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Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

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ABSTRACT

BACKGROUND

The treatment of persistent symptoms attributed to Lyme disease remains controversial. We assessed whether longer-term antibiotic treatment of persistent symptoms attributed to Lyme disease leads to better outcomes than does shorter-term treatment.

METHODS

In a randomized, double-blind, placebo-controlled trial conducted in Europe, we assigned patients with persistent symptoms attributed to Lyme disease — either related temporally to proven Lyme disease or accompanied by a positive IgG or IgM immunoblot assay for *Borrelia burgdorferi* — to receive a 12-week oral course of doxycycline, clarithromycin plus hydroxychloroquine, or placebo. All study groups received open-label intravenous ceftriaxone for 2 weeks before initiating the randomized regimen. The primary outcome measure was health-related quality of life, as assessed by the physical-component summary score of the RAND-36 Health Status Inventory (RAND SF-36) (range, 15 to 61, with higher scores indicating better quality of life), at the end of the treatment period at week 14, after the 2-week course of ceftriaxone and the 12-week course of the randomized study drug or placebo had been completed.

RESULTS

Of the 281 patients who underwent randomization, 280 were included in the modified intention-to-treat analysis (86 patients in the doxycycline group, 96 in the clarithromycin–hydroxychloroquine group, and 98 in the placebo group). The SF-36 physical-component summary score did not differ significantly among the three study groups at the end of the treatment period, with mean scores of 35.0 (95% confidence interval [CI], 33.5 to 36.5) in the doxycycline group, 35.6 (95% CI, 34.2 to 37.1) in the clarithromycin–hydroxychloroquine group, and 34.8 (95% CI, 33.4 to 36.2) in the placebo group ($P=0.69$; a difference of 0.2 [95% CI, –2.4 to 2.8] in the doxycycline group vs. the placebo group and a difference of 0.9 [95% CI, –1.6 to 3.3] in the clarithromycin–hydroxychloroquine group vs. the placebo group); the score also did not differ significantly among the groups at subsequent study visits ($P=0.35$). In all study groups, the SF-36 physical-component summary score increased significantly from baseline to the end of the treatment period ($P<0.001$). The rates of adverse events were similar among the study groups. Four serious adverse events thought to be related to drug use occurred during the 2-week open-label ceftriaxone phase, and no serious drug-related adverse event occurred during the 12-week randomized phase.

CONCLUSIONS

In patients with persistent symptoms attributed to Lyme disease, longer-term antibiotic treatment did not have additional beneficial effects on health-related quality of life beyond those with shorter-term treatment. (Funded by the Netherlands Organization for Health Research and Development ZonMw; PLEASE ClinicalTrials.gov number, NCT01207739.)

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Patients with Lyme disease, which is caused by the *Borrelia burgdorferi* sensu lato complex (including *B. afzelii* and *B. garinii* in Europe), often report persistent symptoms.[1] These symptoms are also referred to as the post–Lyme disease syndrome or chronic Lyme disease and may occur after resolution of an erythema migrans rash or after other — possibly unnoticed — manifestations of early Lyme disease, regardless of whether a patient received initial appropriate antibiotic treatment. Patients present mainly with pain, fatigue, and neurologic or cognitive disturbances.[2,3]

A Quick Take is available at NEJM.org

Previous randomized, clinical trials have not shown convincingly that prolonged antibiotic treatment has beneficial effects in patients with persistent symptoms attributed to Lyme disease.[4-6] Nonetheless, the debate about this issue has continued.[7] Although most guidelines do not recommend antimicrobial therapy for longer than 2 to 4 weeks,[8,9] other guidelines recommend prolonged antibiotic therapy.[10] We performed a randomized, double-blind, clinical trial (Persistent Lyme Empiric Antibiotic Study Europe [PLEASE]) that included three study groups to compare shorter-term treatment (ceftriaxone followed by placebo [placebo group]) with longer-term treatment (ceftriaxone followed by doxycycline [doxycycline group] or ceftriaxone followed by the combination of clarithromycin and hydroxychloroquine [clarithromycin–hydroxychloroquine group]).

Methods

Study Oversight

The trial was approved by the medical ethics review committee Commissie Mensgebonden Onderzoek regio Arnhem–Nijmegen. The study was conducted in accordance with the principles of the most recent version of the Declaration of Helsinki and the International Conference on Harmonisation guidelines on Good Clinical Practice. Written informed consent was provided by all the participants. All the authors take responsibility for the accuracy and completeness of the reported data and vouch for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org) and statistical analysis plan (which is included in the protocol). Details of the protocol and study design have been published previously.[11] The trial was performed at two sites in the Netherlands (Radboud University Medical Center and Sint Maartenskliniek) and was overseen by an independent external data and safety monitoring board.

