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TREATMENT OF CHRONIC BACTERIAL PROSTATITIS WITH LEVOFLOXACIN AND CIPROFLOXACIN LOWERS SERUM PROSTATE SPECIFIC ANTIGEN

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ABSTRACT

Purpose: We compared baseline and post-therapy prostate specific antigen (PSA) in patients with chronic bacterial prostatitis who were treated with levofloxacin or ciprofloxacin.

Materials and Methods: Subset analysis was done using a randomized, multicenter, double-blind, active control trial of 500 mg levofloxacin daily for 28 days vs 500 mg ciprofloxacin twice daily in 28 days in men with chronic bacterial prostatitis.

Results: Of the 377 men in the intent to treat population, including 197 treated with levofloxacin and 180 treated with ciprofloxacin, 35 on levofloxacin and 37 on ciprofloxacin with baseline PSA greater than 4 ng/ml were included in this analysis. Excluded from analysis were 2 levofloxacin treated patients with extremely high PSA at baseline (62 and 103 ng/ml, respectively). Mean baseline PSA ± SD in the patients analyzed was 8.33 ± 4.46 ng/ml, which decreased to 5.36 ± 3.82 ng/ml after therapy. There was no significant difference in the mean change in PSA between the levofloxacin and ciprofloxacin groups. Approximately 42% of patients with increased baseline PSA had a post-therapy PSA of 4 ng/ml or less. Of patients who were microbiologically evaluable and had normalized PSA after therapy levofloxacin eradicated the pathogen in 90.9% (10 of 11). However, of patients in whom post-therapy PSA remained increased the microbiological eradication rate was 69.2% (9 of 13). Similarly 93.3% of the ciprofloxacin group (14 of 15 patients) with normalized post-therapy PSA experienced microbiological eradication compared with 61.5% (8 of 13) with continued increased PSA after therapy.

Conclusions: Approximately 20% of patients diagnosed with chronic bacterial prostatitis had increased PSA. A significant decrease in PSA was observed in these patients after treatment with levofloxacin or ciprofloxacin. An association was observed between bacterial persistence and the likelihood that PSA would return to normal.

KEY WORDS: prostate, prostatitis, ofloxacin, ciprofloxacin, prostate-specific antigen

Chronic bacterial prostatitis is a common diagnosis in men of all ages and demographics, and it results in approximately 2 million office visits yearly in the United States.[1,2] Some controversy exists regarding the role that bacteria may have lay in causing chronic prostatitis as well as which bacteria are responsible for the pathological condition. A definitive diagnosis of chronic bacterial prostatitis (CBP) requires collecting and identifying the infecting pathogen by the Meares-Stamey 4 glass procedure. However, patients with chronic prostatitis are commonly treated empirically with antimicrobials as first line therapy. Due to the wide range of pathogens that may cause CBP and the recently observed trend of increased gram-positive pathogens[3,4] a broad-spectrum agent with gram-positive and gram-negative activity would be ideal. Because of this, fluoroquinolones have become a frequent initial choice for CBP treatment.

Numerous studies have linked prostatitis with an increase in serum prostate specific antigen (PSA).[5–7] However, these groups did not specifically diagnose patients with chronic bacterial prostatitis. PSA has become an important tool in prostate cancer screening[8] and men with serum PSA greater than 4 ng/ml are at higher risk for prostate cancer. These patients are usually referred for a biopsy procedure. However, increased PSA is also associated with conditions other than cancer, such as prostate inflammation, and prostatitis treatment has been shown to decrease PSA in a significant percent of such patients. Treatment of prostatitis with an antimicrobial and/or anti-inflammatory medication may provide a cost-effective approach to decrease the number of negative biopsies.[9,10] Initial prostatitis treatment may also provide a more acceptable alternative in patients who are apprehensive about undergoing transrectal ultrasound guided biopsy.

Using data from a large, randomized, multicenter, double-blind clinical trial we report changes in PSA in patients diagnosed with chronic bacterial prostatitis who underwent fluoroquinolone antimicrobial therapy.[11] Followup PSA was examined in patients with increased baseline PSA and clinical outcomes were analyzed.

MATERIALS AND METHODS

Study design. This report represents a subanalysis from a multicenter, double-blind, randomized trial comparing 500 mg levofloxacin orally daily and 500 mg ciprofloxacin orally twice daily for 28 days for chronic bacterial prostatitis. A description of the study design has been published previous-

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ly.[11] Briefly, men 18 years or older with a clinical diagnosis of CBP were included. CBP was diagnosed based on 3 criteria, namely a history of CBP, current clinical signs and symptoms of prostatitis, and laboratory evidence of bacterial prostatitis. Expressed prostatic secretions or post-prostatic massage specimens were obtained for culture using the Meares-Stamey method.[12] Patients with known prostate cancer or recent transurethral resection of the prostate were excluded from study. Additionally, patients with any gross abnormalities of the prostate gland identified by digital rectal examination were excluded.

