The Effect of a Pure Anti-inflammatory Therapy on Reducing Prostate-specific Antigen Levels in Patients Diagnosed With a Histologic Prostatitis

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OBJECTIVE To investigate the effectiveness and the tolerability of a combined pure anti-inflammatory therapy not associated with antibiotics on reducing PSA levels.

MATERIALS AND METHODS Patients with a previous biopsy negative for prostate cancer and showing persisting level of prostate-specific antigen (PSA) greater than 4 ng/dl were recruited. The specimens of previous biopsy were classified as benign or showing inflammation. Eligible patients were divided into 2 equal groups. In group 1, men with histological findings of inflammation at the previous prostatic biopsy were selected, in group 2, patients without such findings were included. Men of both groups were treated for 3 months with the same pure anti-inflammatory scheme including nimesulide, Serenoa repens, bromelain, and quercetin. After treatment, PSA levels were determined again. Independently by the second PSA determinations, all patients underwent a second 16 core biopsy.

RESULTS A total of 140 patients were enrolled. No adverse reactions were reported. Total PSA lowered from 7.3 ng/mL at baseline to 4.6 ng/mL (P <.0001) after treatment in group 1, and from 7.2 ng/mL to 7 ng/mL (P = .0005) in group 2. Overall, we diagnosed a prostate cancer at the second biopsy in 27 men among 140 (19.2%). The percentage of cancer at re-biopsy was 20% (14 of 70) in group 1 and 18.5% (13 of 70) in group 2. We found no cancer at the second biopsy in cases of PSA reduction below 4 ng/mL in both groups.

CONCLUSION Our protocol was very effective and safe in reducing PSA levels. The second biopsy failed to show prostate cancer in all patients with PSA lower than 4 ng/mL. UROLOGY 94: 198–203, 2016.

Since its introduction into clinical practice, the prostate-specific antigen (PSA) has greatly improved the incidence and the early diagnosis of prostate cancer (PC).[1]

Despite PSA is very selective for prostatic diseases, it is not specific for PC since it can increase even in benign prostatic hyperplasia (BPH) and prostatitis.[2]

A prostate biopsy is usually executed when the total PSA is greater than 4 ng/mL independently on the findings at digital rectal examination (DRE). Prostate biopsy is probably the weakest point of urologic practice since at least the two thirds of this invasive and costly procedure failed to detect a PC.[3] The low detection rate of prostate biopsy is determined by the lack of specificity of PSA that causes challenging diagnostic problems for urologists, additional morbidity, and anxiety for patients, and higher costs for health systems. Histological inflammation of the prostate is a very common finding in biopsy specimens of patients with an elevated PSA and no clinical evidence of prostatitis.[4] Inflammation of the prostate is a recognized cause of PSA elevation in absence of PC.[5] Prostatic inflammation leads to a deterioration of the natural anatomic and physiologic barriers between the prostatic milieu and the bloodstream determining increased PSA levels.[6]

In order to reduce the number of unnecessary prostatic biopsies minimizing the effects of inflammation on PSA elevation, several authors published in the official medical literature various protocols based on the administration of antibiotics alone or in association with anti-inflammatory drugs. By a review of literature, we found 25 studies that have investigated the issue of reducing PSA with the purpose to avoid or delay biopsy. Many of those protocols were very successful reporting a mean PSA reduction from baseline values reaching even the 42%.[7,8]

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However, from the evaluation of the literature, there is still not enough evidence suggesting to avoid a biopsy: reduction of PSA does not imply absence of tumor. Seven studies demonstrated that it is possible to detect a PC even in case of PSA reduction below 2.5 ng/mL.[8-14]

The objectives of this prospective cohort study was to investigate the effectiveness and the tolerability of a combined pure anti-inflammatory therapeutic protocol not associated with antibiotics on reducing PSA levels in cases of PSA elevation. This protocol was based on the contemporary administration of 4 compounds: nimesulide, Serenoa repens (saw palmetto extract), bromelain, and quercetin. As secondary endpoint, the cancer detection rate among those patients whose PSA levels dropped below 4 ng/mL was evaluated.

MATERIALS AND METHODS

Between January 2012 and March 2015, after written informed consent, all patients coming to our center with a normal DRE, a previous biopsy negative for PC, and showing persisting levels of PSA greater than 4 ng/mL were recruited in this prospective cohort study. The same qualified urologist (LG) performed all DREs and it was considered normal if there was no palpable induration, nodule, or suspicion of malignancy. All selected patients underwent a previous 12 core transrectal ultrasonography guided biopsy performed by the same urologist (LG) with a bi-planar technique using a 7.5 MHz probe (GE E8CS) using an automated biopsy gun and an 18 gauge needle. Prostate volume was estimated assuming an ellipsoid shape.

