ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2009; 29 (1): 27-34
1173-2563/09/0001-0027/$49.95/0

Penetration of Orally Administered Prulifloxacin into Human Prostate Tissue

Claudio Giberti,[1] *Fabrizio Gallo*,[1] *Maria T. Rosignoli*,[2] *Alessandro Ruggieri*,[2] *Simona Barattè*,[3] *Rossella Picollo*[2] and *Paolo Dionisio*[2]

1 Department of Surgery, Division of Urology, San Paolo Hospital, Savona, Italy
2 R&D Division, Angelini Pharmaceuticals – ACRAF (Aziende Chimiche Riunite Angelini Francesco) SpA, Rome, Italy
3 Nerviano Medical Sciences Srl, Milan, Italy

Abstract

Background and objective: Prulifloxacin, a fluoroquinolone antibacterial agent, may be a useful addition to the antimicrobial armamentarium against prostatitis once the ability of its active metabolite, ulifloxacin, to penetrate prostatic tissue has been determined. This study set out to evaluate ulifloxacin penetration into the prostate following administration of the oral fluoroquinolone prodrug prulifloxacin in patients undergoing transurethral resection of the prostate (TURP).

Methods: This was a phase I, randomized, open-label, single-centre study involving 20 male Caucasian patients (mean age 63.1 years) requiring TURP for treatment of benign prostatic hyperplasia. Sixteen patients were randomized to receive prulifloxacin; the other four patients were not treated (controls) in order to validate the bioanalytical method. Patients in the active treatment groups were randomized to receive one or three once-daily doses of prulifloxacin 600 mg, with the last administration 3 hours prior to surgery. Central/transitional and peripheral zone prostatic tissue samples were obtained from the 6 o'clock and 9 o'clock positions in the prostate, and blood samples were collected concurrently. Ulifloxacin concentrations were determined in the tissue samples and plasma using liquid chromatography-tandem mass spectrometry. Safety was also assessed.

Results: Prostatic tissue concentrations of ulifloxacin always exceeded those in plasma. Mean ulifloxacin concentrations measured in samples collected from the 6 o'clock central/transitional zone of the prostate were higher in patients who received prulifloxacin for 3 days than in those who received a single dose. Mean prostatic tissue/plasma ulifloxacin concentration ratios after single and repeated prulifloxacin administration ranged from 3.8 to 7.1 and from 3.9 to 9.5, respectively. The highest mean ratio was found in the 6 o'clock central/transitional zone after repeated dosing. Prostatic levels of ulifloxacin were above the minimum inhibitory concentrations for the most common causative pathogens of bacterial prostatitis. No treatment-related toxicities were reported.

Conclusion: These findings confirm the ability of prulifloxacin to penetrate prostatic tissues, indicating high exposure of the target tissue to ulifloxacin and,

therefore, a potential therapeutic role for prulifloxacin in the treatment of bacterial prostatic infections.

Background

Prulifloxacin is a fluoroquinolone antibacterial agent that is rapidly absorbed through the intestinal wall and hydrolysed by paraxonase to the active metabolite ulifloxacin following oral administration.[1,2] Like other fluoroquinolones, ulifloxacin prevents bacterial DNA replication, transcription, repair and recombination through inhibition of bacterial DNA gyrase.[1] It has a broad spectrum of antibacterial activity against Gram-negative and Gram-positive bacteria.[3-5]

The elimination half-life of ulifloxacin is 10–12 hours,[6] allowing prulifloxacin to be administered once daily, thus facilitating patient compliance with treatment. Unchanged ulifloxacin is predominantly eliminated via the kidneys, achieving very high concentrations in the urine up to 48 hours after a single administration.[6] Furthermore, ulifloxacin concentrations in the lungs, gynaecological tissues and urine have been shown to reach values higher than those attained in plasma.[7-9] Prulifloxacin is indicated for the treatment of acute uncomplicated lower urinary tract infections (UTIs) and complicated lower UTIs, as well as for acute exacerbations of chronic bronchitis.

