TWO CONTROLLED TRIALS OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

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ABSTRACT

Background It is controversial whether prolonged antibiotic treatment is effective for patients in whom symptoms persist after the recommended antibiotic treatment for acute Lyme disease.

Methods We conducted two randomized trials: one in 78 patients who were seropositive for IgG antibodies to *Borrelia burgdorferi* at the time of enrollment and the other in 51 patients who were seronegative. The patients received either intravenous ceftriaxone, 2 g daily for 30 days, followed by oral doxycycline, 200 mg daily for 60 days, or matching intravenous and oral placebos. Each patient had well-documented, previously treated Lyme disease but had persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesia, often associated with fatigue. The primary outcome measures were improvement on the physical- and mental-health–component summary scales of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) — a scale measuring the health-related quality of life — on day 180 of the study.

Results After a planned interim analysis, the data and safety monitoring board recommended that the studies be discontinued because data from the first 107 patients indicated that it was highly unlikely that a significant difference in treatment efficacy between the groups would be observed with the planned full enrollment of 260 patients. Base-line assessments documented severe impairment in the patients' health-related quality of life. In intention-to-treat analyses, there were no significant differences in the outcomes with prolonged antibiotic treatment as compared with placebo among either the seropositive or the seronegative patients.

Conclusions There is considerable impairment of health-related quality of life among patients with persistent symptoms despite previous antibiotic treatment for acute Lyme disease. However, in these two trials, treatment with intravenous and oral antibiotics for 90 days did not improve symptoms more than placebo. (N Engl J Med 2001;345:85-92.)

ANTIBIOTIC treatment is highly effective for the acute and late septic manifestations of Lyme disease, which is caused by the tick-borne bacterium *Borrelia burgdorferi*.[1] However, some patients have persistent fatigue, myalgias, arthralgias without arthritis, dysesthesias or paresthesias, or mood and memory disturbances after the standard courses of antibiotics.[2,3] Persistent symptoms have been reported both in patients who are seropositive for antibodies against *B. burgdorferi* and in patients who are seronegative. Although the cause of persistent symptoms has not been determined, their temporal association with *B. burgdorferi* infection has led some physicians to treat patients with prolonged courses of antibiotics. Case reports and uncontrolled trials describe success with prolonged antibiotic therapy, often with a recurrence of the symptoms after the discontinuation of therapy.[4] In view of the substantial morbidity and even death[5] associated with prolonged parenteral antibiotic treatment of Lyme disease, it is important to determine the efficacy of such therapy. We report results from randomized, placebo-controlled, double-blind trials of antibiotic therapy in seropositive and seronegative patients who had chronic symptoms after treatment for Lyme disease.

METHODS

Patients

Patients were recruited by means of advertisements and referrals from physicians. Between July 24, 1997, and November 14, 2000, eligible patients were enrolled in two double-blind, placebo-controlled trials, each conducted at three sites. Patients with a positive Western blot for IgG antibodies against *B. burgdorferi* antigens[6] were enrolled in a study of seropositive patients, and patients who were seronegative were enrolled in a separate study. Seronegative patients were required to have documentation of an erythema migrans skin lesion provided by an experienced physician. We initially planned to enroll 260 patients in the studies (194 seropositive and 66 seronegative patients). Patients were eligible if they were at least 18 years old, had a history of acute Lyme disease acquired in the United States, and had at least one of the following: a history of single or multiple erythema migrans skin lesions, early neurologic or cardiac symptoms attributed to Lyme disease, radiculoneuropathy, or Lyme arthritis. Documentation by a physician of previous treatment of acute Lyme disease with a recommended antibiotic regimen was also required. At the time of enrollment, all patients had one or more of the following symptoms that interfered with their functioning: widespread musculoskeletal pain, cognitive impairment, radicular pain, paresthesias, or dysesthesias. Profound fatigue often accompanied one or more of these symptoms. The chronic symptoms had to have begun within 6 months after the initial infection with *B. burgdorferi* and had to have persisted for at least 6 months but less than 12 years.

