Adalimumab Reduces Pain, Fatigue, and Stiffness in Patients with Ankylosing Spondylitis: Results from the Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis (ATLAS)

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ABSTRACT. ***Objective.*** To evaluate the effect of adalimumab on pain, fatigue, and stiffness in patients with active ankylosing spondylitis (AS).

Methods. The Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis (ATLAS) was an ongoing 5-year study that included an initial 24-week, randomized, placebo-controlled, double-blind period. Patients were randomized to adalimumab 40 mg or placebo by subcutaneous injection every other week. Pain was assessed by the bodily pain domain scores of the Medical Outcomes Study Short Form-36 Health Survey (SF-36) and also by total back pain and nocturnal pain using visual analog scales. Fatigue was measured by the SF-36 vitality domain and question 1 of the Bath AS Disease Activity Index (BASDAI). Morning stiffness was measured by the mean of BASDAI questions 5 and 6.

Results. Of 315 patients enrolled, 208 received adalimumab 40 mg and 107 received placebo. At Week 12, adalimumab-treated patients experienced significant improvement compared with placebo-treated patients in the SF-36 bodily pain score ($p < 0.001$), total back pain score ($p < 0.001$), nocturnal pain score ($p < 0.001$), fatigue ($p < 0.01$), and morning stiffness ($p < 0.001$). Pain, fatigue, and morning stiffness were significantly correlated ($p < 0.001$) with baseline values of patient-reported health-related quality of life (HRQOL), and physical function, and with improvements in these values at Week 12 by regression analysis. Treatment effects occurred rapidly (within 2 wks) and were maintained through 24 weeks of treatment.

Conclusion. Adalimumab significantly improved symptoms of pain, fatigue, and stiffness in patients with AS. Improved symptoms were associated with improved physical function and HRQOL. (First Release May 15 2008; J Rheumatol 2008;35:1346–53)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
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Ankylosing spondylitis (AS) is a chronic, progressive, inflammatory disease primarily affecting the axial skeleton, peripheral joints, and entheses. AS is typically diagnosed between 20 and 40 years of age, and disease progression is associated with pain, joint stiffness, and a loss of spinal mobility that can lead to severe functional disability[1].

The most commonly reported symptoms of AS are pain, fatigue, and stiffness[2-4]. In a longitudinal study, the most prevalent concerns of patients with AS were stiffness (90%), pain (83%), fatigue (62%), and poor sleep (54%)[5]. Pain, fatigue, and stiffness are core components of the Bath AS Disease Activity Index (BASDAI)[6]. Pain and stiffness are also considered by the Assessments in SpondyloArthritis International Society (ASAS) to be important components of the efficacy measures (ASAS20, ASAS40, ASAS 5/6, and partial remission response criteria) recommended for the evaluation of patients with AS[7,8].

The European League Against Rheumatism and ASAS recommend administration of tumor necrosis factor (TNF) antagonists for patients with persistently high disease activity, without requiring disease modifying antirheumatic drug (DMARD) use before or during anti-tumor necrosis factor

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(TNF) treatment[9]. Of the 3 TNF antagonist agents available for the treatment of AS — adalimumab, etanercept, and infliximab — adalimumab is the only fully-human anti-TNF monoclonal antibody. The Adalimumab Trial Evaluating Long-Term Efficacy and Safety for Ankylosing Spondylitis (ATLAS) demonstrated that adalimumab was well-tolerated and efficacious in treating patients with AS[10]. ATLAS also demonstrated that adalimumab significantly improves both health-related quality of life (HRQOL) and physical function in patients with AS[11].

Our objective was to evaluate the effect of adalimumab on pain, fatigue, and morning stiffness and to evaluate the relationship between these symptoms and overall HRQOL and physical function in patients with AS who participated in ATLAS.

