W. Kern, E. Kurrle

Ofloxacin versus Trimethoprim-Sulfamethoxazole for Prevention of Infection in Patients with Acute Leukemia and Granulocytopenia

Summary: In a prospective randomized study we evaluated the efficacy and safety of oral ofloxacin (dosage: 200 mg three times daily) versus trimethoprim-sulfamethoxazole (dosage: 960 mg three times daily) as antibacterial prophylaxis in 128 patients with acute leukemia who received aggressive cytotoxic chemotherapy and were granulocytopenic for a median duration of 30 days. Fewer patients receiving ofloxacin were colonized by *Enterobacteriaceae* (13% versus 90%, $p<0.001$) and *Pseudomonas aeruginosa* (3% versus 14%, $p=0.025$), and developed gram-negative bacterial infection (4% versus 26%, $p=0.002$), whereas the incidence of gram-positive bacterial (19% versus 22%) and fungal (7% versus 14%) infections was similar in both groups. Ofloxacin was significantly better tolerated than trimethoprim-sulfamethoxazole, and shortened the duration of fever ($p=0.02$) and of parenteral antimicrobial therapy for presumed or documented acquired infection ($p=0.01$). Ofloxacin appears to be a safe, effective, well-tolerated alternative to trimethoprim-sulfamethoxazole for preventing gram-negative infection in acute leukemia, but more effective prophylaxis of gram-positive infections is still needed.

Zusammenfassung: *Ofloxacin im Vergleich zu Trimethoprim-Sulfamethoxazol zur Infektionsverhütung bei granulozytopenischen Patienten mit akuter Leukämie.* In einer prospektiven, randomisierten Studie wurden die Wirksamkeit und Verträglichkeit von Ofloxacin (dreimal 200 mg täglich) im Vergleich mit Trimethoprim-Sulfamethoxazol (dreimal 960 mg täglich) als antibakterielle Prophylaxe bei Patienten mit akuter Leukämie geprüft. Beurteilbar waren 128 Patienten, die eine aggressive cytostatische Chemotherapie erhielten, mit einer medianen Granulozytopeniedauer von 30 Tagen. In der Ofloxacin-Gruppe wurde eine Kolonisierung mit *Enterobacteriaceae* (13% gegenüber 90%, $p<0.001$) und *Pseudomonas aeruginosa* (3% gegenüber 14%, $p=0.025$) wesentlich seltener beobachtet als in der Trimethoprim-Sulfamethoxazol-Gruppe. Patienten, die Ofloxacin erhielten, entwickelten auch weniger gramnegative Infektionen (4% gegenüber 26%, $p=0.002$), während die Inzidenz von gram-positiven bakteriellen (19% gegenüber 22%) und von Pilzinfektionen (7% gegenüber 14%) in beiden Gruppen vergleichbar war. Ofloxacin war besser verträglich und verkürzte die Fieberdauer ($p=0.02$) sowie die Dauer der parenteralen antimikrobiellen Behandlung von vermuteten oder dokumentierten erworbenen Infektionen ($p=0.01$). In der Prophylaxe gramnegativer Infektionen bei Patienten mit akuter Leukämie erscheint Ofloxacin daher eine wirksamere und besser verträgliche Alternative zu Trimethoprim-Sulfamethoxazol zu sein. Möglichkeiten einer gezielten Prophylaxe gegen grampositive Infektionen sollten jedoch weiterhin überprüft werden.

