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MAJOR ARTICLE

Effectiveness of Long-term Doxycycline Treatment and Cognitive-Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial

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Background. Approximately 20% of patients with acute Q fever will develop chronic fatigue, referred to as Q fever fatigue syndrome (QFS). The objective of this randomized controlled clinical trial was to assess the efficacy of either long-term treatment with doxycycline or cognitive-behavioral therapy (CBT) in reducing fatigue severity in patients with QFS.

Methods. Adult patients were included who met the QFS criteria according to the Dutch guideline: a new onset of severe fatigue lasting ≥6 months with significant disabilities, related to an acute Q fever infection, without other somatic or psychiatric comorbidity explaining the fatigue. Using block randomization, patients were randomized between oral study medication and CBT (2:1) for 24 weeks. Second, a double-blind randomization between doxycycline (200 mg/day, once daily) and placebo was performed in the medication group. Primary outcome was fatigue severity at end of treatment (EOT; week 26), assessed with the Checklist Individual Strength subscale Fatigue Severity.

Results. Of 155 patients randomized, 154 were included in the intention-to-treat analysis (doxycycline, 52; placebo, 52; CBT, 50). At EOT, fatigue severity was similar between doxycycline (40.8 [95% confidence interval {CI}, 37.3–44.3]) and placebo (37.8 [95% CI, 34.3–41.2]; difference, doxycycline vs placebo, −3.0 [97.5% CI, −8.7 to 2.6]; $P = .45$). Fatigue severity was significantly lower after CBT (31.6 [95% CI, 28.0–35.1]) than after placebo (difference, CBT vs placebo, 6.2 [97.5% CI, .5–11.9]; $P = .03$).

Conclusions. CBT is effective in reducing fatigue severity in QFS patients. Long-term treatment with doxycycline does not reduce fatigue severity in QFS patients compared to placebo.

Clinical Trials Registration. NCT01318356.

Keywords. cognitive-behavioral therapy; *Coxiella burnetii*; doxycycline; placebo; Q fever fatigue syndrome.

Q fever, caused by the gram-negative intracellular coccobacillus *Coxiella burnetii*, is notorious for long-term sequelae. Besides chronic Q fever (ie, persistent *C. burnetii* infection), which occurs in 1%–5% of cases [1], a debilitating fatigue syndrome has been described [2–11]. This Q fever fatigue syndrome (QFS) persists for years in approximately 20% of cases following acute Q fever [2–6, 9–11]. Many QFS patients fulfill the case definition of chronic fatigue syndrome (CFS) [2, 8, 10, 12]. QFS has major health impacts with severe fatigue, substantial disabilities, and reduced quality of life [8, 11, 13–15]. Following the largest Q fever outbreak ever reported [1], which occurred in the Netherlands with >4000 notified patients, the need for an evidence-based treatment regimen increased. The large number of QFS patients had major economical consequences [16]. The pathophysiology of QFS remains to be elucidated, hampering treatment based on etiology.

Long-term treatment with tetracyclines has been reported to improve performance status and reduce fatigue in QFS [4, 17], but subsequent reports have been conflicting [5, 18]. No randomized controlled trials (RCTs) have been performed, and available studies all have major limitations, precluding extrapolation of these results. Cognitive-behavioral therapy (CBT), aimed at fatigue-related cognitions and behavior thought to

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perpetuate symptoms, can reduce symptoms and improve functioning in CFS [19]. A considerable overlap in fatigue-perpetuating factors between QFS and CFS implies that CBT might also reduce fatigue severity in QFS [12].

We performed an RCT (the Qure study) to assess the efficacy of long-term treatment with either doxycycline or CBT in patients with QFS.

METHODS

Study Design, Setting, and Participants

The trial was approved by the Medical Ethical Review Committee region Arnhem-Nijmegen (2011/069, NL35755.091.11) and conducted in compliance with the most recent provisions of the Declaration of Helsinki, the International Conference on Harmonisation guidelines on Good Clinical Practice, and appropriate regulatory requirements. The trial was performed at 2 sites of the Radboud university medical center (Radboudumc): the Radboud Expertise Center for Q fever and the Expert Center for Chronic Fatigue (ECCF). The study protocol has been published [20]. This trial was overseen by an independent monitor.

