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Prulifloxacin versus Levofloxacin in the Treatment of Chronic Bacterial Prostatitis: a Prospective, Randomized, Double-Blind Trial

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Summary

Ninety-six patients with chronic bacterial prostatitis (CBP) and evidence of infection were randomized to receive a 4-week oral course of either prulifloxacin (a new fluoroquinolone) 600 mg or levofloxacin 500 mg once daily. They were evaluated with the Meares-Stamey test and the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) at baseline and one week after therapy completion. Patients with microbiological eradication were evaluated again with the Meares-Stamey test 6 months after therapy completion. The microbiological eradication rate was 72.73% for prulifloxacin and 71.11% for levofloxacin (p=0.86) and the reduction in the NIH-CPSI was 10.75 and 10.73, respectively (p=0.98). Safety was comparable, with 18.18% adverse events for prulifloxacin and 22.22% for levofloxacin (p=0.79). Thus, a 4-week course of prulifloxacin 600 mg once daily is at least as effective and safe as levofloxacin 500 mg once daily in the treatment of CBP.

Key words: **Chronic bacterial prostatitis, Meares-Stamey test, National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), prulifloxacin, levofloxacin, prostatitis.**

INTRODUCTION

Prostatitis is considered the most common outpatient condition in urologic practice in men younger than 50 years [1]. The categories of prostatitis associated with a bacterial etiology are reported to be much less prevalent than those believed to have a non bacterial etiology. Nonetheless, up to 10% of patients evaluated for the so called "chronic prostatitis" are ultimately diagnosed with chronic bacterial prostatitis (CBP), equivalently termed type II prostatitis according to the NIDDK/NIH classification [2].

The Meares-Stamey four-glass test is the traditional and formal method used to evaluate the microbiologic and inflammatory status of the lower urinary tract, and it has been strongly recommended as the test of choice when attempting to diagnose CBP [3].

The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) [4] is a validated reliable and responsive tool to objectively assess the symptom complex in patients with chronic prostatitis and chronic pelvic pain syndrome. Since its development in 1999 it has been translated and validated in multiple languages and is now used in the everyday clinical practice by many centers worldwide [5].

The recommended therapy of patients with CBP is a 4- to 6-week oral course of fluoroquinolones (such as ciprofloxacin and levofloxacin), due to their high oral bioavailability and penetration into the prostatic ducts, wide antibacterial activity against Gram-positive and Gram-negative uropathogens, including

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Pseudomonas aeruginosa, and good safety profile [6]. However, since the various fluoroquinolones have different pharmacokinetic and pharmacodynamic properties and exhibit different microbial resistance patterns, the optimal drug is still being sought [7,8].

Prulifloxacin, the prodrug of ulifloxacin, is a new broad-spectrum oral fluoroquinolone, with greater *in vitro* activity against isolates of Gram-negative bacteria than ciprofloxacin and other fluoroquinolones [9]. Its relatively long half-life and high urinary concentrations allow a once-daily administration. Prulifloxacin has demonstrated good microbiological and clinical efficacy in two recent trials including patients with acute uncomplicated and complicated lower urinary tract infections, and has a better tolerability profile than that of other fluoroquinolones in terms of its cardiological and neurological safety [10,11].

The aim of the present prospective randomized trial was to assess the efficacy and safety of a 4-week regimen of prulifloxacin in comparison with levofloxacin, a reference fluoroquinolone, in the treatment of patients with CBP.

PATIENTS AND METHODS

Patients

After Institutional Review Board approval, 96 consecutive patients referring to our outpatient clinic between June 2005 and March 2006 and diagnosed with CBP were enrolled in the present study. Inclusion criteria were age greater than 18 years and diagnosis of CBP, as confirmed by each of the following: 1) one previous symptomatic episode of bacterial prostatitis of at least 4 weeks' duration or two or more episodes of any duration in the preceding 12 months; 2) current symptoms of prostatitis (such as dysuria, frequency, urgency, suprapubic or perineal discomfort, painful ejaculation); 3) current laboratory evidence of prostatitis with a single uropathogen identified. Exclusion criteria were genitourinary tract abnormalities, history of sexually transmitted diseases, active urethritis, bladder outlet obstruction, previous prostate and urethral surgery, inflammatory bowel disease, neurological diseases affecting the bladder, previous or concomitant malignancies, renal or hepatic failure, known fluoroquinolone hypersensitivity or previous therapy with either of the study drugs (levofloxacin and prulifloxacin). All participants provided a written informed consent.

