ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1993, p. 1214–1218
0066-4804/93/061214-05$02.00/0

Vol. 37, No. 6

Oral Rifampin plus Ofloxacin for Treatment of *Staphylococcus*-Infected Orthopedic Implants

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Received 17 September 1992/Accepted 18 March 1993

We examined the effectiveness and safety of the combination of rifampin plus ofloxacin given orally for treating prosthetic orthopedic implants infected with staphylococci. The prospective cohort study was conducted in a referral public hospital with ambulatory care services between 1985 and 1991. Consecutive patients from whom *Staphylococcus* organisms susceptible to the study drugs were isolated from their orthopedic implants and who had no contraindication to the treatment were eligible for the study. All patients were treated orally with rifampin, 900 mg/day, plus ofloxacin, 600 mg/day. Patients with hip prosthesis infection were treated for 6 months, with removal of any unstable prostheses after 5 months of treatment; patients with knee prosthesis infection were treated for 9 months, with removal of the prosthesis after 6 months of treatment; and patients with infected bone plates were treated for 6 months, with removal of the plate after 3 months of treatment, if necessary. Monthly clinical evaluations were conducted until the completion of the treatment and follow-up or telephone interviews were conducted at 6, 12, 24, 36, 48, and 60 months thereafter. Treatment failures were documented by clinical evaluation, sampling of the infected site for culture and antibiotic activity measurement, and fistulography, if possible. Cure was defined as the absence of clinical, biological, and radiological evidence of infection 6 months after the completion of treatment, treatment failure was defined as the absence of cure, and relapse was defined as the reappearance of infection caused by the same *Staphylococcus* isolate that caused the original infection, regardless of the timing of this secondary infection. Among 51 patients included in the study and evaluable for safety, 4 patients had side effects and were not evaluable for treatment effectiveness; the overall success rate was 74% among 47 patients, with a success rate of 81% for the hip prosthesis group, 69% for the knee prosthesis group, and 69% for the osteosynthesis device group. Eight treatment failures were related to the isolation of a resistant bacterium. The combination of rifampin administered orally plus ofloxacin is a suitable alternative to the conventional long-term intravenous therapy for treatment of orthopedic implants infected with staphylococci.

Infection complicates 0.5 to 1% of hip prostheses (13, 14) and 1 to 2% of knee prostheses (6, 13). *Staphylococcus* species are the cause of 45 to 55% of these infections (1, 7), regardless of the type of implant. The functional prognosis for these types of infections remains poor, despite long-term intravenous antibiotic therapy combined with a one- or two-stage replacement of the orthopedic implant. The availability of fluoroquinolones prompted physicians to propose treatment protocols that included those drugs as alternatives to conventional intravenous treatment. Encouraging preliminary data regarding these trials and data from animal models were published as the present study was being conducted (2). We report herein the results of a prospective study carried out by a single protocol that included rifampin and a fluoroquinolone. The present study included the largest series of *Staphylococcus* species-infected orthopedic implants that has been known to be treated.

MATERIALS AND METHODS

Patients. A patient was included in the present study when all of the following criteria were met. (i) The patient had to have clinical and radiological evidence of an orthopedic implant infection. Evidence of hip prosthesis infection was the presence of at least one of the following: hip prosthesis fistula, hip pain and biological inflammatory syndrome, or radiological prosthesis looseness and biological inflammatory syndrome. Evidence of knee prosthesis infection was the presence of at least one of the following: knee prosthesis fistula, knee pain and biological inflammatory syndrome, or radiological prosthesis looseness and biological inflammatory syndrome. Evidence of osteosynthesis device infection was the presence of at least one of the following: osteosynthesis device fistula, inflammation in the area of the osteosynthesis device, or radiological looseness of the device and biological inflammatory syndrome. The extension of a fistula to the device was confirmed by fistulography with a radiographic contrast agent. A biological inflammatory syndrome included an erythrocyte sedimentation rate of >50 and an elevated level of C-reactive protein. (ii) Leukocytes and gram-positive cocci were present upon direct examination of pus samples, and the same *Staphylococcus* species, as determined by biotyping and antibiotic susceptibility testing, was isolated at least twice from the discharge of a fistula or at least once from joint aspirate or a surgical bone biopsy specimen. (iii) The isolates were susceptible in vitro to both rifampin and ofloxacin. (iv) The patient could have no contraindication to the use of rifampin and ofloxacin. (v) The patients had to be available for follow-up after the completion of treatment (>6 months). All patients who were eligible for the study were included. At the time of inclusion, demographic and clinical data were registered, as were