Study Population

Patients were recruited from October 2010 through June 2013. Eligibility was assessed according to previously described inclusion and exclusion criteria (Table S1 in the Supplementary Appendix, available at NEJM.org).[11] In short, patients with persistent symptoms attributed to Lyme disease (musculoskeletal pain, arthritis, arthralgia, neuralgia, sensory disturbances, dysesthesia, neuropsychological disorders, or cognitive disorders, with or without persistent fatigue) were eligible if these symptoms either were temporally related to an erythema migrans rash or an otherwise proven case of symptomatic Lyme disease or were accompanied by *B. burgdorferi* IgG or IgM antibodies, as confirmed by means of immunoblot assay.

Randomization and Blinding

Patients were randomly assigned to one of three groups in a 1:1:1 ratio. Randomization was computerized and balanced by minimization for age (<40 or ≥40 years), sex, duration of symptoms (<1 or ≥1 year), and baseline Global Health Composite score of the RAND-36 Health Status Inventory (RAND SF-36).[12] The randomization list consisted of consecutive medication numbers entered into a secured Web-based database by an independent Web manager. All personnel involved in the study (except the Web manager and study pharmacist) and all participants were unaware of the study-group assignments.

Intervention

All the patients received treatment with 2000 mg of open-label intravenous ceftriaxone daily for 14 days. Patients were admitted at the study site for ceftriaxone administration during days 1 and 2; subsequent doses were given intravenously by specialized home-care nurses. After the 2-week course of ceftriaxone treatment was completed, the patients received a 12-week oral course of doxycycline (100 mg of doxycycline twice daily combined with a placebo twice daily), clarithromycin–hydroxychloroquine (500 mg of clarithromycin twice daily combined with 200 mg of hydroxychloroquine twice daily), or placebo (two

different placebo capsules twice daily), as randomly assigned in a blinded manner. The study drugs and placebo were prepared as capsules with an identical appearance. Active drugs were purchased as standard tablets through the hospital pharmacy department and were placed inside size 000 capsules; placebos were prepared by filling color-matched size 000 capsules with inactive microcrystalline cellulose. Adherence was verified by means of pill counts, patient diaries, and the Medication Event Monitoring System (AARDEX Group), in which microprocessors in the cap of a medication bottle electronically record each time a bottle is opened.[13] The use of specific concomitant medications was prohibited during the entire study period, as described previously.[11]

OUTCOME MEASURES

Outcomes were assessed with the use of self-completed questionnaires at baseline, at the end of the treatment period at 14 weeks (i.e., when the 2-week course of ceftriaxone and the 12-week randomized phase had been completed), at 26 weeks (12 weeks after the end of the treatment period), at 40 weeks (the end of the trial, 26 weeks after the end of the treatment period), and at 52 weeks after the start of the treatment period. Study visits to evaluate safety were scheduled at weeks 2, 8, and 14 and included a medical history, physical examination, and laboratory investigations. The primary outcome measure was health-related quality of life at the end of the treatment period, as assessed by the physical-component summary score of the RAND SF-36.[12,14] This score is based on the weighted T-scores of the four physical scales of the RAND SF-36 (physical functioning, role limitations due to physical health problems, pain, and general health perceptions). The raw SF-36 physical-component summary score was transformed into a norm-based T-score (range, 15 to 61), with a mean (±SD) score of 50±10 in the general population (higher scores indicate a better physical quality of life).

Main secondary outcomes were physical and mental aspects of health-related quality of life, as assessed with the use of the RAND SF-36,[11] and fatigue, as assessed with the use of the fatigue-severity scale of the Checklist Individual Strength, on which scores range from 8 to 56, with higher scores indicating more fatigue[15] (Table 1).

STATISTICAL ANALYSIS

The primary analyses were performed in the modified intention-to-treat population, which included all patients who were randomly assigned to a study group and received at least one dose of ceftriaxone. In the primary analysis, the three study groups were compared at end of the treatment period by means of analysis of covariance, with sex and baseline SF-36 physical-component summary score as covariates. Missing data were imputed according to the baseline-value-carried-forward method. In secondary analyses, linear mixed models were used to evaluate the duration of the treatment effect in an explorative way, and missing data were imputed with the nearest available observation. All models included the baseline value of the dependent variable, sex, time, study-group assignment, and time-by-treatment interaction. No interim efficacy analysis was performed. Sensitivity analyses included a prespecified per-protocol analysis and alternative imputation techniques. Patients who had major protocol violations, such as receipt of less than 75% of a study drug or placebo, as recorded by microprocessors in the Medication Event Monitoring System caps, or use of prohibited concomitant medication, were excluded from the per-protocol analysis.[11]

A two-sided alpha level of 5% was used to indicate statistical significance, and confidence intervals, when calculated, were 95% confidence intervals. Bonferroni correction was used for pairwise comparisons among the three study groups. Statistical analyses were performed with the use of SPSS software, version 20 (SPSS).

