Adalimumab Improves Sleep and Sleep Quality in Patients with Active Ankylosing Spondylitis

MARTIN RUDWALEIT, KATHERINE GOOCH, BEAT MICHEL, MANFRED HEROLD, ÅKE THÖRNER, ROBERT WONG, MARTINA KRON, NAIJUN CHEN, and HARTMUT KUPPER

ABSTRACT. ***Objective.*** Fatigue and sleep problems are significant in patients with ankylosing spondylitis (AS). This subanalysis of the RHAPSODY study (Review of Safety and Effectiveness with Adalimumab in Patients with Active Ankylosing Spondylitis) was conducted to evaluate the effect of adalimumab on sleep in patients with active AS.

Methods. All patients (n = 1250) had active AS and received adalimumab 40 mg every other week during the 12-week open-label treatment period. Sleep was assessed by the Medical Outcomes Study Sleep Scale (MOS-SS) at screening and Weeks 6, 12, and 20 (optional continuation period). Effect sizes were calculated to determine clinical significance. Paired Student t tests compared the change in the MOS-SS domains from Week 12 to baseline. Correlation coefficients were calculated to determine the relationship between change in sleep domains and other Week 12 clinical and patient-reported outcomes (Bath AS Disease Activity Index, C-reactive protein, nocturnal pain, total back pain, Bath AS Functional Index, patient's global assessment of disease activity, morning stiffness, Short Form-36 Health Survey, and Work Productivity and Activity Impairment questionnaire components).

Results. At Week 12, adalimumab significantly improved sleep in each of the MOS-SS domains ($p < 0.001$). Effect sizes for 3 of the 6 domains (disturbance, –0.69; adequacy, 0.55; somnolence, –0.52) and both sleep problems indices (Index I, –0.68; Index II, –0.77) were moderate, suggesting clinical significance. Change in the MOS-SS Sleep Problem Index II was moderately correlated with change in most clinical and patient-reported outcomes. Sleep improvements were similar in patients with and without radiographically advanced AS.

Conclusion. Adalimumab improves overall sleep and sleep quality in patients with active AS. (J Rheumatol First Release Oct 15 2010; doi:10.3899/jrheum.100213)

Key Indexing Terms:
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From Charité-University Medicine Berlin, Benjamin Franklin Campus, Berlin; Abbott GmbH & Company KG, Ludwigshafen, Germany; Abbott Laboratories, Abbott Park, Illinois, USA; Rheumaklinik und Institut für Physikalische Medizin, Universitätsspital Zürich, Zürich, Switzerland; Universitätsklinik Innsbruck, Innsbruck, Austria; and Mälasjukhuset Eskilstuna, Eskilstuna, Sweden.

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M. Rudwaleit, MD, Medical Department I, Rheumatology, Charité-University Medicine Berlin, Campus Benjamin Franklin; K. Gooch, PhD; N. Chen, MS, Global Health Economics and Outcomes Research, Abbott Laboratories; R. Wong, MD, formerly Abbott Laboratories; B. Michel, MD, Rheumaklinik und Institut für Physikalische Medizin, Universitätsspital Zürich; M. Herold, MD, Rheumaambulanz & Rheumalabor, Klinische Abteilung für Allgemeine Innere Medizin, Universitätsklinik Innsbruck; Å. Thörner, MD, Department of Rheumatology, Mälasjukhuset Eskilstuna; M. Kron, PhD; H. Kupper, MD, Abbott GmbH & Company KG.

Address correspondence to Dr. M. Rudwaleit, Charité-Campus Benjamin Franklin Hospital, Medical Department I, Rheumatology, Hindenburgdamm 30, 12200 Berlin, Germany. E-mail: martin.rudwaleit@charite.de

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Ankylosing spondylitis (AS) is a chronic, progressive, inflammatory disease of the axial skeleton, large peripheral joints, and entheses. AS is the prototype of the spondyloarthritides, a group of disorders that includes sacroiliitis, presence of the HLA-B27 allele, and the development of spinal ankylosis[1]. Over time, continued inflammation can cause the joints and bones to fuse and cause deformity and disability[2].

