0022-5347/04/1712-0734/0
THE JOURNAL OF UROLOGY®

Vol. 171, 734–739, February 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000106191.11936.64

ONCE DAILY, EXTENDED RELEASE CIPROFLOXACIN FOR COMPLICATED URINARY TRACT INFECTIONS AND ACUTE UNCOMPLICATED PYELONEPHRITIS

DAVID A. TALAN,* IRA W. KLIMBERG, LINDSAY E. NICOLLE, JAMES SONG, STEVEN F. KOWALSKY AND DEBORAH A. CHURCH

From the University of California-Los Angeles Medical Center-Olive View (DAT), Sylmar, California, Florida Foundation for Healthcare Research (IWK), Ocala, Florida, Health Sciences Centre, University of Manitoba (LEN), Winnipeg, Manitoba, Canada, and Bayer Pharmaceuticals Corp. (JS, SFK, DAC), West Haven, Connecticut

ABSTRACT

Purpose: We assessed the efficacy and safety of 1,000 mg extended release ciprofloxacin orally once daily vs conventional 500 mg ciprofloxacin orally twice daily, each for 7 to 14 days, in patients with a complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP).

Materials and Methods: In this prospective, randomized, double-blind, North American multicenter clinical trial adults were stratified based on clinical presentation of cUTI or AUP and randomized to extended release ciprofloxacin or ciprofloxacin twice daily. Efficacy valid patients had positive pretherapy urine cultures (10^5 or greater cFU/ml) and pyuria within 48 hours of study entry. Bacteriological and clinical outcomes were assessed at the test of cure visit (5 to 11 days after therapy) and the late followup visit (28 to 42 days after therapy).

Results: The intent to treat population comprised 1,035 patients (extended release ciprofloxacin in 517 and twice daily in 518), of whom 435 were efficacy valid (cUTI in 343 and AUP in 92). For efficacy valid patients (cUTI and AUP combined) bacteriological eradication rates at test of cure were 89% (183 of 206) vs 85% (195 of 229) (95% CI −2.4%, 10.3%) and clinical cure rates were 97% (198 of 205) vs 94% (211 of 225) (95% CI −1.2%, 6.9%) for extended release vs twice daily ciprofloxacin. Late followup outcomes were consistent with test of cure findings. Eradication rates for Escherichia coli, which accounted for 58% of pathogens, were 97% or greater per group. Drug related adverse event rates were similar for extended release and twice daily ciprofloxacin (13% and 14%, respectively).

Conclusions: Extended release ciprofloxacin at a dose of 1,000 mg once daily was as safe and effective as conventional treatment with 500 mg ciprofloxacin twice daily, each given orally for 7 to 14 days in adults with cUTI or AUP. It provides a convenient, once daily, empirical treatment option.

KEY WORDS: urinary tract infections, urinary tract, kidney, ciprofloxacin, pyelonephritis

Complicated (c) urinary tract infections (UTIs) are those occurring in patients with underlying functional, metabolic or anatomical defects of the urinary tract.[1,2] Patients with acute uncomplicated pyelonephritis (AUP) have renal infection but normal genitourinary tracts. Escherichia coli is isolated from 80% of cases of AUP[2] but only from 30% to 60% of cases of cUTI.[3,4]

Patients with cUTI may be difficult to treat because of potential infection with a wide variety of organisms, urinary tract abnormalities, an increased likelihood of resistance[5–7] and a high frequency of recurrent infections. Increasing resistance in E. coli is also a concern.[8] Empirical treatment for cUTI and AUP is usually achieved with a 7 to 14-day course of antibiotics active against anticipated pathogens.[2,9]

A new, once daily, 500 mg extended release formulation of ciprofloxacin (CIP-XR) has been approved for uncomplicated UTI.[10] The 1,000 mg CIP-XR dose described has recently been approved for cUTI and AUP. The new extended release formulation is a bilayer tablet. The first layer releases 35% of the dose immediately after ingestion and the second layer releases the remaining 65% at a slower rate. The convenience of the once daily formulation may enhance patient compliance. In this clinical trial we compared the efficacy and safety of 1,000 mg CIP-XR orally with conventional 500 mg ciprofloxacin orally twice daily (CIP-BID), each given for 7 to 14 days, for the treatment of patients with cUTI or AUP.