The calculation of power was based on a pilot study that included 80 patients with persistent symptoms attributed to Lyme disease.[11] Patients were classified as having a poor or reasonable clinical condition, as assessed during the first clinical consultation at the outpatient clinic. The difference in SF-36 physical-component summary score between patients with a poor clinical condition and those with a reasonable clinical condition was a mean of 3±8 points, which corresponds to the minimal clinically important difference of 2 to 5 points that has been proposed for the SF-36 physical-component summary score.[14] We calculated that a minimum of 75 patients would need to be assigned to each group (225 patients in total) for the study to have 90% power to detect a difference of 3 points at

Table 1. Baseline Characteristics in the Modified Intention-to-Treat Population.*

Characteristic	Doxycycline Group (N=86)	Clarithromycin–Hydroxychloroquine Group (N=96)	Placebo Group (N=98)
Female sex — no. (%)	40 (47)	42 (44)	47 (48)
Age — yr	48.1±12.8	48.2±13.0	50.0±9.7
White race — no. (%)†	84 (98)	96 (100)	98 (100)
Current symptoms — no. (%)‡			
Arthralgia	80 (93)	87 (91)	84 (86)
Musculoskeletal pain	72 (84)	77 (80)	76 (78)
Sensory disturbances	62 (72)	72 (75)	79 (81)
Neuralgia	7 (8)	16 (17)	18 (18)
Neurocognitive symptoms	76 (88)	81 (84)	85 (87)
Fatigue	84 (98)	91 (95)	92 (94)
Duration of symptoms — yr			
Median	2.7	2.7	2.1
Interquartile range	1.3–7.7	1.3–5.4	0.9–5.5
Lyme disease history — no. (%)‡			
Tick bite	47 (55)	46 (48)	60 (61)
Erythema migrans§	25 (29)	26 (27)	27 (28)
Acrodermatitis chronica atrophicans¶	0	1 (1)	2 (2)
Meningoradiculitis‖	1 (1)	9 (9)	5 (5)
Previous antibiotic treatment — no. (%)	75 (87)	86 (90)	89 (91)
Duration — days			
Median	40	30	31
Interquartile range	27–57	21–44	28–58
No. of courses			
Median	2.0	2.0	2.0
Interquartile range	1.0–2.0	1.0–2.0	1.0–2.5
Intravenous treatment — no. (%)	11 (13)	16 (17)	15 (15)
Positive *Borrelia burgdorferi* serology — no. (%)	70 (81)	73 (76)	75 (77)
IgM	25 (29)	21 (22)	35 (36)
IgG	55 (64)	65 (68)	58 (59)
RAND SF-36 score**			
Physical-component summary	30.3±6.3	32.7±7.5	31.8±8.1
Mental-component summary	37.4±9.9	37.1±9.8	37.6±9.6
Global-health composite	32.1±8.0	33.1±8.3	33.0±9.1
Physical-functioning scale	37.3±8.2	40.3±9.9	38.1±9.4
Role–physical scale	28.8±5.9	31.3±9.5	30.3±8.6
Bodily pain scale	35.2±8.3	37.3±8.2	38.1±9.4
General-health scale	35.5±7.7	35.9±7.6	35.9±8.4
Mental-health scale	44.2±9.8	43.6±10.0	44.0±8.5
Role–emotional scale	41.8±15.1	39.9±15.2	42.4±14.8
Social-functioning scale	33.5±12.8	33.8±12.0	34.2±12.2
Vitality scale	38.3±7.1	39.0±7.8	38.3±7.7

Table 1. (Continued.)

Characteristic	Doxycycline Group (N=86)	Clarithromycin–Hydroxychloroquine Group (N=96)	Placebo Group (N=98)
Checklist Individual Strength††			
Total score	101.9±19.4	96.5±20.7	99.3±22.3
Fatigue-severity scale	46.0±8.1	42.7±10.7	43.8±10.6

* Plus–minus values are means ±SD. All study groups received a 2-week course of ceftriaxone before the randomized 12-week course of study drug or placebo. The modified intention-to-treat population included all patients who were randomly assigned to a study group and received at least one dose of ceftriaxone. Between-group differences in characteristics were analyzed with the use of analysis of variance for continuous variables, chi-square tests for proportions, and Fisher's exact test for small numbers (expected frequency <5). Data that were not normally distributed were analyzed with the use of Kruskal–Wallis tests. There were no significant baseline differences among the study groups at a significance level of 0.05. RAND SF-36 denotes the RAND-36 Health Status Inventory.
† Race was self-reported.
‡ Categories are not mutually exclusive.
§ The condition was considered to be temporally related if it was diagnosed by a physician 0 to 4 months before the onset of symptoms.
¶ This condition was considered to be temporally related if it was diagnosed by a physician or biopsy 0 to 4 months before the onset of symptoms.
‖ The condition was considered to be temporally related if it was diagnosed on the basis of intrathecal borrelia antibody production 0 to 4 months before the onset of symptoms.
** The ranges of the RAND SF-36 scores were as follows: physical-component summary, 15 to 61; mental-component summary, 11 to 66; global-health composite, 8 to 65; physical-functioning scale, 16 to 58; role–physical scale, 26 to 56; bodily pain scale, 20 to 60; general-health scale, 20 to 64; mental-health scale, 16 to 66; role–emotional scale, 19 to 54; social-functioning scale, 12 to 57; and vitality scale, 26 to 70. For all scales, higher scores indicate better quality of life.
†† Scores on the Checklist Individual Strength range from 20 to 140 for the total score and from 8 to 56 for the fatigue-severity scale. For both scales, higher scores indicate more fatigue.

a two-sided alpha level of 5% and a reliability coefficient (correlation between consecutive measurements) of 0.7.[16] To compensate for possible loss to follow-up, a study population of at least 255 patients was targeted.

