ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1995, p. 661–667 Vol. 39, No. 3
0066-4804/95/$04.00+0

Comparison of Cefuroxime Axetil and Doxycycline in Treatment of Patients with Early Lyme Disease Associated with Erythema Migrans

STEVEN W. LUGER,[1] PHILIP PAPARONE,[2] GARY P. WORMSER,[3] ROBERT B. NADELMAN,[3] EDGAR GRUNWALDT,[4] GEMA GOMEZ,[5] MICHAEL WISNIEWSKI,[5] AND JEFFREY J. COLLINS[5]*

Old Lyme Family Practice, Old Lyme, Connecticut[1]; Lyme Disease Center for South Jersey, Absecon, New Jersey[2]; Division of Infectious Diseases, Department of Medicine, New York Medical College, Westchester County Medical Center, Valhalla, New York[3]; Shelter Island, New York[4]; and Glaxo Inc., Research Triangle Park, North Carolina[5]

Received 15 September 1994/Returned for modification 7 November 1994/Accepted 16 December 1994

A randomized, multicenter, investigator-blinded clinical trial was undertaken in order to compare the efficacies of cefuroxime axetil and doxycycline in the treatment of patients with Lyme disease associated with erythema migrans. A total of 232 patients with physician-documented erythema migrans were treated orally for 20 days with either cefuroxime axetil, 500 mg twice daily (119 patients), or doxycycline, 100 mg three times daily (113 patients), and clinical evaluations were conducted during treatment (8 to 12 days) and at 1 to 5 days and 1, 3, 6, 9, and 12 months posttreatment. Patients were assessed as to the resolution of erythema migrans and of the signs and symptoms related to early Lyme disease as well as to the prevention of late Lyme disease. A satisfactory clinical outcome (success or improvement) was achieved in 90 of 100 (90%) evaluable patients treated with cefuroxime axetil and in 89 of 94 (95%) patients treated with doxycycline (difference, −5%; 95% confidence interval, −12 to 3%). Patients with paresthesia, arthralgia, or irritability at enrollment were at higher risk for an unsatisfactory clinical outcome at 1 month posttreatment. Of the patients with satisfactory outcomes at 1 month posttreatment who were evaluable at 1 year posttreatment, a satisfactory outcome was achieved in 62 of 65 (95%) and in 53 of 53 (100%) patients treated with cefuroxime axetil and doxycycline, respectively (difference, −5%; 95% confidence interval, −10 to 4%). Twenty-eight percent of patients treated with doxycycline and 17% of those treated with cefuroxime axetil had one or more drug-related adverse events ($P = 0.041$). Doxycycline was associated with more photosensitivity reactions (6% compared with 0% for patients treated with cefuroxime axetil; $P = 0.006$), and cefuroxime axetil was associated with more cases of diarrhea (5% compared with 0% for patients treated with doxycycline; $P = 0.030$). Jarisch-Herxheimer reactions occurred in 12% of the patients in each treatment group. In summary, cefuroxime axetil is well tolerated and appears to be equally as effective as doxycycline in the treatment of early Lyme disease and in preventing the subsequent development of late Lyme disease.

Lyme disease, a tick-transmitted spirochetal infection caused by *Borrelia burgdorferi* (19), is the most common arthropod-transmitted illness in the United States (2). Erythema migrans, the most characteristic manifestation, is the best clinical marker available for identifying patients with early Lyme disease.

Initially, the choice of appropriate antibiotic therapy for patients with Lyme disease had been based on in vitro and in vivo susceptibility data, along with experience in treating other spirochetal infections (20). The results of clinical trials have shown that antibiotics chosen in this manner do not successfully treat infections in all patients (21). Although penicillin and tetracycline were originally considered the antimicrobial agents of choice for the treatment of patients with early Lyme disease (20), they have largely been replaced by amoxicillin and doxycycline as first-line therapy (14) because the latter antibiotics are more active in vitro, demonstrate greater bioavailabilities, and have longer half-lives requiring less frequent dosing. However, no clinical trials have been conducted to confirm directly the expected advantage of amoxicillin and doxycycline over older antibiotics.

The usefulness of antimicrobial agents in the penicillin family is often hampered by allergic reactions reported in up to 10% of the population (11) as well as the need for frequent dosing. Similarly, tetracyclines should not be used in pregnant or breast-feeding women or in children younger than 8 years of age, and these antibiotics need to be used with caution because of photosensitivity reactions associated with their use (16, 17). Another antimicrobial agent without these complications would broaden the antibiotic choices available to the clinician for treating patients with early Lyme disease.

Cefuroxime axetil, an expanded-spectrum oral cephalosporin, was chosen for clinical study because previous in vitro and in vivo studies suggested that it has activity comparable to that of doxycycline against *B. burgdorferi* (1, 7). In addition, cefuroxime axetil is well tolerated, can be dosed twice daily, and has no age contraindication, and photosensitivity reactions have not been reported to be associated with its use (4, 12). An initial study comparing the efficacy and safety of cefuroxime axetil given at 500 mg twice daily with those of doxycycline given at 100 mg three times daily was conducted in 123 early Lyme disease patients with erythema migrans (15). The results

* Corresponding author. Mailing address: Glaxo Inc., 5 Moore Drive, Research Triangle Park, NC 27709. Phone: (919) 941-4739. Fax: (919) 941-3592. [Reprint requests to Steven W. Luger, Kaiser Permanente, 2080 Silas Deane Highway, Rocky Hill, CT 06067. Phone: (203) 258-2900. Fax: (203) 258-2903.]

demonstrated that cefuroxime axetil administered twice daily was as effective as doxycycline administered three times daily not only in the treatment of early Lyme disease but also in preventing the progression to late Lyme disease over the course of a 1-year follow-up period.