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Patients were excluded if they had hypersensitivity to the study medications, had previously received parenteral antibiotic therapy for 60 days or more for their current symptoms, had active inflammatory synovitis, had a coexisting condition that could have accounted for their symptoms, or were unable to discontinue medications that could interfere with the evaluation of their response to the treatment regimen (e.g., narcotic analgesics or prednisone in a dose of 10 mg per day or more). Patients with a positive polymerase-chain-reaction (PCR) test for *B. burgdorferi* DNA in plasma or cerebrospinal fluid at base line were also excluded.

Study Protocols

The study protocols were approved by the institutional review boards for human investigations at the participating centers, and each patient gave written informed consent. A data and safety monitoring board planned an interim analysis after at least 110 subjects had been enrolled. Patients were randomly assigned in a 1:1 ratio to receive either antibiotics or placebo. The antibiotic treatment regimen consisted of intravenous ceftriaxone for 30 consecutive days (2 g per day), followed by oral doxycycline for 60 consecutive days (100 mg twice daily). The patients in the placebo group received an intravenous dextrose solution that was the same color as the ceftriaxone solution and oral placebo capsules identical in appearance to the doxycycline, both for the same lengths of time as the antibiotics were administered. Compliance and safety were monitored by home visits by study nurses every other day during the intravenous-treatment phase and twice (on days 45 and 75) during the oral-treatment phase.

Clinical and laboratory evaluations were performed at screening, at base line, and on days 3, 5, 13, 21, 30, 45, 75, 90, and 180. The base-line evaluation included a complete medical history taking, a detailed physical examination, neuropsychological testing, a lumbar puncture, and sampling of peripheral blood.

Clinical Response

The primary outcome was an improvement in the patients' health-related quality of life, which was measured by means of the Medical Outcomes Study (MOS) 36-item Short-Form General Health Survey (SF-36).[7,8] Additional measures of the health-related quality of life included the MOS scales for pain, cognition, and role functioning (the ability to participate in usual daily activities)[9-11] and a modified version of the Fibromyalgia Impact Questionnaire (FIQ).[12,13] Each of the instruments used to measure the health-related quality of life was administered to study participants at base line and at 30, 90, and 180 days. The SF-36 includes eight multiple-item scales that measure physical functioning, physical limitations on usual role-related activities, bodily pain, general health perceptions, vitality, social functioning, emotional limitations on usual role-related activities, and mental health. These scales provide the basis for calculating the summary scores on the physical component and the mental component of the SF-36.[7,8] The scores range from 0 (worst) to 100 (best). For each of the scales, the mean (±SD) score for members of the general population of the United States without chronic conditions was considered to be 50±10.

To assess changes in the health-related quality of life over time, a change score for each SF-36 summary scale was calculated by subtracting the base-line score from the scores at 30, 90, and 180 days. With the use of 2 SE as the criterion,[8,14] individual patients were classified into three categories of change: those whose follow-up scores did not change more than would be expected by chance (unchanged group); those whose follow-up scores improved by more than 2 SE (improved group); and those whose follow-up scores declined by more than 2 SE (worse group). According to previous studies, a change of 2 SE is 6.5 points on the SF-36 physical-health summary scale and 7.9 points on the SF-36 mental-health summary scale.[8,14] The overall change in health status was calculated for each patient. Patients were categorized as having improved health status if they had better scores on both scales or had a better score on one scale and a score on the other scale that was not worse. Patients were categorized as having worsened health status if they had worse scores on one or both of the scales and as having the same health status if their scores on both the physical- and mental-component scales were unchanged.

