Eur J Clin Microbiol Infect Dis (1998) 17:715–719

Note

Comparison of Oral Cefixime and Intravenous Ceftriaxone followed by Oral Amoxicillin in Disseminated Lyme Borreliosis

J. Oksi, J. Nikoskelainen, M.K. Viljanen

Abstract Two treatment regimens for disseminated Lyme borreliosis (mainly neurologic and musculoskeletal manifestations) were compared in a randomized trial. A group of 30 patients received oral cefixime 200 mg combined with probenecid 500 mg three times daily for 100 days. Another group of 30 patients received intravenous ceftriaxone 2 g daily for 14 days followed by oral amoxicillin 500 mg combined with probenecid 500 mg three times daily for 100 days. There was no statistically significant difference in the outcome of infection between the two groups. However, the total number of patients with relapses or no response at all and the number of positive polymerase chain reaction findings after therapy were greater in the cefixime group. The general outcomes of infection in patients with disseminated Lyme borreliosis after 3–4 months of therapy indicate that prolonged courses of antibiotics may be beneficial in this setting, since 90% of the patients showed excellent or good treatment responses.

Introduction

Optimization of antibiotic therapy for Lyme borreliosis is a controversial subject. The duration of the antibiotic course, the antimicrobial agents used, and the route of administration vary greatly. Most published recommendations favor intravenous antibiotics for 2–4 weeks or, alternatively, oral therapy for 4 weeks. However, clinicians frequently use antibiotic courses longer than recommended. According to a recent questionnaire study, about half of the clinicians working in highly endemic areas in the USA prefer to use antibiotic treatments for 3 or more months in patients with chronic Lyme borreliosis [1]. However, there is no conclusive evidence that long-term treatment can prevent treatment failures.

The clinical outcome of infection after antibiotic therapy is difficult to assess and standardize. Therefore, it is difficult to compare data on treatment efficacies in different clinical studies on disseminated Lyme borreliosis. Microbiologically, the polymerase chain reaction (PCR) is the only reliable method of showing treatment failure, since antibodies to *Borrelia burgdorferi* may persist for years, even after successful therapy. It is poorly understood how often the post-treatment symptoms are caused by immunologic mechanisms or persistent tissue damage and what role a persistent infection may have in the symptomatology of Lyme borreliosis in these patients.

In the present study, two treatment regimens for disseminated Lyme borreliosis were compared in an open randomized trial: oral cefixime 200 mg plus probenicid 500 mg three times daily for 100 days versus intravenous ceftriaxone 2 g daily for 14 days followed by oral amoxicillin 500 mg plus probenicid 500 mg three times daily for 100 days.

Materials and Methods

Sixty-two consecutive patients with disseminated Lyme borreliosis who were originally referred to the Turku University Central Hospital and subsequently diagnosed as having Lyme borreliosis were randomized into two groups. The first group ($n=31$) received cefixime 200 mg combined with probenecid 500 mg three times daily for 100 days. The other group ($n=31$) received intravenous ceftriaxone 2 g daily for 14 days followed by amoxicillin 500 mg combined with probenecid 500 mg three times daily for 100 days. One patient from each group was excluded

J. Oksi (✉), J. Nikoskelainen
Department of Medicine, Turku University Central Hospital, Kiinamyllynkatu 13, FIN-20520 Turku, Finland

J. Oksi
Department of Medical Microbiology, Turku University, Turku, Finland

M.K. Viljanen
National Public Health Institute, Department in Turku, Turku, Finland

from the study because of a change of antimicrobial agents for clinical reasons or because of the patient's refusal to continue therapy. Accordingly, 30 patients in each group completed the courses of therapy. The mean age of the patients was 42.4 years in the cefixime group and 42.7 years in the ceftriaxone/amoxicillin group.

The diagnosis of the patients was based on clinical (according to guidelines developed by the Centers for Disease Control) [2] and laboratory findings. Table 1 shows the symptoms and signs of the patients. Symptoms or signs designated as "second-line" in Table 1 were all additional findings in the patients; i.e., the diagnosis was based on other clinical symptoms and signs. For example, in 22 of the 26 patients with arthralgia or fibromyalgia, the primary symptoms and signs were neurologic. Of the remaining four patients, one had hepatitis, one had a gallium-scintigraphy-positive joint finding, one had erythema nodosum, and one had lymphadenitis and fever. Accordingly, we prefer to classify these patients within the Lyme borreliosis group, since other causes of their symptoms and signs were excluded.