Accepted for publication September 19, 2003.
Study received institutional review board approval.
Presented at annual meeting of American Urological Association, Chicago, Illinois, April 26–May 1, 2003.
* Correspondence and requests for reprints: University of California-Los Angeles Medical Center-Olive View, 14445 Olive View Dr., Sylmar, California 91342 (telephone: 818-364-3107; FAX: 818-364-3268; e-mail: dtalan@ucla.edu).

PATIENTS AND METHODS

Study population. Men and nonpregnant women 18 years or older were eligible for inclusion if they had a clinical diagnosis of cUTI or AUP. Complicated UTI was defined as at least 1 sign or symptom of a lower UTI (eg dysuria or urgency) and at least 1 other condition, namely an indwelling urinary catheter, 100 ml or greater post-void residual urine, neurogenic bladder, obstruction due to nephrolithiasis, tumor or fibrosis, urinary retention due to benign prostatic hypertrophy, bladder cancer or other urological anatomical abnormalities. Criteria for AUP included fever, chills and flank pain with or without costovertebral angle tenderness, nausea or symptoms of lower UTI. Eligible patients had a positive clean catch midstream or catheter obtained urine culture within 48 hours of study enrollment (10^5 cFU/ml or

greater of a causative organism) and pyuria (10 leukocytes per mm^3 or greater in unspun urine or greater than 5 leukocytes per mm^3 in centrifuged urine).

Primary exclusion criteria were pregnancy or lactation, inability to tolerate oral medications, history of prostatitis or epididymitis, renal transplantation, ileal loops or vesicoureteral reflux, infection requiring greater than 14 days of therapy, systemic antimicrobial therapy within 48 hours prior to enrollment or a baseline neutrophil count of less than 1,000 cells per mm^3, CD_4 less than 200 cells per mm^3, aspartate transaminase or alanine transaminase and/or total bilirubin greater than 3 times the upper limit of normal, serum creatinine greater than 3.0 mg/dl or creatinine clearance less than 30 ml per minute per 1.73 m^2. Each patient provided written informed consent.

Study design and antimicrobial therapy. This prospective, double-blind, randomized, multicenter study was done from April 2001 to July 2002 in the United States and Canada. Patients were stratified as having cUTI or AUP and then randomized in a 1:1 ratio to receive 1,000 mg CIP-XR once daily or conventional 500 mg CIP-BID for 7 to 14 days without regard to meals. Study drugs were administered in double-blind, double dummy fashion to mask differences in dosing frequency (once vs twice daily). Thus, each patient received medication and/or matching placebo twice daily. Concomitant systemic antimicrobials with activity against uropathogens were not permitted through the test of cure visit unless treatment failed.

Microbiological and clinical assessments. A clean catch midstream or catheter urine specimen and 2 blood cultures were collected within 48 hours of enrollment. Urine specimens were also collected at the test of cure (5 to 11 days after therapy) and late followup (28 to 42 days after therapy) visits. Additional blood cultures were repeated if baseline cultures were positive. Blood cultures were performed at individual study sites and urine cultures and susceptibility testing were performed at a central laboratory (Covance, Indianapolis, Indiana) using National Committee for Clinical Laboratory Standards.[11] For catheterized patients 2 or more pathogens (10^5 cFU/ml or greater) isolated from baseline urine culture were considered contaminants unless simultaneous blood culture yielded the same pathogen(s). At the test of cure visit bacteriological outcomes were categorized as eradication—original uropathogen(s) 10^5 cFU/ml or greater decreased to less than 10^4 cFU/ml, persistence—10^4 cFU/ml or greater of any original uropathogen, superinfection—10^5 cFU/ml or greater of a uropathogen other than the baseline pathogen(s) during the course of active therapy, new infection—10^5 cFU/ml or greater of a uropathogen other than the baseline pathogen(s) after the end of active therapy or indeterminate—not assessable for any reason, eg posttreatment culture not obtained. At the late followup visit bacteriological responses were defined as continued eradication—causative organism less than 10^4 cFU/ml at test of cure and late followup, eradication with recurrence—causative organism(s) less than 10^4 cFU/ml at test of cure but reappearance of the same organism(s) at 10^4 cFU/ml or greater before or at late followup, persistence—carried forward from test of cure, superinfection—carried forward from test of cure, new infection—carried forward from test of cure plus additional new infections following test of cure or indeterminate—as described.

