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Concise Report

Fatigue in rheumatoid arthritis reflects pain, not disease activity

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***Objective*. We determined the amount of fatigue experienced by patients with RA, and its relationship to synovitis, pain and other common clinical features. We also examined to what extent RA fatigue is improved by disease-modifying antirheumatic drugs (DMARDs) and anti-tumour necrosis factor (TNF) therapy.**

***Methods*. We studied two cohorts of 238 and 274 RA patients cross-sectionally and examined treatment responses in 30 RA patients starting anti-TNF and 54 starting DMARDs followed for 3 and 6 months. We measured fatigue using visual analogue scores (VAS) and Medical Outcomes Study Short Form 36 (SF-36) vitality scores. We recorded the disease activity score for 28 joints and its components (tender/swollen joint counts, patient global assessment, ESR), morning stiffness, health assessment questionnaire, physician global assessment, erosive disease, nodules, rheumatoid factor, concomitant medications and illnesses, and the SF-36 questionnaire.**

***Results*. Fatigue was common in RA patients; over 80% had clinically relevant fatigue (VAS ≥20 mm), over 50% had high levels (VAS ≥50 mm). It was associated with pain and changes in mental health, particularly depression. In each of the two cross-sectional cohorts, this relationship was similar whichever measures of fatigue and mental health were used. Fatigue fell with DMARDs and anti-TNF: before treatment, 87% of patients had high fatigue, after treatment this fell to 50%. These treatment effects were mainly linked to improvements in pain.**

***Conclusions*. High fatigue levels characterize RA and are mainly linked to pain and depression. The association with disease activity is secondary. Fatigue falls with DMARD and anti-TNF therapy. The balance of evidence suggests that fatigue is centrally mediated in established RA.**

KEY WORDS: Rheumatoid arthritis, Fatigue, Clinical assessment, DMARDs, Anti-TNF.

Fatigue is common in rheumatoid arthritis (RA) and its absence characterizes disease remission [1]. Qualitative studies highlight the importance people with RA attribute to fatigue [2, 3]. Between 40 and 80% of RA patients attending specialist clinics have clinically relevant fatigue, which is a feature of active disease [4–7]. By contrast, few cases (under 5%) are in remission [8], in which there is no fatigue. These observations suggest disease activity is one underlying factor in the pathogenesis of fatigue in RA. Surprisingly, the ways in which disease activity influences RA fatigue have not been investigated to any extent. However, interest in this issue has been stimulated by a large randomized controlled trial (RCT) of adalimumab, an anti-TNF agent, which significantly reduced fatigue in RA [9]. The improvement in fatigue was associated with falls in disease activity, providing the best evidence yet that inflammatory synovitis is a potentially important causal factor for RA fatigue. There is relatively little data on whether conventional disease-modifying antirheumatic drugs (DMARDs) reduce fatigue. Only one RCT has looked at this to any extent. It compared leflunomide with methotrexate and showed that both DMARDs improved Medical Outcomes Study Short Form 36 (SF-36) energy and vitality scores, which are equivalent to fatigue measured with specific instruments [10].

Several other factors influence RA fatigue, including psychosocial factors, health beliefs, illness perceptions and poor social support [11, 12]. Fatigue also has strong relationships to pain and depression [4, 5, 7, 11–20]. These inter-relationships led Wolfe to coin the term 'fibromyalgic RA' to describe the subset of patients with high levels of fatigue, pain and depression [21].

Our aim was to define the relative contribution of RA disease activity to fatigue in comparison with factors such as pain and depression in established RA. We examined these inter-relationships in two cross-sectional studies using different instruments to assess fatigue. We also evaluated the comparative effects of DMARDs and anti-TNF on RA fatigue in prospective observational cohorts.