All 60 patients had been symptomatic for more than 2 months prior to the diagnosis and initiation of treatment for disseminated Lyme borreliosis. Twelve (6 in each group) of the 21 patients with a history of erythema migrans had been treated with antibiotics for 10–14 days at the time erythema migrans appeared, and the remaining nine patients were previously untreated for Lyme borreliosis. Twenty-two patients in each group had serum antibodies against *Borrelia burgdorferi*. Nineteen patients in the cefixime group and 18 in the ceftriaxone/amoxicillin group had *Borrelia burgdorferi* DNA in their plasma or cerebrospinal fluid as detected by PCR. Table 1 summarizes these and additional laboratory data of the patients.

Magnetic resonance imaging of the brain was carried out in 40 of 60 patients (20 in each group) using a high-field magnet (1.5 Tesla) with T_2 and T_1 sequences (TR 2500, TE 90 and TR 600, TE 15) and gadolinium enhancement at axial, coronal, and sagittal planes. The magnetic resonance images were abnormal in eight patients in each group. Table 1 lists these findings.

All patients were followed-up for one year after antibiotic therapy commenced. Outcomes of the patients were defined as excellent, good, poor clinical response, or no clinical response. The outcomes of all patients were assessed by the same clinician

Table 1 Symptoms, signs, and laboratory and brain MRI findings in patients with disseminated Lyme borreliosis

	Cefixime group[a] ($n=30$)	Ceftriaxone + amoxicillin group[b] ($n=30$)
Symptoms and signs		
History of erythema migrans	11	10
History of tick bites	6	5
Neurologic manifestations	21	27
Facial paresis	2	3
(Radiculo)meningitis	5	4
Neuritis or radiculitis	4	7
Ataxia or severe vertigo	6	4
Other, "second-line" symptoms and signs (Lyme disease encephalopathy, epilepsy, hemispasticity, dementia, severe cephalalgia, fecal incontinence, photophoby, neuropathy)	4	9
Musculoskeletal manifestations	22	20
Arthritis	10	3
Arthralgia or fibromyalgia ("second-line")	10	16
Myositis	1	0
Other ("acute triggerfinger", myalgia)	1	1
Pericarditis	1	0
Hepatitis	1	2
Recurrent fever episodes	5	4
Laboratory findings		
IgM antibodies	16 of 30	18 of 30
IgG antibodies	10 of 30	9 of 30
IgM and/or IgG antibodies	22 of 30	22 of 30
Intrathecal production of antibodies	2 of 23	0 of 20
Lymphocyte stimulation with *B. burgdorferi*	18 of 19	12 of 13
Culture-positive CSF	1 of 23	0 of 20
PCR-positive plasma	17 of 30	18 of 30
PCR-positive CSF	5 of 23	2 of 20
PCR-positive plasma and/or CSF	19 of 30	18 of 30
Brain MRI findings		
Normal	12 of 20	12 of 20
Multiple small white-matter lesions	6 of 20	6 of 20
Slight atrophy, abnormal in view of age	2 of 20	2 of 20
Cerebral infarction	1 of 20	0 of 20
Encephalitis	0 of 20	1 of 20
Aneurysm	0 of 20	1 of 20

[a] A randomized group who received cefixime 200 mg combined with probenecid 500 mg three times daily for 100 days

[b] A randomized group who first received i.v. ceftriaxone 2 g daily for 14 days followed by amoxicillin 500 mg combined with probenecid 500 mg three times daily for 100 days

CSF, cerebrospinal fluid; PCR, polymerase chain reaction; MRI, magnetic resonance imaging

(J.O.), who also examined all of the patients at different time points.

IgM and IgG antibodies against sonicated *Borrelia burgdorferi* were measured by an in-house EIA using *Borrelia burgdorferi* sensu stricto (B31, ATCC 35210) as antigen [3]. All steps of the EIA were carried out automatically by an Auto-EIA II instrument (Labsystems, Finland). Serum samples were tested at a dilution of 1:100. The results were expressed as relative EIA units. Seropositivity was determined by comparing antibody results from test serum samples with those of 110 healthy controls. The cut-off value for weakly positive results was the mean +2 SD of the controls. Intrathecally produced antibodies against *Borrelia burgdorferi* flagellin were measured using a commercial EIA (Lyme Neuroborreliosis Kit; Dako, Denmark).