All men and nonpregnant, nonlactating women, aged ≥18 years suspected of Q fever-related fatigue were screened for QFS, using standard clinical and laboratory protocols. Eligibility was assessed according to previously described inclusion and exclusion criteria (Supplementary Table 1) [20]. QFS was defined as severe fatigue (score ≥35 on the Checklist Individual Strength [CIS] subscale Fatigue Severity) for ≥6 months, causing significant disabilities (score ≥450 on the Sickness Impact Profile [SIP8]) in daily functioning, not being caused by chronic Q fever or other somatic or psychiatric morbidity, directly related to an acute Q fever infection, and the fatigue should have been either absent before or have significantly increased since the acute Q fever infection. Chronic Q fever was excluded based on negative serum polymerase chain reaction (PCR), Q fever serology (immunoglobulin G phase I titers <1:1024), and absence of signs of endocarditis or vascular infection. All enrolled patients provided written informed consent.

Randomization and Blinding

Patients were randomly assigned to receive either study medication or CBT (2:1 ratio). Second, a double-blind randomization was performed within the medication group, allocating patients to doxycycline or placebo (1:1 ratio). The randomization sequence was computer-generated using block randomization, performed by an independent biostatistician. Allocation concealment was achieved by sealed opaque envelopes with individual codes according to the randomization list, made by an administrative assistant with no affiliation to the project group. The double-blind randomization within the medication condition was performed by the pharmacist. The first randomization list and the double-blind randomization list were made available by the independent biostatistician and the study pharmacist, respectively, to the principal investigator after completion of the study. All trial-related personnel, except the study pharmacist, and participants were masked with regard to the medication group. Allocation to CBT was not blinded.

Interventions

Patients in the medication group were treated with doxycycline 200 mg or placebo, both orally administered once daily, for 24 weeks. Study medication was prepared and labeled by the Clinical Trials Unit department of the Clinical Pharmacy of Radboudumc, according to Good Manufacturing Practice guidelines. Doxycycline was reencapsulated and placebo was prepared as capsules with identical appearance. Study visits were at 4, 8, and 16 weeks after start of treatment, including medical history, physical examination, and laboratory investigation. Patients were excluded if they met the exclusion criteria during treatment with medication (Supplementary Table 2) [20]. Compliance was verified by pill counting. Patients allocated to CBT received approximately 24 weeks of individual CBT, based on the manual of CBT for CFS [20, 21], by trained and supervised cognitive-behavioral therapists [20]. Treatment frequency was determined on individual basis, with intended sessions once every 2 weeks. Details of the assessments per visit have been published [20].

Outcomes

Outcomes were assessed by self-completed questionnaires and laboratory investigation at baseline, 26 weeks (end of treatment period [EOT]), and 28 weeks (end of study [EOS]). The primary outcome measure was fatigue severity at EOT, measured by the CIS subscale Fatigue Severity [22], with a cutoff score of ≥35 as classification for severe fatigue. Clinical meaningful improvement, taking into account whether the magnitude of change on the CIS subscale Fatigue Severity is clinically relevant, was defined as a reliable change index (RCI) × 1.96 plus a CIS Fatigue Severity score of <35 [23]. The RCI was calculated based on the standard deviation of the baseline CIS fatigue score with 0.88 as reliability factor [22]. Secondary outcomes were level of functional impairment at EOT, measured with weighted total score on 8 subscales of the SIP8 with a cutoff score of ≥450 indicating significant disabilities [24], the level of psychological distress at EOT, measured with the total score of the Symptom Checklist 90 (SCL-90) with a low total score reflecting psychological well-being [25], and *C. burnetii* serology (immunofluorescence assay; Focus Diagnostics, Cypress, California) and serum PCR (in-house, real-time PCR directed against insertion sequence IS1111a) at EOS.

Adverse Events

Safety was assessed by monitoring adverse events (AEs) and concomitant drug use. AEs in the medication condition were recorded during the prescheduled study visits, and, if applicable, during the trial when reported by the patient. For patients

allocated to CBT, AEs were monitored at 8 weeks after start of therapy and at EOT.