Biopsy specimens were all analyzed by the same pathologist who classified the results as benign or showing inflammation. Inflammation of the prostate was defined as infiltration of prostate biopsy specimens by inflammatory cells, lymphocytes, plasma cells, or histiocytes. Exclusion criteria were

- age less than 50 or greater than 75 years,
- a suspicious DRE,
- men with evidence of urinary tract infection on urinalysis,
- re-biopsy refused,
- a previous finding of atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia,
- a prior diagnosis of PC,
- an indwelling catheter or previous prostatic surgery of any nature,
- recent instrumentation of the genitourinary tract (less than 6 months),
- any form of hormonal manipulation or a history of allergy to nimesulide.

Eligible patients were divided into 2 equal groups with a 1:1 ratio. In group 1, men with histological findings of inflammation at the previous prostatic biopsy were selected, in group 2, patients without such findings were included.

Men of both groups were treated with the same pure anti-inflammatory combined therapy that included the following: nimesulide 100 mg bi-daily for 1 week each month for 3 months, Serenoa repens 320 mg once a day for 3 months, bromelain 200 mg bi-daily for 3 months, and quercetin 250 mg bi-daily for 3 months.

After such therapy, a second visit was scheduled: the free and total PSA levels were determined again with the same kit and the incidence of adverse reactions due to our treatment protocol was investigated. Independently, by the second PSA determinations, all patients underwent a second set of 16 cores transrectal ultrasonography guided biopsy. The second biopsy was scheduled within 2 weeks since the completion of the anti-inflammatory treatment at which it was used the same scheme of the first biopsy taking 12 cores from the peripheral zone and including 4 more specimens from the transitional zone. All biopsies were performed again by the same urologist and analyzed by the same pathologist.

For statistical analysis, we used the statistical package of Microsoft Excel. A *t*-test was used to evaluate the differences between the 2 groups of the mean values of the following features: age, prostate volume, total PSA at baseline, total PSA after treatment, free to total (F/T) PSA ratio at baseline, and F/T PSA ratio after treatment. We used a chi-square test to evaluate in both groups the effectiveness of our therapeutic regimen in terms of frequencies of PSA normalization, PSA reduction, F/T PSA ratio increase, and cancer at re-biopsy. A Z test on proportion difference was employed to evaluate the incidence of the following features: cancer although PSA reduction, cancer although F/T PSA increase, and cancer although F/T PSA ratio >20%.

We used a *t*-test to calculate the statistical significance of the variations in each group of the mean values at baseline and after treatment of total PSA and of F/T PSA ratio.

RESULTS

Overall, 140 patients respecting eligible criteria were enrolled in this prospective cohort study. Results are summarized in Table 1: data are reported as mean ± standard deviation. The 2 groups did not show statistically significant differences at baseline in terms of age ($P = 0.44$) and total PSA ($P = 0.31$) whereas prostatic volume was higher in subjects without inflammation ($P < .0001$) and the F/T PSA ratio was lower in subject with an histologic diagnosis of prostatitis ($P < .0001$). No adverse reactions were reported due our therapeutic regimen. Total PSA lowered from 7.3 ng/mL at baseline to 4.6 ng/mL after treatment in group 1 ($P < .0001$) and from 7.2 ng/mL to 7 ng/mL ($P = .0005$) in group 2 (Fig. 1). The percentage of mean PSA reduction from baseline to after-treatment values was of 37% in group 1 and 2.7% in group 2. The F/T PSA ratio increased from 18.6% baseline to 21.1% after treatment in group 1 ($P < .0001$) and from 23.5% to 23.6% in group 2 ($P = 0.15$) (Fig. 2).

After our treatment protocol, we assisted to a PSA reduction in 90% of patients (63 of 70) belonging to group 1 and in 62.8% (44 of 70) of patients in group 2 ($P < .0001$). A PSA normalization to levels lower than 4 ng/mL occurred in 35.7% (25 of 70) subjects in group 1 and in 2.9% (2 of 70) individuals in group 2 ($P < .0001$).

