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CEFTRIAXONE COMPARED WITH DOXYCYCLINE FOR THE TREATMENT OF ACUTE DISSEMINATED LYME DISEASE

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ABSTRACT

Background Localized Lyme disease, manifested by erythema migrans, is usually treated with oral doxycycline or amoxicillin. Whether acute disseminated *Borrelia burgdorferi* infection should be treated differently from localized infection is unknown.

Methods We conducted a prospective, open-label, randomized, multicenter study comparing parenteral ceftriaxone (2 g once daily for 14 days) with oral doxycycline (100 mg twice daily for 21 days) in patients with acute disseminated *B. burgdorferi* infection but without meningitis. The erythema migrans skin lesion was required for study entry, and disseminated disease had to be indicated by either multiple erythema migrans lesions or objective evidence of organ involvement.

Results Of 140 patients enrolled, 133 had multiple erythema migrans lesions. Both treatments were highly effective. Rates of clinical cure at the last evaluation were similar among the patients treated with ceftriaxone (85 percent) and those treated with doxycycline (88 percent); treatment was considered to have failed in only one patient in each group. Among patients whose infections were cured, 18 of 67 patients in the ceftriaxone group (27 percent) reported one or more residual symptoms at the last follow-up visit, as did 10 of 71 patients in the doxycycline group (14 percent, $P \geq 0.05$). Mild arthralgia was the most common persistent symptom. Both regimens were well tolerated; only four patients (6 percent) in each group withdrew because of adverse events.

Conclusions In patients with acute disseminated Lyme disease but without meningitis, oral doxycycline and parenterally administered ceftriaxone were equally effective in preventing the late manifestations of disease. (N Engl J Med 1997;337:289-94.)

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LYME disease is an infectious disease caused by the tick-borne spirochete *Borrelia burgdorferi*.¹ Although it is not present in all patients, the earliest and most easily recognized manifestation of *B. burgdorferi* infection is the skin lesion known as erythema migrans. Dissemination of the spirochete to multiple organs and tissues, including the central nervous system, occurs early in the course of infection.²⁻⁴ In studies of patients with erythema migrans, those with multiple lesions or other evidence of acute disseminated disease have been grouped together with patients with only local infection. Therefore it is not known whether patients with acute disseminated infection should be treated differently from patients with local infection.

Treatment for patients with erythema migrans typically involves oral doxycycline or amoxicillin,⁵⁻⁷ and most patients treated with either of these agents for local infection have an excellent response. However, not all patients given oral antibiotics for early disease have a favorable outcome,^{8,9} perhaps because the drugs have insufficient activity against borrelia in the central nervous system.¹⁰

Ceftriaxone is highly active against *B. burgdorferi* and reaches high levels in the cerebrospinal fluid and synovial fluid.^{10,11} Treatment with ceftriaxone is effective in acute disseminated Lyme disease, including that manifested by neuroborreliosis, carditis, and meningitis.¹¹⁻¹³ We conducted a study to compare the effectiveness and tolerability of parenteral ceftriaxone and

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standard oral therapy in patients with acute disseminated *B. burgdorferi* infection but without meningitis.

METHODS

Study Sample

Patients who had been in areas where Lyme disease is endemic, who were eight years of age or older, and who had acute disseminated Lyme borreliosis were eligible for enrollment in this open-label, controlled, randomized, multicenter study. The study was conducted between May 1990 and June 1994. Erythema migrans, defined as an expanding, annular, erythematous skin lesion at least 5 cm in diameter, was required for study entry. Disseminated disease was considered present if the patient had one or more of the following: more than one erythema migrans lesion; carditis manifested by heart block; neurologic abnormalities (seventh-cranial-nerve palsy or radiculitis of less than three months' duration); and acute large-joint arthritis.

