Fatigue is an independent outcome measure and is sensitive to change in patients with psoriatic arthritis

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Received on October 12, 2009; accepted in revised form on January 8, 2010.

ABSTRACT

Objective. *This pilot study examined sensitivity to change and relative independence of fatigue as an outcome measure in patients with psoriatic arthritis (PsA) following anti-TNF therapy.*

Methods. *Patients with PsA commencing anti-TNF therapy were evaluated at baseline and at 3 months. Fatigue was measured using a 0-10 numeric rating scale (NRS). This was a one-dimensional 11-point NRS with anchors of 0 (none) and 10 (a great deal). The words 'none' and 'a great deal' were placed under the NRS corresponding to the anchors 0 and 10, respectively. Sensitivity to change of fatigue was compared with recognised core outcomes and determined by calculating the standardised response means. Multiple regression analysis was employed to determine predictors of fatigue and their independent variance.*

Results. *Forty-one patients were evaluated. Mean (SD) fatigue levels were 5.6 (2.3) and 3.6 (2.2) (p=0.001) at baseline and at 3-months, respectively. Using the SRM, fatigue ranked sixth relative to the other measures demonstrating a moderate sensitivity to change. Noteworthy was the observation that fatigue was ranked higher than CRP. The relative independent variance in fatigue of 27% was greater than that of the core clinical measures: HAQ 21%, TJC 14%, Pain 4%, SJC 0.4%, GH 0.4%, and less than that of the laboratory measure CRP 33%.*

Conclusion. *This study demonstrated that fatigue is an independent outcome measure and is sensitive to change in patients with PsA.*

Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis and usually seronegative for rheumatoid factor (1, 2). It is a multisystem disorder which presents with a variety of patterns of cutaneous, axial skeleton and peripheral musculoskeletal manifestations. The burden of these combined disease entities has been demonstrated in terms of quality of life. Similar to rheumatoid arthritis (RA) (3, 4), pain, function and fatigue are the patient reported outcomes most frequently prioritised by patients with PsA (5).

Monitoring the course of PsA not only includes the evaluation of disease activity in the joints and skin, but also the impact of diverse features of the disease, such as fatigue, on many areas of life (6). Work to agree a 'core set' of measures for outcome studies in PsA (7), similar to the RA 'core set', was advanced through the expert 'Group for Research and Assessment of Psoriasis and Psoriatic Arthritis' (GRAPPA) initiative, (7), and further refined through the OMERACT process (8). Six core domains agreed include: peripheral joint activity count, skin activity, pain, patient global assessment, physical function, and health related quality of life. Fatigue was among other domains agreed as important, but not mandatory, for inclusion in all clinical trials or observational studies (6). Moreover, it was recommended that further research was required to elucidate its relationship to pain and to determine the best instrument to assess fatigue.

The purpose of this pilot study was to further contribute to this research agenda. Fatigue, as an outcome measure, was examined in two ways. Firstly, the discriminatory property of a the single dimension measurement scale in use was evaluated (9) and secondly, predictors of fatigue as well as the independent contribution made by fatigue to the assessment of PsA were explored.

Methods

Patient selection

This study formed part of an internal department clinical evaluation of biologic therapies, services, processes and outcome measures in preparation for the establishment of a formal database. Patients with PsA, diagnosed by a rheumatologist (10), who were prescribed anti-TNF therapy were evaluated prospectively according to a predetermined clinical protocol. Data were subsequently extracted from hospital clinical records and assessed retrospectively as part of good clinical practice review. Patient information was anonymised; neither audit nor ethical approval was required at the time this study was conducted.

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Clinical assessment

Clinical assessments were performed before and 3 months after commencement of anti-TNF therapy. Clinical measures included the ACR core set of outcome measures (11), and an assessment of fatigue, using a numeric rating scale (NRS). The six core outcomes measured included pain; 0-28 swollen joint count (SJC); 0-28 tender joint count (TJC); patient global health (GH); health assessment questionnaire (HAQ); and the acute phase marker CRP. Fatigue severity was quantified using a one-dimensional 11-point numeric rating scale (NRS) with anchors of 0 (none) and 10 (a great deal). The words 'none' and 'a great deal' were placed under the NRS corresponding to the anchors 0 and 10, respectively. These data were collected at a time when clinical measures were confined to the ACR core set. Neither data relating to skin assessment nor to the clinical subsets were captured on patients. The data collection period predated the establishment of a consensus on core domains for assessment of outcome in PsA (6).

