

Early changes in fatigue and cytokine concentration following etanercept treatment in rheumatoid arthritis

Aim: To study early changes in fatigue, disease activity and cytokines within individual patients with rheumatoid arthritis (RA) following etanercept treatment. **Methods:** 12-week prospective observational study of 21 RA patients starting etanercept therapy. DAS28, fatigue, IL-1 β , IL-4, IL-6, IL-8 and IL-1ra were measured. **Results:** DAS28, fatigue and IL-6 improved significantly by 40% compared with baseline values in the first 4 weeks ($P < 0.05$), but followed different time courses. The main improvement in IL-6 occurred by week 2, fatigue (BRAF MDQ) by week 3 and DAS28 by week 4. At week 3 improvement of DAS28 (24%) was significantly less than BRAF MDQ (42%, $P < 0.003$) and IL-6 (43%, $P < 0.03$). **Conclusion:** Fatigue improved faster than disease activity, suggesting that fatigue may be mediated via a different pathway.

Keywords: biologic therapies • cytokines • fatigue • IL-6 • rheumatoid arthritis

Fatigue is a major symptom in rheumatoid arthritis (RA), with a reported prevalence of up to 88% [1]. Patients report that fatigue can be as debilitating for them as pain [2]. Additionally, fatigue severity may be a better predictor of quality of life than pain, joint tenderness or disease activity [3]. Fatigue is now included in the core set of outcomes measures for RA clinical trials [4].

The efficacy of etanercept in controlling disease activity, inhibition of radiographic damage and improvement in physical function has been shown in several clinical trials [5]. However, studies examining fatigue response following biological therapies are sparse. Fatigue has a multifactorial etiology and various processes have been postulated including inflammatory cytokines [6]; hormonal imbalances [7]; reduction in tissue oxygenation [8]; external factors such as medication; and nonclinical factors such as psychosocial issues (coping, mood and illness beliefs) [9]. Biological therapies may have an impact on fatigue directly or indirectly by improving disease activity. Early improvement in fatigue following biological therapies

supports the concept that proinflammatory cytokines play a major role.

In a placebo-controlled trial in 234 patients with active RA, etanercept resulted in a 25% improvement in the vitality domain of the SF-36 after 3 months of treatment [5]. A trial of adalimumab resulted in a statistically significant improvement in fatigue measured by the functional assessment of chronic illness therapy-fatigue scale [10]. Following etanercept treatment a significant improvement in fatigue occurred as early as 2 weeks [11]. Furthermore, the 36% mean reduction in fatigue was sustained for up to 46 months following etanercept treatment [11].

To date, no studies have looked at the relationship between fatigue, cytokines and disease activity within individual patients in the first few weeks following biologic treatment. This time frame might be important in understanding the underlying pathoetiology of fatigue. Therefore, the aim of this study was to determine, in patients with RA starting etanercept therapy for clinical indications, whether fatigue improves more quickly

Cecilia Mercieca^{*1}, Samy Zakout², John Kirwan¹, Mohammed Sharif³ & Elaine Smith²

¹Academic Rheumatology Unit, University of Bristol, University Hospitals Bristol NHS Foundation Trust, Bristol, BS2 8HW, UK

²Department of Rheumatology, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, GL1 3NN, UK

³School of Clinical Sciences, Southmead Hospital, University of Bristol, Bristol, BS10 5NH, UK

*Author for correspondence: merciecacecilia@gmail.com

and relates more closely to particular proinflammatory cytokines compared with measures of disease activity in the first 12 weeks of treatment.