MATERIALS AND METHODS

Patients and study design. ATLAS was a multicenter, randomized, double-blind, placebo-controlled, Phase III study designed to demonstrate the safety and efficacy of adalimumab in patients with active AS (ClinicalTrials.gov NCT00085644). Complete methodologic details of ATLAS have been published[10]. Patients who were at least 18 years of age were recruited from 43 sites (21 in the United States and 22 in Europe). Eligibility criteria included a diagnosis of AS according to the modified New York criteria[12] and an inadequate response or intolerance to at least 1 nonsteroidal antiinflammatory drug (NSAID). Patients for whom 1 or more DMARD had failed were also allowed to participate. Patients were randomized in a 2:1 ratio to receive either adalimumab 40 mg or placebo subcutaneously every other week for 24 weeks (Abbott Laboratories, Abbott Park, IL, USA). Participants who did not achieve at least a 20% response according to the ASAS criteria for improvement (ASAS20) at Weeks 12, 16, or 20 were eligible to receive open-label treatment with adalimumab 40 mg every other week. After Week 24, patients were treated with adalimumab in an open-label extension period for up to 5 years.

Patient-reported outcome (PRO) measures. Total back pain: The total back pain measure assessed the amount of back pain at any time during the previous week. Total back pain was scored by patients on a 0–100-mm visual analog scale (VAS).

Nocturnal pain: The nocturnal pain measure assessed the amount of back pain at night during the past week. Nocturnal pain was scored by patients on a 0–100-mm VAS.

Medical Outcomes Study Short Form-36 Health Survey (SF-36): The SF-36 is a generic health status instrument developed for use in primary care settings and chronic disease populations[13]. The SF-36 consists of the following 8 domains: physical function, bodily pain, role limitations–physical, general health, vitality, social function, role limitations–emotional, and mental health. In ATLAS, the bodily pain domain was used to evaluate overall pain and the vitality domain (which includes energy level and fatigue) was used to evaluate overall fatigue. All domains assessed by the SF-36 questionnaire require patients to consider a 4-week recall period. Each domain score ranges from 0 to 100, with higher scores reflecting better health status. The SF-36 domain scores have excellent reliability and good construct validity across the general population in the US and across many chronic disease populations[13,14], including patients with AS[15-19]. A difference of 5 to 10 points in an SF-36 domain score is considered the minimum clinically important difference[20].

Bath AS Disease Activity Index (BASDAI): The BASDAI is a construct index using patient-reported measures of disease activity in AS. These include measures of severity of fatigue, spinal and peripheral joint pain, localized tenderness, and morning stiffness (both qualitative and quantitative responses are required)[6]. Fatigue was evaluated on a 0–10-cm VAS using question 1 of the BASDAI questionnaire, "How would you describe the overall level of fatigue/tiredness you have?". Morning stiffness (both intensity and duration) was scored as the mean of BASDAI questions 5 and 6, which are reported by the patient on a 0–10-cm VAS. Question 5 of the BASDAI, "How would you describe the overall level of morning stiffness you have had from the time you wake up?", was assessed on a range from none to very severe. Question 6, "How long does your morning stiffness last from the time you wake up?", was assessed on an hourly scale from 0 to 2 or more hours.

Bath AS Functional Index (BASFI): The original BASFI used a VAS in which the final score was the mean of 10 questions related to daily activities; each question was answered using a 0–10-cm VAS, where 0 indicated that the activity was performed without difficulty and 10 indicated that the activity was impossible to perform[21]. In our study, the BASFI score was assessed using a 0 to 10 scale.

AS Quality-of-Life Questionnaire (ASQOL): The ASQOL is a needs-based disease-specific instrument designed to measure HRQOL in patients with AS[22]. Patients answer yes or no to 18 items that assess the current effect of AS on their HRQOL.

Schedule of assessments: Total back pain, nocturnal pain, BASDAI measures of fatigue and morning stiffness, and BASFI were assessed at baseline and at Weeks 2, 4, 8, 12, 16, 20, and 24. The SF-36 and ASQOL were completed at baseline and at Weeks 12 and 24.

Statistical analysis. Efficacy analyses of the pain, fatigue, and morning stiffness endpoints were performed on the intention-to-treat population, defined as all randomized patients who received at least 1 dose of the study medication. Mean changes in continuous variables from baseline to Weeks 12 and 24 were compared for adalimumab and placebo treatment groups using analysis of covariance (ANCOVA). Each ANCOVA model included a factor for treatment and was adjusted for baseline. For analyses of continuous variables, the last observation was carried forward to record patient data for those who missed an assessment or elected to enter open-label treatment before Week 24.