Some of the most prevalent quality of life (QOL) concerns in AS include stiffness, pain, fatigue, and poor sleep[3]. In patients with osteoarthritis, pain has been associated with poor functioning, less sleep, and increased healthcare resource use[4]. A similar relationship between pain, sleep, and health outcomes for patients with AS has been demonstrated[3]. Sleep disturbances have been positively correlated to pain and fatigue in patients with rheumatic disorders[5]. Severe pain, stiffness, and more functional impairment are associated with an increase in utilization of healthcare resources in patients with rheumatism[6]. Pain has been correlated with difficulty in getting to sleep and a worse quality of sleep in patients with AS; pain was also correlated with

sleep disruption[7]. Adalimumab, a fully human anti-tumor necrosis factor (anti-TNF) antibody, was shown to significantly reduce pain and fatigue in patients with active AS[8].

Sleep problems are important concerns in patients with AS[9]. Hultgren, *et al*[10] found that a significantly greater percentage of both male and female patients with AS reported too little sleep compared to the general population ($p < 0.0001$), which the authors attributed primarily to pain. Results of a study evaluating infliximab treatment in patients with rheumatoid arthritis (RA) suggest a relationship between improved sleep and inhibition of circulating TNF concentrations[11]. Winkler[12] showed that sulfasalazine administration in patients with AS led to significant improvement in the duration of articular morning stiffness and reduced disturbances of sleep compared with placebo. Similarly, Taylor, *et al*[13] found that patients with AS treated with sulfasalazine had significant improvement in sleep disturbance ($p < 0.05$); however, the placebo group also experienced the same improvement.

In this subanalysis of the RHAPSODY (Review of Safety and Effectiveness with Adalimumab in Patients with Active Ankylosing Spondylitis) study, the Medical Outcomes Study Sleep Scale (MOS-SS) was used to assess sleep attributes. The MOS-SS is a validated, self-administered instrument designed to assess the quality of sleep[14]. The MOS-SS was originally developed as part of the MOS to assess the sleep problems in patients with varying illnesses and comorbidities and was found to have good overall measurement properties in determining sleep problems in a medically diverse population[14]. Several studies using the MOS-SS have demonstrated the construct validity, reliability, and responsiveness to change in patients with various health concerns, including neuropathic pain[15,16] and RA[17].

The purpose of this analysis was to evaluate the effect of adalimumab on sleep in patients with active AS and to determine whether treatment with adalimumab could improve sleep and subsequent QOL. Patients with radiographic Stage V AS were included to assess whether adalimumab could affect the sleep of patients with widespread spinal fusion.

MATERIALS AND METHODS

RHAPSODY was an open-label, multinational, multicenter, Phase IIIb study designed to further assess the safety and efficacy, including the effect on sleep, of adalimumab in the treatment of patients with active AS who were also receiving standard therapy for the symptoms of AS (ClinicalTrials.gov Identifier NCT00478660). A total of 1250 patients were enrolled at 211 sites in 15 European countries[18,19,20]. This study was conducted according to the guidelines of the International Conference on Harmonisation and the Declaration of Helsinki, informed consent was obtained from each patient, and each participating site received ethics approval.

Study population. Major inclusion criteria included adult male and female patients with active AS who had a score on the Bath AS Disease Activity Index (BASDAI) ≥ 4 at the screening visit, an unsatisfactory response to standard AS therapies including a minimum of failing (or intolerance of) at least 1 nonsteroidal antiinflammatory drug, and no history of or current acute inflammatory joint disease of origin other than AS.