Prostatitis is a common outpatient condition seen in urological practice. The incidence of physician-diagnosed prostatitis is 4.9 cases per 1000 person-years, with a high prevalence of prostatitis symptoms, a rate that is quite comparable to those of ischaemic heart disease and diabetes mellitus.[10] Bacterial prostatitis has proven to be a difficult condition to treat, probably in part due to inappropriate drug penetration within prostatic tissues and fluid. Indeed, there are vast differences in the ability of various antibacterial agents to penetrate prostatic tissue, with penetration being dependent on a number of factors including absorption, plasma protein binding, lipid solubility, intercompartment pH gradient, and biotransformation.[11] Several fluoroquinolones have been shown to achieve prostatic tissue concentrations higher than those achieved in plasma.[11] As a result of their favourable pharmacokinetic profiles and broad-spectrum activity, fluoroquinolones are currently recommended for the treatment of acute or chronic bacterial prostatitis.[12]

Enterobacteriaceae, especially *Escherichia coli*, are frequently involved as causative agents of bacterial prostatitis.[13,14] Prulifloxacin has demonstrated potent activity against these organisms[3-5] and may, therefore, prove to be a useful addition to the antimicrobial armamentarium against prostatitis once the ability of its active metabolite to penetrate prostatic tissue is established and quantified.

The aim of this study was to evaluate the extent of ulifloxacin penetration into the prostate gland following two different schedules of administration of prulifloxacin in patients admitted for transurethral resection of the prostate (TURP). The secondary objective of the study was to evaluate the safety profile of prulifloxacin.

Methods

This phase I, randomized open-label study was conducted at the Division of Urology, San Paolo Hospital, Savona, Italy, in accordance with World Medical Assembly and Good Clinical Practice guidelines, and with the approval of the local Ethics Committee. All patients provided written informed consent prior to being admitted to the study. Being a preliminary pilot study, the number of patients enrolled was not determined on a statistical basis.

Eligible patients were male Caucasian inpatients between 50 and 70 years of age and requiring TURP for the treatment of benign prostatic hyperplasia. Patients with known or suspected hypersensitivity to fluoroquinolone antimicrobials, who had received treatment with antimicrobials within 1 week prior to receiving prulifloxacin or experimental drugs in the 4 weeks preceding the study, who had impaired liver or renal function, who had evidence of infection within 48 hours prior to surgery, or who had an

indwelling catheter for 48 hours or more prior to surgery were excluded from the study. Patients were also considered ineligible if they had valvular heart disease requiring prophylaxis for cardiac endocarditis, gastrointestinal disease or a history of malabsorption, malignant neoplasms or epilepsy.

Patients were enrolled and screened 7–10 days before the administration of prulifloxacin. Each patient's medical history was determined, and patients underwent a physical examination, assessment of vital signs, ECG, virological tests and laboratory analyses.

Prostatic tissue samples from a control group of patients who did not receive prulifloxacin were used to validate the liquid chromatography-mass spectrometry (LC-MS/MS) bioanalytical method. Enrolment of these patients was completed before commencing enrolment for the active treatment groups. Patients eligible for treatment with prulifloxacin were assigned to treatment sequentially according to a randomization list, and following a progressive order. No blinding procedures were implemented. Patients received either one tablet of prulifloxacin 600 mg approximately 3 hours prior to surgery, or three tablets of prulifloxacin 600 mg once daily for 3 days, with the last administration occurring 3 hours prior to surgery. A margin of 30 minutes either side of the target time for drug administration was allowed. The final dose of prulifloxacin was administered by the investigators; compliance was otherwise assessed using tablet counts. Safety was assessed by monitoring adverse events for 48 hours following surgery. Emergent signs and symptoms were reported in case report forms.

Because of the explorative nature of the trial, the sample size was not based on a power calculation. For this reason, only descriptive statistics (mean, standard deviation, minimum and maximum) were applied. Taking into account the small number of enrolled patients, inferential statistics were not implemented. Observed plasma concentrations were plotted against tissue concentrations and linear regression analysis was applied. Statistical analyses were performed using SAS for Windows, version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Tissue Sampling and Assays

Eight samples of prostatic tissue were collected from each patient: two samples from the central/transitional zone and two samples from the peripheral zone at the 6 o'clock position and two samples from the central/transitional zone and two samples from the peripheral zone at the 9 o'clock position. During surgery, the bladder was continuously irrigated with sterile saline, thereby minimizing the possibility of contamination of the tissue samples by blood and urine. In addition, samples were rinsed after collection with normal saline and stored at −20°C until analysis.