Regression analyses were used to determine the cross-sectional relationship between measures of patient-reported pain, fatigue, and stiffness and overall HRQOL (measured by ASQOL) and physical function (measured by BASFI). Three regression models were specified using baseline scores. Model 1 included selected demographic (age, sex) and clinical variables (duration of AS, physician's global assessment of disease activity). Pain, fatigue, and stiffness measures were added to Models 2 and 3, using total back pain, BASDAI fatigue, and BASDAI stiffness scores for Model 2 and using SF-36 bodily pain domain, SF-36 vitality domain, and BASDAI stiffness scores for Model 3. The regression analysis substituting SF-36 bodily pain and vitality scores for back pain and BASDAI scores was designed to determine the generalizability of these findings to multi-item pain- and fatigue-related scales.

Similar models were used to determine the association between the changes from baseline to Week 12 in measures of pain, fatigue, and stiffness symptoms and also the changes from baseline to Week 12 in measures of overall HRQOL, function, and physician-assessed disease activity.

RESULTS

Patients. A total of 315 patients with active AS participated in ATLAS; 208 were randomized to receive adalimumab and 107, to receive placebo. Most patients were Caucasian (95.6%), male (74.9%), and positive for the HLA-B27 allele (78.7%). The average age was 42.2 years, and mean disease duration was 10.6 years. The 12-week, double-blind study period was completed by 98.1% of adalimumab-treated patients and 96.3% of placebo-treated patients. By Week 24, 94.0% of randomized patients remained in the study.

Baseline assessments. Baseline demographic and clinical

characteristics were similar between treatment groups, and there were no statistically significant differences in mean baseline pain, fatigue, or morning stiffness scores (Table 1). A summary of baseline SF-36 scale scores for all patients in ATLAS is presented in Figure 1.

Efficacy results. Mean changes from baseline to Weeks 12 and 24 in pain, fatigue, and stiffness scores for both adalimumab- and placebo-treated patients are summarized in Table 2.

Pain assessments: Rapid and statistically significant improvement occurred as early as 2 weeks for adalimumab-treated patients compared with placebo-treated patients for total back pain scores [–19.5 (95% confidence interval [CI] –22.3 to –16.7) vs –3.3 (95% CI –7.2 to 0.6)] and nocturnal back pain scores [–20.1 (95% CI –23.1 to –17.1) vs –4.9 (95% CI –9.1 to –0.8)]. By Week 12, the mean total back pain score improved by 27.3 points (95% CI –30.8 to –23.9) in adalimumab-treated patients compared with 8.4 points (95% CI –13.2 to –3.6) in placebo-treated patients. The mean nocturnal pain score improved by 26.0 points (95% CI –29.5 to –22.5) in the adalimumab group compared with 8.0 points (95% CI –12.9 to –3.1) in the placebo group at Week 12. There was also significant improvement in SF-36 bodily pain scores at Week 12 for patients treated with adalimumab compared with placebo (19.4 vs 6.2; $p < 0.001$). Significant improvements in all 3 pain measures were sustained through Week 24 (Table 2).

Fatigue assessments: After 2 weeks of treatment, adalimumab-treated patients reported significant improvement in fatigue compared with placebo-treated patients (BASDAI fatigue, –1.1 vs –0.3; $p < 0.001$). By Week 12, fatigue scores improved by 2.2 points (95% CI –2.5 to –1.8) in adalimumab-treated patients compared with 0.7 points (95% CI –1.2 to –0.2) in placebo-treated patients. The reduction in fatigue as measured by BASDAI question 1 was maintained through Week 24 in the adalimumab group (Table 2). Further, the mean change from baseline to Week 12 in SF-36 vitality scores improved more in the adalimumab group compared with the placebo group (12.9 vs 6.8; $p < 0.01$), and this mag-

Table 1. Baseline demographics and clinical characteristics. Except where indicated, all values are mean ± standard deviation.

