

The three As of chronic prostatitis therapy: antibiotics, α -blockers and anti-inflammatories. What is the evidence?

J. CURTIS NICKEL

Department of Urology, Queen's University, Kingston, Ontario, Canada

Accepted for publication 20 August 2004

KEYWORDS

prostatitis, chronic pelvic pain syndrome, antibiotics, α -blockers, anti-inflammatories

INTRODUCTION

The three most common medications prescribed by physicians for treating chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) include antibiotics, α -blockers and anti-inflammatories [1]. Until recently there has been no conclusive evidence to judge their efficacy in ameliorating CP/CPPS symptoms in clinical practice [2]. The general acceptance of a definition and classification system for CP was reported in [3], and the development of a validated outcome symptom index in [4], the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI); this has stimulated much clinical research to evaluate the most common treatments used in CP/CPPS.

CP/CPPS or NIH Category III CP is defined as the presence of genitourinary pain in the absence of a defined uropathogen, using standard culture techniques [3]. For clinical trials, a further list of exclusions has been suggested that can be adapted for the specific indication being tested [5,6]. The NIH-CPSI measures the three major domains of prostatitis, i.e. pain (0–21), urinary symptoms (0–10) and impact on quality of life (0–12), for a total score of 0–43 [4]. A treatment effect between active therapy and placebo groups (a difference between the groups compared to baseline) of 4 points appears to be clinically significant, while in individual patients a 25% or 6-point decrease in total NIH-CPSI is a clinically perceptible improvement (patients achieving this improvement can be categorized as 'responders') [7,8]. These advances have now generated the clinical data and evidence needed to evaluate

the use of antibiotics, α -blockers and anti-inflammatories in CP/CPPS.

ANTIBIOTICS

Antibiotics are the most common first-line therapy for all the prostatitis syndromes [1,2], despite the consistent finding that only \approx 5% of these men have definite bacterial infection. Uncontrolled studies [9] suggested that antibiotics significantly improve the symptom complex associated with the very common diagnosis of CP/CPPS. A European consensus report concluded that a trial of antibiotic therapy for category IIIA inflammatory CPPS was justified, but not for category IIIB non-inflammatory CPPS [10], although the recommendations were not based on strong evidence. This weak evidence and subsequent recommendations for antibiotic use in CP/CPPS have significant ramifications for clinical practice.

The Canadian Prostatitis Research Group undertook the first multicentre, randomized placebo-controlled trial to evaluate the safety and efficacy of antibiotic therapy compared to placebo in men with a clinical diagnosis of CP/CPPS [11] (Table 1 [11–18]). Men with an NIH diagnosis of CP/CPPS (specifically, no infection localized to prostate) were randomized to levofloxacin (45 men) or placebo (35) for 6 weeks. Both groups had a progressive improvement in symptoms, measured by the NIH-CPSI, but the difference in response was not statistically or clinically significant at the end of treatment (6 weeks) or follow-up visits (12 weeks). At 6 and 12 weeks the levofloxacin group had a decrease of 5.4 and 5.6 points, respectively, in the mean total NIH-CPSI from baseline, compared to a decrease of 2.9 and 3.1 points for the placebo group (the treatment effect at 6 weeks was -3.2 ; $P > 0.05$). A third of patients in the antibiotic group were

considered responders (25% decrease in NIH-CPSI), compared with 31% of the placebo group ($P > 0.05$). This pilot placebo-controlled study was the first to show that a trial of antibiotic therapy in men diagnosed with CP/CPPS resulted in an improvement in symptoms that was not significantly different from placebo at the end of treatment or follow-up.

What are the clinical implications of this study? The study was too small to detect a differential treatment effect in patients who have been recently symptomatic (in the described study, the mean duration of symptoms was 5.5–7.6 years), in Category IIIA (inflammatory) compared to Category IIIB (non-inflammatory) CPPS, or in patients who had not been previously treated with antibiotics (in that study, 80–83% had been). Alexander *et al.* [12] recently reported initial findings from the NIH Chronic Prostatitis Collaborative Research Network Randomized Controlled Trial comparing ciprofloxacin, tamsulosin and the combination of ciprofloxacin and tamsulosin, with placebo. In this 6-week study, which enrolled very chronic, heavily pre-treated patients with CP/CPPS, it was reported that men treated with ciprofloxacin (\pm tamsulosin) fared no better than patients treated with placebo. The final report describing the study should be available within the next year.