Overall in our study, we diagnosed a PC at the second biopsy in 27 men among 140 (19.2%). The percentage of cancer at re-biopsy was 20% (14 of 70) in group 1 and 18.5% (13 of 70) in group 2 ($P = 0.83$). A cancer at re-biopsy although PSA reduction was found in 20.6% (13 of 63) individuals in group 1 and in 13.6% (6 of 44) of patients with no findings of prostatic inflammation ($P = .167$). A PC at the second biopsy although an in-

Table 1. Results (mean ± standard deviation)

	Group 1 Histological Inflammation	Group 2 Absence of Histological Inflammation	*P* Value	Statistic Test Employed
Age	61.2 ± 7.5	61.3 ± 3.7	.444	*t* test
Prostate volume (mL)	53.6 ± 14.6	62 ± 13.4	<.0001	*t* test
Total PSA baseline (ng/mL)	7.3 ± 1.8	7.2 ± 1.7	.312	*t* test
Total PSA after treatment (ng/mL)	4.6 ± 1.7	7 ± 2	<.0001	*t* test
F/T PSA ratio baseline (%)	18.6 ± 3.1	23.5 ± 3.1	<.0001	*t* test
F/T PSA ratio after treatment (%)	21.1 ± 2.8	23.6 ± 3	<.0001	*t* test
Mean PSA reduction from baseline values (%)	37% (from 7.3 to 4.6)	2.7% (from 7.2 to 7)		
Mean F/T PSA ratio increase from baseline values (%)	13.4% (from 18.6 to 21.1)	0.4% (from 23.5 to 23.6)		
PSA normalization (%)	35.7% (25 of 70)	2.9% (2 of 70)	<.0001	Chi-square
PSA reduction (%)	90% (63 of 70)	62.8% (44 of 70)	<.0001	Chi-square
F/T PSA ratio increase (%)	85.7% (60 of 70)	61.4% (43 of 70)	<.0001	Chi-square
Cancer at re-biopsy (%)	20% (14 of 70)	18.5% (13 of 70)	.830	Chi-square
Cancer although PSA reduction (%)	20.6% (13 of 63)	13.6% (6 of 44)	.167	Z-test
Cancer although F/T PSA increase (%)	57.1% (8 of 14)	53.8% (7 of 13)	.431	Z-test
Cancer although F/T PSA ratio >20% (%)	21.4% (3 of 14)	61.5% (8 of 13)	<.0001	Z-test
Cancer although PSA normalization (%)	0% (0 of 25)	0% (0 of 2)		

F/T, free to total; PSA, prostate-specific antigen.

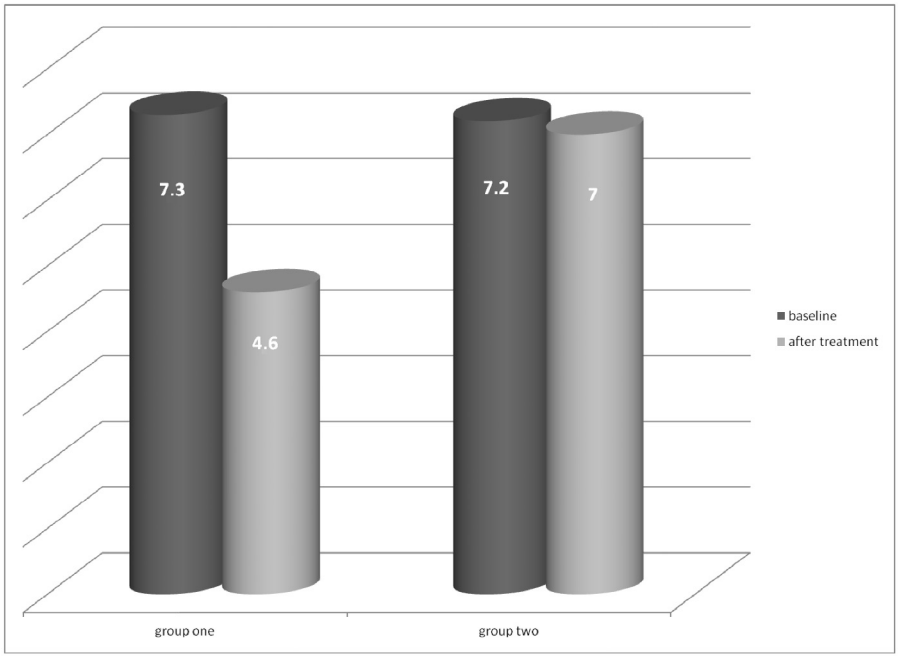

Figure 1. Total PSA at baseline and after treatment (ng/mL).

crease in the F/T PSA ratio was detected in 57.1% (8 of 14) patients in group 1 and in 53.8% (7 of 13) of men belonging to group 2 ($P = .43$). We diagnosed a PC even in cases of F/T PSA ratio higher than 20% in the 21.4% (3 of 14) of cases in group 1 and in 61.5% (8 of 13) on men included in group 2 ($P < .0001$).

We found no cancer at the second biopsy in cases of PSA reduction below 4 ng/mL in both groups.