Characteristic	Placebo, n = 107	Adalimumab 40 mg Every Other Week, n = 208
Age, yrs	43.4 ± 11.3	41.7 ± 11.7
Male, n (%)	79 (73.8)	157 (75.5)
White, n (%)	99 (92.5)	202 (97.1)
Body weight, kg	79.8 ± 18.4	81.9 ± 17.8
Disease duration, yrs	10.0 ± 8.3	11.3 ± 10.0
Total back pain, 0–100-mm VAS	67.2 ± 21.5	64.4 ± 20.9
Nocturnal pain, 0–100-mm VAS	64.6 ± 24.0	60.7 ± 23.5
BASDAI fatigue, 0–10-cm VAS	6.7 ± 1.9	6.5 ± 2.0
BASDAI stiffness, 0–10-cm VAS	6.7 ± 1.9	6.7 ± 2.0
Short Form-36 bodily pain domain, 0–100	29.8 ± 15.0	31.7 ± 16.7
Short Form-36 vitality domain, 0–100	34.0 ± 16.5	32.6 ± 18.0

BASDAI fatigue was the mean of question 1; BASDAI stiffness was the mean of questions 5 and 6. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, VAS: visual analog scale.

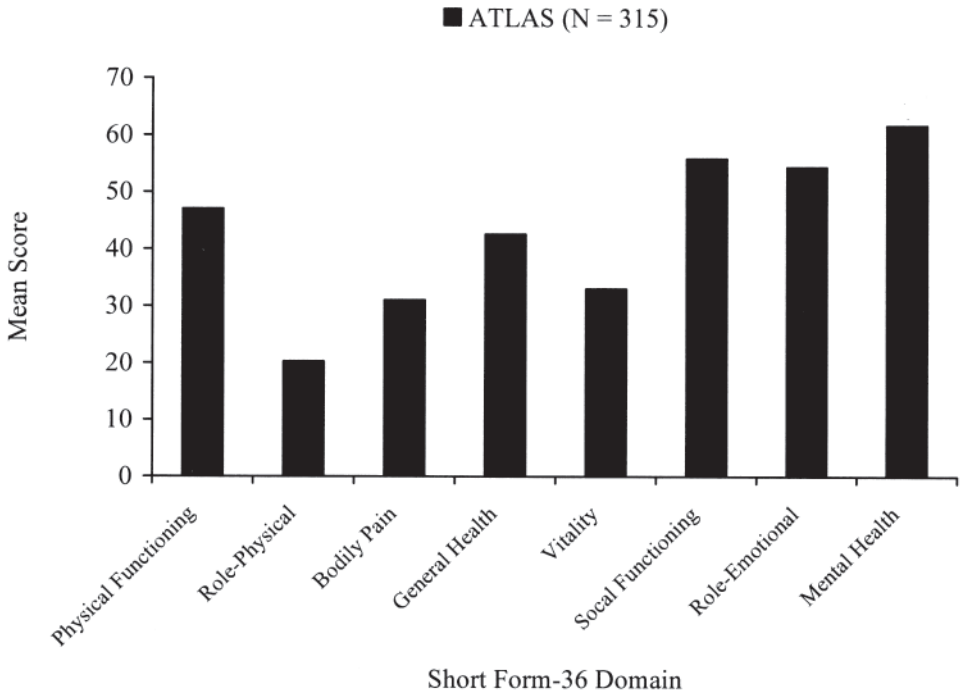

Figure 1. Mean SF-36 Health Survey domain scores for all patients with ankylosing spondylitis (AS) who participated in Adalimumab Trial Evaluating Long-Term Efficacy and Safety for AS (ATLAS).

Table 2. Summary of mean changes from baseline to Week 12 and from baseline to Week 24, by treatment group. All values are the adjusted mean ± SEM.

Patient-Reported Outcome Measure	Baseline to Week 12 Placebo, n = 107	Adalimumab, n = 208	p	Baseline to Week 24 Placebo, n = 107	Adalimumab, n = 208	p
Pain assessment						
Total back pain	–8.4 ± 2.4	–27.3 ± 1.8	< 0.001	–8.9 ± 2.5	–27.7 ± 1.8	< 0.001
Nocturnal pain	–8.0 ± 2.5	–26.0 ± 1.8	< 0.001	–8.7 ± 2.6	–27.3 ± 1.9	< 0.001
SF-36 bodily pain domain	6.2 ± 2.0	19.4 ± 1.4	< 0.001	6.7 ± 2.0	20.7 ± 1.5	< 0.001
Fatigue assessment						
BASDAI fatigue	–0.7 ± 0.3	–2.2 ± 0.2	< 0.001	–0.6 ± 0.3	–2.4 ± 0.2	< 0.001
SF-36 vitality domain	6.8 ± 1.8	12.9 ± 1.3	0.005	5.9 ± 1.9	14.5 ± 1.3	< 0.001
Stiffness assessment						
BASDAI stiffness	–1.2 ± 0.2	–3.0 ± 0.2	< 0.001	–1.1 ± 0.3	–3.1 ± 0.2	< 0.001

p values are a comparison between placebo and adalimumab treatment groups of the means from analysis of covariance with treatment and baseline values as covariates. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, SF-36: Short-Form 36 Health Survey.