Introduction

Bacterial infections remain a frequent cause of morbidity and mortality in patients who receive aggressive cytotoxic therapy for acute leukemia [1]. One of the major attempts at preventing infection in these patients has been the use of oral antibacterial agents that are capable to suppress aerobic gram-negative bacilli in the gastrointestinal tract flora during the periods of profound granulocytopenia [2, 3]. Although a reduction in the incidence of severe infections could be shown, this approach has remained controversial, mainly because most reports failed to document increased remission rates or prolonged survival [4–6]. Among the best studied and most widely used oral regimens for infection prevention in acute leukemia is trimethoprim-sulfamethoxazole, either given alone or together with polymyxin B or colistin. Trimethoprim-sulfamethoxazole prophylaxis has been found to be more effective than oral non-absorbable agents, presumably due to its systemic antibacterial activity besides its effect on the digestive tract flora [4]. The overall efficacy of trimethoprim-sulfamethoxazole prophylaxis may, however, be limited for several reasons. Adverse effects may be frequent and may significantly lower patient compliance [7–9]. There is a certain potential of myelosuppression or other adverse hematologic effects [9–12]. Trimethoprim-sulfamethoxazole has poor activity against *Pseudomonas aeruginosa*, and the emergence of resistant strains of *Enterobacteriaceae* during treatment now appears to be common [13–17].

Newer fluorinated quinolones have been studied as an alternative to previous prophylactic regimens for infection prevention in acute leukemia. Studies in healthy volunteers and in patients have shown that newer quinolones are able to effectively suppress gram-negative aerobic ba-

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Dr. *W. Kern*, Prof. Dr. *E. Kurrle*, Medizinische Universitätsklinik und Poliklinik, Robert-Koch-Straße 8, W-7900 Ulm, Germany.

cilli in the digestive tract without exerting profound effects on the anaerobic fecal flora [18–19]. Controlled studies with norfloxacin have shown that this effect indeed may lead to a more effective prevention of gram-negative bacillary infection in patients with neutropenia as compared to no prophylactic treatment [20, 21], oral non-absorbable drugs [21, 22] and trimethoprim-sulfamethoxazole [21, 23, 24]. The incidence of febrile episodes and documented gram-positive infections, however, remained largely unaffected by norfloxacin prophylaxis. Similar results have been reported for ciprofloxacin in a relatively small study conducted by *Dekker* and colleagues [25].

Of other possible fluoroquinolone candidate drugs ofloxacin might prove especially useful. Serum and saliva levels after oral therapy with ofloxacin are substantially greater than those achieved with norfloxacin or ciprofloxacin [26–28] while its *in vitro* activity against gram-positive potential pathogens is better than that of norfloxacin and appears to be as effective as that of ciprofloxacin [29, 30]. We therefore studied the efficacy and safety of oral ofloxacin for the prevention of infection in patients with acute leukemia.

Patients and Methods

Patient selection: Adult patients with acute leukemia admitted to receive chemotherapy for remission induction or intensive consolidation were eligible for participation in the study. After informed consent had been obtained patients were randomized to receive prophylactic treatment with either oral ofloxacin or with trimethoprim-sulfamethoxazole. Patients were stratified according to whether fever and/or infection was present on admission, and according to the type of the planned cytotoxic chemotherapy.

Infection prophylaxis: One group of patients received ofloxacin tablets (200 mg) three times daily. The other group received trimethoprim-sulfamethoxazole tablets (960 mg) three times daily. Both groups of patients received oral amphotericin B (500 mg four times daily) suspension to prevent overgrowth of yeasts. Prophylactic treatment was started on admission or at the time of initiation of antileukemic chemotherapy. No other prophylactic measures were taken. Patients received standard hospital diet, and were nursed on open wards. Prophylactic treatment was continued until granulocyte counts reached 1,000 cells per µl, or antileukemic treatment was terminated because of other reasons.

Microbiological surveillance: Surveillance cultures from feces, oropharynx and urine were obtained on admission and twice weekly during the study period. MacConkey agar, chocolate agar, blood agar (with 7% defibrinated sheep blood), and Sabouraud's dextrose agar were used for subcultures. Species differentiation was done by standard methods. API 20 E and API 20 NE test strips were used for gram-negative bacilli, and DNase and coagulase assays were used for staphylococci. Antimicrobial susceptibility testing was done using the agar dilution method on Iso-Sensitest agar (Oxoid). The breakpoints for susceptibility and resistance were 1 and 4 mg ofloxacin per liter, and 40 and 160 mg trimethoprim-sulfamethoxazole (1:19 ratio) per liter, respectively.

