silodosin on each symptom assessed by IPSS questionnaire.

Materials and methods: Study participants (N = 923) were men aged ≥50 years with IPSS ≥13 and Qmax 4–15 mL/s. They received silodosin 8 mg or placebo once daily for 12 weeks. Patient responses to 7 IPSS questions were collected at weeks 0 (baseline), 0.5, 1, 2, 4, and 12 and scored on a 6-point scale. Efficacy of silodosin versus placebo was assessed by analysis of covariance.

Results: For each symptom, the 2 treatment groups had similar mean baseline scores. Decrease in score from baseline (mean ± standard deviation) to last observation was significantly greater with silodosin than with placebo for all symptoms ($P < 0.005$); symptom improvement with silodosin (versus placebo) was greatest for weak stream (silodosin, −1.1 ± 1.4 versus placebo, −0.5 ± 1.2; $P < 0.0001$) and smallest for nocturia (silodosin, −0.6 ± 1.1 versus placebo, −0.4 ± 1.2; $P = 0.0037$). Compared with placebo, silodosin significantly improved nocturia within 1 week (silodosin, −0.5 ± 1.07 versus placebo, −0.3 ± 1.05; $P = 0.009$) and all other symptoms within 3 to 4 days ($P < 0.01$).

Conclusions: Silodosin significantly improved all BPH-associated symptoms assessed by IPSS questionnaire within the first week of treatment. All improvements were maintained over the 12-week study period.

Keywords: BPH, symptoms, rapid onset, silodosin, α_{1A}-adrenoceptor antagonist

Introduction

Benign prostatic hyperplasia (BPH) is a chronic condition often associated with lower urinary tract symptoms (LUTS). The severity of BPH-related LUTS appears to depend, at least in part, on smooth muscle tone in the prostate and bladder neck, which is mediated by α_{1A}-adrenoceptors.[1,2] α-Blockers (α_1-adrenoceptor antagonists) have become the therapy of choice for patients with BPH-related LUTS because they provide effective symptom relief, are generally well tolerated, and are relatively inexpensive.[3] However, α-blockers vary in their propensity to cause blood pressure-related adverse events, which have been attributed to the blockade of α_{1B}-adrenoceptors in arterial vessels.[2,4,5]

Correspondence: Marc Gittelman
South Florida Medical Research, 21st Century Oncology/UroMedix-Aventura Division, 21150 Biscayne Boulevard, Suite 300, Aventura, FL 33180, USA
Tel +1 305-931-8080
Fax +1 305-931-7024
Email mgittelman@southfloridamedicalresearch.com

submit your manuscript | www.dovepress.com
Dovepress
DOI: 10.2147/OAJU.S15333

Silodosin is an α-blocker that recently has been approved in the United States (US) for treatment of the signs and symptoms of BPH. The pharmacological properties of silodosin are characterized by an exceptionally high selectivity for the α_{1A}- versus α_{1B}-adrenoceptor subtype.[6,7] Moreover, silodosin has been shown to be highly selective for prostatic versus vascular tissue.[8–10] Consistent with this observation, results from phase III clinical studies suggest that silodosin carries minimal risk for orthostatic hypotension and overall has excellent cardiovascular tolerability.[11,12]

Combined efficacy results from the phase III clinical studies showed that silodosin can promote rapid and significant improvement in BPH-associated urinary symptoms and peak urinary flow rate and can substantially improve LUTS-related quality of life.[11] Overall symptom improvement was evaluated on the basis of aggregate patient scores for 7 distinct symptoms addressed by the International Prostate Symptom Score (IPSS) questionnaire. This post hoc analysis determined the effect of silodosin on each of the 7 symptoms.

Materials and methods

Patients and study design

This post hoc analysis of combined data from two 12-week randomized, double-blind, placebo-controlled US studies (NCT00224107, NCT00224120, at www.clinicaltrials.gov) evaluated the efficacy and safety of silodosin for the treatment of signs and symptoms of BPH. The study has been described in detail and overall results published.[11] Briefly, study participants were at least 50 years of age with an IPSS greater than 13, a peak urinary flow rate (Qmax) of 4 to 15 mL/s, and a postvoid residual volume less than 250 mL. Patients first received single-blind treatment with placebo for 4 weeks. Those with at least a 30% decrease in IPSS or an increase in Qmax of 3 mL/s or greater during the placebo run-in period were excluded from randomization. Eligible patients were randomly assigned (1:1) to double-blind treatment with placebo or silodosin 8 mg once daily with breakfast for 12 weeks. The primary end point was the change in IPSS from baseline to the last observation. IPSS was assessed during clinical visits at weeks 0 (baseline), 1, 2, 4, and 12 and by phone interview on day 3 or 4 of the first week (week 0.5).

