REVIEWS OF INFECTIOUS DISEASES • VOL. 10, SUPPLEMENT 1 • JANUARY–FEBRUARY 1988
 0162-0886/88/1001-0132$02.00

SESSION 14

Comparative Studies of Fluoroquinolones in the Treatment of Urinary Tract Infections

R. Malinverni and M. P. Glauser

From the Medizinische Universitätsklinik, Inselspital, Bern, and the Division of Infectious Diseases, Department of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

The results of comparative trials of fluoroquinolones for the treatment of uncomplicated and complicated urinary tract infections (UTI) were reviewed. Several randomized, comparative trials showed that in uncomplicated UTI norfloxacin, ciprofloxacin, and ofloxacin were at least as effective as trimethoprim-sulfamethoxazole (TMP-SMZ) and amoxicillin and usually more effective than nalidixic acid, pipemidic acid, and nitrofurantoin. Comparative trials of single-dose regimens have, however, been limited. A few randomized, comparative trials have shown that in complicated UTI norfloxacin, ciprofloxacin, and ofloxacin were at least as effective as amoxicillin and TMP-SMZ and usually more effective than pipemidic acid. Moreover, preliminary results indicate that fluoroquinolones might be effective for the oral treatment of complicated UTI that are difficult to treat, especially those due to *Pseudomonas aeruginosa*. Comparative trials are needed to establish the value of fluoroquinolones for chronic bacterial prostatitis. There are no conclusive data on fluoroquinolone treatment of UTI in patients with renal failure. Emergence of resistant pathogens during therapy with fluoroquinolones has been infrequent but might be more frequent in complicated UTI caused by *P. aeruginosa*.

Although highly effective and well-established antibiotic regimens are available for the treatment of urinary tract infection (UTI), there is a need for new antimicrobial agents, especially for the treatment of outpatients with UTI that are difficult to treat and for which most of the drugs available for oral treatment are ineffective.

The fluoroquinolones have several properties that suggest their potential clinical utility for the treatment of UTI, including high activity in vitro against virtually all urinary tract pathogens and good absorption after oral administration that results in prolonged high levels of drug in urine [1].

The methodologic problems associated with open and comparative trials evaluating the efficacy of new antibiotics for the treatment of UTI have recently been reviewed [2]. For this review of the efficacy of fluoroquinolones for the treatment of UTI, we have emphasized those studies that have both sufficient data for a clear classification of UTI and data on follow-up urine cultures 4–6 weeks after the end of treatment (unless otherwise mentioned). In this evaluation, bacteriologic cure (sterile urine) was considered as the end point of antibiotic treatment since the definitions of clinical response, when stated, varied from one study to another and symptoms may disappear in the absence of bacteriologic cure. In table 1, which outlines the efficacy of fluoroquinolone treatment of UTI by infecting organism, only data from studies (noncomparative and comparative) that provided sufficient information to permit a clear classification of UTI were taken into account. We will consider and analyze separately the uncomplicated and the complicated UTI.

Uncomplicated UTI is an infection occurring in a patient without anatomic or functional abnormalities of the urinary tract. Such infections are amenable to either a single dose or to very short-term treatment [3–5]. In contrast, complicated UTI will be considered as those that occur during pregnancy or in patients with anatomic or functional abnormalities of the urinary tract, those in patients with debilitating underlying diseases such as diabetes mellitus, or those in patients presenting with the clinical picture of acute pyelonephritis. The treatment of complicated UTI should be more prolonged than

We thank Mrs. Kathrin Zsirmik and Mrs. Alexandra Bloch for typing the manuscript.

Please address requests for reprints to R. Malinverni, Medizinische Universitätsklinik, Inselspital, CH-3010 Bern, Switzerland.

Table 1. Rates of eradication of organisms after fluoroquinolone treatment of urinary tract infections (UTI).

