ELSEVIER

INFLAMMATION AND ANTI-INFLAMMATORY THERAPY IN CHRONIC PROSTATITIS

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ABSTRACT

Anti-inflammatory medications have been used for the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), given that inflammation and pain are traditionally associated with this condition. The National Institutes of Health (NIH) classification divides category III into (1) category IIIA—patients with white blood cells (WBCs) in their expressed prostatic secretions, post–prostate massage urine (voided bladder urine-3 [VB_3]) or semen; and (2) category IIIB—those without WBCs. However, recent studies indicate that the ability of WBC count alone to distinguish men with symptoms from those without appears limited. Other markers of inflammation, such as cytokines, may correlate better with clinical findings. The mechanisms of inflammation continue to be investigated, including contributions from reactive oxygen species, autoimmune response, neurogenic inflammation, and even endocrine dysfunction. There have been few controlled studies of anti-inflammatory therapy for chronic prostatitis. In the only randomized double-blind placebo-controlled trial, the NIH-Chronic Prostatitis Symptom Index (CPSI) total, domain, and pain scores significantly decreased from baseline in all groups, but the difference was not statistically significant. Other medications that have some theoretic anti-inflammatory properties have shown promising early results. Further study of currently available anti-inflammatory medications may be warranted, especially in longer trials, which may allow resolution of the significant placebo effect commonly seen in the short term in men with CPPS. Further discussion is needed to either validate, modify, or abolish the distinction between category IIIA and IIIB in the NIH classification. UROLOGY **60:** 29–34, 2002.

The use of anti-inflammatory medications for the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) makes empiric sense given that inflammation and pain are traditionally associated with this condition. Although pain is unarguably the predominant symptom in chronic prostatitis and forms the cornerstone of the National Institutes of Health (NIH) criteria for making this diagnosis,[1] the data to support the view that inflammation is an integral part of this syndrome are less compelling. The NIH classification divides category III (chronic pelvic pain syndrome) as follows: (1) category IIIA, patients with white blood cells (WBCs) in their expressed prostatic secretions (EPS), post–prostate massage urine (voided bladder-3 [VB_3]), or semen, and (2) category IIIB, those without WBCs. This distinction has never been validated, and there is not a direct correlation between inflammation in the EPS and seminal plasma.[2] However, identification of sites and types of inflammatory changes associated with CPPS may provide potential approaches for therapy.

A basic question to ask is whether men with symptoms of pelvic pain have any greater number of WBCs in their EPS than men without symptoms. In the EPS of 119 individuals with no clinical evidence of urinary tract inflammation, only 13 had $\geq$10 WBCs per high-power field.[3] This study indicates that although there is potentially a cutoff point for WBCs to distinguish the 2 groups, inflammation can also be found in asymptomatic men. Recent data from the Chronic Prostatitis Collaborative Research Network (CPCRN) compared WBC counts in 487 men with CP and 120 asymptomatic control subjects.[4] The only significant difference in WBC count in the 2 groups was a greater number of leukocytes in the initial stream urine

Michel A. Pontari is a co-patent holder along with Merck & Co., Inc., for the use of cyclooxengase-2 in chronic prostatitis and is a Vioxx and Proscar study investigator funded by Merck & Company, Inc.

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0090-4295/02/$22.00
PII S0090-4295(02)02381-6

(VB_1) of the prostatitis group. Thus, the ability of the WBC count alone to distinguish men with symptoms from those without symptoms appears limited.

Several groups have looked at cytokine levels in both seminal plasma and EPS. Elevated levels of tumor necrosis factor-α (TNF-α) and interleukin-1β have been reported in seminal plasma.[5] Interleukin-8 has also been reported to be increased in seminal plasma in category IIIA as compared with either IIIB or control subjects.[6] In the 2 studies looking at seminal plasma, although there were no elevations in interleukin-1β and TNF-α, both studies found that the 2 cytokines correlated with each other. However, neither correlated with WBC counts in any of the 4-glass urine specimens. Nadler *et al.*[7] found elevated levels of interleukin-1β and TNF-α levels in EPS in category IIIA as opposed to IIIB patients and control subjects. No correlation between these cytokines and WBC counts was noted. The EPS of patients with category IV prostatitis (asymptomatic inflammation), or asymptomatic inflammation, also contained elevated levels of these 2 cytokines. Hochreiter *et al.*[8] reported that EPS levels of interleukin-8 and epithelial neutrophil activating factor-78 were significantly elevated in categories IIIA, IV, and I over control subjects and category IIIB patients.