Clinical response to the study drug was assessed on day 3, 4 or 5 of therapy, and at the test of cure and late followup visits. At test of cure clinical response was defined as cure—resolution or improvement of signs and symptoms related to infection, such that no additional antimicrobial therapy was administered or required, failure—no apparent response to therapy, persistent signs/symptoms, reappearance of signs/symptoms at or before test of cure or additional antimicrobial therapy for the current infection, or indeterminate—no evaluation possible. At late followup clinical response was defined as continued cure—continued absence of all signs/symptoms related to infection, such that additional antimicrobial therapy was not needed, failure—carried forward from test of cure, relapse—patients graded as cure at test of cure who had reappearance of signs/symptoms related to the current infection requiring antimicrobial therapy or indeterminate—no evaluation possible.

Safety and efficacy populations. All patients who received at least 1 dose of study drug comprised the safety (intent to treat) population and were evaluated for clinical outcomes and monitored through the test of cure visit for adverse events. Serious adverse events were captured through the late followup visit. The efficacy valid subpopulation was evaluated for bacteriological and clinical outcomes. It consisted of patients who met certain criteria, namely bacteriological outcome determined at test of cure unless the clinical outcome was early treatment failure, study drug received for a minimum of 3 days if a clinical outcome of failure or a minimum of 7 days if a clinical outcome of cure at test of cure, received no other concomitant antimicrobial agent active against urinary tract pathogens through test of cure unless failure occurred, bacterial pathogen had in vitro susceptibility to ciprofloxacin (minimal inhibitory concentration [MIC] 2 mg/l or less) and adherence to study medication (received at least 80% of the prescribed study drug dose).

Statistical analyses. The primary objective of this study was to evaluate whether CIP-XR was noninferior compared with CIP-BID based on the microbiological eradication rate at the test of cure visit for the efficacy valid population. With 435 patients valid for efficacy and a maximum allowable delta of 10% (ie difference in true failure rates) this study had 85% power to detect noninferiority between the 2 study arms (1-sided $\alpha = 0.025$). Secondary objectives were to assess bacteriological success at late followup, and clinical success at test of cure and late followup. Additional analysis of infection strata (cUTI vs AUP) by treatment interaction for the primary efficacy variable was performed using the Breslow-Day test.[12] All statistical analyses were performed using SAS 8.2 (SAS Institute, Inc., Cary, North Carolina) software.

Categorical baseline medical variables were analyzed using the chi-square test. For continuous variables a 1-way ANOVA model was used to compare the 2 treatment groups. Adverse events were tabulated by type (using COSTART) and frequency for all events and for drug related events.

For test of cure and late followup bacteriological and clinical responses the differences between eradication and cure rates were estimated using the 95% CI generated with a Mantel-Haenszel weighting procedure based on infection type. Noninferiority in terms of eradication rates was defined statistically as the lower limit of the 2-sided 95% CI with the weighted difference between treatment groups greater than −10%.

RESULTS

Patient population. There were 1,042 patients randomized from 100 centers, including 92 from the United States and 8 from Canada, and 1,035 comprised the safety population. The efficacy valid population included 435 patients, of whom 206 received CIP-XR (cUTI in 166 and AUP in 40) and 229 received CIP-BID (cUTI in 177 and AUP in 52). Exclusion from the efficacy valid population was primarily for less than 10^5 cFU/ml uropathogen at baseline (311 of 600 cases or 62%) or an inappropriately collected urine specimen (121 of 600 or 20%). Primary causes of the 210 premature discontinuations were protocol violation in 84 of 210 patients (40%) and adverse event in 48 of 210 (23%), that is 24% and 22% who received CIP-XR and CIP-BID, respectively.

Baseline demographics and disease characteristics were

similar for the 2 ciprofloxacin treatment groups (the 2 strata combined) for the efficacy valid population (table 1). Most evaluable patients had cUTI rather than AUP (343 vs 92). The mean age of patients with cUTI was higher than for those with AUP (about 66 vs about 41 years) and the AUP stratum was primarily female (83%). Within each stratum (cUTI or AUP) the 2 treatment groups were well balanced with respect to demographic and medical characteristics as well as disease severity and symptom prevalence. The most common underlying conditions for cUTI included 100 ml or greater post-void residual urine in 39% of cases, neurogenic bladder in 33%, obstructive uropathy in 25% and benign prostatic hypertrophy with urinary retention in 20%. An indwelling bladder catheter was present in 6% of patients, and 2% and 3% of the CIP-XR and CIP-BID groups, respectively, had catheters placed following study entry.