nitude of improvement was maintained through Week 24 (14.5 vs 5.9; $p < 0.001$).

Morning stiffness assessments: At Week 12, adalimumab treatment was associated with significantly greater reduction of morning stiffness compared with placebo treatment (–3.0 vs –1.2; $p < 0.001$). Statistically significant improvements with adalimumab treatment were measured as early as Week 2 (–2.0 for adalimumab-treated patients vs –0.6 for placebo-treated patients; $p < 0.001$) and were maintained through Week 24 (–3.1 for the adalimumab group vs –1.1 for the placebo group; $p < 0.001$).

Relationship between patient-reported symptoms and overall physical function and HRQOL. Results of the cross-sectional regression analyses are summarized in Tables 3 and 4 and results of the longitudinal regression analyses are summarized in Tables 5 and 6. Overall, these analyses indicated a significant association between symptoms of pain, fatigue, and stiffness and measures of patient-reported physical function and HRQOL. In addition, improvement in these 3 symptoms contributed significantly to the improvement in patient-reported physical function and HRQOL.

Physical function: In the cross-sectional regression analysis, the selected demographic and clinical variables explained 27% of the variance in physical function (i.e., BASFI scores; Table 3). The addition of total back pain, BASDAI fatigue, and BASDAI stiffness scores in Model 2

Table 3. Association between baseline symptoms of pain, fatigue, and stiffness and patient-reported physical function.

Independent Variables	Dependent Variable BASFI Score Model 1 Estimate	p	Model 2* Estimate	p	Model 3† Estimate	p
Age	0.4552	< 0.0001	0.3868	< 0.0001	0.3921	< 0.0001
Weight	0.0617	0.0389	0.0360	0.1709	0.0420	0.1057
Disease duration	0.0001	0.7479	0.0006	0.0783	0.0005	0.1166
Sex	–4.9196	0.0688	–2.0140	0.3997	–2.2349	0.3421
Baseline physician global assessment of disease activity	0.4693	< 0.0001	0.2675	< 0.0001	0.2371	< 0.0001
Baseline stiffness			1.8789	0.0009	2.0115	0.0002
Baseline pain			0.2531	< 0.0001	–0.4576	< 0.0001
Baseline fatigue			1.9113	0.0008	–0.1380	0.0214
R^2	0.2696		0.4462		0.4733	

*Model 2 included BASDAI question 1 as the measure of fatigue; total back pain as measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. † Model 3 included SF-36 vitality domain as the measure of fatigue; SF-36 bodily pain as the measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath AS Function Index, SF-36: Short-Form 36 Health Survey.

Table 4. Association between baseline symptoms of pain, fatigue, and stiffness and patient-reported health-related quality of life.

	Dependent Variable ASQOL Score					
	Model 1		Model 2*		Model 3†	
Independent Variables	Estimate	p	Estimate	p	Estimate	p
Age	0.0341	0.1308	0.0245	0.2302	0.0223	0.2044
Weight	0.0075	0.2281	0.0032	0.5609	0.0001	0.9890
Disease duration	–0.0001	0.0893	–0.0001	0.4177	–0.0001	0.3259
Sex	–1.6918	0.0027	–1.0413	0.0404	–0.7348	0.0965
Baseline physician global assessment of disease activity	0.0715	< 0.0001	0.0348	0.0030	0.0248	0.0177
Baseline stiffness			0.3229	0.0069	0.2280	0.0213
Baseline pain			0.0320	0.0080	–0.0965	≤ 0.0001
Baseline fatigue			0.5759	< 0.0001	–0.0817	< 0.0001
R^2	0.1543		0.3332		0.5021	

*Model 2 included BASDAI question 1 as the measure of fatigue; total back pain as measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. † Model 3 included SF-36 vitality domain as the measure of fatigue; SF-36 bodily pain as the measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. ASQOL: Ankylosing Spondylitis Quality-of-Life Questionnaire, BASDAI: Bath AS Disease Activity Index, SF-36: Short-Form 36 Health Survey.

