Journal of Psychosomatic Research 116 (2019) 62–67

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Long-term effect of cognitive behavioural therapy and doxycycline treatment for patients with Q fever fatigue syndrome: One-year follow-up of the Qure study

Ruud P.H. Raijmakers[a,b,*], Stephan P. Keijmel[a,b], Evi M.C. Breukers[a], Gijs Bleijenberg[c], Jos W.M. van der Meer[a,b], Chantal P. Bleeker-Rovers[a,b,*], Hans Knoop[c,d]

[a] Radboud Expert Center for Q Fever, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Department of Internal Medicine, Division of Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands
[c] Expert Center for Chronic Fatigue, Department of Medical Psychology, VU University Medical Centre, Amsterdam, The Netherlands
[d] Department of Medical Psychology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Q fever fatigue syndrome
Coxiella burnetii
Therapy
Cognitive behavioural therapy
Doxycycline
Follow-up

ABSTRACT

Background: Previously, we reported a randomized placebo-controlled trial, the Qure study, showing that cognitive behavioural therapy (CBT), and not doxycycline, was significantly more effective than placebo in reducing fatigue severity in Q fever fatigue syndrome (QFS) patients. This follow-up study evaluates the long-term effect of these treatment regimens, 1 year after completion of the original trial.

Methods: All patients who completed the Qure study, CBT (n = 50), doxycycline (n = 52), and placebo (n = 52), were included in this follow-up study. Between twelve and fifteen months after end of treatment (EOT), patients filled out web-based questionnaires including the main outcome measure fatigue severity, assessed with the Checklist Individual Strength (CIS), subscale fatigue severity.

Results: Fatigue severity in the CBT, but not doxycycline or placebo, group was significantly increased at follow-up compared to EOT (respective means 39.5 [95% CI, 36.2–42.9] and 31.3 [95% CI, 27.5–35.1], mean difference 8.2 [95% CI, 4.9–11.6]; $P < .001$). Fatigue severity scores of CBT (adjusted mean 39.8 [95% CI, 36.1–43.4]) and doxycycline (adjusted mean 41.0 [95% CI, 37.5–44.6]) groups did not significantly differ from the placebo group (adjusted mean 37.1 [95% CI, 33.6–40.7]; $P = .92$ and $P = .38$, respectively).

Conclusion: The beneficial effect of CBT on fatigue severity at EOT was not maintained 1 year thereafter. Due to its initial beneficial effect and side effects of long-term doxycycline use, we still recommend CBT as treatment for QFS. We suggest further investigation on tailoring CBT more to QFS, possibly followed by booster sessions.

1. Introduction

Q fever is a zoonosis caused by the intracellular Gram-negative bacterium *Coxiella burnetii.* Transmission to humans occurs primarily through inhalation of contaminated aerosols spread by bodily fluids, e.g. milk, urine, feces, and most importantly parturient fluids, of infected animals, most commonly goats and sheep [1–4]. Due to a vast increase in goat farming between 1983 and 2009, the Netherlands experienced the largest Q fever outbreak ever reported between 2007 and 2011 [5,6]. It is estimated that at least 44.000 people became infected, of whom over 4.000 were notified as having a symptomatic infection [7,8], i.e., acute Q fever. This number is probably an underestimation as the infection is thought to remain asymptomatic in approximately 60% of patients [5,7,9,10].

Patients with acute Q fever have a variety of symptoms, many of which are non-specific. Most common are flu-like symptoms, pneumonia, or hepatitis [1,3,10]. Following infection with *C. burnetii*, both symptomatic and asymptomatic, around 1–5% of patients eventually develop chronic Q fever or persistent focalized infection, usually manifesting as endocarditis or infection of pre-existing aneurysms or vascular prostheses [1,3,10,11]. A more common long-term sequela following infection with *C. burnetii* is Q fever fatigue syndrome (QFS).

* Corresponding authors at: Department of Internal Medicine, Division of Infectious Diseases 463, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

E-mail addresses: Ruud.Raijmakers@radboudumc.nl (R.P.H. Raijmakers), Stephan.Keijmel@radboudumc.nl (S.P. Keijmel), Evi.Breukers@radboudumc.nl (E.M.C. Breukers), Gijs.Bleijenberg@radboudumc.nl (G. Bleijenberg), Jos.vanderMeer@radboudumc.nl (J.W.M. van der Meer), Chantal.Bleeker-Rovers@radboudumc.nl (C.P. Bleeker-Rovers), Hans.knoop@amc.uva.nl (H. Knoop).

https://doi.org/10.1016/j.jpsychores.2018.11.007
Received 4 September 2018; Received in revised form 9 November 2018; Accepted 10 November 2018

Although most patients recover from their acute Q fever infection within the first 6 months, around 20% remain chronically fatigued [12]. This fatigue is frequently accompanied by other symptoms [12]. QFS leads to impairment in daily functioning and general health status, contributing to the high Q fever-related economic costs of the Dutch outbreak and emphasizing the necessity for an adequate treatment of this debilitating syndrome [12–17].

