Assessment of fatigue in the management of patients with ankylosing spondylitis

E. Dernis-Labous, M. Messow and M. Dougados

**Background.** Pain, stiffness, functional impairment, range of motion and quality of life are the main conventional domains used in studies evaluating ankylosing spondylitis (AS). However, fatigue has been reported as the major complaint of AS patients.

**Objectives.** To evaluate fatigue as a potential independent domain in comparison with the ‘conventional’ ones and to evaluate the sensitivity to change after non-steroidal anti-inflammatory drug (NSAID) therapy.

**Methods.** Patients were classified as having painful AS (modified New York criteria). The following variables were recorded at baseline and after 6 weeks of therapy (either placebo or NSAIDs): pain (VAS), function (Bath Ankylosing Spondylitis Functional Index), patient’s global assessment (VAS), inflammation (night pain), morning stiffness, metrology (Schober test, finger-to-floor) and fatigue using 0–100 VAS scale. Analysis consisted of (i) the prevalence of fatigue (VAS value of at least 50 mm), (ii) the independence of the information evaluated using a regression model, and (iii) the sensitivity to change, by calculating the standardized response mean (mean change/s.d. change) (SRM) between placebo and NSAID group.

**Results.** Fatigue was considered important in 401 patients (out of 639: 63%). The information provided by the variables ‘pain’, ‘function’ and ‘global assessment’ explained only 44% of the variability of the variable ‘fatigue’ (similar analyses considering ‘pain’ on the one hand and ‘function’ on the other hand as the dependent variables showed an $R^2$ value of 34 and 60%, respectively). The NSAID treatment effect (SRM) was higher for the variables ‘pain’ and ‘function’ (0.76 and 0.71, respectively) than for the variable ‘fatigue’ (0.34).

**Conclusion.** This study strongly suggests that fatigue should be considered as an independent domain to be systematically evaluated in AS patients and that conventional therapy such as NSAIDs have a lower effect on this domain than on pain or functional impairment.

**Key words:** Fatigue, Ankylosing spondylitis.

Fatigue can be defined either as a progressive impairment of generating capacity of muscle (peripheral or muscle fatigue) or a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a feeling of weariness, sleepiness and irritability [1]. Fatigue is the enduring subjective sensation of general tiredness or ‘exhaustion’. In healthy subjects the phenomenon is of natural occurrence, but in patients it is considered a lack of energy [2].

The prevalence of fatigue in healthy adults varies from 14 to 25% [1] with gender difference (14 and 20% in males and females, respectively) [3, 4]. The lifetime prevalence is 24% in the general population. Fatigue is present in a wide variety of medical illnesses such as...
anaemia, thyroid diseases, renal failure, liver, pulmonary or cardiovascular disturbances and clinically apparent depression [2]. Fatigue is strongly associated with psychological factors and sleep disturbance [1]. In the elderly, fatigue is related to various factors: psychosocial factors (such as depression, anxiety and social support), physical inactivity, musculoskeletal factors, high body mass index, deterioration of cardiovascular function and reduced aerobic work capacity [4]. Therefore, fatigue can be explained by (i) demographic factors, (ii) psychological and social factors and (iii) disease-related variables.

Most patients with rheumatic diseases complain of chronic generalized fatigue (i.e. lupus, rheumatoid arthritis, Sjögren’s disease) [1, 5–7]. In rheumatoid arthritis, 80 to 93% of patients complain of fatigue. Patients with rheumatoid arthritis reported a higher fatigue score than age- and sex-matched controls in degree of severity and impact of fatigue [3].

In ankylosing spondylitis, pain, fatigue and stiffness are the most commonly reported symptoms [8–10]. In a survey of 1950 patients suffering from ankylosing spondylitis, which addressed the domain considered as the most disabling, pain was considered the predominant disabling domain by 34% of the patients, stiffness by 25% and fatigue by 6% [8]. Fatigue has been considered so important by some experts that it was included in a core set of variables that evaluate the symptomatic severity of the disease. For example, the Bath team of rheumatologists proposed a construct index—the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)—evaluating five domains, including fatigue (the four others are axial pain, peripheral pain, enthesiopathy pain and stiffness) [11].

Moreover, fatigue was considered as an important domain by the Assessments in Ankylosing Spondylitis (ASAS) group [12]. The ASAS task force is an international group of experts dealing with outcome measures in ankylosing spondylitis. Through different approaches this group proposed a set of clinical and biological variables that should be considered when conducting clinical studies in AS. The ASAS group suggested that fatigue be evaluated, but they emphasized the lack of relevant tools to evaluate it.