Other aspects of the inflammatory response in men with CPPS include levels of reactive oxygen species (ROS) or free radicals. Neutrophils release ROS in response to antigenic stimulation. Shahed and Shoskes[9] measured levels of ROS in EPS, with the hypothesis that infection by gram-positive bacteria in category IIIA, but not prostatic colonization, results in oxidative stress because tissue injury by definition follows infection and not colonization. Their category IIIA patients had significantly higher oxidative stress levels than did their category IIIB patients. Oxidative stress levels, however, were independent of leukocyte count in the EPS and, therefore, were not a marker per se of leukocytes but rather were a marker of tissue injury. Less oxidative stress was subsequently detected in the EPS after clinically successful treatment with oral antibiotic or antioxidant. Increased oxidative stress, which does not correlate with WBC count, has been reported in the seminal plasma also of men with CPPS.[10] The oxidative stress may also result directly in prostate pain. Shahed and Shoskes[11] also proposed that oxidative stress in category III patients increases prostaglandin E_2 (PGE_2) levels, which in turn lower β-endorphin levels,[12] contributing to the pain of prostatitis. PGE_2 levels in their patients were 4 to 6 times higher than in their asymptomatic control subjects.[11] Although not significant, a trend to lower levels was seen in category IIIB versus IIIA. After treatment with either an antibiotic or antioxidant, β-endorphin levels were significantly higher and PGE_2 levels were significantly lower.

Several studies indicate that the inflammatory response in men with CPPS may be autoimmune. The EPS of CPPS patients contain markers for cytotoxic T cells, a cell type not typical of antimicrobial immunity but more consistent with autoimmune inflammation or secondary remodeling of injured tissue.[9] A proposal for the target autoantigen is prostate-specific antigen.[13] Another proposal is that the immune response in men with CPPS is a shift from the type 1 to type 2 T-cell response. Type 1 is cell-mediated immunity, and type 2 is humoral (antibody) immunity. Type 2 is associated with disease states favoring antibody production and tissue destruction. If type 2 is greater than type 1, then this will result in increased mast cell proliferation, activation, life span, and increased tissue injury. Wong *et al.*[14] found a correlation between the ratio of interleukin-10 and interleukin-2 with nerve growth factor and stem cell factor to support this concept. Interleukin-2 is a type 1 stimulant, and interleukin-10 is associated with type 2 response.

Other factors involved in the inflammatory response that may offer opportunities for therapy have been reported. Cho *et al.*[15] from the Seattle group used color Doppler ultrasonography to show marked increases in flow to the prostatic capsule and parenchyma in category IIIA and IIIB patients compared with control subjects. If vascular congestion itself or the delivery of inflammatory cells from this vascular congestion, with resultant cytokine production, contributes to pain, then therapy aimed at reducing prostatic blood flow may be helpful. Also contributing to prostatic inflammation may be hormonal factors. Morón *et al.*[16] showed that in the rat model of autoimmune prostatitis, early castration improved thymic function and decreased the development of autoimmune prostatitis as the rats aged. In the Wistar rat, implantation of estradiol-17β results in prostate inflammation.[17] Other studies have shown that coadministration of testosterone (but not dihydrotestosterone) along with estrogen is protective against inflammation and is also blocked by bromocriptine, implicating prolactin in the inflammatory response.[18,19] Recent data on possible genetic alterations in patients with CPPS also make a compelling argument for the possible role of endocrine factors. Krieger and Riley[20] found differences in frequency of alleles of the phosphoglycerate kinase 1 (PGK1) gene between CPPS patients and control subjects. The PGK1 gene differed in the number of short tandem repeats. The PGK1 gene in the region assessed has been found to be associated with familial prostate cancer, hypospadias,

and androgen insensitivity. Another gene in the same region of the X chromosome, Xq11 to Xq13, is the androgen receptor. These findings lead to the question of whether androgen insensitivity or dysfunction is involved in the pathogenesis of CPPS.