One blood sample was withdrawn concomitantly with each tissue collection to allow comparisons of drug concentrations in these different areas of the prostate. Intravenous blood samples were collected using S-Monovette® heparinized lithium tubes (Sarstedt, Leicester, Leicestershire, UK). Within 20 minutes of collection, plasma was separated by centrifugation, transferred into two polypropylene tubes (at least 1.5 mL of plasma each), and stored at −20°C until analysis.

After oral administration the prodrug prulifloxacin is undetectable in biological fluids, being almost quantitatively transformed into the active metabolite ulifloxacin. Concentrations of ulifloxacin were determined in human plasma and prostatic tissue by validated LC-MS/MS bioanalytical methods with a calibration range of 50–10 000 ng/mL or ng/g, respectively. A prestudy validation of the methods for measurement of ulifloxacin in plasma and prostatic tissue was performed to assess the following parameters: linearity, precision, accuracy, selectivity, sensitivity (lower limit of quantitation [LLQ]), recovery, matrix effects and carry-over.

Plasma and tissue samples were analysed using calibration standards prepared in the same matrix as samples spiked with ulifloxacin. Eight calibration standards (excluding blanks) in duplicate and six quality control samples (QCs) [spiked at 150, 200 and 7500 ng/mL, each in duplicate] were run within each batch. The batch was considered acceptable if 75% of calibrants showed accuracy within 15% (±20% at the LLQ) of the nominal value and at least

67% (four of six) of the QCs were within ±15% of their respective nominal values and at least 50% of QCs were within ±15% of nominal value at each concentration.

Aliquots of human plasma (10 μL) were added with 20 μL of internal standard (IS, ciprofloxacin 1000 ng/mL) and 400 μL of 0.1% formic acid in acetonitrile into 96 well plate. Following vortex mixing and centrifugation (20 minutes at 2060 g, 6°C), an aliquot of the supernatant (280 μL) was transferred into a second 96 well plate, dried under nitrogen gas at 40°C and the residue was reconstituted with 150 μL of a mixture containing water, acetonitrile and formic acid (79.9/20/0.1, v/v/v) and injected onto the LC-MS/MS system.

Human prostate tissue was added to nine volumes of Dulbecco's phosphate buffered saline and homogenized using an Ultrasonic Processor (Hielscher Ultrasonics, GmbH, Teltow, Germany). Aliquots of 20 μL of IS ciprofloxacin 1000 ng/mL and 0.1% formic acid 400 μL in acetonitrile were then added to 40 μL of the homogenates in 96 well plate and the samples processed as for plasma samples.

The LC-MS/MS apparatus consisted of an Agilent 1100 high-performance liquid chromatography system (Agilent Technologies, Milan, Italy), a CTC PAL autosampler (Alfatech, Genoa, Italy) and a Sciex API3000™ triple quadrupole mass spectrometer with a Turbo Ion Spray™ (Applied Biosystems, Milan, Italy) in positive ion mode with multiple reaction monitoring. The following mass/charge ratios (m/z) were used to monitor precursor → product ions: 350.2 → 248.2 for ulifloxacin and 332.2 → 288.2 for ciprofloxacin. A Chromolith® RP C18 column (50 × 4.6 mm, 3.5 μm) [Merck, Darmstadt, Germany) was used. The analytes were eluted, under gradient conditions, using a mobile phase containing 0.1% formic acid in water and methanol. The flow rate was 1 mL/minute and a split was used to reduce the flow rate directed to the mass spectrometer to 0.3 mL/minute. The retention times of ulifloxacin and ciprofloxacin were about 1.8 and 1.7 minutes, respectively.

