Comparison of Azithromycin and Cefadroxil for the Treatment of Uncomplicated Skin and Skin Structure Infections

Maureen B. Jennings, DPM; James M. McCarty, MD; Neil M. Scheffler, DPM; Anthony D. Puopolo, MD; Constance D. Rothermel, PhD

In this multicenter, investigator-blind trial, we compared the efficacy and safety of azithromycin and cefadroxil for the treatment of uncomplicated skin and skin structure infections (SSSIs). A total of 296 patients were randomized to receive either azithromycin (500 mg on day 1, followed by 250 mg once a day on days 2 to 5) or cefadroxil (500 mg twice a day for 10 days). Outpatients, ranging in age from 18 to 75 years, with acute uncomplicated SSSIs were enrolled in the study. Clinical and bacteriologic response was assessed between days 10 and 13 (primary end point) and between days 28 and 32. In a modified intent-to-treat analysis, clinical success rates assessed between days 10 and 13 were 97% (111/114) for azithromycin and 96% (101/105) for cefadroxil (P=.717). For azithromycin and cefadroxil, corresponding rates of bacteriologic eradication for Staphylococcus aureus *were 94% (64/68) and 86% (60/70), respectively, and for* Streptococcus pyogenes*, 80% (4/5) and 100% (6/6), respectively. Clinical success rates assessed between days 28 and 32 were 100% (82/82) for azithromycin compared with 90% (75/83) for cefadroxil (P=.007). Corresponding rates of eradication for* S aureus *were 100% (59/59) versus 89% (56/63), respectively; and for* S pyogenes*, 100% (4/4) versus 83% (5/6), respectively. The incidence of treatment-related adverse events was similar in the 2 treatment groups. However, 5 of the 139 patients (4%) in the cefadroxil group discontinued therapy because of treatment-related adverse events compared with none of the 152 patients in the azithromycin group (P=.02). Five-day therapy with azithromycin was as effective as 10-day therapy with cefadroxil for treating uncomplicated SSSIs.*

Cutis. 2003;72:240-244.

Uncomplicated skin and skin structure infections (SSSIs) are among the most common problems encountered in medical practice[1] and include impetigo, erysipelas, cellulitis, folliculitis, and simple abscesses. SSSIs commonly are caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.[2]

Mild to moderate uncomplicated SSSIs usually respond to appropriate oral antimicrobial therapy, and first-generation cephalosporins and antistaphylococcal penicillins are often the drugs of choice.[2] Azithromycin, an azalide antibiotic, has a prolonged half-life of 68 hours,[3] which allows for once-daily dosing and shorter regimens for treating a wide range of infections. In previous studies of SSSIs, azithromycin has demonstrated clinical and bacteriologic efficacy comparable to that of

Accepted for publication March 14, 2003.

Dr. Jennings is from the New York College of Podiatric Medicine, New York. Dr. McCarty is from the Valley Children's Medical Group, Madera, California. Dr. Scheffler is from the American Center for Foot Health Research, Baltimore, Maryland. Dr. Puopolo is from the Milford Emergency Associates, Milford, Massachusetts. Dr. Rothermel is from Pfizer Inc, New York, New York.

This study was supported by a research grant from Pfizer Inc. Dr. Rothermel is an employee of and owns stock in Pfizer Inc. The other authors report no conflict of interest.

Reprints: Maureen B. Jennings, DPM, New York College of Podiatric Medicine, 1800 Park Ave, New York, NY 10035 (e-mail: mjennin@nycpm.edu).

dicloxacillin in adults[4] and to that of dicloxacillin,[5] flucloxacillin,[5] or cefaclor[6] in children.

In this study, we compared the efficacy and safety of a 5-day regimen of once-daily azithromycin with a 10-day regimen of twice-daily cefadroxil for the treatment of patients with uncomplicated SSSIs. Results for a subset of patients (40) in this trial have been reported previously.[7]

Methods

Patients—Patients were eligible for the study if they were outpatients between the ages of 18 and 75 years and had signs or symptoms of an acute SSSI that warranted treatment with oral antibiotics.

Women of childbearing age were required to have a negative pregnancy test before entry in the study and were to use adequate contraception both during and for 3 months after the end of the study. Types of infections appropriate for inclusion in this study included primary pyodermas (cellulitis, folliculitis, furuncles, carbuncles, paronychia, ecthyma, and erysipelas) and secondary bacterial infections complicating preexisting skin lesions, such as traumatic lesions (abrasions, wounds), eczematous dermatitis, exfoliative erythrodermas, dermatophytosis, vesicular or bullous eruptions (varicella, pemphigus), and intertrigo. Patients were excluded if they had a history of hypersensitivity to macrolides or β-lactams, chronic skin ulcers or infected burns, use of systemic or topical antibiotics within 72 hours of study enrollment, concurrent topical or systemic steroid therapy, use of an investigational drug within the previous 30 days, or other clinically significant medical conditions (hematologic, immunologic, renal, hepatic, or cardiovascular disease; psychiatric disorders; or alcohol or drug dependency). Also excluded were patients not suitable for outpatient therapy, including elderly debilitated patients, or those with hospital-acquired infections, known or suspected bacteremia, or significant underlying health problems that could compromise response to therapy.