Three additional multiple-item scales from the MOS were used as secondary measures of cognitive functioning, pain, and functioning in role-related activities.[9-11,15] Clinical response was also measured with the use of the modified version of the FIQ, for which the scores range from 0 (best) to 110 (worst). This version of the FIQ has been validated for patients who have persistent symptoms after treatment for Lyme disease.[13] In a control population without chronic illness, the mean total score on the modified FIQ was 14.0, whereas the mean for patients with chronic Lyme disease after treatment was 50.2.[13] Previous studies have indicated that a change of 16.0 points is clinically meaningful.[16-19]

Laboratory Studies

Western blotting for IgG antibodies against *B. burgdorferi* antigens was performed with the IgG MarBlot (MarDx Diagnostics, Carlsbad, Calif.) according to the manufacturer's instructions.[6] The intrathecal production of antibodies against *B. burgdorferi* was measured as previously described.[20] Base-line specimens of cerebrospinal fluid and plasma specimens obtained at base line and on days 3, 5, 21, and 45 were tested by PCR for the presence of *B. burgdorferi* DNA, as previously described.[21] All samples of cerebrospinal fluid were cultured in Barbour–Stoenner–Kelly II medium to detect *B. burgdorferi* and were monitored by dark-field microscopy for six weeks.[22] Some blood samples were cultured for *B. burgdorferi* in hypertonic medium.[23]

Adverse Events

Adverse events and changes in laboratory values were evaluated and graded with the use of scales derived from the Common Toxicity Criteria of the National Cancer Institute.

Compliance

Compliance with the regimen of medications was assessed by counts of both the number of doses of the intravenous medication the patients received and the pills they had remaining. The actual pill counts were compared with the number of pills that the patient should have had remaining at the time of the home visit by a nurse on day 75.

Statistical Analysis

The primary analysis was an intention-to-treat analysis of all the patients enrolled in the studies. The primary clinical end point was the proportion of patients whose condition was categorized as improved, unchanged, and worse on the basis of the summary scores for the mental and physical components of the SF-36 at 180 days. Patients who withdrew from the study were categorized as having worsened health status on both of these scales.

The study of seropositive patients was designed to have a power of 90 percent, with a 5 percent level of significance in a two-sided test and a sample size of 194, to detect a difference of 25 percent between the antibiotic group and the placebo group in the proportion of patients with improved health status.[24] With the enrollment of 66 patients, the study of seronegative patients would have 80 percent power, with a 5 percent level of significance in a two-sided test, to detect a 35 percent difference between the antibiotic group and the placebo group.[24]