Type of infection, fluoroquinolone	Percentage of strains eradicated after treatment (total no. isolated before treatment)*						
	Coagulase-negative staphylococci	Enterococci	*Escherichia coli*	*Proteus* species	*Klebsiella* species	*Pseudomonas aeruginosa*	*Enterobacter* species
Uncomplicated UTI							
Norfloxacin	94 (32)	. . .	93 (228)	100 (17)	58 (12)	100 (8)	100 (5)
Ciprofloxacin	87 (15)	100 (7)	96 (266)	100 (10)	100 (6)	. . .	. . .
Ofloxacin	. . .	100 (8)	94 (97)	94 (18)	100 (8)	. . .	. . .
Enoxacin	. . .	. . .	99 (107)	. . .	. . .	. . .	. . .
Pefloxacin	. . .	. . .	88 (48)	. . .	100 (5)	100 (5)	. . .
Complicated UTI							
Norfloxacin	. . .	100 (5)	96 (27)	. . .	. . .	81 (36)	. . .
Ciprofloxacin	100 (5)	100 (5)	98 (93)	100 (35)	85 (27)	54 (112)	100 (10)
Ofloxacin	89 (19)	94 (36)	94 (65)	93 (29)	78 (27)	67 (52)	75 (8)
Enoxacin	. . .	100 (22)	75 (12)	. . .	. . .	79 (38)	. . .
Pefloxacin	100 (5)	. . .	95 (62)	95 (20)	100 (6)	. . .	. . .

NOTE. Data are from [10–53] and from data on file, Laboratoire Roger Bellon (Neuilly-sur-Seine, France).

* The minimum number of strains required to be reported in this table was five. The total number of strains isolated before treatment was calculated by summarizing the data from all trials that used one of the fluoroquinolones for the treatment of uncomplicated or complicated UTI. Eradication rates (%) were the number of isolates of one bacterial species eradicated at follow-up divided by the total number of isolates of the same species found before treatment.

that of uncomplicated UTI since relapses frequently occur after short-term treatment [4] and even after courses of therapy longer than 10–14 days [5, 6]. There are suggestions that 6 weeks of antibiotic therapy may be needed to eradicate complicated (relapsing) infections, as shown in women with upper UTI [7], in renal transplant recipients [8], and in men with recurrent UTI [9].

Because the treatment of both uncomplicated and complicated UTI are relatively well standardized and because most antibacterial agents that achieve reasonable antibacterial activity in the urine are effective for the treatment of UTI, it is not surprising that the new quinolones have shown good activity in open, noncomparative studies. Even placebo therapy might achieve a cure rate of up to 50% in female patients with acute symptomatic UTI. Thus, this review will consider only those studies that have compared in a prospective, randomized fashion fluoroquinolone therapy with well-established regimens. In addition, we will also consider those studies that have tested in a prospective way various dosages or durations of treatment of fluoroquinolones. Finally, this review will analyze the results of open trials specifically aimed at treating UTI caused by *Pseudomonas aeruginosa*, for which no alternative orally administrable drugs are presently available.

Efficacy of Fluoroquinolone Treatment of UTI, by Organisms

Table 1 summarizes the data on the rates of eradication of different organisms from the urinary tract after treatment with five fluoroquinolones. Obviously, a precise comparison of the eradication rate for one drug with that for another was not possible since the duration of treatment varied considerably from one study to another. Furthermore, although in the majority of studies, follow-up cultures were performed 4–6 weeks after the end of treatment, in some studies such cultures were done as early as 7–9 days after completion of therapy. Finally, only a small number of UTI due to gram-positive organisms were included in these studies, since all studies excluded strains resistant in vitro, a common pattern, especially among enterococci tested against fluoroquinolones.

Randomized Trials with Fluoroquinolones for the Treatment of Uncomplicated UTI

Trials aimed at defining optimal treatment regimens. Rugendorff and Schneider [54] treated 59 women with acute infections with either a single dose of norfloxacin (800 mg) or a 3-day course (800 mg

daily) and reported a slightly, but not significantly, better cure rate after the 3-day regimen (93.7%) than after the single dose (85.2%).

Graeff et al. [55] reported that a 3-day course of ciprofloxacin (200 mg daily) was not significantly superior to a single dose (250 mg) for the treatment of postoperative UTI in 100 gynecologic patients. Garlando et al. [25] recently studied two single-dose regimens of ciprofloxacin (either 100 mg or 250 mg orally) for the treatment of acute UTI in 38 women. The cure rates in the two groups (89% and 84%, respectively) were similar, but two of four episodes due to *Staphylococcus saprophyticus*, as compared with only three of 34 due to gram-negative Enterobacteriaceae, could not be cured. The rate of killing by ciprofloxacin of *S. saprophyticus* in vitro was significantly slower than that of four strains of *Escherichia coli*.