Study Design—This was a randomized, investigator-blind, comparative trial conducted at 10 centers in the United States. Patients were assigned randomly to receive either azithromycin (500 mg on day 1, followed by 250 mg once a day on days 2 to 5) or cefadroxil (500 mg twice a day for 10 days). The study was approved by the Institutional Review Board at each study center, and informed consent was obtained from each patient.

Data Collection—Data were collected at 4 time points. The baseline visit (day 1) included a medical history, physical examination, signs and symptoms assessment, and clinical laboratory tests (hematology, serum chemistry, and urinalysis). The baseline clinical assessment was substantiated by Gram stain and culture of material obtained from the infection site. Pathogens were identified, and susceptibility to both study drugs was determined by disk diffusion, according to the National Committee for Clinical Laboratory Standards.[8] Additional assessments were performed between days 5 and 7, 10 and 13, and 28 and 32 and included evaluation of clinical signs and symptoms, concomitant illness or concurrent medication, clinical and bacteriologic response (including the collection of material for culture, if available), and safety assessments (including laboratory tests).

Response to Therapy—Assessment of clinical and bacteriologic efficacy included both modified intent-to-treat (MITT) and per protocol analyses. Generally, the MITT population is more representative of the patients encountered in clinical practice. The clinical MITT population included all patients who had received at least one dose of study drug, had the appropriate baseline diagnosis, and had one follow-up evaluation. Bacteriologically, evaluable MITT patients included clinical MITT patients who had a pathogen isolated at baseline. The per protocol population included clinical MITT patients who had received at least 50% of the total dose of study drug, had received no additional antibiotics during the study, had a susceptible baseline pathogen, and had an evaluation between days 10 and 13. The primary efficacy end point was the clinical response obtained between days 10 and 13. Clinical response was defined as *cure* (complete resolution of pretreatment signs and symptoms), *improvement* (partial resolution of signs and symptoms, without the need for additional antibiotic therapy), or *failure* (no change or worsening of signs and symptoms, or requirement for additional antibiotic therapy).

The secondary efficacy end point was the bacteriologic response obtained between days 10 and 13 and was defined as *eradication* (elimination of baseline pathogen, or absence of material for culture in patients with a clinical response of cure or improvement), *persistence* (presence of baseline pathogen between days 10 and 13), *recurrence* (presence of baseline pathogen between days 28 and 30 in patients whose response between days 10 and 13 was eradication), and *superinfection* (presence of a new pathogen, accompanied by persistence or worsening of signs and symptoms of infection).

Safety—All patients who received at least one dose of study drug were included in the safety analysis. Safety data included adverse events summarized by the investigator's assessment of severity

Table 1.

Demographic and Baseline Characteristics

Characteristic	Azithromycin (n=152)	Cefadroxil (n=139)
Mean age±SD, y	33.9±13.9	32.3±14.0
Sex, n		
Female	68	59
Male	84	80
Mean weight, kg		
Female	75.2	75.0
Male	85.1	84.6
Race, n		
White	93	86
Black	26	23
Asian	2	2
Other	31	28
Diagnosis, n*		
Primary pyoderma	133	114
Secondary bacterial infection	19	25
Other	8	3

*Some patients had more than one primary diagnosis.

(mild, moderate, or severe) and laboratory analyses (hematology, clinical chemistry, and urinalysis).

Statistics—The log-rank test was used to analyze demographic characteristics and clinical response rates. Safety data were assessed with the χ^2-square test or Fisher exact test, as appropriate. All statistical tests were 2 tailed, and significance was assessed at the 5% level.

Results

Patient Demographics—A total of 296 patients were randomized to either azithromycin (152) or cefadroxil (144). However, 5 patients in the cefadroxil group discontinued therapy because of adverse events. Of the remaining 291 patients, 152 in the azithromycin group and 139 in the cefadroxil group received study drug and were included in the safety analysis. The 2 groups were well matched as to demographics and baseline diagnosis (Table 1). The clinical MITT population included 279 patients (azithromycin, 145; cefadroxil, 134), of whom 219 (azithromycin, 114; cefadroxil, 105) were evaluable between days 10 and 13. Failure to meet both inclusion or exclusion criteria was the most common reason for nonevaluability at this visit. Between days 28 and 32, 165 MITT patients were clinically evaluable (azithromycin, 82; cefadroxil, 83). Failure to meet both inclusion or exclusion criteria and no visit between days 28 and 32 were the most common reasons for nonevaluability. Among clinically evaluable MITT patients, 173 had a pathogen isolated at baseline and were bacteriologically evaluable between days 10 and 13 (azithromycin, 88; cefadroxil, 85).

Response to Therapy—The MITT analysis demonstrated comparable rates of clinical success (cure or improvement) for azithromycin and cefadroxil when assessed between days 10 and 13: 111/114 (97%) and 101/105 (96%), respectively ($P=.717$). The rate of clinical success (cure) obtained between days 28 and 32 for azithromycin was significantly higher than that for cefadroxil: 82/82 (100%) versus 75/83 (90%), respectively ($P=.007$). The per protocol analysis demonstrated comparable clinical suc-

Table 2.