Patients & methods

Consecutive patients meeting the entry criteria were invited to take part at two rheumatology outpatient departments in Southwest England. The inclusion criteria were patients RA [12] and active disease defined by a disease activity score (DAS28) ≥ 5.1 , in whom two previous disease-modifying antirheumatic drugs (DMARDs) had failed to control disease activity. Patients taking prednisolone had to be on a stable dose prior to and throughout the study period and taking no more than 10 mg daily. Concomitant DMARDs included methotrexate, sulphasalazine and leflunomide and no changes in DMARD doses were made during the study. Patients were assessed at baseline prior to starting etanercept and then at weeks 1–4, 8 and 12 after starting treatment. All patients received 50 mg etanercept weekly by subcutaneous injection. At each visit the following assessments were carried out: DAS28; the Hospital Anxiety and Depression questionnaire; the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAFF NRS); and the Bristol Rheumatoid Arthritis Multidimensional Fatigue Questionnaire (BRAFF MDQ) [14]. The BRAFF NRS consists of three single-item questions measuring fatigue severity, fatigue effect and coping using numerical rating scales. The 20-item BRAFF MDQ has a global score and four subscales (physical fatigue, living with fatigue, cognitive fatigue and emotional fatigue). Both questionnaires, specific for RA, have greater validity in RA than other fatigue questionnaires, and are reliable and sensitive to change [13–15].

At each visit blood was collected into a chilled syringe between noon and 1 p.m. IL-6 shows circadian variation which peaks early in the morning. The logistics of the study precluded measurement at this time. It was therefore ensured that blood for cytokine levels was taken between midday and 1 p.m., allowing comparison across the different measurements. After collection blood was placed into a chilled EDTA blood tube then immediately centrifuged for 7 min at 5750 rpm. Plasma was separated by pipetting into small plastic aliquot containers, placed on dry ice for rapid freezing, then stored at -20°C for up to 48 h before storage at -70°C until assayed. Plasma IL-1 β , IL-4, IL-6, IL-8 and IL-1ra were measured using MSD[®] V-PLEX assay kits (BABS Biomarker Services, Welwyn Garden City, UK). The assays were carried out in several batches and the intra and interassay variations were less than 20% for all cytokines.

Ethical approval for the study was granted by the North Somerset and South Bristol Research Ethics Committee (08/H0106/93) and recruited patients gave written consent.

A paired *t*-test was used to compare proportion improvement from baseline at each time point. A second planned analysis included only patients with high fatigue scores (BRAFF NRS ≥ 6) at baseline. This was because some patients with high DAS scores (the clinical criterion for initiating treatment) might not have high fatigue scores, so could not contribute to observations specifically related to a reduction in fatigue. Pearson's correlation was used to study the strength of the association between IL-6, fatigue and disease activity.

Results

Two patients initially included withdrew due to adverse effects; an infected toe ulcer at week 2 and a painful erythematous skin rash at week 7, and have not been included in the analysis. A further 21 patients (16 female) were recruited. The mean age was 59.8 years (standard deviation [SD] 12.4) and the mean C-reactive protein (CRP) was 10.7 (SD 14.6). At baseline the mean DAS28 was 5.7 (SD 0.8), mean BRAFF MDQ 38.4 (14.89) and IL-6 2.99 pg/ml (SD 2.76).

Fifteen patients achieved an improvement in DAS28 ≥ 1.2 by week 12. Following etanercept treatment disease activity, fatigue and IL-6 all showed significant improvement by week 2 ($P < 0.05$). By week 12 the improvement in DAS28 was 39%, BRAFF MDQ 39% and IL-6 40% compared with baseline (Table 1). Of the cytokines measured, IL-6 was the only one to show a significant change from baseline following treatment. There was no consistent pattern of change in IL-1 β , IL-4, IL-8 and IL-1ra. The Hospital Anxiety and Depression questionnaire did not show a significant correlation with the fatigue.

In the planned secondary analysis, four patients with low baseline fatigue were excluded. These patients were treated with etanercept because of a high DAS28, but could not contribute to our observations about change in fatigue. The remaining 17 patients showed a substantial improvement from baseline in IL-6 by week 2, BRAFF MDQ by week 3 and DAS28 by week 4 (Figure 1A). These differences were greatest at week 3, when a *t*-test showed that improvement in DAS28 (24%) was significantly different from that in BRAFF MDQ (42%, $P < 0.003$) and IL-6 (43%, $P < 0.03$) but improvement in BRAFF MDQ and IL-6 were not significantly different ($P = 0.84$).