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS

Approximately 1200 patients were screened. The most frequent reasons for ineligibility were negative serologic findings combined with Lyme disease that was either unproven or temporally unrelated to symptoms, a coexisting condition that could account for the patient's symptoms, or known unacceptable side effects from the active study drugs. Of all eligible patients, fewer than 10% declined to participate. A total of 281 patients underwent randomization, and 280 started the oral course of the study drug or placebo (Fig. 1). Table 1 shows the baseline characteristics of patients included in the modified intention-to-treat analysis; there were no significant baseline differences among the study groups. The randomized oral regimen (active study drug or placebo) was completed by 252 patients (90.0%): 76 of 86 patients (88.4%) in the doxycycline group, 84 of 96 patients (87.5%) in the clarithromycin–hydroxychloroquine group, and 92 of 98 patients (93.9%) in the placebo group (P=0.28) (Fig. 1).

No differences in adherence were recorded among the study groups (P=0.50); 75 patients (87.2%) in the doxycycline group, 78 (81.3%) in the clarithromycin–hydroxychloroquine group, and 84 (85.7%) in the placebo group took at least 75% of the assigned study medication or placebo, as recorded by the microprocessors on the Medication Event Monitoring System caps (Fig. 1).

OUTCOMES

The primary outcome in the modified intention-to-treat analysis (i.e., the mean health-related quality of life at the end of the treatment period, as indicated by the SF-36 physical-component summary score, corrected for baseline SF-36 physical-component summary score and sex) did not differ significantly among the study groups (P=0.69) (Table 2). With respect to the secondary outcomes, the mean SF-36 physical-component summary score among all patients in the