Study design. Our study included a screening period, a study treatment period (Day 1 through Week 12), an optional study continuation period (Week 12 through Week 20), and a 70-day followup telephone call to assess safety. During the treatment period, patients received adalimumab 40 mg (Abbott Laboratories, Abbott Park, IL, USA) every other week subcutaneously. Assessments were completed on Day 1, Week 2, Week 6, Week 12, and Week 20. Patients with active uveitis flares in the year before enrollment were allowed to continue adalimumab treatment through Week 20. Also, patients who lived in countries where adalimumab was not yet commercially available at Week 12 were allowed to continue receiving adalimumab through Week 20.

Sleep assessments. The MOS-SS consists of 12 items that assess 6 domains of sleep activities: sleep disturbance (4 attributes: length of time to fall asleep, restless sleep, trouble falling asleep, and trouble getting back to sleep), daytime somnolence (3 attributes: feel drowsy during the day, trouble staying awake during the day, and daytime naps), perceived sleep adequacy (2 attributes: enough sleep to feel rested and feel you get the amount of sleep needed), awaken short of breath or with headache (1 attribute), snoring (1 attribute), and sleep quantity (1 attribute). In addition to the 6 subscale scores, the MOS-SS yields 2 sleep problem indices, which further assess sleep problems using composite scores. The Sleep Problem Index I incorporates 6 of the 12 MOS-SS items and the Sleep Problem Index II (overall sleep problems) includes 9 of the 12 items.

The MOS-SS questionnaire was completed by each patient at baseline (screening) and on Weeks 6, 12, and 20 (for those patients participating in the continuation period). Patients reported the frequency of each problem experienced during the previous 4 weeks. Each item was rated on a 6-point scale ranging from "none of the time" to "all of the time," except for sleep quantity, which was measured in hours. Apart from sleep quantity, each item was transformed to a 0 to 100–point range so that the worst possible score was 0 and the best was 100. Items that were left blank were excluded when the scale scores were calculated. Scores represent the average for all items in the scale that the respondent answered. Sleep quantity and an additional measure, optimal sleep, were based on the average number of hours of sleep each night during the previous 4 weeks.

Clinical measures. Clinical response in AS to adalimumab was measured by the Assessment of SpondyloArthritis international Society criteria (ASAS20, ASAS40, and ASAS 5/6), as described[21].

Disease activity, symptoms, and patient function were assessed by the BASDAI, the Bath AS Functional Index (BASFI), and additional visual analog scales (VAS). The BASFI is a 0 to 10–cm VAS completed by the patient to assess physical function. The patient also assessed his/her disease activity, total back pain, and nocturnal pain intensity during the previous week using VAS scales ranging from 0 (none) to 100 mm (severe or worst possible). Morning stiffness was also assessed as part of the BASDAI questionnaire. C-reactive protein (CRP) concentration, a serologic biomarker of inflammation, was also measured.

Patient-reported outcomes. Patient-reported outcomes included 2 additional questionnaires, the Short Form-36 Health Survey (SF-36)[22] and the Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) questionnaire[23]. The SF-36 measures health-related QOL in 8 domains: physical function, role limitations-physical, role limitations-emotional, vitality, general health, bodily pain, social function, and mental health. Each domain is scored on a scale of 0–100 points, with greater scores indicating better QOL. The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were also derived. The WPAI-SHP is a quantitative measure of reduced productivity during work and nonwork activities. The WPAI-SHP includes 4 components: (1) percentage of work time missed because of AS, (2) percentage of impairment caused by AS while working, (3) percentage of other activity impairment caused by AS (i.e., activities outside of work), and (4) the overall percentage of work impairment caused by AS.

Radiographic staging. Radiographic staging of AS severity was performed as described by Braun, *et al*[24]. In this classification, Stage I is defined as

Grade II or greater bilateral radiographic sacroiliitis, Stage II is minor radiographic evidence of spinal involvement in ≤ 1 spinal segment (≤ 3 vertebrae, which equals < 15% of the spine), Stage III is moderate radiographic evidence of spinal involvement in ≤ 2 spinal segments (4–12 vertebrae, which equals 15% to < 50% of the spine), Stage IV is radiographic evidence of spinal involvement in > 2 spinal segments (13–19 vertebrae, which equals 50% to < 80% of the spine), and Stage V is widespread (≥ 80%) fusion of the spine (≥ 20 vertebrae).