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TABLE 1. Clinical characteristics of and outcomes for of 22 patients with staphylococcal infections of their hip prostheses[a]

Case no.	Time of delay to infection (mo)	Clinical presentation	Diagnostic procedure	Microorganism isolated	Prosthesis removal	Outcome	Follow-up (mo)
1	1	P, I	Puncture	*S. aureus*	No	Failure, resistant *S. aureus*	
2	2	Fi	Fistula	CNS	No	Cure	18
3	11	P, I, L	Biopsy	CNS	Yes	Cure	12
4	30	P, I	Biopsy	*S. aureus*	No	Intolerance	
5	36	I, L	Biopsy	CNS	Yes	Cure	30
6	30	Fi	Fistula	*S. aureus*	No	Failure, resistant, CNS	
7	2	Fi	Fistula	*S. aureus*	No	Cure	33
8	28	P, I, L	Puncture	*S. aureus*	Yes	Cure	24
9	6	Fi	Fistula	*S. aureus*	No	Failure	
10	9	P, I, L	Puncture	CNS	Yes	Cure	18
11	12	Fi	Fistula	CNS	No	Cure	22
12	1	Fi	Fistula	CNS	No	Cure	17
13	1	Fe, I	Biopsy	CNS	No	Cure	12
14	32	P, I, L	Biopsy	CNS	Yes	Cure	33
15	25	Fi	Puncture	CNS	No	Failure	
16	30	Fi	Fistula	*S. aureus*	No	Cure	57
17	7	I, L	Biopsy	*S. aureus*	Yes	Cure	35
18	24	I, L	Biopsy	CNS	Yes	Cure	61
19	1	Fe, I, L	Biopsy	*S. aureus*	Yes	Cure	21
20	130	Fe, P, I, L	Biopsy	*S. aureus*	Yes	Cure	9
21	48	I, L	Puncture	*S. aureus*	Yes	Cure	33
22	60	P, I, L	Biopsy	CNS	No	Cure	15

[a] Fe, fever; P, pain; Fi, fistula; L, loosened prosthesis; I, inflammatory syndrome; CNS, coagulase-negative staphylococcus.

laboratory data, including blood and differential counts, hepatic enzyme levels, erythrocyte sedimentation rate, C-reactive protein levels, and radiological data. When available, pus was sampled by using a compress or a swab; when not available, pus was sampled by needle aspiration of the prosthesis or by surgical biopsy when three consecutive aspirations remained sterile. Direct microscopic examination of the pus after Gram staining ensured the presence of polymorphonuclear leukocytes and bacteria. The isolation procedure has been described previously (21). Briefly, in parallel with conventional isolation procedures, we used a lysis-centrifugation method with the rapid freezing in liquid nitrogen of the culture material that was obtained; this was followed by thawing at 37°C. Identification of the bacteria and antibiotic susceptibility tests were performed by using AutoSCAN-4 (American Microscan, Mahwah, N.J.), and the results were confirmed, if necessary, by conventional methods: with the API systems (API System, Montalieu-Vercieu, France) for the identification of bacteria and the agar diffusion method for antibiotic susceptibility tests.

Treatment protocol. Ofloxacin, 200 mg three times a day, and rifampin, 900 mg once a day, were administered orally. The overall design of the treatment protocol depended on the type of infection. (i) For patients with hip prosthesis infections, antibiotics were administrated orally for a total of 6 months. In the case of an unstable prosthesis only, one-stage removal and reimplantation of the hip prosthesis was performed after 5 months of antibiotic treatment; in other cases, the prosthetic material was conserved. (ii) For patients with knee prosthesis infection, oral antibiotics were administered for 6 months before and 3 months after one- or two-stage removal and reimplantation of the prosthesis for all the patients (regardless of whether the prosthesis was stable). (iii) For patients with osteosynthesis devices, antibiotics were administered orally for 6 months, with the foreign body removed after 3 months of therapy, if necessary.