Evaluation: Patients were daily examined for fever and signs of infection, and for clinical and laboratory manifestations of possible side effects. In cases of suspected infection appropriate diagnostic studies were performed, and cultures were taken from blood and from other possibly infected clinical sites. Fever was defined as an axillary temperature of more than 38°C, and infections were classified as described previously [7]. All febrile patients were initially treated with empiric parenteral antibiotic combination therapy (usually piperacillin/netilmicin), while the oral prophylactic regimens were continued. Patients were deemed evaluable for efficacy only if they had received at least 14 or more days of prophylaxis and at least seven or more days of prophylaxis while being granulocytopenic (less than 1,000 cells per µl). All microorganisms that were cultured from surveillance sites after more than one week of prophylaxis were considered colonizing organisms. When they appeared only in single cultures and had not been isolated before this period they were considered to be transient strains.

Statistical analysis: Chi-square analysis or Fisher's exact test were used to compare differences in proportions. Differences in medians and means were analysed by Wilcoxon's rank-sum test. Life table analysis with the log-rank test was used in order to compare the times until the first fever or infection after appearance of granulocytopenia. For this analysis only patients without fever and/or infection on admisssion were evaluated. All tests were done with two-sided hypotheses.

Results

Patient Characteristics

A total of 160 patients were entered into the trial. Four patients died within 48 h after admission. Four patients could not be evaluated because of incomplete data. Eight patients did not receive chemotherapy or did not become granulocytopenic, and nine patients were excluded because of other protocol violations. Of the 135 remaining patients 128 (70 in the group receiving ofloxacin, and 58 in the group receiving trimethoprim- sulfamethoxazole) completed more than 14 days of prophylaxis and were evaluated for efficacy. The patients in both groups were similar in age, sex distribution, underlying disease, proportion of patients with fever and/or infection on admission, duration of granulocytopenia, and total duration of the study period (Table 1).

Tolerance and Side Effects

Adverse effects probably attributable to the study drugs were more frequent in the group receiving trimethoprim-sulfamethoxazole (Table 2). Seven patients receiving ofloxacin versus 23 patients receiving trimethoprim-sulfamethoxazole experienced any adverse effects (10% versus 36%, $p = 0.001$). In patients who completed more than two weeks of prophylaxis a similar incidence of adverse effects was observed (9% versus 29%, $p = 0.005$).

Most adverse effects were gastrointestinal intolerance and skin rashes in both groups (Table 2). Prophylactic treatment was discontinued because of adverse effects in 5 ofloxacin recipients and in 19 trimethoprim-sulfamethoxazole recipients ($p = 0.002$).

Surveillance Cultures

Ofloxacin recipients were significantly less likely to be col-

Infection 19 (1991) No. 2

Table 1: Patient characteristics.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Patients, n	70	58
Median age, yrs (range)	40.5 (16–68)	42.5 (16–67)
Sex (male/female), n	44/26	38/20
Underlying disease, n		
AML	49	42
ALL/AUL	21	16
Relapse	21	11
Treatment, n		
Remission induction	30	20
Remission induction/ consolidation	20	21
Consolidation	20	17
Patients receiving high dose cytosine arabinoside	12	10
Infection or fever on admission, n	19	20
Granulocytopenic (<1,000 cells/µl) episodes, n	103	91
Median duration of granulocytopenia, days (range)		
<100 cells/µl	14 (0–59)	16 (0–48)
<1,000 cells/µl	28.5 (10–81)	36 (7–85)

Note: all differences were statistically not significant.