Cerebrospinal fluid or blood specimens were inoculated into tubes containing BSK-II medium and incubated at 30 °C. The tubes were examined macroscopically twice weekly and passaged once weekly for at least 2 months. Dark-field microscopy was carried out if the color of the culture medium indicated growth. The final identification of cultured spirochetes was based on the results of PCR. One milliliter of sample (plasma or cerebrospinal fluid) was centrifuged (Eppendorf Microfuge; 13 000 rpm, 10 min), 800 µl of the supernatant was removed, and the remaining 200 µl was mixed with 300 µl of sodium dodecyl sulfate (SDS) solution (0.1 M NaOH, 2 M NaCl, and 0.5% SDS). After incubation at 80 °C for 15 min, 200 µl of 0.1 M Tris-HCl (pH 8) was added. After SDS treatments, DNA was extracted with phenol-chloroform, precipitated with ethanol, and finally dissolved in Tris-EDTA buffer [4]. A 5 µl volume of extracted DNA was added into the reaction tube. The specific target chosen for the PCR was a DNA fragment from the flagellin gene sequence of *Borrelia burgdorferi*.

The PCR was run as described earlier with primers WK1 and FL7, resulting in a 497 bp PCR product [5–7]. Each PCR run included a positive control containing DNA extracted from a reference strain (B31) of *Borrelia burgdorferi* sensu stricto (ATCC 35210). Every sixth tube of each run was used as a negative control subjected to all of the described sample treatments. The negative controls remained negative on each run. One hundred blood donors living in the Turku area provided control samples for the PCR assay with primers WK1 and FL7: one of these samples was positive. The sensitivity of the PCR [7] was found to be 10–100 *Borrelia burgdorferi* cells per reaction. The PCR used was highly specific for *Borrelia burgdorferi* sensu lato. Other *Borrelia* species (*Borrelia hermsii*, *Borrelia parkeri*, and *Borrelia turicatae*) and treponemes (*Treponema denticola*, *Treponema pectinovorum*, *Treponema socranskii*, and *Treponema vincentii*) gave negative results.

Results and Discussion

The follow-up visits (2–4 by each patient) of the 60 patients (30 in each group) took place at the end of therapy, 3–4 months thereafter, and 1 year after the antibiotic therapy was commenced. Prior to each follow-up visit, serum antibodies against *Borrelia burgdorferi* were measured, and PCR to detect borrelial DNA in the plasma was performed. The case reports of two of the patients have been previously published [8, 9].

Table 2 shows the outcome of infection, determined 1 year after antibiotic therapy commenced. This table also presents laboratory findings of patients at the end of the follow-up period. Twelve patients in each group

Table 2 Outcome of infection, follow-up laboratory findings, and adverse effects of antibiotics in patients with disseminated Lyme borreliosis treated with oral antibiotics only or intravenous followed by oral antibiotic therapy

	Cefixime group[a] ($n=30$)	Ceftriaxone + amoxicillin group[b] ($n=30$)
Outcome		
Excellent clinical response	12	12
Good clinical response	14	16
No clinical response	3	1
Clinical relapse after good clinical response	1[c]	1
Follow-up laboratory findings		
Significant decrease of antibody level (if initially positive)	18 of 23	17 of 22
Positive PCR after treatment	3[d] of 30	0 of 30
Adverse effects		
No adverse effects (except possible Herxheimer-like reactions)	28	26
Nausea causing noncompliance with drug regimen	0	1
Diarrhea and positive culture of *C. difficile* in stool	2	2
Other antibiotic-associated diarrhea	0	1
Possible prolonged Herxheimer-like reactions, including fever, transient rash, marked worsening of symptoms, or cardiac arrhythmia	12	18
Allergic reactions	0	0

[a] A randomized group who received cefixime 200 mg combined with probenecid 500 mg three times daily for 100 days

[b] A randomized group who first received i.v. ceftriaxone 2 g daily for 14 days followed by amoxicillin 500 mg combined with probenecid 500 mg three times daily for 100 days

[c] In addition, two patients relapsed during follow-up and received a 28-day course of i.v. ceftriaxone before the end of 1 year of follow-up

[d] Two patients during 1 year of follow-up; the third patient was PCR-positive 33 months after initiation of antibiotic therapy

PCR, polymerase chain reaction

were asymptomatic ("excellent clinical response") at the end of follow-up. Fourteen patients in the cefixime group and 16 patients in the ceftriaxone/amoxicillin group had markedly milder symptoms, or negligible residual symptoms ("good clinical response"). None of the patients was found to have a poor clinical response. However, four patients in the cefixime group and two patients in the ceftriaxone/amoxicilin group showed no clinical response or experienced a recurrence of symptoms after a temporary improvement ("relapse after good clinical response").