Chromatograms were integrated to measure peak areas using Analyst™ version 1.4.1 (Applied Biosystems, Streetsville, ON, Canada) and the data were transferred to Watson™ LIMS (Laboratory Information Management System) [Thermo Fisher Scientific, Waltham, MA, USA] for standard curve regression, curve fitting and data management. A weighted linear regression function (weight: 1/concentration squared) was used to fit calibration lines and consequently to calculate ulifloxacin concentrations in QCs and in human plasma and prostate samples.

Results

Intrastudy Validation

Validation results indicated adequate method sensitivity (LLQ), selectivity, carry-over, extraction recovery, matrix effect, linearity, precision and accuracy over the nominal range of 50.0–10 000 ng/mL in plasma and 50–10 000 ng/g in prostatic tissue. Recovery of ulifloxacin from the matrices was high (≥80%) and the carry-over effect was negligible. Therefore, the methods used were applicable to pharmacokinetic studies of prulifloxacin.

The intrastudy validation results confirmed good performance for the bioanalytical method. Six analytical batches were accepted throughout the study (one for plasma and five for tissues). The calibration curves, constructed with eight calibrators (excluding blanks and including the LLQ and the upper limit of quantitation) were linear in the tested range with accuracy of the calibrators within 100 ± 15% of the nominal values. The coefficients of determination (R^2) were always higher than 0.99.

The accuracy of the QCs was within 100 ± 20% of the nominal values in at least five of six samples analysed within each bioanalytical session.

Patient Characteristics

Twenty male Caucasian patients requiring TURP because of benign prostatic disease were enrolled, including four control patients. Sixteen patients were randomized to receive prulifloxacin 600 mg as

Table I. Baseline characteristics of the study population

Variable	Controls (n = 4)	Prulifloxacin 600 mg (n = 16)	
		single dose (n = 8)	3 doses (n = 8)
Mean age [y (± SD)]	62.2 (± 4.99)	62.6 (± 4.72)	64.1 (± 3.14)
Mean height [cm (± SD)]	168.5 (± 5.97)	173.2 (± 10.28)	167.8 (± 4.97)
Mean bodyweight [kg (± SD)]	70.5 (± 11.12)	74.8 (± 10.48)	76.4 (± 8.14)
Diagnosis on admission (n)			
BPH	4	7	8
BPH + urethral stenosis		1	
Mean prostate weight [g (± SD)]	30.0 ± 4.4	32.4 ± 4.7	29.0 ± 8.0

BPH = benign prostatic hyperplasia.

single or 3-day repeated administrations. Table I shows the demographic and baseline characteristics of the study patients, including the mean prostate weight in each study group. The mean age was 63.1 years (range 54–70 years). Baseline laboratory values and vital signs were similar between treatment groups. Fourteen patients reported 35 concomitant medications. Of these, four patients were in the control group and five patients each were in the prulifloxacin single- and 3-dose treatment groups. Compliance for study medication was 100% and all patients completed the trial and were evaluable for pharmacokinetic and safety evaluations.

Drug Bioavailability

Blood sampling was always performed concomitantly with tissue collections. Because of logistical and technical issues related to surgery, some differences between the theoretical target time (3 hours from the last dose intake) and the actual sampling time were recorded. These differences ranged between −1 and +50 minutes.

Prostatic tissue concentrations of ulifloxacin always exceeded those in plasma. Mean ulifloxacin concentrations measured in samples collected from the 6 o'clock central/transitional zone of the prostate were higher in patients who received prulifloxacin for 3 days than in those who received a single dose (table II). These findings were not fully replicated in samples collected from the 9 o'clock zone (table II).

Mean prostatic tissue/plasma ulifloxacin concentration ratios after single and repeated prulifloxacin administrations ranged from 3.8 to 7.1 and from 3.9 to 9.5, respectively (table III). The highest mean ratio was found in the 6 o'clock central/transitional zone after repeated dosing.

Figure 1 shows the results of the linear regression. Statistical analysis showed a significant slope with a nonsignificant intercept, indicating a proportional increase between tissue and plasma ulifloxacin concentrations.

