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Prulifloxacin versus Ciprofloxacin in the Treatment of Adults with Complicated Urinary Tract Infections

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Key Words
Complicated UTI · Prulifloxacin · Ciprofloxacin

Abstract
Introduction: The present study was performed to evaluate the efficacy and safety of a 10-day regimen of prulifloxacin 600 mg once daily as compared to ciprofloxacin 500 mg twice daily in the treatment of patients with complicated urinary tract infections (UTIs). ***Materials and Methods:*** 257 patients (mean age ± SD 62.3 ± 16.5) were enrolled and orally treated with prulifloxacin (127 patients) or ciprofloxacin (130 patients). The study was designed as a randomized, double-blind, double-dummy, controlled clinical trial. The primary efficacy parameter was the eradication of infecting strains ($<10^3$ cfu/ml). The clinical outcome and tolerability were also assessed. ***Results:*** At baseline, the most common infecting strains were *Escherichia coli* (62.8%), *Proteus mirabilis* (7.1%) and *Klebsiella pneumoniae* (4.1%). At the early follow-up, the rate of patients showing successful treatment was 90.8% in the prulifloxacin group, and 77.8% in the ciprofloxacin group (p = 0.008). A positive clinical outcome was observed in 94.8 and 93.3% of prulifloxacin- and ciprofloxacin-treated patients. Both drugs were well tolerated. Two patients dropped out for treatment-related adverse events. ***Conclusions:*** The high urinary concentrations of prulifloxacin, combined with a broad-spectrum antimicrobial activity, allow its use in the empiric therapy of UTIs.

Introduction

Symptomatic urinary tract infections (UTIs) are associated with substantial morbidity and significant expenditures, and represent a major health problem throughout the Western world [1, 2]. The growing incidence of resistance among common urinary tract pathogens, particularly *Escherichia coli* and *Enterococcus*, to traditional antimicrobial therapies has changed the therapeutic approach to UTIs, and fluoroquinolone antimicrobial agents have taken on an expanding role. Actually, the recent Infectious Diseases Society of America clinical management guidelines for UTI recommend fluoroquinolones as first-line therapy for uncomplicated UTI in areas where resistance is likely to be of concern [3]. Fluoroquinolones have demonstrated high bacteriologic and clinical cure rates, as well as low rates of resistance, among most common uropathogens.

Whereas almost all fluoroquinolones give equivalent results with short-term therapy of acute uncomplicated cystitis, the empiric therapy of patients with complicated

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UTI should be chosen based on a sufficiently high urinary bactericidal activity against Gram-negative as well as Gram-positive uropathogens [4]. Moreover, the specific pharmacokinetic and pharmacodynamic properties of the drug should be considered, giving the preference to antibacterial agents with high and prolonged urinary concentrations and a broad spectrum of activity.

Based on the results of the published clinical studies, a dosage of 500 mg ciprofloxacin twice daily, 500 mg levofloxacin once daily, or 400 mg gatifloxacin once daily may be effective and comparable dosage regimens in the treatment of severe complicated UTI [4].

Prulifloxacin, the prodrug of ulifloxacin, is a new fluoroquinolone oral antibacterial agent with a broad spectrum of in vitro activity against various Gram-negative and Gram-positive bacteria [5]. The in vitro activity of ulifloxacin is generally greater than that of ciprofloxacin and other fluoroquinolones against isolates of Gram-negative bacteria, including *E. coli, Klebsiella* spp., *Proteus, Providencia* and *Morganella* spp., *Pseudomonas aeruginosa, Moraxella catarrhalis* and *Haemophilus* spp. [6, 7]. Against Gram-positive bacteria, such as *Streptococcus* spp., *S. aureus, Enterococcus* spp. and coagulase-negative staphylococci, the in vitro activity of ulifloxacin is generally similar to or greater than that of ciprofloxacin, but lower than that of moxifloxacin [7].

After absorption from the gastrointestinal tract, prulifloxacin is rapidly and extensively metabolized to ulifloxacin, the active compound [5]. The relatively long terminal half-life and the very high urinary concentrations of ulifloxacin up to 24 h from administration, often exceeding at 48 h more than 10 times the MIC values of the most frequent uropathogens, allow a once-daily administration in patients with urinary infections [8].