A sustained reduction in the 'severity of fatigue' and 'effect of fatigue' scales of the BRAFF NRS was noted (Figure 1B) but not of 'coping with fatigue.' There was an improvement in all subscales of BRAFF MDQ

(physical, living, cognition and emotion) by week 12. The greatest improvement occurred in the subscale living (60.2%), followed by cognition (42.9%), physical (35.5%) and emotion (28.8%). Figure 1b.

Discussion

Persistent severe fatigue is a major debilitating symptom for RA patients [1]. Patients ranked 'less fatigue' among the top eight treatment outcomes [2]. RA fatigue is strongly associated with quality of life, overall health status and work productivity [3]. However, few studies have reported fatigue as an outcome measure.

Improvement in fatigue following biotherapies [4] suggests that an immunological mechanism may partly contribute to RA fatigue, which may be directly related to disease activity or indirectly related through different unknown biological pathways. A significant reduction in fatigue was observed at weeks 2, 4 and 8 following etanercept treatment and this was sustained for up to 46 months [4]. A meta-analysis of biotherapies in established RA which included 10 randomized controlled trials and 3837 patients showed a modest effect size of 0.45 (95% CI 0.31, 0.58) for the control of fatigue [16]. The authors reported a number of limitations including heterogeneity of the population, the multifactorial etiology of fatigue, and that disease activity was the main inclusion criterion rather than fatigue. Further, only studies using functional assessment of chronic illness therapy-fatigue and SF-36-V scores were included.

Whether and how biotherapies improve fatigue in RA is unclear. Fatigue probably results from the interplay of pain, functional disability, inflammation, coping and psychosocial factors which vary over time [1]. Several hypotheses about how cytokines can contribute to fatigue have been postulated. Studies support IL-1 as an important regulator of the sickness behavior in animals [17] and autoimmune conditions [6]. TNF, IL-1 and IL-6 have been reported to cause hypothalamic–pituitary–adrenal axis dysregulation [7]. Injection of IL-6 induces fatigue in healthy volunteers [18].

Our study supports the concept that fatigue may be mediated by a different biological pathway to that of disease activity as they follow different time courses in response to etanercept treatment. Fatigue reached a plateau at week 3 while disease activity continued to improve throughout the 12 weeks of the study. From the clinical perspective it is useful to note that further improvement in fatigue is unlikely after 3 weeks of therapy and that other interventions are required if fatigue is still an important symptom. It would be interesting to study whether different biologic therapies show different efficacy on fatigue.

The BRAF scales [14] enable a multidimensional assessment of fatigue rather than focusing solely on severity levels. The subscale living with fatigue showed the greatest improvement while coping with fatigue did not improve suggesting that pharmacological interventions do not affect the different dimensions in the same way. The disconnect between fatigue severity, the impact this has on the patients' lives, and the patient perceived ability to cope with fatigue has been shown in other studies [14,15]. These observations support a multimodal approach to management incorporating pharmacological and non-pharmacological interventions. Measurement of different dimensions of fatigue could potentially enable a more personalized and timely treatment approach. The lack of association between fatigue and self-reported pain and depression could be explained by the short time frame as well as the fact that these patients have been suffering from RA for quite some time. We were purposefully concentrating on relatively rapid changes in this study.

One limitation of our study is the relatively small number of patients. Due to intra-assay variations it is possible that some smaller changes in other cytokines apart from IL-6 were not detected. Future studies might concentrate on having larger numbers of patients followed more intensively over a relatively short time period. Also, fatigue is multifactorial and social factors were not assessed in our study. Given the short period over which the measures changed we do not think that changes in social factors would have taken place.

Table 1. Percentage change from baseline following etanercept therapy in 21 patients.