In the interim analysis of the primary outcome, the O'Brien–Fleming adjustment for multiple testing and the B-value stochastic curtailment method were used.[25] The primary outcome for each trial was analyzed by the chi-square test with individual type I error rates of 0.05. The efficacy of the treatment in each trial was estimated as the difference in risk (with 95 percent confidence interval). Secondary outcomes included improvement or worsening as measured by the SF-36 at 30 and 90 days, the total FIQ score, and the MOS pain, cognition, and role-functioning scores at 30, 90, and 180 days.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	SEROPOSITIVE PATIENTS		SERONEGATIVE PATIENTS		ALL PATIENTS	
	ANTIBIOTIC GROUP (N=39)	PLACEBO GROUP (N=39)	ANTIBIOTIC GROUP (N=25)	PLACEBO GROUP (N=26)	ANTIBIOTIC GROUP (N=64)	PLACEBO GROUP (N=65)
Age — yr	55±14	54±14	52±14	51±11	54±14	53±13
Female sex — no. (%)	17 (44)	16 (41)	15 (60)	13 (50)	32 (50)	29 (45)
White race — no. (%)	35 (90)	36 (92)	25 (100)	24 (92)	60 (94)	60 (92)
Symptoms of acute disease — no. (%)						
History of tick bite	39 (100)	39 (100)	25 (100)	26 (100)	64 (100)	65 (100)
Erythema migrans lesion	24 (62)	24 (62)	25 (100)	26 (100)	49 (77)	50 (77)
Arthralgia or myalgia	26 (67)	32 (82)	17 (68)	22 (85)	43 (67)	54 (83)†
Neurologic symptoms	17 (44)	14 (36)	10 (40)	12 (46)	27 (42)	26 (40)
Previous antibiotic treatment						
Number of courses	2.9±1.3	2.6±1.3	3.2±1.5	2.8±1.4	3.0±1.4	2.7±1.3
Duration — days						
Median	71	60	57	49	66	50
Interquartile range	42–113	42–98	33–120	31–83	41–116	35–90
Current symptoms — no. (%)						
Arthralgia or myalgia	36 (92)	35 (90)	23 (92)	25 (96)	59 (92)	60 (92)
Neurocognitive symptoms	31 (79)	22 (56)‡	20 (80)	20 (77)	51 (80)	42 (65)
Dysesthesia	18 (46)	17 (44)	10 (40)	13 (50)	28 (44)	30 (46)
Fatigue or malaise	36 (92)	34 (87)	23 (92)	23 (88)	59 (92)	57 (88)
Headache	16 (41)	12 (31)	12 (48)	14 (54)	28 (44)	26 (40)
Sleep disturbance	20 (51)	19 (49)	10 (40)	18 (69)†	30 (47)	37 (57)
Duration of symptoms — yr	4.5±3.0	4.1±2.5	4.8±3.2	4.3±3.3	4.7±3.0	4.2±2.8
Fibromyalgia tender points	4.7±5.6	3.2±4.3	4.6±4.3	5.6±4.5	4.6±5.1	4.2±4.5
Cerebrospinal fluid findings						
Pleocytosis (white-cell count, >5/mm³) — no. (%)	2 (5)	0	3 (12)	1 (4)	5 (8)	1 (2)
Elevated protein level (>45 mg/dl) — no. (%)	10 (26)	9 (23)	7 (28)	7 (27)	17 (27)	16 (25)
Positive culture for *B. burgdorferi* — no. positive/no. of cultures	0/39	0/39	0/25	0/26	0/64	0/64
Positive PCR results for *B. burgdorferi* DNA — no. positive/no. of tests						
Cerebrospinal fluid	0/39	0/39	0/25	0/26	0/64	0/64
Blood at base line	0/39	0/39	0/25	0/26	0/64	0/65
Blood during treatment	0/141	0/139	0/87	0/91	0/228	0/230
SF-36 scores§						
Physical component	33.1±9.9	34.8±9.9	35.8±8.6	36.7±7.8	34.2±9.4	35.5±9.1
Mental component	43.4±11.6	45.1±11.8	46.7±9.7	38.4±12.7¶	44.7±10.9	42.5±12.5
MOS scores‖						
Pain	49.9±24.8	55.6±22.5	63.0±21.6	46.2±23.5¶	55.1±24.3	52.0±23.2
Cognition	54.2±22.7	69.3±21.6**	53.3±20.0	54.5±21.5	53.9±21.5	63.5±22.6¶
Role functioning	53.5±33.4	51.3±30.4	56.0±32.9	57.3±35.4	54.5±33.0	53.7±32.3
Fibromyalgia Impact Questionnaire††	58.4±19.7	50.3±21.7	47.9±15.2	61.6±20.1‡‡	54.3±18.7	54.7±21.6

*Plus–minus values are means ±SD. Patients were considered to be seropositive if they had a Western blot indicating substantial levels of serum IgG antibodies to *Borrelia burgdorferi* at the time of enrollment in the study; patients were considered to be seronegative if they had a negative Western blot. The antibiotic treatment regimen for those in the antibiotic group was intravenous ceftriaxone (2 g per day) for 30 consecutive days, followed by oral doxycycline (200 mg per day) for 60 consecutive days.

†P=0.04.

‡P=0.03.

§The summary scores on the physical and mental components of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) are shown. The scores range from 0 (worst) to 100 (best). The general population of the United States without chronic conditions is assigned a mean (±SD) score of 50±10.

¶P=0.01.

‖Multiple-item scales from the Medical Outcomes Study (MOS) were used to measure pain, cognitive functioning, and functioning in role-related activities. For each scale, the range of scores is 0 to 100, with higher scores indicating greater pain, better cognitive functioning, and less limitation, respectively.

