0022-5347/03/1692-0592/0
THE JOURNAL OF UROLOGY®

Vol. 169, 592–596, February 2003
Printed in U.S.A.
DOI: 10.1097/01.ju.0000042927.45683.6c

TERAZOSIN THERAPY FOR CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME: A RANDOMIZED, PLACEBO CONTROLLED TRIAL

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ABSTRACT

Purpose: We evaluate terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome.

Materials and Methods: The study included 100, 20 to-50-year-old subjects who met the consensus criteria for chronic prostatitis/chronic pelvic pain syndrome and had not received previous α-blockers. Subjects were randomized to receive terazosin with dose escalation from 1 to 5 mg. daily or placebo for 14 weeks. The primary criterion for response was scoring 2 or less ("delighted-to-mostly satisfied") on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) quality of life item. The secondary criterion for response was greater than 50% reduction in NIH-CPSI pain score at 14 weeks. Other outcomes included total and NIH-CPSI domain scores, International Prostate Symptom Score, peak urinary flow rate, post-void residual urine and adverse effects.

Results: Using the primary criterion 24 of 43 evaluable subjects (56%) responded in the terazosin group compared to 14 of 43 (36%) in the placebo group ($p = 0.03$). Using the secondary criterion 26 of 43 subjects (60%) responded in the terazosin group compared to 16 of 43 (37%) in the placebo group ($p = 0.03$). The terazosin group had greater reductions ($p < 0.05$) in NIH-CPSI total score, individual domain scores and International Prostate Symptom Score than the placebo group. There was no difference in peak urinary flow rate or post-void residual. In the terazosin group 18 patients (42%) had side effects compared to 9 (21%) in the placebo group ($p = 0.04$).

Conclusions: Terazosin proved superior to placebo for patients with chronic prostatitis/chronic pelvic pain syndrome who had not received α-blockers previously.

KEY WORDS: prostate, chronic disease, pelvic pain, prostatitis, drug therapy

Chronic prostatitis/chronic pelvic pain syndrome afflicts 2% to 10% of men.[1,2] It decreases quality of life[3] and causes major economic losses.[4] Despite its importance as a cause of morbidity, there are only limited evidence based treatment recommendations. No drug or surgical procedure has proven to have lasting benefits. During the last 30 years many treatments have been investigated in pilot studies, including α-blockers, antibiotics, nonsteroidal anti-inflammatory agents, pentosan polysulfate, allopurinol, quercetine, finasteride, trice-weekly ejaculation, transurethral and "subtotal" prostate resection, transurethral incision of the prostate, balloon dilation, hyperthermia, transurethral needle ablation and radical prostatectomy.[5] This wide variety of treatments clearly reflects patient and clinician frustrations.

Because symptoms of chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia (BPH) overlap somewhat, investigators hypothesized that drugs effective for BPH might help some patients with chronic prostatitis/chronic pelvic pain syndrome. Urodynamic studies suggested that some patients have functional obstruction at the bladder neck or external urethral sphincter.[6] Several studies demonstrated that α-blockers improved chronic prostatitis/chronic pelvic pain syndrome symptoms. Osborn et al reported a 3-arm crossover study with placebo, baclofen and phenoxybenzamine, a nonselective α-blocker.[7] This study was difficult to interpret because it involved baclofen, a striated muscle relaxant, and there was no washout period among the treatment arms. Neal and Moon reported symptomatic improvement with terazosin, a selective α-blocker, but it was difficult to discern the true treatment benefits from the natural history of chronic prostatitis in this open label study.[8] de la Rossette[9] and Lacquaniti[10] et al reported randomized, placebo controlled studies using selective α-blockers. de la Rossette et al studied only 25 patients,[9] while Lacquaniti et al did not specify their diagnostic criteria.[10] Despite these limitations, α-blockers are among the most frequently prescribed drugs for chronic prostatitis. We determine the effectiveness of terazosin therapy for patients who met the National Institutes of Health (NIH) consensus definition for chronic prostatitis/chronic pelvic pain syndrome in a randomized, placebo controlled study.