We excluded pregnant or nursing women and patients with evidence of syphilis, meningitis, or collagen vascular disease; current symptoms of Lyme disease for which they had previously received treatment; a serious underlying disease that precluded the evaluation of the response to treatment; gallbladder disease; or hypersensitivity to ceftriaxone or doxycycline. Patients treated with antimicrobial agents effective in Lyme disease within 48 hours before study entry or treated with an investigational compound within two weeks before study entry were also excluded, as were patients with meningitis or encephalitis.

Concurrent treatment with other antimicrobial agents or corticosteroids was not permitted during the treatment period. We instructed investigators not to prescribe other antibiotics known to be effective in the treatment of Lyme disease until after the patients had been evaluated three months after study treatment. The study protocol was approved by the institutional review boards of the participating institutions, and all patients gave written informed consent before enrollment, in accordance with the 1983 Declaration of Helsinki.

Study Design

After it was determined that they fulfilled the criteria for participation in the study, we randomly assigned eligible patients to receive either ceftriaxone (2 g once daily [50 mg per kilogram of body weight, up to 2 g, in the case of children]), administered either intravenously or intramuscularly, at the discretion of the investigator, for 14 days or doxycycline (100 mg twice daily [4.4 mg per kilogram, up to 100 mg twice daily, for children weighing up to 45.5 kg]) administered orally for 21 days. Before receiving the study medication, the patients underwent a physical examination. Patients with signs of meningitis or neurologic involvement underwent lumbar puncture at the discretion of the investigator. We photographed erythema migrans lesions, and the same investigator evaluated all photos. We performed serologic tests for syphilis (with the Venereal Disease Research Laboratory test), rheumatoid factor, and antinuclear antibodies at base line. We repeated the examinations weekly during therapy and three, six, and nine months after the completion of therapy. At base line and at all subsequent visits, we evaluated clinical signs and symptoms and ranked them as to severity (mild, moderate, or severe), and we recorded any adverse events. We obtained blood samples for use in hematologic and blood-chemistry tests at base line and weekly during therapy.

Clinical Evaluation

At each of the three follow-up visits, investigators classified each patient's clinical response as a cure (indicated by the resolution of objective clinical findings of Lyme disease); as a treatment failure (indicated by objective signs compatible with clinically active Lyme disease, including evidence of arthritis or neurologic disease); or as not assessable (because of improper dose or length of treatment, concomitant antimicrobial therapy, failure to meet the

entry criteria, withdrawal from the study because of severe adverse events, or death).

Serologic Testing

Serum samples were obtained at base line and at each follow-up visit for measurement of specific antibody reactivity to *B. burgdorferi* with use of an enzyme-linked immunosorbent assay (ELISA) and Western blotting.^{14,15} Only values on the ELISA that were greater than 3 SD above the mean for negative controls were considered positive. Western blots were interpreted according to the recommendations of the Centers for Disease Control and Prevention (CDC).¹⁵

Statistical Analysis

We calculated the rates of clinical cure three, six, and nine months after treatment and at the last evaluation for each patient, regardless of when it occurred. The primary variable with respect to efficacy was the clinical-cure rate (number of patients cured divided by the total number that could be evaluated) at the last visit. We calculated the 95 percent confidence interval for the difference in rates of cure (the rate in the ceftriaxone group minus that in the doxycycline group) at the last evaluation.

We used Fisher's exact test for all nominal categorical comparisons, and we used the chi-square test to compare the distribution of patients among age groups. Statistical significance was considered indicated by a two-sided P value ≤ 0.05 .

RESULTS

Characteristics of Patients

Of the 140 patients enrolled, 68 were randomly assigned to receive parenteral ceftriaxone and 72 to receive oral doxycycline. A total of five patients assigned to ceftriaxone (7 percent) and seven patients in the doxycycline group (10 percent) discontinued treatment prematurely. Of these patients, four in each treatment group withdrew because of adverse events; the remaining patients left the study for administrative reasons. Subsequently, one additional patient in each group who had begun treatment was judged not to have erythema migrans. Fifty-eight of the 68 patients in the ceftriaxone group (85 percent) and 62 of the 72 patients in the doxycycline group (86 percent) were evaluated at the nine-month follow-up visit. Before enrollment, 34 patients underwent lumbar puncture; 27 of them were excluded from the study because they had meningitis. All 27 were treated with ceftriaxone.