Two patients (classified as clinical treatment failures during follow-up) in the cefixime group were positive by PCR with plasma samples obtained several months after the end of the therapy. These two patients and two other patients who relapsed clinically were retreated with a 4-week intravenous course of ceftriaxone 2 g daily. One of the two patients with only clinical signs of relapse had progressive symptoms and signs despite intravenous ceftriaxone, and her plasma sample obtained in February 1997, 33 months after initiation of the first antibiotic therapy for Lyme borreliosis, was again PCR-positive. Thus, this patient was the third in the cefixime group to be positive by PCR after antibiotic therapy (Table 2).

The patients experienced frequent adverse effects (Table 2) during antibiotic therapy. However, these effects included worsening of initial symptoms, new symptoms, and low-grade fever or transient rashes, all of which could be classified as possible prolonged Herxheimer-like reactions during the first few weeks of antibiotic therapy. Allergic reactions or severe adverse effects causing discontinuation of the therapy were not observed. Some patients reported slight to moderate diarrhea, which disappeared during treatment. One patient developed diarrhea 2 weeks before the completion of therapy, but it resolved shortly thereafter. Daily intake of products containing *Lactobacillus* GG were recommended to every patient on antibiotics to prevent or treat diarrhea. Four of the 60 patients developed moderate diarrhea with culture-positive *Clostridium difficile* and were treated with metronidazole. All 60 patients completed the randomized antibiotic course for Lyme borreliosis.

Approximately 3 weeks after the initiation of antibiotic therapy, four patients (2 in each group) developed a generalized rash, but continuation of the therapy did not worsen the rash. Surprisingly, the rash disappeared even without cessation of the drug or during a break of a couple of days in the antibiotic therapy, and it did not reappear. Therefore, these rashes were probable Jarisch-Herxheimer reactions, although they appeared quite late. One patient suddenly developed transient deafness during the therapy, although she had no history of auditory symptoms. The other symptoms (Table 2) that were classified as Herxheimer-like reactions were usually mild, localized, and transient rashes or marked worsening of initial symptoms and signs.

In some patients direct demonstration of *Borrelia burgdorferi* DNA may confirm a persistent infection several months after therapy. In our study this occurred in two patients randomized to receive oral cefixime for 100 days but in no patient randomized to receive intravenous ceftriaxone for 14 days followed by oral amoxicillin for 100 days (difference not statistically significant, chi-square test). However, the small size of the patient groups allows no further conclusions on the superiority of intravenous treatment versus oral treatment on its own. It should be noted that during the follow-up period, the two patients in the cefixime group with PCR-positive findings had a clinical relapse and received intravenous ceftriaxone for 28 days, which probably altered the classification of their outcome since one of them became asymptomatic and one had a good clinical response. Therefore, in fact, six (instead of 4 at the end of follow-up, Table 2) of the 30 patients in the cefixime group experienced relapse or had no clinical response, whereas the number of patients in the ceftriaxone/amoxicillin group was two of 30 (difference not statistically significant, chi-square test).

The general outcomes of infection in patients with disseminated Lyme borreliosis after 3–4 months of therapy indicate that prolonged courses of antibiotics may be beneficial in this setting, since 90% of our patients showed excellent or good treatment responses. The low clinical relapse rate is markedly lower than the level earlier reported among patients treated with shorter courses of antibiotics [10–13]. Only two randomized drug trials (intravenous penicillin G or oral doxycycline for 14 days [14]; intravenous ceftriaxone for 14 days or oral doxycycline for 21 days [15]) have been carried out in patients with disseminated Lyme borreliosis. In one of the trials [14], outcomes were excellent without any treatment failures. In the other trial [15], conducted among patients with acute disseminated Lyme disease (mainly multiple erythema migrans), the rates of clinical cure were 85% and 88% in patients receiving ceftriaxone and doxycycline, respectively. However, at the last follow-up visit, the patients in the ceftriaxone group reported persistent symptoms much more frequently (27% of the patients) than one would expect with the clinical cure rates defined by the investigators.