Statistical Analysis

Following the Dutch Q fever outbreak, the number of new cases decreased drastically and several studies concurrently investigated health-related aspects following acute Q fever, limiting the number of eligible patients. Because there were only a limited number of patients available for participation, a traditional power analysis was not possible. Instead, we performed an analysis to estimate the effect size that has to be assumed for a power of 80%. The maximum number of available patients was estimated as 180 (60 patients per arm). Assuming a 20% dropout rate, this left a sample size of 50 patients per arm. This sample size was divided by a design factor of 0.884 ($1–0.34^2$), with 0.34 being the correlation between fatigue severity at baseline and EOT [26], leaving a sample size of 56. Using G*Power software (version 3.1.5) based on a sample size of 56, a power of 0.80, and an α of .05, a moderate effect size of 0.53 needed to be assumed to obtain a power of 0.8 for demonstrating a significant difference.

Primary analyses were performed on the data of all participants who completed the postintervention measurements, irrespective of whether or not they completed the treatment: intention-to-treat was the basis for all analyses. In the primary analysis, each of the experimental groups (doxycycline and CBT) was compared to the placebo group at EOT using analysis of covariance with the EOT CIS fatigue score as dependent measure, baseline CIS fatigue score as covariate, and the condition as fixed factor. For the secondary outcome measures, the same analysis was repeated but with the EOT secondary outcome measures as dependent variable and scores at baseline as covariate. No interim analyses were undertaken. Two-sided 5% significance levels were used. Because primary and secondary analyses entailed 2 separate hypotheses, Bonferroni correction was used, which means that reported *P* values are twice the *P* values found in the analyses. Also, when reporting estimated effects, 97.5% confidence intervals (CIs) were used. Statistical analyses were performed blinded for group allocation, using SPSS version 22 and SAS version 9.2 software.

RESULTS

Figure 1 shows the trial profile. In total, 438 patients with suspected QFS were screened for eligibility. The most prevalent reason for ineligibility was another cause for the fatigue. Of the 221 patients meeting the QFS criteria, 21 were not eligible for study participation and 44 refused participation (22%). Between May 2011 and January 2015, 156 patients signed informed consent and were randomized; of these, 155 started treatment, either doxycycline (n = 52), placebo (n = 52), or CBT (n = 51). One patient refused double-blind randomization after allocation to the medication group, and received no treatment. There were no significant baseline differences between the treatment groups (Table 1; Supplementary Table 3). The intention-to-treat analysis included 154 patients. There was a median of 1.0 pill left at EOT in both the doxycycline and placebo groups. In the CBT group, patients received a median of 9 sessions (interquartile range, 7.50–11.25). Treatment was completed by 142 patients (92%): doxycycline, 49 (94%); placebo, 50 (96%); and CBT, 43 (84%). During CBT, 1 patient withdrew informed consent, and the other 7 patients discontinued treatment because they could not adhere to the therapy for various reasons.

Primary Endpoint

The primary endpoint in the intention-to-treat analysis, fatigue severity at EOT adjusted for baseline fatigue severity, did not significantly differ between doxycycline (40.8 [95% CI, 37.3–44.3]) and placebo (37.8 [95% CI, 34.3–41.2]; difference, doxycycline vs placebo, −3.0 [97.5% CI, −8.7 to 2.6]; $P = .45$), and was significantly lower after CBT (31.6 [95% CI, 28.0–35.1]) than after placebo (difference, CBT vs placebo, 6.2 [97.5% CI, .5–11.9]; $P = .03$) (Table 2; Figure 2). Clinically meaningful improvement, that is, a reduction of 9 points on the CIS subscale Fatigue Severity plus a score of <35, was reached by 44% of patients: doxycycline, 31%; placebo, 46%; CBT, 56% ($P = .04$; Supplementary Table 4).