Microbiological efficacy. Of the 1,035 intent to treat patients 641 had pretherapy uropathogens (674) isolated (10^5 cFU/ml or greater), including 49 with a total of 51 ciprofloxacin resistant (MIC 4 mg/l or greater) organisms. By stratum pre-therapy ciprofloxacin resistance was observed in 46 of the 815 patients with cUTI (5.6%) and in 3 of the 220 with AUP (1.4%). The most common resistant pathogens were E. coli (20 of 383 cases or 5%) and Enterococcus faecalis (8 of 75 or 11%). According to the protocol patients with baseline ciprofloxacin resistant pathogens were excluded from the efficacy analysis.

The distribution of pre-therapy pathogens in efficacy valid cases was comparable for the 2 treatment groups (table 2). A total of 12 patients (CIP-XR in 7 and CIP-BID in 5 or 2.8%) had bacteremia at baseline, including E. coli in 11 (cUTI in 2 and AUP in 9) and Klebsiella pneumoniae in 1 with AUP. At test of cure 95% and 93% of all uropathogens were eradicated by CIP-XR and CIP-BID, respectively.

For all efficacy valid cases eradication at the test of cure visit was achieved in 88.8% and 85.2% of those treated with CIP-XR and CIP-BID, respectively (95% CI −2.4, 10.3, table 3). All 12 patients with baseline bacteremia had eradication from urine at test of cure, of whom 10 also had the bloodborne organism eradicated. Two cases without repeat blood cultures were classified as indeterminate.

Of patients with cUTI at test of cure eradication was achieved in 89.2% and 81.4% of CIP-XR and CIP-BID recipients, respectively. Test of cure eradication rates for AUP cases were 87.5% and 98.1%, respectively. These differences for CIP-XR and CIP-BID for the cUTI and AUP strata ($p = 0.008$) suggests that a different treatment effect was present between the cUTI and AUP groups. When patients were stratified by cUTI or AUP, no differences in demographics, baseline medical characteristics or the severity of signs and symptoms were found before therapy between the treatment groups. In 3 patients with AUP who received CIP-XR a new infection developed due to Enterococcus species compared with 0 with AUP in the CIP-BID group. For the cUTI stratum the difference in eradication rates is also explained by a higher rate of new infections in patients receiving CIP-BID vs CIP-XR (14 vs 5). Approximately half of the patients with new infections were asymptomatic and received no additional antimicrobial therapy (2 of 3 with AUP on CIP-XR, 8 of 14 with cUTI on CIP-BID and 2 of 5 with cUTI on CIP-XR).

Five patients with cUTI (3 on CIP-XR and 2 on CIP-BID) had organisms that became resistant to ciprofloxacin during the study (MIC 4 mg/l or greater). Three persistent uropathogens that were initially susceptible at baseline had an MIC of 16 mg/l at test of cure, namely Staphylococcus aureus in a CIP-XR case, and E. coli and E. faecalis in 2 CIP-BID cases, respectively. The patients with S. aureus and E. faecalis achieved clinical cure, while the remaining patient had an indeterminate clinical response. At the late followup visit 2 recurrent organisms had developed resistance to ciprofloxacin, namely E. coli with an MIC of 16 mg/l in extended release patients. One of these patients remained clinically cured at the followup visit and the other experienced clinical relapse.

Clinical efficacy. In efficacy valid patients at test of cure clinical cure was achieved in 96.6% of those on CIP-XR vs. 93.8% of those on CIP-BID (95% CI −1.2, 6.9, table 4). The

TABLE 1. *Demographic and baseline medical characteristics*

Variable	Efficacy Valid Population		Intent to Treat Population	
	CIP-XR	CIP-BID	CIP-XR	CIP-BID
No. pts	206	229	517	518
Mean age ± SD (range)	60.1 ± 19.1 (18–96)	61.2 ± 19.4 (18–92)	58.9 ± 20.2 (18–97)	59.9 ± 19.9 (18–94)
No. women (%)	118 (57)	127 (55)	298 (58)	299 (58)
No. race (%):				
White	168 (82)	177 (77)	410 (79)	414 (80)
Black	19 (9)	27 (12)	55 (11)	48 (9)
Hispanic	18 (9)	24 (10)	48 (9)	53 (10)
Asian	1 (less than 1)	1 (less than 1)	3 (less than 1)	3 (less than 1)
American Indian	0	0	1 (less than 1)	0
Mean days infection ± SD	4.7 ± 9.1	4.4 ± 4.7	4.7 ± 8.3	4.5 ± 5.3
No. health status at study entry (%):				
Excellent/good	167 (81)	178 (78)	404 (78)	402 (78)
Fair	37 (18)	49 (21)	108 (21)	110 (21)
Poor	2 (1)	2 (1)	5 (less than 1)	6 (1)
No. AUP (%):				
No. pts	40	52	109	111
Mean age ± SD (range)	41.3 ± 17.2 (18–81)	40.2 ± 15.7 (18–83)	39.6 ± 16.7 (18–81)	40.1 ± 16.8 (18–84)
No. women (%)	33 (82)	43 (83)	97 (89)	96 (86)
No. cUTI (%):				
No. pts	166	177	408	407
Mean age ± SD (range)	64.6 ± 16.6 (19–96)	67.4 ± 15.9 (23–92)	64.1 ± 17.7 (19–97)	65.3 ± 17.1 (21–94)
No. women (%)	85 (51)	84 (47)	201 (49)	203 (50)
No. underlying conditions (%):				
0	—	—	8 (2)	8 (2)
1	119 (72)	140 (79)	283 (69)	306 (75)
2	41 (25)	33 (19)	105 (26)	86 (21)
3–4	6 (3)	4 (2)	12 (3)	7 (2)