Statistical analysis. All patients who received at least 1 adalimumab injection were included in the analyses. Categorical data were analyzed by frequency and percentage, and quantitative data were analyzed by mean, SD, minimum, median, and maximum.

For comparison of Week 12 and baseline values of patient-reported outcomes and MOS-SS, paired Student t tests were applied. Unpaired Student t tests were calculated to compare nocturnal pain and MOS-SS (baseline values, Week-12 values, and changes from baseline to Week 12) between the subgroups of patients with complete spinal fusion (Stage V AS) and those with nonadvanced radiographic changes.

Spearman's rank correlation coefficient was calculated to assess the correlation between the change from baseline to Week 12 in the MOS-SS domains and change in clinical (CRP, BASDAI, morning stiffness from BASDAI, BASFI) and patient-reported outcomes [nocturnal pain, total back pain, patient's global assessment of disease activity (PGA), SF-36, WPAI-SHP]. Correlations of 0.0 to 0.2 are considered negligible; 0.2 to 0.4, weak; 0.4 to 0.7, moderate; 0.7 to 0.9, strong; and 0.9 to 1.0, very strong[25]. Associations between the ASAS response variables (ASAS20, ASAS40, ASAS 5/6)[20] at Week 12 and change from baseline to Week 12 in the MOS-SS Sleep Problem Index II were assessed by calculating OR with 95% CI and p values in logistic regression models using change in MOS-SS Sleep Problem Index II as a continuous explanatory variable and each ASAS response as dichotomous dependent variables.

Multiple linear regression analyses were performed to identify baseline factors (among them age, sex, AS duration, presence of advanced AS at baseline, BASDAI at baseline, and prior TNF antagonist use) associated with having an effect on the change of MOS-SS domains from baseline to Week 12. A separate model was fitted for each MOS-SS domain. Baseline factors showing an association of $p < 0.2$ in simple regression models were included in the final model.

Effect sizes (ES) were calculated to assess the magnitude of the effect of adalimumab treatment on the change in MOS-SS domains. ES was measured as the mean change from the baseline to Week 12, divided by the SD of the change in score[26]. Cohen's rule[26] was applied in determination of whether ES were to be considered small (< 0.5), moderate (0.5–0.8), or large (> 0.8)[27].

All statistical tests were explorative. P values < 0.05 were considered significant. Data were analyzed using SAS version 8.2 (SAS Inc., Cary, NC, USA).

RESULTS

Patient disposition and adalimumab treatment duration. A total of 1250 patients with active AS were enrolled and received at least 1 dose of adalimumab. The mean duration of exposure to adalimumab during the study was 106 days. Most patients (90.8%) completed the study; 661 patients completed Week 12 and 474 patients completed Week 20. A total of 115 (9.2%) patients withdrew from the study prematurely. Adverse events were the most common reason for discontinuation (66 patients, 5.3%). Other reasons for discontinuation included withdrawal of consent (11 patients, 0.9%), loss to followup (3 patients, 0.4%), unsatisfactory therapeutic effect (13 patients, 1.7%), and protocol violation (9 patients, 1.2%).

Patient characteristics at baseline. The majority of patients were male (71.3%), white (97.1%), and HLA-B27–positive (82.1%). The mean age of patients was 43.6 years (± 11.4), and the mean duration of AS since diagnosis was 11.0 years (± 9.8). Forty-one patients had Stage V AS, according to radiographic staging[24].