Secondary Endpoints

At EOT, the mean SIP8 total score did not differ significantly between either doxycycline and placebo (difference, doxycycline vs placebo, −137.7 [97.5% CI, −409.9 to 134.6]; $P = .51$) or CBT and placebo (difference, CBT vs placebo, 177.0 [97.5% CI, −98.3 to 452.3]; $P = .30$). Doxycycline yielded no difference in SCL-90 total score compared with placebo (difference, doxycycline vs placebo, −6.5 [97.5% CI, −18.7 to 5.7]; $P = .45$), whereas the SCL-90 total score significantly improved after CBT compared with placebo (difference, CBT vs placebo, 15.6 [97.5% CI, 3.3–27.8]; $P = .010$). At EOS, the majority of patients had stable or declining antibody titers compared to baseline, and the number of patients with declining titers was similar in all groups (Supplementary Tables 3 and 5). *Coxiella burnetii* PCR remained negative in all patients.

Adverse Events

Overall, 138 (90%) patients reported at least 1 AE, and 2 (1%) AEs of gastrointestinal origin led to study discontinuation, both in the doxycycline group. In the doxycycline group, both the total number of AEs and the median number of AEs per patients were highest, and fewer patients reported no AEs (Supplementary Table 6). No serious adverse events (SAEs) occurred during treatment with doxycycline. Two SAEs were reported in the placebo group. One patient who had not yet started treatment was admitted to hospital with urosepsis. The