Follow-up. Monthly clinical follow-up was performed; this included a 3-month laboratory follow-up, including blood and differential counts, erythrocyte sedimentation rate, and hepatic enzyme levels. In case of treatment failure, the evaluation procedure included the following: a clinical check for the patient's compliance, conventional radiography and fistulography, and bacteriological evaluation, including determinations of antibiotic activities in the material discharged from the fistula, as reported previously (21), and in the patient's urine. The identification and biotype indicated by the AutoSCAN-4 and the antibiotic susceptibility pattern of the organism isolated from a patient at the time of treatment failure were compared with those of the isolate at the time of diagnosis. Molecular techniques were not used to demonstrate the identities of the isolates. Antibiotic treatment was stopped when no clinical, biological, or radiological evidence of infection was present following the completion of the treatment protocol or at any time during the documented treatment failure. Examinations at 6, 12, 24, 36, 48, and 60 months after the completion of therapy were performed either by a visit or by a telephone interview with the patient. The follow-up interview included questions about the use of analgesics or nonsteroidal medications, pain and signs of dysfunction, physical examination, and radiological evaluation by the surgeon. We report here results only for those patients with a follow-up of >6 months.

RESULTS

Fifty-one patients included in the present study between January 1987 and November 1991 were evaluable. Among these, patient 4 stopped the 2-week treatment after developing a skin allergy that was presumably related to ofloxacin, patients 31 and 40 stopped treatment after they had gastrointestinal side effects, and patient 32 stopped treatment after he developed polyarthralgia. Forty-seven patients who were evaluable for treatment efficacy included 21 patients with hip prosthesis infection (Table 1), 13 patients with knee prosthesis infection (Table 2), and 13 patients with infection of a foreign body, including percutaneous traction pins in two

TABLE 2. Clinical characteristics of and outcomes for 15 patients with staphylococcal infection of their knee prostheses[a]

Case no.	Time of delay to infection (mo)	Clinical presentation	Diagnostic procedure	Microorganism isolated	Prosthesis removal	Outcome	Follow-up (mo)
23	5	P, I	Biopsy	CNS	Yes	Failure, resistant CNS	
24	29	P, I	Puncture	*S. aureus*	Yes	Cure	35
25	7	P, I	Puncture	CNS	Yes	Cure	15
26	1	Fe, P, I	Biopsy	*S. aureus*	Yes	Cure	37
27	4	P, Fi, L	Fistula	*S. aureus*	No	Failure	
28	30	Fi	Fistula	*S. aureus*	Yes	Cure	26
29	20	I, L	Biopsy	CNS	Yes	Cure	30
30	24	P, L	Biopsy	CNS	Yes	Failure	
31	8	Fe, I, L	Puncture	CNS	No	Intolerance	
32	16	P, I	Puncture	CNS	No	Intolerance	
33	3	P, I	Biopsy	CNS	Yes	Cure	45
34	3	Fi	Fistula	*S. aureus*	Yes	Cure	23
35	40	Fe, P, I	Biopsy	*S. aureus*	No	Cure	27
36	33	Fi	Fistula	CNS	No	Cure	21
37	12	Fi	Fistula	*S. aureus*	No	Failure, resistant *S. aureus*	

[a] Fe, fever; P, pain; Fi, fistula; L, loosened prosthesis; I, inflammatory syndrome; CNS, coagulase-negative staphylococcus.

patients (patients 39 and 49), plates in eight patients (patients 38, 40, 43, 44, 45, 46, 47, and 48), wires in two patients (patients 41 and 51), and intramedullary nails in two patients (patients 42 and 50) (Table 3). Overall, the 27 males and the 20 females who were evaluable for treatment efficacy and safety had a median age of 52 years. All patients included in the study had clinical or radiological evidence of device infection, and they all fulfilled the case definition. Fistulas were present in 23 of 51 (45%) patients. *Staphylococcus* species were isolated from the pus of the fistula discharge in 20 of 51 (39%) patients, after puncture of the infected site in 15 of 51 (29.5%) patients and after surgical biopsy of the infected site in 16 of 51 (31.5%) patients. The time delay between the surgical implantation of the orthopedic device and the laboratory-confirmed diagnosis of infection ranged from 1 to 130 months. The time delay was <3 months in 14 of 51 (27.5) patients and >12 months in 22 of 51 (43%) patients. The overall treatment success rate was 74% (35 of 47 patients), with success rates of 81% (17 of 21 patients) for patients with hip prosthesis infection, 69% (9 of 13 patients) for patients with knee prosthesis infection, and 69% (9 of 13 patients) for patients with other device infections. Thirteen of 21 patients (62%) were cured without prosthesis removal, and 23 of 26 patients (88%) were cured with prosthesis removal. Those rates were determined after a posttreatment follow-up of 7 to 61 months (average, 24 months). The results according to the causative staphylococcal species are presented in Table 4. Twenty of 26 patients (77%) with *Staphylococcus aureus* infection were cured, and 16 of 21 patients (76%) with coagulase-negative *Staphylococcus* infection were cured. In two patients with infected knee prostheses (patients 35 and 36), cure was obtained, even though their knee prostheses were not removed as recommended in the study design, because of old age (patients 36) and the refusal of patient 35 to undergo surgery. Three treatment failures in patients with *S. aureus* hip prosthesis infections (patients 1, 6, and 9) were related to the isolation of a resistant coagulase-negative *Staphylococcus* species, and treatment failure in patient 15 was related to the isolation of *Enterobacter intermedium*. Two treatment failures (patients 23 and 37) were related to the isolation of resistant staphylococci and two treatment failures were not confirmed by culture (patients 27 and 30). Three treatment failures (patients 42, 43, and 46) were related to the isolation of a resistant *Staphylococcus* species identical to the one isolated at the time of diagnosis. Treatment failure in patient 49, whose bone plate was infected with *S. aureus*, was related to