None of the differences between the treatment groups were statistically significant.

TABLE 2. *Overall bacteriological eradication rates by uropathogen at test of cure assessment in efficacy valid population*

Organism	No. CIP-XR/Total No. (%)			No. CIP-BID/Total No. (%)		
	Overall	cUTI	AUP	Overall	cUTI	AUP
All pathogens	202/212 (95)	163/171 (95)	39/41 (95)	222/239 (93)	167/183 (91)	55/56 (98)
E. coli	126/130 (97)	91/94 (97)	35/36 (97)	131/133 (99)	90/92 (98)	41/41 (100)
K. pneumoniae	22/23 (96)	20/21 (95)	2/2 (100)	21/25 (84)	19/23 (83)	2/2 (100)
E. faecalis	17/18 (94)	17/17 (100)	0/1	19/27 (70)	14/21 (67)	5/6 (83)
Proteus mirabilis	11/12 (92)	11/12 (92)	0	13/13 (100)	10/10 (100)	3/3 (100)
Enterobacter species	6/6 (100)	6/6 (100)	0	9/9 (100)	9/9 (100)	0
Citrobacter species	5/6 (83)	5/6 (83)	0	6/7 (86)	5/6 (83)	1/1 (100)
S. aureus	4/6 (67)	4/6 (67)	0	3/4 (75)	2/3 (67)	1/1 (100)
K. oxytoca	1/1 (100)	1/1 (100)	0	6/7 (86)	6/7 (86)	0
Pseudomonas aeruginosa	4/4 (100)	3/3 (100)	1/1 (100)	3/3 (100)	3/3 (100)	0
Serratia marcescens	2/2 (100)	2/2 (100)	0	4/4 (100)	4/4 (100)	0
Miscellaneous*	4/4 (100)	3/3 (100)	1/1 (100)	7/7 (100)	5/5 (100)	2/2 (100)

Some patients had more than 1 causative organism, and pathogens showing indeterminate bacteriological responses at test of cure, which occurred only in patients with cUTI, were excluded (indeterminate responses were for CIP-XR K. pneumoniae in 2, E. faecalis in 1 and E. faecium in 1, and for CIP-BID P. mirabilis in 1).

* For CIP-XR S. saprophyticus in 2 patients, E. faecium in 1 and Burkholderia cepacia in 1, and for CIP-BID S. saprophyticus in 2, Morganella morganii in 2, Providencia rettgeri in 2 and Weeksella virosa in 1.

TABLE 3. *Microbiological response of efficacy valid patients with complicated UTI and acute uncomplicated pyelonephritis*