Bacteriologic Eradication Rates (% Isolates), Modified Intent-to-Treat Population

	No. of Patients (%)	
	Azithromycin	Cefadroxil
Days 10–13*	(n=88)	(n=85)
Staphylococcus aureus	64/68 (94)	60/70 (86)
Streptococcus pyogenes	4/5 (80)	6/6 (100)
Streptococcus agalactiae	9/9 (100)	11/11 (100)
Other†	35/39 (90)	37/38 (97)
Total	112/121 (93)	114/125 (91)
Days 28–32*	(n=74)	(n=74)
S aureus	59/59 (100)	56/63 (89)
S pyogenes	4/4 (100)	5/6 (83)
S agalactiae	7/7 (100)	12/12 (100)
Other†	29/29 (100)	21/26 (81)
Total	99/99 (100)	94/107 (88)

*Some patients had more than one pathogen.
†Includes anaerobic gram-negative rod, *Pseudomonas aeruginosa, Haemophilus parainfluenzae, Bacteroides melaninogenicus, Proteus mirabilis, Klebsiella oxytoca, Escherichia coli, Acinetobacter* species, streptococcus species, *Enterobacter cloacae*, and enterococcus group D.

cess rates in the 2 treatment groups at both end points: between days 10 and 13, azithromycin 60/61 (98%) versus cefadroxil 72/75 (96%), $P=.425$; and between days 28 and 32, azithromycin 53/53 (100%) versus cefadroxil 61/66 (92%), $P=.079$.

Bacteriologic eradication rates for the MITT population, overall and stratified by pathogen, were comparable in the 2 treatment groups (Table 2). Bacteriologic eradication rates obtained between days 10 and 13 in the per protocol population were consistent with those in the MITT group and were similar for the 2 antibiotics: azithromycin 73/75 (97%), with 2 persistent *S aureus* isolates; and cefadroxil 95/104 (91%), with 9 persistent *S aureus* isolates. Eradication rates obtained between days 28 and 32 were as follows: azithromycin 65/65 (100%), with no persistent isolates; and cefadroxil 78/88 (89%), with 5 persistent *S aureus* isolates.

Safety—All patients who received at least one dose of study drug were included in the safety analysis. Rates of treatment-related adverse events in the azithromycin and cefadroxil groups were 24% (37/152) and 28% (39/139), respectively ($P=.50$). Differences in treatment-related laboratory abnormalities also were not statistically significant ($P=.194$). Among patients in the cefadroxil group, 5 of 139 patients (4%) discontinued therapy because of treatment-related adverse events versus none of the 152 patients in the azithromycin group ($P=.02$). Reasons for discontinuation in the cefadroxil group included gastrointestinal complaints (2 patients), dysuria (1 patient), urticaria (1 patient), and joint pain (1 patient).

Treatment-related adverse events occurring in 3% or more of patients are shown in Table 3. One patient in the azithromycin group experienced a serious adverse event (hospitalization due to angina and dyspnea). The patient subsequently recovered.

Comment

Treatment options for uncomplicated SSSIs typically include a 10-day regimen of either a first-generation cephalosporin or an antistaphylococcal penicillin. In this study, we compared 5 days of

Table 3.

Treatment-Related Adverse Events Occurring in 3% or More of Patients

Event	No. of Patients (%)	
	Azithromycin (n=152)	Cefadroxil (n=139)
Nervous system		
Headache	9 (6)	8 (6)
Dizziness	1 (<1)	7 (5)
Gastrointestinal		
Diarrhea	9 (6)	5 (4)
Nausea	4 (3)	5 (4)
Dyspepsia	5 (3)	2 (1)
Abdominal pain	5 (3)	5 (4)

once-daily azithromycin with 10 days of twice-daily cefadroxil. Results are generally consistent with the findings of Mallory,[9] who demonstrated comparable clinical and bacteriologic efficacy for 5-day therapy with azithromycin compared with 10-day therapy with cephalexin for treating uncomplicated SSSIs. Furthermore, Daniel[10] reported that 5-day azithromycin was as effective as, and better tolerated than, a 7-day regimen of either erythromycin or cloxacillin.

Safety and efficacy are primary considerations when selecting an antibiotic. In addition, a favorable side effect profile and ease of administration are important attributes for both physicians and patients. In fact, antibiotic regimens featuring fewer daily doses and shorter treatment durations improve compliance.[11,12]

In summary, 5-day therapy with azithromycin demonstrated clinical and bacteriologic efficacy comparable to that of 10-day therapy with cefadroxil and was associated with a lower rate of treatment-related discontinuations. These results support consideration of azithromycin as a treatment option in the management of uncomplicated SSSIs.

Acknowledgment—The authors acknowledge the contributions of the following investigators who participated in this trial: Stanley C. Parman, MD; Paul L Sheitel, DPM; Max E. Reddeck, MD; Kim M. Feldhaus, MD; Howard R. Fox, DPM; Anne W. Lucky, MD; and Mark L. Lipton, DPM.

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