TABLE 3. Clinical characteristics of and outcomes for 14 patients with staphylococcal infection of osteosynthesis devices[a]

Case no.	Time of delay to infection (mo)	Clinical presentation	Localization	Type of device	Diagnostic procedure	Microorganism isolated	Device removal	Outcome	Follow-up (mo)
38	3	P, I	Femur	PL	Puncture	*S. aureus*	No	Cure	16
39	2	Fi, I	Phalanx	TP	Fistula	*S. aureus*	Yes	Cure	19
40	4	Fi	Ankle	PL	Fistula	*S. aureus*	No	Intolerance	
41	5	P, I	Phalanx	W	Puncture	CNS	No	Cure	36
42	5	Fi, I	Tibia	IMN	Puncture	CNS	No	Failure, resistant CNS	
43	1	Fi	Tibia	PL	Fistula	CNS	No	Failure, resistant CNS	
44	4	Fi	Tibia	PL	Fistula	*S. aureus*	No	Cure	12
45	4	P, I	Tibia	PL	Puncture	*S. aureus*	Yes	Cure	14
46	35	Fi	Tibia	PL	Fistula	*S. aureus*	No	Failure, resistant *S. aureus*	
47	1	Fi	Tibia	PL	Fistula	CNS	Yes	Cure	13
48	4	P, I	Ankle	PL	Puncture	*S. aureus*	Yes	Cure	11
49	1	P, Fi	Tibia	TP	Fistula	*S. aureus*	Yes	Failure, resistant CNS	
50	12	Fi	Tibia	IMN	Puncture	*S. aureus*	Yes	Cure	7
51	5	Fi	Wrist	W	Fistula	*S. aureus*	Yes	Cure	9

[a] Fe, fever; P, pain; Fi, fistula; L, loosened device; I, inflammatory syndrome; TP, traction pins; PL, plate; IMN, intramedullary nail; W, wire; CNS, coagulase-negative staphylococcus.

TABLE 4. Study results according to the causative staphylococcal species for 47 patients evaluable for efficacy

Prosthesis group	No. of patients cured/total no. treated			
	S. aureus		Coagulase-negative staphylococci	
	Antibiotics alone	Device removed	Antibiotics alone	Device removed
Hip	2/5	5/5	5/6	5/5
Knee	1/3	4/4	1/1	3/5
Other devices	5/6	2/3	1/3	1/1
Total	6/11	14/15	7/10	9/11

the isolation of a resistant coagulase-negative *Staphylococcus* species.