A treatment strategy with proven efficacy for QFS has long remained elusive [12]. A handful of studies have tried to assess the effectiveness of antibiotic treatment with tetracyclines [18–20]. However, these studies showed conflicting results and lack a valid trial design. Cognitive behavioural therapy (CBT) is an effective treatment for chronic fatigue syndrome (CFS) [21] and was thought to be, because of its striking overlap in symptoms, also be effective as treatment for QFS [22,23].

We previously published the results of the first and until now only randomized placebo-controlled trial for QFS treatment, the Qure study [24,25], comparing CBT and doxycycline treatment with placebo treatment [12]. This trial demonstrated a beneficial effect in reducing fatigue severity for CBT, but not doxycycline, compared to placebo treatment. For the present study we investigated whether this beneficial effect is sustained over time. In CFS it was shown that the beneficial effects of CBT lasted for at least 18 months following completion of therapy [26,27], although significant relapse did occur after this period in about half of the patients who had a favourable response directly following CBT [28]. Therefore, we evaluated whether the beneficial effect of CBT in QFS patients persisted 1 year after completion of therapy and compared the outcomes of CBT and doxycycline at follow-up with those of patients from the placebo group.

2. Methods

2.1. Patients

In this study, patients who participated in the Qure study (Clinical Trials Registration: NCT01318356 [25]) were contacted one year after completion of the study. In the original trial, 156 men and non-lactating women aged ≥18 years who were diagnosed with QFS [29], were included and equally randomized with a 1:2 ratio between two treatment groups; CBT (n = 51) and medication (n = 105). In the medication group, a second double-blinded randomization was performed between doxycycline and placebo treatment with a 1:1 ratio [24], which was refused by one patient leaving a total of 155 patients who started with the interventions. A total of 154 participants were included in the intention-to-treat (ITT) analysis of the Qure study; CBT (n = 50; 1 patient refused any further contact after withdrawing consent during CBT), doxycycline (n = 52), and placebo (n = 52); all 154 patients were contacted for follow-up assessment.

2.2. Procedures

At least twelve months (with extension to a maximum of fifteen months) after completing end of treatment (EOT) assessments in the original trial, patients were sent an e-mail by a research assistant (LV) with an invitation to participate in the follow-up assessment. In this email, the purpose of the follow-up was explained, and a link to web-based questionnaires was provided. If patients did not respond within 1 to 2 weeks, they were contacted again by e-mail. In case the web-based follow-up was not completed after the reminder, within 1 to 2 weeks, and patients had not indicated that they did not want to participate, they were contacted by phone by the research assistant to establish the reason for not responding and were asked again for their cooperation. In case the patient indicated that he or she would fill out the questionnaire but did not do so, the primary investigator (SPK) contacted the patient personally. If this was not successful, the patient was regarded as having dropped out.

2.3. Ethics

All participants provided written informed consent for participation in the Qure study, which also included a follow-up measurement. The Qure study was approved by the Medical Ethics Review Committee Region Arnhem-Nijmegen (registration number 2011/069, NL35755.091.11).

2.4. Outcome variables

Fatigue severity was the primary outcome of the Qure study measured with the subscale fatigue severity of the Checklist Individual Strength (CIS, Cronbach's alpha 0.83–0.93) [30]. Patients with a cut-off score ≥ 35 were classified as severely fatigued [31,32]. 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 subscale on fatigue severity score of < 35 [33]. The RCI was calculated based on the standard deviation of the baseline CIS subscale on fatigue severity score (4.87) of the original Qure study with 0.88 as reliability factor (= 4.28) [30]. The RCI score is then multiplied with 1.96 (=8.40), and signifies a minimal drop of nine points on the CIS subscale fatigue severity. Clinical meaningful improvement was calculated at EOT and follow-up. Functional impairment was a secondary outcome and was measured with the total score on Sickness Impact Profile-8 (SIP8, Cronbach's alpha 0.91) [34]. Patients with a cut-off score of ≥450 were classified as functionally impaired [35].