Previously published data showed that the efficacy of a single dose of prulifloxacin 600 mg is equivalent to that of a single dose of pefloxacin 800 mg, in the treatment of women with acute uncomplicated UTIs [9]. The present study was performed to evaluate the efficacy and safety of a 10-day regimen of prulifloxacin 600 mg once daily as compared to ciprofloxacin 500 mg twice daily in the treatment of patients with complicated UTIs.

Materials and Methods

Patients

Adult in- and outpatients aged 18–85 years with complicated UTI, as defined by the presence of indwelling catheter, intermittent catheterization, residual urine ≥ 50 ml after voiding, prostatic hypertrophy, obstructive uropathy, vesicoureteral reflux or other urologic abnormalities were eligible in the trial. UTI was confirmed by pyuria (WBC $\geq 10/mm^3$) and culture of a midstream urinary specimen exhibiting $\geq 10^5$ cfu/ml of bacterial strains susceptible or moderately susceptible to both drugs. Any combination of dysuria, urgency, frequency, suprapubic pain, and fever was also requested. Patients with prostatitis, vesiculitis, epididymitis, known quinolone hypersensitivity, pregnancy and lactation, significant renal or hepatic impairment, concurrent infections or recent antibiotic therapy, were excluded from study participation.

Study Design

This randomized, double-blind, double-dummy, ciprofloxacin-controlled clinical trial was performed at 11 Italian and 8 French centers. The study protocol was approved by the Ethics Committees and all patients provided written informed consent before participating in the study.

The patients were randomized to receive oral prulifloxacin 600 mg once daily or oral ciprofloxacin 500 mg twice daily for 10 days. They were assessed at baseline (visit 1), on days 5–7 during treatment (visit 2), 5–7 days after completion of therapy (visit 3, early follow-up) and 4 weeks after the end of treatment (visit 4, long-term follow-up). Microbiological assessments were performed at each visit. At baseline, demographic characteristics, physical examination and medical history were recorded. Before and after treatment, biochemical, hematological analyses, and urinalysis were assessed.

Efficacy and Tolerability Parameters

The primary parameter for the evaluation of efficacy was the eradication of infecting strains ($<10^3$ cfu/ml). Microbiological assessments were expressed as follows: *eradication* (the pathogen observed at baseline was not found at the early follow-up), *persistence* (the original pathogen was still observed at the early follow-up, though not found at visit 2), and *superinfection* (a new pathogen was found at the early follow-up). Patients with eradication at the early follow-up (endpoint) were considered as a success for statistical purposes.

At the long-term follow-up assessments, the presence of infecting strains in patients with sterile urine at endpoint was defined as eradication with relapse (the pathogen observed at baseline and disappeared at endpoint, was found again at the long-term follow-up) or eradication with reinfection (the pathogen observed at baseline was not found at endpoint and long-term follow-up, but a new pathogen was found at long-term follow-up).

The identification and susceptibility tests for isolated microorganisms in the urine were performed according to the National Committee for Clinical Laboratory Standards [10]. Susceptibility for prulifloxacin was defined as follows: susceptible (zone diameter ≥ 21 mm corresponding to MIC ≤ 1 μg/ml), resistant (zone diameter ≤ 15 mm corresponding to MIC ≥ 4 μg/ml); all the strains showing a zone diameter of 16–20 mm were defined as moderately susceptible [5].

Clinical treatment failure was defined as the persistence of fever (>37.5°C) and/or no improvement in severity of all symptoms reported at baseline (dysuria, urgency, frequency, suprapubic pain). Biological safety was determined by means of hematology, clinical chemistry and urine analyses performed before and after treatment. Tolerability was assessed by monitoring adverse events.