At baseline, 941 of 1190 (79.1%) patients had greater than normal CRP concentrations. Mean scores for BASDAI, BASFI, and nocturnal pain were 6.3, 5.4, and 61.7, respectively (Table 1). Mean baseline scores on items on the MOS-SS ranged from 20.4 (sleep short of breath or headache) to 49.3 (sleep disturbances); patients reported an average of 6.2 hours of sleep per day (Table 1).

Sleep assessments. At Week 6, improvements were observed for all sleep domains, as measured by the MOS-SS. Sleep adequacy and sleep quantity scores increased, while sleep disturbance, snoring, shortness of breath or headache, somnolence, and sleep problems (Sleep Problems Indices I and II) declined (Table 2). These improvements were statistically significant at Week 12 ($p < 0.001$; Table 2). The improvement of optimal sleep occurred as early as Week 6 (47.7%) and persisted through Week 12 (51.5%) and Week 20 (54.5%), compared with baseline (35.1%).

The ES for changes in snoring, shortness of breath, and sleep quantity patterns were small. The ES for disturbance, adequacy, somnolence, and Sleep Problem Indices I and II were moderate, indicating more clinically meaningful changes (Table 3). In addition, the mean number of hours of

Table 1. Baseline characteristics of study participants.

Characteristic	Adalimumab, n = 1250	
	n	Mean ± SD
Quantitative assessments		
BASDAI, 0–10	1248	6.3 ± 1.4
BASFI, 0–10	1245	5.4 ± 2.2
Nocturnal pain, 0–100 VAS	1250	61.7 ± 24.9
CRP, mg/dl (normal 0.007–0.49)	1190	2.0 ± 2.4
WPAI-SHP questionnaire components, %		
Work time missed (employed patients)	626	15.7 ± 28.7
Impairment while working (employed patients)	674	48.8 ± 26.5
Overall work impairment (employed patients)	602	52.5 ± 28.2
Activity impairment	1231	62.2 ± 24.0
MOS-SS domains		
Sleep disturbances, 0–100	1248	49.3 ± 25.1
Snoring, 0–100	1212	38.8 ± 31.8
Sleep short of breath or headache, 0–100	1245	20.4 ± 24.7
Sleep adequacy, 0–100	1248	36.3 ± 25.2
Daytime somnolence, 0–100	1248	41.0 ± 22.1
Sleep problems index, I, 0–100	1248	45.9 ± 19.2
Sleep problems index II, 0–100	1248	48.1 ± 19.0
Sleep quantity, hours/day	1156	6.2 ± 1.4

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: BAS Functional Index; VAS: visual analog scale; CRP: C-reactive protein; WPAI-SHP: Work Productivity and Activity Impairment-Specific Health Problem; MOS-SS: Medical Outcomes Study Sleep Scale.

Table 2. Changes in Medical Outcomes Study Sleep Scale domains and nocturnal pain from baseline to Week 20. P values for change from baseline to Week 12 are from paired Student t tests. Measures are 0–100 linear scale except for sleep quantity.