2.5. Statistical analysis

Statistical analysis was performed using SPSS 22.0.01 (SPSS Inc., Chicago, IL) and significance was assumed at a P value of < 0.05. Analyses were primarily based on an ITT analysis. In case of significant differences in the primary analysis, a sensitivity analysis will be performed on the basis of worst case imputation, i.e. maximal values on the outcome measures for missing data. In addition, a per-protocol analysis was conducted, excluding those patients who did not fully complete their allocated treatment (n = 12; CBT n = 7, doxycycline n = 3, and placebo n = 2), or followed additional treatment, i.e. CBT, (n = 15; doxycycline n = 8 and placebo n = 7) during follow-up. Between-group differences in baseline characteristics and duration of follow-up period were analysed with analysis of variance. Within-group comparisons between EOT and follow-up scores were done with pairwise t-tests. ANCOVA was used for between-group comparisons, adjusted for baseline scores. The CBT and doxycycline group were compared to the placebo group. In these analyses, follow-up scores on outcome measures were used as dependent, treatment strategy as fixed factor and scores at baseline of the Qure study as covariate. A Bonferroni correction was applied to adjust for multiple comparisons.

3. Results

Fig. 1 shows the trial profile. All 154 patients who participated in the study completed EOT and follow-up assessments and were included in the ITT analysis; CBT (n = 50), doxycycline (n = 52), and placebo (n = 52). Eight patients with doxycycline and 7 patients with placebo as allocated treatment received CBT during their follow-up period. Twelve patients stopped their treatment before EOT (CBT n = 7, doxycycline n = 3, and placebo n = 2) but did complete both EOT and follow-up assessments. There were no missing data, therefore, no imputation strategy was required. The total patient group consisted of 80 men and 74 women with a mean age of 43.8 (SD ± 12.1) at baseline. There were no significant differences in patient characteristics between treatment groups at baseline assessment of the Qure study (Table 1) [25]. The mean follow-up period from EOT assessment was 13.2 months (SD ± 1.3). No significant difference in follow-up period