Patients in the two treatment groups were generally well matched with respect to demographic characteristics (age and sex) and the base-line severity of symptoms ($P \geq 0.090$) (Table 1). Sixty-two patients in the ceftriaxone group (91 percent) and 71 in the doxycycline group (99 percent) had multiple erythema migrans lesions at study entry. The mean time from the appearance of erythema migrans to the start of treatment was 9 days in the ceftriaxone group and 10 days in the doxycycline group. Swelling of the joints was noted in four patients in the ceftriaxone group and five in the doxycycline group. However, at base line, the patients in the ceftriaxone group had a higher prevalence of seventh-cranial-

nerve palsy (7, vs. 3 in the doxycycline group), arthralgia (38 vs. 30), and carditis (7 vs. 2).

Serologic Testing

Ninety-nine of the 140 patients (71 percent) were positive for *B. burgdorferi* on ELISA at entry into the study. Eighty-six of the 99 patients with a positive ELISA had two or more bands on the Western blot; 30 patients had more than five bands. Sixty-four of these 99 patients met the current CDC criteria for a positive Western blot. Forty-eight of the 64 met the criteria for a positive Western blot with respect to IgM but not IgG. Reactivity to the 41-kd flagellin band was the most common type and was observed for 92 percent of the patients who were positive on ELISA. Reactivity to outer surface protein C was the next most common, occurring in 64 percent of the patients (unpublished data). Of the 29 percent who were ELISA-negative, only 10 subsequently seroconverted.

Assessment of Clinical Response

Because of inadequate follow-up or early discontinuation of the antibiotic because of adverse events, the clinical responses of nine ceftriaxone-treated patients and eight doxycycline-treated patients could not be assessed. Therefore, the responses of 59 of the 68 patients in the ceftriaxone group and 64 of the 72 in the doxycycline group could be evaluated. Fifty-eight of the 68 patients given ceftriaxone (85 percent) and 63 of the 72 patients given doxycycline (88 percent) were considered clinically cured (Table 2). The 95 percent confidence interval for the 3 percent difference between the groups (-15.0 to 10.6 percent) indicates the virtual equivalence of the two treatments in this study.

One patient in each treatment group had objective evidence of Lyme disease at the last evaluation (i.e., treatment failed). A patient in the ceftriaxone group who presented with seventh-cranial-nerve palsy and normal results on lumbar puncture continued to have palsy at the three-month follow-up and was given ceftriaxone for an additional five weeks. Despite treatment, the palsy persisted. In a second patient, large-joint arthritis developed during treatment with doxycycline; this patient also had fatigue, joint swelling, limitation of joint movement, arthralgia, and myalgia; he subsequently received intravenous ceftriaxone for three weeks and had a complete resolution of all signs and symptoms.

Although only 1 patient in each treatment group had objective evidence of treatment failure at the last evaluation, 18 of 67 patients in the ceftriaxone group and 10 of 71 in the doxycycline group reported residual symptoms at their last evaluation ($P \geq 0.05$). As Table 3 shows, 14 patients in the ceftriaxone group reported arthralgia, and 6 reported fatigue; in the doxycycline group, 6 reported arthralgia, and 5 fatigue. The majority of persistent symptoms were