α -BLOCKERS

CP/CPPS is characterized by pain and discomfort in the perineum, pelvis, testicles and penis, and is associated with obstructive and irritative voiding symptoms. Dysfunctional high-pressure voiding (and possibly, related intraprostatic ductal reflux) is thought to be implicated in the pathogenesis of CP/CPPS. α -Blockers, which have become the cornerstone of treating the voiding symptoms of BPH, have become a

TABLE 1 Randomized placebo-controlled trials assessing antibiotics, α -blockers and anti-inflammatories in CP/CPPS, using the accepted NIH definition of the condition and the validated NIH-CPSI as the outcome measure

Drug [ref]	Date	Weeks	N patients		Treatment effect*	Response rate	
			Active	Placebo		Active	Placebo
Levofloxacin [11]	2003	6	45	35	-3.2	33	31
Ciprofloxacin† [12]	2004	6	98	98	-1.3	16	23
Terazosin [13]	2003	14	43	43	-4.1	56	36
Alfuzosin [14]	2003	24	17	20	-6.1	65	24
Tamsulosin [15]	2004	6	27	30	-3.6	52	33
Tamsulosin‡ [12]	2004	6	98	98	0.4	17	22
Rofecoxib [16]	2003	6		59			40
25 mg			53		-0.7	46	
50 mg			49		-2.0	63	
Quercetin [17]	1999	4	15	13	-6.5	67	20
Pentosan polysulphate [18]	2003	16	51	49	-2.7	37	18

*Difference between treatment and placebo groups vs baseline; †Ciprofloxacin (\pm tamsulosin) vs no ciprofloxacin (\pm tamsulosin) in a 2×2 factorial designed randomized controlled trial (initial results [12]); ‡Tamsulosin (\pm ciprofloxacin) vs no tamsulosin (\pm ciprofloxacin) in a 2×2 factorial designed randomized controlled trial (initial results [12]).

therapeutic tool for the physician treating CP/CPPS.

There have been many uncontrolled reports and several randomized placebo-controlled studies of α -blockers ameliorating the symptoms of CP (chronic nonbacterial prostatitis and prostatodynia). It was very difficult to assess the response of patients to α -blockers from these early trials. The researchers used different definitions of the prostatitis symptoms, variable inclusion/exclusion criteria, and did not have available a validated outcome variable, e.g. a symptom index. Studies designed and reported since the NIH definition of CP/CPPS was accepted [3], and the NIH-CPSI was developed and validated [4], have allowed a critical examination of the efficacy of these agents in CP/CPPS.

Cheah *et al.* [13] randomized 86 patients with chronic prostatitis to either terazosin or placebo for 14 weeks. Patients on terazosin had a reduction by half in the mean symptom score, vs 37% in the placebo-treated group ($P = 0.001$). Terazosin resulted in a modest but significant improvement in all domains of the NIH-CPSI (treatment effect for total NIH-CPSI, -4.1 ; $P < 0.05$).

Mehik *et al.* [14] followed 19 patients randomized to 6 months of alfuzosin

treatment and 20 to 6 months of placebo therapy, and both groups were followed for a further 6 months after discontinuing the active or placebo medication. Patients in the alfuzosin group had significantly better amelioration of symptoms than in the placebo group, and that was evident at 4 months, becoming even more clinically significant by 6 months (treatment effect, -6.1 ; $P = 0.01$). At 6 months, two-thirds of patients on alfuzosin were rated as responders, vs 24% of the placebo group (a responder being categorized as any patient with a 25% decrease in total NIH-CPSI from baseline). At the end of the 6-month active-treatment phase, patients on placebo deteriorated quickly back to their baseline level. Patients on alfuzosin also deteriorated, but not to the same extent, and were still better at 12 months than patients who had been previously treated with placebo. However, this important trial shows that long-term α -blocker therapy is required before there is significant amelioration of symptoms, and that α -blocker therapy may have to be continued for longer than was originally thought (>6 months).