Table II. Mean ulifloxacin concentrations (± SD) in plasma and prostatic tissue samples in patients who received prulifloxacin prior to transurethral resection of the prostate

Variable	Prulifloxacin 600 mg (n = 16)	
	single dose (n = 8)	3 doses (n = 8)
Plasma (μg/mL)	0.47 (± 0.31)	0.49 (± 0.26)
Prostatic tissue (μg/g)		
6 o'clock position	2.7 (± 2.2)	4.2 (± 4.3)
central/transitional zone	2.5 (± 2.1)	5.5 (± 5.7)
peripheral zone	2.9 (± 2.5)	2.9 (± 1.9)
9 o'clock position	2.4 (± 2.1)	2.0 (± 1.6)
central/transitional zone	1.9 (± 1.8)	2.1 (± 1.4)
peripheral zone	3.0 (± 2.4)	1.9 (± 2.0)

Table III. Mean prostatic tissue to plasma ratios (± SD) of ulifloxacin concentrations in patients who received prulifloxacin prior to transurethral resection of the prostate

Prostatic tissue position/zone	Prulifloxacin 600 mg (n = 16)	
	single dose (n = 8)	3 doses (n = 8)
6 o'clock position	5.8 (± 2.1)	7.6 (± 5.0)
central/transitional zone	5.2 (± 2.0)	9.5 (± 6.3)
peripheral zone	6.3 (± 2.3)	5.7 (± 2.6)
9 o'clock position	5.4 (± 4.7)	4.3 (± 1.9)
central/transitional zone	3.8 (± 1.2)	4.6 (± 2.1)
peripheral zone	7.1 (± 6.4)	3.9 (± 1.9)

Safety

No serious adverse events and no treatment-related adverse events occurred. One patient in the untreated control group reported a single episode of cutaneous rash, which spontaneously resolved within a few hours.

Discussion

The results of this study showed that after single and repeated administrations of prulifloxacin 600 mg, high ulifloxacin concentrations were reached in prostatic tissue.

As expected, ulifloxacin plasma concentrations in our study were relatively low compared with previous reported data.[6] However, in that study, blood samples were taken at the time of peak concentration of the drug (0.75–1 hours), whereas in the current study, blood samples were collected approximately 3 hours after the last prulifloxacin dose, which was chosen as the earliest practicable sampling point given the time needed for anaesthesia and surgical procedures. Sampling procedures were carefully implemented to avoid contamination by blood and urine, although negligible interference cannot be definitely excluded.

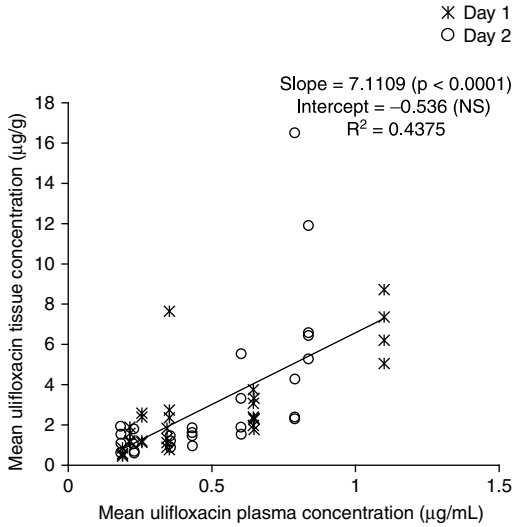

Fig. 1. Correlation between tissue and plasma ulifloxacin concentrations. **NS** = not significant; **R2** = coefficient of determination.

After single and 3-day repeated administrations of prulifloxacin 600 mg, ulifloxacin tissue concentrations were always higher than those reached in plasma. When data were pooled, the mean (± SD) prostatic ulifloxacin concentrations after single and repeated administrations were 2.6 ± 2.2 and 3.1 ± 3.4 µg/g, respectively, indicating drug accumulation in the prostate over time. Higher penetration of ulifloxacin in the 6 o'clock position compared with the 9 o'clock sampling zone was observed, and this was more evident after repeated administration of prulifloxacin. This is probably because the major blood vessels of the prostate pass through the gland predominantly at the 5 and 7 o'clock positions, thereby resulting in a higher drug concentration at the 6 o'clock position, as has previously been reported in a comparative trial investigating the distribution of ofloxacin and ciprofloxacin in prostatic tissue.[15]