TABLE 1. BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	CEFTRIAXONE (N=68)	DOXYCYCLINE (N=72)
Sex — no. (%)		
Male	43 (63)	44 (61)
Female	25 (37)	28 (39)
Age — yr		
Mean \pm SD	42.1 \pm 17.8	43.1 \pm 18.1
Range	10–85	7–84†
Mean time (\pm SD) from erythema migrans to treatment — days	8.57 \pm 8.32	9.93 \pm 13.71
Most frequent symptoms — no. (%)‡		
Arthralgia		
Mild	19 (28)	10 (14)
Moderate	15 (22)	16 (22)
Severe	3 (4)	4 (6)
Fever or chills		
Mild	11 (16)	16 (23)
Moderate	16 (24)	21 (30)
Severe	7 (10)	10 (14)
Fatigue		
Mild	14 (21)	17 (24)
Moderate	27 (40)	31 (43)
Severe	13 (19)	13 (18)
Headache		
Mild	20 (30)	23 (32)
Moderate	17 (25)	10 (14)
Severe	9 (13)	16 (22)
Stiff neck		
Mild	11 (16)	17 (24)
Moderate	7 (10)	12 (17)
Severe	3 (4)	2 (3)
Carditis	7 (10)	2 (3)

*For details of the two study treatments, see the Methods section.

†Although the enrollment of a seven-year-old was a protocol violation, he was included in the analysis since the reason for the exclusion of those under the age of eight was the effect of doxycycline on the teeth.

‡Symptoms were assessed in 67 patients in the ceftriaxone group and 72 in the doxycycline group, except for fever, with respect to which only 71 doxycycline-treated patients were assessed.

mild and did not interfere with daily activities. Only one patient in each group reported severe arthralgia. The one patient in the doxycycline group who reported severe arthralgia at the last follow-up had a history of multiple dorsal and lumbar fractures with diffusely demineralized osseous structures. Fatigue was uncommon among the patients, and in none of them was it severe.

Safety

Drug-related adverse events were more frequent in the ceftriaxone group (39 of 68 patients [57 percent]) than in the doxycycline group (31 of 72 [43 percent], $P = 0.128$). Gastrointestinal events were reported by more patients given ceftriaxone (41 percent) than patients given doxycycline (25 percent,

TABLE 2. INVESTIGATORS' ASSESSMENT OF CLINICAL RESPONSES AT EACH FOLLOW-UP EVALUATION.*

EVALUATION	TOTAL NO.	CLINICAL CURE		TREATMENT FAILURE		NOT ASSESSABLE†	
		CEFTRI- AXONE	DOXY- CYCLINE	CEFTRI- AXONE	DOXY- CYCLINE	CEFTRI- AXONE	DOXY- CYCLINE
number of patients (percent)							
3 mo	127	55 (92)	63 (94)	1 (2)	1 (1)	4 (7)	3 (4)
6 mo	119	51 (88)	54 (89)	0	0	7 (12)	7 (11)
9 mo	120	56 (97)	58 (94)	0	0	2 (3)	4 (6)
Last‡	140	58 (85)	63 (88)	1 (1)	1 (1)	9 (13)	8 (11)

*The numbers of patients whose outcomes could be assessed at the three-month, six-month, and nine-month follow-up visits were 60, 58, and 58, respectively, in the ceftriaxone group, and 67, 61, and 62, respectively, in the doxycycline group. All patients' outcomes could be assessed at the last follow-up contact, by definition, regardless of when it occurred. Because of rounding, percentages for a treatment group at a particular follow-up visit may not total 100.

†The most frequent reasons for patients' not being able to be assessed included inadequate follow-up, death, or withdrawal because of adverse events.

‡The 95 percent confidence interval for the difference in the rate of clinical cure at the last evaluation (the rate in the ceftriaxone group minus that in the doxycycline group, or 3 percent) was -15.0 to 10.6 percent.

TABLE 3. THE MOST COMMON PERSISTENT SYMPTOMS AT THE LAST FOLLOW-UP VISIT, ACCORDING TO TREATMENT GROUP.*

SYMPTOM	CEFTRIAZONE (N=18)			DOXYCYCLINE (N=10)		
	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
no. of patients						
Arthralgia	11	2	1	4	1	1
Backache	2	0	0	1	0	0
Fatigue	5	1	0	4	1	0
Headache	1	1	0	0	0	0
Irritability	3	1	0	0	0	0
Malaise	5	0	0	1	0	0
Myalgia	3	0	1	1	1	1
Stiff neck	2	0	0	0	0	0

*Some patients had more than one symptom.

