Chronic Prostate Inflammation Predicts Symptom Progression in Patients with Chronic Prostatitis/Chronic Pelvic Pain

J. Curtis Nickel,* Stephen J. Freedland, Ramiro Castro-Santamaria† and Daniel M. Moreira

From the Department of Urology, Queen's University, Kingston, Ontario, Canada, Division of Urology, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California, Global R&D, GlaxoSmithKline Inc., King of Prussia, Pennsylvania, and Department of Urology, University of Illinois at Chicago, Chicago, Illinois

Purpose: We examined the 4-year longitudinal association between histological prostate inflammation and chronic prostatitis/chronic pelvic pain syndrome. We also studied the development of new and progressing existing chronic prostatitis/chronic pelvic pain syndrome in men randomized to placebo in the REDUCE (REduction by DUtasteride of prostate Cancer Events) population.

Materials and Methods: At multiple time points during 4 years univariable and multivariable analyses were performed between acute and chronic inflammation detected on baseline biopsies and the incidence of chronic pelvic pain syndrome-like symptoms, defined as a positive response to CPSI (Chronic Prostatitis Symptom Index) question 1a—perineal pain and/or question 2b—ejaculatory pain and a total pain subscore of at least 4, and progression of chronic prostatitis/chronic pelvic pain syndrome, defined as a 4-point or greater increase from baseline in total CPSI score, in patients with a baseline categorization of chronic prostatitis/chronic pelvic pain syndrome.

Results: Of the 4,109 men in the study acute and chronic inflammation was detected in 641 (15.6%) and 3,216 (78.3%), respectively. Chronic prostatitis/chronic pelvic pain syndrome symptom status was available for 2816 at baseline. Chronic prostatitis/chronic pelvic pain syndrome-like symptoms developed in 317 of 2,150 men without the condition at baseline who had followup data. Acute and chronic inflammation was not associated with the incidence of the symptoms ($p > 0.1$). At a median followup of 12.0 months 109 of 145 men with baseline chronic prostatitis/chronic pelvic pain syndrome and followup data showed symptomatic progression. Chronic but not acute inflammation was significantly associated with shorter time to progression on univariable and multivariable analyses ($p = 0.029$ and 0.018, respectively).

Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome

CPSI = Chronic Prostatitis Symptom Index

I-PSS = International Prostate Symptom Score

PSA = prostate specific antigen

PV = prostate volume

PVR = post-void residual urine volume

REDUCE = REduction by DUtasteride of prostate Cancer Events

Accepted for publication January 5, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

ClinicalTrials.gov Identifier: NCT00056407.

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

† Financial interest and/or other relationship with GlaxoSmithKline.

Editor's Note: This article is the ••• of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages ••• and •••.

0022-5347/17/1981-0001/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2017.01.035
Vol. 198, 1-7, July 2017
Printed in U.S.A.

Conclusions: Inflammation is not associated with an increased risk of chronic prostatitis/chronic pelvic pain syndrome. However, chronic inflammation predicts the risk of symptomatic progression in men in whom chronic prostatitis/chronic pelvic pain syndrome symptoms have been identified.

Key Words: prostate, prostatitis, pelvic pain, inflammation, chronic pain

THE clinical diagnosis of prostatitis has traditionally been linked to prostate infection and inflammation. In the last half century we came to realize that that the majority of men diagnosed with prostatitis do not have active infection and they were referred to as having nonbacterial or abacterial prostatitis. However, the symptoms experienced by these men were still believed to be due to prostate inflammation. These patients are now classified as having CP/CPPS category III.[1] They can be even further categorized as those with demonstrable inflammation in prostate specimen urine and prostatic fluid specimens (category IIIA) and those with no demonstrable inflammation in these specimens (category IIIB). To further complicate things, we now understand that men may have prostate inflammation but remain asymptomatic (category IV).

Research to date has shown a relative disconnection between prostate inflammation and the syndrome of CP/CPPS. Studies have indicated no apparent association of inflammation in EPS/VB3 (expressed prostatic secretion/voided bladder 3) with symptom severity,[2] histological inflammation, or CP/CPPS diagnosis[3] or symptoms.[4] Furthermore, there appears to be no clinically significant difference between inflammation in men with CP/CPPS and asymptomatic controls,[5] and no differential treatment benefits of inflammation stratification.[6,7]

We do not know the relevance of histological inflammation and its relationship to CP/CPPS symptoms. Does evidence of inflammation in the prostate predict CP/CPPS outcomes, prevalence (symptoms), incidence (development of symptoms), severity (symptoms) and/or progression (increase in symptoms)?