	No. CIP-XR (%)	No. CIP-BID (%)	95% CI
Test of cure 5–11 days after therapy			
Both strata combined:	206	229	
Eradication	183 (88.8)	195 (85.2)	−2.4, 10.3
Persistence	10 (4.9)	17 (7.4)	
Superinfection	5 (2.4)	3 (1.3)	
New infection	8 (3.9)	14 (6.1)	
cUTI:	166	177	
Eradication	148 (89.2)	144 (81.4)	
Persistence	8 (4.8)	16 (9.0)	
Superinfection	5 (3.0)	3 (1.7)	
New infection	5 (3.0)	14 (7.9)	
AUP:	40	52	
Eradication	35 (87.5)	51 (98.1)	
Persistence	2 (5.0)	1 (1.9)	
New infection	3 (7.5)	0	
Late followup 28–42 days after therapy			
Both strata combined:	179	188	
Continued eradication	124 (69.3)	115 (61.2)	−0.8, 18.6
Eradication with recurrence	19 (10.6)	18 (9.6)	
Persistence	10 (5.6)	17 (9.0)	
Superinfection	5 (2.8)	2 (1.1)	
New infection*	21 (11.7)	36 (19.1)	
cUTI:	146	145	
Continued eradication	99 (67.8)	80 (55.2)	
Eradication with recurrence	18 (12.3)	15 (10.3)	
Persistence	8 (5.5)	16 (11.0)	
Superinfection	5 (3.4)	2 (1.4)†	
New infection	16 (11.0)	32 (22.1)	
AUP:	33	43	
Continued eradication	25 (75.8)	35 (81.4)	
Eradication with recurrence	1 (3.0)	3 (7.0)	
Persistence	2 (6.0)	1 (2.3)	
New infection	5 (15.2)	4 (9.3)	

Indeterminate responses were excluded.

* The most common pathogens causing new infections were E. faecalis in 7 patients on CIP-XR and 6 on CIP-BID, and S. aureus in 4 on CIP-BID.

† Recurrent original pre-therapy pathogen in 1 patient with cUTI and superinfection at test of cure who was reclassified as eradication with recurrence at late followup.

rate of clinical cure in cUTI cases was 96.4% and 93.1% for CIP-XR and CIP-BID, and the corresponding rates for AUP were 97.5% and 96.2%, respectively. At the late followup visit continued clinical cure was reported in 82.9% of CIP-XR and 80.6% of CIP-BID treated patients. The intent to treat population showed almost identical results for the 2 ciprofloxacin arms (table 4).

Safety. Of the 1,035 patients who received at least 1 dose of study drug and were evaluated for safety adverse event rates were the same for the 2 treatment arms (31.9%) (table 5). Drug related events were reported by 13.2% of CIP-XR and 13.5% of CIP-BID treated patients with the most common drug related events being nausea, diarrhea, vaginal moniliasis, headache and dizziness. One patient receiving CIP-BID had a possibly drug related, serious adverse event, that is a perforated duodenum with unconfirmed Helicobacter pylori infection.

Study drug was prematurely discontinued due to an adverse event in 48 patients, of whom 28 (16 on CIP-XR and 12 on CIP-BID) experienced 1 or greater possible/probable drug related adverse event (table 5). Primary events resulting in discontinuations in the 2 treatment groups were gastrointestinal (ie nausea, vomiting or diarrhea) and dizziness. Four patients with cUTI (3 receiving CIP-XR and 1 receiving CIP-BID) died during the study or followup but none of the deaths was judged to be related to the study drug. The respective causes of death were acute renal failure, respiratory failure and sudden death probably due to worsening congestive heart failure in the CIP-XR cases and renal cell carcinoma in the CIP-BID case.

TABLE 4. *Clinical cure rates*

	No. Efficacy Valid Population (%)		No. Intent to Treat Population (%)	
	CIP-XR	CIP-BID	CIP-XR	CIP-BID
Test of cure 5–11 days after therapy				
Overall:	205	225	379	407
Cure	198 (96.6)	211 (93.8)*	343 (90.5)	368 (90.4)
Failure	7 (3.4)	14 (6.2)	36 (9.5)	39 (9.6)
cUTI:	165	173	297	316
Cure	159 (96.4)	161 (93.1)	267 (89.9)	281 (88.9)
Failure	5 (3.6)	12 (6.9)	30 (10.1)	35 (11.1)
AUP:	40	52	82	91
Cure	39 (97.5)	50 (96.2)	76 (92.7)	87 (95.6)
Failure	1 (2.5)	2 (3.8)	6 (7.3)	4 (4.4)
Late followup 28–42 days after therapy				
Overall:	181	187	332	347
Continued cure	150 (82.9)	151 (80.7)†	258 (77.7)	270 (77.8)
Failure	8 (4.4)	16 (8.6)	41 (12.3)	43 (12.4)
Relapse	23 (12.7)	20 (10.7)	33 (9.9)	34 (9.8)
cUTI:	145	143	258	275
Continued cure	120 (82.8)	109 (76.2)	198 (76.7)	202 (73.4)
Failure	7 (4.8)	14 (9.8)	35 (13.6)	39 (14.2)
Relapse	18 (12.4)	20 (14.0)	25 (9.7)	34 (12.4)
AUP:	36	44	74	72
Continued cure	30 (83.3)	42 (95.5)	60 (81.1)	68 (94.4)
Failure	1 (2.8)	2 (4.5)	6 (8.1)	4 (5.6)
Relapse	5 (13.9)	0	8 (10.8)	0

Indeterminate responses were excluded.
* 95% CI −1.2, 6.9.
† 95% CI −5.4, 10.4.

