Silodosin for Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Results of a Phase II Multicenter, Double-Blind, Placebo Controlled Study

J. Curtis Nickel,*,† Michael P. O'Leary,‡ Herbert Lepor,§ Kim E. Caramelli,‡ Heather Thomas,‡ Lawrence A. Hill‡ and Gary E. Hoel‡

From Queen's University, Kingston, Ontario, Canada (JCN), Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts (MPO), New York University School of Medicine, New York, New York (HL), and Watson Laboratories, Salt Lake City, Utah (KEC, HT, LAH, GEH)

Purpose: We evaluated the efficacy and safety of 2 doses of silodosin vs placebo in men with moderate to severe abacterial chronic prostatitis/chronic pelvic pain syndrome who had not been treated previously with α-blockers for chronic prostatitis/chronic pelvic pain syndrome.

Materials and Methods: In this multicenter, randomized, double-blind, phase II study, men 18 years old or older with chronic prostatitis/chronic pelvic pain syndrome, a total National Institutes of Health Chronic Prostatitis Symptom Index score of 15 or greater and a National Institutes of Health Chronic Prostatitis Symptom Index pain score of 8 or greater received 4 or 8 mg silodosin, or placebo once daily for 12 weeks. The primary efficacy end point was change from baseline to week 12 in National Institutes of Health Chronic Prostatitis Symptom Index total score.

Results: Of 151 patients (mean age 48 years) 52 received 4 mg silodosin, 45 received 8 mg silodosin and 54 received placebo. Silodosin 4 mg was associated with a significant decrease in total National Institutes of Health Chronic Prostatitis Symptom Index score (mean $\pm$ SD change –12.1 $\pm$ 9.3) vs placebo (−8.5 $\pm$ 7.2, p = 0.0224), including a decrease in urinary symptom (−2.2 $\pm$ 2.7, placebo −1.3 $\pm$ 3.0, p = 0.0102) and quality of life (−4.1 $\pm$ 3.1, placebo −2.7 $\pm$ 2.5, p = 0.0099) subscores. The 4 mg dose of silodosin also significantly increased Medical Outcomes Study Short Form 12 physical component scores (4.2 $\pm$ 8.1, placebo 1.7 $\pm$ 9.0, p = 0.0492). During global response assessment 56% of patients receiving 4 mg silodosin vs 29% receiving placebo reported moderate or marked improvement (p = 0.0069). Increasing the dose of silodosin to 8 mg resulted in no incremental treatment effects.

Conclusions: Silodosin 4 mg relieved symptoms and improved quality of life in men with chronic prostatitis/chronic pelvic pain syndrome but its efficacy requires confirmation in additional studies.

Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome

GRA = global response assessment

HRQoL = health related quality of life

ITT = intent to treat

LOCF = last observation carried forward

LUTS = lower urinary tract symptoms

NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index

OC = observed cases

RE = retrograde ejaculation

SF-12 = Medical Outcomes Study Short Form 12

Key Words: prostatitis, drug therapy, adrenergic alpha-antagonists, KMD 3213 [supplementary concept]

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Clinical Trial Registration NCT00740779 (www.clinicaltrials.gov).

* Correspondence: Department of Urology, Queen's University, Kingston General Hospital, 76 Stuart St., Kingston, Ontario, Canada K7L 2V7 (telephone: 613-548-2497; FAX: 613-545-1970; e-mail: jcn@queensu.ca).

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SUCCESSFUL management of chronic prostatitis presents a difficult challenge for physicians and patients because of the lack of effective evidence-based, disease specific treatment options. Prostatitis-like symptoms are relatively common in adult men, with an estimated prevalence in North America ranging from 2.2% to 9.7%.[1,2] At least 90% of all cases of chronic prostatitis are attributable to abacterial chronic prostatitis/chronic pelvic pain syndrome.[3] CP/CPPS is characterized by urogenital pain and variable LUTS in the absence of urinary tract infection,[4] and the associated symptoms can be debilitating.[5–7] A cross-sectional study by the Chronic Prostatitis Collaborative Research Network of 278 men using validated HRQoL indices such as the quality of life impact subscore of the NIH-CPSI and SF-12 demonstrated that CP/CPPS is associated with impairment of disease specific as well as general mental and physical HRQoL.[6]