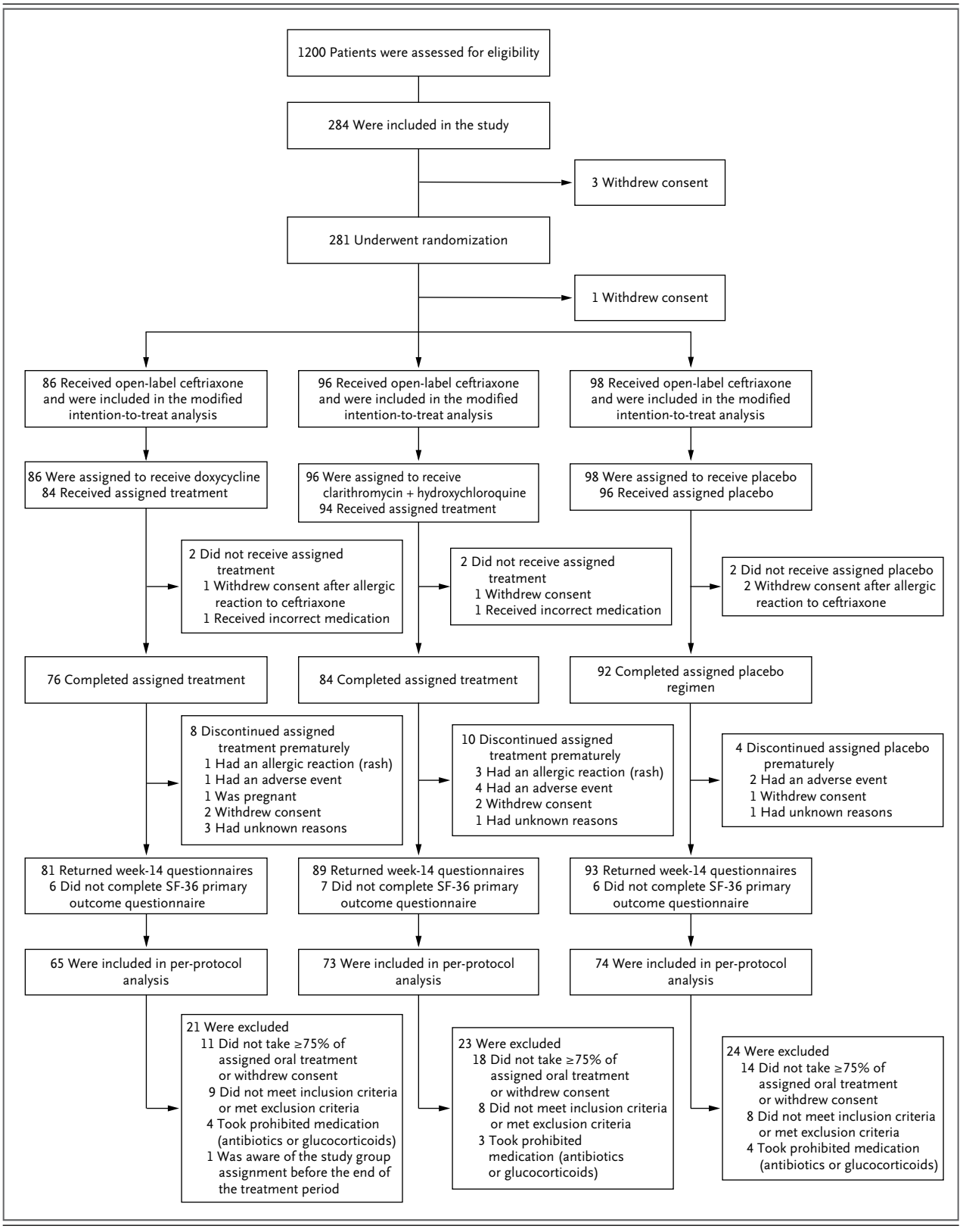

Figure 1 (facing page). Enrollment, Randomization, and Analysis.

Some patients were excluded from the per-protocol analysis because of two or more reasons. Premature discontinuation was defined as discontinuation of the study drug or placebo 7 days or more before the scheduled end of the treatment period, as recorded by microprocessors in the Medication Event Monitoring System caps that were used to track adherence. Week 14 was the end of the treatment period, after the 2-week course of ceftriaxone and the 12-week course of the randomized study drug or placebo had been completed. SF-36 denotes RAND-36 Health Status Inventory.

modified intention-to-treat analysis increased from 31.8 at baseline to 36.4 at the end of the treatment period (difference, 4.6 points; 95% confidence interval [CI], 3.6 to 5.5; P<0.001). At weeks 26, 40, and 52, the SF-36 physical-component summary score remained higher than the baseline score but did not change significantly from the score at the end of the treatment period in any of the study groups (Fig. 2). None of the secondary outcome measures at the end of the treatment period differed significantly among the study groups (Table 2). Mixed-model analyses did not show any additional longer-term treatment effect with respect to the SF-36 physical-component summary score or any of the secondary outcomes; P values for time-by-treatment interaction ranged from 0.14 to 0.90, and there was no significant difference among the study groups in the SF-36 physical-component summary score (P=0.35) or any other secondary outcome measure at any time point during follow-up. All sensitivity analyses yielded results similar to those of the main analyses. Specifically, the results were not quantitatively different when alternate imputation techniques were used for missing data (Table S4 in the Supplementary Appendix). The per-protocol analysis, which included 212 patients (Fig. 1), yielded similar results to the modified intention-to-treat analysis at the end of the treatment period and during follow-up across the three study groups.

SAFETY

Overall, 205 patients (73.2%) reported at least one adverse event, 9 patients (3.2%) had a serious adverse event, and 19 patients (6.8%) had an adverse event that led to discontinuation of the study drug (Table 3). Most adverse events were grade 1 or 2 according to the criteria of the AIDS Clinical Trials Group for grading the severity of adverse events among adults (Table S3 in the Supplementary Appendix).

During the 2-week open-label ceftriaxone phase, 131 patients (46.8%) reported at least one adverse event. Most of these adverse events were judged to be drug-related, and rash and diarrhea were the most common events. No catheter-associated infections were reported. In 6 patients, an allergic adverse event led to the discontinuation of ceftriaxone. Five serious adverse events were reported, four of which were allergic reactions related to ceftriaxone use.

During the 12-week randomized phase, 134 patients (47.9%) had at least one adverse event (Table 3), most of which were judged to be drug-related. The percentage of patients with adverse events from any cause and with drug-related adverse events did not differ significantly among the study groups (P=0.27 and P=0.14, respectively). Photosensitivity and nausea were the most common events in the doxycycline group. Nausea and diarrhea were the most common events in the clarithromycin–hydroxychloroquine group, and rash was significantly more prevalent in that group than in either of the other two groups (P=0.01). Fourteen patients (5.0%) discontinued the randomized active drug or placebo because of an adverse event; the number of patients who discontinued their assigned regimen did not differ significantly among the three study groups (P=0.49). Four serious adverse events were reported, none of which were drug-related.