We previously reported a previous cross-sectional examination of baseline data on all patients enrolled in the REDUCE trial, a 4-year, phase 3, placebo controlled study to determine whether daily dutasteride 0.5 mg reduces the risk of biopsy detectable prostate cancer.[8] That study failed to show any significant relationship between the presence of prostate inflammation and CP/CPPS-like symptoms.[4] Entrance criteria for REDUCE included a prostate cancer negative biopsy prior to enrolment with a priori evaluation of the inflammatory status of the tissue.[8]

In the current study we examined the 4-year longitudinal association between CP/CPPS-like symptoms, the development of new CP/CPPS, the progression of existing CP/CPPS and histological prostate inflammation in the men randomized to placebo in the REDUCE population.

METHODS

The design of REDUCE was described previously.[8] Briefly, eligible men were 50 to 75 years old and had serum PSA 2.5 or greater, or 3.0 ng/ml according to age (50 to 60 or 60 to 75 years, respectively) but 10 ng/ml or less and a single negative prostate biopsy (6 to 12 cores) within 6 months of enrollment. Men were excluded from study if they had a history of prostate cancer, high grade intraepithelial neoplasia, atypical small acinar proliferation or PV greater than 80 cm^3, underwent previous prostate surgery or had I-PSS 25 or greater, or 20 or greater on α-blockers.

At the screening and randomization visits data on demographics, medical history, physical examination, PV measured by ultrasonography, PSA, I-PSS, quality of life, peak urinary flow and PVR were collected. Participants were randomized in double-blind fashion to receive oral dutasteride 0.5 mg or placebo daily and they were followed every 6 months for 4 years.

Baseline biopsies had been performed before the start of the study and were reread centrally elsewhere. Acute and chronic prostate inflammation was coded as present or absent.[9,10] Chronic inflammation consisted mainly of lymphocytes and a variable number of plasma cells and macrophages. Acute inflammation consisted of neutrophilic infiltrate.

Patients were followed every 6 months at clinical visits, when peak urinary flow, PVR, I-PSS, CPSI and quality of life were determined. Medical and surgical history was also updated.

The protocol was approved by the institutional review board at each research site and all participants provided written informed consent. Of the 8,231 men enrolled in the study 4,126 (50.1%) were randomized to receive placebo and were included in study. We excluded 17 men (less than 1%) due to missing data on baseline acute and chronic inflammation, which resulted in a final study sample of 4,109.

Univariable comparisons of baseline characteristics between men with vs without baseline acute and chronic prostate inflammation were performed using the chi-square test for categorical data and the Student t-test for continuous variables. The association of acute and chronic baseline inflammation with CPSI scores at multiple time points were plotted and evaluated with the Student's t-test. The association of acute and chronic inflammation in baseline prostate biopsies with time to

the development and progression of CP/CPPS-like symptoms was estimated and plotted with the Kaplan-Meier method. This was compared between groups with the log rank test on univariable analysis and with the Cox proportional hazards model on univariable and multivariable analyses.

CP/CPPS was defined as a positive response to CPSI question 1a (perineal pain) and/or question 2b (ejaculatory pain), and a total pain subscore of at least 4.[11] Moderate to severe CP/CPPS was defined as a positive response to CPSI question 1a and/or question 2b, and a total pain subscore of at least 8.[11] Progression of CP/CPPS was defined as an increase 4 or more points from baseline total CPSI score in patients with baseline CP/CPPS.[12]

Multivariable analysis was controlled for baseline age in years (continuous), race (white or other), body mass index in kg/m^2 (continuous), digital rectal examination (coded as normal or abnormal), PV in cm^3 (continuous), PSA in ng/ml (continuous), I-PSS (continuous), quality of life (continuous), CPSI (continuous), peak urinary flow in ml per second (continuous) and PVR in ml (continuous). All covariates were determined at baseline.

All statistical analyses were 2-tailed and performed using R 3.2.1 (https://www.r-project.org/) with p <0.05 considered statistically significant.

RESULTS

Of the 4,109 men included in the study 3,733 (90.8%) were white. Mean ± SD age was 62.7 ± 6.1 years, mean body mass index was 27.4 ± 4.2 kg/m^2, mean PSA was 5.9 ± 2.0 ng/ml and mean PV was 45.8 ± 18.8 cm^3. Mean peak flow was 14.7 ± 19.5 ml per second and mean PVR was 46 ± 48 ml.