Table 1. Characteristics of patients at baseline

	Prulifloxacin (n = 127)	Ciprofloxacin (n = 130)
Male/female	35/92	39/91
In-/outpatients	25/102	27/103
Age (mean ± SD), years	62.29 ± 17.11	62.35 ± 15.98
Weight (mean ± SD), kg	67.38 ± 13.59*	66.40 ± 11.50
Bacteriuria ($\geq 10^5$ cfu/ml) with pyuria, %	89.8	91.5
Hematuria (micro/macro), %	55.1	50
Fever (>37.5°C), %	29.9	24.6

* n = 125.

Table 2. Bacteriological response (eradication/total) by pretreatment pathogens

	Prulifloxacin n (%)	Ciprofloxacin n (%)
Escherichia coli (n = 136)	66/67 (98.5)	65/69 (94.2)
Proteus mirabilis (n = 16)	7/7 (100)	9/9 (100)
Klebsiella pneumoniae (n = 8)	4/4 (100)	4/4 (100)
Pseudomonas aeruginosa (n = 8)	3/3 (100)	3/5 (60)
Enterococcus faecalis (n = 5)	4/4 (100)	1/1 (100)
Others (n = 35)	15/16 (93.7)	18/19 (94.7)
Total (n = 208)	99/101 (98.0)	100/107 (93.5)

Statistical Analysis

The sample size was determined to demonstrate the equivalence of treatments by a non-inferiority trial [11]. Assuming an eradication rate of 85% for ciprofloxacin, a prefixed producer's risk of 20%, a maximum difference of 15% between test and control drugs and a one-tailed confidence level of 95%, the sample size required was of at least 94 patients per treatment group [12].

Efficacy analyses were performed on the intention-to-treat (ITT) and the per-protocol (PP) populations. The ITT population was defined as all the randomized patients with baseline urine culture exhibiting an infecting strain $>10^3$ cfu/ml and final microbiological assessment. The PP population was defined as all the randomized patients with an infecting strain $\geq 10^5$ cfu/ml and pyuria, treatment compliance ≥ 80%, not assuming concomitantly other antibacterial agents, and with the final assessments. Patients withdrawn for drug-related adverse events or lack of efficacy were considered failures. All the treated patients were included in the tolerability analyses.

To demonstrate the equivalence hypothesis, the lower limit of the one-tailed 95% confidence interval (CI) for the difference between the efficacy rates should not exceed 15%.

Results

A total of 257 patients entered the study, 127 randomly treated with prulifloxacin 600 mg once daily, and 130 with ciprofloxacin 500 mg twice daily. Patients' characteristics are summarized in table 1. At baseline, clinical signs and symptoms occurred alike for frequency and severity in the two treatment groups.

The most common complications of UTIs reported upon admission were functional or anatomical abnormalities (51% of the patients), prostatic hypertrophy (12.1%) and obstructive uropathy (11.3%). *E. coli* was the prevalent infecting strain isolated at baseline (62.8%), followed by *Proteus mirabilis* (7.1%), *Klebsiella pneumoniae* (4.1%), *Enterococcus* spp. (4.1%) and *P. aeruginosa* (3.7%). Eight patients showed multibacterial infections. Fifteen strains (mainly *E. coli* and *Enterococcus* spp.) resulted in being resistant to both prulifloxacin and ciprofloxacin, while 2 and 3 infecting strains were resistant to prulifloxacin or ciprofloxacin only, respectively. In particular, 4.6 and 5.9% of the baseline *E. coli* isolates resulted in being resistant to prulifloxacin and ciprofloxacin, respectively.

Two hundred and two patients were assessed at endpoint. Fifty-five patients were not assessed at endpoint or were withdrawn from the study, due to the presence of baseline strains resistant to one or both of the test medications, inadequate or contaminated urine samples, adverse events or lack of efficacy. Patients withdrawn from the study for treatment-related adverse events (1 patient per treatment group) or for lack of efficacy (2 patients in the ciprofloxacin group) were included in the efficacy analyses as treatment failures.

The microbiological and clinical responses were assessed in the ITT and PP populations. The ITT population consisted of 206 patients (the 202 who completed the study plus 4 patients withdrawn for treatment-related adverse events or lack of efficacy), 98 treated with prulifloxacin and 108 treated with ciprofloxacin. The PP population consisted of 193 patients (94 in the prulifloxacin and 99 in the ciprofloxacin group), after exclusion of 13 patients due to protocol violations. Results hereinafter presented refer to the ITT population, unless otherwise stated.