Ludwig [46] treated 43 patients with either a 1-day course (200 mg) or a 3-day course of ofloxacin and reported similar cure rates (91% and 95%) for the two regimens.

Randomized, comparative trials. The results of randomized, comparative trials are summarized in table 2. Norfloxacin was compared with trimethoprim-sulfamethoxazole (TMP-SMZ) in several randomized, comparative trials for the treatment of uncomplicated UTI [10–17, 56, 59]. In each trial, norfloxacin was at least as effective as TMP-SMZ. In a large trial including 323 patients, norfloxacin (800 mg daily for 3–10 days) was significantly more effective (97% cure rate) than TMP-SMZ (90% cure rate) [59]. In the largest randomized, double-blind multicenter study, which included more than 600 patients, two norfloxacin regimens (400 or 800 mg daily) were compared with TMP-SMZ (320/1,600 mg daily) given for 7 days [60]. A minority of the patients had recurrent UTI (~25%) or UTI complicated by factors such as structural abnormalities of the urinary tract, stones, or diabetes mellitus (~15%). The bacteriologic efficacy 4 weeks after the end of treatment was similar in all treatment groups (88%–89%). However, the lower dose of norfloxacin (400 mg) was less effective than the higher dose (800 mg) and than TMP-SMZ for UTI in men and for patients with complicated UTI.

Among those trials that determined bacterial susceptibilities after norfloxacin therapy [10–13, 15–17], only one therapeutic failure was due to superinfection with a resistant group B streptococcal strain [16]. One study compared a single dose of norfloxacin (1,200 mg) to a single dose of TMP-SMZ (480/2,400 mg) for the treatment of uncomplicated UTI in 43 women: the cure rates were similar (88% and 82%, respectively) [17]. The two failures (relapses) after norfloxacin therapy were due to strains of *S. saprophyticus* (that were still susceptible to norfloxacin in vitro). When norfloxacin was compared with nalidixic acid and pipemidic acid, norfloxacin was significantly more effective [18, 61]. Finally, norfloxacin was slightly, but not significantly, more effective than amoxicillin for the treatment of uncomplicated UTI in geriatric patients [62].

Henry et al. [36] treated 65 women in a prospective, randomized, double-blind study with either ciprofloxacin (500 mg daily) or TMP-SMZ (320/1,600 mg daily) for 10 days. They reported a slightly better cure rate after ciprofloxacin (100%) than after TMP-SMZ (94%) therapy. Moreover, ciprofloxacin was significantly less toxic. Newsom et al. [38] reported a higher cure rate after a 5-day course of ciprofloxacin (200 mg daily) than after trimethoprim alone (400 mg daily) in 32 geriatric patients with uncomplicated UTI. In one study of 75 hospital inpatients (50% with complicated UTI), two ciprofloxacin regimens (200 mg and 500 mg daily) given during 5 days were compared with TMP-SMZ (320/1,600 mg daily) [37]. Only the two ciprofloxacin groups included patients with infections due to *P. aeruginosa* or *Acinetobacter* species. In spite of this, both ciprofloxacin regimens were at least as effective as TMP-SMZ. In a further study of 60 patients with uncomplicated and complicated UTI, ciprofloxacin (500 mg daily) was significantly superior to TMP-SMZ (320/1,600 mg daily) given for 7–10 days [63]. In a limited study, ciprofloxacin appeared more effective than nalidixic acid [26].

Several randomized, comparative studies of ofloxacin (usually given for 3–5 days) for the treatment of uncomplicated UTI were performed in Europe [64]. Overall, ofloxacin had an efficacy similar to that of TMP-SMZ. Similarly, one study from the United States compared two regimens of ofloxacin (400 mg and 600 mg daily) to TMP-SMZ (320/1,600) given for 7 days to 39 women with uncomplicated UTI. Bacteriologic cure was achieved in all patients [65]. Ofloxacin was more effective than nitrofurantoin for the treatment of uncomplicated UTI in two studies [66, 67]. When compared with pipemidic acid, ofloxacin was significantly more effective, but

Table 2. Results of randomized comparative trials of fluoroquinolones for the treatment of uncomplicated urinary tract infections.