Acute prostate inflammation was observed in 641 baseline biopsies (15.6%) (table 1). Acute baseline inflammation was associated with younger age, lower baseline PSA and slightly better baseline quality of life (all p <0.05). Chronic prostate inflammation was observed in 3,216 baseline biopsies (78.3%) (table 1). Chronic baseline inflammation was associated with older age, nonwhite race, lower baseline PSA, larger prostates, higher baseline I-PSS, worse baseline quality of life, higher baseline PVR and higher CPSI (all p <0.05). Figure 1 shows the association of CPSI at multiple time points with baseline acute and chronic inflammation, respectively. The noticeable increase in CPSI at 24 months in the inflammation and no inflammation groups was likely a temporary increase in CP/CPPS-like symptoms associated with the mandated 2-year biopsy.

Of the 4,109 men in the study 2,816 had available CP/CPPS status at baseline. CPSI had been validated in all languages in this multicenter international study. A total of 2,626 men (93.3%) did not have a history of baseline CP/CPPS, of whom 2,150 had followup data available and were included in the analysis of CP/CPPS development. CP/CPPS developed in 317 men. Median followup was not achieved even after 50 months. Acute and chronic inflammation was not associated with the incidence of CP/CPPS on univariable or multivariable analysis (table 2 and fig. 2).

A total of 190 men (6.7%) had a history of CP/CPPS at baseline, of whom 145 had followup data

Table 1. *Baseline patient characteristics by baseline acute or chronic prostate inflammation*

	Acute Inflammation			Chronic Inflammation		
	Absent	Present	p Value*	Absent	Present	p Value*
No. pts (%)	3,468 (84.4)	641 (15.6)	—	893 (21.7)	3,126 (78.3)	—
Mean ± SD age	62.9 ± 6.1	62.1 ± 6.2	0.006	62.3 ± 6.3	62.9 ± 6.0	0.011
No. race (%):			0.457			0.012
White	3,156 (91.0)	577 (90.0)		831 (93.1)	2,902 (90.3)	
Other	311 (9.0)	54 (10.0)		62 (6.9)	313 (9.7)	
Mean ± SD body mass index (kg/m^2)	27.4 ± 4.2	27.4 ± 4.0	0.901	27.4 ± 3.8	27.4 ± 4.3	0.936
No. digital rectal examination (%):			0.721			0.299
Normal	3,329 (96.2)	611 (95.8)		863 (96.7)	3,077 (95.9)	
Abnormal	133 (3.8)	27 (4.2)		29 (3.3)	131 (4.1)	
Mean ± SD PSA (ng/ml)	5.9 ± 2.0	5.7 ± 1.9	0.009	6.1 ± 2.0	5.9 ± 2.0	0.016
Mean ± SD Prostate vol (cm^3)	46.0 ± 18.3	44.4 ± 21.1	0.061	43.3 ± 18.9	46.5 ± 18.7	<0.001
Mean ± SD I-PSS	9.3 ± 5.7	9.5 ± 6.0	0.578	8.8 ± 5.6	9.5 ± 5.8	0.001
Mean ± SD quality of life	2.1 ± 1.4	2.0 ± 1.3	0.014	2.0 ± 1.4	2.1 ± 1.4	0.031
Mean ± SD peak flow (ml/sec)	14.7 ± 20.1	14.7 ± 8.5	0.940	14.8 ± 7.5	14.7 ± 21.7	0.821
Mean ± SD PVR (ml)	47 ± 48	44 ± 49	0.246	43 ± 47	47 ± 48	0.024
Mean ± SD CPSI	6.5 ± 5.5	6.3 ± 5.3	0.469	6.1 ± 5.4	6.6 ± 5.5	0.086
Mean ± SD CPSI CP/CPPS†	14.7 ± 5.9	14.0 ± 4.9	0.508	14.2 ± 5.6	14.8 ± 5.8	0.592
No. CP/CPPS (%):			0.411			0.523
No	2,185 (93.1)	441 (94.2)		536 (92.6)	2,090 (93.4)	
Yes	163 (6.9)	27 (5.8)		43 (7.4)	147 (6.6)	
No. moderate/severe CP/CPPS (%):			0.706			0.587
No	2,291 (97.6)	458 (97.9)		567 (97.9)	2,182 (97.5)	
Yes	57 (2.4)	10 (2.1)		12 (2.1)	55 (2.5)	

*Chi-square test for categorical variables and Student t-test for continuous variables.
†In 190 patients.