The present replicate study, which used a design similar to that reported previously (15) but involving more study centers, was conducted in order to confirm the previous results with a larger number of study patients.

(This study was presented in part at the V International Conference on Lyme Borreliosis, Arlington, Va., 30 May to 2 June 1992, the 6th European Congress of Clinical Microbiology and Infectious Diseases, Seville, Spain, 28 to 31 March 1993, and the VI International Conference on Lyme Borreliosis, Bologna, Italy, 19 to 22 June 1994.)

MATERIALS AND METHODS

Study design. Patients were enrolled between May and November 1990 into the randomized, investigator-blinded, multicenter trial described here. Outpatients 12 years of age or older weighing at least 45 kg (100 lbs) who were diagnosed with early Lyme disease confirmed by the presence of physician-documented erythema migrans (with or without systemic manifestations of infection) were candidates for enrollment in the study. The number of erythema migrans lesions was recorded, and the primary lesion was measured and (in nearly all cases) photographed.

Patients were excluded if they were pregnant or lactating, if they had a history of serious adverse reactions to any cephalosporin or tetracycline drug or an immediate hypersensitivity reaction to any penicillin, if they had gastrointestinal disorders that would interfere with the absorption of orally administered antimicrobial agents, if they received therapy with any systemic antimicrobial agent with known activity against *B. burgdorferi* within 10 days before enrollment, or if they had unstable concomitant underlying conditions compromising the ability to respond to infection. To ensure enrollment of patients with similar characteristics at each study center, investigators at each site kept a record of potentially eligible patients who were considered for study entry but who were not enrolled. The study protocol was approved by the institutional review board at each center, and written informed consent was obtained from all patients.

Treatment. Patients were randomly assigned to receive either cefuroxime axetil (Ceftin; Glaxo Inc., Research Triangle Park, N.C.), 500 mg twice daily, or doxycycline (doxycycline hyclate; E. R. Squibb & Sons, Inc., Princeton, N.J.), 100 mg three times daily, according to a computer-generated randomization scheme. The 300-mg dose of doxycycline is the dose recommended by the manufacturer for the treatment of syphilis (16), another spirochetal illness. An additional reason for selecting treatment with doxycycline at 100 mg three times daily rather than the more commonly used regimen of 100 mg twice daily was to provide a standard with a high degree of efficacy for comparison with cefuroxime axetil, which was thought to be important given the limited data available on the treatment of early Lyme disease with this oral cephalosporin. Patients were instructed to take cefuroxime axetil after eating, when drug absorption is enhanced (5), whereas doxycycline was administered without regard to meals. To minimize possible gastrointestinal side effects, however, patients were encouraged to take doxycycline with milk or yogurt. All patients were provided with Bullfrog 36 sunscreen (Chattem, Inc., Chattanooga, Tenn.) to protect against possible photosensitivity reactions and were instructed to wear sunglasses when exposed to sunlight. Each patient received a 20-day supply of drug. A minimum of 12 days of therapy, with uninterrupted dosing in the first 5 days, was required for a patient to be considered evaluable. To maintain investigator blinding, medication was dispensed by the study coordinator, and patients were instructed not to discuss their study medication with the investigator conducting the clinical evaluations.

Efficacy assessment. A complete medical history and physical examination were done at the time of patient enrollment. A complete blood count, clinical chemistry testing, electrocardiographic evaluation, and urinalysis were done at this time. Serum for Lyme disease serologic assessment (immunoglobulin M [IgM] and IgG antibodies analyzed by enzyme-linked immunosorbent assay [ELISA] and immunofluorescence assay) was collected at the initial visit and at all subsequent scheduled visits as part of an independent serologic research study.

To assess the response to therapy, repeat physical examinations and clinical evaluations were done 8 to 12 days after starting treatment as well as 1 to 5 days and 1 month after completing treatment. Follow-up laboratory tests and electrocardiographic evaluations were done at the first posttreatment visit. To assess patient compliance, a qualitative microbiologic assay was used to determine the presence of antimicrobial drug in a urine sample collected at the during-treatment visit. In addition, patient medication containers were examined by the study coordinator, who counted the remaining pills at the second patient visit and collected the containers after the completion of therapy. To determine whether patients successfully treated for early Lyme disease developed signs and symptoms of late Lyme disease, subsequent evaluations were made at patient visits 3 and 12 months posttreatment and by telephone contacts 6 and 9 months posttreatment. Patients were seen at unscheduled visits if an examination was indicated by their clinical condition.

The efficacy of antimicrobial treatment for early Lyme disease was evaluated on the basis of the clinical response at 1 month posttreatment. The clinical signs and symptoms evaluated and ranked as to severity (mild, moderate, severe) at all patient visits included splenomegaly, radiculopathy, regional and generalized lymphadenopathy, malaise, irritability, fatigue, jaw pain, headache, chills, stiff neck, paresthesia, myalgia, arthralgia, arthritis, pleuritis, backache, nausea, vomiting, diarrhea, sore throat, and fever. The clinical response of each patient at 1 month posttreatment was categorized as follows: (i) success (resolution of erythema migrans rash and other clinical signs and symptoms by the posttreatment visit on days 1 to 5, with a continued asymptomatic state through the 1-month posttreatment follow-up period), (ii) improvement (resolution of erythema rash but incomplete resolution of any other clinical signs and symptoms of early Lyme disease by the posttreatment visit on days 1 to 5, with further improvement or complete resolution by the 1-month posttreatment follow-up visit), (iii) failure (no improvement in erythema migrans rash or other clinical signs and symptoms of early Lyme disease by the posttreatment visit on days 1 to 5), or (iv) recurrence (success or improvement but with recurrence of erythema migrans rash or other signs and symptoms of early Lyme disease by the 1-month posttreatment follow-up visit). Patients were considered to be clinically unevaluable if they received less than 12 days of treatment with a study drug, if their antimicrobial treatment was interrupted in the first 5 days of therapy, if their enrollment violated the selection criteria, if they received concomitant treatment with a nonstudy antibiotic, if they failed to complete the posttreatment visits, if they withdrew from the study because of an adverse event, or if they showed evidence of poor compliance with therapy (absence of antibacterial activity in the urine specimen obtained during treatment or returned medication indicating less than 12 days of dosing).