Table 2: Adverse effects.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Patients entered, n	80	80
Patients with adverse effects, n[a]	7 (1)	23 (6)
Rash	3 (–)	8 (4)
Gastrointestinal	2 (–)	13 (1)
Central nervous system	1 (1)	–
Liver	1 (–)	–
Hematologic	–	3 (1)
Patients discontinuing prophylaxis because of adverse effects	5	19

Note: [a]numbers in brackets indicate number of patients with early side effects excluded from analysis of efficacy.

onized with gram-negative bacilli at surveillance sites than were the patients receiving trimethoprim-sulfamethoxazole (Table 3). Ofloxacin provided better protection against colonization especially with *Enterobacteriaceae*. After more than one week of prophylaxis, nine patients receiving ofloxacin compared with 52 patients receiving trimethoprim-sulfamethoxazole had at least one surveillance culture positive for *Enterobacteriaceae* (13% versus 90%, $p<0.001$). Most of these strains were transient in ofloxacin recipients, whereas the majority of patients in the trimethoprim-sulfamethoxazole group were persistently colonized (6% versus 76%, $p<0.001$).

Strains of *Enterobacteriaceae* resistant to the prophylactic

Table 3: Colonization at surveillance sites by gram-negative bacilli.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Patients colonized by, n[a]		
Any gram-negative	35 (15)	55 (48)
Enterobacteriaceae	9 (4)	52 (44)
Escherichia coli	2 (–)	52 (39)
Klebsiella spp.	4 (2)	12 (7)
others	7 (2)	24 (15)
Pseudomonas aeruginosa	2 (1)	8 (4)
Other gram-negative	32 (11)	23 (5)
Acinetobacter spp. non-aeruginosa	18 (3)	11 (2)
Pseudomonas spp.	19 (8)	17 (2)
others	9 (4)	7 (–)

Note: [a]numbers in brackets indicate number of patients with persistent colonization of indicated organism.

agent were cultured from surveillance sites in five ofloxacin recipients and in 48 trimethoprim-sulfamethoxazole recipients (7% versus 79%, $p<0.001$), respectively (Table 4). In the ofloxacin group these strains included *Klebsiella ozaenae* (one patient), *Enterobacter agglomerans* (one patient), and *Citrobacter freundii* (four patients). Resistant strains of *Enterobacteriaceae* in the trimethoprim-sulfamethoxazole group were *Escherichia coli* (41 patients), *Klebsiella pneumoniae* (seven patients), *Klebsiella oxytoca* (four patients), *Citrobacter freundii* (14 patients), *Citrobacter diversus* (one patient), *Proteus* spp. (11 patients), *Enterobacter* spp. (four patients), and *Hafnia alvei* (one patient). Ofloxacin recipients were also less likely to be colonized by *Pseudomonas aeruginosa* (3% versus 14%, $p=0.025$ by Fisher's exact test) (Table 3), whereas the proportions of patients colonized by gram-negative bacilli other than *Pseudomonas aeruginosa* and *Enterobacteriaceae* were similar in both groups (Table 3). These organisms included non-aeruginosa *Pseudomonas* spp., *Acinetobacter* spp. and other non-fermentative bacilli. They appeared more likely to be resistant to the prophylactic agent in the ofloxacin group (Table 4): 30 ofloxacin recipients versus 15 trimethoprim-sulfamethoxazole recipients were colonized by resistant gram-negative bacilli other than *Pseudomonas aeruginosa* or *Enterobacteriaceae* (43% versus 26%, $p=0.069$).