Agents	No. of patients	Dosage (mg/day)	Duration (days)	Bacteriologic cure rate (%)	Reference(s)
Norfloxacin		800*		75–100	
vs.	816		10†		10–17, 56–59
Trimethoprim-sulfamethoxazole (TMP-SMZ)		320/1,600		70–100	
Norfloxacin		800		96	
vs.	110		3		18
Nalidixic acid		1,980		82	
Norfloxacin		800		91	
vs.	197		10		61
Pipemidic acid		750		79	
Norfloxacin		800		83	
vs.	91		7		62
Amoxicillin		750		74	
Ciprofloxacin		500		100	
vs.	65		10		36
TMP-SMZ		320/1,600		94	
Ciprofloxacin		200		94	
vs.	32		5		38
TMP		400		60	
Ciprofloxacin		200		71	
vs.	19		7		26
Nalidixic acid		2,000		33	
Ofloxacin		100		81	
vs.	72		3–5		64
TMP-SMZ		320/1,600		80	
Ofloxacin		100	3–5	94	
vs.	189				64
Nalidixic acid		4,000	7	77	
Ofloxacin		200	3	78/91	
vs.	123				66, 67
Nitrofurantoin		300	7	66/77	
Ofloxacin		200	3	81	
vs.	50				43
Pipemidic acid		800	5	55	
Enoxacin		300		99	
vs.	252		7		52
Pipemidic acid		750		90	

* In two studies [11, 56] the daily dose was 400 mg; one study [17] compared a single dose of norfloxacin (1,200 mg) and TMP-SMZ (480/2,400 mg).

† Duration of treatment was 10 days in seven of 12 trials [10–14, 56, 58], 7–10 days in two trials [15, 16], 7 days in one trial [57], 3–10 days in one trial [59], and a single dose in one trial [17].

the follow-up period was short (1 week) [43]. Moreover, ofloxacin was compared with nalidixic acid for the treatment of uncomplicated UTI and achieved a higher rate of cure [64].

Kamidono et al. [52] compared enoxacin with pipemidic acid for the treatment of acute uncomplicated cystitis in women and observed a significantly higher cure rate with enoxacin, but no follow-up cultures were performed. In conclusion, fluoroquinolones were at least as effective as other well-

Table 3. Results of randomized comparative trials of fluoroquinolones for the treatment of complicated urinary tract infections.

Agents	No. of patients	Dosage (mg/day)	Duration (days)	Bacteriologic cure rate (%)	Reference(s)
Norfloxacin		800		95	
vs.	40		7		19
Amoxicillin		750		75	
Norfloxacin		800		63/75	
vs.	530		5		68, 69
Pipemidic acid		2,000		48/62	
Norfloxacin		800		93	
vs.	109		28–42		70
Trimethoprim-sulfamethoxazole (TMP-SMZ)		320/1,600		80	
Norfloxacin		800		100	
vs.	28		14–42		24
Parenteral therapy (β-lactam ± aminoglycoside)				88	
Ciprofloxacin		500		63	
vs.	61		10		71
TMP-SMZ		320/1,600		45	
Ciprofloxacin		200 (iv)		88	
vs.	40		Not stated		72
Mezlocillin		4,000		57	
Ofloxacin		400		82	
vs.	425		7		64
TMP-SMZ		320/1,600		80	
Ofloxacin		400		96	
vs.	50		7		64
Amoxicillin + clavulanic acid		1,875		57	
Ofloxacin		600		89	
vs.	228		5		42
Pipemidic acid		2,000		72	
Enoxacin		600		89	
vs.	393		5		52
Pipemidic acid		2,000		68	

established antimicrobial agents, but in the majority of the trials, the duration of therapy for uncomplicated UTI was too long.

Randomized, Comparative Trials for the Treatment of Complicated UTI

The results of some randomized, comparative trials of treatment of complicated UTI are summarized in table 3. When norfloxacin was compared with amoxicillin for the treatment of complicated UTI in geriatric patients, it proved slightly, but not significantly, better than amoxicillin [19]. Norfloxacin was superior to pipemidic acid in two double-blind randomized studies [68, 69]. However, in both studies the follow-up period may have been inadequate. Sabbaj et al. [70] treated 109 men with recurrent UTI with either norfloxacin or TMP-SMZ for 4–6 weeks and reported a significantly higher cure rate with norfloxacin. In an open, comparative study, 28 patients with complicated UTI due to organisms resistant to aminoglycosides and TMP-SMZ were treated orally with norfloxacin or with a parenteral regimen (usually a β-lactam plus an aminoglycoside) for 2–6 weeks [24]. Norfloxacin cured more patients (100%) than did the parenteral regimens (88%), but the follow-up period may have been inadequate for all patients.