Table 5. Association between the change from baseline to Week 12 in symptoms of pain, fatigue, and stiffness and patient-reported physical function.

	Dependent Variable: Change in BASFI Score From Baseline to Week 12					
	Model 1		Model 2*		Model 3†	
Independent Variables	Estimate	p	Estimate	p	Estimate	p
Age	0.1701	0.1352	–0.1441	0.0572	–0.1654	0.0366
Weight	0.0221	0.4792	–0.0055	0.7885	0.0018	0.9334
Disease duration	–0.0001	0.7301	0.0003	0.2902	0.0004	0.1638
Sex	–3.0698	0.2777	0.4554	0.8040	–0.1206	0.9495
Baseline physician global assessment of disease activity	–0.0237	0.6980	–0.0075	0.8497	0.0039	0.9249
Change in stiffness			1.9780	< 0.0001	2.9593	< 0.0001
Change in pain			0.2773	< 0.0001	–0.2142	< 0.0001
Change in fatigue			1.5909	< 0.0001	–0.2559	< 0.0001
R^2	0.0141		0.5941		0.5594	

*Model 2 included BASDAI question 1 as the measure of fatigue; total back pain as measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. † Model 3 included SF-36 vitality domain as the measure of fatigue; SF-36 bodily pain as the measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stifness. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath AS Functional Index, SF-36: Short-Form 36 Health Survey.

explained 45% of the variance in physical function; each symptom made a significant contribution to the explanation of variance (all $p < 0.001$). The results for Models 2 and 3 were nearly identical. Switching the pain measure to the SF-36 bodily pain domain and the fatigue measure to the SF-36 vitality domain in Model 3 accounted for 47% of the variance in physical function scores.

In the longitudinal regression analysis, demographic and baseline clinical characteristics accounted for only 1.4% of the variance in baseline to Week 12 changes in BASFI scores (Table 5). Adding the mean changes from baseline to Week 12 in the total back pain, BASDAI fatigue, and BASDAI stiffness scores significantly contributed (all $p < 0.0001$) to the regression model for BASFI change scores and increased the amount of explained variance to 59% (Model 2). For Model 3, changing the measures of pain and fatigue to the SF-36 bodily pain and vitality domain scores increased the amount of explained variance to 56%.

Overall HRQOL: The demographic and clinical measures included in cross-sectional Model 1 explained 15% of the variance in ASQOL scores (Table 4). The addition of total back pain, BASDAI fatigue, and stiffness scores

Table 6. Association between the change from baseline to Week 12 in symptoms of pain, fatigue, and stiffness and patient-reported health-related quality of life.

	Dependent Variable: Change in ASQOL Score From Baseline to Week 12					
	Model 1		Model 2*		Model 3†	
Independent Variables	Estimate	p	Estimate	p	Estimate	p
Age	0.0611	0.0073	0.0039	0.8177	–0.0007	0.9623
Weight	–0.0014	0.8221	–0.0065	0.1609	–0.0063	0.1278
Disease duration	–0.0001	0.3852	0.000002	0.9709	0.00003	0.5828
Sex	–0.2078	0.7119	0.3502	0.3980	0.4799	0.1966
Baseline physician global assessment of disease activity	–0.0085	0.4846	–0.0080	0.3706	–0.0066	0.4185
Change in stiffness			0.3712	0.0001	0.3382	< 0.0001
Change in pain			0.0326	0.0002	–0.0597	< 0.0001
Change in fatigue			0.4347	< 0.0001	–0.0751	< 0.0001
R^2	0.0256		0.4867		0.5899	

*Model 2 included BASDAI question 1 as the measure of fatigue; total back pain as measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. † Model 3 included SF-36 vitality domain as the measure of fatigue; SF-36 bodily pain as the measure of pain; and the mean of BASDAI questions 5 and 6 as the measure of stiffness. ASQOL: Ankylosing Spondylitis Quality-of-Life Questionnaire, BASDAI: Bath AS Disease Activity Index, SF-36: Short-Form 36 Health Survey.

increased the amount of explained variance in ASQOL scores to 33% (Model 2), and the inclusion of the SF-36 bodily pain and vitality and BASDAI stiffness scores increased the amount of explained variance to 50% (Model 3). The different patient-rated pain, fatigue, and stiffness scores all significantly contributed to these regression models (all $p < 0.03$).