**P=0.004.

††The modified Fibromyalgia Impact Questionnaire has a range of scores from 0 (best) to 110 (worst). In a control population without chronic illness, the mean total score on the modified questionnaire was 14.0.

‡‡P=0.009.

RESULTS

Characteristics of the Patients

A total of 129 patients were enrolled in the studies (78 seropositive and 51 seronegative). The base-line characteristics of the patients are shown in Table 1. A total of 42 (33 percent) of the patients had previously received intravenous antibiotic treatment for a mean (±SD) of 30±12 days. All other previous treatment consisted of oral antibiotics. There were no significant differences between the seropositive patients and the seronegative patients other than the presence or absence of serum antibodies to *B. burgdorferi*. All cultures of cerebrospinal fluid in standard Barbour–Stoenner–Kelly II medium and of blood in hypertonic medium were negative for *B. burgdorferi*. *B. burgdorferi* DNA was not detected in any base-line sample of cerebrospinal fluid or blood, nor was it detected in any of the blood samples obtained during the treatment phase (on days 3, 5, 21, and 45). Given a cutoff of 1.2 for the ratio of antibody against *B. burgdorferi* in cerebrospinal fluid to antibody in serum, the intrathecal production of antibody was detected in eight patients (five in the combined antibiotic groups and three in the combined placebo groups).

Treatment was discontinued in 14 patients (8 seropositive and 6 seronegative). The reasons for the discontinuation of treatment were similar across the groups of patients. An adverse event was the reason for the discontinuation of treatment in three of the patients in the combined antibiotic groups (5 percent) and three of those in the combined placebo groups (5 percent). Treatment was discontinued in the other eight patients for reasons other than an adverse event.

In the combined population of both studies, the mean base-line summary score for the physical component of the SF-36 was approximately 1.5 SD below that of age-matched members of the general population of the United States who did not have a chronic illness, and the mean base-line summary score for the mental component was approximately 0.5 SD below that of such a control group. Similarly, the base-line FIQ scores were markedly abnormal.

Compliance

All patients who completed 180 days in one of the trials took at least 75 percent of the prescribed medications. There were no differences between the treatment groups in either the seropositive or the seronegative study in patients' compliance with medication.

Efficacy

The interim analysis was performed with the use of data on 107 patients who had completed 180 days in one of the trials. This analysis indicated that there was a 1.4 percent chance in the seropositive study and a 4.0 percent chance in the seronegative study that a significant difference in the efficacy of treatment between the antibiotic group and the placebo group would be observed when the full projected enrollment was reached. An analysis that included the patients in both studies indicated that there was a 3.9 percent chance of observing a significant difference at full enrollment. Because of the lack of efficacy of the antibiotic treatment at the time of the interim analysis, the data and safety monitoring board recommended discontinuation of the active treatment of enrolled patients and of further enrollment in the treatment phase of the studies.

The responses of the 115 patients who were enrolled in the studies at least 180 days before enrollment was stopped are shown in Table 2 and Figure 1. Intention-to-treat analyses at 30, 90, and 180 days showed no significant differences in the measures of the health-related quality of life between the patients in the antibiotic groups and those in the placebo groups in the seropositive study, the seronegative study, or both studies combined.

In the combined study populations, changes in the score on the modified FIQ at 180 days also revealed no significant differences between the antibiotic groups and the placebo groups. We defined a decrease of 25 percent from the base-line score on the modified FIQ as indicative of clinical improvement and an increase of 25 percent as indicative of clinical worsening. Given these definitions, 28 of the 51 patients in the combined antibiotic groups (55 percent) had improved health status as measured by the FIQ at 180 days, as compared with 22 of the 53 patients in the combined placebo groups (42 percent) ($P=0.17$). Conversely, 14 percent of the patients in the antibiotic groups (7 of 51) had worsened health status as measured by the FIQ at 180 days, as compared with 19 percent (10 of 53) in the placebo groups ($P=0.48$). Separate comparisons of the FIQ scores in the antibiotic group and the placebo group of the seropositive study and of those in the two treatment groups in the seronegative study found no statistically significant differences according to treatment.