DISCUSSION

In this randomized, double-blind trial involving patients with persistent symptoms attributed to Lyme disease, prolonged antibiotic treatment (ceftriaxone followed by 12 weeks of either doxycycline or clarithromycin–hydroxychloroquine) did not lead to a better health-related quality of life than that with shorter-term treatment (ceftriaxone followed by placebo). Patients with persistent symptoms attributed to Lyme disease have a poor quality of life, as has been reported in previous studies[5,6,17,18]; the low baseline RAND SF-36 scores of the patients in our trial also reflect the poor quality of life among

Table 2. Treatment Effect at the End of the Treatment Period in the Modified Intention-to-Treat Population.*

Outcome	Doxycycline Group (N = 86)	Clarithromycin–Hydroxychloroquine Group (N = 96)	Placebo Group (N = 98)	P Value†	Doxycycline Group vs. Placebo Group	Clarithromycin–Hydroxychloroquine Group vs. Placebo Group
	score (95% CI)				*difference in score (95% CI)‡*	
Primary outcome: SF-36 physical-component summary§	35.0 (33.5 to 36.5)	35.6 (34.2 to 37.1)	34.8 (33.4 to 36.2)	0.69	0.2 (–2.4 to 2.8)	0.9 (–1.6 to 3.3)
Secondary outcomes						
RAND SF-36§						
Mental-component summary	40.2 (38.6 to 41.9)	40.5 (38.9 to 42.1)	40.1 (38.6 to 41.7)	0.94	0.1 (–2.7 to 2.9)	0.4 (–2.3 to 3.1)
Global-health composite	36.1 (34.5 to 37.8)	36.6 (35.1 to 38.1)	36.0 (34.5 to 37.5)	0.85	0.1 (–2.6 to 2.9)	0.6 (–2.1 to 3.2)
Physical-functioning scale	41.9 (40.5 to 43.3)	42.1 (40.8 to 43.4)	41.0 (39.7 to 42.3)	0.44	0.9 (–1.4 to 3.2)	1.1 (–1.1 to 3.4)
Role–physical scale	33.6 (31.6 to 35.6)	34.4 (32.5 to 36.3)	33.9 (32.0 to 35.8)	0.84	–0.3 (–3.7 to 3.1)	0.5 (–2.8 to 3.8)
Bodily pain scale	39.1 (37.5 to 40.7)	40.5 (39.0 to 41.9)	39.4 (37.9 to 40.9)	0.42	–0.3 (–2.9 to 2.4)	1.1 (–1.5 to 3.6)
General-health scale	37.1 (35.6 to 38.6)	38.4 (37.0 to 39.8)	37.5 (36.2 to 38.9)	0.41	–0.4 (–2.9 to 2.0)	0.9 (–1.5 to 3.3)
Mental-health scale	45.1 (43.8 to 46.4)	45.2 (43.9 to 46.4)	45.1 (43.9 to 46.4)	1.00	0.0 (–2.3 to 2.2)	0.0 (–2.1 to 2.2)
Role–emotional scale	44.7 (42.4 to 47.0)	41.4 (39.2 to 43.6)	42.6 (40.4 to 44.8)	0.11	2.1 (–1.7 to 6.0)	–1.2 (–5.0 to 2.6)
Social-functioning scale	36.3 (34.2 to 38.4)	38.5 (36.6 to 40.5)	37.5 (35.6 to 39.5)	0.32	–1.2 (–4.7 to 2.3)	1.0 (–2.4 to 4.4)
Vitality scale	42.5 (40.9 to 44.0)	42.4 (41.0 to 43.9)	41.9 (40.5 to 43.4)	0.85	0.5 (–2.0 to 3.1)	0.5 (–2.0 to 3.0)
Checklist Individual Strength¶						
Total score	88.7 (84.4 to 92.9)	87.1 (83.0 to 91.1)	88.4 (84.4 to 92.4)	0.84	0.3 (–6.9 to 7.4)	–1.3 (–8.3 to 5.6)
Fatigue-severity scale	39.4 (37.3 to 41.5)	38.6 (36.6 to 40.5)	38.3 (36.3 to 40.2)	0.73	1.1 (–2.4 to 4.6)	0.3 (–3.1 to 3.7)

* All study groups first received a 2-week course of ceftriaxone before the randomized 12-week course of study drug or placebo. P values were derived by analysis of covariance. All scores are adjusted for sex and baseline SF-36 physical-component summary score.
† Bonferroni correction was used for pairwise comparisons among the three study groups.
‡ Group differences should exceed 2 to 4 T-points (exact number of points varies for each scale) to indicate minimally important differences on all RAND SF-36 scales.[14]
§ The ranges of the RAND SF-36 scores were as follows: RAND SF-36 physical-component summary, 15 to 61; mental-component summary, 11 to 66; global-health composite, 8 to 65; physical-functioning scale, 16 to 58; role–physical scale, 26 to 56; bodily pain scale, 20 to 60; general-health scale, 20 to 64; mental-health scale, 16 to 66; role–emotional scale, 19 to 54; social-functioning scale, 12 to 57; and vitality scale, 26 to 70. For all scales, higher scores indicate better quality of life.
¶ Scores on the Checklist Individual Strength range from 20 to 140 for the total score and from 8 to 56 for the fatigue-severity scale. For both scales, higher scores indicate more fatigue.