MATERIALS AND METHODS

Subject selection. Patients who met the clinical criteria for chronic prostatitis/chronic pelvic pain syndrome[11] were recruited during a prostatitis awareness campaign targeting a diverse population in Northern Malaysia[2] and from those seeking treatment at participating hospitals. Eligibility requirements included age between 20 and 50 years, score of 1 or greater on items 1 and 2 (presence of pelvic pain and quality of life) and 4 or greater on item 9 ("mostly dissatisfied," "unhappy" or "terrible") of the National Institutes of

Accepted for publication August 16, 2002.
Supported by an unrestricted grant from Abbott Laboratories, Malaysia.
* Financial interest and/or other relationship with Abbott Laboratories.
† Requests for reprints: Department of Urological Surgery, University of Washington School of Medicine, VA Puget Sound Health Care System, 1660 S. Columbian Way, Seattle, Washington 98108.

Health Chronic Prostatitis Symptom Index (NIH-CPSI),[12] symptoms for 3 or greater months and a desire to be treated. Potential subjects were excluded from study if they met criteria for chronic bacterial prostatitis after lower urinary tract localization studies,[13] had previous urinary tract infection or a uropathogen documented within the last year, had significant medical problems, had any NIH consensus exclusion criteria,[11] had been treated with α-blockers previously or were taking medications that could affect lower urinary tract function.

Study design and procedures (fig. 1). The protocol adhered to the International Committee of Harmonization guidelines for Good Clinical Practice and was approved by a Joint School of Pharmaceutical Sciences, University of Science Malaysia-Penang Hospital Committee on Clinical Studies. Each subject had a baseline NIH-CPSI score, International Prostate Symptom Score (I-PSS),[14] peak urinary flow rate and post-void residual urine. In addition, prostate size was measured by ultrasound and serum prostate specific antigen (PSA) was determined (normal range less than 4 ng./ml.).

Subjects were assigned following a random number table to receive either terazosin or placebo. The terazosin dosage was 1 mg. for 4 days, 2 mg. for 10 days and 5 mg. for 12 weeks. Placebo tablets compounded from lactose had a similar appearance to terazosin tablets. Subjects were assessed for treatment outcomes at weeks 2, 6 and 14. Patients were not permitted to take other medications for chronic prostatitis/chronic pelvic pain syndrome or those that affect the lower urinary tract function during the study. They were asked to report new medications at each clinic visit.

Outcomes. Because prostatitis is associated with substantial reduction in quality of life,[3] the primary outcome measure was the NIH-CPSI quality of life item, and the primary criterion for response was a score of 0 to 2 ("delighted" to "mostly satisfied") at week 14 (compared to 4 to 6, "mostly dissatisfied" to "terrible" at baseline). Since all patients had pelvic pain, the secondary criterion for response was a greater than 50% reduction in the baseline NIH-CPSI pain domain score. Other outcomes included mean NIH-CPSI total score and the individual domain scores, I-PSS, peak urinary flow rate and post-void residual between treatment groups. Also during each followup visit subjects were asked if they experienced any adverse effects.

The NIH-CPSI, a prostatitis specific symptom index developed and validated in North America,[12] evaluates 3 domains (pain, urinary and quality of life impact), and has been recommended as an outcome measure in research trials.[5] The I-PSS, peak urinary flow rate and post-void residual were analyzed because patients with chronic prostatitis/chronic pelvic pain syndrome often experience urinary tract symptoms that terazosin might ameliorate. The NIH-CPSI and the I-PSS were translated into other major languages (Malay and Chinese) spoken by the local population with the accuracy verified by back translation into English as described