The clinical outcome of patients with *Borrelia burgdorferi* infection after antibiotic therapy is difficult to assess and standardize. It is therefore difficult to compare clinical studies on treatment efficacies in patients with disseminated Lyme borreliosis. Our patients with disseminated Lyme borreliosis did not have multiple erythema migrans lesions (which is an infrequent manifestation of Lyme borreliosis in Europe), and they had a longer duration of symptoms

than did patients with acute disseminated Lyme borreliosis [15].

It is possible that oral cefixime for 3 months in disseminated Lyme borreliosis is as effective as a 2-week course of intravenous ceftriaxone followed by oral amoxicillin for 3 months. The number of patients in the present study was too small to show a statistically significant difference between the two groups of patients with different treatment strategies. However, the total number of patients with relapses or no response at all and the number of positive PCR findings after therapy were greater in the cefixime group. Longer antibiotic courses were not compared against shorter ones, since the duration of treatment was nearly the same in both groups. Carefully controlled double-blind trials are needed to determine whether patients who receive longer courses of antibiotics are at an advantage, since Lyme borreliosis can probably cause late symptoms through immunologic mechanisms.

Acknowledgements This study was supported by the Maud Kuistila Foundation, the Finnish Medical Foundation, and the Orion Corporation Research Foundation. The language of the manuscript was revised by Simo Merne, M.A. Condensed parts of this paper were presented at the First International Meeting on the Therapy of Infections, 27–30 November 1996, Florence, Italy.

References

1. Ziska M, Demarest F, Donta ST: Physicians' preferences in the diagnosis and treatment of Lyme disease in the United States. Infection (1996) 24:182–186
2. Centers for Disease Control: Case definitions for public health surveillance/Lyme disease. Morbidity and Mortality Weekly Report (1990) 39:19–21
3. Viljanen MK, Punnonen J: The effect of storage of antigen-coated polystyrene microwells on the detection of antibodies against *Borrelia burgdorferi* by enzyme immunoassay (EIA). Journal of Immunological Methods (1989) 124:137–141
4. Hance AJ, Grandchamp B, Lévy-Frébault V, Lecossier D, Rauzier J, Bocart D, Gicquel B: Detection and identification of mycobacteria by amplification of mycobacterial DNA. Molecular Microbiology (1989) 3:843–849
5. Krüger WH, Pulz M: Detection of *Borrelia burgdorferi* in cerebrospinal fluid by the polymerase chain reaction. Journal of Medical Microbiology (1991) 35:98–102
6. Picken RN: Polymerase chain reaction primers and probes derived from flagellin gene sequences for specific detection of the agents of Lyme disease and North American relapsing fever. Journal of Clinical Microbiology (1992) 30:99–114
7. He QS, Marjamäki M, Soini H, Mertsola J, Viljanen MK: Primers are decisive for sensitivity of PCR. Biotechniques (1994) 17:82–85
8. Oksi J, Marjamäki M, Koski K, Nikoskelainen J, Viljanen MK: Bilateral facial palsy and meningitis caused by borrelia double infection. Lancet (1995) 345:1583–1584
9. Oksi J, Kalimo H, Marttila RJ, Marjamäki M, Sonninen P, Nikoskelainen J, Viljanen MK: Intracranial aneurysms in three patients with disseminated Lyme borreliosis – cause or chance association? Journal of Neurology, Neurosurgery and Psychiatry (1998) 64:636–642
10. Maiwald M, Stockinger C, Hassler D, von-Knebel-Doeberitz M, Sonntag HG: Evaluation of the detection of *Borrelia burgdorferi* DNA in urine samples by polymerase chain reaction. Infection (1995) 23:173–179
11. Halperin J, Keller T, Whitman M: PCR-based detection of CSF *Borrelia burgdorferi* as a predictor of treatment response in CNS Lyme borreliosis. In: Axford JS, Rees DHE (eds): Lyme borreliosis. Plenum Press, New York (1994) pp 295–301
12. Rahn DW, Malawista SE: Lyme disease: recommendations for diagnosis and treatment. Annals of Internal Medicine (1991) 114:472–481
13. Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ: Treatment of late Lyme borreliosis – randomised comparison of ceftriaxone and penicillin. Lancet (1988) i: 1191–1194
14. Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B: Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. Neurology (1994) 44:1203–1207
15. Dattwyler RJ, Luft BJ, Kunkel MJ, Finkel MF, Wormser GP, Rush TJ, Grunwaldt E, Agger WA, Franklin M, Oswald D, Cockey L, Maladorno D: Ceftriaxone compared with doxycycline for treatment of acute disseminated Lyme disease. New England Journal of Medicine (1997) 337:289–294