Weeks of treatment	1		2		3		4		8		12	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
BRAF severity	3.7	(28.6)	10.2	(16.1)	25.9	(21.7)	22.5	(27.3)	16.9	(30)	33.7	(16)
BRAF effect	14.1	(15.2)	11.7	(15.7)	27.9	(22.9)	22.4	(28.8)	29.7	(20.1)	34.7	(16.4)
BRAF coping	-27.9	(42.9)	-18.4	(41.3)	-27.1	(49.9)	-53.1	(74)	-65.3	(99.1)	-61.1	(100.1)
BRAF MDQ	10.4	(18.7)	15.6	(16.4)	29.6	(22.1)	28.0	(22.1)	28.2	(23.1)	38.5	(16.5)
DAS28	19.9	(7.6)	23.8	(7.6)	24.6	(6.7)	31.4	(6.3)	34.9	(9.4)	38.8	(10.1)
IL-6	24.9	(29)	44.9	(19.6)	44.4	(16.8)	41.2	(16.9)	37.6	(30.9)	39.5	(31.6)

BRAF: Bristol Rheumatoid Arthritis Fatigue; BRAF MDQ: Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire.

Finally, the main entry criterion for starting etanercept was high disease activity rather than fatigue. To allow for this, our planned second analysis was performed excluding the small proportion of our patients with low

fatigue scores at baseline. The strengths of this study are the early serial measurements which enabled a detailed multidimensional study of fatigue, disease activity and cytokine which has not been previously explored.