P=0.049). Notably, 25 ceftriaxone-treated patients (37 percent) but only 4 doxycycline-treated patients (6 percent) reported diarrhea (P<0.001). Only one patient in the ceftriaxone group had severe diarrhea; that patient was found to have *Clostridium difficile* infection. Headache, nausea, vomiting, and weight loss led to the discontinuation of doxycycline in another patient. Twice as many patients in the doxycycline group (nine, or 12 percent) as in the ceftriaxone group (four, or 6 percent; P=0.246) had dermatologic reactions, primarily photosensitivity reactions. Urticaria developed in two patients in each treatment group. Another patient in the ceftriaxone group had angioedema (edema of the lips, with dysphagia) after five days of treatment; the angioedema

resolved after the discontinuation of ceftriaxone and the institution of therapy with diphenhydramine. Five patients in the ceftriaxone group (7 percent) had mild phlebitis related to the intravenous line. Another patient in the ceftriaxone group discontinued therapy because of drug-induced fever. All but one of these reactions (drug-induced fever on day 12) occurred within the first week of treatment with either ceftriaxone or doxycycline. Seven patients receiving ceftriaxone and four receiving doxycycline had minor, transient abnormalities on laboratory tests.

A 77-year-old woman had gastrointestinal hemorrhage on the sixth day of doxycycline treatment. The patient had had severe abdominal pain on days 4 and 5 and was found to have a duodenal ulcer, a hiatal hernia with reflux, and hepatic cysts. Doxycycline was discontinued on day 6. One patient assigned to ceftriaxone died 27 days after completing 14 days of therapy. This patient had throbbing pain in his left arm and radiating pain to his chest and arm one week after finishing treatment. He was referred to a neurologist. The patient died 21 days later; at autopsy, the cause of death was listed as probable cardiac arrhythmia secondary to ischemia and the effects of drugs (alcohol, nortriptyline, and amitriptyline). There was no evidence of residual Lyme disease, such as carditis.

DISCUSSION

This study specifically addressed the treatment of acute disseminated *B. burgdorferi* infection, unlike previous studies that have lumped patients with early local and disseminated infection together.^{6,7,16-18} Be-

cause we excluded patients who had meningitis, the number of patients with active neurologic disease in this study was small. Most patients (95 percent) had multiple erythema migrans lesions. We found that oral doxycycline (100 mg twice daily for 21 days) had efficacy similar to that of ceftriaxone (2 g administered intravenously or intramuscularly once daily for 14 days) in the treatment of acute disseminated Lyme disease. Both groups had an excellent response to treatment; only one patient in each treatment group had objective evidence of active disease after treatment. It is possible that the one patient in the ceftriaxone group in whom treatment was considered to have failed because of the persistence of seventh-cranial-nerve palsy did not represent a true treatment failure. Rather, the persistent palsy may have been due to permanent damage to the nerve at the time of infection.

The rates of clinical response in this study are close to those in previous reports. Nadelman et al. considered 88 percent of their patients to be clinically cured 1 month after treatment with doxycycline (100 mg three times a day for 20 days).¹⁶ Ninety-two percent of the subjects continued to have a satisfactory outcome one year after treatment. In a retrospective summary of the available literature, Magid et al. reported good responses to oral doxycycline in 95 percent of the cases of acute localized or disseminated disease.¹⁹ Pfister et al. reported that 90 percent of patients with neurologic sequelae of Lyme disease had a favorable outcome after treatment with intravenous ceftriaxone.¹¹ The one treatment failure in the doxycycline group in our study was in a patient who responded to treatment with a three-week course of intravenous ceftriaxone.