Febrile Episodes and Acquired Infections

More patients in the ofloxacin group than in the trimethoprim-sulfamethoxazole group remained free of acquired infections and febrile episodes (31% versus 16%, $p=0.059$) (Table 5). The duration of fever for acquired episodes was shorter in ofloxacin recipients (median: 3 versus 7 days, $p=0.02$), and the overall proportion of granulocytopenic days spent febrile smaller (21% versus 28%, $p<0.001$) (Table 5). Differences in the proportions of febrile days during granulocytopenia were observed at all granulocyte levels and were independent of whether the patients were or were not infected on admission (data not

Table 4: Colonization at surveillance sites in each group by gram-negative bacilli resistant to the study drug.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Patients colonized by, n. (%)		
Any resistant[a] gram-negative	32 (46%)	48 (83%)
Resistant strains of *Enterobacteriaceae*	5 (7%)	46 (79%)
Escherichia coli	–	41
Klebsiella spp.	1	11
Enterobacter spp.	1	4
Proteus spp.	–	11
Citrobacter spp.	4	15
Hafnia alvei	–	1
Resistant strains of *Pseudomonas aeruginosa*	1 (1%)	8 (14%)
Other resistant gram-negative bacilli	30 (43%)	15 (26%)
Acinetobacter spp.	16	6
Other non-fermenters	10	17
Haemophilus spp.	–	1

Note: [a]resistance was defined as minimal inhibitory concentration > 4 mg/l (ofloxacin) or > 160 mg/l (trimethoprim-sulfamethoxazole).

Table 5: Fever and acquired infections.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Granulocytopenic episodes without fever, n	43 (42%)	25 (27%)
Proportion of granulocytopenic days spent febrile, %[a]	21%	28%
Patients remaining free of acquired infections, and febrile episodes, n	22 (31%)	9 (16%)
Median duration of fever for acquired episodes, days[b] (range)	3.0 (0–40)	7.0 (0–49)
Patients with acquired infections, n[c]	36 (51%)	41 (71%)
Acquired infections, n	47	57
Microbiologically documented (bacteremia)	22 (14)	39 (29)
Clinically documented	25	18
Unexplained fever episodes, n	19	16
Fatal infections, n	6	3

Note: [a]$p < 0.001$ by Chi square analysis;
[b]$p = 0.02$ by Wilcoxon's rank sum test;
[c]$p = 0.04$ by Chi square analysis.

shown). The times until first fever in patients who were initially free of infection were similar in both groups (mean: 15.1 versus 12.3 days, $p = 0.18$ by log rank test analysis). There were 47 acquired documented infections in 36 ofloxacin recipients compared with 57 documented infections in 41 patients receiving trimethoprim-sulfamethoxazole prophylaxis (51% versus 71%, $p = 0.04$) (Table 5). The number of patients with bacteremia/fungemia (14 versus 23, $p = 0.025$), and the number of bacteremic/fungemic infections (14 versus 29) were lower among ofloxacin recipients, whereas no significant differences were noted between both groups in terms of microbiologically documented infections without bacteremia, clinically documented infections, and unexplained fever episodes (Table 5). Similar results were obtained when patients with or without fever on admission and patients receiving only one or more than one course of chemotherapy were separately analysed (data not shown).

Table 6: Proportion of patients with microbiologically documented infections.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Patients with microbiologically documented infections, n (%)		
Gram-negative bacterial infection[a]	3 (4%)	15 (26%)
Gram-positive bacterial infection	13 (19%)	13 (22%)
Fungal infection	5 (7%)	8 (14%)
Patients with bacteremia/fungemia, n (%)		
Gram-negative bacteremia[a]	1 (1%)	13 (22%)
Gram-positive bacteremia	13 (19%)	12 (21%)
Fungemia	–	2 (3%)

Note: [a]$p < 0.01$ by Chi square analysis.

Table 7: Organisms isolated from patients with microbiologically documented acquired infections.

Organism	Ofloxacin	Trimethoprim-sulfamethoxazole
Gram-negative bacteria		
Escherichia coli	–	13 (12)
Klebsiella pneumoniae	–	5 (3)
Pseudomonas aeruginosa	1	1
Pseudomonas fluorescens	1	–
Acinetobacter sp.	1 (1)	–
Gram-positive bacteria		
Staphylococcus aureus	3 (2)	1 (1)
Coagulase-negative staphylococci	3 (3)	8 (8)
Viridans group streptococci	6 (6)	7 (7)
Other streptococci	1 (1)	1
Corynebacterium group JK	2 (2)	2 (2)
Fungi		
Candida sp.	2	6 (2)
Aspergillus sp.	3	2

Note: Numbers in brackets indicate organisms isolated from blood.