Another hypothesis is that of neurogenic inflammation. This is a particularly attractive idea, given that pain is a prominent part of the CPPS syndrome. In humans, there is evidence for abnormally retained activity in the external urinary sphincter with voiding in approximately 80% of men with CPPS undergoing urodynamics.[21] This idea is supported by an animal study in which irritation of the prostate and simultaneous administration of Evans blue intravenously in the rat results in upregulation of c-*fos* at the L6 to S1 spinal cord level, and peripherally there is plasma extravasation manifest as blue dots on the skin at such sites as the scrotum, abdomen, and lower back, corresponding to the prostate dermatome.[22] This finding was also seen with bladder irritation. Interestingly, in another study, the semen of men with spinal cord injury contained ROS in 97% of cases, compared with 40% of infertile men and 15% of control subjects, indicating that neurologic injury is associated with changes in semen similar to those seen in men with CPPS.[23]

RELATION BETWEEN INFLAMMATION AND SYMPTOMS

Does inflammation correlate with symptoms? In the CPCRN Cohort study, the presence of WBC correlates poorly with symptoms.[24] This study looked at 278 men with CPPS. Category IIIA was defined as 5+ WBC in EPS or 1+ in voided bladder specimen after EPS (VB_3) or semen. Urethral inflammation was defined as 1+ WBC in VB_1. Fifty-six percent had urethral inflammation, 51% had 5+ WBC in EPS, and 87% were classified as category IIIA. None of the Chronic Prostatitis Symptom Index (CPSI) measures, including subsets for pain, urinary symptoms, and quality of life, were different for WBC subgroups. The overall rank correlation between WBC and urinary symptoms was nonsignificant and weak. Another argument against the association of inflammation and symptoms is that category IIIB patients have symptoms but no inflammation, and conversely category IV patients have inflammation but no symptoms.

Although WBCs do not correlate with symptoms, other markers of inflammation may have a stronger association. Ruggieri *et al.*[6] found no correlation between levels of interleukin-1β and TNF-α in seminal plasma and symptoms. However, Hochreiter *et al.*[25] found that cytokine levels in EPS changed in association with symptoms. In the absence of antibiotic treatment, 80% of patients showed increased cytokines (by a mean of 1725%) when symptoms developed, and a mean decrease of 49% when symptoms disappeared. Increases or decreases in cytokine levels also correlated with WBC levels in EPS. When antibiotics were given, cytokine levels decreased in 93% of the cases (mean decrease 51%), regardless of changes in symptoms or inflammatory status. Thus, it is also possible that although static measurements of immune mediators may not correlate with symptoms, changes in the levels of these mediators may be clinically meaningful.

ANTI-INFLAMMATORY THERAPY

There have been few trials of anti-inflammatory therapy for chronic prostatitis, and only 1 randomized double-blind placebo-controlled trial. Small studies of less mainstream anti-inflammatory medications have been reported using seaprose S[26] and nimesulide.[27] In 2001, a randomized placebo-controlled trial of rofecoxib (Vioxx, Merck & Co., Whitehouse Station, NJ), a cyclooxygenase (COX)-2 inhibitor, was completed.[28] COX-1 is the constitutive isoform found in virtually all cell types; the COX-2 isoform is undetectable in most tissues but is rapidly induced in inflammation.[29] In vivo, COX-2 can continue to be synthesized for days or weeks given the persistence of an appropriate stimulus.[30] COX-2 may play a role in chronic nonbacterial prostatitis. Compared with normal men, EPS and semen of men with CP/CPPS have higher levels of the inflammatory cytokines interleukin-1β and TNF-α.[5,7] These cytokines upregulate COX-2 gene expression, which may further contribute to inflammation.[31,32] In the reported study, a tota1 of 161 patients were randomized to treatment with rofecoxib 50 mg, 25 mg, or placebo. The NIH-CPSI total, domain, and pain scores significantly decreased from baseline in all groups, and although the mean scores numerically favored the rofecoxib groups, the difference was not statistically significant among groups. There was a trend for a higher percentage of patients with a 25% or 6-point improvement in total score on rofecoxib versus placebo, with the difference being significantly different ($P < 0.05$) for the 50 mg rofecoxib group. Patient global assessment of pain, response to therapy, and disease activity also favored rofecoxib over placebo ($P < 0.05$, $P = 0.07$, $P = 0.06$, respectively). Altogether, 79% of the patients on 50 mg rofecoxib versus 59% on placebo reported no pain or mild pain, and 56% of patients on rofecoxib versus 27% on placebo also experienced significant improvement in quality of life ($P < 0.005$). Rofecoxib was generally well tolerated.