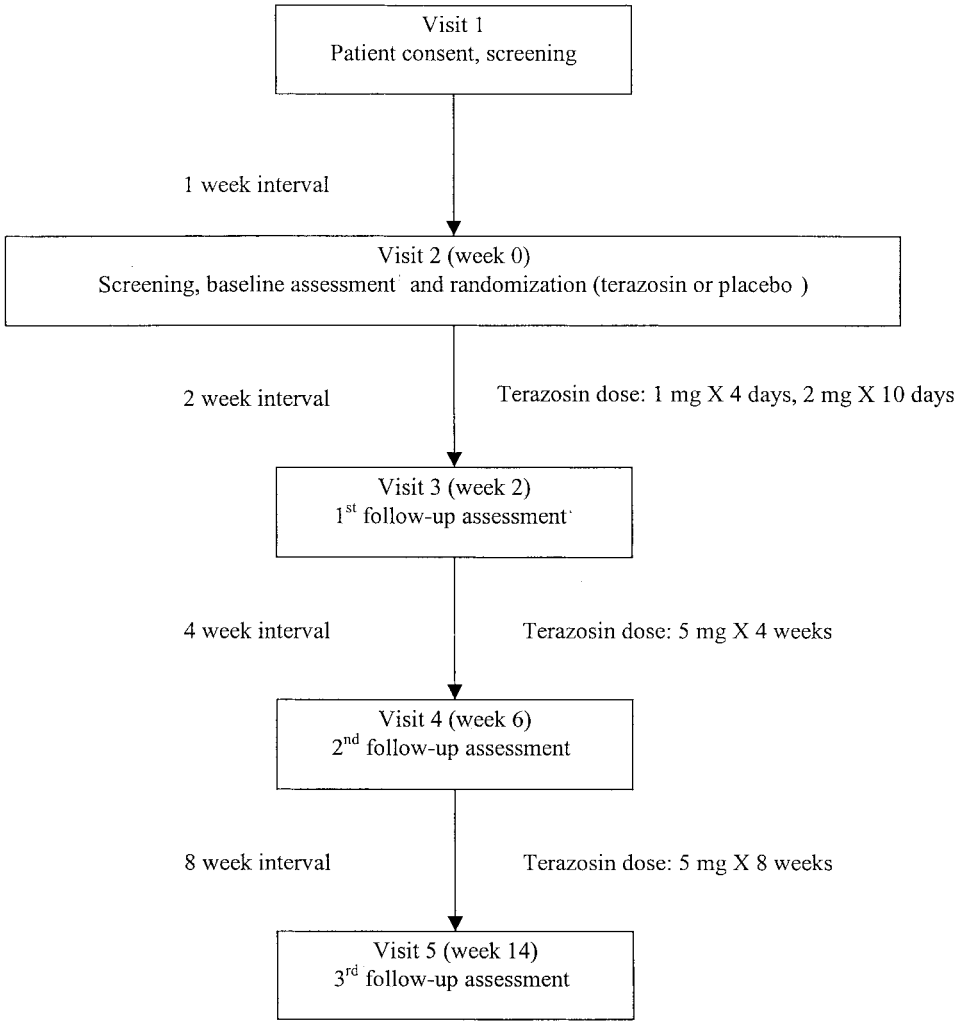

FIG. 1. Primary (NIH-CPSI quality of life item), secondary (NIH-CPSI pain domain) and other (NIH-CPSI urinary and quality of life impact domains and total score, I-PSS, peak urinary flow rate, post-void residual and adverse effects) outcomes were measured at baseline and each followup visit. Placebo tablets had similar appearance to terazosin tablets at all dose levels.

previously.[2] Peak urinary flow rate was measured using a weight transducer flow meter with values considered evaluable only if the voided volume was at least 150 ml. Post-void residual was measured by transabdominal ultrasound.

Statistical analyses. A sample size of 80 subjects (40 per arm) was powered for a difference of at least 30% between the terazosin ($p_1 = 60\%$) and placebo groups ($p_2 = 30\%$) with a 95% CI ($\alpha = 0.05$) and statistical power of 80% ($\beta = 0.2$).[15] Allowing for 20% dropout the enrollment goal was 100 subjects.

Prostate size and PSA at baseline were compared using the Student t test, and for age the Mann-Whitney U statistic was calculated. Chi-square statistics were calculated to compare racial distributions, duration of symptoms, as well as proportion of responders between treatment groups. Analysis of variance procedures for a 2-factorial, split-plot experimental design[16] were used to evaluate outcome parameters between the treatment groups. Within group changes for each parameter were assessed using the extended Tukey test, and $p < 0.05$ was considered significant.

RESULTS

Demographics and clinical presentation. Between April 1, 2000 and September 30, 2001, 100 subjects were recruited for study. The terazosin and placebo groups were comparable at baseline in all variables assessed (tables 1 and 2). There were more subjects with a symptom duration of 3 to 6 months in the terazosin group compared to the placebo group, while the reverse was true for symptom duration of 7 to 12 months and greater than 12 months. However this difference was not statistically significant. The terazosin group also appeared to have higher mean NIH-CPSI domain and I-PSS scores compared to the placebo group but these differences were not significant and were not reflected in the median scores. Of the 100 subjects 86 completed all followup assessments. The dropout rate was 14% in both groups. Reasons for dropout included "did not have time" (5 patients), "moved to another town/country" (4) and "ineffective treatment" (2). We could not contact the 3 remaining subjects.