Study design

At study entry, which preceded by 5 to 7 days the start of therapy, all patients were evaluated with a thorough medical history, complete physical examination, NIH-CPSI, which has recently been translated and validated in Italian [5], and the Meares-Stamey four-glass test. Infection was confirmed by isolating the pathogen on the basis of the standard cut-off points, i.e. an at least 10-fold increase in the bacterial colony-forming unit concentration in the expressed prostatic secretions (EPS) and/or voided urine after prostate massage (VB3) compared to initial voided urine. Evidence of increased leukocyte count (>10 white blood cells per high power field) in the EPS and/or VB3 was mandatory for diagnosis. All organisms were identified using standard procedures and tested for antimicrobial susceptibility by disk diffusion assay. Additional exclusion criteria at this point were isolation of pathogens other than *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa* and *Enterococci* spp., which are the only etiologically recognized organisms of CBP according to the European Association of Urology guidelines on urinary tract infections [6], and microbial resistance to levofloxacin. Levofloxacin is regularly tested by the clinical laboratory of our hospital with National Committee for Clinical Laboratory Standards susceptibility breakpoints of 0.25-2.8 μg/ml for Gram-positive and 0.5-4.8 μg/ml for Gram-negative bacteria, and its resistance rate for uropathogens has been shown to be comparable to that of prulifloxacin in a recent report exploring microbial resistance patterns in four areas of Italy [12].

Patients were then randomized by a computer-generated schedule to receive a 4-week oral course of either prulifloxacin 600 mg once daily or levofloxacin 500 mg once daily. All tablets were over-encapsulated and delivered by a specialized research nurse of the outpatient clinic to maintain double blinding.

On visit 1 (2 weeks after therapy start) the NIH-CPSI was administered but no microbiological assessment was performed. On visit 2 (one week after therapy completion) the NIH-CPSI was administered and the Meares-Stamey test was performed. On visit 3 (6 months after therapy completion) patients found to have a microbiological eradication on visit 2 were evaluated for recurrent prostate infection with a new Meares-Stamey test.

Treatment-emergent adverse events, defined as any adverse event first occurring or worsening after randomization, were monitored at each visit and their severity and relationship to study drug was also recorded.

Study endpoints and statistical analysis

The primary endpoint was microbiologic efficacy, as assessed by the overall eradication rate of the infecting strains. The secondary endpoints were clinical efficacy, as assessed by NIH-CPSI reduction, recurrent infection rate at 6 months and safety, as assessed by evaluating all treatment-emergent adverse events. All analyses were conducted on an intent-to-treat basis. Two-sided 95% confidence intervals (CI) were computed around the difference

(prulifloxacin minus levofloxacin) in evaluating noninferiority. Noninferiority would be established if the upper boundary of the 95% CI was less than 20% and the CI crossed zero. Logistic regression was used to evaluate the association between the improvement in the NIH-CPSI score and Meares-Stamey test results at visit 2. The association was expressed in terms of odds ratio (OR) and the precision of the estimates was indicated by 95% CI. Differences in patient characteristics between the two groups of subjects were calculated by Fisher's exact test for categorical variables and by Wilcoxon rank sum test for continuous variables. Values of p were considered significant when ≤0.05 and marginally significant or indicative of a trend when ranging between 0.05 and 0.1. All statistical analyses were performed with SAS v9.1 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 96 patients were enrolled in the present trial and randomized to prulifloxacin (n=48) or levofloxacin (n=48) treatment. Median age was 42 years (range 32 to 58). The two groups were comparable with regard to clinical baseline characteristics (*Table 1*).

TABLE 1 - *Patient characteristics for the two groups at baseline.*

	Prulifloxacin group (n=48)	Levofloxacin group (n=48)	p
Age in years, median (range)	44 (31-58)	44 (30-54)	0.87
Episodes of bacterial prostatitis within 12 months prior to study entry, median (range)	3 (1-6)	3 (1-5)	0.71
NIH-CPSI score, mean (range)	17.22 (8-25)	17.33 (9-27)	0.81

Two patients in each group were lost to follow-up. Two men in the prulifloxacin group and one in the levofloxacin group dropped out for treatment-related adverse events. Consequently, 44 patients in the prulifloxacin group and 45 patients in the levofloxacin group were suitable for the final analysis.