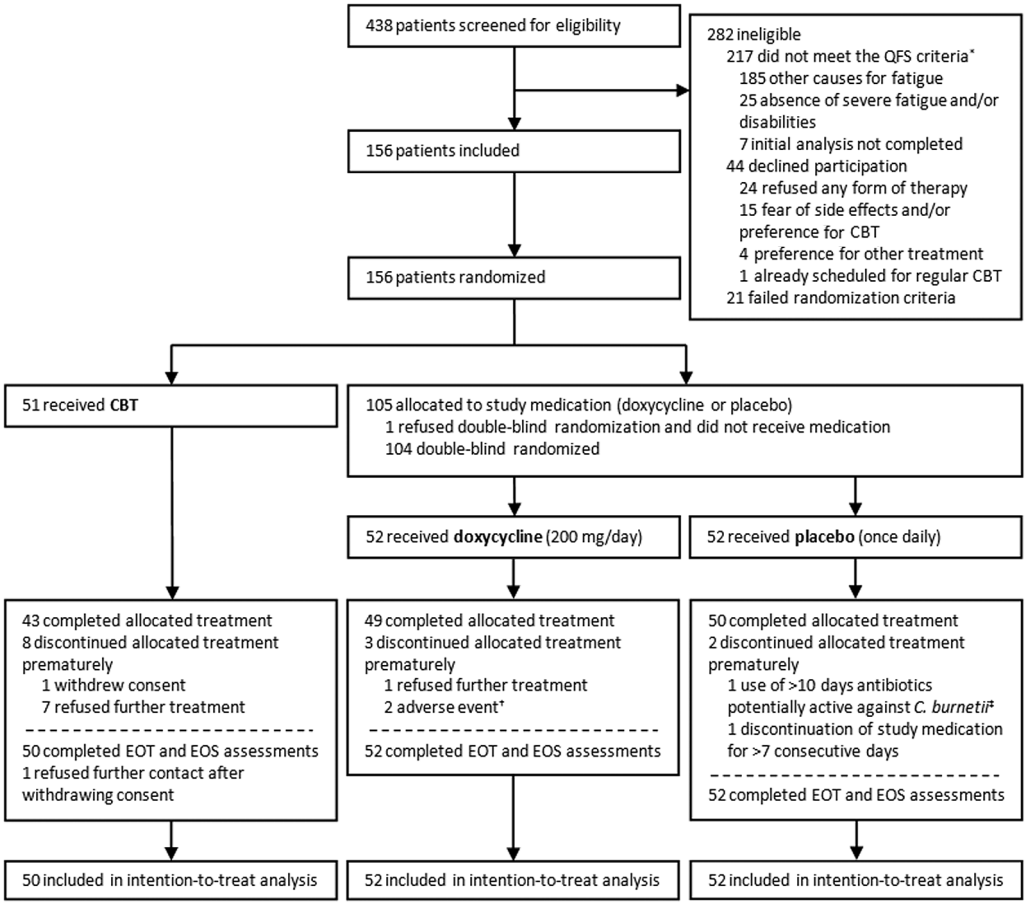

Figure 1. Trial profile. Primary analyses were based on intention-to-treat and included the data of all patients who completed the end of treatment (EOT) and end of study (EOS) assessments. *As described in the study protocol [20], including a cutoff score of ≥35 on the Checklist Individual Strength subscale Fatigue Severity, and a cutoff score of ≥450 on the Sickness Impact Profile 8 total score to classify severe fatigue and substantial fatigue-related disabilities. †Leading to discontinuation of study medication for >7 consecutive days. ‡Use of ciprofloxacin of 14 days because of prostatitis. Abbreviations: CBT, cognitive-behavioral therapy; EOS, end of study; EOT, end of treatment; QFS, Q fever fatigue syndrome; SIP8, Sickness Impact Profile.

Table 1. Baseline Characteristics of All Included Patients with Q Fever Fatigue Syndrome[a]

Characteristic	Doxycycline (n = 52)	Placebo (n = 52)	CBT (n = 51)
Female sex, No. (%)	29 (56)	20 (38)	25 (49)
Age, y, mean ± SD	43.6 ± 10.2	44.6 ± 12.3	43.3 ± 13.7
Duration of symptoms, mo			
Median	36.00	37.50	40.00
Interquartile range	24.25–57.00	25.50–50.75	22.00–59.00
CIS subscale Fatigue Severity, mean ± SD	51.4 ± 4.7	50.2 ± 4.8	49.7 ± 4.7
SIP8 total score, mean ± SD	1304.9 ± 537.7	1295.1 ± 593.7	1369.4 ± 646.7
SCL-90 total score, mean ± SD	152.2 ± 31.4	159.1 ± 41.0	156.4 ± 35.0
IFA, No. (%)			
IgM phase I	24 (46)	28 (54)	25 (49)
IgM phase II	30 (58)	32 (62)	32 (63)
IgG phase I	45 (87)	42 (81)	40 (78)
IgG phase II	52 (100)	50 (96)	49 (96)
Negative *Coxiella burnetii* PCR, No. (%)	52 (100)	52 (100)	51 (100)

Abbreviations: CBT, cognitive-behavioral therapy; CIS, Checklist Individual Strength; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; SCL-90, Symptom Checklist 90; SD, standard deviation; SIP8, Sickness Impact Profile.

[a]Between-group differences in primary and secondary outcome characteristics at baseline were analyzed with analysis of variance for continuous variables.

Table 2. Treatment Effect on Primary and Secondary Endpoints for Patients Included in the Intention-to-Treat Analysis[a]

Outcome	Doxycycline (n = 52), Mean (95% CI)	Placebo (n = 52), Mean (95% CI)	CBT (n = 50), Mean (95% CI)	Dox vs Placebo, *P* Value[b]	Dox vs Placebo, Difference (97.5% CI)	Dox vs Placebo, Standardized Effect Size[c]	CBT vs Placebo, *P* Value[b]	CBT vs Placebo, Difference (97.5% CI)	CBT vs Placebo, Standardized Effect Size[c]
Primary endpoint									
CIS subscale Fatigue Severity	40.8 (37.3–44.3)	37.8 (34.3–41.2)	31.6 (28.0–35.1)	.45	−3.0 (−8.7 to 2.6)	0.24	.03	6.2 (.5–11.9)	0.49
Secondary endpoints: questionnaires									
SIP8 total score	1101.5 (933.5–1269.6)	963.8 (795.8–1131.9)	786.8 (615.3–958.3)	.51	−137.7 (−409.9 to 134.6)	0.20	.30	177.0 (−98.3 to 452.3)	0.26
SCL-90 total score	149.2 (141.6–156.7)	142.6 (135.1–150.1)	127.1 (119.4–134.7)	.45	−6.5 (−18.7 to 5.7)	0.18	.01	15.6 (3.3–27.8)	0.43
Secondary endpoints: serology and PCR, No. (%)									
IFA									
IgM phase I	24 (46)	28 (54)	20 (40)	.68	NA	NA	.36	NA	NA
IgM phase II	27 (52)	32 (62)	29 (58)	1.0	NA	NA	1.0	NA	NA
IgG phase I	43 (83)	39 (75)	37 (74)	.87	NA	NA	1.0	NA	NA
IgG phase II	51 (98)	50 (96)	46 (92)	.33	NA	NA	.36	NA	NA
Negative *C. burnetii* PCR	52 (100)	52 (100)	50 (100)	NA	NA	NA	NA	NA	NA