COMMENT

This study concerns one of the most challenging dilemma for urologic community: the clinical management of patients who show persisting abnormal PSA levels with a concomitant negative biopsy and a normal DRE.

Since the first study performed by Jeanette Potts from Cleveland published on the Journal of Urology in 2000, other 24 authors spent great efforts to validate the best

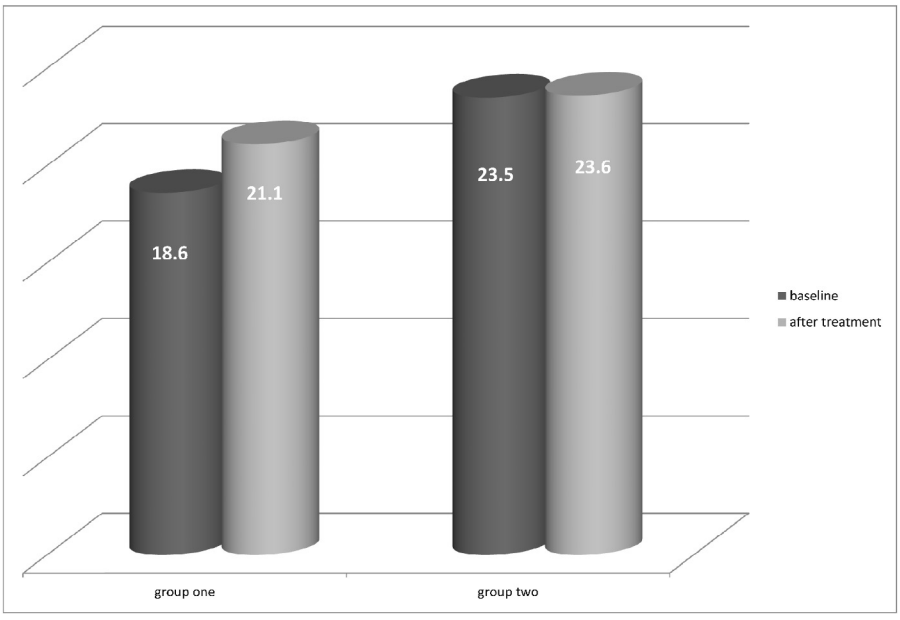

Figure 2. F–T PSA at baseline and after treatment (%).

therapeutic regimen in order to minimize the effects of prostate inflammation in increasing PSA. The goals of these studies were to reduce the number of unnecessary biopsies and to increase the detection rate for PC of this costly and invasive diagnostic procedure.

From the analysis of the published literatures about this very interesting topic, several causes for reflections have arisen.

(1) The grade of the effectiveness of such various protocols in reducing PSA values was extremely variable: the highest rate of mean total PSA reduction from its baseline values was 42%, achieved by Bulbul and Azab, whereas the lowest was 2.5% reported by Dirim and coworkers.[7,8,15] Surprisingly, two authors reported an increase of PSA values despite antibiotic or anti-inflammatory treatment.[9,16]

(2) Although PSA reduction or PSA normalization was achieved, there is not enough evidence to suggest to avoid a biopsy: reduction of PSA does not imply absence of tumor. Seven of 12 studies, in which a prostatic biopsy was executed despite PSA normalization, demonstrated that it is possible to detect a PC even in case of PSA reduction below 2.5 ng/dl.[8-14]

(3) Although it is well recognized that only 5%-10% of all prostatic inflammations are caused by bacteria, 24 among 25 protocols used an antibiotic.[17] In all studies, the antibiotic was a quinolone (ciprofloxacine, levofloxacine, or ofloxacine). In one study by Magri et al, azithromycin was added in order to eradicate a possible chlamydia infection.[18] The only published protocol that did not employ antibiotics was the one published by Candiano and coworkers who use a combined therapy with phytotherapic agents.[19]

(4) Six studies among 25 associated quinolones with a non-steroidal anti-inflammatory drugs (NSAID). Employed NSAIDs were 100 mg ketoprofen administered rectally for 5 days[20]; piroxicam 20 mg/day for 6 weeks[8,16]; ibuprofen or celecoxib for 4 weeks[21]; diclofenac sodium 75 mg slow release once a day, for 2-3 weeks[22]; not reported.[23]

(5) Only in 2 studies among 24, there was a rational use of antibiotics that were administered in cases of a proven bacteric prostatitis (National Institutes of Health classification type II).[18,23] The remaining 22 studies prescribed antibiotics although the presence of a bacteric infection even at culture analysis of the expressed prostatic secretion was excluded.