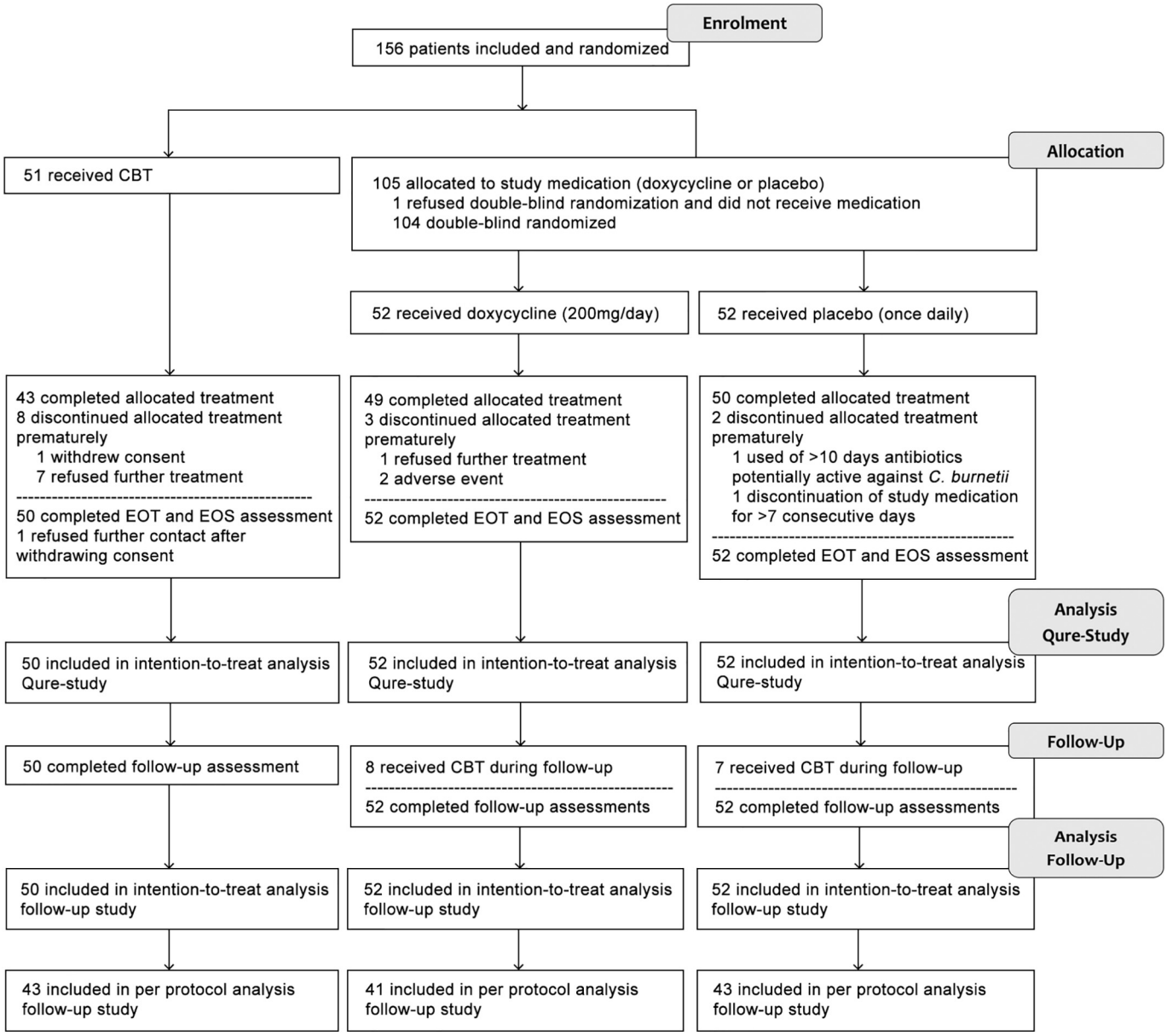

Fig. 1. Trial profile of the Qure study.
Analyses were based on an intention-to-treat method and included the data of all 154 patients who completed follow-up assessment. Abbreviations: *QFS*, Q fever fatigue syndrome; *CBT*, cognitive behavioural therapy; *EOT*, end of treatment; *EOS*, end of study.

Table 1
Characteristics at baseline assessment [25] of all patients who completed follow-up assessment.

Characteristics	Doxycycline (*n* = 52)	Placebo (n = 52)	CBT (n = 50)
Female sex, No. (%)	29 (56)	20 (38)	25 (50)
Age, y, mean ± SD	43.6 ± 10.2	44.6 ± 12.3	43.1 ± 13.7
Duration of symptoms, mo			
Median	36.00	37.50	39.50
Interquartile range	24.50–57.00	25.50–50.75	22.00–58.25
CIS subscale fatigue severity score, mean ± SD	51.4 ± 4.7	50.2 ± 4.8	49.5 ± 4.7
SIP8 total score, mean ± SD	1304.9 ± 537.7	1295.1 ± 593.7	1369.8 ± 653.3

Questionnaires on fatigue, i.e. CIS subscale fatigue severity, and functional impairment, i.e. SIP8, were used. Patients with a CIS subscale fatigue severity cut-off score of ≥35 were classified as severely fatigued. Patients with a SIP8 total cut-off score of ≥450 were classified as functionally impaired.
Abbreviations: *CBT*, cognitive behavioural therapy; *SD*, standard deviation; *CIS*, Checklist Individual Strength; *SIP8*, Sickness Impact Profile8.

Table 2
Mean scores on fatigue severity and functional impairment by treatment group at baseline, EOT and follow-up[a].

	Mean (95% CI)			Change score[b] (95% CI)	*P* value
	Baseline	EOT	Follow-up		
Fatigue severity *(CIS subscale fatigue severity)*					
CBT	49.5 (48.2–50.9)	31.3 (27.5–35.1)	39.5 (36.2–42.9)	8.2 (4.9–11.6)	< 0.001
Doxycycline	51.4 (50.1–52.7)	41.1 (37.7–44.5)	41.3 (37.6–45.1)	0.2 (−3.2–3.5)	0.91
Placebo	50.2 (48.9–51.5)	37.7 (34.2–41.3)	37.1 (33.4–40.8)	−0.6 (−4.0–2.7)	0.70
Functional impairment *(SIP8 total score)*					
CBT	1369.8 (1184.1–1555.5)	811.8 (607.5–1016.1)	880.6 (662.8–1098.5)	68.8 (−93.5–231.1)	0.40
Doxycycline	1304.9 (1155.2–1454.6)	1092.1 (890.3–1294.0)	1057.9 (843.7–1272.2)	−34.2 (−184.7–116.4)	0.65
Placebo	1295.1 (1129.8–1460.4)	949.3 (778.1–1120.4)	853.0 (661.3–1044.7)	−96.2 (−242.8–50.3)	0.19

Questionnaires on fatigue, i.e. CIS subscale fatigue severity, and functional impairment, i.e. SIP8, were used. Patients with a CIS subscale fatigue severity cut-off score of ≥35 were classified as severely fatigued. Patients with a SIP8 total cut-off score of ≥450 were classified as functionally impaired.
Abbreviations: *SD*, standard deviation; *EOT*, end of treatment; *CIS*, Checklist Individual Strength; *CBT*, cognitive behavioural therapy; *SIP8*, Sickness Impact Profile8.
[a] *P* values were based on paired *t*-test comparisons.
[b] Change score: follow-up scores compared to EOT scores.