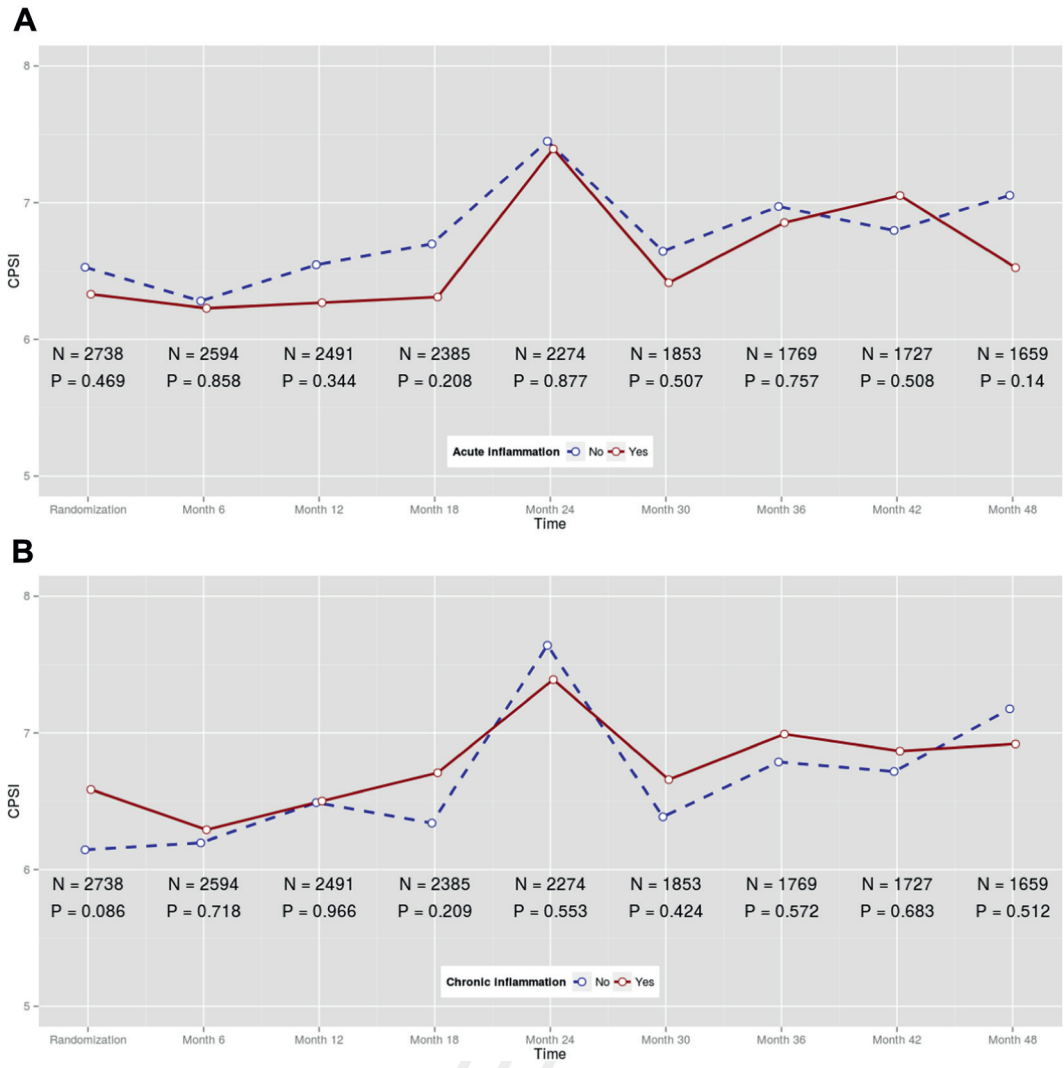

Figure 1. Mean chronic CP/CPPS symptom index. *A*, by acute inflammation. *B*, by chronic inflammation.

and were included in the analysis of CP/CPPS progression. At a median followup of 12.0 months CP/CPPS progression had developed in 109 men.

Acute inflammation was not associated with CP/CPPS progression on univariable or multivariable analyses (table 2 and fig. 3, *A*). Conversely, chronic inflammation was significantly associated with shorter time to CP/CPPS progression on univariable or multivariable analysis (table 2 and fig. 3, *B*).