The identified uropathogens at study entry were: *Escherichia coli* in 15 and 16 patients, *Klebsiella pneumoniae* in 8 and 6 patients, *Proteus mirabilis* in 7 and 6 patients, *P. aeruginosa* in 2 and 4 patients and *Enterococcus faecalis* in 12 and 13 patients in the prulifloxacin and levofloxacin groups, respectively.

Of the 44 patients treated with prulifloxacin, 32 (72.73%) had a negative Meares-Stamey test at visit 2, and in the group treated with levofloxacin, 32 patients out of 45 (71.11%) had a negative test (p=0.86). The 95% confidence interval for the observed 1.62 difference was -16.74 to 19.76 (-18.23 to 21.21 including the continuity correction). The eradication rates for the single bacteria are detailed in *Table 2*.

TABLE 2 - *Eradication rate for the single bacteria in the assessable patients.*

	Prulifloxacin group (n=44)	Levofloxacin group (n=45)
Escherichia coli	12/15 (80%)	12/16 (75%)
Klebsiella pneumoniae	6/8 (75%)	4/6 (66.67%)
Proteus mirabilis	5/7 (71.42%)	4/6 (66.67%)
Pseudomonas aeruginosa	1/2 (50%)	2/4 (50%)
Enterococcus faecalis	8/12 (66.67%)	10/13 (76.92%)
overall	**32/44 (72.73%)**	**32/45 (71.11%)**

The average reduction in the NIH-CPSI score from study entry to visit 2 was 10.75 (from 17.22 to 6.47) in the group treated with prulifloxacin and 10.73 (from 17.33 to 6.6) in the group treated with levofloxacin. The reduction was statistically significant both in patients treated with prulifloxacin and in those treated with levofloxacin (p-value of paired t-test <0.0001 in both groups). The difference in the score reduction (0.017) was not statistically significant (p=0.98). When considering the average reduction in the NIH-CPSI score from study entry to visit 1, this was higher in the prulifloxacin group than in the levofloxacin group (5.29 vs 4.80, respectively), but the difference was only marginally significant (p=0.1).

There was a statistically significant relationship between the improvement in the NIH-CPSI score from baseline visit to day 35 and Meares-Stamey test results on day 35 in both groups, that is, patients with greater reduction in the score were more likely to have negative Meares-Stamey test on day 35 (p=0.001 for prulifloxacin and p=0.02 for levofloxacin). Considering all patients, the likelihood of having a negative Meares-Stamey test on day 35 per each one-point decrease in the NIH-CPSI score from baseline to day 35 increased by 63% (OR=1.63; 95%CI: 1.30-2.03). In the prulifloxacin group it increased by 41% (OR=1.41; 95%CI: 1.14-1.73) and in the levofloxacin group by approximately 4 times (OR=4.11; 95%CI: 1.30-2.03).

At visit 3 five patients in the prulifloxacin group and 11 in the levofloxacin group had a positive

Meares-Stamey test, the difference being only marginally significant (p=0.1 when considering all patients and p=0.08 when considering only patients with negative Meares-Stamey test at visit 2).

Both drugs were well tolerated. Eight out of 44 patients (18.18%) in the prulifloxacin group and 10 out of 45 men (22.22%) in the levofloxacin group experienced treatment-related adverse events, with no significant difference (p=0.79). Five and three patients in the prulifloxacin group had diarrhoea and skin rash, respectively. One patient with either complication discontinued the medication due to severity. Five, three and two patients in the levofloxacin group had gastric pain, headache and nausea, respectively. One patient with severe gastric pain dropped out.

DISCUSSION

The present single-center study is, to the best of our knowledge, the first prospective randomized trial that has ever tested prulifloxacin, a new fluoroquinolone drug with broad-spectrum antimicrobial activity and high urinary concentrations, in the treatment of CBP. Our results seem to indicate an equivalent microbiological and clinical efficacy and a comparable safety profile of prulifloxacin to those of levofloxacin, which is a reference drug for bacterial prostatitis.