Patients who had satisfactory clinical responses (success or improvement) at 1 month posttreatment were followed until 1 year posttreatment to determine whether they subsequently developed signs and symptoms of late Lyme disease. The clinical response of each patient at this time was categorized as follows: (i) success (no signs or symptoms of late Lyme disease [for example, arthralgia, fatigue, arthritis, carditis, neurologic disease] throughout the 1-year follow-up period), (ii) improvement (some signs or symptoms consistent with late Lyme disease but no objective evidence of active disease during the 1-year follow-up period), or (iii) failure (signs or symptoms of late Lyme disease, including seropositivity for antibodies to *B. burgdorferi* at the time of assessment during or at the completion of the 1-year follow-up period). In the case of equivocal clinical findings of late Lyme disease, the distinction between the assessment of a patient as an improvement or failure during the 1-year follow-up period reflected, in addition to the serologic evidence, the investigator's evaluation of the patient's overall clinical condition. Patients were considered to be clinically unevaluable if they were lost to follow-up or if they developed evidence of early Lyme disease (for example, erythema migrans) because of recurrence or reinfection during the 1-year follow-up period.

Safety assessment. The safety of the study drugs was assessed by recording adverse events and by monitoring laboratory values during and after the completion of treatment. The investigator evaluated the severities of all adverse events and determined whether an event was related to the study drug. Jarisch-Herxheimer reactions were recorded as adverse events. The occurrence of such a reaction was determined by patient interview at the during-treatment visit. A Jarisch-Herxheimer reaction was defined as an intensification of symptoms within the first 24 h of antimicrobial use (20).

Statistical analyses. The two treatments were compared with respect to satisfactory (success or improvement) and unsatisfactory (failure or recurrence) clinical responses by using a Mantel-Haenszel statistic controlling for investigational center (10). Other comparisons between cefuroxime axetil and doxycycline were done by Fisher's exact test.

Signs and symptoms of Lyme disease were compared by using a scoring system based on the investigator assessment of the severity of each clinical sign and symptom (not present = 0, mild = 1, moderate = 2, severe = 3). The scores for individual signs and symptoms were summed at each visit to produce a total symptom score. These total symptom scores were compared between treatments at each visit by using a van Elteren statistic (22) to control for investigational center.

The rate of study dropouts was compared between treatment groups by using a Mantel-Haenszel statistic controlling for investigational center. Incidence rates for adverse events were compared between treatment groups for all adverse events and for those deemed by the investigator to be drug related. To define incidence, an adverse event in a patient experiencing the adverse event more than one time was counted only once. Analysis was done by a two-tailed exact test (8) for each type of event, grouped by body system and over all body systems. In all cases, a P value of less than or equal to 0.05 was considered to indicate statistical significance.

TABLE 1. Characteristics of erythema migrans at study enrollment

Characteristic	Cefuroxime axetil (n = 119)	Doxycycline (n = 113)	P value
Presence of EM[a] lesion (no. [%] of patients)	117 (98.3)	113 (100)	0.15[b]
Presence of multiple EM lesions (no. [%] of patients)	20 (16.8)	12 (10.6)	0.14[b]
No. of EM lesions			
Mean ± SEM	3.03 ± 0.93	1.75 ± 0.31	
Median	1.00	1.00	0.17[c]
Range	0–100	1–25	
Size of primary EM lesion (cm^2)			
Mean ± SEM	79 ± 10	106 ± 14	
Median	54	64	0.62[c]
Range	2–980	3–810	
Days since lesion first observed			
Mean	6.94 ± 1.04	6.04 ± 0.69	
Median	4.00	4.00	0.66[c]
Range	1–90	1–60	
Systemic manifestations[d]	94 (79.0)	84 (74.3)	0.41[b]

[a] EM, erythema migrans.
[b] The analysis performed was a Mantel-Haenzsel test controlling for investigational center.
[c] The analysis performed was a van Elteren (22) test (two-tailed).
[d] Presence of Lyme disease signs and symptoms in addition to erythema migrans.

TABLE 2. Clinical efficacies of cefuroxime axetil and doxycycline in the treatment of early Lyme disease

Clinical outcome	No. of patients[a]	
	Cefuroxime axetil	Doxycycline
Success	67 (67.0)	68 (72.3)
Improvement	23 (23.0)	21 (22.3)
Satisfactory[b]	90 (90.0)	89 (94.7)
Failure	7 (7.0)	4 (4.3)
Recurrence	3 (3.0)	1 (1.1)
Unsatisfactory	10 (10.0)	5 (5.3)
Total, evaluable patients	100	94
Unevaluable	19	19
Total, all patients	119	113

[a] Numbers in parentheses indicate percentage of evaluable patients.
[b] Pairwise comparison of satisfactory outcome was performed by Fisher's exact test: cefuroxime axetil versus doxycycline, P = 0.250. The number of patients with a satisfactory outcome was the number of patients who were treatment successes plus the number of patients who showed improvement.
[c] The number of patients with an unsatisfactory outcome was the number of patients who were treatment failures plus the number of patients who had recurrences.