Investigators obtained serum samples for PSA analysis from all white men older than 50 years and all black men older than 40 years. At physician discretion other patients may also have had PSA analysis performed. Patient assessments were performed at study entry, study days 7 and 21, and between days 33 and 46, that is 5 to 18 days after the last dose of active drug for post-therapy analysis.

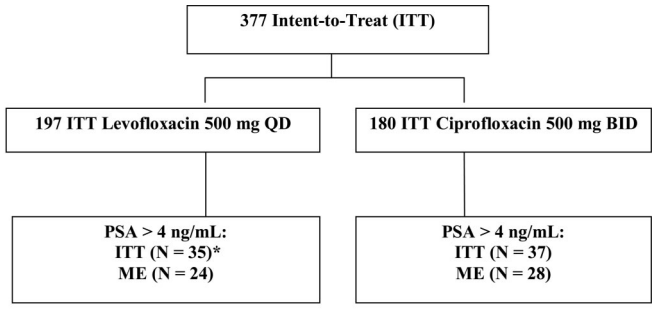
Clinical and microbiological assessment. Clinical assessments after therapy were determined by the investigator using certain criteria, including clinical cure—all signs and symptoms of the current prostatitis episode had resolved or remitted to the subject normal pre-infection baseline, clinical improvement—clear, appreciable improvement in the degree of signs and symptoms of the current prostatitis episode, such that no additional antibacterial therapy was required, and clinical failure—no appreciable improvement or worsening in the signs and symptoms of the current prostatitis episode. Clinical success was defined as clinical cure or improvement.

Microbiological assessment was based on post-therapy culture results using certain criteria, namely eradicated—absence of the admission pathogen(s) on post-therapy culture obtained in the absence of potentially effective systemic antimicrobials, persisted—continued presence of the admission pathogen in the post-therapy culture and presumed persisted—presumed presence of the admission pathogen after therapy in subjects with clinical failure in whom no test of cure culture was taken or a negative culture was obtained after modification of study therapy.

Statistical analysis. The Student t test was used to compare the change in post-therapy PSA from baseline in the treatment groups. Statistical tests of hypotheses were done at the 2-sided 5% significance level.

RESULTS

Patient disposition and characteristics. In the clinical trial, the total intent to treat (ITT) population consisted of 377 patients, including 197 randomized to receive levofloxacin and 180 randomized to receive ciprofloxacin (see figure). PSA was determined obtained at baseline and after therapy in 320 patients, including 169 in the levofloxacin group and 151 in the ciprofloxacin group. Of these patients 37 (21.9%) in the levofloxacin group and 37 (24.5%) in the ciprofloxacin group had increased serum PSA at baseline (greater than 4 ng/ml). Two patients in the levofloxacin treated group were excluded due to extremely high PSA at baseline (62 and 103 ng/ml), which remained highly increased after therapy (59 and 92 ng/ml, respectively). The reason for these high values was possibly a condition other than chronic bacterial prostatitis, although no followup information was obtained on these patients. A total of 24 and 28 patients receiving levofloxacin or ciprofloxacin, respectively, were microbiologically evaluable (ME), defined as having culture samples obtained at baseline and after therapy for analysis.



*Two patients treated with levofloxacin were excluded due to exceedingly high PSA values (62 and 103 ng/mL)

Disposition of patients included in clinical trial. *QD*, daily. *BID*, twice daily. Asterisk indicates 2 levofloxacin treated patients who were excluded from analysis due to extremely high PSA (62 and 103 ng/ml, respectively).

The 2 treatment groups showed similar baseline characteristics (table 1). The levofloxacin treatment group had a larger proportion of patients older than 65 years, although the difference was not significant. The ciprofloxacin group had slightly higher mean baseline PSA and each treatment group underwent a comparable average treatment duration. Of 35 levofloxacin treated patients 12 (34.3%) and 9 of 37 (24.3%) on ciprofloxacin were administered nonsteroidal anti-inflammatory drugs (NSAIDs) during the study.

PSA analysis after therapy. In all patients with measured baseline and after therapy PSA (318, not including 2 with extremely high baseline and post-therapy PSA) mean PSA $\pm$ SD decreased from 3.03 $\pm$ 3.67 to 2.05 $\pm$ 2.76 ng/ml (mean change -0.98 ± 2.14, $p < 0.0001$). In patients with baseline PSA less than 4 ng/ml (246) mean PSA decreased from 1.48 $\pm$ 1.02 to 1.09 $\pm$ 1.21 ng/ml (mean change -0.38 ± 1.09, $p < 0.0001$).