Gram-negative bacteria were less frequently isolated as causative organisms from patients receiving ofloxacin prophylaxis (Tables 6 and 7). There were three gram-negative bacterial infections in the ofloxacin group. Interestingly, all three infections (one of which was accompanied by bacteremia) were catheter-related, one requiring no antibacterial treatment but surgical incision. In the trimethoprim-

Infection 19 (1991) No. 2

Table 8: Antimicrobial therapy for acquired suspected or proven infections.

	Ofloxacin	Trimethoprim-sulfamethoxazole
Patients requiring antimicrobial therapy, n (%)	46 (66%)	47 (81%)
Duration of antibacterial therapy		
Percentage of study days[a]	19%	29%
Median duration, days[b]	7.0	13.5
(range)	(0–45)	0–51
Duration of antifungal therapy		
Percentage of study days[a]	3%	6%
Median duration, days	0	0
(range)	(0–20)	(0–32)

Note: [a]$p < 0.001$ by Chi square analysis;
[b]$p = 0.01$ by Wilcoxon's rank sum test.

sulfamethoxazole group 15 patients developed 18 gram-negative bacterial infections (three patients had recurrent gram-negative infection) involving 19 gram-negative organisms. Fifteen of these infections were bacteremic. The difference between both groups in the number of patients developing gram-negative bacterial infections was statistically significant (4% versus 26%, $p = 0.002$). The number of patients with gram-positive bacterial (19% versus 22%, $p = 0.75$) and fungal infections (7% versus 14%, $p = 0.34$) was similar in both groups. All infecting bacterial organisms were resistant to the respective prophylactic agent in both groups.

No significant differences were found between the sites of acquired infections in both groups. Upper and lower respiratory tract involvement and catheter-related infections were the most frequently documented sites in both ofloxacin and trimethoprim-sulfamethoxazole recipients (data not shown).

Fatal Infections

There were six fatal infections in the ofloxacin group compared with three in the trimethoprim-sulfamethoxazole group (9% versus 5%, $p = 0.69$). Fatal infections were caused by *Aspergillus* pneumonia, disseminated *Candida* infection, and bacteremia by *Klebsiella oxytoca* in the trimethoprim-sulfamethoxazole recipients. In the ofloxacin group fatal infections included two cases of *Staphylococcus aureus* bacteremia, one patient with bacteremia by *Staphylococcus epidermidis*, two patients with pneumonia of uncertain etiology, and one patient with a clinical diagnose of sepsis and severe mucositis in whom blood cultures failed to grow an organism. One of the patients with pneumonia probably had cytomegalovirus pneumonia complicated by pulmonary hemorrhage. The other patient was admitted with pneumonia, did not respond to broad spectrum antibacterial and antifungal therapy, and to empiric therapy with trimethoprim-sulfamethoxazole, and died with unresolving pneumonia and refractory leukemia.

Antimicrobial Therapy

Forty-six patients in the ofloxacin group required parenteral antimicrobial therapy for presumed or documented acquired infection compared with 47 patients in the trimethoprim-sulfamethoxazole group (66% versus 81%, $p = 0.08$). Similar results (67% versus 79%, $p = 0.3$) were obtained for patients who were free of fever or infection on admission. The median duration of antibacterial and antifungal therapy for acquired infections and febrile episodes is shown in Table 8. The median duration of antibacterial therapy was shorter in ofloxacin recipients than in trimethoprim-sulfamethoxazole recipients (7.0 versus 13.5 days, $p = 0.01$).