Statistics

Sensitivity to change and its comparison with that of the core set outcome measures was demonstrated using a paired-samples *t*-test and the standardised response mean (SRM) (12). It is suggested that standardised effect sizes of 0.2–0.5 should be regarded as small, 0.5–0.8 as moderate, and above 0.8 as large. The association between fatigue and the six core measures at each time point was examined through univariate linear regression analysis. The independent contribution of fatigue measurement to the assessment of PsA, relative to the core set variables, was calculated through multiple regression analysis using backward deletion technique (13). The data utilised were the change in values at 3 months of both fatigue and each of the six core outcome measures. This statistical approach was utilised previously in a patient cohort with RA (14, 15).

Results

Clinical and demographic details

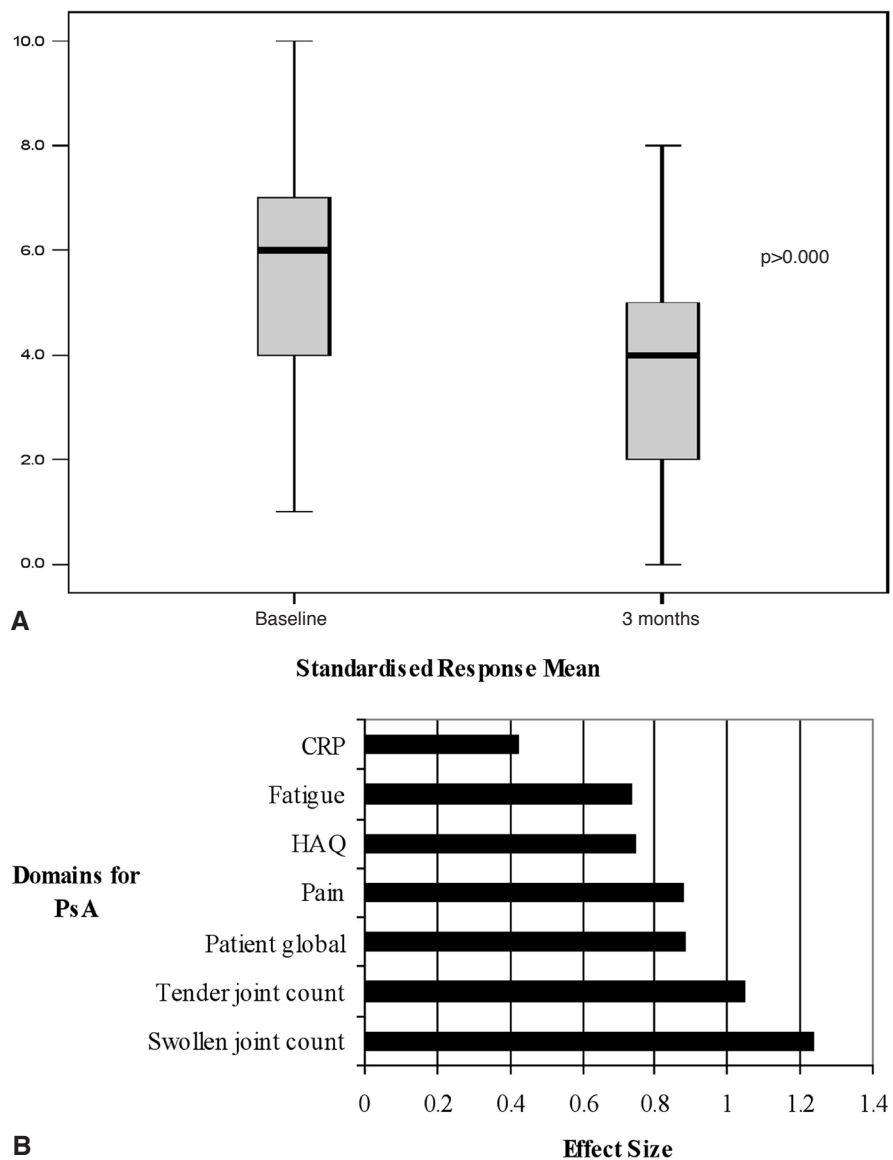Forty-one successive patients were evaluated, twenty two (54%) were fe-