RESULTS

Two hundred thirty-two patients were enrolled in the study, of whom 119 were treated with cefuroxime axetil and 113 were treated with doxycycline. In both treatment groups approximately three-fifths (61 to 63%) of the patients were male, nearly all patients (97%) were white, and the patients' average age was in the mid-40s (45 to 47 years old). With the exception of two cefuroxime axetil-treated patients who had misdiagnosed skin lesions (one with ringworm and the other with a herpes lesion), all study patients showed one or more erythema migrans lesions at the time of enrollment (Table 1). Although a greater proportion of patients in the cefuroxime axetil group had multiple erythema migrans lesions at enrollment (17% compared with 11% in the doxycycline group), this difference was not statistically significant (P = 0.144). While patients in the cefuroxime axetil group also had a somewhat greater mean number of erythema migrans lesions than did doxycycline-treated patients, the average size of the primary lesion was slightly larger in the latter group. The mean duration of erythema migrans before treatment was slightly longer in the cefuroxime axetil group, although the median duration was identical in both treatment groups (4 days). The percentage of patients showing signs and symptoms of early Lyme disease other than erythema migrans was also similar in the two treatment groups. Review of the logs of potentially eligible patients not enrolled in the study kept at each site indicated that patients with similar characteristics participated at all study centers.

Clinical outcome. The clinical outcomes for the patients in the two treatment groups at 1 month posttreatment are summarized in Table 2. Of the 232 patients enrolled, 194 (84%) were clinically evaluable. A satisfactory clinical response (success or improvement) was obtained in 90 of 100 (90%) (95% confidence interval [CI], 84 to 96%) and in 89 of 94 (95%) (95% CI, 90 to 99%) evaluable patients treated with cefuroxime axetil or doxycycline, respectively (difference, −5%; 95% CI, −12 to 3%). Seven cefuroxime axetil-treated patients failed to respond to treatment, and three patients in this group were assessed as clinical recurrences. Four doxycycline-treated patients failed to respond to treatment, and one was classified as a clinical recurrence. In addition to erythema migrans, which was still present in 8 of the 15 study patients with unsatisfactory clinical outcomes (failure or recurrence) at 1 month posttreatment, these patients continued to report various complaints, including arthralgia, myalgia, paresthesia, fatigue, irritability, headache, and stiff neck (Table 3).

Of the 15 patients with unsatisfactory clinical outcomes, 3 were withdrawn from the study early because of their poor response to treatment, and 4 received treatment with alternative oral antibiotics (2 with amoxicillin and 2 with doxycycline). All four of the patients retreated with antibiotics were significantly improved at 1 year posttreatment. Of the remaining 11 patients not retreated with antibiotics, 6 were lost to follow-up and could not be assessed at 1 year posttreatment (although 1 of these was asymptomatic at 9 months posttreatment), 3 were significantly improved at 1 year posttreatment, and 2 patients had little or no resolution of symptoms. One of these patients reported severe arthralgias, recurrent (non-erythema migrans) rashes, and persistent fatigue. This patient also complained of joint swelling, particularly of the ankles, but this swelling could not be confirmed by the physician. The second patient, according to the patient's mother, reported persistent fatigue and fibromyalgia, but this was not verified by physician examination. Nineteen patients in each group were unevaluable for various reasons, including deviation from the protocol (10 patients), failure to complete follow-up visits (9 patients), withdrawal because of an adverse event (5 patients), and enrollment in violation of the selection criteria (5 patients).

The symptom scoring system described in Materials and Methods was used to monitor the clinical responses of patients with early Lyme disease to treatment with cefuroxime axetil or doxycycline. Treatment with both regimens resulted in a steady decrease in the number and severity of signs and symptoms; no

TABLE 3. Signs and symptoms present at 1 month posttreatment in study patients with an unsatisfactory clinical outcome

Study drug	Patient no.	Clinical outcome[a]	Residual signs and symptoms at 1 m posttreatment	
			Erythema migrans	Other[b]
Cefuroxime axetil	2	F	+	None
	8[c]	F	−	Arthralgia (mi), fatigue (mi)
	9	F	+	None
	19	F	+	Malaise (m), arthralgia (mi), paresthesia (mi), fatigue (mi), backache (mi)
	25[d]	F	+	Arthralgia (s), myalgia (s), fatigue (m), stiff neck (mi), headache (mi), malaise (mi), irritability (mi)
	43	F	+	Paresthesia (mi), stiff neck (mi), fatigue (mi), nausea (mi)
	108	F	+	None
	5	R	−	Fatigue (m), arthralgia (mi), arthritis (mi), irritability (mi)
	8[c,d]	R	+	Myalgia (mi), paresthesia (mi), stiff neck (mi), headache (mi)
	10[e]	R	−	Arthralgia (m), myalgia (m), arthritis (m)
Doxycycline	11	F	−	Arthralgia (mi), fatigue (mi), headache (mi), backache (mi), irritability (mi)
	48	F	−	Arthralgia (mi), myalgia (mi), paresthesia (mi), fatigue (mi), headache (mi), irritability (mi), chills (mi)
	103	F	−	Irritability (m), myalgia (mi), arthritis (mi), stiff neck (mi), fatigue (mi), headache (mi), jaw pain (mi)
	141	F	+	None
	7	R	−	Arthralgia (m), myalgia (m), radiculopathy (m), stiff neck (m), fatigue (m), headache (m), backache (m)