Boerema et al. [71] compared ciprofloxacin with TMP-SMZ for complicated UTI in male and female patients with anatomic or functional disorders of the urinary tract. Four to 6 weeks after therapy, the cure rate among patients treated with ciprofloxacin was higher (63%) than that among those treated with TMP-SMZ (45%). Similarly, Peters [72] found a higher cure rate 4 weeks after the end of therapy in 20 urologic patients treated iv with ciprofloxacin than in patients treated with mezlocillin.

Ofloxacin was compared with TMP-SMZ in several randomized studies of Europe for the treatment of complicated UTI [64]. The cure rates reported for the two regimens were similar. A smaller number of patients were included in trials comparing ofloxacin with a fixed combination of amoxicillin plus clavulanic acid [64]. Bacteriologic cures were observed in more patients treated with ofloxacin than in those treated with amoxicillin plus clavulanic acid. In a large double-blind trial in Japan that compared ofloxacin with pipemidic acid for the treatment of UTI complicated by factors such as neurogenic bladder dysfunction, lithiasis, obstruction, or neoplasms, ofloxacin was significantly more effective than pipemidic acid [42]. However, it is unclear in that study when follow-up cultures were performed.

Enoxacin was compared with pipemidic acid for the treatment of complicated UTI, and a significantly higher cure rate was reported for patients treated with enoxacin, but no follow-up cultures were performed [52].

In conclusion, the new quinolones were at least as effective as TMP-SMZ or amoxicillin for the treatment of complicated UTI. In this setting, however, in some trials the duration of therapy was clearly too short and adequate follow-up cultures often were missing.

Fluoroquinolones for the Treatment of UTI Due to *P. aeruginosa*

Leigh and Emmanuel [20] observed an 84% cure rate in 19 patients with complicated UTI (paraplegia, multiple sclerosis, or other compromised bladder function; prostatic neoplasia, or indwelling catheters) due to *P. aeruginosa* and to *Pseudomonas fluorescens* after norfloxacin (800 mg daily) given for 5–10 days. However, follow-up cultures were not adequate for all patients. In this study, one of three failures occurred in a patient with a UTI caused by a resistant strain of *P. aeruginosa*. Boerema and Van Saene [23] treated 16 similar patients with *P. aeruginosa* UTI with norfloxacin (400–800 mg daily) for 3 months and reported a 75% cure rate, but three of four failures were infections due to resistant strains of *P. aeruginosa*. Sauerwein and Bauernfeind [73] reported a 43% cure rate in 52 paraplegic patients with recurrent UTI (due primarily to *P. aeruginosa*) 1 week after the end of a 10-day course of norfloxacin (800 mg daily) and observed the emergence of resistance in three (11%) of 28 *P. aeruginosa* strains after therapy. Westenfelder et al. [74] treated 60 patients (14 of whom were infected with *P. aeruginosa*) with UTI and obstructions of the lower or upper urinary tract, which in most patients were due to malignancy, with norfloxacin (800 mg daily) for 7–9 days and observed a bacteriologic cure rate of 91% after 5–9 days of therapy; in the *P. aeruginosa* infection that did not respond to therapy, resistance developed.