Analysis

This post hoc analysis evaluated changes in individual symptom scores as assessed by IPSS questions. All randomized study participants (N = 923) who provided baseline data for the primary efficacy variable (total IPSS) were included in the analysis; 466 patients received silodosin and 457 received placebo.[11] The IPSS questionnaire assesses 7 distinct urinary symptoms. Frequency (question [Q2]), urgency (Q4), and nocturia (Q7) are classified as irritative symptoms. Incomplete emptying (Q1), intermittency (Q3), weak stream (Q5), and straining (Q6) are classified as obstructive symptoms. Severity of each symptom is scored on a 6-point scale.[13]

Mean changes in score from baseline with 95% confidence intervals (CIs) were calculated for observed cases at each time point. For additional analyses at week 12, the last post-baseline observation was carried forward to impute missing data. Comparison of treatment effects was performed by analysis of covariance (ANCOVA), with baseline as a covariate. No adjustments were made for multiple statistical comparisons. ANCOVA results were reported as *P* values (for the test of null hypothesis of no difference between treatments). A 2-sided significance level of 5% was applied to all statistical tests.

Results

For each IPSS symptom, mean baseline values for the silodosin and placebo groups were similar (Table 1). Mean baseline scores ranged from 2.2 points for straining to 3.6 points for weak stream (Table 1). For each IPSS symptom, improvement from baseline to week 12 (last observation carried forward) was significantly greater in patients who received silodosin than in those who received placebo (Table 2). The difference between silodosin-related and placebo-related mean changes from baseline to week 12 (last observation carried forward) was smallest for nocturia (0.2 points) and greatest for weak stream (0.6 points) (Table 2).

Table 1 Baseline values for individual symptoms assessed by the IPSS questionnaire

Baseline, mean (SD)	Silodosin (n = 466)	Placebo (n = 457)
Irritative symptoms		
Frequency (Q2)	3.5 (1.10)	3.5 (1.05)
Urgency (Q4)	3.0 (1.32)	3.0 (1.27)
Nocturia (Q7)	2.8 (1.19)	2.8 (1.19)
Obstructive symptoms		
Incomplete emptying (Q1)	3.1 (1.27)	3.1 (1.25)
Intermittency (Q3)	3.1 (1.25)	3.1 (1.31)
Weak stream (Q5)	3.6 (1.16)	3.6 (1.16)
Straining (Q6)	2.2 (1.43)	2.2 (1.37)

Abbreviations: IPSS, International Prostate Symptom Scores; Q, question; SD, standard deviation.

All symptom improvements occurred rapidly. Maximum or close to maximum improvement with silodosin versus placebo was achieved at 0.5 or 1 week (Figure 1). For all IPSS symptoms except nocturia, the difference in improvement between silodosin and placebo treatment groups was significant at week 0.5 (observed cases). For nocturia, the difference between treatments was significant at week 1 (Table 2). Symptom improvement with silodosin, expressed as mean percentage reduction in IPSS from baseline to the last observation, ranged from 16.7% for nocturia to 38.2% for straining. Mean symptom improvement was 20.7% and 24.0% for frequency and urgency, respectively, and 25.2% (incomplete emptying) or greater for all obstructive symptoms (Figure 2). In contrast, mean symptom improvement with placebo was 10.9% (frequency) or less for irritative symptoms and 16.9% (straining) or less for obstructive symptoms (Figure 2).

Discussion

Combined efficacy data from 2 phase III studies with a total of 923 patients demonstrated that once-daily administration of silodosin 8 mg rapidly led to significant improvement