It surprised us that a greater number of patients in the ceftriaxone group than in the doxycycline group reported persistent symptoms at the last evaluation. Among the patients whose infections were cured, 18 of 67 patients in the ceftriaxone group (27 percent) reported one or more residual symptoms at the last follow-up visit, as did 10 of 71 patients in the doxycycline group (14 percent, $P \geq 0.05$). Arthralgia was the most frequent persistent symptom in both treatment groups. To evaluate the relative severity of arthralgia, we examined the use of nonsteroidal antiinflammatory agents (NSAIDs) between the three-month and nine-month follow-up visits at the two centers that enrolled the greatest number of patients. Of 32 patients, only 2 in each treatment group reported taking NSAIDs. Three reported taking aspirin — two for antiplatelet activity (one in each group) and one (in the ceftriaxone group) for occasional headaches; the fourth patient (in the doxycycline group) reported taking ibuprofen for elbow pain. Thus, it does not appear that the persistent arthralgia reported in either group was clinically important or that ceftriaxone-treated pa-

tients required more frequent analgesic treatment than doxycycline-treated patients.

The clinical significance of the persistent symptoms is difficult to assess. Early studies of Lyme disease focused primarily on the most severe outcomes of the disease, and in the past, patients with minor symptoms have generally been considered to have a favorable outcome.^{6,16,18} Although there are several possible explanations for the presence of residual symptoms — including continued infection, an immunologic process, permanent tissue damage resulting from the initial infection,²⁰ and coinfection with another tick-borne pathogen — the cause of post-treatment symptoms remains to be addressed in future studies.

Signs and symptoms attributable to the nervous or musculoskeletal system have been noted by other investigators. Two separate, large, retrospective studies of patients treated for early Lyme disease found a surprisingly high incidence of continued signs and symptoms, especially if treatment was delayed.^{8,9} Shadick et al.⁸ found that 34 percent of patients in a suburban area of highly endemic disease just north of Boston who had been treated for early Lyme disease had long-term sequelae, including arthritis, arthralgia, cognitive impairment, and neuropathy. A similar investigation carried out in Westchester County, New York,⁹ found that 114 of the 215 patients studied (53 percent) had persistent signs and symptoms, including neurologic, cardiac, and musculoskeletal disorders. Of the 114 patients with ongoing problems, 35 (31 percent) had clinically important fatigue and arthralgia as their chief symptoms. These retrospective studies suggest that perhaps more attention should be paid to minor post-treatment symptoms. Although arthralgia and fatigue have been reported after the administration of both oral and parenteral antibiotics for early Lyme disease,^{6,16-18} the incidence is generally low. Mild arthralgia, fatigue, and headache were noted after therapy with intravenous ceftriaxone and oral penicillin,¹⁷ and arthralgia was noted after oral treatment with amoxicillin plus probenecid or with doxycycline.⁶ One year after treatment with cefuroxime axetil or doxycycline, approximately 10 percent of patients reported the persistence of mild-to-severe fatigue, arthralgia, and myalgia.¹⁶

Although 58 percent of ceftriaxone-treated patients and 43 percent of doxycycline-treated patients reported drug-related adverse events, these events were generally mild; serious events were uncommon. The types of adverse events in the two treatment groups differed, with ceftriaxone-treated patients most frequently reporting diarrhea (37 percent) and doxycycline-treated patients most frequently reporting photosensitivity and rash (13 percent). Diarrhea is a well-known side effect of ceftriaxone.²¹ Photosensitivity after treatment with doxycycline has been re-

ported by others^{7,16} and may be lessened by the use of ultraviolet A and B blockers or by having patients avoid direct sunlight while receiving treatment.

This study confirms the current practice of using orally administered doxycycline as first-line therapy for acute disseminated Lyme disease. However, for patients in whom tetracycline is contraindicated or who have allergies to penicillin, parenterally administered ceftriaxone offers a treatment option that is as effective as doxycycline in the treatment of acute disseminated Lyme disease.

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