In the field of urological infections, prulifloxacin has already been tested in two multicenter randomized clinical trials. In the first, it showed comparable efficacy to pefloxacin as single-dose therapy in women with acute uncomplicated urinary tract infections [10]. In the second, it exhibited a similar eradication rate to ciprofloxacin in the treatment of complicated urinary tract infections in both sexes [11]. Tolerability of prulifloxacin was high in both studies.

The rationale for testing prulifloxacin in CBP patients derives from *in vitro* data. Recent studies have, in fact, shown that ulifloxacin, the active metabolite of prulifloxacin, has greater penetration within bacteria compared to levofloxacin, ciprofloxacin and gatifloxacin [13,14]. It has also been demonstrated that ulifloxacin easily enters macrophages and polymorphonuclear neutrophils, thereby killing bacteria directly or rendering them more prone to phagocytic action [15]. Both are highly desirable properties in the CBP setting, since most antibiotics are known to have a low diffusion capability into chronically inflamed/infected prostate ducts [16]. In addition, ulifloxacin has been found to stimulate the synthesis of several cytokines, such as IL-6, IL-8 and TNF-α, which may play a key role in mediating and possibly antagonizing the infective process in the prostate *in vivo* by enhancing the local immune response [17].

Our results are in accordance with those reported by Bundrick *et al* in a recent multicenter trial comparing levofloxacin to ciprofloxacin in the treatment of CBP [18], in that approximately three quarters of patients showed eradication of the infecting strain after the 4-week course of fluoroquinolone therapy. Moreover, similarly to the findings of the same study, a relatively high proportion (approximately one quarter) of Gram-positive pathogens was isolated in our patients, thus emphasizing the necessity of a broad-spectrum antibiotic coverage when treating this disease entity.

As an additional outcome measure, in the current study we evaluated the clinical efficacy of the drug treatment, since we believe that in patients with CBP, besides microbiological eradication, improvement of the symptom complex should be a fundamental goal of therapeutic efforts, and currently appropriate and validated tools, such as the NIH-CPSI questionnaire, are available to assess it. Our results demonstrated a significant reduction in the NIH-CPSI score from study entry to treatment completion in both groups, which was obtained in the vast majority of patients. This finding has never been previously reported in the literature. Moreover, we observed a greater, albeit not significant, reduction in the NIH-CPSI after 2 weeks of treatment in the prulifloxacin group compared to levofloxacin group. Based on this trend, we can speculate that prulifloxacin may lead to faster clinical improvement, so that even a shorter course of treatment might be sufficient. This could have been substantiated by microbiological data, but a Meares-Stamey test was not performed at that time, since the ongoing medication was deemed to possibly inhibit the growth of pathogens.

Interestingly, there appeared to be a significant association between microbiological eradication and clinical improvement, assessed with the NIH-CPSI score. If this finding is substantiated by additional, large-sampled studies, the symptom scoring system might be used to monitor treatment efficacy, replacing the more complicated, time-consuming and costly Meares-Stamey test.

A further point deserving comment in our study is a lower, albeit only marginally significant, proportion of patients treated with prulifloxacin having recurrent prostate infection at 6-month follow-up visit compared to levofloxacin. On the basis of this trend, we postulate that the difference in long-term microbiological success may be due to the above mentioned chemical properties of the active metabolite, which, by means of its putative direct action on the chemotaxis of neutrophils and other phagocytes, presumably creates an unfavorable milieu against persisting or re-infecting bacteria. Additional *in vitro* and *in vivo* studies are eagerly awaited to clarify this issue.

The main limitation of our study is the relatively small number of patients per arm, which may have lowered the statistical power to detect a difference with regard to the secondary endpoints, especially

the 6-month re-infection rate. Furthermore, unlike levofloxacin, microbial resistance to prulifloxacin by the disk diffusion assay was not tested, thus possibly biasing its true efficacy rate.

In conclusion, the present results suggest that prulifloxacin 600 mg orally once daily is at least as effective and safe as levofloxacin 500 mg orally administered once daily for 4 weeks in the management of patients with CBP. Therapy with both drugs enables the great majority of patients to achieve microbiological eradication of the infecting strain and to significantly improve the symptom complex. Multicenter randomized trials of adequate size are needed to confirm our findings.

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