There are other medications that are not nonsteroidal anti-inflammatory drugs (NSAIDs) but

likely exert an anti-inflammatory effect in treating the symptoms of CPPS. Pentosan polysulfate (PPS) is a semisynthetic mucopolysaccharide, which is chemically and structurally similar to naturally occurring glycosaminoglycans that form a protective barrier in the urinary epithelium. Beneficial effects have been reported with doses of 200 mg po bid[33] and 100 mg po tid.[34] A recent randomized placebo-controlled trial used 900 mg given orally qd for 16 weeks versus placebo: there was a moderate or marked clinical global improvement with PPS, 36.7% versus placebo 17.8% ($P = 0.04$).[35] A 50% reduction in total NIH-CPSI score was seen with PPS, 20% versus 8% placebo. Thus, PPS may be another alternative for men with CPPS. Another medication likely having anti-inflammatory effects is finasteride. In patients with category IIIA prostatitis, 6 months of therapy with finasteride versus placebo resulted in a 50% improvement in global assessment in 44% of patients on finasteride and 27% on placebo.[36] Another class of medications that may be exerting anti-inflammatory effects is antibiotics. Ciprofloxacin and ofloxacin reduce ROS generated by neutrophils.[37] Ciprofloxacin also inhibits endothelial cell production of interleukin-6 in response to TNF and interleukin-1,[38] and tetracycline inhibits nitric oxide synthase production by macrophages.[39]

FUTURE OF ANTI-INFLAMMATORY THERAPY

An important element in directing future anti-inflammatory therapy will be basic research into the inflammatory response seen in men with CPPS, especially the concept of non–WBC-associated inflammation. An example of therapy directed at recent findings of elevated TNF-α levels is an ongoing trial of etanercept (Embrel, Immunex Corporation, Seattle, WA), which binds TNF-α.[40] Other potential targets of intervention include mast cell degranulation and alterations in hormones. Further trials with currently available anti-inflammatory medications may be warranted, with changes in trial design. Longer trials with NSAIDs, such as rofecoxib, may allow resolution of the significant placebo effect commonly seen in the short term in men with CPPS. Further discussion is needed to validate, modify, or abolish the distinction between category IIIA and IIIB in the NIH classification.

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DISCUSSION FOLLOWING DR. PONTARI'S PRESENTATION

Scott I. Zeitlin, MD (Los Angeles, California): Is there a length of time to which you would limit the use of pentosan polysulfate?

Michel Pontari, MD (Philadelphia, Pennsylvania): There is probably a significant placebo effect, but at 3 months, those effects tend to decrease, as occurred in the saw palmetto trial done by Dr. Steve Kaplan.[1] In terms of doing a study, I think you take it up to 3 months. Clinically, I do not have an answer for that question. My patients are given it for several months.

Anthony J. Schaeffer, MD (Chicago, Illinois): How do the researchers using pentosan for interstitial cystitis interpret the data?

Dr. Pontari: The longer you use it, the more benefit you may have, with patients getting better out to 3 years.

J. Curtis Nickel, MD (Kingston, Ontario, Canada): In our prospective study in interstitial cystitis patients, there was a continued response out to 38 weeks, which did not plateau. There was no dose effect. There was no difference between 300 mg and 900 mg.[2]

Dr. Pontari: So if you are going to use pentosan polysulfate, it sounds like 100 mg tid might be as good as 300 mg tid.

John N. Krieger, MD (Seattle, Washington): You told us about inflammation and anti-inflammatory therapy, and rofecoxib is an anti-inflammatory agent. Can you interpret the results of that study in terms of who had evidence of white blood cells and who did not?

Dr. Nickel: We tried. The numbers are too small: 50 patients in either group. It was a pilot study, and the interpretation of the results depends on how you define your categories. The categories IIIA and IIIB can use different cut points, 10 white blood cells, 5 white blood cells. Different categorizations got different numbers, and that is why we did not pursue it. The study was too underpowered to allow a subanalysis.[3]

Dr. Zeitlin: Are you going to repeat the study for different protocols?

Dr. Nickel: The problem was that we might have used the wrong endpoint. We used the National Institutes of Health/Chronic Prostatitis Symptom Index (NIH-CPSI). Merck & Co., Inc., the study sponsor, initially interpreted the study as only mildly supportive. But subsequently we have done 4 or 5 more studies in other therapies, and this treatment has come up with some of the best results. Every study shows that the NIH-CPSI is not emerging to be as sensitive a test as we had