Methods

Patients

We studied RA patients who met the criteria of the American College of Rheumatology and were attending out-patient clinics in southeast London. We performed both clinical association and treatment response studies and looked at two patient groups

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TABLE 1. Details of patients enrolled in clinical association and treatment response studies

	Clinical association studies		Treatment response studies	
	Initial ($n=238$)	Second ($n=274$)	DMARDs ($n=54$)	Anti-TNF ($n=30$)
Demographic details				
Mean age, yr (range)	60 (26–85)	64 (24–91)	60 (33–82)	53 (22–81)
Sex (F:M)	4:1	3:1	3:1	14:1
Mean disease duration, yr (range)	11 (0–37)	12 (1–52)	10 (1–42)	15 (1–33)
Clinical measures				
High fatigue (VAS $\geq$50 mm)	129 (54%)	138 (50%)	34 (63%)	26 (87%)
Clinically relevant fatigue (VAS $\geq$20 mm)	200 (84%)	222 (81%)	49 (91%)	29 (97%)
Mean fatigue (S.D.)	49 (26.9)	49 (28.1)	56 (27.2)	67 (21.9)
Mean pain (S.D.)	47 (27.9)	46 (27.7)	61 (25.2)	65 (21.9)
Mean DAS 28 (range)	4.4 (0.5–8.1)	4.7 (0.8–8.5)	5.7 (2.7–8.5)	6.1 (3.7–7.8)
Bivariate (Spearman's) correlations with VAS fatigue				
DAS	$r=0.48$ ($P<0.001$)	$r=0.47$ ($P<0.001$)	$r=0.69$ ($P<0.001$)[a]	$r=0.43$ ($P=0.019$)[a]
Pain	$r=0.68$ ($P<0.001$)	$r=0.66$ ($P<0.001$)	$r=0.63$ ($P<0.001$)[a]	$r=0.65$ ($P<0.001$)[a]

[a]Correlation with change in both measures.

in each (Table 1). The initial clinical association study assessed fatigue using a visual analogue scale (VAS); the second clinical association study also used the vitality scale of the SF-36 as an alternative measure of fatigue. The two treatment response studies evaluated patients either starting DMARDs and remaining on treatment for 6 months or patients starting anti-TNF and remaining on treatment for 3 months; patients who stopped treatment for any reason were excluded.

Assessment of fatigue

Fatigue was measured using a 100 mm VAS and the vitality subscale of the SF-36 questionnaire [22].

Other assessments

Demographic data (age, sex and disease duration), information on treatment (current DMARDs and anti-TNF), pain (100 mm VAS), disease activity score (DAS) for 28-joint counts and its constituent components (28 tender joint count, 28 swollen joint count, patient global assessment and ESR) were recorded in all cases. In the treatment response studies, the clinical assessments were recorded before and after 3 or 6 months of treatment.

In the clinical association studies, data were also collected on early morning stiffness (EMS) in minutes, the modified health assessment questionnaire [23] (HAQ) score and the physician global assessment score. Patients in the initial study were assessed for the presence of erosive disease, nodules, rheumatoid factor, haemoglobin, creatinine, all concomitant medications and illnesses.

Analysis

Simple descriptive analyses (including mean and S.D.) were applied to the main data in all groups. Regression analyses were used to examine the factors influencing fatigue in the clinical association studies using the Statistical Package for the Social Sciences (SPSS® 11 for Windows). Simple linear regressions were used to study the individual effects of continuous variables, such as age, pain, physical assessment and DAS. The effects of binary variables were assessed with two-sample independent *t*-tests. To determine the key factors that contribute to fatigue in RA, the simple linear regression was followed by a multiple linear regression model fitted to all the variables in a stepwise manner, paying special attention to multi-collinearities, interactions and potential mediating relationships.

As fatigue measured by the SF-36 vitality score was not normally distributed, the results were categorized into three categories: low, normal and high energy scores. Simple ordinal regressions were used to study the individual effects of continuous variables followed by fitting a multiple ordinal regression model to all the variables. The effects of binary variables were assessed with two-sample independent *t*-tests. To assess the effects of treatment, two-sample independent *t*-tests and bivariate Spearman's correlations were used.

Results

Frequency of fatigue

RA patients had high fatigue levels (Table 1); 80% of patients had clinically relevant fatigue (VAS score $\geq$20 mm) and over 50% had high fatigue scores (VAS score $\geq$50 mm). Fatigue was also assessed using the SF-36 energy and vitality score (range 0–100). The lower the score the more severe the fatigue. The mean SF-36 energy and vitality score in our cohort was 51, which is substantially less that in than normal UK populations, who have reported mean scores of 61–65.