Adverse Events

At least one study-related adverse event occurred in 16 of the 64 patients in the combined antibiotic groups (25 percent) and 11 of the 65 patients in the combined placebo groups (17 percent). Most of the adverse events were minor and resolved without intervention or sequelae. However, the two patients in whom a study-related serious adverse event occurred were both in the antibiotic group. During intravenous treatment, one had a life-threatening pulmonary embolism and the other had fever, anemia, and gastrointestinal bleeding. Although the overall rate of adverse events was not significantly different in the two treatment groups, rash, diarrhea, and vaginal pruritus occurred more frequently among the patients in the antibiotic groups (9 of 64 patients) than among those in the placebo groups (2 of 65 patients). There were

TABLE 2. CLINICAL RESPONSES AT 180 DAYS.*

SF-36 OUTCOME CATEGORY	SEROPOSITIVE PATIENTS				SERONEGATIVE PATIENTS				ALL PATIENTS			
	ANTIBIOTIC GROUP (N=35)	PLACEBO GROUP (N=35)	DIFFERENCE IN RISK	P VALUE	ANTIBIOTIC GROUP (N=22)	PLACEBO GROUP (N=23)	DIFFERENCE IN RISK	P VALUE	ANTIBIOTIC GROUPS (N=57)	PLACEBO GROUPS (N=58)	DIFFERENCE IN RISK	P VALUE
	no. (%)		% (95% CI)		no. (%)		% (95% CI)		no. (%)		% (95% CI)	
Physical component				0.96				0.34				0.55
Improved	11 (31)	10 (29)	3 (−19 to 24)		9 (41)	5 (22)	19 (−7 to 46)		20 (35)	15 (26)	9 (−8 to 26)	
Unchanged	16 (46)	17 (49)			9 (41)	11 (48)			25 (44)	28 (48)		
Worse	8 (23)	8 (23)	0 (−20 to 20)		4 (18)	7 (30)	−12 (−37 to 13)		12 (21)	15 (26)	−5 (−20 to 11)	
Mental component				0.46				0.71				0.87
Improved	11 (31)	16 (46)	−14 (−37 to 8)		8 (36)	6 (26)	10 (−17 to 37)		19 (33)	22 (38)	−5 (−22 to 13)	
Unchanged	16 (46)	12 (34)			9 (41)	12 (52)			25 (44)	24 (41)		
Worse	8 (23)	7 (20)	3 (−16 to 22)		5 (23)	5 (22)	1 (−23 to 25)		13 (23)	12 (21)	2 (−13 to 17)	
Total				0.96				0.58				0.90
Improved	13 (37)	14 (40)	−3 (−26 to 20)		10 (45)	7 (30)	15 (−13 to 43)		23 (40)	21 (36)	4 (−14 to 22)	
Unchanged	10 (29)	9 (26)			6 (27)	8 (35)			16 (28)	17 (29)		
Worse	12 (34)	12 (34)	0 (−22 to 22)		6 (27)	8 (35)	−8 (−34 to 19)		18 (32)	20 (34)	−3 (−20 to 14)	

*Patients were considered to be seropositive if they had a Western blot indicating substantial levels of serum IgG antibodies to *Borrelia burgdorferi* at the time of enrollment in the study; patients were considered to be seronegative if they had a negative Western blot. The antibiotic treatment regimen for those in the antibiotic group was intravenous ceftriaxone (2 g per day) for 30 consecutive days, followed by oral doxycycline (200 mg per day) for 60 consecutive days. The difference in risk is the proportion of patients with improved or worse scores in the antibiotic group minus the proportion with improved or worse scores in the placebo group. P values were derived by the chi-square test for the comparison of the antibiotic group with the placebo group across the three outcome categories of "improved," "unchanged," and "worse." SF-36 denotes Medical Outcomes Study 36-item Short-Form General Health Survey, and CI confidence interval.

no infections associated with the intravenous catheter, and there were no deaths.