Table 2 shows the eradication rate of infecting strains, in each treatment group. At the endpoint, only 9 patients showed persistence (2 in the prulifloxacin group and 7 in the ciprofloxacin group), while 20 patients (6 prulifloxa-

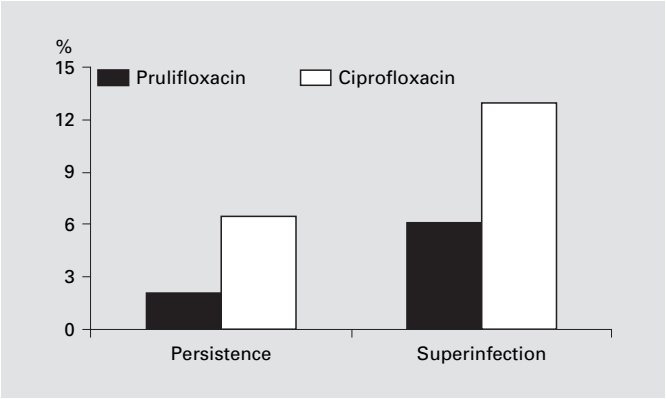

Fig. 1. Percentages of patients with microbiological failures at the endpoint (ITT population).

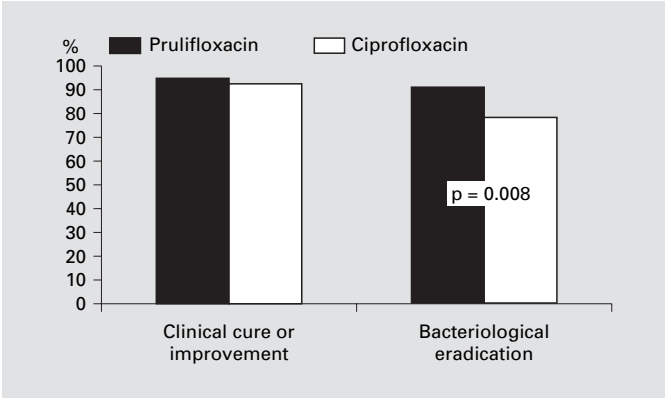

Fig. 2. Clinical and microbiological results at the endpoint (percentages of patients; ITT population).

cin and 14 ciprofloxacin) had superinfection (fig. 1). The rate of superinfection was alike in in- and outpatients (8 vs. 12), and was mainly related to the presence of resistant *Enterococcus* strains.

At the endpoint, the percentages of patients showing successful treatment were 90.8% (95% CI 85.1–96.5) in the prulifloxacin group, and 77.8% (95% CI 69.9–85.6) in the ciprofloxacin group. The lower limit of the one-tailed 95% CI of the difference between treatments was 4.9%, which demonstrated the higher efficacy of prulifloxacin compared to ciprofloxacin. Actually, the Z-test performed on these data showed a significant difference in favor of prulifloxacin ($Z = 2.63$, $p = 0.008$). Similar results were observed in the PP population (90.4 vs. 80.8%; 95% CI 84.5–96.4 and 73.1–88.6, respectively).

From a clinical viewpoint, the percentages of success at the endpoint were 94.8% (95% CI 90.4–99.2; n = 97) in the prulifloxacin group and 93.3% (95% CI 88.5–98.1; n = 104) in the ciprofloxacin group. No statistically significant differences between groups were detected. Figure 2 shows the rates of patients with successful clinical and microbiological results at the endpoint.

One hundred and sixty-one (82 prulifloxacin, 79 ciprofloxacin) out of 173 patients with successful treatment at endpoint, were followed-up for 4 weeks after completion of the therapy. Eighteen patients (21.9%; 95% CI 13.0–30.9) in the prulifloxacin group and 14 (17.7%; 95% CI 9.3–26.1) in the ciprofloxacin group showed relapse (8 prulifloxacin, 8 ciprofloxacin) or reinfection (10 prulifloxacin, 6 ciprofloxacin). At this time point, a clinical deterioration was evidenced in 14.6% (95% CI 7.0–22.3) and 13.9% (95% CI 6.3–21.6) of patients in the prulifloxacin and ciprofloxacin group, respectively. No statistically significant differences between groups were found for either microbiological and clinical parameters.