Abbreviations: CBT, cognitive-behavioral therapy; *C. burnetii*, *Coxiella burnetii*; CI, confidence interval; CIS, Checklist Individual Strength; Dox, doxycycline; IFA, immunofluorescence assay; IgG, immunoglobulin G; IgM, immunoglobulin M; NA, not applicable; PCR, polymerase chain reaction; SCL-90, Symptom Checklist 90; SIP8, Sickness Impact Profile.

[a] *P* values were based on analysis of covariance. All scores are adjusted for baseline.

[b] Pairwise comparisons between treatment arms with Bonferroni correction.

[c] Standardized effect sizes are computed as difference scores divided by the pooled standard deviation of the postmeasurements.

other patient was admitted for clinical evaluation of preexisting cardiological symptoms, which yielded no diagnosis. In the CBT group, 42 (84%) patients reported at least 1 AE. No SAE occurred during CBT treatment.

DISCUSSION

In this RCT in QFS patients, long-term treatment with doxycycline was associated with a reduction in fatigue severity compared to baseline, but no more than with placebo, whereas CBT proved to be effective in reducing fatigue severity and the level of psychological distress compared to placebo. None of the treatment regimens showed a significant effect on functional impairment. Significantly more QFS patients showed a clinically meaningful improvement in fatigue following CBT.

This study is the first RCT evaluating both long-term treatment with doxycycline and CBT in QFS patients. The finding that long-term treatment with doxycycline was no more effective than placebo was contrary to previously published results [4, 17]. Both Arashima et al [4] and Iwakami et al [17] reported clinical improvement in QFS patients who received tetracycline treatment for 3 months. In the former uncontrolled open-label study [4], 20 patients were treated with minocycline 200 mg/day (n = 18), levofloxacin 200 mg/day, or erythromycin 400 mg/day. In the latter pilot study [17], 58 patients (54 with assumed QFS) received minocycline 100 mg/day (n = 29), doxycycline 100 mg/day (n = 26), or levofloxacin 200 mg/day (n = 3). However, both studies lacked a clear description of the criteria for QFS, and included patients who were *C. burnetii* PCR positive at baseline, indicating chronic Q fever; such patients might benefit from antibiotic treatment because of persistent infection. In our study, patients with a possible persistent (chronic) Q fever infection—based on clinical signs, serology, and PCR results—were not included. Furthermore, both previous studies included patients with a symptom duration of 1–4 months, whereas it is known that the percentage of patients experiencing severe fatigue decreases in the first months following acute Q fever while only a subset of patients will experience persistent fatigue [9, 11]. In contrast to these positive studies, in a case series of QFS patients [5] and in a case report [18], long-term treatment with a tetracycline showed inconsistent results. This study with a longer duration of antibiotic administration does not support long-term treatment with doxycycline for QFS, and such treatment should not be advised. These results will hopefully prevent discussions on the value of long-term antibiotic treatment for QFS and prevent patients from unnecessary prolonged antimicrobial therapy. This has already been seen in the treatment of prolonged symptoms attributed to Lyme disease, which eventually also proved ineffective [27]. In addition, most AEs occurred in the doxycycline group, including the highest median number of AEs per patient. In contrast to doxycycline, 2 SAEs were noticed in the placebo group; none of these were drug related. In this study, the observed placebo effect is