Nickel *et al.* [15] randomized 57 men with CP/CPPS to tamsulosin 0.4 mg or placebo, after a 2-week placebo run-in, and followed the two groups for 6 weeks using the NIH-CPSI (total and domain subscores). After 6 weeks

patients treated with tamsulosin had a statistically significant treatment effect (-3.6 ; $P = 0.04$) compared to those on placebo. There was no significant treatment effect in patients who had mild symptoms (25th percentile, -1.6 points; $P = 0.53$). Patients with severe symptoms (75th percentile) had a statistically and clinically significant response over placebo (treatment effect, -8.3 points; $P < 0.01$). This pilot study showed that tamsulosin was significantly better than placebo, particularly in men with moderate and severe CP/CPPS. Most of the patients in these three studies were naïve to previous α -blocker therapy.

In contrast, the initial results from the NIH Chronic Prostatitis Collaborative Research Network Randomized Controlled Trial [12], comparing 6 weeks ciprofloxacin, tamsulosin and their combination to placebo, enrolled intensely pre-treated patients. In this recently reported study, patients treated with tamsulosin (\pm ciprofloxacin) did not improve significantly more than patients treated with placebo. The final report of the study should be available within the next year.

α -Blockers appear to have a role in treating CP/CPPS; they seem to work best in men who are naïve to these agents, have moderate to severe symptoms, and who are willing to stay on therapy for >6 weeks.

ANTI-INFLAMMATORIES

The primary symptoms of CP/CPPS are perineal, lower abdominal, testicular, penile and ejaculatory pain [1–4]. Relief of the pain and discomfort associated with CP is a primary goal of therapy. NSAID therapy remains one of the most common empirical treatments for the pain and inflammation associated with CP/CPPS [1], but only one randomized placebo-controlled study is available to assess this therapy [16]; 161 patients diagnosed with nonbacterial CP were randomized to 6 weeks of rofecoxib 25 mg, 50 mg or placebo in a 6-week double-blind multicentre study. Although there was a positive treatment effect, it was not statistically significant for either 25 mg (-0.7) or 50 mg rofecoxib (-2.0). However, there was a trend for the percentage of patients with a 25% (or 6-point) improvement in total score to be better on rofecoxib than placebo, with the difference being significantly different ($P < 0.05$) for the 50 mg group (63% vs 40%

for placebo). The patients' overall assessment of pain, response to therapy and disease activity also favoured rofecoxib over placebo ($P < 0.05$, 0.07 and 0.06, respectively). Of the patients on 50 mg rofecoxib, 79%, vs 59% on placebo, reported no or mild pain, and 56% of patients on 50 mg rofecoxib, vs 27% on placebo, also had a significant improvement in quality of life ($P < 0.005$).

Quercetin is a naturally occurring bioflavonoid found in green tea, red wine and onions, and has many anti-inflammatory mechanisms [17]. In a small randomized placebo-controlled study, Shoskes *et al.* [17] showed that 15 patients randomized to quercetin had a mean improvement of 7.9 points in total NIH-CPSI, compared with 1.4 in the 13 patients receiving placebo (treatment effect -6.5 , $P = 0.003$). Ten of the patients taking the bioflavonoid had at least a 25% improvement in symptoms, compared with two taking placebo.

Pentosan polysulphate sodium is a plant-derived, cross-linked, semi-synthetic mucopolysaccharide with a xylan backbone; it produces modest improvements in symptoms compared with placebo in patients diagnosed with interstitial cystitis, another enigmatic condition characterized by pelvic pain and irritative voiding symptoms. Its mechanism of action is generally unknown, but it is hypothesized that some of its effect is probably secondary to its anti-inflammatory actions. In a pilot study designed to assess the possible beneficial effects of this drug in men with CP/CPSP, 100 men with CP/CPSP were randomized to 16 weeks of treatment with 900 mg/day pentosan polysulphate (three times the usual dose used in interstitial cystitis) or placebo [18]. For this study, a standard 7-point subjective overall assessment was the primary endpoint. There was a statistically significant benefit in the pentosan polysulphate group compared with the placebo group (37% vs 18% responders, respectively; $P < 0.05$). The treatment effect (total NIH-CPSI) was statistically significant at 12 weeks, and remained numerically superior (-2.7), but not statistically significant, at 16 weeks.