DISCUSSION

The primary goals of these studies in patients with symptoms that persist after recommended antibiotic treatment for Lyme disease were to characterize the impairment in health-related quality of life among such patients and to determine the efficacy of prolonged treatment with antibiotics. The effect of chronic Lyme disease on the health-related quality of life was substantial in both seropositive and seronegative patients. The deficits in physical health status as measured by the SF-36 were equivalent to those observed in patients with congestive heart failure or osteoarthritis and were more than 0.5 SD greater than the impairment observed in patients with type 2 diabetes or a recent myocardial infarction.[7,8] Chronic pain was an important contributor to the impairment of physical health and was similar to that reported by patients with osteoarthritis.[7,8] The impairment of mental health status was similar to that observed in patients with subthreshold lifetime depression (a depressive disorder that does not meet all of the criteria for major depression of the *Diagnostic and Statistical Manual of Mental Disorders,* third edition).[7,8,26] The study patients also had some impairment in cognitive functioning. Their base-line FIQ scores reflected the impairments in health status that were evident in the SF-36 scores and were similar to those in previous studies of patients with fibromyalgia or those with chronic Lyme disease after treatment.[8-13]

The administration of placebo and treatment with a regimen of parenteral ceftriaxone for 30 days, followed by oral doxycycline for 60 days, had similar effects on the patients' health-related quality of life. This antibiotic-treatment regimen was selected because of the in vitro and in vivo activity of both of these antibiotics against *B. burgdorferi* and because they are effective for the treatment of neuroborreliosis.[1] Experience with other chronic infectious diseases caused by persistent bacteria (e.g., syphilis, tuberculosis, and helicobacter infection) suggests that it is unlikely that more prolonged antibiotic therapy or a different combination of antibiotics would result in greater improvement than was observed in this study.

Although we used both conventional and hypertonic culture mediums to isolate *B. burgdorferi* in base-line samples of cerebrospinal fluid and blood and used PCR to detect *B. burgdorferi* DNA in base-line samples of blood and cerebrospinal fluid as well as samples of blood collected during treatment, we did not find evidence of persistent infection with *B. burgdorferi* in these patients. There was no evidence of *B. burgdorferi* in a total of more than 700 different blood and cerebrospinal fluid samples from the 129 patients in these studies.

The placebo groups in these studies provide a view of the natural history of symptoms among patients with chronic Lyme disease after treatment. Dur-