Feature	n	Adalimumab, n = 1250 Absolute Change, Mean ± SD	p
Sleep disturbance			
Week 6	1227	–13.9 ± 21.4	< 0.001
Week 12	1206	–15.3 ± 22.2	< 0.001
Week 20	492	–17.2 ± 23.4	< 0.001
Snoring			
Week 6	1168	–3.6 ± 21.9	< 0.001
Week 12	1151	–4.3 ± 22.7	< 0.001
Week 20	463	–2.6 ± 22.2	0.011
Awaken short of breath or with headache			
Week 6	1221	–4.6 ± 23.5	< 0.001
Week 12	1198	–4.1 ± 22.8	< 0.001
Week 20	489	–3.0 ± 21.4	0.002
Sleep adequacy			
Week 6	1227	13.6 ± 27.0	< 0.001
Week 12	1205	15.2 ± 27.6	< 0.001
Week 20	492	15.6 ± 28.3	< 0.001
Daytime somnolence			
Week 6	1226	–8.9 ± 19.0	< 0.001
Week 12	1205	–10.4 ± 20.1	< 0.001
Week 20	492	–12.7 ± 21.4	< 0.001
Sleep Problems Index I			
Week 6	1227	–11.1 + 16.9	< 0.001
Week 12	1206	–12.2 ± 17.9	< 0.001
Week 20	492	–13.2 ± 18.1	< 0.001
Sleep Problems Index II			
Week 6	1227	–12.1 ± 16.3	< 0.001
Week 12	1206	–13.4 ± 17.4	< 0.001
Week 20	492	–14.8 ± 17.9	< 0.001
Sleep quantity (hours/day)			
Week 6	1037	0.4 ± 1.2	< 0.001
Week 12	1029	0.4 ± 1.3	< 0.001
Week 20	425	0.5 ± 1.3	< 0.001
Nocturnal pain			
Week 6	1232	–32.4 ± 29.5	< 0.001
Week 12	1206	–34.2 ± 30.0	< 0.001
Week 20	491	–36.9 ± 29.8	< 0.001

sleep per night increased from 6.2 hours at baseline to 6.6 hours at both Week 6 and Week 12. By Week 20, patients were sleeping for a mean of 6.7 hours per night.

Correlation of sleep with clinical and patient-reported outcomes. Overall, treatment with adalimumab resulted in improvement in clinical and patient-reported outcomes at Week 12 (Table 4). The change in MOS-SS Sleep Problem Index II was positively correlated with improvements in clinical measures such as BASDAI score, CRP concentration, nocturnal pain, total back pain, BASFI score, PGA, and morning stiffness (Table 5). To investigate the relationship between fatigue and sleep, we also assessed correlations between Question 1 on the BASDAI and the MOS-SS domains. Greater degrees of fatigue were negatively correlated with sleep adequacy (correlation coefficient, –0.36) and quantity (correlation coefficient, –0.17) and were positively correlated with overall sleep problems (correlation coefficient, 0.43). These correlations were small but significant for an association between improvements in fatigue and sleep (all $p < 0.001$).

Table 3. Effect size based on mean change in Medical Outcomes Study Sleep Scale domains from baseline to Week 12. Effect sizes are calculated by dividing the mean change from baseline to Week 12 by the SD of the change in score.

Medical Outcomes Study Sleep Scale Domain	Absolute Change From Baseline to Week 12, Mean ± SD	Effect Size	
Disturbance	–15.3 ± 22.2	–0.69	Moderate
Snoring	–4.3 ± 22.7	–0.19	Small
Awaken short of breath or with headache	–4.1 ± 22.8	–0.18	Small
Adequacy	15.2 ± 27.6	0.55	Moderate
Somnolence	–10.4 ± 20.1	–0.52	Moderate
Sleep Problems Index I	–12.2 ± 17.9	–0.68	Moderate
Sleep problems Index II	–13.4 ± 17.4	–0.77	Moderate
Quantity	0.4 ± 1.3	0.31	Small

Results of the WPAI-SHP indicated a reduction in the percentage of work time missed, percentage of impairment while working, percentage of overall work impairment, and percentage of activity impairment. The improvement in MOS-SS Sleep Problem Index II was correlated with the increases in QOL as measured by the SF-36 PCS and the SF-36 MCS. Correlations ranged between 0.384 and 0.466 (absolute values) for all measures, with the exception of CRP (0.163) and percentage of work time missed (0.224). The strongest correlations were between MOS-SS Sleep Problem Index II and percentage of overall work impairment (0.466) and between MOS-SS Sleep Problem Index II and nocturnal pain (0.463).

The greater the reduction in the Sleep Problem Index II (overall sleep), the greater the chance of a clinical response, as measured by the ASAS20 at Weeks 6 and 12 and both ASAS40 and ASAS 5/6 at Week 12 (Table 6). This association was observed as early as 6 weeks after initiation of adalimumab treatment.