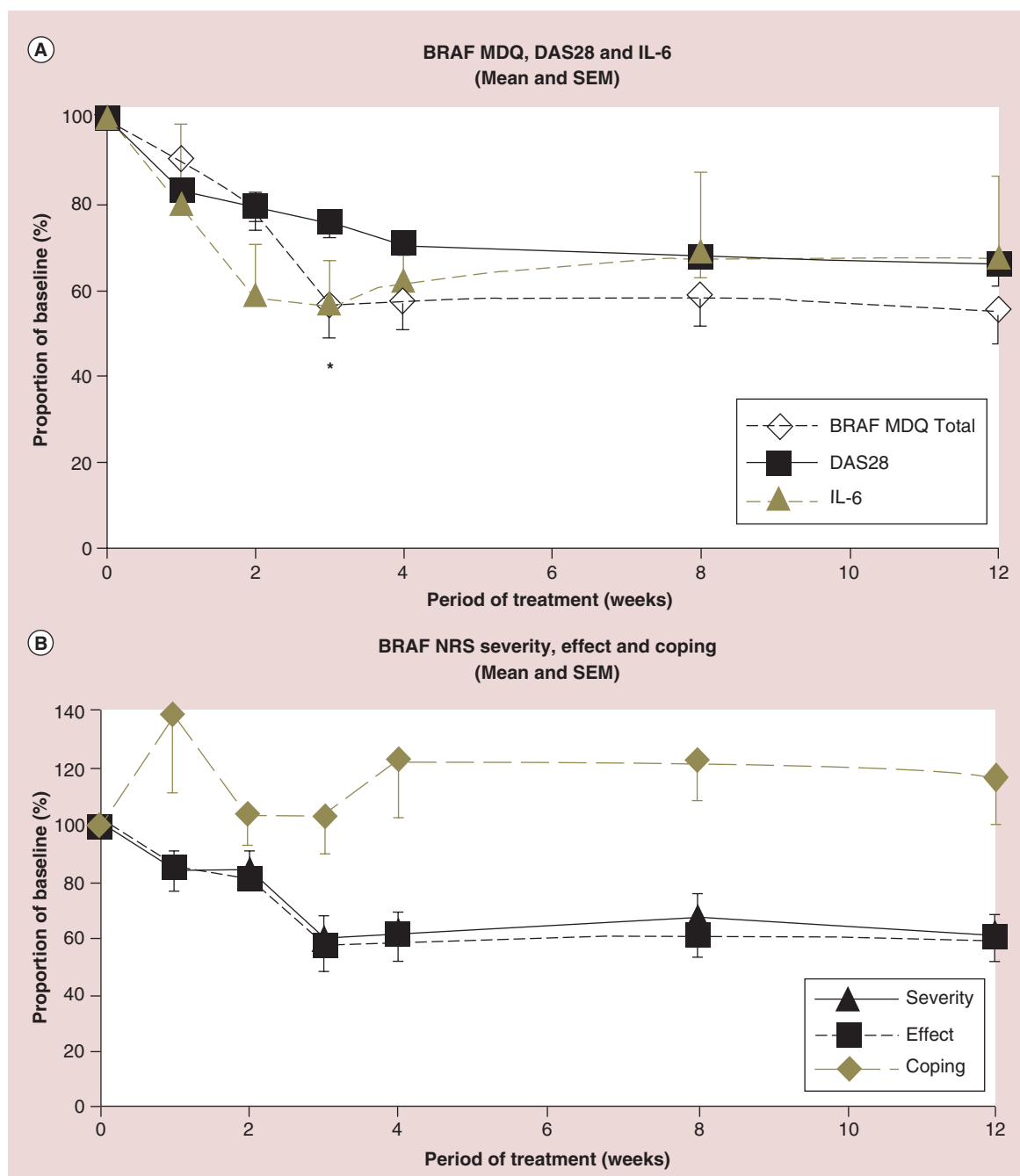


Figure 1. Percentage change from baseline following etanercept treatment of patients with high baseline fatigue score (n=17). (A) Fatigue (Bristol Rheumatoid Arthritis Multidimensional Fatigue Questionnaire), disease activity (DAS28) and IL-6 change from baseline following etanercept treatment of patients who had high levels of fatigue at baseline defined as Bristol Rheumatoid Arthritis Fatigue severity numerical rating scale ≥ 6 (n = 17). *At week 3 improvement in DAS28 (24%) was significantly different from that in BRAF MDQ (42%, $P < 0.003$) and IL-6 (43%, $P < 0.03$). **(B)** Change from baseline of the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale of severity, effect and coping of patients who had high levels of fatigue at baseline defined as Bristol Rheumatoid Arthritis Fatigue severity numerical rating scale ≥ 6 (n = 17). BRAF: Bristol Rheumatoid Arthritis Fatigue; NRS: Numerical Rating Scale.

Conclusion

There was a significant improvement in fatigue and disease activity following etanercept treatment, and IL-6 was the only cytokine which showed a significant response. The reduction in IL-6 occurred rapidly and preceded an improvement in fatigue, which improved faster than disease activity, raising the possibility that fatigue could be mediated via a different biological pathway.

Future perspective

Over the last decade new therapeutic options have become available for RA patients. However, few studies have looked at the effect of biologics on fatigue. More intensive investigation of the early changes in cytokines and symptoms following biological therapy in a larger number of patients may provide more information about the mechanisms of fatigue in RA.

Financial & competing interests disclosure

This was an investigator-initiated and -managed study, but was funded fully and in advance by an unconditional educational grant from Pfizer Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- Fatigue is an important symptom in rheumatoid arthritis (RA) and improvement following biological therapies supports the concept that cytokines play a role.
- Few studies have looked at fatigue response following biological therapies.

Methods

- Prospective observational study of 21 patients with active RA starting etanercept therapy assessed at baseline, 1–4, 8 and 12 weeks.
- Assessments included DAS28, and fatigue questionnaires (Bristol Rheumatoid Arthritis Multidimensional Fatigue Questionnaire (BRAFMQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale fatigue scales). Plasma IL-1 β , IL-4, IL-6, IL-8 and IL-1ra were measured at each visit.
- A planned analysis of patients with high baseline fatigue was undertaken.

Results

- DAS28, fatigue and IL-6 all improved significantly by 40% ($P < 0.05$) compared with baseline values but followed different time courses in the first 4 weeks.
- In patients with high baseline fatigue, the main improvement in IL-6 occurred by week 2, fatigue (BRAFMQ) by week 3 and DAS28 by week 4.
- At week 3 improvement in DAS28 (24%) was significantly less than in BRAFMQ (47%, $P < 0.003$) and IL-6 (43%, $P < 0.03$).

Conclusion

- Disease activity, fatigue and IL-6 concentrations follow different early time courses after etanercept treatment, suggesting that fatigue may be mediated via a different pathway.
- Studying early post-treatment cytokine and symptom changes may help elucidate the mechanisms of RA fatigue.

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