On the whole, prulifloxacin and ciprofloxacin were well tolerated. Two patients dropped out for treatment-related adverse events: 1 patient (prulifloxacin) for moderate rash and pruritus, and 1 patient (ciprofloxacin) for severe gastric pain. The most frequent treatment-related adverse event was gastric pain, reported in 4.7% of the prulifloxacin-treated and 5.7% of the ciprofloxacin-treated patients (table 3). Treatment-related adverse events involved the digestive body system in 8.6% of the prulifloxacin group patients, and in 8.5% of the ciprofloxacin group patients. Neither clinically significant differences in vital signs compared to baseline nor changes in clinically relevant hematology or chemistry were observed.

During the study period, one non-treatment-related serious adverse event occurred in the ciprofloxacin group: 13 days after the completion of therapy, a 60-year-old male patient was hospitalized in the intensive care unit for bronchial congestion and severe respiratory distress due to Mendelson syndrome related to Holmes disease. The patient's condition worsened and resulted in death (37 days after hospitalization). This event was considered not treatment-related.

Discussion

In this double-blind, randomized study, efficacy and safety of prulifloxacin 600 mg once daily were compared with those of ciprofloxacin 500 mg twice daily, both administered orally in patients with complicated UTIs.

Table 3. Incidence of patients (%) with treatment-related adverse events

	Prulifloxacin (n = 127)	Ciprofloxacin (n = 130)
Diarrhea	–	1 (0.8)
Gastric pain	6 (4.7)	7 (5.4)
Gastritis	2 (1.6)	1 (0.8)
Gastrointestinal disorder	1 (0.8)	1 (0.8)
Nausea	1 (0.8)	1 (0.8)
Increased γ-GT	1 (0.8)	–
Rash/pruritus	1 (0.8)	1 (0.8)
Taste perversion	1 (0.8)	–

As expected, the most commonly isolated pathogen at baseline was *E. coli*, which showed an incidence of resistance to both drugs of approximately 4–6%, definitely lower than that generally reported for trimethoprim-sulfamethoxazole, the current 'gold standard' therapy in UTIs [3, 13].

At the early follow-up, high bacterial eradication rates of pretreatment strains were detected with both prulifloxacin and ciprofloxacin (table 2). Microbiological failures were mainly due to superinfections, more frequent in ciprofloxacin-treated patients. The rates of successful treatment were 90.8 and 77.8% in the prulifloxacin and ciprofloxacin group, respectively ($p = 0.008$). The difference was no longer significant at the long-term follow-up, and there were no differences in the clinical parameter. At the early follow-up, a positive clinical outcome was reached with a very similar incidence in both treatment groups, approximately 95% (prulifloxacin) and 93% (ciprofloxacin), indicating that in some patients reporting improved signs and symptoms, the infecting strains were not eradicated. This is probably due to a suppression of the pathogen virulence characteristics, related to the presence of the antimicrobial agent, which produces an improvement in the host inflammatory response and clinical emergences, but without bacterial eradication [14].

Sustained eradication up to 4 weeks after treatment was reported in 78.1 and 82.3% of the patients in the prulifloxacin and ciprofloxacin group, respectively. Similar results at long-term follow-ups were reported in other studies performed with ciprofloxacin and gatifloxacin [15, 16].

In this study, prulifloxacin showed a very good safety profile, definitely comparable to the reference medication. Most of the events observed were of mild to moderate severity. Biological monitoring did not show any clinically significant variations.