Results of the multiple linear regression analyses showed that older age was associated with significantly less improvement in sleep disturbance ($p < 0.001$), sleep adequacy ($p = 0.027$), somnolence ($p < 0.001$), and the Sleep Problem Index II ($p < 0.001$). More severe AS (determined by baseline BASDAI scores) was associated with greater improvement in 6 of the 8 sleep domains, excluding snoring and sleep adequacy (data not shown), and both sleep indices. Previous TNF antagonist use was associated with less improvement in sleep disturbance ($p < 0.001$), sleep adequacy ($p < 0.001$), sleep quantity ($p = 0.002$), optimal sleep ($p = 0.005$), and the Sleep Problem Index II ($p <$

Table 4. Mean change of clinical and patient-reported outcomes from baseline to Week 12. All quality-of-life measures were assessed at baseline (obtained at screening); the change is from baseline to Week 12. P values for change from baseline to Week 12 are from paired Student t tests.

Assessment	n	Mean Change ± SD	p
BASDAI, 0–10	1204	–3.3 ± 2.3	< 0.001
C-reactive protein, mg/dl	772	–1.4 ± 2.5	< 0.001
Nocturnal pain, 0–100 VAS	1206	–34.2 ± 30.0	< 0.001
Total back pain, 0–100 VAS	1205	–32.9 ± 28.4	< 0.001
BASFI, 0–10	1201	–2.2 ± 2.3	< 0.001
PGA, 0–100 VAS	1203	–35.3 ± 30.0	< 0.001
Morning stiffness, hours	1205	–3.7 ± 2.7	< 0.001
SF-36 PCS, 0–100	1168	10.1 ± 10.2	< 0.001
SF-36 MCS, 0–100	1168	5.9 ± 11.3	< 0.001
WPAI-SHP, %			
Work time missed (employed patients)	489	–6.5 ± 25.9	< 0.001
Impairment while working (employed patients)	577	–23.1 ± 28.1	< 0.001
Overall work impairment (employed patients)	470	–25.2 ± 29.3	< 0.001
Activity impairment	1163	–26.7 ± 28.6	< 0.001

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: visual analog scale; BASFI: BAS Functional Index; PGA: Patient's Global Assessment of disease activity; SF-36; Short-Form 36 Health Survey; PCS: Physical Component Summary; MCS: Mental Component Summary; WPAI-SHP: Work Productivity and Activity Impairment-Specific Health Problem.

Table 5. Spearman correlation of change in Medical Outcomes Study Sleep Scale domains with change in clinical and patient-reported outcomes at Week 12. Correlations of 0.0 to 0.2 are considered negligible; 0.2 to 0.4 weak; 0.4 to 0.7 moderate; 0.7 to 0.9 strong; and 0.9 to 1.0 very strong. All quality-of-life measures were assessed at baseline (obtained at screening); the change is from baseline to Week 12.

Outcome Assessment	Medical Outcomes Study Sleep Scale Domain				
	Disturbance	Adequacy	Somnolence	Sleep Problems Index II	Quantity
BASDAI	0.381	–0.345	0.355	0.455	–0.215
CRP	0.175	–0.108	0.152	0.163	–0.106
Nocturnal pain	0.422	–0.352	0.281	0.463	–0.243
Total back pain	0.365	–0.322	0.295	0.428	–0.203
BASFI	0.384	–0.312	0.328	0.434	–0.213
PGA	0.386	–0.332	0.332	0.449	–0.207
Morning stiffness	0.351	–0.291	0.307	0.399	–0.172
SF-36 PCS	–0.318	0.345	–0.337	–0.412	0.179
SF-36 MCS	–0.322	0.285	–0.299	–0.384	0.177
WPAI-SHP (%)					
Work time missed (employed patients)	0.200	–0.167	0.174	0.224	–0.126
Impairment while working (employed patients)	0.379	–0.337	0.297	0.452	–0.159
Overall work impairment (employed patients)	0.382	–0.353	0.363	0.466	–0.151
Activity impairment	0.368	–0.361	0.343	0.455	–0.212

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; BASFI: BAS Functional Index; PGA: Patient's Global Assessment of disease activity; SF-36; Short-Form 36 Health Survey; PCS: Physical Component Summary; MCS: Mental Component Summary; WPAI-SHP: Work Productivity and Activity Impairment-Specific Health Problem.