Fig. 1. Sensitivity of fatigue measurement to change in PsA following 3 months treatment with TNF-α blockade (**A**). Each box plot indicates the lower and upper quartiles, the central line is the median, and the whiskers indicate the extreme values.
(**B**) The standardised response means (SRM) were used to index responsiveness of fatigue and compare it with that of the core and other important domains in PsA.

male. Mean age ± SD (range), years was 45±12.7 (15-73), mean disease duration, years 10±8.7 (0–36). Prescribed biologic therapies included etanercept 27 (66%), adalimumab 12 (29%), infliximab 2 (5%). Mean (range) baseline clinical measures included pain VAS 5.3 (0–9) mm, TJC 15.4 (0–55), SJC 14.5 (0–35), patient global health (GH) 5.8 (0–10), HAQ 1.00 (0–2.5), CRP 18.1 (1–88) (0-4 mg/L), and fatigue 5.7 (1–10).

Sensitivity to change

At baseline, mean (SD) fatigue scores were 5.71 (2.32). At 3 months, fatigue

scores had fallen to 3.96 (2.06) ($p<0.000$) (Fig. 1A). Sensitivity to change of fatigue was further examined comparing it with the sensitivity to change of the core set. Fatigue, which demonstrated a moderate sensitivity to change, ranked sixth relative to the other measures (Fig. 1B). Noteworthy was the observation that fatigue was ranked higher than CRP.

Correlates, predictors and independence of fatigue

Univariate regression analyses of the relationship between fatigue and the individual measures were similar at both time

Table I. Univariate linear regression analysis of fatigue and core domains for PsA at baseline and 3 months.

Variable	r	β Coefficient	SE(β)	t-value	*p*-value	R² (%)
Baseline Fatigue						
GH	0.538	0.536	0.135	3.981	0.000*	0.289 (29)
HAQ	0.477	1.582	0.569	3.394	0.002*	0.228 (23)
Pain	0.472	0.434	0.130	3.339	0.002*	0.222 (22)
CRP	0.261	0.030	0.019	1.643	0.109	0.068 (7)
TJC	0.189	0.034	0.029	1.189	0.242	0.036 (4)
SJC	0.051	0.013	0.041	0.317	0.753	0.003 (0)
3-month Fatigue						
GH	0.613	0.619	0.131	4.736	0.000*	0.376 (38)
HAQ	0.549	1.703	0.432	3.942	0.000**	0.302 (30)
Pain	0.529	0.480	0.123	3.892	0.000*	0.280 (28)
TJC	0.319	0.090	0.044	2.023	0.051	0.102 (10)
CRP	0.025	0.004	0.028	0.146	0.885	0.001 (0)
SJC	-0.004	-0.003	0.098	-0.026	0.979	0.000 (0)

*Correlation is significant at 0.01 level (2-tailed);
**Correlation is significant at 0.05 level (2-tailed).

Table II. Regression of core set variables and fatigue*.

Measure (Change 0-3 months)	R Multiple Correlation	R² Explained Variance (%)	1-R² Unexplained Variance (%)	Relative Unexplained Variance (%)
CRP	0.36	0.13 (13)	0.87 (87)	33
Fatigue	0.53	0.28 (28)	0.72 (72)	27
HAQ	0.68	0.46 (46)	0.54 (54)	21
Tender joint count	0.79	0.62 (62)	0.38 (38)	14
Pain	0.95	0.90 (90)	0.1 (10)	4
Swollen joint count	0.99	0.99 (99)	0.01 (1)	0.4
Global Health	0.99	0.99 (99)	0.01 (1)	0.4

*Firstly, fatigue and then each one of the 6 core outcome measures were taken as the dependent variable and regressed in turn against all the other outcomes together (independent variables).
R: multiple correlation coefficient with changes in the linear combination of the rest of the measures;
R²: coefficient of determination or explained variance; proportion of variance in the measure associated;
1-R²: proportion of variance not predicted by the rest of the measures; Relative unexplained variance: unexplained variance multiplied by 100 and divided by the sum of all the unexplained variances.

points. At baseline, fatigue significantly correlated with global health (r=0.54, *p*=0.000), HAQ (r=0.47, *p*=0.002) and pain (r=0.47, *p*=0.002). Findings were similar at 3-month follow up: global health (r=0.61, *p*=0.000), HAQ r=0.55, *p*=0.000), pain (0.53, *p*=0.000). At baseline and (3 months) GH, HAQ and pain explained 29% (38%); 23% (30%); and 22% (28%) of the variance in NRS fatigue scores, respectively (Table I). The examination of the independent contribution of fatigue to the assessment of outcome at 3-months, relative to the other 6 core domains, are shown in Table II: CRP (33%), fatigue (27%) had HAQ (21%) had the highest relative values. The measures that made the lowest independent contribution to assessment of outcome were SJC and GH, at 0.04% each (Table II).