Clinical association studies: simple regression

The initial clinical association study showed that VAS fatigue scores were significantly correlated with disease activity measures, including DAS and VAS pain (Table 1), and also HAQ ($r=0.51$, $P<0.001$) and early morning stiffness ($r=0.46$, $P<0.001$). In addition, there were significant associations with some comorbidities, number of concomitant diseases, depression (fatigue score 68.6 *vs* 47.6, $P=0.002$) and fibromyalgia (fatigue score 72.1 *vs* 47.7, $P=0.001$), and some prescribed drugs (methotrexate, tramadol and paracetamol). Fatigue was not associated with other DMARDs (sulphasalazine, hydroxychloroquine, leflunomide, gold, azathioprine, cyclosporin, d-penicillamine), anti-TNF therapy (etanercept, adalimumab, infliximab) and steroids. It was also unrelated to age, disease duration, sex, rheumatoid factor, rheumatoid nodules, anaemia, diabetes mellitus, and renal, respiratory or ischaemic heart disease.

The second clinical association study (alternative measure study) showed similar significant correlations between VAS fatigue scores and both DAS and VAS pain scores (Table 1). The SF-36 energy and vitality scores correlated (Spearman's rank correlation)

strongly with fatigue VAS scores ($r = 0.58$, $P < 0.001$). Correlations with measures of disease activity were similar whether fatigue was measured using the VAS or the SF-36 energy and vitality score: SF-36 energy and vitality score (DAS, $r = 0.41$, $P < 0.001$; HAQ, $r = 0.46$, $P < 0.001$), VAS fatigue (DAS, $r = 0.47$, $P < 0.001$; HAQ, $r = 0.46$, $P < 0.001$). SF-36 mental health scores also showed a significant relationship with SF-36 energy and vitality score ($r = 0.6$, $P < 0.001$) as well as VAS fatigue ($r = 0.46$, $P < 0.001$).

Clinical association studies: multiple regression

Multiple linear regression in the initial clinical association study showed that five variables explained 53% of variation in VAS fatigue scores (Table 2). Pain had the strongest association, then HAQ and depression. Methotrexate and erosive disease had negative associations, indicating that patients receiving methotrexate had less fatigue and that those without erosions had more fatigue.

Multiple linear regression in the second study showed that three variables explained 53% of the variation in VAS fatigue scores (Table 2). Pain had the strongest positive association, followed by SF-36 mental health score (in an inverse scale a negative association indicates a positive relationship) and patient global assessment. Finally, an ordinal regression model of the relationships of SF-36 energy and vitality scores showed that three variables had significant associations: HAQ and pain had the strongest association followed by SF-mental health scores (Table 2).

Treatment response study

DMARDs. Over 6 months, VAS fatigue scores fell from a mean of 56 to 49 ($P = 0.176$). Before treatment, 34 (63%) of the patients had high levels of fatigue (VAS scores ≥ 50 mm); after treatment this fell to 26 (48%). The fall in VAS fatigue scores correlated with improvements in pain and DAS 28 ($r = 0.63$, $P < 0.001$ and $r = 0.69$, $P < 0.001$, respectively). The effect sizes of DMARD therapy on DAS, pain and fatigue were 79, 66 and 42%, respectively.

Anti-TNF. Prior to treatment, the VAS fatigue score of anti-TNF treated patients was statistically significantly higher than that of DMARD treated patients (67 *vs* 56, $P = 0.04$) although after treatment it was similar in the two groups (50 *vs* 49). Over 3 months there was a mean fall in VAS fatigue score from 67 to 50 ($P = 0.009$). Before treatment, 26 (87%) of patients had high levels of fatigue (VAS score ≥ 50 mm); after treatment this fell to 15 (50%). The falls in VAS fatigue scores correlated with improvements in pain and DAS 28 ($r = 0.65$, $P < 0.001$ and $r = 0.43$, $P = 0.019$, respectively). The effect sizes of anti-TNF therapy on DAS, pain and fatigue were 128, 80 and 73%, respectively.