Table 2. *Association of baseline prostate inflammation with CP/CPPS development and progression*

Baseline Prostate Inflammation	Univariable		Multivariable*	
	HR (95% CI)	p Value*	HR (95% CI)	p Value*
Development:				
Acute	1.101 (0.827–1.467)	0.509	1.102 (0.819–1.484)	0.520
Chronic	1.278 (0.947–1.724)	0.109	1.245 (0.910–1.703)	0.171
Progression:				
Acute	1.206 (0.705–2.063)	0.493	1.444 (0.787–2.649)	0.236
Chronic	1.741 (1.058–2.863)	0.029	1.949 (1.124–3.379)	0.018

* Controlled for baseline age, race, body mass index, digital rectal examination, prostate volume, PSA, I-PSS, quality of life, chronic CP/CPPS symptom index, peak urinary flow and PVR.

DISCUSSION

During the 4-year longitudinal study men with CP/CPPS symptoms randomized to placebo treatment in the REDUCE study in whom chronic prostate inflammation was identified in the baseline biopsy had greater symptom progression than men without prostate inflammation. However, the presence of prostate inflammation did not predict an increased prevalence of CP/CPPS, increased severity of CP/CPPS-like symptoms or increased risk of CP/CPPS-like symptoms with time in men who were asymptomatic at baseline.

The presence of inflammatory cells in the prostate indicates activation of the immune response.