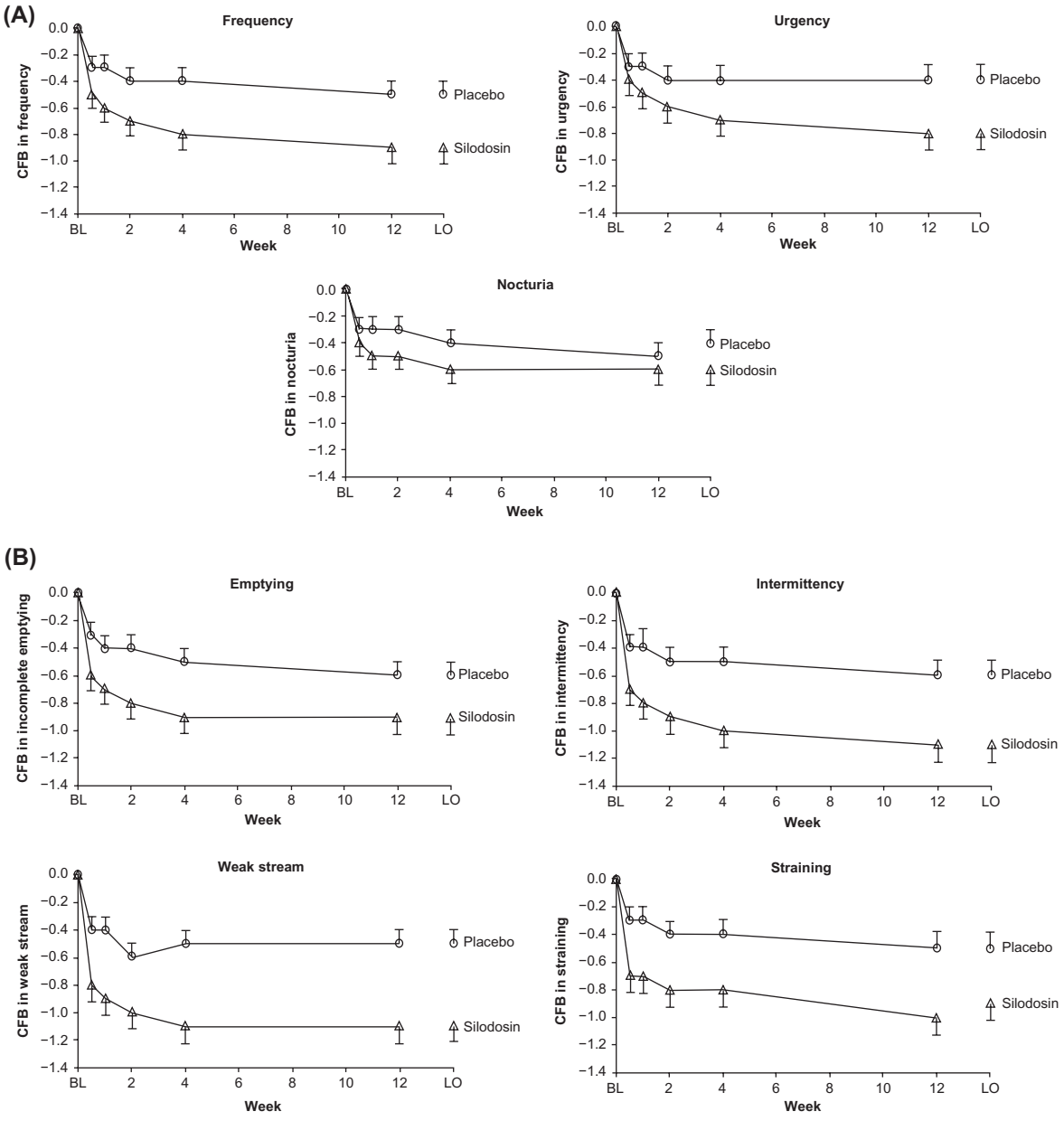

Figure 1 Change from baseline (week 0) in score for specific International Prostate Symptom Score (IPSS) irritative (**A**) or obstructive (**B**) symptoms. Error bars indicate 95% confidence intervals.

Abbreviations: BL, baseline; CFB, change from baseline; LO, last observation after baseline.

Table 2 Differences in treatment-related IPSS changes from baseline[a]