[a] F, failure; R, recurrence.
[b] mi, mild; m, moderate; s, severe.
[c] Two patients at separate study centers were identified as patient 8.
[d] Patient was withdrawn from the study at the completion of treatment.
[e] Patient was withdrawn from the study two weeks posttreatment.

significant differences were observed at any of the scheduled visits up to and including that at 1 year posttreatment (Fig. 1). Analysis of the pretreatment symptom scores for the 15 study patients with unsatisfactory clinical outcomes indicates somewhat higher symptom scores in this patient subset at the time of enrollment, although this difference was not statistically significant (unsatisfactory responders, 6.2; all other patients, 4.6; $P = 0.286$). In a retrospective analysis, the presence of three particular signs and symptoms at enrollment was independently associated with subsequent treatment failure in these patients compared with the signs and symptoms in patients with satisfactory outcomes: paresthesia (47 versus 6%; $P < 0.001$), arthralgia (53 versus 22%; $P = 0.008$), and irritability (40 versus 17%; $P = 0.032$).

Of the 189 patients with satisfactory clinical responses at 1 month posttreatment, 180 were followed during the 1-year follow-up period, and 118 of these were evaluable at 1 year posttreatment. Of these patients, 62 of 65 (95%) (95% CI, 90

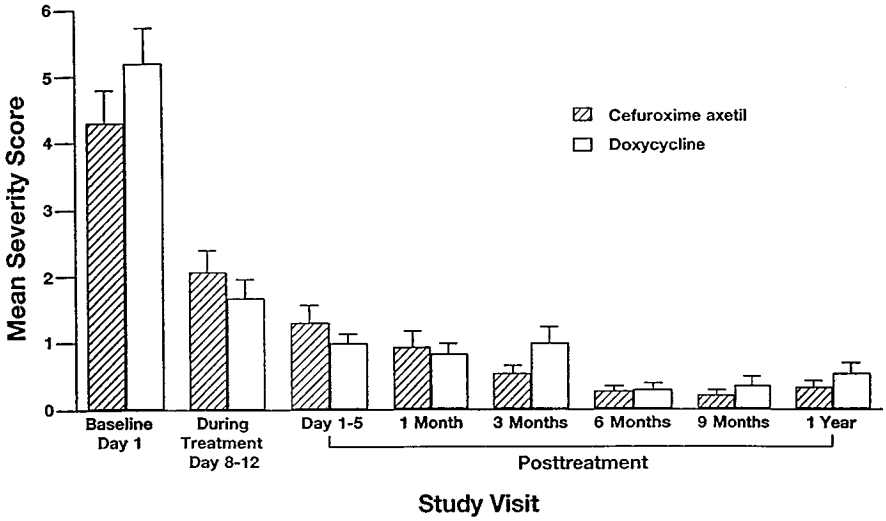

FIG. 1. Comparison of Lyme disease symptom severity in patients treated with cefuroxime axetil or doxycycline. A large number of clinical signs and symptoms (see Materials and Methods) were evaluated at each patient visit or telephone assessment and were ranked as to their severity by using a numerical scoring system (not present = 0, mild = 1, moderate = 2, severe = 3). The severity scores for each sign or symptom for an individual patient were added to yield an overall patient severity score at each visit or telephone assessment. These scores were averaged to provide a mean severity score for each treatment group at each study visit. T bars indicate the standard error of the mean.

TABLE 4. Clinical efficacy of cefuroxime axetil and doxycycline in the prevention of late lyme disease in successfully treated early lyme disease patients

Clinical outcome	No. of patients[a]	
	Cefuroxime axetil	Doxycycline
Success	57 (87.7)	48 (90.6)
Improvement	5 (7.7)	5 (9.4)
Satisfactory[b]	62 (95.4)	53 (100.0)
Failure	3 (4.6)	0 (0.0)
Total, evaluable patients	65	53
Unevaluable	26	36
Total, all patients	91	89

[a] Numbers in parentheses indicate percentage of evaluable patients.
[b] Pairwise comparison of satisfactory outcome was performed by Fisher's exact test: cefuroxime axetil vs. doxycycline, $P = 0.127$. The number of patients with a satisfactory outcome was the number of patients who were treatment successes plus the number of patients who showed improvement.

to 100%) cefuroxime-treated patients and 53 of 53 (100%) (95% CI, 100 to 100%) doxycycline-treated patients had satisfactory clinical outcomes (success or improvement) at 1 year posttreatment (Table 4) (the difference in satisfactory outcomes was −5%; 95% CI, −10 to 4%). Thus, nearly all patients who had a satisfactory clinical response at 1 month posttreatment failed to show symptoms of late Lyme disease during the 1-year follow-up period.

Sixty-two patients (26 in the cefuroxime axetil group and 36 in the doxycycline group) followed during the 1-year posttreatment period were unevaluable for various reasons, including loss to follow-up (45 patients) (which included the development of early Lyme disease because of reinfection [2 patients] or recurrence [5 patients]), use of non-study antibiotics (12 patients), and deviation from the protocol (5 patients).