Discussion

This pilot study provides further evidence of the validity of fatigue as an outcome measure in PsA. The sensitivity to change of fatigue in patients prescribed anti TNF therapy was demonstrated. The primary correlates and predictors of fatigue, namely GH, function and pain were similar before and after therapy. The unique contribution of fatigue to the assessment of outcome in PsA was also demonstrated at 3 months. The patient reported outcomes fatigue, and HAQ contributed most unique information. In agreement with previous findings, this suggests that fatigue is an important independent outcome in the comprehensive assessment of PsA, as opposed to being subsumed under other measures (16).

To date, relatively few studies have been

undertaken to compare the performance of single item scales versus multidimensional scales in the assessment of fatigue in PsA. The most widely utilised instruments to measure fatigue in PsA include the Fatigue Severity Scale (FSS) and the Functional Assessment of Chronic Illness Therapy (FACIT). While both are regarded as one-dimensional tools, they do contain 9 and 13 points respectively (17). They are most frequently employed in clinical trials as opposed to routine clinical practice. A modified version of the FSS has been shown to distinguish between patients with PsA and controls, and to correlate with disease activity (18). The validity and reliability of the FACIT in the measurement of fatigue in PsA has been demonstrated (17). However, such multiple question tools carry both responder and administrator burden and are of limited use in daily clinical practice (19, 20). This study provides new information on the measurement properties of a one-dimensional fatigue scale in PsA.

The ability to measure change is regarded as an essential criterion of all measurement instruments (9). Both the responsiveness and sensitivity to change of the NRS was previously demonstrated in patients with RA (15). This study confirms the responsiveness of the NRS in PsA, by detecting statistically significant difference in fatigue levels 3 months after commencing anti TNF therapy and its moderate sensitivity to change when compared the core set measures. Fatigue has been recently recognised as an important patient reported symptom in PsA and specific data in relation to its appropriate assessment and management are limited (17, 21, 22). This study provides new evidence on the suitability of a single item NRS for quantifying fatigue in PsA.

It has been suggested that fatigue in PsA is a domain which could be subsumed under patient global health assessment (22). However, through both the GRAPPA (5) and OMERACT process (6), the importance of fatigue as a patient reported outcome has been endorsed. Though further study was recommended to examine its relationship with or possible redundancy in relation to other disease related factors (6, 21).

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This study confirms the association between the outcomes of global health, function and pain using a single item NRS. A recent large cross-sectional study of PsA demonstrated that fatigue is associated with pain, female sex, physical functional disability, medication status and psychological distress. It was also demonstrated that measuring fatigue provided information on disease outcome additional to that provided by the core set (21). Fatigue has been shown to make a unique contribution to the assessment of outcome in RA in a similar biologic therapy longitudinal observational study (15). This concise report provides evidence which supports previous findings on the uniqueness of fatigue in the assessment of outcome in PsA.

Agreement exists on the importance of fatigue as a patient reported outcome across the major chronic rheumatic diseases such as RA, PsA and systemic lupus erythematous. Moreover, assessment of fatigue provides important information on the assessment of health related quality of life in these respective disease groups (4, 14, 15, 21, 23-24).

The feasibility of single item one-dimensional scales is an important determinant of their successful use in daily clinical practice. Moreover, it is an important consideration in instrument choice to ensure ongoing assessment of this patient reported outcome (20). Limitations of this study include the small sample size, lack of data on psychosocial variables, sleep, skin assessment, and on the comparative performance between one and multi-dimensional scales used to measure fatigue in PsA. Furthermore, the interpretation of the multiple regression needs to be cautious as the ratio of cases to independent variables is low (25). These limitations including assessment of psoriasis will be addressed in future studies.

In conclusion, this pilot study demonstrated that a one-dimensional measure of fatigue is sensitive to change in patients with PsA. The interventional nature of the study contributes to the validity of this observation. Further evidence of the unique contribution to the assessment of disease outcome in PsA highlights the clinical importance of fatigue in the comprehensive assessment of disease in order to optimise treatment interventions, and quality of life.

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