PROSTATITIS

No benefit of α-blockers for chronic prostatitis

Florian M. E. Wagenlehner and Wolfgang Weidner

A randomized controlled trial has questioned the widespread use of the α-blocker alfuzosin as an empirical treatment for chronic prostatitis–chronic pelvic pain syndrome. Instead, only a small subgroup of patients might benefit from this therapy.

On the basis of the available evidence, α-blockers have been recommended as a first-line therapy for patients with chronic prostatitis–chronic pelvic pain syndrome (CP–CPPS), particularly for α-blocker-naive men with moderate symptoms of relatively recent onset.[1] The large randomized controlled trial by Nickel *et al.*[2] investigated the utility of 12 weeks' treatment with the α-blocker alfuzosin (10 mg per day) for relief of symptoms in men with CP–CPPS. The results of this study contradict the widespread urological practice of offering α-blocker therapy to men with CP–CPPS for symptomatic improvement.

> ...the use of α-blockers for CP–CPPS has been widespread in recent years

Prostatitis is a heterogeneous condition characterized by genitourinary pain and lower urinary tract symptoms.[3] The prevalence of symptoms suggestive of prostatitis in the general male population ranges between 2.2% and 13.8%, according to different studies.[1] CP–CPPS is the most common prostatitis subtype, with a heterogeneous and largely unknown etiology.

Men with CP–CPPS are often prescribed α-blockers for several reasons. First, these agents are effective and recommended in men with lower urinary tract symptoms resulting from benign prostatic hyperplasia.[4] Second, α_1-adrenergic receptors located in the central nervous system have been implicated in long-term pain syndromes.[5] Third, α-blockers might reduce neurogenic inflammation.[6] Finally, α-blockers might reduce bladder outlet obstruction,[7] which is regarded as one etiologic cause of CP–CPPS.[1]

Nickel *et al.*[2] defined a patient as having CP–CPPS if their duration of symptoms was longer than 6 weeks and their total score on the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) was ≥12. Important exclusion criteria were previous use of α-blockers, urinary tract infection, symptomatic genital herpes, unilateral orchialgia, genitourinary cancer, inflammatory bowel disease, urethral stricture, prostate or bladder surgery and neurologic disease affecting the bladder. These exclusion criteria are integral to the quality of the study, because the diagnosis of CP–CPPS relies to a certain extent on the exclusion of other diseases. During the study, patients were evaluated primarily by the NIH-CPSI score, and secondarily by the McGill Pain Questionnaire, the Medical Outcomes Study Short Form Health Survey 12, the Hospital Anxiety and Depression Scale, the International Index of Erectile Function and the Male Sexual Health Questionnaire.

In total, 272 men were randomized to receive alfuzosin or placebo, and 233 completed the 12-week study period. Within the intention-to-treat analysis population, the two study groups had similar baseline characteristics, although the total NIH-CPSI score was somewhat higher in the placebo group than in the alfuzosin group (mean 25.1 versus 23.8; $P = 0.06$); this difference is unlikely to have affected the study results. Patients in both groups had a mean pain subscore of approximately 11, a urinary symptoms subscore of approximately 5, and a quality of life impact subscore of approximately 5, which indicates that patients included in the study had significant CP–CPPS symptoms. The proportion of patients who met the primary end point—a decrease of at least 4 points in their total NIH-CPSI score from baseline to 12 weeks—was 49.3% in both groups (absolute rate difference 0.1%, 95% CI –11.2, 11.0; $P = 0.99$). Overall, patients who received alfuzosin had a mean decrease in the total NIH-CPSI score of 7.1 points, compared with 6.5 points for those who received placebo ($P = 0.70$). One-third of patients in each group reported a marked or moderate improvement in symptoms on a Global Response Assessment. With regard to secondary outcome measures, only the Male Sexual Health Questionnaire scores showed a difference between groups, with a greater improvement in the alfuzosin group (mean increase 1.7 versus 0.6 points; $P = 0.06$), which is unlikely to be clinically relevant. Nickel *et al.*[2] conclude that alfuzosin should not be used to treat symptoms of CP–CPPS.

> Nickel *et al.* conclude that alfuzosin should not be used to treat symptoms of CP–CPPS

Several studies have demonstrated a positive effect of α-blockers on the outcomes of patients with CP–CPPS. Mehik *et al.*[8] found that 17 patients treated with alfuzosin (5 mg twice daily) had a modest, but statistically significant, improvement in NIH-CPSI score compared with 20 individuals who received placebo. Nickel *et al.*[9] previously studied 58 patients who were randomized to receive 0.4 mg per day tamsulosin or placebo. The total NIH-CPSI score improved significantly in the patients who received α-blocker therapy

compared with placebo; this beneficial effect was greatest in those men who had the most severe symptoms. Cheah *et al.*[10] randomly allocated 100 men with CP–CPPS to receive 5 mg terazosin or placebo. Terazosin proved superior to placebo for symptomatic relief in α-blocker-naive patients. By contrast, Alexander *et al.*[11] randomized 196 men with long-lasting CP–CPPS to receive ciprofloxacin, tamsulosin, both drugs, or placebo. Ciprofloxacin and tamsulosin did not substantially reduce symptoms in those patients. Nevertheless, despite some negative results, the use of α-blockers for CP–CPPS has been widespread in recent years.