These arguments prompted us to conduct a study to evaluate the prevalence, the clinical relevance and the effect of NSAID therapy on fatigue in a large sample of AS patients.

Patients and methods

Patients

The information collected on patients who participated in two large randomized NSAID trials was used. These studies were reported previously and both were double-blind, placebo-controlled, 6-week trials. [11, 13]. Briefly, out-patients with active disease fulfilling the modified New York criteria for ankylosing spondylitis entered the study. Informed consent was obtained for all patients. All the patients had, at entry, a spinal active disease defined by a level of pain (visual analogue scale, VAS, 100 mm) of at least 40 mm, 2 to 14 days after NSAID discontinuation, and a flare defined by an increase in pain level of at least 30% between the time of NSAID discontinuation and baseline.

Assessment criteria

Fatigue was evaluated using the first item of the BASDAI questionnaire: ‘How would you describe the overall level of fatigue/tiredness you have?’ The answer was recorded using a 0–100 VAS scale (0 = the absence of fatigue and 100 = worst condition imaginable).

Other outcome variables evaluated six further domains: (i) pain was assessed using a 0–100 mm VAS; (ii) patient’s global assessment of disease activity using a 0–100 mm VAS; (iii) functional impairment scale, using the Bath Ankylosing Spondylitis Functional Index (BASFI 0–100: 0 = performed without difficulty and 100 = impossible to perform), which focuses on 10 questions related to daily activities, measured on a visual analogue scale in which the final score is the mean of the value of the 10 questions; (iv) stiffness, using the morning stiffness intensity and duration (0–100 mm VAS); (v) range of motion, using different metrological instruments: chest expansion, finger-to-floor distance, modified Schober test; and (vi) inflammation, using C-reactive protein (CRP; mg/l) and night disturbance (Likert scale).

Statistical analysis

The first step of the analysis was evaluation of the prevalence of fatigue in painful ankylosing spondylitis. For this purpose, we have evaluated the distribution of the level of fatigue using a 0–100 mm VAS in the whole population at baseline. Moreover, and in accordance with a previous study in this field [14], the presence of fatigue was defined as a VAS value of at least 50 mm. This analysis was made on the data collected at baseline.

In order to assess the construct validity of the variable, we have evaluated the correlation between this variable and the other ones considered to be related to the ankylosing spondylitis process (pain, functional impairment, inflammation, range of motion). Using this technique as previously evaluated in different diseases, it was anticipated that such a coefficient for convergent construct validity would fall between 0.2 and 0.6 [15].

The second step was to evaluate the characteristics of patients with or without fatigue (defined by a fatigue VAS of at least 50 mm). For this purpose, we conducted both univariate and multivariate analyses.

The third step was the evaluation of the specificity of the domain ‘fatigue’. For this purpose, and as a preliminary analysis, we conducted multivariate analyses in which pain, functional impairment and patient’s global assessment were defined consecutively as the dependent variable and all the other variables the independent variables. With this technique a coefficient of regression $R^2$ provided a value between 0 and 1. In this model, a value close to 0 means that the information given by the tested variable is indeed not linked to the other variables and that it can be considered as independent or specific. These analyses were conducted not only at baseline in the entire group of patients (while the patients had a painful disabling disease), but also at week 6 in the subgroup of patients who were receiving active treatment (NSAIDs), i.e. while most of them had a stabilized disease.

The fourth step consisted of evaluation of the discriminant capacity and the sensitivity to change of the variable ‘fatigue’ in comparison with the other variables. For this purpose the standardized response mean (SRM; the ratio of the mean
change over the standard deviation of the change) was calculated for the placebo and NSAID groups [16]. The difference between the SRM in the placebo and in the active treatment group yields an evaluation of the discriminant capacity of the variable. A value higher than 0.60 is usually considered as a relevant discriminant capacity, and a value below 0.20 is usually considered of no relevance [16].

Ethical approval was obtained for the studies and consent was obtained for all the patients.

**Results**

**Patients and study course**

Table 1 summarizes the characteristics of the 639 evaluated patients (473 in the first trial and 166 in the second). There were no statistically significant differences in the baseline characteristics between the patients in the active and in the placebo group. During the 6 weeks of the study, 155 patients withdrew owing to lack of efficacy or toxicity.