When samples collected at the 6 and 9 o'clock positions were considered together with ulifoxacin concentrations in peripheral versus central/transitional zones (figure 2), the highest ulifloxacin concentrations were seen in the central/transitional zone in some patients, although in general there was a

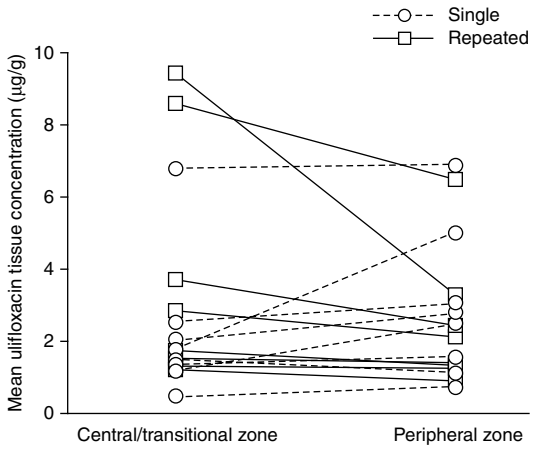

Fig. 2. Intraindividual comparison of ulifloxacin concentrations in central/transitional and peripheral zones after single and repeated administration of prulifloxacin.

relatively homogeneous distribution of the drug throughout the prostate. Similar results have been observed with lomefloxacin.[16] The acceptably high ulifloxacin concentrations also observed in the peripheral zone of the prostate have potential clinical significance since this zone is more frequently the site of infection in bacterial prostatitis.[17]

Regression analysis showed that ulifloxacin concentration in prostate tissue increased proportionally with ulifloxacin plasma levels. After repeated prulifloxacin administration, a situation that more closely resembles use of antibacterials in bacterial prostatitis, the mean tissue/plasma ratio ranged from 3.9 to 9.5, a ratio higher than that previously reported for ciprofloxacin, ofloxacin and lomefloxacin,[15,16,18] and indicating very good penetration of the drug into prostate. This result confirms the capacity for ulifloxacin to penetrate target tissues, as previously reported for lung and gynaecological tissues.[8,9]

The causative agents of chronic bacterial prostatitis include mainly Gram-negative strains, most frequently *E. coli*, and, to a lesser extent, *Klebsiella* spp., *Proteus* spp., *Enterococci* spp, *Serratia* spp. and *Pseudomonas aeruginosa*.[13,14] The prostatic concentrations of ulifloxacin achieved in this study were generally above the minimum inhibitory concentration required to inhibit growth of 90% of isolates involved in prostatic bacterial infections,[3-5] and therefore a good efficacy profile for prulifloxacin in the treatment of patients with prostatic infections may be predicted. Indeed, a recent double-blind, clinical trial comparing prulifloxacin and levofloxacin in the treatment of chronic bacterial prostatitis confirmed a comparable rate of eradication for these two drugs.[19] The limited sample size of this study does not allow any definite conclusions to be drawn. However, the results of this study, when considered in light of the broad antimicrobial spectrum of prulifloxacin, particularly against *P. aeruginosa*,[20] and the ability of the drug to penetrate into prostate tissue, call for wider clinical trials.

Importantly, the safety profile of prulifloxacin in this study was also very favourable with no drug-related adverse events being reported.

Conclusion

The findings of this study confirm the ability of prulifloxacin to penetrate prostatic tissue, resulting in high exposure of the target tissue to ulifloxacin and, thereby, a potential therapeutic role of prulifloxacin in the treatment of bacterial prostatic infections.