IPSS questions	Week	Change from baseline, mean (SD)		
		Silodosin (n = 466)	Placebo (n = 457)	*P* value[b]
Irritative symptoms				
Frequency (Q2)	0.5	−0.5 (1.08)	−0.3 (0.96)	0.0002
	12	−0.9 (1.34)	−0.5 (1.16)	<0.0001
Urgency (Q4)	0.5	−0.4 (1.21)	−0.3 (1.14)	0.0075
	12	−0.8 (1.36)	−0.4 (1.27)	<0.0001
Nocturia (Q7)	0.5	−0.4 (1.06)	−0.3 (1.03)	0.0968
	1	−0.5 (1.07)	−0.3 (1.05)	0.0091
	12	−0.6 (1.14)	−0.4 (1.15)	0.0037
Obstructive symptoms				
Incomplete emptying (Q1)	0.5	−0.6 (1.14)	−0.3 (0.97)	<0.0001
	12	−0.9 (1.42)	−0.6 (1.22)	<0.0001
Intermittency (Q3)	0.5	−0.7 (1.19)	−0.4 (1.10)	0.0002
	12	−1.1 (1.41)	−0.6 (1.33)	<0.0001
Weak stream (Q5)	0.5	−0.8 (1.29)	−0.4 (1.03)	<0.0001
	12	−1.1 (1.41)	−0.5 (1.21)	<0.0001
Straining (Q6)	0.5	−0.7 (1.16)	−0.3 (1.21)	<0.0001
	12	−0.9 (1.32)	−0.5 (1.24)	<0.0001

Notes: [a]Week 12 (last observation carried forward); [b]Silodosin versus placebo.
Abbreviations: IPSS, International Prostate Symptom Score; Q, question; SD, standard deviation.

in total IPSS and irritative and obstructive symptom subscores[11] and statistically significant improvement (versus placebo) in each of the 7 individual symptoms assessed by the IPSS questionnaire. Except for nocturia, significant improvement was achieved by day 3 or 4 – the earliest assessment time point after treatment initiation. Nocturia improved significantly within 1 week of treatment initiation. A previous analysis of patients' responses to IPSS Q8, which assesses quality of life related to BPH-associated urinary symptoms, showed that patients who received silodosin generally experienced substantially greater improvement in symptom-related quality of life than those who received placebo.[11]

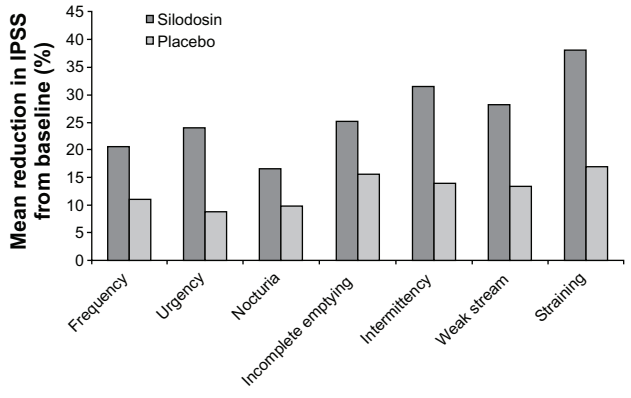

Figure 2 Symptom improvement (mean reduction in International Prostate Symptom Scores [IPSS] from baseline to last observation) as a percentage of baseline values.

Given that IPSS subscores for specific symptoms usually are not reported for individual patients, the clinical significance of some of the improvements demonstrated by our analysis is difficult to gauge. Consideration of whether a treatment effect is clinically meaningful is further complicated by the magnitude of positive placebo effect that is often seen when BPH-related LUTS are assessed by questionnaire.[14] Validation of the original American Urological Association symptom index, which comprises the 7 symptom-related items of the IPSS, showed a variable degree of correlation of each item with the overall score, ranging from 0.54 to 0.83.[13] The study recorded mean changes in scores following prostatectomy of −1.5 (frequency), −1.0 (urgency), −0.8 (nocturia), −1.5 (emptying), −1.8 (intermittency), −2.4 (weak stream), and −1.6 (hesitancy).[13] In light of these data, the mean changes from baseline to week 12 observed in our study appear to be of clinical significance, particularly those observed for all irritative symptoms (Table 2). Reductions over 12 weeks in total IPSS were 6.4 points for silodosin and 3.5 points for placebo.[11] This illustrates a highly significant treatment effect of silodosin in terms of statistical significance compared with the placebo effect[11] and clinically meaningful symptom improvement.[15] In this post hoc analysis, silodosin on average improved each symptom score (except that for nocturia) by 21% to 38% over the baseline score. These values are substantially higher than the corresponding values for placebo (8.8% to 17%).

The results of this analysis support previous observations that silodosin is a fast-acting agent that provides significant BPH symptom relief within a few days. The short duration of the study precludes evaluation of the long-term effect (beyond 12 weeks) of silodosin on each of the 7 IPSS symptoms. In a 40-week open-label extension of the 2 placebo-controlled phase III studies of silodosin, patients who had received silodosin in the double-blind studies on average maintained symptom improvement with continued silodosin treatment during the open-label study. In the open-label study, symptoms also were assessed by IPSS total score and IPSS irritative and obstructive subscores.[12]

Conclusion

Silodosin, a highly uroselective α-blocker, rapidly and significantly improved all irritative and obstructive BPH-related symptoms assessed by the IPSS questionnaire, and the improvements were maintained over the study period of 12 weeks. Together with the previously reported evidence of its efficacy and excellent cardiovascular tolerability,[11,12] our results support consideration of silodosin as a valuable new treatment option for patients with symptomatic BPH.