FUTURE CONSIDERATIONS

CP/CPSP is a difficult clinical condition to treat; antibiotics, α -blockers and anti-inflammatories appear to benefit patients

with CP syndromes, but do not produce spectacular cure rates. A trend toward combined therapy is developing, not only in BPH [19], but also in prostatitis [8,20]. It seems very reasonable that other novel therapies or multimodal therapeutic strategies with α -blockers and other potentially beneficial agents that have independent actions (e.g. antibiotics, α -blockers, anti-inflammatory agents) should be evaluated in prospective, randomized placebo-controlled trials

ACKNOWLEDGEMENTS AND DISCLOSURE

Dr Nickel's Prostatitis Research Clinic is supported in part by peer-reviewed funding from the National Institutes of Health NIDDK. He has been a consultant with Bayer, Ortho-McNeil, Boehringer-Ingelheim, Sanofi-Synthelabo and Farr Laboratories.

CONFLICT OF INTEREST

None declared.

REFERENCES

- Schaeffer AJ, Landis JR, Knauss JS *et al.* Demographic and clinical characteristics of men with chronic prostatitis: The NIH chronic prostatitis cohort (CPC) study. *J Urol* 2002; **168**: 593–8
- McNaughton Collins M, MacDonald R, Wilt TJ. Diagnosis and treatment of chronic abacterial prostatitis: a systematic review. *Ann Intern Med* 2000; **133**: 367–81
- Krieger JN, Nyberg LM, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA* 1999; **282**: 236–7
- Litwin MS, McNaughton-Collins M, Fowler FJ *et al.* The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. *J Urol* 1999; **162**: 369–75
- Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis. consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. *Urology* 1999; **54**: 229–33
- Propert KJ, Alexander RB, Nickel JC *et al.* The design of a multi-center

randomized clinical trial for chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2002; **59**: 870–6

- Turner JA, Ciol MA, Korff M, Berger R. Validity and responsiveness of the national institutes of health chronic prostatitis symptom index. *J Urol* 2003; **169**: 580–3
- Shoskes DA, Hakim L, Ghoniem G, Jackson CL. Long-term results of multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome. *J Urol* 2003; **169**: 1406–10
- Nickel JC, Downey J, Johnston B, Clark J. Predictors of response to antibiotic therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical study. *J Urol* 2001; **165**: 1539–44
- Bjerklund-Johansen TE, Gruneberg RN, Guibert J *et al.* The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. *Eur Urol* 1998; **34**: 457–66
- Nickel JC, Downey J, Clark J *et al.* Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multi-center trial. *Urology* 2003; **62**: 614–7
- Alexander RB, Propert KJ, Schaeffer AJ *et al.* A randomized trial of ciprofloxacin and tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome. *J Urol* 2004; **171** (Suppl): 61 (A232)
- Cheah PY, Liong ML, Yuen KH *et al.* Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. *J Urol* 2003; **169**: 592–6
- Mehik A, Alas P, Nickel JC, Sarpola A, Helstrom PJ. Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. *Urology* 2003; **62**: 425–9
- Nickel JC, Narayan P, McKay J, Doyle C. Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double-blind trial. *J Urol* 2004; **171**: 1594–7
- Nickel JC, Pontari M, Moon T *et al.* A randomized, placebo-controlled, multicenter study to evaluate the safety and efficacy of rofecoxib in the treatment of chronic nonbacterial prostatitis. *J Urol* 2003; **169**: 1401–5
- Shoskes DA, Zeitlin SI, Shahed A, Rajfer J. Quercetin in men with category III

chronic prostatitis: a preliminary prospective, double-blind, placebo control trial. *Urology* 1999; **54**: 960–3

- 18 **Nickel JC, Forrest J, Tomera KM, Hernandez-Graulau J, Moon TD, Schaeffer AJ.** Effects of pentosan polysulfate sodium in men with chronic pelvic pain syndrome: a multi-center randomized, placebo-controlled study. *J Urol* 2002; **167** (Suppl.): 63, A248
- 19 **McConnell JD, Roehrborn CG, Bautista**

OM et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *NEJM* 2003; **349**: 2384–449

- 20 **Nickel JC, Downey J, Ardern D, Clark J, Nickel K.** Failure of monotherapy strategy for the treatment of difficult chronic prostatitis/chronic pelvic pain syndrome patients. *J Urol* 2004; **172**: 551–4

Correspondence: J. Curtis Nickel, Department of Urology, Queen's University, Kingston General Hospital, Kingston, Ontario, Canada, K7L 2V7.
e-mail: jcn@post.queensu.ca

Abbreviations: CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index.