In patients with increased PSA at baseline (greater than 4 ng/ml) measurements after therapy showed a significant decrease in mean PSA from 8.33 $\pm$ 4.46 to 5.36 $\pm$ 3.82 ng/ml ($p < 0.0001$). Mean PSA was decreased by 2.81 ng/ml in those treated with levofloxacin and by 3.13 ng/ml in ciprofloxacin treated patients (levofloxacin vs ciprofloxacin $p = 0.687$, table 2). Similar decreases were observed in mean PSA in the ME population. Additionally, 11 of 24 ME patients (45.8%) treated with levofloxacin had a post-therapy PSA of 4 ng/ml or less compared with 15 of 28 ME patients (53.6%) treated with ciprofloxacin.

Clinical and microbiological outcomes in these patients were compared between treatment groups based on post-therapy PSA (tables 3 and 4). In the ME population levofloxacin and ciprofloxacin achieved greater than 90% clinical success and microbiological eradication in patients with normalized PSA (4 ng/ml or less) after therapy. However, success rates were much lower in patients with continued increased PSA after therapy (less than 70% clinical or microbiological success in the ME population with levofloxacin or ciprofloxacin treatment). There were no significant differences in clinical or microbiological outcomes between treatment groups regardless of PSA after therapy.

DISCUSSION

This analysis suggests that antimicrobial therapy in patients with chronic bacterial prostatitis may result in a subsequent decrease in PSA. All patients with or without increased PSA at baseline showed a significant decrease in mean PSA after fluoroquinolone treatment. The patient population with CBP and increased PSA (greater than 4 ng/ml) at baseline experienced a decrease in mean PSA of 8.33 ng/ml at baseline to 5.36 ng/ml at the post-therapy evaluation ($p < 0.0001$). Overall 30 of 72 patients (42%) with increased PSA at baseline had normalized PSA after fluoroquinolone treatment. This is in agreement with previous studies showing that treatment of chronic prostatitis

TABLE 1. *Patient demographics and baseline characteristics*

	Levofloxacin		Ciprofloxacin	
	ITT	ME	ITT	ME
No. pts	35	24	37	28
Age:				
Mean ± SD	63.0 ± 10.2	63.0 ± 10.1	59.2 ± 11.5	57.6 ± 10.3
Range	42–81	49–81	31–82	31–75
No. age category (%):				
45 or Younger	1 (2.9)	0	5 (13.5)	4 (14.3)
46–64	18 (51.4)	14 (58.3)	20 (54.1)	17 (60.7)
65 or Older	16 (45.7)	10 (41.7)	12 (32.4)	7 (25.0)
No. race (%):				
White	27 (77.1)	17 (70.8)	28 (75.7)	20 (71.4)
Black	5 (14.3)	5 (20.8)	5 (13.5)	4 (14.3)
Other	3 (8.6)	2 (8.3)	4 (10.8)	4 (14.3)
Mean wt ± SD (kg)	85.8 ± 13.1	86.7 ± 13.0	86.6 ± 15.3	85.5 ± 12.0
Baseline PSA (ng/ml):				
Mean ± SD	7.88 ± 3.60	7.73 ± 3.52	8.76 ± 5.15	8.88 ± 4.96
Range	4.0–18.4	4.0–18.4	4.1–22.0	4.1–22.0
Mean therapy duration ± SD (days)	26.9 ± 6.2	28.1 ± 0.4	27.3 ± 5.3	27.7 ± 2.6

TABLE 2. *PSA at baseline and after therapy in ITT and ME populations*

Treatment	No. Pts	Mean PSA ± SD (ng/ml)	
		Baseline	After Therapy
ITT:			
Levofloxacin	35	7.88 ± 3.60	5.07 ± 2.65
Ciprofloxacin	37	8.76 ± 5.15	5.63 ± 4.70
ME:			
Levofloxacin	24	7.73 ± 3.52	4.89 ± 2.56
Ciprofloxacin	28	8.88 ± 4.96	5.09 ± 4.34

with antimicrobials and anti-inflammatory drugs can decrease serum PSA to within the normal range in a significant percent of men.[9,13] Interestingly patients in this study with baseline PSA less than 4 ng/ml also experienced a significant decrease in mean PSA after antimicrobial therapy.

The PSA test provides an important tool for screening in men at higher risk for prostate cancer. However, because PSA is tumor associated and not tumor specific, other physiological conditions besides cancer can increase serum PSA and lead to potentially unnecessary biopsy procedures that increase patient inconvenience and overall medical costs.[14] Some estimates suggest that as many as two-thirds of biopsies recommended by increased PSA are negative for prostate cancer.[15,16] Antimicrobial treatment in patients with increased PSA and confirmed or suspected CBP may eliminate the need for some biopsies and decrease the number of unnecessary procedures. However, further research is needed to understand more fully the long-term effects of antimicrobial treatment and PSA.