Acknowledgements

This work was supported by a grant from Angelini Pharmaceuticals – ACRAF (Aziende Chimiche Riunite Angelini Francesco) SpA Medical writing assistance for the preparation of this manuscript was provided by Andrea Bothwell, Wolters Kluwer Health, and her assistance was funded by Angelini Pharmaceuticals – ACRAF SpA. Paolo Dionisio, Rossella Picollo, Maria T. Rosignoli and Alessandro Ruggieri are employees of Angelini Pharmaceuticals – ACRAF SpA. The other authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Keam SJ, Perry CM. Prulifloxacin. Drugs 2004; 64 (19): 2221-34
2. Tougou K, Nakamura A, Watanabe S, et al. Paraxonase has a major role in the hydrolysis of prulifloxacin (NM441), a prodrug of a new antibacterial agent. Drug Metab Dispos 1997; 26: 355-9
3. Prats G, Roig C, Mirò E, et al. In vitro activity of the active metabolite of prulifloxacin (AF 3013) compared with six other

fluoroquinolones. Eur J Clin Microbiol Infect Dis 2002; 21 (4): 328-34
4. 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 (12): 3616-22
5. Gualco L, Schito AM, Schito GC, et al. In vitro activity of prulifloxacin against *Escherichia coli* isolated from urinary tract infections and the biological cost of prulifloxacin resistance. Int J Antimicrob Agents 2007; 29 (6): 679-87
6. Picollo R, Brion N, Gualano V, et al. Pharmacokinetics and tolerability of prulifloxacin after single oral administration. Arzneimittelforschung 2003; 53 (3): 201-5
7. Nakashima M, Uematsu T, Kosuge K, et al. Pharmacokinetics and safety of NM441, a new quinolone, in healthy male volunteers. J Clin Pharmacol 1994; 34: 930-7
8. Concia E, Allegranzi B, Ciottoli GB, et al. Penetration of orally administered prulifloxacin into human lung tissue. Clin Pharmacokinet 2005; 44 (12): 1287-94
9. Gorlero F, Lorenzi P, Rosignoli MT, et al. Penetration of prulifloxacin into gynaecological tissues after single and repeated oral administrations. Drugs R D 2007; 8 (6): 373-81
10. Krieger JN, Lee SW, Jeon J, et al. Epidemiology of prostatitis. Int J Antimicrob Agents 2008; 31 Suppl. 1: S85-90
11. Charalabopoulos K, Karachalios G, Baltogiannis D, et al. Penetration of antimicrobial agents into the prostate. Chemotherapy 2003; 49 (6): 269-79
12. Naber KG. Management of bacterial prostatitis: what's new? BJU Int 2008; 101 Suppl. 3: 7-10
13. Etienne M, Chavanet P, Sibert L, et al. Acute bacterial prostatitis: heterogeneity in diagnostic criteria and management. Retrospective multicentric analysis of 371 patients diagnosed with acute prostatitis. BMC Infect Dis 2008; 8: 12
14. Bartoletti R, Cai T, Mondaini N, et al. Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: results of a multicenter case-control observational study. J Urol 2007; 178 (6): 2411-5
15. Png JC, Tan E, Foo KT, et al. A comparative study of the distribution of ofloxacin and ciprofloxacin in prostatic tissues after simultaneous oral ingestion. Br J Urol 1997; 79 (5): 781-4
16. Kovarik JM, de Hond JA, Hoepelman IM, et al. Intraprostatic distribution of lomefloxacin following multiple-dose administration. Antimicrob Agents Chemother 1990; 34 (12): 2398-401
17. McNeal JE. The prostate and prostatic urethra: a morphologic synthesis. J Urol 1972; 107 (6): 1008-16
18. Boerema JB, Dalhoff A, Debruyne FM. Ciprofloxacin distribution in prostatic tissue and fluid following oral administration. Chemotherapy 1985; 31 (1): 13-8
19. Giannarini G, Mogorovich A, Valent F, et al. Prulifloxacin versus levofloxacin in the treatment of chronic bacterial prostatitis: a prospective, randomized, double-blind trial. J Chemother 2007; 19 (3): 304-8
20. Roveta S, Schito AM, Marchese A, et al. Microbiological rationale for the utilisation of prulifloxacin, a new fluoroquinolone, in the eradication of serious infections caused by *Pseudomonas aeruginosa*. Int J Antimicrob Agents 2005; 26 (5): 366-72

Correspondence: Dr *Paolo Dionisio*, R&D Division, Angelini Pharmaceuticals – ACRAF (Aziende Chimiche Riunite Angelini Francesco) SpA P. le della Stazione snc, S. Palomba Pomezia, Rome, I-00040, Italy.
E-mail: p.dionisio@angelini.it