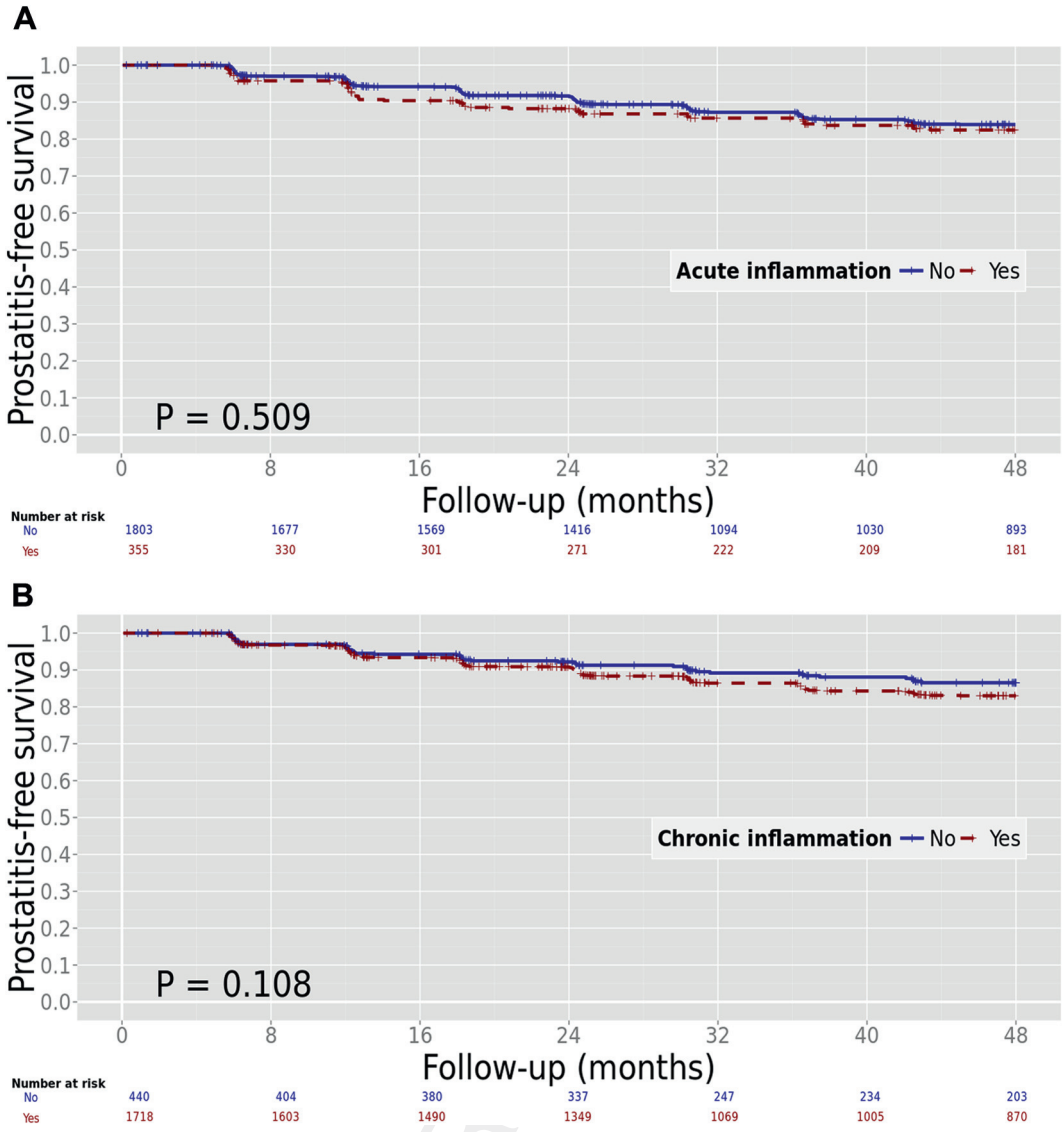

Figure 2. Association of baseline prostate inflammation with CP/CPPS-free survival (*PFS*). *A,* acute inflammation. *B,* chronic inflammation.

Chronic inflammation develops when there is persistent irritation or injury. An immune response is the culmination of a complex series of interactions among tissue, leukocytes/lymphocytes and a network of coordinating chemokines and cytokines, of which all can be heavily influenced by the microenvironment.

The difference between the groups of men with and without CP/CPPS-like symptoms at baseline may lie in the composition of the immune infiltrate and the cytokine milieu in the prostate, which are conditions that cannot be discerned by simple histological grading. We hypothesize that in men without symptoms the regulatory immune populations (eg regulatory T cells) are able to keep the proinflammatory reaction in check or the cytokine milieu is biased toward a less destructive response (Th2 vs Th17/Th1).

In mouse models a situation such as this can be recreated when there is over expression of a self-antigen in the gut along with the production of T cells that recognize this self antigen. In these mice chronic cellular infiltration of the lamina propria of the intestine develops but they do not have intestinal damage because self-reactive cells are held in check by the regulatory network.[13] The inflammation is sustained due to persistent expression of the self-antigen but it is restrained by the regulatory network, which prevents uncontrolled and potentially more destructive proinflammatory responses.

The homeostatic proliferation of memory/activated effector CD4+ T cells, which occurs with age,