The longitudinal regression models for ASQOL scores also demonstrated the significant associations between changes in pain, fatigue, and stiffness scores (all $p < 0.0003$) and changes in overall HRQOL (Table 6). In Model 2, the addition of the 3 symptom measures increased the variance explained to 49%, and in Model 3, the variance explained in changes in ASQOL scores was increased to 59%.

DISCUSSION

ATLAS demonstrated that adalimumab was well tolerated in patients with AS and improved clinical signs and symptoms, mobility, and C-reactive protein concentrations[10]. Improvements in overall physical function and HRQOL were significantly greater for adalimumab- versus placebo-treated patients at Week 12, and these improvements were maintained throughout the 24-week study period[11]. Our analysis demonstrated that adalimumab therapy significantly improved PRO measures of pain, fatigue, and stiffness in patients with active AS.

Active AS severely reduces HRQOL[17]. Patients with AS experience chronic pain and stiffness, which in turn limits their abilities to perform various activities of daily living[17]. Fatigue, defined as an enduring, subjective sensation of generalized tiredness or exhaustion, has also been increasingly recognized as an important outcome measure in AS[3,5,23-25].

In this report, there were significant differences between adalimumab and placebo treatments on measures of pain, stiffness, and fatigue. After 12 and 24 weeks of treatment, the adalimumab group reported significant improvements in PRO measures for total back pain, nocturnal pain, and SF-36 bodily pain domain scores compared with the placebo group. Fatigue, as measured by both BASDAI fatigue and SF-36 vitality domain scores, and stiffness also improved significantly in the adalimumab-treated group compared with the placebo-treated group. Symptom improvement occurred early in the course of treatment. Further, the improvement in pain and fatigue as measured by the SF-36 bodily pain and vitality domain scores exceeded the 5 to 10 points required to attain a minimum important difference, suggesting that adalimumab treatment results in clinically meaningful improvement in patients with AS.

Regression analysis indicated a significant association between the symptoms of pain, fatigue, and stiffness and PRO measures of overall HRQOL and physical function at baseline. Improvement in these 3 symptoms contributed significantly to the improvement of overall HRQOL and physical function. These results are consistent with other studies indicating that symptoms of pain, fatigue, and stiffness are the most troubling to patients and are significantly associated with reduced HRQOL and functioning in patients with AS[26]. Our results also suggest that treatment with adalimumab has a clinically important effect from the patient's perspective.

The clinical benefit of TNF antagonists for the treatment of AS has been well established[27-30]. Several placebo-controlled trials have demonstrated the significant and sustained efficacy of TNF blockade in improvement in symptoms, function, and HRQOL in patients with AS[8,11,17,27,28,31]. However, ATLAS is the first study to specifically identify

the effect of anti-TNF treatment (adalimumab) on the 3 major concerns (i.e., pain, fatigue, and stiffness) of patients with AS[32]. Our findings complement and extend the reported clinical benefits of TNF antagonist treatment for patients with AS[11,16,27,29,30].

There are a few limitations associated with the HRQOL assessments in our study. A substantial percentage of randomly assigned patients entered therapy with open-label adalimumab after 12 weeks. Last-observation-carried-forward analysis was used, but large numbers of patients discontinuing randomized study treatment may have compromised interpretation of results after the 12-week visit. Endpoints were also based on PRO, and it is unknown whether expectations for improvements in clinical and functional outcomes influenced results. However, the validity of clinical criteria-based PRO, specifically BASDAI and BASFI, has been established[32].

This is the first study to specifically identify the effect of adalimumab treatment on the leading causes of disability and discomfort in patients with AS, including pain, fatigue, and stiffness. Adalimumab treatment resulted in statistically significant and clinically meaningful improvements in measures of pain, fatigue, and stiffness in patients with AS. These symptom improvements were associated with significant improvements in overall HRQOL and physical function.

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