these patients. At the 14-week visit at the end of the treatment period, the mean SF-36 physical-component summary score had improved significantly from baseline regardless of the study-group assignment, but quality of life remained below that of the general population. Similar improvements over time, regardless of study-group assignment, were reported by Kaplan et al., who compared placebo with ceftriaxone followed by doxycycline for persistent symptoms attributed to Lyme disease.[19]

Whether improvement in the SF-36 physical-component summary score at the end of the treatment period is a beneficial effect of shorter-term antibiotic therapy or a nonspecific effect caused by the low level of baseline functioning, expectations associated with treatment, or placebo effects remains unclear, because all the patients had received 2 weeks of open-label antibiotics before entering into the longer-term randomized study-drug or placebo phase. No significant differences among the study groups were found for any of the secondary outcomes at the end of the treatment period. In addition, no significant changes over time were observed during the 26-week follow-up after the end of the treatment period in any of the study groups.

Although we did not find a significant benefit of longer-term antibiotic therapy, we did find that there were side effects from the use of antibiotics; however, these side effects were similar among the study groups. The majority of patients (68.6%) reported a drug-related adverse event. During the open-label ceftriaxone phase, the incidence of serious adverse events was low; no patient had a serious adverse event related to the use of catheters, and 4 of 280 patients (1.4%) had allergic reactions. During the randomized phase, photosensitivity related to doxycycline use and rash related to clarithromycin–hydroxychloroquine use were the most common adverse events, and no serious adverse event was thought to be related to the randomized study drugs or placebo.

Specific efforts were made to ensure that the patients adhered to the study regimens. Using the Medication Event Monitoring System caps, we recorded that 22 patients (7.9%) discontinued treatment 7 days or more before the end of the treatment period at week 14. In a sensitivity analysis that included the 212 patients who were more than 75% adherent to the study regimen, as determined by electronic medication bottle caps, and had no major protocol violations, no significant difference was shown among the study groups.

The findings of the current trial contribute to the findings of prior work.[4-6,18] Our results are consistent with those from the randomized, placebo-controlled trials by Klempner et al.,[5] who did not identify a benefit from treatment with ceftriaxone followed by doxycycline for a total of 90 days. However, these trials had been performed in North America, and Lyme disease in Europe is caused by different borrelia species.[20] The trials by Klempner et al.[5] have been the subject of divergent opinions because they were discontinued prematurely after an interim analysis had indicated that a significant difference in efficacy was unlikely to be reached. Therefore, although the results are statistically

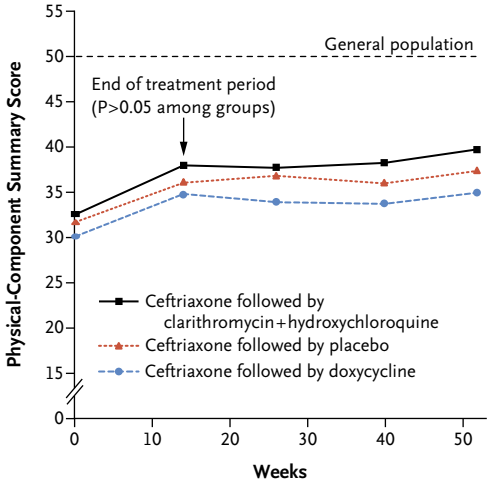

Figure 2. Physical-Component Summary Scores.
Shown is the mean SF-36 physical-component summary score for each study group at baseline and at subsequent study visits (nonimputed values). The SF-36 physical-component summary score is based on the weighted T-scores of the four physical RAND SF-36 scales (physical functioning, role limitations due to physical health problems, pain, and general health perceptions). The raw SF-36 physical-component summary score was transformed into a norm-based T-score (range, 15 to 61), with a mean (±SD) score of 50±10 in the general population (higher scores indicate a better physical quality of life). The P value was derived by means of analysis of covariance at the end of the treatment period at 14 weeks, with adjustment for sex and baseline SF-36 physical-component summary score.

Table 3. Adverse Events in the Modified Intention-to-Treat Population.*

Type of Event	Total (N=280)	Open-Label Phase (N=280)	Randomized Phase			P Value
			Doxycycline Group (N=86)	Clarithromycin–Hydroxychloroquine Group (N=96)	Placebo Group (N=98)	
			no. of participants (percent)			
Any adverse event†	205 (73.2)	131 (46.8)	47 (54.7)	45 (46.9)	42 (42.9)	0.27
Any drug-related adverse event†	192 (68.6)	127 (45.4)	42 (48.8)	42 (43.8)	34 (34.7)	0.14
Discontinued treatment owing to adverse event†	19 (6.8)	6 (2.1)	3 (3.5)	7 (7.3)	4 (4.1)	0.49‡
Any serious adverse event	9 (3.2)	5 (1.8)	3 (3.5)	1 (1.0)	0	0.08‡
Most common adverse events						
Diarrhea	91 (32.5)	72 (25.7)	4 (4.7)	9 (9.4)	6 (6.1)	0.43
Nausea	44 (15.7)	20 (7.1)	9 (10.5)	10 (10.4)	5 (5.1)	0.31
Rash†	31 (11.1)	23 (8.2)	1 (1.2)	8 (8.3)	1 (1.0)	0.01‡
Mucosal fungal infection	20 (7.1)	8 (2.9)	5 (5.8)	4 (4.2)	3 (3.1)	0.66‡
Photosensitivity	19 (6.8)	2 (0.7)	16 (18.6)	0	1 (1.0)	<0.001
Headache	16 (5.7)	12 (4.3)	0	2 (2.1)	2 (2.0)	0.55‡
Dizziness	16 (5.7)	3 (1.1)	3 (3.5)	5 (5.2)	5 (5.1)	0.88‡
Visual impairment	16 (5.7)	1 (0.4)	1 (1.2)	4 (4.2)	10 (10.2)	0.02‡