**Prevalence of fatigue**

A VAS fatigue value greater than 50 mm was observed in 63% of patients at entry (401/639). Figure 1 shows the distribution of the variable VAS fatigue 0–100 mm.

**Characteristics of the patients with regard to the presence or absence of fatigue**

Table 1 summarizes the main characteristics of the patients with or without fatigue (defined by a fatigue VAS above or below 50 mm). Patients with a fatigue VAS above 50 mm also had a more painful (VAS pain) and disabling (BASDAI) disease. There was a higher prevalence of women in the patients with fatigue (see Table 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole (n = 639)</th>
<th>Fatigue (+) (n = 401)</th>
<th>Fatigue (−) (n = 238)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41.7 ± 11.9</td>
<td>42.1 ± 11.9</td>
<td>40.9 ± 11.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex [male/female (%F)]</td>
<td>484/155 (32)</td>
<td>115/286 (29)</td>
<td>40/198 (17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>12.1 ± 9.5</td>
<td>11.8 ± 9.0</td>
<td>12.5 ± 10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Global pain (VAS)</td>
<td>69.9 ± 16.5</td>
<td>74.5 ± 15.3</td>
<td>62.2 ± 15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Axial pain (VAS)</td>
<td>65.7 ± 21.8</td>
<td>73.9 ± 17.1</td>
<td>51.8 ± 21.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral pain (VAS)</td>
<td>28.2 ± 29.1</td>
<td>33.7 ± 31.5</td>
<td>18.8 ± 21.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global assessment patient (VAS)</td>
<td>63.1 ± 20.4</td>
<td>69.1 ± 18.3</td>
<td>53 ± 19.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BASFI</td>
<td>48.3 ± 22.3</td>
<td>56.7 ± 20.4</td>
<td>34.3 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning stiffness intensity (VAS)</td>
<td>61.1 ± 25.5</td>
<td>67.8 ± 23.8</td>
<td>49.7 ± 24.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning stiffness duration (VAS)</td>
<td>54.4 ± 31.2</td>
<td>59.8 ± 31.0</td>
<td>45.2 ± 29.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>13 ± 16</td>
<td>11.9 ± 15.3</td>
<td>14.9 ± 16.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Finger-to-floor (cm)</td>
<td>49.4 ± 29.8</td>
<td>52.2 ± 30.2</td>
<td>44.8 ± 28.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Schober index</td>
<td>72.6 ± 15.3</td>
<td>72.6 ± 15.4</td>
<td>72.6 ± 15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Chest expansion (mm)</td>
<td>61.2 ± 21.6</td>
<td>63.2 ± 21.1</td>
<td>57.8 ± 22</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*a’Fatigue +’ group compared with ‘fatigue −’ group.

**Distribution of the variable fatigue**

![Distribution of the variable fatigue](image)

Fig. 1. Distribution of the variable fatigue (VAS 100 mm) in 639 patients suffering from active painful ankylosing spondylitis.
**Construct validity**

The coefficient of correlation between the studied variable (fatigue) and the variables previously considered to reflect the activity of the disease are given in Table 2. Such coefficients of correlation fall in the expected range between 0.2 and 0.6 [except for one variable evaluating the domain ‘inflammation’ (CRP) and for all the variables evaluating the domain ‘range of motion’].

**Evaluation of the specificity of the domain fatigue**

At baseline, the multivariate analyses considering pain (VAS), functional impairment (BASFI) and patient’s global assessment of disease activity (VAS) as the dependant variable and all the other outcomes as the independent variables showed $R^2$ values of 60, 61 and 48% respectively. The same analysis in which fatigue was considered as the dependant variable showed an $R^2$ value of 46%. In others words, all the outcome variables (except pain, but including function, patient’s global assessment, stiffness assessment, range of motion, inflammation and fatigue) accounted for 60% of the variance in pain. The same analysis concluded that all the outcome variables (except fatigue, but including function, patient’s global assessment, stiffness assessment, range of motion, inflammation and pain) accounted for 46% of the variance in fatigue.

The same multivariate analysis performed at week 6 showed $R^2$ values of 86, 83, 77 and 63%, when considering pain, global assessment, functional impairment and fatigue as the dependant variables, respectively.

**Discriminant capacity of outcome variables**

Table 3 summarizes the changes observed during placebo and NSAID treatment and the standardized response mean of each evaluated outcome variable.

A value over 0.60 (considered as a relevant discriminant capacity) was obtained for the variable night disturbance (0.61). A value below 0.20 (considered as a poor discriminant capacity) was observed for the variables CRP and peripheral pain (0.17 and 0.17, respectively). A value of 0.35 was obtained for the variable fatigue.