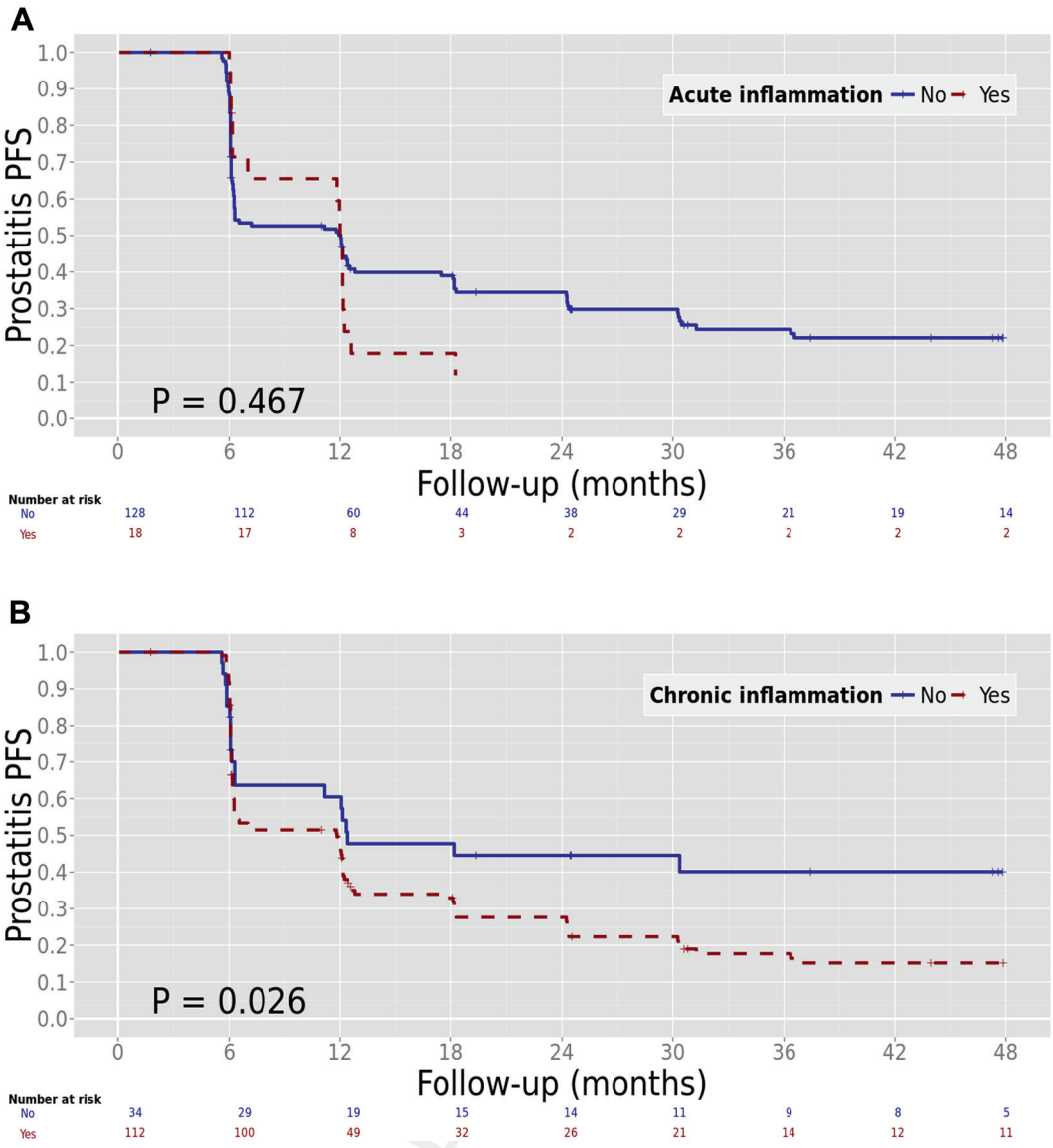

Figure 3. Association of baseline prostate inflammation with CP/CPPS progression-free survival (*PFS*). *A*, acute inflammation. *B*, chronic inflammation.

may also contribute to symptom progression and it supports the correlation of higher baseline chronic inflammation and older age.[14] Additional evidence exists that as we age, the regulatory T-cell population becomes unbalanced and may lose the ability to suppress interleukin-17 producing cells,[15] which drive the pathology of many autoimmune diseases. Interleukin-17 was recently implicated in pelvic pain in animal models of experimental CP/CPPS[16] and neuropathic pain,[17] and it is up-regulated in patients with ESSIC (International Society for the Study of Bladder Pain Syndrome) type 3C interstitial cystitis/bladder pain syndrome.[18]

In other words in patients with CP/CPPS who have chronic inflammation but no symptoms the immune system may remain balanced and ready to induce an active response but uncontrolled progression is prevented by regulatory mechanisms. In patients with symptomatic CP/CPPS the balance has tipped and disease can progress. Why progressive symptoms develop in some men and not in others may come down to complex interactions among genetics (eg polymorphisms in cytokine loci, neurological and endocrine), environmental triggers (eg trauma, diet and infection) and psychosocial factors.[19] We do not have data from this study to confirm this hypothesis but our observations support other studies suggesting that an immunological process is involved in men in whom CP/CPPS has developed.[19]

The major limitation of this study is that it was a cancer prevention study and we evaluated

CP/CPPS-like symptoms in the placebo group only, although the analysis was planned a priori. We found that patients randomized to dutasteride in this longitudinal analysis would have had CP/CPPS end points reduced with time.[20] This would have complicated any evaluation of the effect of baseline inflammation on CP/CPPS progression if we had included the treatment arm in attempt to increase study power.

Furthermore, men with severe BPH and/or lower urinary tract symptoms (PV greater than 80 cm^3 and/or baseline I-PSS 25 or greater, or 20 or greater on α-blockers) were not included in REDUCE. There was no control to determine how or even whether bothersome CP/CPPS symptoms were treated. We have not addressed all confounding associations among prostate inflammation, CP/CPPS symptoms, BPH/lower urinary tract symptoms (the REDUCE population was enriched with patients with BPH secondary to enrollment criteria), prostate size and/or the increased risk of prostate cancer in this population.

Also, we believe that the observations noted in this study are likely real in this population of men but they may not be generalizable to a population who would not have been eligible to enroll in REDUCE, that is men not at risk for prostate cancer.

The obvious strength of this analysis is that to our knowledge it is the largest and longest longitudinal study evaluating the association between inflammation and CP/CPPS-like symptoms.