Efficacy. Figure 2 shows a box plot of the NIH-CPSI quality of life score for patients in the terazosin and placebo groups at baseline and all followup visits. Median quality of life score decreased to 2 in the terazosin group, and decreased to 4 and plateaued after week 2 in the placebo group. Of 43 subjects 24 (56%) responded in the terazosin group and 14 of 43 subjects (33%) responded in the placebo group (chi square 4.7, df 1, $p = 0.03$, fig. 2). Of 43 subjects 26 (60%) in the terazosin group had greater than 50% reduction in baseline pain score at week 14 compared to 16 of 43 subjects (37%) in the placebo group (chi square 4.6, df 1, $p = 0.03$).

The terazosin group had a 57% reduction in mean NIH-CPSI total score (25.1 ± 7.1 at baseline to 10.8 ± 9.0 at week 14, $p < 0.001$) versus a 37% decrease in the placebo group (27.2 ± 7.7 at baseline to 17.0 ± 12.1 at week 14, $p < 0.001$). The 57% reduction in NIH-CPSI total score in the terazosin group was 1.5-fold greater than the 37% reduction in the placebo group after 14 weeks ($p = 0.01$). Improvements in NIH-CPSI pain, urinary and quality of life impact domains in the terazosin group were each significantly greater ($p < 0.05$) than those in the placebo group after 14 weeks.

The terazosin group experienced a 62% reduction in mean I-PSS (12.1 ± 9.8 at baseline to 4.6 ± 6.0 at week 14) than the 35% in the placebo group (14.1 ± 2.3 at baseline to 9.1 ± 3.9 at week 14, $p = 0.03$). There was no difference between the groups in regard to peak urinary flow rate (terazosin 15.4 ± 6.9 to 18.7 ± 8.1 ml. per second in terazosin and placebo 18.1 ± 2.3 to 19.7 ± 3.9 ml. per second). There was also no difference in post-void residual (terazosin 24.8 ± 25.6 to 17.1 ± 20.8 ml. and placebo 20.6 ± 24.5 to 16.0 ± 18.1 ml.).

In the terazosin group 18 of 43 (42%) patients complained of side effects compared to 9 of 43 patients (21%) in the placebo group (chi-square 4.4, df 1, $p = 0.04$). Side effects in the terazosin and placebo groups included dizziness (7 versus 2 patients), asthenia (7 versus 3), postural hypotension (1 versus 0), palpitation (1 versus 2), flu syndrome (1 versus 0), drowsiness (2 versus 1), headache (2 versus 2) and rashes (0 versus 1). No patient withdrew from study because of side effects.

Responders in the terazosin group had lower NIH-CPSI pain scores at baseline (mean 10.5, SD 2.9) than nonresponders (mean 13.1, SD 3.5, $p = 0.01$). Malays were most likely to respond (78.6%) followed by Chinese (64.3%), Indians (50.0%) and other races (11.1%) (chi square 10.7, df 3, $p = 0.01$). Parameters that were not associated with response included age, baseline urinary and quality of life impact domains, NIH total score, I-PSS, peak urinary flow rate, post-void residual and symptom duration. In contrast, within the placebo group there was no difference between responders and nonresponders in any parameter assessed.

DISCUSSION

Terazosin proved superior to placebo therapy for patients with chronic prostatitis/chronic pelvic pain syndrome who had a quality of life score of 4 or greater (mostly dissatisfied) and had not received previous treatment with α-blockers. Because prostatitis reduces quality of life substantially,[3] global quality of life assessment was selected as the primary outcome measure. After 14 weeks 56% of subjects in the terazosin group had a quality of life at least "mostly satisfied" (primary response criterion) compared to 33% in the placebo group. Of subjects in the terazosin group 60% had a greater than 50% reduction in the NIH-CPSI pain score (secondary response criterion) compared to 37% in the placebo group ($p = 0.03$). Other outcomes were consistent with these findings. Improvements in the mean NIH-CPSI total and domain scores as well as the I-PSS at the final visit were all greater in the terazosin group ($p < 0.05$). Patients who had lower baseline pain scores or were of ethnic Malay or Chinese origin were more likely to respond to terazosin. Our data also suggest that 5 mg. terazosin should be given for at least 14

TABLE 1. *Comparison of baseline demographic and clinical characteristics of patients*