Discussion

The present study demonstrates the usefulness of oral ofloxacin for prevention of bacterial infections in patients with acute leukemia who receive aggressive cytotoxic chemotherapy. Compared with trimethoprim-sulfamethoxazole the advantages of ofloxacin treatment were better tolerance, a significant reduction in the incidence of gram-negative bacterial infection, and a shorter duration of fever and of parenteral antimicrobial therapy for acquired presumed or documented infection. The reduced incidence of gram-negative bacterial infections was paralleled by a better protection against colonization by *Enterobacteriaceae* and *P. aeruginosa*.

The efficacy of trimethoprim-sulfamethoxazole prophylaxis appeared to be compromised by the high rate of colonization and infection by strains of *Enterobacteriaceae* that were resistant to this agent. The proportion of patients colonized by trimethoprim-sulfamethoxazole-resistant *Enterobacteriaceae* was higher than reported in many previous studies. Geographical differences and differences in microbiologic surveillance may account for this finding [10, 13, 15–17, 31]. The addition of a polymyxin to trimethoprim-sulfamethoxazole as suggested in a previous study [32], might have been more effective in preventing colonization and subsequent infection by trimethoprim-sulfamethoxazole-resistant gram-negative organisms. Due to the large number of tablets to be administered the compliance with this regimen, however, is likely to be poorer than with either agent alone [17]. Colonization and infection by resistant gram-negative bacteria has also been documented during prophylaxis with polymyxin B or colistin alone or combined with trimethoprim-sulfamethoxazole or vancomycin [17, 22, 32–36]. The overall gain in efficacy through the addition of a polymyxin to trimethoprim-sulfamethoxazole may therefore be minimal.

Ofloxacin did not completely prevent colonization by gram-negative bacilli. Particularly the so-called non-fermenters (other than *Pseudomonas aeruginosa*) were frequently cultured from surveillance sites. The majority of these organisms were resistant to ofloxacin, and two patients developed catheter-related infections due to such

organisms (in addition to one with a catheter-related *Pseudomonas aeruginosa* infection). Similar observations, though at varying rates, have been made in other studies of fluoroquinolone prophylaxis [20, 22–25, 27, 34, 36, 37]. Although the proportions of patients colonized by gram-negative bacilli other than *Pseudomonas aeruginosa* and *Enterobacteriaceae* were not significantly different between both groups these organisms appeared to be more frequently resistant to the respective prophylactic agent in the ofloxacin group than in the trimethoprim-sulfamethoxazole group. This is consistent with previously published *in vitro* studies [38, 39].

A small percentage of ofloxacin recipients harboured resistant strains of *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Resistance to fluoroquinolones in *Enterobacteriaceae* is uncommon in clinical isolates, and has only recently been described [40–42]. Certain species of *Enterobacteriaceae* such as *Citrobacter*, *Serratia*, or *Enterobacter* spp. may be more prone to the development of quinolone resistance than *Escherichia coli* and others. Although we did not observe infections caused by such strains, with the more intense use of fluoroquinolones in the community and in inpatients this possibility must be borne in mind.

There also seems to be a small percentage of patients who develop infections due to *Pseudomonas aeruginosa* despite prophylaxis with fluoroquinolones. Only one patient in the present series had an infection due to *Pseudomonas aeruginosa* during ofloxacin treatment, but the incidence may be higher with lower doses [27]. Such infections have repeatedly been reported in norfloxacin recipients [20, 24, 28, 43], or during prophylaxis with pefloxacin in granulocytopenic patients (*Devaux, I., Laurent, C., Hill, C., Andremont, A., Tancrède, C.*: 3rd Int. Symp. New Quinol. 1990, abstr. no. 222; *Archimbaud, E., Guyotat, D., Maupas, J., Plotton, C., Nageotte, A., Devaux, Y., Fiere, D.*: 3rd Int. Symp. New Quinol. 1990, abstr. no. 198). A recent study indicates that there may be a certain risk of nosocomial spread of such strains [44]. This may limit the usefulness of fluoroquinolone prophylaxis in the future.