**Discussion**

This study confirms the relatively high prevalence of fatigue in patients suffering from ankylosing spondylitis. Such fatigue is correlated with painful and disabling disease but should be considered as a specific domain (independent from pain or functional impairment). This study also suggests that fatigue is not well controlled by NSAID therapy.

This study was conducted in patients with axial involvement of the disease, using a simple VAS scale to evaluate the intensity of fatigue. Additionally, the discriminant capacity of fatigue was evaluated in NSAID trials considering NSAIDs as the gold standard for therapy.
Assessment of fatigue in AS

Table 3. Standardized response mean (mean change/s.d. mean change)

<table>
<thead>
<tr>
<th>Variable</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASFI</td>
<td>0.59</td>
</tr>
<tr>
<td>Patient’s global assessment (VAS)</td>
<td>0.56</td>
</tr>
<tr>
<td>Axial pain (VAS)</td>
<td>0.51</td>
</tr>
<tr>
<td>Morning stiffness, duration (VAS)</td>
<td>0.46</td>
</tr>
<tr>
<td>Morning stiffness, intensity (VAS)</td>
<td>0.40</td>
</tr>
<tr>
<td>Finger-to-floor</td>
<td>0.41</td>
</tr>
<tr>
<td>Chest expansion</td>
<td>0.37</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.35</td>
</tr>
<tr>
<td>Schober</td>
<td>0.22</td>
</tr>
<tr>
<td>CRP</td>
<td>0.17</td>
</tr>
<tr>
<td>Peripheral pain (VAS)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Focusing on axial involvement of the disease helped deal with a homogeneous group of patients. However, these results cannot be generalized to other patients, which underlines the need to evaluate fatigue in other clinical manifestations of spondylarthropathy; for instance, to determine whether results are similar in patients suffering from peripheral articular arthritis or enthesiopathy.

Fatigue was evaluated using a simple VAS scale. VAS represents a single dimension of fatigue (severity or degree), but does not include other dimensions such as duration. The VAS scale is a comprehensive tool that measures fatigue severity as well as other individual components of fatigue [1]. The multidimensional assessment of fatigue (MAF) scale contains 16 items and measures five dimensions of fatigue (degree, severity, distress, impact on activities of daily living, timing of the fatigue over the past week). VAS level of fatigue is one component of the MAF scale and has established reliability and validity in adults with rheumatoid arthritis [3], ankylosing spondylitis [8] and also in non-rheumatic diseases [2]. Moreover, it might be of interest to note whether such fatigue is permanent, or mainly experienced in the morning or in the evening. Such detailed information was not available in our study.

Van Tubergen [14] used both the VAS scale and the multidimensional fatigue inventory (MFI) scale to evaluate fatigue in 812 patients with ankylosing spondylitis. MFI consists of 20 items covering five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity and mental fatigue. They concluded that BASDAI fatigue (VAS) and MFI had equal properties with respect to responsiveness and reproducibility but, as expected, MFI provided more insight into specific dimensions of fatigue.

As previously reported we confirmed that fatigue is commonly observed (65% of the patients reported by Calin [8] and 62.7% in the present study). Such levels of fatigue might be influenced by antidepressants [17]. It has been reported that antidepressants are frequently prescribed in patients with painful ankylosing spondylitis. Such information was not available in our study and therefore the impact of such therapy on the level of fatigue in ankylosing spondylitis remains to be further evaluated. In epidemiological and/or therapeutic studies, the clinical level of disease activity is usually assessed by the level of pain and functional disability (considering de facto that other domains such as fatigue are dependent on these two major domains). This study confirms the existence of a correlation between fatigue and these domains, arguing in favour of an acceptable construct validity [15]. However, the analyses we conducted strongly suggest that fatigue should be considered as an independent and specific domain, like pain, functional impairment and patient’s global assessment.

This study confirms that NSAID therapy is a very efficient symptomatic therapy with a strong reduction of pain, functional impairment and patient’s global assessment. In contrast, the change in the level of fatigue after NSAID therapy is of lower magnitude. These results suggest that there is a neglected goal in the management of ankylosing spondylitis. The recently reported data obtained after other treatments such anti-tumour necrosis factor (TNF) therapies are interesting to consider in this respect. Fatigue should be included as a specific outcome variable in studies of new agents such as anti-TNFα therapy.

The authors have declared no conflicts of interest.

References