Leigh et al. [39] reported a 63% cure rate in 27 UTI due to *P. aeruginosa* that were treated with ciprofloxacin (400–500 mg daily) for 5 days in patients with abnormalities of the urinary tract and reported development of resistance in three of 10 failures. Brown et al. [40] treated 16 patients with chronic (>2 months duration) *P. aeruginosa* UTI with ciprofloxacin (100–500 mg daily) for 2 weeks and reported a 44% cure rate 8 weeks after the end of treatment, observing emergence of resistance in one case of failure. As a part of a comparative trial, Williams and Grüneberg [37] treated 18 hospital inpatients with *P. aeruginosa* UTI with ciprofloxacin (200–500 mg daily) for 5 days, observing a cure rate of 72% without emergence of resistance. Van Poppel et al. [28] treated 29 patients with UTI (38% of which were due to multiresistant *P. aeruginosa*) and neurogenic bladder dysfunction with ciprofloxacin (200 mg daily) for 7 days and reported a 48% cure rate after 1 week but only a 17% cure rate after 1 month; one *P. aeruginosa* strain developed resistance. Using a higher dose regimen (1,000 mg of ciprofloxacin daily), Saavedra et al. [75] treated 28 patients (20 with pseudomonal infections) with urinary tract obstructions for a mean duration of 12 days, with a cure rate at 4 weeks of 35%. A total of 26 patients with UTI due to *P. aeruginosa* were treated with ciprofloxacin (1,000 mg daily) usually for 10 days in three open studies that included other infections [27, 29, 30]. Ninety-two percent of these patients were cured, but the follow-up period was only 1 week. Kumazawa et al. [31] treated 62 patients with complicated UTI due to *P. aeruginosa* and observed bac-

teriologic cure in 72.6% after ciprofloxacin therapy (400 mg daily for 5–14 days). Unfortunately, it is unclear when follow-up cultures were performed.

In conclusion, the patient's underlying conditions, the dosages, and the durations of administration of the fluoroquinolones varied considerably among these studies, complicating a conclusive interpretation of the results. Nevertheless, the orally administered fluoroquinolones have been effective against urinary *P. aeruginosa* infections, but emergence of resistant strains was observed repeatedly.

Fluoroquinolones for the Treatment of Prostatitis

The results of treatment of bacterial prostatitis with fluoroquinolones are summarized in table 4. Bologna et al. [76] treated 20 patients with chronic relapsing prostatitis with a 10-day course of norfloxacin (800 mg daily). Four weeks after the end of the treatment, bacteriologic cure was observed in 85% of the patients. In a comparative study Sabbaj et al. [70] treated 25 male patients with recurrent UTI and culture-positive prostatic fluid or ejaculate with norfloxacin for 4–6 weeks and reported a 92% cure rate at follow-up cultures at 1–3 weeks. Ciprofloxacin (1,000 mg daily) was tested by Guibert et al. [32] for the treatment of 26 patients with acute (28-day treatment) and chronic (84-day treatment) prostatitis due primarily to *E. coli*. After 6 weeks, bacteriologic cure had occurred in 77% of the patients. Suzuki et al. [77] treated 22 patients (four with acute and 18 with chronic prostatitis) with ofloxacin (300–600 mg daily) for 5–21 days. The segmented urine culture technique was used, and an overall rate of bacteriologic cure of 82% was reported. All eight gram-negative infections were eradicated, whereas only 10 of 14 gram-positive coccal infections were eradicated. No follow-up cultures were performed in this study after the end of the treatment. Finally, pefloxacin (800 mg daily) was given to 33 patients with acute or recurrent prostatitis for a median duration of 28 days; the bacteriologic cure rate was 63% in patients followed up for up to 3 months (data on file, Laboratoire Roger Bellon, Neuilly-sur-Seine, France).

Treatment of Patients with Renal Failure

The urinary recovery of fluoroquinolones decreases as impairment of renal function progresses, but drug concentrations may remain above the MIC for most urinary pathogens [1, 78]. Thus, fluoroquinolone treatment of UTI in patients with different levels of renal failure is of special clinical interest. However, the vast majority of controlled clinical trials have excluded patients with impaired renal function. Only a few clinical studies [39, 40, 47, 53] involved patients with renal failure. In one study [53], treatment of UTI with enoxacin failed in three of five patients with mild to severe renal failure (plasma creatinine levels, 1.8–3.8 mg/100 mL) and structural abnormalities of the urinary tract; it is notable that the three failures occurred in patients with the highest creatinine levels. Brown et al. [40] described a failure in a patient with chronic UTI due to *P. aeruginosa* and severe renal failure in whom concentrations of ciprofloxacin in urine were similar (1 mg/L) to the MIC for the organism. Schulz and Dörfler [47] observed a 71% cure rate among 15 patients with mild to severe renal failure (plasma creatinine levels, 1.2–10 mg/100 mL), and four patients undergoing hemodialysis, whose doses of ofloxacin were adjusted (100–400 mg daily). Two of the four patients receiving dialysis were cured, but one of these patients was cured only after the dose of ofloxacin was doubled. The therapeutic response was negatively affected by concomitant treatment with antacids, which are known to interfere with the gastrointestinal absorption of fluoroquinolones.