In conclusion, our comprehensive longitudinal evaluation of patients in REDUCE randomized to placebo for 4 years confirmed that while chronic inflammation is not associated with a greater risk of CP/CPPS-like symptoms, it predicts symptom progression in men identified with CP/CPPS at baseline.

ACKNOWLEDGMENTS

Dr. Jennifer Cross assisted with immunological interpretation of results. Baseline biopsies were reread at Bostwick Laboratories.

REFERENCES

1. Krieger JN, Nyberg L and Nickel JC: NIH consensus definition and classification of prostatitis. JAMA 1999; **282:** 236.
2. Schaeffer AJ, Knauss JS, Landis JR et al: Leukocyte and bacterial counts do not correlate with severity of symptoms in men with chronic prostatitis: the National Institutes of Health Chronic Prostatitis Cohort Study. J Urol 2002; **168:** 1048.
3. True LD, Berger RE, Rothman I et al: Prostate histopathology and the chronic prostatitis/chronic pelvic pain syndrome: a prospective biopsy study. J Urol 1999; **162:** 2014.
4. Nickel JC, Roehrborn CG, O'Leary MP et al: Examination of the relationship between symptoms of CP/CPPS and histologic inflammation: baseline data from the REDUCE chemoprevention trial. J Urol 2007; **178:** 896.
5. Nickel JC, Alexander RB, Schaeffer AJ et al: Leukocytes and bacteria in men with chronic prostatitis/chronic pelvic pain syndrome compared to asymptomatic controls. J Urol 2003; **170:** 818.
6. Nickel JC: The three As of chronic prostatitis therapy: antibiotics, alpha-blockers and anti-inflammatories. What is the evidence? BJU Int 2004; **94:** 1230.
7. Anothaisintawee T, Attia J, Nickel JC et al: The management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. JAMA 2011; **305:** 78.
8. Andriole GL, Bostwick DG, Brawley OW et al: Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010; **362:** 1192.
9. Nickel JC, True LD, Kreiger JN et al: Consensus development of a histopathological classification system for chronic prostatic inflammation. Br J Urol Int 2001; **87:** 797.
10. Nickel JC, Roehrborn CG, Castro-Santamaria R et al: Chronic prostate inflammation is associated with severity and progression of benign prostatic hyperplasia, lower urinary tract symptoms and risk of acute urinary retention. J Urol 2016; **196:** 1493.
11. Nickel JC, Downey J, Hunter D and Clark J: Prevalance of prostatitis-like symptoms in a population based study employing the NIH-chronic prostatitis symptom index (NIH-CPSI). J Urol 2001; **165:** 842.
12. Propert KJ, Wang Y, Alexander R et al; Chronic Prostatitis Collaborative Research Network: Responsiveness of the NIH-CPSI. QOL Res 2006; **15:** 299.
13. Westendorf AM, Templin M, Geffers R et al: CD4+ T cell mediated intestinal immunity: chronic inflammation versus immune regulation. Gut 2005; **54:** 60.
14. Moro-García MA, Alonso-Arias R and López-Larrea C: When aging reaches CD4+ T-cells: phenotypic and functional changes. Front Immunol 2013; **10:** 107.
15. Sun L, Hurez VJ, Thibodeaux SR et al: Aged regulatory T cells protect from autoimmune inflammation despite reduced STAT3 activation and decreased constraint of IL-17 producing T cells. Aging Cell 2012; **11:** 509.
16. Murphy SF, Schaeffer AJ, Done J et al: IL17 mediates pelvic pain in experimental autoimmune prostatitis (EAP). PLoS One 2015; **10:** e0125623.
17. Kim CF and Moalem-Taylor G: Interleukin-17 contributes to neuroinflammation and neuropathic pain following peripheral nerve injury in mice. J Pain 2011; **12:** 370.
18. Logadottir Y, Delbro D, Fall M et al: Cytokine expression in patients with bladder pain syndrome/interstitial cystitis ESSIC type 3C. J Urol 2014; **192:** 1564.
19. Pontari M: Etiology of chronic prostatitis/chronic pelvic pain syndrome: psychoimmunoneurendocrine dysfunction (PINE syndrome) or just a really bad infection? World J Urol 2013; **31:** 725.
20. Nickel JC, Roehrborn C, Montorsi F et al: Dutasteride reduces CP/CPPS symptoms compared with placebo in men enrolled in the REDUCE study. J Urol 2011; **186:** 1313.