Discussion

Fatigue is a dominant symptom in RA. In keeping with previous reports [11–20], we showed that it is strongly associated with pain. Patients with active RA had high levels of fatigue, but multiple regression analyses show that this relationship was less important than the association with pain. Patients diagnosed with either fibromyalgia and/or depression have higher levels of fatigue. These conditions coaggregate and after adjustment with multivariate analysis, depression is the only comorbidity invariably associated with fatigue. Other comorbidities, including cardiovascular and respiratory diseases, were not directly related. Several other factors

TABLE 2. Factors contributing to fatigue in initial and alternative measure association studies

Initial clinical association study ($n = 238$)						Alternative measure clinical association study ($n = 274$)				
			95% confidence interval					95% confidence interval		
	Variable	Coefficient	Lower	Upper	P	Variable	Coefficient	Lower	Upper	P
Fatigue (VAS)[a]	Pain (VAS)	0.50	0.39	0.61	0.0001	Fatigue (VAS)[b]	0.44	0.28	0.60	0.0001
Adjusted $R^2 = 0.53$	Modified HAQ	7.17	3.25	11.09	0.0001	Adjusted $R^2 = 0.53$	−0.39	−0.51	−0.27	0.0001
	Depression	10.73	1.18	20.29	0.03		0.16	0.02	0.31	0.03
	Methotrexate	−8.08	−13.00	−3.17	0.001	Energy and vitality	1.95	1.35	2.81	0.0001
	Erosive disease	−7.47	−12.62	−2.32	0.01	(SF-36)[c]	1.02	1.01	1.03	0.0001
						Odds ratio	0.95	0.94	0.97	0.0001

Fatigue was assessed using VAS and the SF-36 vitality scale. Analysis was by multiple linear regression.
[a]Excluded variables: DAS 28, tender joint count, swollen joint count, physician global assessment, patient global assessment, ESR, EMS, age, disease duration, sex, seropositivity, rheumatoid nodules, haemoglobin, creatinine, diabetes mellitus, hypothyroidism, respiratory disease, ischaemic heart disease, number of concomitant diseases, fibromyalgia, tramadol, paracetamol, sulphasalazine, hydroxychloroquine, leflunomide, gold, azathioprine, cyclosporin, d-penicillamine, anti-TNF therapy, corticosteroids.
[b]Excluded variables: DAS 28, TJC, SJC, physician global assessment, HAQ, EMS, CRP, ESR, age, sex, disease duration.
[c]Excluded variables: DAS 28, tender joint count, swollen joint count, physician global assessment, patient global assessment, EMS, CRP, ESR, age, sex, disease duration.

are associated with fatigue scores. HAQ scores were positively associated, indicating that patients with high fatigue levels are markedly disabled. Methotrexate use and erosive disease had negative relationships. This suggests that methotrexate use is associated with lower levels of fatigue, which may have two explanations: firstly, patients who are treated with methotrexate have a better outcome; secondly, the non-methotrexate-treated patients represent a different subset of RA patients. The association of non-erosive disease and higher fatigue scores may also represent a specific subset of RA patients in this population. Interestingly, we found no association between fatigue and age or disease duration, indicating that peripheral features like muscle mass, which decreases with age, and disease duration are unimportant. Therefore, fatigue in RA is likely to be central in origin.

RCTs provide some evidence that adalimumab [9], methotrexate and leflunomide [10] reduce fatigue. These falls in fatigue accompanied decreases in disease activity. Our observational studies show that in routine practice fatigue falls when active RA is treated with anti-TNF and to a lesser extent with DMARDs. These falls mirror decreases in DAS scores and pain. Although Wolfe and Michaud [24] found similar levels of fatigue in RA patients on anti-TNF therapy and those not receiving biologicals, they did not measure fatigue levels prior to commencement of anti-TNF and their results are best explained by confounding by indication. Indeed, our data indicate that patients started on anti-TNF therapy have higher fatigue scores at baseline. TNF receptors have been identified on neurons [25] and chronic inflammation is associated with up-regulation of these TNF receptors [26]. TNF has also been implicated in pain pathways [27]; thus, in conditions such as RA the increase in TNF levels may contribute to chronic inflammatory pain. The improvement in pain and fatigue with anti-TNF therapy may be due to a direct central effect through interaction with sensory neurons.