* Data are the number of patients who had at least one event of a given type (% of study group). All patients received a 2-week course of ceftriaxone treatment (open-label phase), after which patients were randomly assigned to receive a 12-week oral course of doxycycline, clarithromycin–hydroxychloroquine, or placebo (randomized phase).

† The total is not a sum of the two trial phases because some patients had an adverse event during both phases. P values were derived from the chi-square test for the comparisons of the three study groups during the randomized phase.

‡ Fisher's exact test was used when the numbers were small (expected frequency <5).

valid, the value of prolonged antibiotic therapy for patients with Lyme disease has been based on a study population of approximately 115 patients. Others have suggested that the trials by Klempner et al. were underpowered as a result of an optimistic estimate of the size of the treatment effect.[7] In a pilot study, we determined that the clinically relevant treatment effect on the SF-36 physical-component summary score was 3 points, as was recommended by the SF-36 Health Survey.[14] None of the differences among the study groups were found to exceed the minimal clinically relevant difference for each of the RAND SF-36 scales, which varies between 2 and 4 across scales.[14] Whereas earlier trials might have been influenced by baseline differences, we included baseline health-related quality of life as a covariate.

Three other small, placebo-controlled trials have addressed prolonged treatment for persistent symptoms attributed to Lyme disease and showed positive effects for some outcomes only.[4,6,18] Krupp et al.[4] reported a significant treatment effect of ceftriaxone on fatigue, but not on cognitive function, at follow-up. Fallon et al. found a beneficial effect of ceftriaxone on neurocognitive performance at week 12, but the effect was not sustained to week 24.[18] Cameron et al. reported beneficial effects of amoxicillin on mental-health scores, but not on physical health, in a subgroup of patients.[6] Although several noncomparative, open-label studies have shown beneficial effects of prolonged antimicrobial treatment, including the regimens used in the current study,[21-24] randomized, controlled trials of prolonged antimicrobial treatment have not confirmed those effects.

The current trial has several limitations.

First, patients received open-label antibiotics for 2 weeks before the randomized phase. Consequently, the study was designed to compare longer-term therapy with shorter-term therapy, rather than with placebo as was done in previous trials.[4,5,18] Although we did not identify any benefit of longer-term therapy, the question of whether a 2-week regimen of antibiotics is superior to withholding any therapy in our patient population remains unanswered. We chose not to include a study group that received only placebo because it was judged to be unethical to withhold treatment from patients who might have an infection at baseline that had not yet been treated. We selected ceftriaxone because it is considered the treatment of choice for disseminated Lyme disease.[5,8] Thus, although 14 weeks of antimicrobial therapy did not provide a clinical benefit for patients with persistent symptoms attributed to Lyme disease, our results cannot show whether our study may have included patients with undiagnosed active *B. burgdorferi* infection, who have benefited from ceftriaxone treatment.

This trial, as well as previous trials,[4-6,18] was aimed at the treatment of patients with persistent, notably distressing or impairing symptoms that emerged after well-documented Lyme disease. We acknowledge that the cause of these persistent symptoms is unclear and that these patients may be heterogeneous with respect to the pathogenesis or the duration and severity of the symptoms — which reflects the heterogeneity of the population seen in clinical practice. We prevented an imbalance in baseline characteristics among the study groups by performing a randomization balanced for duration of symptoms (<1 or ≥1 year) and baseline RAND SF-36 score. Finally, it may be argued that 14 weeks of treatment is insufficient to show a beneficial treatment effect. However, whereas prolonged antimicrobial treatment is not uncommon for various infectious diseases,[25,26] the purpose of prolonged therapy for such diseases is for the prevention of microbiologic relapse rather than for a delayed onset of clinical alleviation of signs or symptoms. We are not aware of any infectious disease in which the initial effect on signs, symptoms, and laboratory findings is delayed beyond the first 3 months of effective therapy.

In conclusion, the current trial suggests that 14 weeks of antimicrobial therapy does not provide clinical benefit beyond that with shorter-term treatment among patients who present with fatigue or musculoskeletal, neuropsychological, or cognitive disorders that are temporally related to prior Lyme disease or accompanied by positive *B. burgdorferi* serologic findings.

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