TABLE 5. *Adverse events*

Adverse Event	No. CIP-XR (%)	No. CIP-BID (%)
Total pts	517	518
All reported events:	165 (31.9)	165 (31.9)
Mild to moderate intensity	130 (25.1)	137 (26.4)
Severe intensity	35 (6.8)	28 (5.4)
At least 1 drug related event	68 (13.2)	70 (13.5)
Specific drug related events:*		
Nausea	15 (2.9)	15 (2.9)
Diarrhea	12 (2.3)	7 (1.4)
Vaginal moniliasis	9 (1.7)	7 (1.4)
Headache	7 (1.4)	8 (1.5)
Dizziness	9 (1.7)	3 (0.5)
	28 (5.4)	25 (4.8)
Serious events†	0	1 (less than 1)
Premature discontinuations:		
Due to any event	28 (5.4)	20 (3.9)
Due to drug related events	16 (3.1)	12 (2.3)

* Only events occurring in 1.5% or greater of patients in either treatment group.
† Events that were fatal, life threatening, required hospitalization, resulted in disability or otherwise endangered the patient.

DISCUSSION

This large clinical trial of patients with cUTI and AUP shows that a new, once daily, extended release ciprofloxacin formulation was at least as effective as the conventional, twice daily ciprofloxacin tablet regimen based on bacteriological and clinical responses. More than 85% of the evaluable patients in the 2 treatment groups achieved bacteriological eradication at short-term followup and more than 93% were clinically cured. Bacteriological and clinical success continued at the late followup visit and remained similar in the 2 treatment groups. Overall this trial of once daily, extended release ciprofloxacin shows similar eradication rates as previous investigations of conventional twice daily ciprofloxacin in patients with cUTI and AUP.[8, 13–18]

An inconsistent treatment effect was observed between patients with AUP (higher eradication rate with CIP-BID) and those with cUTI (higher eradication rate with CIP-XR). The significance of this result is not obvious since the clinical cure rates were similar, many of the patients with new infections were asymptomatic and no difference in eradication rates between treatments was observed for either stratum when the rate was analyzed by pretreatment causative organism. Because this study was not designed to examine responses in patient subpopulations, the observed treatment difference may be attributable to the size of the AUP and cUTI patient groups.

The uropathogens isolated were consistent with those in previous reports.[1, 9, 19] In patients with cUTI E. coli was the most common uropathogen (54%), followed by K. pneumoniae and E. faecalis (12% each). The majority of patients with AUP (84%) were infected with E. coli. Overall ciprofloxacin eradicated greater than 97% of baseline E. coli urinary isolates and 100% (10 of 10 cases) of evaluable E. coli bloodstream isolates. The emergence of resistance to ciprofloxacin (4 mg/l or greater) was uncommon, being seen in 5 of the 435 patients (1.1%), of whom all experienced persistent or recurrent infections (E. coli in 3, E. faecalis in 1 and S. aureus in 1) and of whom 3 achieved clinical cure.

Empirical therapy with a fluoroquinolone is recommended for many patients because of the increased likelihood of pathogens other than E. coli with cUTI and the increasing recognition of clinically important rates of trimethoprim/sulfamethoxazole resistant E. coli in cUTI and AUP,[6, 8, 9, 20] which increase the likelihood of clinical failure.[8] The emergence of E. coli resistance to first generation cephalosporins has also been noted.[5] Due to such developments empirical treatment for UTI has shifted toward more potent antimicrobial agents that have a history of low rates of in vitro resistance to common uropathogens.[9]

A limitation of this study was that patients with baseline ciprofloxacin resistant pathogens were excluded. However, the rate of E. coli resistance to ciprofloxacin among these North American community acquired isolates was low at approximately 5%. Also, patients with certain conditions (a history of prostatitis or epididymitis, renal transplantation, ileal loops or vesicoureteral reflux) were excluded due to the necessity of surgical or other interventions.