Of the available treatment options for CP/CPPS none has consistently demonstrated efficacy in clinical studies.[5] A common treatment of CP/CPPS is the administration of α_1-adrenergic receptor antagonists (α-blockers) with proven efficacy in relieving LUTS associated with BPH. Because these agents have the ability to block α_1-mediated signaling in various physiological systems, including the lower urinary tract and the central nervous system,[8] they may potentially ameliorate CP/CPPS associated LUTS and pain by mitigating peripheral and central neuropathy and/or improving voiding functions.[9] However, results from clinical studies that evaluated the effects of α-blockers in patients with CP/CPPS have been inconclusive and contradictory. A number of randomized, placebo controlled, phase II studies of terazosin, alfuzosin and tamsulosin showed promising efficacy.[10–12] In addition, results of a systematic review and meta-analysis of data from 11 CP/CPPS randomized placebo controlled studies that met strict inclusion criteria indicated that the use of α-blockers provided a statistically significant clinical benefit.[13] However, 2 multicenter, randomized, placebo controlled studies included in this analysis, 1 of tamsulosin and the other a large study of alfuzosin, failed to demonstrate significant symptom improvement in patients with CP/CPPS.[14,15]

Silodosin, a highly selective α_{1A}-adrenoceptor antagonist, is an effective treatment approved by the United States Food and Drug Administration for men with BPH associated LUTS.[16,17] The present pilot study evaluates the efficacy and safety of 2 doses of silodosin (4 and 8 mg once daily) compared with placebo in patients with moderate to severe abacterial CP/CPPS not previously treated with α-blockers for this condition.

MATERIALS AND METHODS

Study Design

This 12-week, multicenter, double-blind, placebo controlled, phase II study (ClinicalTrials.gov identifier NCT00740779) was conducted between September 2008 and October 2009. The protocol was approved by an institutional review board before study initiation, and the study was conducted in accordance with the Declaration of Helsinki and the United States Code of Federal Regulations. The primary end point was change from baseline to week 12 in the NIH-CPSI total score. Secondary end points included safety; change from baseline in the NIH-CPSI pain, urinary and HRQoL subscores; and change from baseline in SF-12 physical and mental component scores. In addition, responder analyses were conducted for GRA and NIH-CPSI at week 12. GRA responders were defined as subjects who indicated markedly or moderately improved on the 7-point GRA scale. NIH-CPSI responders were defined as subjects who had a decrease of 6 or more points in the NIH-CPSI total score.[18,19]

Sample size calculation was based on published values for treatment and placebo associated changes from baseline in NIH-CPSI total.[14] A difference of 5.2 between treatment groups was calculated as the detectable difference if $\alpha = 0.025$, $\sigma = 7.3$, power = 0.9 and there were 50 subjects in each treatment group.

Participants

Study participants were recruited from 32 centers across the United States, including mostly community based practices and a few university medical centers. Eligible participants were men 18 years or older with CP/CPPS who had a total NIH-CPSI score of at least 15, and a NIH-CPSI pain score of at least 8 at screening, had experienced pain in the pelvic region for at least 3 months before screening and previously had not received α-blocker therapy for CP/CPPS. Patients were excluded from the study if they had participated in a study of an investigational agent within the last 30 days, had experienced 2 or more urinary tract infections within the previous 12 months, or had medical conditions potentially precluding safe study participation or affecting study results such as significant postural hypotension, abnormal test results of digital rectal examination (except benign prostate enlargement), prostate specific antigen greater than 10.0 ng/ml and liver or renal insufficiency. Patients treated with medications that might confound study results, such as 5α-reductase inhibitors, tricyclic antidepressants, androgens and ketoconazole, had to undergo appropriate washout periods to be eligible. All eligible patients provided informed written consent.

Treatments and Assessments

Patients were randomized 1:1:1 to receive 4 or 8 mg silodosin, or placebo once daily with food at breakfast for