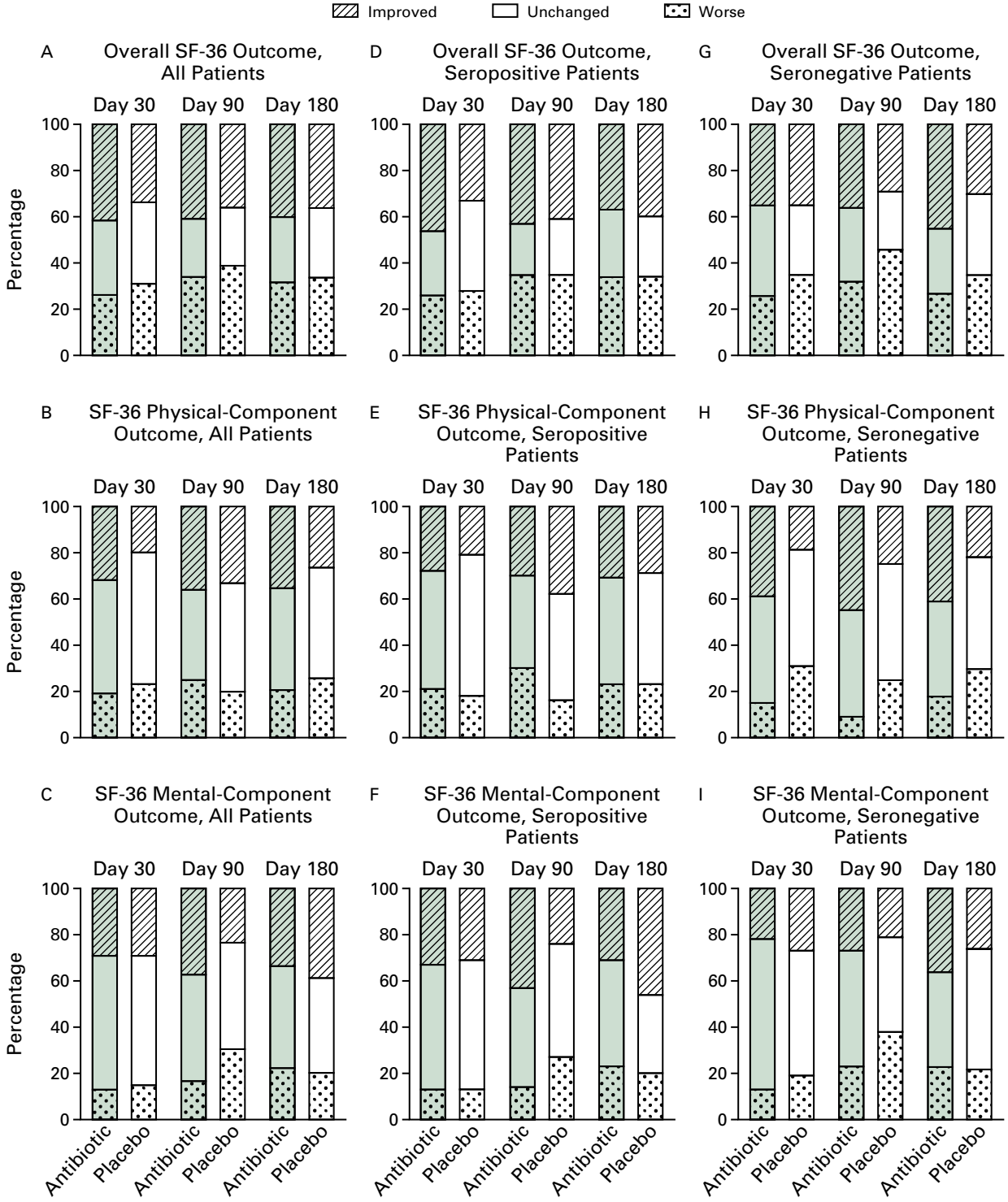

Figure 1. Change or Lack of Change from Base Line in the Health-Related Quality of Life as Measured by the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).

Results are shown for the overall outcome (Panel A, all patients; Panel D, seropositive patients; Panel G, seronegative patients); the physical component (Panel B, all patients; Panel E, seropositive patients; Panel H, seronegative patients); and the mental component (Panel C, all patients; Panel F, seropositive patients; Panel I, seronegative patients). The scores of patients in the antibiotic group are compared with those of patients in the placebo group at the end of intravenous treatment (day 30), at the end of oral treatment (day 90), and 3 months after the completion of treatment (day 180). Statistical tests comparing the scores in the antibiotic group with those in the placebo group showed no statistically significant difference at any of the time points.

ing the six-month evaluation period, we observed improvement in health status in 36 percent of patients, worsening health status in 39 percent, and no significant change in 25 percent. A similar relation between the administration of placebo and health-related quality of life has been reported previously among patients with other rheumatologic diseases that do not appear to be related to persistent infection. For example, a randomized, placebo-controlled trial in patients with mild-to-moderate rheumatoid arthritis found an improved clinical response after 48 weeks of placebo treatment in 39 to 41 percent of patients, as compared with 54 to 56 percent of patients treated with minocycline.[27]

In summary, patients with chronic musculoskeletal pain, neurocognitive symptoms, or both that persist after antibiotic treatment for well-documented Lyme disease have considerable impairment in their health-related quality of life. The patients enrolled in these studies did not have evidence of persistent infection by *B. burgdorferi*, as judged on the basis of the available microbiologic and molecular methods of detection. There were no significant differences between clinical responses of patients who received intravenous and oral antibiotics for 90 days and those of patients who received placebo.

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