(6) Phytotherapic agents were used in 3 studies of which in 2 were associated with quinolone and in 1 given in monotherapy.[18,19,24]

(7) The effectiveness of quinolones in reducing PSA seems to be related more on their anti-inflammatory effects due to inhibition of IL6 than on their pure antibacterial properties.

Thus, our review of literature demonstrates the common abuse of antibiotics inside the urologic community that are paradoxically prescribed even in cases of proven absence of infection. Eggener et al reported 1 case of urosepsys after prostatic biopsy due to the onset of resistance determined by irrational employ of antibiotics.[9]

The present study investigated the effectiveness of a pure anti-inflammatory therapeutic protocol on reducing PSA in patients with abnormal PSA levels and a previous histologic diagnosis of prostatic inflammation. To the best of our knowledge this is the first prospective trial to use a pure anti-inflammatory therapy not associated with antibiotics for this purpose. Our protocol consisted of a very effective, common, and inexpensive NSAID (nimesulide) associated with 3 phytotherapic agents (Serenoa repens, bromelain, and quercetin). All these principles have already

showed their effectiveness on treatment of prostatitis in previous published trials.[25-28]

The 2 groups did not show statistically significant differences in terms of age and total PSA at baseline although prostatic volume was higher in subjects without inflammation. This finding can be justified by the fact that PSA elevation was determined by a higher prostatic volume (BPH) in group 2 and by the presence of an inflammation in group 1.

After our treatment protocol, we found a statistically significant higher reduction in total PSA value in patients with histological findings of prostatic inflammation. The percentage of mean PSA reduction from baseline to after-treatment values was of 37% in group 1 (from 7.3 ng/mL to 4.6 ng/mL) and of 2.7% (from 7.2 ng/mL to 7 ng/mL) in group 2. Thus, the anti-inflammatory therapy was much more effective in patients with a certified histologic diagnosis of prostatitis. These data are fundamental to explain the extreme variability in terms of effectiveness reported by the numerous protocols published in the official medical literature: an anti-inflammatory or antibiotic therapy is effective and justified in cases of prostatic inflammation or infection, whereas is useless, costly, and potentially dangerous in the other cases (BPH, latent PC).

In our study the F/T PSA ratio was statistically significantly lower in patients with histologic inflammation: 18.6% in group 1 vs 23.5% in group 2. These data showed that prostatitis reduces the F/T ratio and can dangerously mislead urologists in their clinical practice simulating a PC. Our protocol was even effective in increasing F/T ratio only in cases of prostatitis: we found an increase in main F/T ratio values after treatment compared with its baseline values of 13.4% (from 18.6% to 21.1%) in group 1 and of 0.4% (from 23.5% to 23.6%) in group 2. A statistically significant increase in F/T ratio after an antibiotic or anti-inflammatory therapy was reported even by Kaygisiz, Lorente, and Toktas, whereas Erol, Faydaci, Baltaci, and Dirim found an increase but not significant.[12-16,22,29]

Overall, in our study, we diagnosed a PC at the second 16 cores biopsy in 27 among 140 men (19.2%). We did not find differences in terms of cancer at re-biopsy among the 2 groups: 20% (14 of 70) in group 1 vs 18.5% (13 of 70) in group 2.

Our study showed that a F/T PSA ratio increase after therapy above 20% cannot be used as a criterion to avoid a second biopsy: 3 patients in group 1 and 8 patients in group 2 were diagnosed with a PC although this condition was achieved.

A PSA normalization after our protocol to levels lower than 4 ng/mL occurred in 35.7% subjects (25 of 70) in group and in 2.9% individuals (2 of 70) in group 2. We found PC in nobody of these 27 men even using a 16 cores scheme at second biopsy.

Basing on these data, physicians might consider the option to avoid or delay a second biopsy in patients who received a diagnosis of histologic prostatitis whose total PSA levels reduced below 4 ng/mL after such anti-inflammatory protocol. This option could be especially valid for patients who experienced major distress and adverse reactions at first prostate biopsy and who showed a negative emotive approach in repeating this invasive diagnostic procedure. However, due the limited number of patients included in this trial, this option can be considered only investigative and requires a careful and extensive patients' information about the potential risks and benefits of this practice. We encourage further trials with a larger number of patients to confirm the findings of this study.

CONCLUSION

An anti-inflammatory therapeutic protocol not associated with antibiotics with nimesulide, Serenoa repens, bromelain, and quercetin given for 3 months was very effective and safe in reducing PSA levels and in increasing F/T PSA ratio in patients previously diagnosed with a histologic inflammation of the prostate. The second biopsy failed to show PC in all patients with PSA lower than 4 ng/mL after anti-inflammatory therapy.

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