The three cefuroxime axetil-treated patients assessed as clinical failures during the 1-year follow-up period showed a variety of Lyme disease-related symptoms, including arthritis, arthralgia, cognitive dysfunction, and headache; these symptoms were moderate to severe in intensity (Table 5). All of these patients were serologically reactive for anti-*B. burgdorferi* IgG antibodies at the time that they were assessed as clinical failures. Two of the three patients classified as clinical failures received treatment with alternative antibiotics, one with oral agents and one with a parenteral antibiotic. The patient retreated with a parenteral antibiotic was significantly improved by 1 year posttreatment, while the patient retreated with oral antibiotics was lost to follow-up and could not be assessed at 1 year posttreatment. The third patient, who was not retreated with antibiotic, had no resolution of symptoms at 1 year posttreatment.

TABLE 5. Signs and symptoms present during the 1-year posttreatment follow-up period in study patients treated with cefuroxime axetil assessed as long-term clinical failures

Patient no.	Residual signs and symptoms at withdrawal during the 1-year posttreatment follow-up period[a]	Study duration (mo posttreatment)[b]
19	Headache (s), vertigo (s), dizziness (s), cognitive dysfunction (m)	9
28	Arthritis (m)	9
36	Arthritis (m), arthralgia (m)	7

[a] None of the patients had erythema migrans lesions and all patients were positive for anti-*B. burgdorferi* IgG antibodies by ELISA and or immunofluorescence assay at the time of withdrawal. mi, mild; m, moderate; s, severe.
[b] Patients were withdrawn from the study when they were assessed as clinical failures at the indicated times.

No neurologic or cardiac complications were observed at 1 month or less posttreatment. One patient treated with cefuroxime axetil developed what was believed to be Lyme arthritis, characterized by small effusions, tenderness, and warmth of the left ankle, by the 1-month posttreatment visit. This patient's symptoms improved after a second course of oral antibiotics. Two possible additional cases of Lyme arthritis, as defined by objective swelling, pain on motion, or warmth in the affected joints on physical examination (21), were noted in cefuroxime axetil-treated patients assessed as clinical failures at 7 and 9 months posttreatment, respectively. One of these patients, who had a 5-year history of degenerative spondylosis of the lumbar spine, complained of aching knees while in the study. There was no evidence of effusion and her knees were not tapped or X rayed. The second patient developed inflammation of the left ankle while in the study, with no radiographic evidence of degenerative joint disease, although slight osteoporosis was noted. A history of gout was revealed upon questioning, and the ankle inflammation resolved upon treatment with colchicine and indomethacin (Indocin), although the patient complained of intermittent swelling and pain. For both of these patients, the investigator considered it equally likely that the arthritis-like symptoms which occurred in these patients while in the study were related to their preexisting conditions rather than reflecting the development of Lyme arthritis.

Adverse events. One or more drug-related adverse events were reported by significantly more doxycycline-treated patients than by cefuroxime axetil-treated patients (28.3 compared with 16.8%; $P = 0.041$) (Table 6). In addition, the natures of the most commonly reported adverse events differed considerably between the two treatment groups. A significantly increased incidence of drug-related adverse events affecting the skin was reported by doxycycline-treated patients ($P = 0.009$; 10% compared with 2% for the cefuroxime axetil group), reflecting the development of skin photosensitivity reactions in 6% of these patients compared with none in the cefuroxime axetil group ($P = 0.006$). All patients with such reactions claimed to be applying their sun block regularly. One patient in the cefuroxime axetil group experienced urticaria, and another developed a skin eruption. Although the incidence of adverse events related to the gastrointestinal system was similar in the two treatment groups, the reported incidence of diarrhea was significantly higher in cefuroxime axetil-treated patients ($P = 0.030$; 5% compared with 0% in doxycycline-treated patients). No patient in either group developed *Clostridium difficile*-associated colitis. One cefuroxime axetil-treated patient developed mild anemia that may have been drug related. Eight patients withdrew from the trial because of drug-related adverse events, three of whom were treated with cefuroxime axetil (diarrhea and dizziness, diarrhea and stomach cramps, and urticaria) and five of whom were treated with doxycycline (chest discomfort and burning, chest pain and shortness of breath, rash, and stomach pain in two patients).

Jarisch-Herxheimer reactions. The incidence of Jarisch-Herxheimer reactions in cefuroxime axetil-treated patients was nearly identical to that observed in doxycycline-treated patients (11.8% compared with 11.5%), in contrast to the threefold greater incidence reported in cefuroxime axetil-treated patients in the previous study (15). These reactions were tran-

TABLE 6. Drug-related adverse events reported by patients with early Lyme disease treated with cefuroxime axetil or doxycycline[a]

Adverse event	No. (%) of patients		*P* value[b]
	Cefuroxime axetil (*n* = 119)	Doxycycline (*n* = 113)	
Skin			
Photosensitivity	0 (0.0)	7 (6.2)	0.006
Urticaria	1 (0.8)	0 (0.0)	
Rash, skin eruption	1 (0.8)	2 (1.8)	
Other skin events	0 (0.0)	2 (1.8)	
Total patients with one or more skin events	2 (1.7)	11 (9.7)	0.009
Gastrointestinal system			
Diarrhea	6 (5.0)	0 (0.0)	0.030
Nausea	3 (2.5)	4 (3.5)	
Gastric pain/upset	1 (0.8)	3 (2.7)	
Other gastrointestinal events	3 (2.5)	5 (4.4)	
Total patients with one or more gastrointestinal events	9 (7.6)	10 (8.8)	0.813
Hematologic anemia	1 (0.8)	0 (0.0)	
Other	5 (4.2)	5 (4.4)	
Total patients with one or more drug-related events	20 (16.8)	32 (28.3)	0.041

[a] Adverse events are not necessarily additive since some patients reported more than one adverse event.
[b] Incidence of adverse events was compared by a two-tailed Fisher's exact test.

sient, usually lasting 1 to 2 days, and in no case did they result in the withdrawal of the patients from the study.