Characteristics	Terazosin	Placebo	p Value
No. pts.	43	43	
Median age (range)	36 (24–49)	35 (20–50)	0.68 (Mann Whitney U)
% Racial distribution:			0.68 (chi-square)
Chinese	32.6	37.2	
Malay	32.6	20.9	
Indian	14.0	16.3	
Others	20.6	25.6	
% Symptom duration (mos.):			0.32 (chi-square)
3–6	39.5	30.2	
7–12	46.5	53.5	
Greater than 12	14.0	16.3	
Mean prostate size (SD)	13.7 (4.2)	13.7 (3.5)	0.99 (t test)
Mean ng./ml. PSA (SD)	0.67 (0.64)	0.96 (1.89)	0.06 (t test)

TABLE 2. *Other outcome measures*

Wk.	Mean (SD)/Median					Mean (SD)	
	NIH-CPSI Total Score (item 1 to 9)	NIH-CPSI Pain (item 1 to 4)	NIH-CPSI Urinary (items 5 and 6)	NIH-CPSI Quality of Life Impact (items 7 to 9)	I-PSS	Peak Urinary Flow Rate (ml./sec.)*	Post-Void Residual (ml.)
Terazosin:							
0†,‡	25.1 (7.1)/27	11.7 (3.4)/12	5.1 (3.7)/5	8.3 (2.6)/9	12.1 (9.8)/11	15.4 (6.9)	24.8 (25.6)
2§	16.1 (7.2)/16	7.0 (4.3)/7	3.1 (2.6)/3	5.8 (2.8)/6	7.8 (6.2)/6	17.6 (7.4)	21.3 (24.0)
6	13.4 (7.6)/12	6.4 (5.2)/7	2.5 (2.8)/2	4.3 (3.3)/4	6.5 (6.6)/5	17.7 (7.5)	21.5 (21.4)
14	10.8 (9.0)/10	5.2 (5.7)/3	2.0 (2.8)/0	3.6 (3.4)/3	4.6 (6.0)/2	18.7 (8.1)	17.7 (20.8)
Placebo:							
0†	27.2 (7.7)/27	12.6 (3.7)/13	5.4 (3.7)/5	8.9 (2.3)/9	14.1 (9.3)/14	18.1 (8.3)	20.6 (24.5)
2	20.4 (9.7)/19	9.3 (5.3)/9	4.4 (3.5)/5	6.6 (3.5)/6	10.9 (8.7)/11	18.9 (7.2)	19.6 (20.5)
6	18.1 (10.2)/17	7.9 (5.8)/8	4.1 (3.6)/4	5.6 (3.5)/6	10.0 (9.0)/7	18.5 (7.1)	16.2 (22.0)
14	17.0 (12.1)/17	7.8 (6.7)/8	3.6 (3.6)/4	5.5 (3.9)/6	9.1 (8.7)/6	19.7 (7.6)	16.0 (18.1)

* Voided volume of at least 150 ml.).
† No significant difference between the terazosin and placebo groups with regard to baseline outcome parameters.
‡ Terazosin dose was escalated from 1 mg. daily for 4 days to 2 mg. daily for 10 days.
§ From week 2 and after terazosin dose was 5 mg. daily.