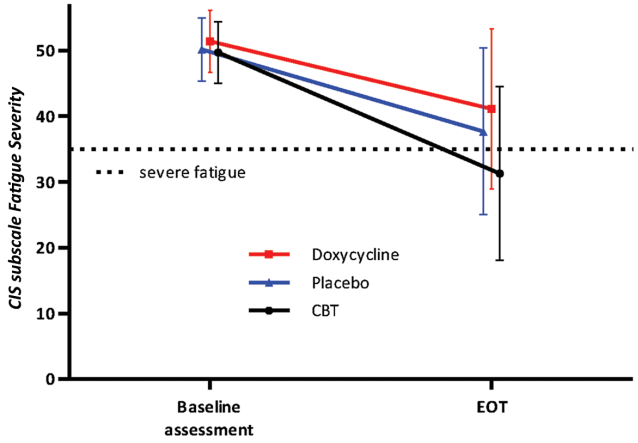

Figure 2. Mean fatigue severity and standard deviation per treatment group at baseline and at end of treatment (EOT), 26 weeks, measured with the Checklist Individual Strength subscale Fatigue Severity with a severity range from 8 to 56. Higher scores indicate a higher level of fatigue. Patients with a cutoff score of ≥35 are classified as severely fatigued. Abbreviations: CBT, cognitive-behavioral therapy; CIS, Checklist Individual Strength; EOT, end of treatment.

remarkably high. This can be explained by the regular follow-up visits during the treatment course, which included standard advice on how to manage chronic fatigue (eg, regulation of bedtimes, quitting sleeping during the day, and maintaining mental and physical activities as much as possible). For several years no standard care was available for QFS patients, and this study, the initiation of which was partly patient-driven, provided support for patients.

CBT had significantly better results than placebo in all but 1 of the secondary outcomes. In addition, the positive effect of CBT on fatigue severity was also clinically relevant. CBT is effective in reducing symptoms and improving functioning in CFS patients [19] and in chronic fatigue in chronic illnesses [28–30]. CBT is a complex intervention, encompassing a stepwise increase in physical activity and challenging dysfunctional fatigue-related beliefs. A change in beliefs about fatigue and the ability to become active seems to mediate the positive effects in CBT for CFS [31]. Previously, an overlap in fatigue-related and cognitive-behavioral variables between QFS and CFS was found, but the relationship between perpetuating factors and fatigue as is found in CFS could not be confirmed in QFS [12]. Although CBT proved effective in reducing fatigue and psychological distress in QFS patients as well, it remains unclear whether the process of change during CBT in QFS is similar to that in CFS [31]. Different processes involved in the perpetuation of disabilities might explain the absence of effect of CBT on functional impairment, for which CBT for CFS has proven efficacy [32–34]. However, this might also be due to the inclusion of patients with moderate levels of overall impairment (SIP8 total score ≥450) [32–34] and, thus, less opportunity for improvement. The mean number of AEs per patient was lowest in the CBT group, and no SAE occurred in this group. Therefore, patients need not be concerned about safety if CBT is performed by qualified and trained therapists [35].

The effectiveness of CBT does not imply that the cause of QFS is psychological. Several hypotheses regarding the etiology of QFS exist, varying from a biopsychological etiology with *C. burnetii* acting as trigger for fatigue development [6] and the determination of symptoms by host and genetic factors [36], to cytokine dysregulation, supported by low levels of *C. burnetii* DNA found in bone marrow aspirates, thin-needle liver biopsies, and blood mononuclear cells [37–39]. In addition, it should be noted that prevalence of chronic fatigue differs between studies in different countries [40]. Although this could be due to a real difference in prevalence, this could also be explained by different research methods. Nevertheless, further research into the etiology is necessary.

The present findings are strengthened by the high therapy compliance in all groups and low number of dropouts and missing data. This study also has limitations. It was not designed to compare doxycycline and CBT directly, due to the limited number of available patients. However, as the EOT scores in the doxycycline group were similar to placebo, with even higher mean scores, the results imply a favorable effect of CBT. As masking for CBT was not possible, this trial was partly blinded. CBT was directly compared to placebo plus usual care, which might explain some of the differences observed as patients in the CBT group clearly know they are being treated. Due to the maximum number of available patients, it was not possible to include a control group without any form of treatment. Finally, it is unclear whether the detected effects will be sustained over time. To evaluate the long-term beneficial effects of CBT, as has been shown for CBT for CFS [41], patients are currently surveyed by poststudy questionnaires 12–15 months posttreatment. Furthermore, a mediation analysis is planned to identify cognitive and behavioral variables that mediate the positive effect of CBT on fatigue in QFS.

In conclusion, CBT is effective in reducing fatigue severity and the level of psychological distress in QFS patients. Long-term treatment with doxycycline does not significantly reduce fatigue severity in QFS patients and should not be advised.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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