Table 4. Results of the treatment of bacterial prostatitis with fluoroquinolones.

Agent	No. of patients	Dosage (mg/day)	Duration (days)	Follow-up (weeks)	Bacteriologic cure rate (%)	Reference
Norfloxacin	20	800	10	4	85	76
Norfloxacin	25	800	28–42	1–3	92	70
Ciprofloxacin	26	1,000	28/84	6	77	32
Ofloxacin	22	300–600	5–21	End of treatment	82	77
Pefloxacin	33	800	28	12	63	*

* Data on file, Laboratoire Roger Bellon (Neuilly-sur-Seine, France).

Conclusions

For the treatment of uncomplicated UTI, randomized comparative trials of norfloxacin, ciprofloxacin, and ofloxacin have conclusively shown these drugs to be at least as effective as TMP-SMZ and amoxicillin and usually superior to nalidixic acid, pipemidic acid, and nitrofurantoin. In some trials, however, the duration of treatment was >3 days, thus raising the question of whether such relatively prolonged treatment was actually necessary – considering that conventional short-term treatment has been effective in such conditions.

Comparative trials of single-dose regimens have been limited, and in two studies, treatment failures have been attributed to the poor susceptibility of gram-positive cocci such as *S. saprophyticus* after single doses of norfloxacin or ciprofloxacin. Clearly, the use of short-term treatment for uncomplicated UTI requires careful, additional studies, but some authors have questioned the interest of the sponsors of such studies for the short-term approach in the management of uncomplicated UTI [79].

For the treatment of complicated UTI, norfloxacin, ciprofloxacin, and ofloxacin have demonstrated good efficacy and were at least as effective as amoxicillin and TMP-SMZ and were usually superior to pipemidic acid. In these trials, however, the duration of treatment was relatively short when one considers the necessity for prolonged administration of antibiotics for complicated UTI.

The few published reports of the outcome of clinical trials of oral treatment of complicated UTI due to *P. aeruginosa* have indicated that the fluoroquinolones may be remarkably effective in this setting. Unfortunately, too many trials that include complicated infections lack the data on follow-up 4–6 weeks after the end of the treatment that are critical in evaluating efficacy. This follow-up period might be especially important when considering the possibility of emergence of resistant organisms during fluoroquinolone treatment, as has been observed in other clinical settings such as osteoarticular or pulmonary infections.

The pharmacokinetic characteristics of fluoroquinolones suggest a possible role for the treatment of chronic bacterial prostatitis [1]. Limited, noncomparative clinical trials suggest that the fluoroquinolones are effective in this condition. Clearly, careful confirmatory clinical trials with microbiologically well-documented infections and follow-up cultures for several months after discontinuation of treatment are urgently needed to conclusively establish a role for the fluoroquinolones in the treatment of this chronic condition.

The development of resistance to the fluoroquinolones might be related in part to the presence at the infected site of concentrations of the antibiotic that are barely inhibitory and that thus may permit the growth of more resistant bacterial subpopulations. Fluoroquinolones produce very high concentrations of drug in the urine, and the emergence of resistance in pathogens of the urinary tract during therapy with fluoroquinolones has been observed only infrequently among organisms other than *P. aeruginosa*. However, preliminary data have indicated that emergence of resistant *P. aeruginosa* during fluoroquinolone therapy for complicated UTI might be a significant problem.

Since the fluoroquinolones are excreted, in part, by the kidney and their urinary recovery decreases as renal function decreases, the treatment of UTI in patients with renal failure should be investigated carefully. The excellent activity of these compounds in vitro and their lack of significant nephrotoxicity make them potentially usable and safe in this setting. However, at present only a few anecdotal reports of the use of these agents in this setting are available, and it is not possible to make a valid conclusion. Controlled trials involving patients with different stages of renal failure are needed, and special attention should be paid to the emergence of resistance. Whether the widespread use of these agents for the treatment of UTI will select resistant strains at other body sites, as has been observed in some French institutions after the widespread use of pefloxacin, is uncertain [80].

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