If fatigue is to be used as an RA outcome measure, it is crucial to identify the best assessment instrument. VAS fatigue scores are simple and reproducible; however, multidimensional assessments may provide a more complete picture and improve our understanding of the clinical relationships of fatigue. We found similar results using VAS scores and SF-36 energy and vitality scores, and when Wolfe [28] compared VAS scores with three multidimensional fatigue scales he also found that the VAS fatigue scale performed favourably compared with more detailed scales. Nevertheless, other validated and detailed instruments that measure RA fatigue, such as the Multidimensional Assessment of Fatigue (MAF) [5] and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [29], may prove more valuable, especially for studies which assess the mechanism of fatigue rather than use it simply as another outcome measure.

In conclusion, high fatigue levels are common in RA and are mainly linked to pain and depression. The association with disease activity is secondary. Fatigue falls with DMARD and anti-TNF therapy. The balance of evidence suggests that fatigue is centrally mediated in established RA.

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References

1. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15.
2. Carr A, Hewlett S, Hughes R, Mitchell H, Ryan S, Carr M, Kirwan J. Rheumatology outcomes: the patient's perspective. J Rheumatol 2003;30:880–3.
3. Ahlmen M, Nordenskiold U, Archenholtz B *et al.* Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients. Rheumatol 2005;44:105–10.
4. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995;22:639–43.
5. Belza BL, Henke CJ, Yelin EH *et al.* Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res 1993;42:93–9.
6. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15.
7. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–17.
8. Balsa A, Carmona L, Gonzalez-Alvaro I *et al.* Value of Disease Activity Score 28 (DAS 28) and DAS 28-3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis. J Rheumatol 2004;31:40–6.
9. Weinblatt ME, Keystone EC, Furst DE *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35–45.
10. Strand V, Scott DL, Emery P *et al.* Leflunomide Rheumatoid Arthritis Investigators Groups. Physical function and health related quality of life: analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, or methotrexate in patients with active rheumatoid arthritis. J Rheumatol 2005;32:590–601.
11. Huyser BA, Parker JC, Thoreson R *et al.* Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998;41:2230–7.
12. Riemsma RP, Rasker JJ, Taal E *et al.* Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. Br J Rheumatol 1998;37:1042–6.
13. Rupp I, Boshuizen H, Jacobi C *et al.* Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis Care Res 2004;51:578–85.
14. Tack B. Self-reported fatigue in rheumatoid arthritis: a pilot study. Arthritis Care Res 1990;3:154–7.
15. Fifield J, Tennen H, Reisine S, McQuillan J. Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. Arthritis Rheum 1998;41:1851–7.
16. Wolfe F, Michaud K. Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: an investigation in 24,831 patients. J Rheumatol 2004;31:2115–20.
17. Suurmeijer TP, Waltz M, Moum T *et al.* Quality of life profiles in the first years of rheumatoid arthritis: results from the EURIDISS longitudinal study. Arthritis Rheum 2001;45:111–21.
18. Fifield J, McQuillan J, Tennen H *et al.* History of affective disorder and the temporal trajectory of fatigue in rheumatoid arthritis. Ann Behav Med 2001;23:34–41.
19. Crosby LJ. Factors which contribute to fatigue associated with rheumatoid arthritis. J Adv Nurs 1991;16:974–81.
20. Jump RL, Fifield J, Tennen H, Reisine S, Giuliano AJ. History of affective disorder and the experience of fatigue in rheumatoid arthritis. Arthritis Rheum 2004;51:239–45.
21. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. J Rheumatol 2004; 31:695–700.

22. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
23. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
24. Wolfe F, Michaud K. Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: an investigation in 24,831 patients. J Rheumatol 2004;31:2115–20.
25. Pollock J, McFarlane SM, Connell MC *et al*. TNF-alpha receptors simultaneously activate Ca2+ mobilisation and stress kinases in cultured sensory neurones. Neuropharmacology 2002;42:93–106.
26. Inglis JJ, Nissim A, Lees DM, Hunt SP, Chernajovsky Y, Kidd BL. The differential contribution of tumour necrosis factor to thermal and mechanical hyperalgesia during chronic inflammation. Arthritis Res Ther 2005;7:R807–16.
27. Empl M, Renaud S, Erne B *et al*. TNF alpha expression in painful and nonpainful neuropathies. Neurology 2001;56:1371–7.
28. Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. J Rheumatol 2004;31: 1896–902.
29. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 2005;32:811–9.