The treatment of patients with CP–CPPS is complicated by the heterogeneous etiology of this syndrome, which can ultimately merge in a common symptomatology. In addition, studies of CP–CPPS treatments have been constrained by the difficulty of evaluating a single treatment option in a patient population with heterogeneous and largely unknown etiology. In this regard, the use of a placebo arm is essential. Means of investigating the underlying etiology of CP–CPPS before the initiation of treatment have been suggested, but none has been universally accepted. The exclusion of an infectious origin in patients with CP–CPPS is mandatory, and should be done by a four-glass or two-glass test.[1] In the study by Nickel and colleagues,[2] exclusion of an infectious origin was done on the basis of midstream urine culture only, which might fail to diagnose cases of chronic bacterial prostatitis. Although rare, this etiology mandates antibacterial treatment. Subvesical obstruction might also be an etiology of CP–CPPS by causing retrograde influx of urine into the prostate. Additional testing of urodynamic parameters—at the least, investigation of uroflowmetry, postvoid residual urine volume and bladder wall thickness—might be beneficial to identify if a subvesical obstruction is present. Future studies should identify patients with subvesical obstruction and test whether these individuals represent a subgroup of patients with CP–CPPS who benefit from α-blocker medication, as these agents have proven efficacy in patients with bladder outlet obstruction.[7]

The study by Nickel *et al.*[2] is an excellent clinical trial, with sufficient statistical power to refute the use of α-blockers in patients with CP–CPPS. A subgroup of patients with subvesical obstruction or voiding dysfunction, however, might benefit from these agents, which should be tested in a clinical trial that includes assessment of urodynamic parameters. In the future, treatment of CP–CPPS with α-blockers should perhaps be reserved for those patients with proven subvesical obstruction.

*Department of Urology and Pediatric Urology, Justus-Liebig-University Giessen, Germany (**FME Wagenlehner, W Weidner**).*

Correspondence: FME Wagenlehner, Department of Urology and Pediatric Urology, University Hospital Giessen and Marburg GmbH—Giessen, Justus-Liebig-University Giessen, Rudolf-Buchheim-Strasse 7, D-35385 Giessen, Germany
wagenlehner@aol.com

doi:10.1038/nrurol.2009.45

Competing interests
The authors declared no competing interests.

1. Schaeffer, A. J. *et al*. The assessment and management of male pelvic pain syndrome, including prostatitis. In *Male Lower Urinary Tract Dysfunction, Evaluation and Management: 6th International Conference on New Developments in Prostate Cancer and Prostate Diseases* (eds McConnell, J. *et al.*) 341–385 (Health Publications, Paris, 2006).
2. Nickel, J. C. *et al*. Alfuzosin and symptoms of chronic prostatitis–chronic pelvic pain syndrome. *N. Engl. J. Med.* **359**, 2663–2673 (2008).
3. Schaeffer, A. J. Clinical practice. Chronic prostatitis and the chronic pelvic pain syndrome. *N. Engl. J. Med.* **355**, 1690–1698 (2006).
4. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J. Urol.* **170**, 530–547 (2003).
5. Andersson, K. E. & Gratzke, C. Pharmacology of α_1-adrenoceptor antagonists in the lower urinary tract and central nervous system. *Nat. Clin. Pract. Urol.* **4**, 368–378 (2007).
6. Geppetti, P., Nassini, R., Materazzi, S. & Benemei, S. The concept of neurogenic inflammation. *BJU Int.* **101 (Suppl. 3)**, 2–6 (2008).
7. Lepor, H. Role of α-adrenergic blockers in the treatment of benign prostatic hyperplasia. *Prostate Suppl.* **3**, 75–84 (1990).
8. Mehik, A., Alas, P., Nickel, J. C., Sarpola, A. & Helstrom, P. J. Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. *Urology* **62**, 425–429 (2003).
9. Nickel, J. C., Narayan, P., McKay, J. & Doyle, C. Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J. Urol.* **171**, 1594–1597 (2004).
10. Cheah, P. Y. *et al*. Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. *J. Urol.* **169**, 592–596 (2003).
11. Alexander, R. B. *et al*. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. *Ann. Intern. Med.* **141**, 581–589 (2004).

PROSTATE CANCER

Regeneration of interest in the prostate

Anne T. Collins and Norman J. Maitland

The growth of prostate acini from single cell implants in mice is a major breakthrough. Such results have important clinical implications, and will ultimately change the treatment paradigm for prostatic disease.

The prostate gland exhibits a remarkable capacity to regenerate after successive cycles of castration and restoration of normal androgen levels, which has been attributed to the existence of a small population of hormone-insensitive cells with stem cell properties. Such cells are highly relevant to our understanding of normal prostate development, carcinogenesis and response to castration. The purification of these putative stem cells, to the exclusion of the majority (>99%) of other cell types, has, however, long remained an experimental challenge. The paper by Leong and colleagues,[1] which describes the regeneration of vestigial prostate glands in mice from single epithelial cell implants, is, therefore, of considerable interest to both basic and clinical scientists.

This topic is not new: Isaacs and Coffey[2] postulated the existence of androgen-independent tissue stem cells in the prostate more than 20 years ago, having observed regeneration of rat prostate after repeated cycles of androgen deprivation and replacement. Their model is generally accepted to hold not only for normal prostate, but also