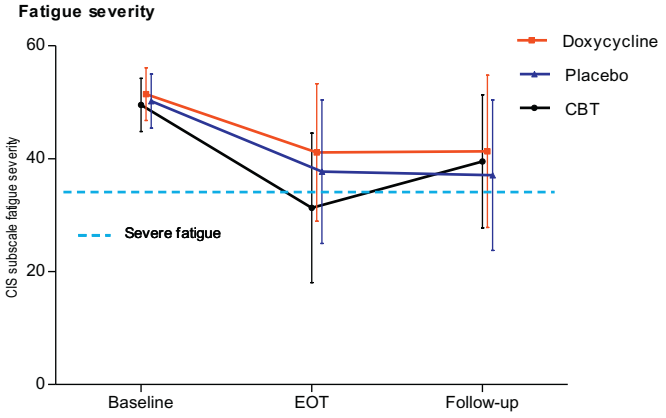

Fig. 2. Mean scores of fatigue severity by treatment group at baseline, EOT and follow-up.
The CIS subscale fatigue severity questionnaire was used. Patients with a CIS subscale fatigue severity cut-off score of ≥35 were classified as severely fatigued. Values are means and error bars are standard deviations. Abbreviations: *CBT*, cognitive behavioural therapy; *CIS*, checklist individual strength; *EOT*, end of treatment.

was found between groups (*P* = .10).

3.1. Primary endpoint

In the CBT group, mean fatigue severity had significantly increased at follow-up compared to EOT assessment (39.5 [95% CI, 36.2–42.9] and 31.3 [95% CI, 27.5–35.1] respectively, mean difference 8.2 [95% CI, 4.9–11.6]) (*P* < .001). There were no significant differences in mean fatigue severity between EOT and follow-up assessment in the doxycycline (41.1 [95% CI, 37.7–44.5] and 41.3 [95% CI, 37.6–45.1] respectively, *P* = .91) and placebo group (37.7 [95% CI, 34.2–41.3] and 37.1 [95% CI, 33.4–40.8] respectively, *P* = .70) (Table 2, Fig. 2).

No significant differences in fatigue severity at follow-up were found between the CBT (adjusted mean 39.8 [95% CI, 36.1–43.4]) and placebo group (adjusted mean 37.1 [95% CI, 33.6–40.7]) (*P* = .92), or doxycycline (adjusted mean 41.0 [95% CI, 37.5–44.6]) and placebo group (*P* = .38) (Table 3, Fig. 2).

3.2. Secondary endpoints

No significant differences in mean functional impairment scores were found between EOT and follow-up assessment in the CBT (811.8 [95% CI, 607.5–1016.1] and 880.6 [95% CI, 662.8–1098.5] respectively, *P* = .40), doxycycline (1092.1 [95% CI, 890.3–1294.0] and 1057.9 [95% CI, 843.7–1272.2] respectively, *P* = .65), or placebo group (949.3 [95% CI, 778.1–1120.4] and 853.0 [95% CI, 661.3–1044.7] respectively, *P* = .19) (Table 2, Fig. 2).

No significant differences in functional impairment at follow-up were found between the CBT (adjusted mean 858.1 [95% CI, 665.7–1050.5]) and placebo group (adjusted mean 866.2 [95% CI, 677.6–1054.7]) (*P* = 1.00), or doxycycline (adjusted mean 1066.4 [95% CI, 877.9–1254.9]) and placebo group (*P* = .42) (Table 3, Fig. 2). Clinical meaningful improvement, defined as a 9-point reduction on the CIS subscale fatigue severity together with a score < 35 at EOT and follow-up respectively, was reached by 31% and 29% of patients in the doxycycline; 46% and 40% of patients in the placebo condition; and 56% and 24% of patients in the CBT group, showing a significant relapse in the latter (*P* = .01). While a significant difference between groups was seen at EOT (*P* = .03), this was no longer the case at follow-up (*P* = .18) (Supplementary Table1).

3.3. Additional per-protocol analysis

Performing a per-protocol analysis yielded no difference in results. No significant differences in fatigue severity were found between the CBT (adjusted mean 39.2 [95% CI, 35.3–43.1]) and placebo group (adjusted mean 36.8 [95% CI, 32.9–40.7]) (*P* > .99), or doxycycline (adjusted mean 41.1 [95% CI, 37.1–45.1]) and placebo group (*P* = .41).

In the CBT group, mean fatigue severity significantly increased at follow-up compared to EOT assessment (39.1 [95% CI, 35.5–42.6] and 30.4 [95% CI, 26.6–34.4] respectively, mean difference 8.6 [95% CI, 4.8–12.4]) (*P* < .001). There were no significant changes in fatigue severity between EOT and follow-up assessments in the doxycycline (39.1 [95% CI, 35.2–43.1] and 41.4 [95% CI, 37.1–45.7] respectively, *P* = .22) and placebo group (36.5 [95% CI, 32.6–40.5] and 36.7 [95% CI, 32.6–40.9] respectively, *P* = .90).