DISCUSSION

Although successful antibiotic therapy for erythema migrans was first achieved in 1948 (6), it was not until 1980 that tetracycline and penicillin were shown to speed the resolution of erythema migrans and possibly prevent the subsequent development of arthritis (21). However, despite the encouraging results reported in this landmark study, many patients still had significant residual symptoms following antibiotic treatment. In an effort to improve upon these results, higher doses of antimicrobial agents, longer durations of therapy, and new antimicrobial agents have been tried (3, 13).

The present replicate study, modeled after a similar but smaller trial conducted previously (15), was designed to assess the available objective findings and to quantitate as accurately as possible subjective symptoms. A follow-up period of 1 year was chosen both to examine the onset of late symptoms and to evaluate the persistence of minor symptoms over an extended period of time.

In the resolution of early Lyme disease, a satisfactory clinical response, defined as success or improvement at the 1-month posttreatment visit, was seen in 90 of 100 (90%) evaluable cefuroxime axetil-treated patients and in 89 of 94 (95%) evaluable-treated doxycycline-treated patients (compared with 93 and 89% satisfactory outcomes, respectively, in the previous study [15]). These results suggest that 500 mg of cefuroxime axetil administered twice daily is as effective as doxycycline administered at 100 mg three times daily in the resolution of early Lyme disease symptoms. The rates of satisfactory responses achieved in the present study are similar to those reported in other studies (2, 13, 15, 20).

With respect to the prevention of late Lyme disease, patients given both treatment regimens, as in the previous study (15), had excellent outcomes, with 95% (62 of 65) of evaluable cefuroxime axetil-treated patients having satisfactory responses at 1 year posttreatment (two patients who were treatment failures developed arthritis and one patient reported severe headaches and vertigo) and 100% (53 of 53) of evaluable doxycycline-treated patients having satisfactory outcomes (90 and 92% of patients had satisfactory outcomes, respectively, at 1 year posttreatment in the previous study [15]). In contrast to the previous study, patients who were assessed as clinically improved at 1 month posttreatment were no more likely to become clinical failures during or at completion of the 1-year follow-up period than were patients who were judged to be clinical successes at 1 month posttreatment (4% compared with 2%; $P = 0.545$).

Finally, there appeared to be no difference between the efficacy of the cefuroxime axetil and doxycycline treatment regimens in the prevention of the post-Lyme syndrome, as assessed by the persistence of symptoms at 1 month posttreatment (23 and 22%, respectively) and at 1 year posttreatment (8 and 9%, respectively).

In contrast to the similar clinical efficacy outcomes achieved with both study drugs, there were significant differences in the incidence of drug-related adverse events. One or more drug-related adverse events occurred in 17% of patients receiving cefuroxime axetil, whereas they occurred in 28% of those treated with doxycycline ($P = 0.041$). There were more skin-associated adverse events, particularly photosensitivity reactions, in the doxycycline group ($P = 0.006$), even though a potent sunscreen was provided to all study patients. However, the use of doxycycline 100 mg three times daily rather than the more commonly used regimen of 100 mg twice daily may have contributed to the level of photosensitivity reactions observed. The association of photosensitivity reactions with doxycycline treatment may be especially problematic for a spring and summer infection such as Lyme disease, when patients may be unable or unwilling to avoid sun exposure. Although the total number of gastrointestinal adverse events were comparable in the two treatment groups, more drug-related diarrhea was reported in the patients receiving cefuroxime axetil ($P = 0.030$).

In summary, the present results indicate that while there was no significant difference in the efficacies of the two antimicrobial regimens compared in the study, significant differences in the adverse event profiles were seen. In a situation such as this, how is the clinician to decide which antibiotic to use for the treatment of patients with early Lyme disease? As in any choice of medication, factors of efficacy need to be balanced by the safety, side effect profile, cost, and dosing convenience of the medication.

Prior studies have suggested that certain factors may identify Lyme disease patients at increased risk for treatment failure. One study found that the initial severity of illness correlated with the occurrence of minor late symptoms (20). A second small study found that patients with symptoms suggestive of dysesthesias (e.g., headache and neck ache) may be at higher risk for treatment failure (13). The current study found that patients presenting at enrollment with paresthesia, arthralgia, or irritability were more likely to respond unsatisfactorily to treatment of their early Lyme disease. Confirmation of these data by further study is important since the identification of the clinical signs or symptoms of early Lyme disease which are reliable risk factors could allow more aggressive or alternative treatment (e.g., parenteral antimicrobial agents) of appropriate patients.

The results of the present study support the inclusion of cefuroxime axetil in the group of antibiotics effective in the treatment of patients with early Lyme disease. However, the study was not designed to answer certain questions that face clinicians treating patients with Lyme disease. Why is a 100% success rate not achieved in resolving the symptoms of early Lyme disease if *B. burgdorferi* is susceptible to the antimicrobial agent used in treatment? Does the persistence of minor symptoms represent treatment failure, and are these symptoms related to the persistence of viable spirochetes? While it is known that genetic differences exist in the response of patients with Lyme arthritis to treatment (18), are there other host factors (e.g., gender, hormones, immunocompetency) that put patients at risk for treatment failure? Does coinfection with another organism (e.g., *Babesia microti* [9]) account for the failure of antimicrobial agents to cure some patients? Until these and other questions concerning Lyme disease are answered by rigorously designed clinical trials, physicians will continue to have excellent success in treating most patients with Lyme disease but will be frustrated by their inability to help the small minority of nonresponding or relapsing patients.