CONCLUSIONS

This study demonstrates that the efficacy and tolerability of extended release ciprofloxacin at a dose of 1,000 mg were similar to those of a conventional twice daily dose of 500 mg ciprofloxacin as 7 to 14-day treatment for adults with cUTI or AUP. The emergence of ciprofloxacin resistance was low in the 2 study arms. Extended release ciprofloxacin offers the

convenience of once daily dosing as well as a side effect profile comparable to that of conventional twice daily ciprofloxacin. Extended release ciprofloxacin at a dose of 1,000 mg is an effective once daily treatment for cUTI and AUP.

Teresa Tartaglione, Amy Plofker and Brian Shearer critically reviewed the manuscript.

REFERENCES

1. Ronald, A.: The etiology of urinary tract infection: traditional and emerging pathogens. Am J Med, suppl., **113:** 14S, 2002
2. Stamm, W. E. and Hooton, T. M.: Management of urinary tract infections in adults. N Engl J Med, **329:** 1328, 1993
3. Gorbach, S., Bartlett, J., Falagas, M. and Hamer, D.: Infectious diseases in clinical practice. In: 1999 Guidelines for Infectious Diseases in Primary Care. Baltimore: Lippincott Williams & Wilkins, pp. 68–69, 1998
4. Nicolle, L. E., Louie, T. J., Dubois, J., Martel, A., Harding, G. K. and Sinave, C. P.: Treatment of complicated urinary tract infections with lomefloxacin compared with that with trimethoprim-sulfamethoxazole. Antimicrob Agents Chemother, **38:** 1368, 1994
5. Gupta, K., Scholes, D. and Stamm, W. E.: Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. JAMA, **281:** 736, 1999
6. Gupta, K., Sahm, D. F., Mayfield, D. and Stamm, W. E.: Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: a nationwide analysis. Clin Infect Dis, **33:** 89, 2001
7. Raz, R., Chazan, B., Kennes, Y., Colodner, R., Rottensterich, E., Dan, M. et al: Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. Clin Infect Dis, **34:** 1165, 2002
8. Talan, D. A., Stamm, W. E., Hooton, T. M., Moran, G. J., Burke, T., Iravani, A. et al: Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial. JAMA, **283:** 1583, 2000
9. Warren, J. W., Abrutyn, E., Hebel, J. R., Johnson, J. R., Schaeffer, A. J. and Stamm, W. E.: Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis, **29:** 745, 1999
10. Henry, D. C., Jr., Bettis, R. B., Riffer, E., Haverstock, D. C., Kowalsky, S. F., Manning, K. et al: Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. Clin Ther, **24:** 2088, 2002
11. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 5th ed. National Committee for Clinical Laboratory Standards, Document M7–A5. Wayne, Pennsylvania: National Committee for Clinical Laboratory Standards, 2000
12. Breslow, N. E. and Day, N. E.: Statistical methods in cancer research. Volume I—The analysis of case-control studies. IARC Sci Publ, **32:** 5, 1980
13. Cox, C. E., Marbury, T. C., Pittman, W. G., Brown, G. L., Auerbach, S. M., Fox, B. C. et al: A randomized, double-blind, multicenter comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection and pyelonephritis. Clin Ther, **24:** 223, 2002
14. Naber, K. G., di Silverio, F., Geddes, A. and Guibert, J.: Comparative efficacy of sparfloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection. J Antimicrob Chemother, suppl., **37:** 135, 1996
15. Harding, G., Nicolle, L., Wenman, W., Richards, G., Louie, T., Martel, A. et al: Randomised comparison of oral ciprofloxacin vs standard parenteral therapy in the treatment of complicated urinary tract infections. Drugs, suppl., **45:** 333, 1993
16. Cox, C. E.: A comparison of the safety and efficacy of lomefloxacin and ciprofloxacin in the treatment of complicated or recurrent urinary tract infections. Am J Med, **92:** 82S, 1992
17. Fang, G. D., Brennen, C., Wagener, M., Swanson, D., Hilf, M., Zadecky, L. et al: Use of ciprofloxacin versus use of aminoglycosides for therapy of complicated urinary tract infection: prospective, randomized clinical and pharmacokinetic study. Antimicrob Agents Chemother, **35:** 1849, 1991
18. Mombelli, G., Pezzoli, R., Pinoja-Lutz, G., Monotti, R., Marone, C. and Franciolli, M.: Oral vs intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. Arch Intern Med, **159:** 53, 1999
19. Ronald, A. R. and Harding, G. K.: Complicated urinary tract infections. Infect Dis Clin North Am, **11:** 583, 1997
20. Mazzulli, T.: Resistance trends in urinary tract pathogens and impact on management. J Urol, **168:** 1720, 2002