4. Discussion

In this follow-up investigation of the Qure study, we found that the beneficial effect of CBT was not sustained at 1-year follow-up. Fatigue severity had significantly increased in the CBT group and there was no longer a significant difference in fatigue severity between CBT and placebo at follow-up. Patients who had received doxycycline or placebo reported no significant change in fatigue severity between EOT and follow-up. Directly following treatment there were no significant differences in levels of functional impairment for CBT or doxycycline compared to placebo. At follow-up, levels of functional impairment did not significantly differ from EOT in all treatment groups.

Table 3
Treatment effect on primary and secondary endpoints for all patients who completed follow-up assessment.

Outcome	Doxycycline (n = 52) Mean (95% CI)[a]	Placebo (n = 52) Mean (95% CI)[a]	CBT (n = 50) Mean (95% CI)[a]	Doxycycline vs Placebo P value[b]	Doxycycline vs Placebo, Mean Difference (95% CI)	CBT vs Placebo, P value[b]	CBT vs Placebo, Mean Difference (95% CI)
Fatigue severity *(CIS subscale fatigue severity)*	41.0 (37.5–44.6)	37.1 (33.6–40.7)	39.8 (36.1–43.4)	0.38	−3.9 (−10.1 to 2.3)	0.92	−2.6 (−8.8 to 3.6)
Functional impairment *(SIP8 total score)*	1066.4 (877.9–1254.9)	866.2 (677.6–1054.7)	858.1 (665.7–1050.5)	0.42	−200.2 (−526.8–126.4)	> 0.99	8.1 (−322.2–338.3)

Questionnaires on fatigue, i.e. CIS subscale fatigue severity, and functional impairment, i.e. SIP8, were used. Patients with a CIS subscale fatigue severity cut-off score of ≥ 35 were classified as severely fatigued. Patients with a SIP8 total cut-off score of ≥ 450 were classified as functionally impaired.
Abbreviations: *CI*, confidence interval; *CBT*, cognitive behavioural therapy; *CIS*, Checklist Individual Strength; *SIP8*, Sickness Impact Profile8.
[a] Mean follow-up scores represents follow-up scores adjusted for baseline.
[b] *P* values were based on analysis of covariance. Follow-up scores are adjusted for baseline.

It was previously shown that the positive effects of CBT for CFS, a similar condition, are sustained for at least 18 months following EOT [28]. A possible explanation for the discrepancy with our findings could lie in the fact that CBT was not sufficiently effective in reducing functional impairment at EOT in QFS patients, an observation that persists in the long-term (Table 3, Supplementary Fig.1). CBT for CFS often has a positive effect on both fatigue severity and functional impairment [36,37]. Throughout this study, all patients were functionally impaired. It is conceivable that persisting functional impairment leads to a constant confrontation with limitations caused by an impaired health status which could eventually lead to an increase in fatigue severity [38]. In addition, it can be noted that patients received a median of 9 CBT sessions in the original trial, which, although effective for fatigue severity, might be insufficient to address perceived functional impairment. As noted in the original trial, there was a trend towards a beneficial effect of CBT on functional impairment.

An alternative explanation could be the recurrent negative media attention in the Netherlands for Q fever since the outbreak of 2007, frequently reminding patients of their complaints and possible unfavourable long-term outcome of QFS. Moreover, a large lawsuit, in which patients collectively sued the Dutch government for negligence during the Q fever outbreak, was still pending during the follow-up period. This encouraged patients to supply attorneys with proof of diagnosis and constantly reminded them of their often dire financial situation and perceived lack of social support. It was previously shown that such lawsuits and perceived lack of social support are associated with poor treatment outcome of CBT or maintenance of symptoms [39,40]. It may be that negative media attention, perceive lack of support and pending lawsuits had a negative effect on the course of fatigue following CBT in the Qure study.

Perhaps the contrast in effect of CBT for QFS and CFS can also be explained by the fact that CBT for QFS was based on the treatment protocol of CBT for CFS [24], aimed at changing cognitive-behavioural factors that perpetuate fatigue in CFS [41]. This protocol is based on a model of perpetuating factors in CFS [41]. However, this CFS model does not fully apply to QFS, as, for example, it was previously shown that QFS patients exhibit stronger somatic attributions than CFS patients and show a less strong relation between fatigue-related beliefs and fatigue [22]. It is likely that not all relevant perpetuating factors for QFS have yet been identified and were therefore not addressed during CBT. It could be postulated that such inappropriately addressed perpetuating factors contributed to the relapse in fatigue severity at 1-year follow-up. The fact that there was a positive effect of CBT directly following CBT however speaks against this hypothesis. One could however also assume that the unknown and unaddressed perpetuating factors in QFS are responsible for the relapse.