ACKNOWLEDGMENTS

We thank Nancy Smith, Cathy Donahue, Maureen Lang, Pam Paparone, Gilda Forseter, and Diane Holmgren, for valuable contributions to the study. We gratefully acknowledge the participation of Daniel Cameron, Sam Donta, Elliot Frank, Leonard Sigal, and Keith Sinusas and their staffs.

Funding for the study was provided by a grant from Glaxo Inc.

REFERENCES

1. **Agger, W. A., S. M. Callister, and D. A. Jobe.** 1992. In vitro susceptibilities of *Borrelia burgdorferi* to five oral cephalosporins and ceftriaxone. Antimicrob. Agents Chemother. **36:**1788–1790.
2. **MMWR.** 1991. Lyme disease surveillance—United States, 1990–1991. Morbid. Mortal. Weekly Rep. **40:**417–421.
3. **Dattwyler, R. J., D. J. Volkman, S. M. Conaty, S. P. Platkin, and B. J. Luft.** 1990. Treatment of early Lyme borreliosis, a randomized trial comparing amoxicillin plus probenecid to doxycycline in patients with erythema migrans. Lancet **336:**1404–1406.
4. **Emmerson, A. M.** 1988. Cefuroxime axetil. J. Antimicrob. Chemother. **22:** 101–104.
5. **Finn, A., A. Straughn, M. Meyer, and J. Chubb.** 1987. Effect of dose and food on the bioavailability of cefuroxime axetil. Biopharm. Drug Dispos. **8:**519–526.
6. **Hollstrom, E.** 1951. Successful treatment of erythema migrans Afzelius. Acta Dermato-Venereol. **31:**235–243.
7. **Johnson, R. C., C. B. Kodner, P. J. Jurkovich, and J. J. Collins.** 1990. Comparative in vitro and in vivo susceptibilities of the Lyme disease spirochete *Borrelia burgdorferi* to cefuroxime and other antimicrobial agents. Antimicrob. Agents Chemother. **34:**2133–2136.
8. **Kendall, M., and A. Stuart.** 1979. The advanced theory of statistics, vol. 2. MacMillan Publishing Company, Inc., New York.
9. **Krause, P. J., S. R. Telford, R. Ryan, A. B. Hurta, I. Kwasnik, S. Luger, J. Niederman, M. Gerber, and A. Spielman.** 1991. Geographical and temporal distribution of babesial infection in Connecticut. J. Clin. Microbiol. **29:**1–4.
10. **Landis, R. J., E. R. Heyman, and G. G. Koch.** 1978. Average partial association in three-way contingency tables: a review and discussion of alternative tests. Int. Stat. Rev. **46:**237–254.
11. **Mandell, G. L., and M. A. Sande.** 1990. Antimicrobial agents. Penicillins, cephalosporins, and other beta-lactam antibiotics, p. 1081–1083. *In* A. G. Gilman, T. W. Rall, A. S. Neis, and P. Taylor (ed.), Goodman and Gillman's the pharmacologic basis of therapeutics, 8th ed. Pergamon Press, New York.
12. **Marx, M. A., and W. K. Fant.** 1988. Cefuroxime axetil. Drug Intell. Clin. Pharmacol. **22:**651–658.
13. **Massarotti, E. M., S. W. Luger, D. W. Rahn, R. P. Messner, J. Wong, R. C. Johnson, and A. C. Steere.** 1992. Treatment of Lyme disease. Am. J. Med. **92:**396–403.
14. **Medical Letter.** 1992. Treatment of Lyme disease. Med. Lett. Drugs Ther. **34:**95–98.
15. **Nadelman, R. B., S. W. Luger, E. Frank, M. Wisniewski, J. J. Collins, and G. P. Wormser.** 1992. Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. Ann. Intern. Med. **117:**273–280.
16. **E. R. Squibb & Sons, Inc.** 1991. Doxycycline hyclate, tablets and capsules (package insert). E. R. Squibb & Sons, Inc., Princeton, N.J.
17. **Standiford, H. C.** 1990. Tetracyclines and chloramphenicol, p. 284–295. *In* G. L. Mandell, R. G. Douglas, and J. E. Bennett (ed.), Principles and practice of infectious disease, 3rd ed. Churchill Livingstone, New York.
18. **Steere, A. C., E. Dwyer, and R. Winchester.** 1990. Association of chronic Lyme arthritis with HLA-DR4 and HLA-DR2 alleles. N. Engl. J. Med. **323:**219–223.
19. **Steere, A. C., R. L. Grodzicki, A. N. Kornblatt, J. E. Craft, A. G. Barbour, W. Burgdorfer, G. P. Schmid, E. Johnson, and S. E. Malawista.** 1983. The spirochetal etiology of Lyme disease. N. Engl. J. Med. **308:**733–740.
20. **Steere, A. C., G. J. Hutchinson, D. W. Rahn, L. H. Sigal, J. E. Craft, E. T. DeSanna, and S. E. Malawista.** 1983. Treatment of the early manifestations of Lyme disease. Ann. Intern. Med. **99:**22–26.
21. **Steere, A. C., S. E. Malawista, J. H. Newman, P. H. Speiler, and N. H. Bartenhagen.** 1980. Antibiotic therapy in Lyme disease. Ann. Intern. Med. **93:**1–8.
22. **van Elteren, P. H.** 1960. On the combination of independent two-samples tests of Wilcoxon. Bull. Int. Stat. Inst. **37:**351–361.