This study demonstrates an association between PSA normalization after treatment, and clinical and microbiological outcomes. Patients who had normalized PSA after therapy were more likely to have experienced clinical and microbiological success with fluoroquinolone treatment for CBP. In the ME population pathogen eradication occurred in 92.3% of patients (24 of 26) who had PSA at or below 4 ng/ml after therapy compared with 65.4% (17 of 26) of those with continued increased PSA. The reason for this remains unclear, although successful eradication of infection may result in decreased prostate inflammation, which is an important factor in increased PSA.[6] Results were comparable between the levofloxacin and ciprofloxacin treatment groups and, as reported earlier, the 2 treatments were well tolerated.[11]

A number of limitations to this study must be addressed. A control group was not included to determine if the absence of fluoroquinolone treatment or the use of anti-inflammatory medication alone would result in decreased PSA in patients with chronic bacterial prostatitis. Of the 72 patients included in this analysis 21 (29.2%) received NSAIDs during the course of this study. Treatment of chronic prostatitis with a combination of antimicrobials and anti-inflammatory agents has been previously shown to decrease PSA.[9] However, the role of NSAID therapy alone on decreasing PSA has not been well documented. Additionally, although increased PSA in patients in this study was assumed to be caused by prostatitis, no ultrasound or biopsy procedures were performed to exclude other causes of increased PSA. Two patients with extremely high PSA were not included in this analysis because PSA remained highly increased after therapy. The reason for the increase is unknown. There was no long-term followup of these 2 patients to determine if decreased PSA was maintained. However, the long-term (6-month) clinical success of CBP treatment was comparable between levofloxacin and ciprofloxacin treated patients.[11] Long-term followup PSA values were not obtained. This report only includes patients with proven or suspected chronic bacterial prostati-

TABLE 3. *Clinical success based on post-therapy PSA*

Post-Therapy PSA (ng/ml)	No. ITT (%)			No. ME (%)		
	Levofloxacin	Ciprofloxacin	95% CI*	Levofloxacin	Ciprofloxacin	95% CI
Overall	35	37		24	28	
4 or Less:†	14	16		11	15	
Success	12 (85.7)	15 (93.8)	−33.4, 17.4	10 (90.9)	14 (93.3)	−28.1, 23.3
Failure	2 (14.3)	1 (6.3)		1 (9.1)	1 (6.7)	
Greater than 4:	21	21		13	13	
Success	14 (66.7)	15 (71.4)	−35.1, 25.5	9 (69.2)	9 (69.2)	−39.3, 39.3
Failure	5 (23.8)	5 (23.8)		4 (30.8)	4 (30.8)	
Unknown	2 (9.5)	1 (4.8)		0	0	

No patients had an unknown outcome.
* All patients with clinical failure or an unknown outcome were combined.

TABLE 4. *Microbiological eradication based on post-therapy PSA*

Post-Therapy PSA (ng/ml)	No. ITT (%)			No. ME (%)		
	Levofloxacin	Ciprofloxacin	95% CI*	Levofloxacin	Ciprofloxacin	95% CI
Overall	35	37		24	28	
4 or Less:	14	16		11	15	
Eradicated	11 (78.6)	14 (87.5)	−39.4, 21.6	10 (90.9)	14 (93.3)	−28.1, 23.3
Persisted	1 (7.1)	1 (6.3)		1 (9.1)	1 (6.7)	
Unknown	2 (14.3)	1 (6.3)		0	0	
Greater than 4:	21	21		13	13	
Eradicated	11 (52.4)	10 (47.6)	−27.8, 37.4	9 (69.2)	8 (61.5)	−32.6, 48.0
Persisted	5 (23.8)	6 (28.6)		4 (30.8)	5 (38.5)	
Unknown	5 (23.8)	5 (23.8)		0	0	

* All patients in persisted and unknown categories were combined.

tis diagnosed by the standard 4 glass test. Results in men with asymptomatic prostatitis were not included in this analysis, although they may be an important group to consider in future studies since they may have a positive 4 glass test, as do symptomatic patients.[4] The effect of antimicrobials on PSA levels in patients with nonbacterial prostatitis was not considered in this study.

CONCLUSIONS

Fluoroquinolone treatment in men with chronic bacterial prostatitis and increased PSA resulted in decreased mean PSA after therapy (8.33 to 5.36 ng/ml). ME patients who had normalized PSA after therapy were more likely to have experienced clinical and microbiological success than patients with continued increased PSA (greater than 90% overall vs less than 70%). Results were comparable between the levofloxacin and ciprofloxacin treatment groups. Additional research is needed but it appears that in patients diagnosed with CBP and increased PSA an antimicrobial regimen may provide more acceptable initial treatment than proceeding directly to prostate biopsy.

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