A mediation analysis is currently being conducted with data of the present study, investigating which changes in cognitive-behavioural variables mediated the initial beneficial effect of CBT at EOT, but also the subsequent relapse in fatigue severity at follow-up [42]. This information can be used to design booster sessions aimed at the mediators relevant for improving long-term outcome following CBT. Booster sessions have shown to be effective in maintaining the beneficial effects of CBT for other disorders, like depression, and could also be tailored specifically for QFS, based on the results of the mediation analysis [43].

As a limitation for this study, it should be noted that follow-up questionnaires were filled out at home. Thus, patients could not be interviewed at follow-up to clarify other possible causes of an increase in fatigue severity, e.g. co-morbidities, dire financial situations, work-related issues, and relational problems.

In conclusion, the majority of QFS patients who initially benefited from CBT did not maintain this effect in the long-term. Several mechanisms may underlie this observation. Due to its initial positive effect and side effects of long-term doxycycline use, CBT is still advised as therapy of choice for QFS patients. At present, it is still the only well-investigated treatment modality for QFS patients with a positive effect.

Further research is necessary to elucidate the aetiology of relapse that occurs following CBT for QFS. We suggest further investigation on tailoring CBT more to QFS, possibly followed by booster sessions which may help to maintain the initial beneficial effect of CBT.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2018.11.007.

Conflict of interest

There were no conflicts of interest.

Acknowledgements

This work was supported by The Netherlands Organization for Health Research and Development (ID ZonMw 50-51800-98-006) and received additional funding from Q-support (ID UMCN140410-01).