In terms of preventing gram-positive bacterial infections both ofloxacin and trimethoprim-sulfamethoxazole appeared to be largely ineffective. Gram-positive organisms are now commonly recognized as a cause of major infections following aggressive cytotoxic chemotherapy [45]. They usually include coagulase-negative staphylococci [46], viridans group streptococci [47– 49], and, less frequently, diphtheroids and *Staphylococcus aureus*, often show primary resistance, or may rapidly develop resistance to newer quinolones [50–53, *Kern, W., Bürger, B., Rozdzinski, E.*: 10th Int. Symp. Gnotobiol. 1990, abstr. no. P-62). On the basis of clinical studies [20– 24] it has been suggested that gram-positive bacterial infections might be more common with norfloxacin than with other prophylactic regimens including trimethoprim-sulfamethoxazole. A recent study concluded that trimethoprim-sulfamethoxazole also might be more effective in the prevention of gram-positive infection than ciprofloxacin [36; *Daenen, S.*: 10th Int. Symp. Gnotobiol. 1990, abstr. no. 64). In the present and previous studies [31,34] comparing ofloxacin with trimethoprim-sulfamethoxazole or with vancomycin/polymyxin there was no evidence for a higher incidence of gram-positive infections among ofloxacin recipients. This suggests that the higher intrinsic activity and higher serum and tissue concentrations of ofloxacin compared with norfloxacin or ciprofloxacin may result in some beneficial effect on the prevention of gram-positive infections, but, in the absence of large comparative studies, the significance of this effect is uncertain. Differences in clinical efficacy between norfloxacin and ciprofloxacin have been suggested previously [28], and recently been confirmed in a large comparative study [54]. It is important to note that quinolone-resistant coagulase-negative staphylococci and viridans group streptococci caused persistent colonization in the majority of ofloxacin recipients in this study. Similar observations have been reported in studies witt ciprofloxacin, norfloxacin, and pefloxacin indicating that despite differing intrinsic activities, pharmacokinetic properties, and possibly clinical efficacy none of these agents while given for antibacterial prophylaxis in the immunocompromised host appears to provide adequate coverage of significant gram-positive bacterial pathogens.

Adverse effects that were probably attributable to the study drugs were observed in less than ten percent of ofloxacin recipients. This is consistent with previous studies using quinolone antibacterial prophylaxis in the immunocompromised patient with rates of adverse effects not exceeding ten percent. As in the study by *Liang* and colleagues [31] and in other studies [40], trimethoprim-sulfamethoxazole was significantly less well tolerated. Particularly gastrointestinal intolerance, but also skin reactions were more frequent among trimethoprim-sulfamethoxazole recipients. As in several previous trials the duration of granulocytopenia was slightly longer in the group receiving trimethoprim-sulfamethoxazole, but the difference was statistically not significant. Whether the observed differences in the present and previous studies were effects caused by trimethoprim- sulfamethoxazole, however, remains unclear.

Due to the large number of patients needed to assess with a sufficient statistical power any beneficial effect of antimicrobial prophylaxis on mortality both the reduction of infection-related morbidity and of total consumption of systemic antibiotics will remain the probably best estimates of the efficacy of antimicrobial prophylaxis in the immunocomprised patient [6]. Many previous reports failed to show decreased total use of systemic antibiotics. The reduced incidence of febrile episodes and documented infections among ofloxacin recipients was accompanied by a shorter duration of systemic antimicrobial therapy. Ofloxacin while reducing the discomfort and side effects associated with trimethoprim-sulfamethoxazole therefore seems to be a suitable agent for infection prevention in acute leukemia. Future studies are needed to monitor the emergence of quinolone resistance during prophylaxis and to assess the role of additional agents with better coverage of gram-positive bacterial pathogens.

Infection 19 (1991) No. 2

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