Acknowledgment

This study was funded by Watson Laboratories, Inc. Scientific Connexions (Newtown, Pennsylvania) provided medical writing and editorial assistance, with funding from Watson Pharma, Inc.

Disclosure

All of the authors have financial and/or other relationships with Watson Laboratories. LS Marks also has a financial and/or other relationship with Allergan, American Medical Systems, Astellas, Bayer, Beckman Coulter, Diagnostic Ultrasound, GTX, GlaxoSmithKline, Gen-Probe, Indevus, Light Sciences Oncology, Lilly/ICOS, Merck, Novartis, Onconome, Pfizer, sanofi-aventis, and Solvay, as well as with NIH, CapCURE, Pardee Foundation, and Seder Foundation.

References

1. Marshall I, Burt RP, Chapple CR. Noradrenaline contractions of human prostate mediated by α_{1A}-(α_{1C}-) adrenoceptor subtype. *Br J Pharmacol*. 1995;115:781–786.
2. Schwinn DA, Roehrborn CG. α_1-Adrenoceptor subtypes and lower urinary tract symptoms. *Int J Urol*. 2008;15:193–199.
3. Lepor H. Alpha blockers for the treatment of benign prostatic hyperplasia. *Rev Urol*. 2007;9:181–190.
4. Hatano A, Takahashi H, Tamaki M, Komeyama T, Koizumi T, Takeda M. Pharmacological evidence of distinct alpha 1-adrenoceptor subtypes mediating the contraction of human prostatic urethra and peripheral artery. *Br J Pharmacol*. 1994;113:723–728.
5. Rudner XL, Berkowitz DE, Booth JV, et al. Subtype specific regulation of human vascular alpha(1)-adrenergic receptors by vessel bed and age. *Circulation*. 1999;100:2336–2343.
6. Shibata K, Foglar R, Horie K, et al. KMD-3213, a novel, potent, α_{1A}-adrenoceptor-selective antagonist: characterization using recombinant human α_1-adrenoceptors and native tissues. *Mol Pharmacol*. 1995; 48:250–258.
7. Yamada S, Okura T, Kimura R. In vivo demonstration of α_{1A}-adrenoceptor subtype selectivity of KMD-3213 in rat tissues. *J Pharmacol Exp Ther*. 2001;296:160–167.
8. Murata S, Taniguchi T, Takahashi M, Okada K, Akiyama K, Muramatsu I. Tissue selectivity of KMD-3213, an α_1-adrenoreceptor antagonist, in human prostate and vasculature. *J Urol*. 2000; 164:578–583.
9. Yamagishi R, Akiyama K, Nakamura S, et al. Effect of KMD-3213, an α_{1a}-adrenoceptor-selective antagonist, on the contractions of rabbit prostate and rabbit and rat aorta. *Eur J Pharmacol*. 1996;315:73–79.
10. Akiyama K, Hora M, Tatemichi S, et al. KMD-3213, a uroselective and long-acting α_{1A}-adrenoceptor antagonist, tested in a novel rat model. *J Pharmacol Exp Ther*. 1999;291:81–91.
11. Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Rapid efficacy of the highly selective α_{1A}-adrenoceptor antagonist silodosin in men with signs and symptoms of benign prostatic hyperplasia: pooled results of 2 phase 3 studies. *J Urol*. 2009;181:2634–2640.
12. Marks LS, Gittelman MC, Hill LA, Volinn W, Hoel G. Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. *Urology*. 2009; 74:1318–1322.
13. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148:1549–1557. Discussion 1564.
14. Madersbacher S, Marszalek M, Lackner J, Berger P, Schatzl G. The long-term outcome of medical therapy for BPH. *Eur Urol*. 2007;51:1522–1533.
15. American Urological Association. Clinical Guidelines: Management of BPH (2003/Updated 2006). Chapter 1: AUA Guidelines on the Management of Benign Prostatic Hyperplasia: Diagnosis and Treatment Recommendations. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=bph. Accessed 2009 May 14.