References

[1] N.R. Parker, J.H. Barralet, A.M. Bell, Q fever, Lancet 367 (9511) (2006) 679–688.
[2] M.G.P. Stoker, B.P. Marmion, The spread of Q fever from animals to man: the natural history of a rickettsial disease, Bull. World Health Organ. 13 (5) (1955) 781–806.
[3] C. Eldin, et al., From Q fever to Coxiella burnetii infection: a paradigm change, Clin. Microbiol. Rev. 30 (1) (2017) 115–190.
[4] N. Arricau Bouvery, et al., Experimental Coxiella burnetii infection in pregnant goats: excretion routes, Vet. Res. 34 (4) (2003) 423–433.
[5] C.E. Delsing, B.J. Kullberg, C.P. Bleeker-Rovers, Q fever in the Netherlands from 2007 to 2010, Neth. J. Med. 68 (12) (2010) 382–387.
[6] H.I. Roest, et al., The Q fever epidemic in the Netherlands: history, onset, response and reflection, Epidemiol. Infect. 139 (1) (2011) 1–12.
[7] W. Van der Hoek, et al., Relation between Q fever notifications and Coxiella burnetii infections during the 2009 outbreak in The Netherlands, Euro Surveill. (2012) 17(3).
[8] L.M. Kampschreur, et al., Screening for Coxiella burnetii seroprevalence in chronic Q fever high-risk groups reveals the magnitude of the Dutch Q fever outbreak, Epidemiol. Infect. 141 (4) (2013) 847–851.
[9] M. Maurin, D. Raoult, Q fever, Clin. Microbiol. Rev. 12 (4) (1999) 518–553.
[10] D. Raoult, T. Marrie, J. Mege, Natural history and pathophysiology of Q fever, Lancet Infect. Dis. 5 (4) (2005) 219–226.
[11] M.C. Wegdam-Blans, et al., Chronic Q fever: review of the literature and a proposal of new diagnostic criteria, J. Inf. Secur. 64 (3) (2012) 247–259.
[12] G. Morroy, et al., Fatigue following acute Q-Fever: a systematic literature review, PLoS One 11 (5) (2016) e0155884.
[13] J.A. van Loenhout, et al., Q-fever patients suffer from impaired health status long after the acute phase of the illness: results from a 24-month cohort study, J. Inf. Secur. 70 (3) (2015) 237–246.
[14] J.A. van Loenhout, et al., Severely impaired health status of non-notified Q fever patients leads to an underestimation of the true burden of disease, Epidemiol. Infect. 143 (12) (2015) 2580–2587.
[15] G.J. Limonard, et al., Detailed analysis of health status of Q fever patients 1 year after the first Dutch outbreak: a case-control study, QJM 103 (12) (2010) 953–958.
[16] G.J. Limonard, et al., Persistence of impaired health status of Q fever patients 4 years after the first Dutch outbreak, Epidemiol. Infect. 144 (6) (2016) 1142–1147.
[17] G. Morroy, et al., The health status of a village population, 7 years after a major Q fever outbreak, Epidemiol. Infect. 144 (6) (2016) 1153–1162.
[18] D. Ledina, et al., Chronic fatigue syndrome after Q fever, Med. Sci. Monit. 13 (7) (2007) (p. Cs88–92).
[19] Y. Arashima, et al., Improvement of chronic nonspecific symptoms by long-term minocycline treatment in Japanese patients with Coxiella burnetii infection considered to have post-Q fever fatigue syndrome, Intern. Med. 43 (1) (2004) 49–54.
[20] E. Iwakami, et al., Treatment of chronic fatigue syndrome with antibiotics: pilot study assessing the involvement of Coxiella burnetii infection, Intern. Med. 44 (12) (2005) 1258–1263.
[21] J.R. Price, et al., Cognitive behaviour therapy for chronic fatigue syndrome in adults, Cochrane Database Syst. Rev. (3) (2008) (p. Cd001027).
[22] S.P. Keijmel, et al., A comparison of patients with Q fever fatigue syndrome and patients with chronic fatigue syndrome with a focus on inflammatory markers and possible fatigue perpetuating cognitions and behaviour, J. Psychosom. Res. 79 (4) (2015) 295–302.
[23] I. Hickie, et al., Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study, BMJ 333 (7568) (2006) 575.
[24] S.P. Keijmel, et al., The Qure study: Q fever fatigue syndrome–response to treatment; a randomized placebo-controlled trial, BMC Infect. Dis. 13 (2013) 157.
[25] S.P. Keijmel, et al., 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, Clin. Infect. Dis. 64 (8) (2017) 998–1005.
[26] P. Powell, et al., Patient education to encourage graded exercise in chronic fatigue syndrome. 2-Year follow-up of randomised controlled trial, Br. J. Psychiatry 184 (2004) 142–146.
[27] A. Deale, et al., Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study, Am. J. Psychiatry 158 (12) (2001) 2038–2042.
[28] A. Janse, et al., Long-term follow-up after cognitive behaviour therapy for chronic fatigue syndrome, J. Psychosom. Res. 97 (2017) 45–51.
[29] *Dutch guideline Q fever fatigue syndrome*http://www.rivm.nl/.
[30] J.H. Vercoulen, et al., Dimensional assessment of chronic fatigue syndrome, J. Psychosom. Res. 38 (5) (1994) 383–392.
[31] J.H.M. Vercoulen, G. Bleijenberg, *De Checklist Individual Strength (CIS)* Gedragstherapie, 32 (1999), pp. 131–136.
[32] M. Worm-Smeitink, et al., The assessment of fatigue: psychometric qualities and norms for the Checklist individual strength, J. Psychosom. Res. 98 (2017) 40–46.
[33] N.S. Jacobson, P. Truax, Clinical significance: a statistical approach to defining meaningful change in psychotherapy research, J. Consult. Clin. Psychol. 59 (1) (1991) 12–19.
[34] A.F. de Bruin, et al., Sickness Impact Profile: the state of the art of a generic functional status measure, Soc. Sci. Med. 35 (8) (1992) 1003–1014.
[35] H.M. Jacobs, et al., The sickness impact profile; results of an evaluation study of the Dutch version, Ned. Tijdschr. Geneeskd. 134 (40) (1990) 1950–1954.
[36] H. Knoop, et al., Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome? Psychother. Psychosom. 76 (3) (2007) 171–176.
[37] S.P. van der Werf, et al., Natural course and predicting self-reported improvement in patients with chronic fatigue syndrome with a relatively short illness duration, J. Psychosom. Res. 53 (3) (2002) 749–753.
[38] M.J. Heins, et al., Possible detrimental effects of cognitive behaviour therapy for chronic fatigue syndrome, Psychother. Psychosom. 79 (4) (2010) 249–256.
[39] A. Deale, T. Chalder, S. Wessely, Illness beliefs and treatment outcome in chronic fatigue syndrome, J. Psychosom. Res. 45 (1) (1998) 77–83.
[40] J.B. Prins, et al., Social support and the persistence of complaints in chronic fatigue syndrome, Psychother. Psychosom. 73 (3) (2004) 174–182.
[41] J.H. Vercoulen, et al., The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model, J. Psychosom. Res. 45 (6) (1998) 507–517.
[42] L.E. van den Akker, et al., Cognitive behavioural therapy for MS-related fatigue explained: a longitudinal mediation analysis, J. Psychosom. Res. 106 (2018) 13–24.
[43] M.M. Weissman, Psychotherapy in the maintenance treatment of depression, Br. J. Psychiatry Suppl. 26 (1994) 42–50.