Conclusions

The very good efficacy of the 10-day prulifloxacin 600 mg once-daily regimen is probably the result of its elevated and prolonged urinary concentrations combined with a broad spectrum of activity [6–8]. The antibacterial activity of prulifloxacin against Gram-positive bacteria and particularly against Gram-negative bacteria most commonly found in UTIs, allows its use in the empiric therapy of UTIs, the current treatment trend [17, 18]. In fact, in the absence of evidence-based guidelines, fluoroquinolones with a broad spectrum of activity against the expected uropathogens and antipseudomonal activity are suggested for the initial empiric treatment of patients with complicated UTIs [1]. In this context, prulifloxacin could have some advantages. However, the empiric therapeutic approach might not be appropriate for serious UTIs in adults, including complicated UTIs requiring hospitalization or nosocomial infections, where the etiology and resistance patterns are not predictable, and require confirmation by culture and susceptibility tests [19].

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References

1 Williams DH, Schaeffer AJ: Current concepts in urinary tract infections. Minerva Urol Nefrol 2004;56:15–31.
2 Talan DA, Naber KG, Palou J, Elkharrat D: Extended-release ciprofloxacin (Cipro XR) for treatment of urinary tract infections. Int J Antimicrob Agents 2004;23(suppl 1):S54–S66.
3 Schaeffer AJ: The expanding role of fluoroquinolones. Dis Mon 2003;49:129–147.
4 Naber KG: Which fluoroquinolones are suitable for the treatment of urinary tract infections? Int J Antimicrob Agents 2001;17:331–341.
5 Keam SJ, Perry CM: Prulifloxacin. Drugs 2004;64:2221–2234.
6 Prats G, Roig C, Miro E, Navarro F, Mirelis B: In vitro activity of the active metabolite of prulifloxacin (AF 3013) compared with six other fluoroquinolones. Eur J Clin Microbiol Infect Dis 2002;21:328–334.
7 Montanari MP, Mingoia M, Varaldo PE: In vitro antibacterial activities of AF 3013, the active metabolite of prulifloxacin, against nosocomial and community Italian isolates. Antimicrob Agents Chemother 2001;45:3616–3622.
8 Picollo R, Brion N, Gualano V, Millérioux L, Marchetti M, Rosignoli MT, Dionisio P: Pharmacokinetics and tolerability of prulifloxacin after single oral administration. Arzneimittelforschung 2003;53:201–205.
9 Cervigni M, Orticelli G, Bologna M, Natale F, Salvatori E, Di Loreto G, Dionisio P: Single-dose prulifloxacin versus single dose pefloxacin in the treatment of acute uncomplicated urinary tract infection in women. Urogynaecol Int J 2003;17:69–77.
10 National Committee for Clinical Laboratory Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests, ed 6. Approved Standard M2-A6. Wayne/Pa, NCCLS, 1997.
11 Committee for Proprietary Medicinal Products: Points to consider on biostatistical/methodological issue arising from recent CPMP discussion on licensing applications: Superiority, non-inferiority and equivalence. CPMP/EWP/482/99, London, Sept 23, 1999.
12 Jones B, Jarvis P, Lewis JA, Ebbutt AF: Trials to assess equivalence: The importance of rigorous methods. BMJ 1996;313:36–39.
13 Alonso Sanz M, Abad Becquer MI: Phenotypes of resistance in community urinary tract isolates of *Escherichia coli*: Therapeutic implications. Med Clin (Barc) 2003;120:361–364.
14 Lorian V, Ernst J: Effects of antibiotics on bacterial structure and their pathogenicity. Pathol Biol (Paris) 1987;35:1370–1376.
15 Cox CE, Marbury TC, Pittman WG, Brown GL, Auerbach SM, Fox BC, Yang JY: A randomized, double-blind, multicenter comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection and pyelonephritis. Clin Ther 2002;24:223–236.
16 Krcmery S, Naber KG, German Ciprofloxacin UTI Study Group: Ciprofloxacin once versus twice daily in the treatment of complicated urinary tract infections. Int J Antimicrob Agents 1999;11:133–138.
17 Gesser RM, McCarroll K, Teppler H, Woods GL: Efficacy of ertapenem in the treatment of serious infections caused by Enterobacteriaceae: Analysis of pooled clinical trial data. J Antimicrob Chemother 2003;51:1253–1260.
18 Krieger JN: Urinary tract infections: What's new? J Urol 2002;168:2351–2358.
19 Carson C, Naber KG: Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. Drugs 2004;64:1359–1373.