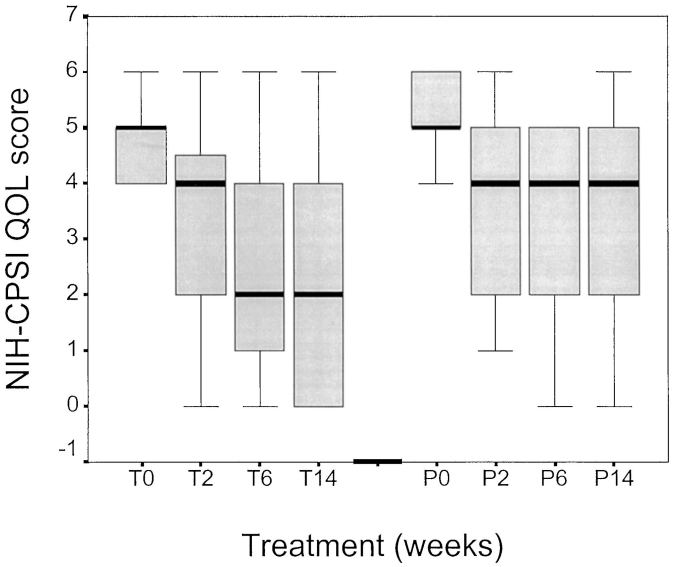

FIG. 2. Box plot of NIH-CPSI quality of life (*QOL*) score (primary outcome measure) of subjects who completed treatment with either terazosin or placebo (43 in each arm). Bold line represents median score, upper and lower bounds of box 25th to 75th percentiles, respectively, and bars maximum and minimum scores. At clinical end point of 14 weeks 56% responded to therapy (NIH-CPSI quality of life score 0 to 2, "mostly satisfied to delighted") in terazosin group compared to 33% in placebo group (chi-square 4.7, df 1, $p = 0.03$). *T0, T2, T6, T14*, terazosin treatment at weeks 0, 2, 6 and 14. *P0, P2, P6, P14*, placebo treatment at weeks 0, 2, 6 and 14.

weeks to obtain maximum response (fig. 2 and table 2). These findings agree with previous data suggesting that terazosin and perhaps other α-blockers may have a role in treating chronic prostatitis/chronic pelvic pain syndrome, especially in patients who have not been treated previously with these drugs. Our findings also agree with earlier recommendations that α-blockers merit priority for research in chronic prostatitis/chronic pelvic pain syndrome.[5] Based on the primary and secondary response criteria, the results obtained were quite similar (56% and 60% for the terazosin group), suggesting that pelvic pain was an important determining factor in quality of life, consistent with published data that pelvic pain symptoms represent the predominant symptoms of chronic prostatitis/chronic pelvic pain syndrome.[4, 17]

Terazosin improved lower urinary tract symptoms as documented by decreases in the NIH-CPSI and I-PSS. However, there was no difference in the mean peak urinary flow rate or post-void residual values between the terazosin and placebo groups. It is possible that terazosin improved the prostatitis symptoms by mechanisms other than changes in bladder outlet function. Mayo et al found that few patients referred to their prostatitis clinic had bladder outlet obstruction.[18] Urodynamic assessments of select patients in this study revealed no patients with bladder outlet obstruction (data not shown). α Receptors are reported to be present in the human bladder[19] and may mediate relief of irritative urinary symptoms experienced by subjects in this study. Also, an animal study showed that α receptors exist in the spinal cord and ganglia, suggesting that terazosin may affect these areas in the central nervous system.[20]

Differences in the response rate of subjects from different ethnic groups in our study suggest the possibility that there might be more than 1 mechanism involved in the etiology of chronic prostatitis/chronic pelvic pain syndrome. For example, the lowest rate of responders was among subjects of other ethnic origins, mainly foreign unskilled workers. It is possible that they experienced greater stress that might exacerbate prostatitis symptoms.

Our findings emphasize the importance of a placebo group and double-blind assessment in studies of chronic prostatitis/chronic pelvic pain syndrome. The study was powered to detect a difference between the terazosin and placebo groups despite the high placebo effect observed (33%). The population included carefully selected subjects who met the NIH consensus criteria for chronic prostatitis/chronic pelvic pain syndrome. No subject was older than 50 years or had been treated previously with α-blockers. We used the NIH-CPSI and other established outcome measures for patient assessment. As terazosin was tittered to 5 mg. daily and given for 14 weeks, we do not know the efficacy of higher doses or longer duration of treatment. We also do not know if terazosin changed the natural history of chronic prostatitis/chronic pelvic pain syndrome.

CONCLUSIONS

Terazosin proved superior to placebo therapy for chronic prostatitis/chronic pelvic pain syndrome as documented by significant reductions in NIH-CPSI quality of life and pain scores. In addition, terazosin also reduced the urinary and quality of life impact scores of the NIH-CPSI as well as the I-PSS. Our results support use of terazosin in patients with chronic prostatitis/chronic pelvic pain syndrome who have not been treated previously with α-blockers. These findings support the need for further studies to determine the clinical characteristics of patients most likely to respond to α-blockers, and the optimal drug, dose and duration of therapy.

Drs. Chong Siang Tan, Chek Lang Ding, Chit Sin Loh and Keong Tatt Foo provided advice, support and comments; Dr. Prashanta K. Das and Mr. Leng Chee Leong provided laboratory support, and Mr. Kok Heng Heng, Ms. Siew Kin Yang,

Ms. Nohana Arif, Ms. Colina Wong and Ms. Jayalakshmi Nagor assisted with the clinical work.

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