DISCUSSION

Infections of orthopedic implants are associated with considerable morbidity and extremely high costs. Simple surgical drainage and then nonstandardized antibiotic therapy result in a mere 20% success rate (4). Short-term intravenous therapy in combination with a one- or two-stage removal of the infected orthopedic implant results in a 35% success rate (12), whereas a shift to long-term antibiotic therapy results in an almost 90% success rate (8, 13). Recently, protocols proposed for the treatment of patients with infected orthopedic implants are mainly based on the favorable pharmacokinetics of newer antibiotics and on their low MICs for *Staphylococcus* species. In the animal model, rifampin alone was able to sterilize *S. aureus*-infected tissue cages when it was administered less than 12 h after challenge (16). Treatment failures have been related to rifampin-resistant variants. Likewise, ciprofloxacin alone failed to cure experimental *Staphylococcus epidermidis* tissue cage infections (17), but the combination of ciprofloxacin plus rifampin resulted in a 100% success rate. The combination of fleroxacin with rifampin resulted in a 41% cure rate in an *S. aureus* foreign body infection model (2). The addition of vancomycin to the fleroxacin-rifampin combination significantly increased the cure rate (92%) and the rapidity of sterilization of the foreign body. These experiments led to the conclusions that in vitro susceptibility results for isolates obtained from foreign bodies are not predictive of in vivo effectiveness, the combination of rifampin with fluoroquinolones is more effective than monotherapy, and the addition of vancomycin to rifampin plus fluoroquinolones increases the combination's effectiveness. The discrepancies between low in vitro MICs and in vivo treatment failures have been related to the poor penetration of the antibiotics in the infected site, the particular glycocalyx biofilm covering the bacteria (5), and the particular anaerobic environment of the bacteria (11). We propose that *Staphylococcus* species may exist partially intracellularly in the macrophages of patients with orthopedic implant infections, as suggested by the effectiveness of cell lysis systems in the recovery of *Staphylococcus* species from fistula discharges (21). In regard to this hypothesis, the combination of rifampin with fluoroquinolones adds two antibiotics with high levels of intracellular penetration and activity against intracellular *Staphylococcus* species (9, 15, 20). A few clinical studies reported the effectiveness of rifampin in combination with other drugs for the treatment of *Staphylococcus*-infected orthopedic implants. Among four previously reported patients with *Staphylococcus* species infections of their orthopedic implants who were treated with various regimens, all of which included rifampin, two patients were cured and two had persistant, sterile drainages (10). Among 10 patients with *Staphylococcus* species-infected orthopedic implants, 8 were cured by various antibiotic regimens, all of which included rifampin (18). In the present series of patients, the two treatment failures were related to prolonged infection, and antimicrobial therapy was inappropriate. A few clinical reports (3, 19) regarding the use of the fluoroquinolones against orthopedic implant infections have been published. Among nine patients with orthopedic implants, seven were cured with pefloxacin alone and two treatment failures were related to the emergence of pefloxacin-resistant isolates (3). The combination of pefloxacin with rifampin resulted in a 100% cure rate among three additional patients with orthopedic implants (3). Those preliminary reports indicate that rifampin and fluoroquinolones used alone are able to cure *Staphylococcus* species-infected orthopedic implants, with most treatment failures related to the emergence of antibiotic-resistant isolates. It has been suggested from studies in animals that the combination of rifampin plus fluoroquinolones prevented later treatment failures (2). In our study, the overall success rate of 74% competes with the results of conventional long-term antibiotic therapy combined with removal of the infected implant and confirms recent data (18). In particular, 62% of patients were cured without orthopedic device removal. Apart from four cases of side effects, the treatment failures that we noted were related to the isolation of resistant staphylococci in most cases. The isolation of a resistant *Staphylococcus* species in those cases led us to hypothesize that those isolates had not been recognized at the time of diagnosis, despite our efforts to ensure the correct microbiological diagnosis. Indeed, diagnosis of staphylococcal infection remains difficult, especially when coagulase-negative staphylococci are isolated from the orthopedic device. No clinical, biological, or radiological sign by itself provides evidence of device infection. The predictive value of these signs, however, is stronger for a fistula extended to the device and when several other signs of infection are present. When direct examination of the pus discloses leukocytes and gram-positive cocci and when multiple separate specimens from the device yield the same coagulase-negative species, it is likely that this species is truly pathogenic and not a contaminant. The patients included in the present study fulfilled these criteria. It is noteworthy that the treatment failure rates differed among the three groups that we studied, with there being a worse prognosis for bone plate infections. Those data indicate that it is possible to cure orthopedic implant infections caused by *Staphylococcus* species by using the combination of rifampin with fluoroquinolone administered orally for a prolonged period of time. Because the results that we obtained compete with those of conventional long-term intravenous antibiotic therapy, for first-line therapy, we propose use of the combination of rifampin plus fluoroquinolones combined with one-stage removal of the implant for unstable hip prostheses and for all knee prostheses whenever possible.

ACKNOWLEDGMENT

We acknowledge E. Rubinstein for helpful discussions and review of the manuscript.

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