0.001). Duration of AS was associated only with more improvement in somnolence (p = 0.001).

At baseline, the 41 patients with advanced AS had worse snoring (p = 0.002), sleep adequacy (p < 0.001), Sleep Problem Index I (p < 0.001), and Sleep Problem Index II (p = 0.001) than patients without advanced AS. At Week 12, patients with advanced AS had worse sleep disturbance (p = 0.023), sleep adequacy (p < 0.001), Sleep Problem Index I (p < 0.001), and Sleep Problem Index II (p = 0.001) than patients without advanced AS. However, the improvement in sleep domains from baseline to Week 12 was similar between patients with and without advanced AS. The changes from baseline to Week 12 in the Sleep Problem Index I were –13.3 ± 16.9 and –12.8 ± 17.7 for patients with and without advanced AS (p = 0.841), respectively. Similarly for the Sleep Problem Index II, the changes were –15.3 ± 17.3 and –13.9 ± 17.2 for patients with and without advanced AS (p = 0.605), respectively.

Table 6. Logistic model for assessing the effect of change of Medical Outcomes Study Sleep Scale Sleep problems Index II on ASAS response.

Dependent Variable	OR (95% CI)	p
ASAS20 at Week 6	0.959 (0.950–0.968)	< 0.0001
ASAS20 at Week 12	0.941 (0.932–0.951)	< 0.0001
ASAS40 at Week 12	0.946 (0.938–0.955)	< 0.0001
ASAS 5/6 at Week 12	0.956 (0.946–0.966)	< 0.0001

ASAS: Assessment of SpondyloArthritis international Society.

Safety. Rudwaleit and colleagues[18,19,20] have reported the safety findings of this study. The results reported here demonstrate no new safety signals compared with other adalimumab-treated patients with active AS[28].

DISCUSSION

The results of our cohort study suggest that adalimumab is effective at improving overall sleep and sleep quality, as measured by the MOS-SS, for patients with active AS. After 12 weeks of adalimumab treatment, sleep disturbance, snoring, shortness of breath or headache upon awakening, somnolence, and scores on the Sleep Problem Index II (overall sleep) had significantly decreased. Similarly, there were significant increases in sleep adequacy and sleep quantity compared with baseline. These improvements in sleep occurred concurrently with corresponding decreases in clinical symptoms and disease activity as assessed by the reduction of CRP concentrations, nocturnal pain, total back pain, morning stiffness, PGA, and BASDAI, as well as simultaneous increases in functioning as assessed by the BASFI, SF-36 PCS, and SF-36 MCS. The SF-36 is a QOL measurement, and QOL improvements have been associated with improvement in sleep[29]. In addition, there were reductions in work time missed, work impairment, and activity impairment as measured by the WPAI-SHP questionnaire. Correlation analyses showed moderate relationships between changes in the MOS-SS Sleep Problem Index II and changes in clinical measures and patient-reported outcomes at Week 12. Improvements were observed as early as Week 6. These results suggest that adalimumab treatment can improve poor sleep quality and patterns experienced by patients with AS.

In patients with RA, Wells and colleagues[29,30] concluded that the standardized response mean of the MOS-SS following the intervention was found to be small to moderate, as was the relative efficiency of the MOS-SS to detect treatment effect. A MOS-SS ES range of –0.56 to –1.42 was reported by de la Loge and Viala[31] following treatment of patients with chronic pain. In studies of patients with neuropathic pain, large ES were reported for sleep disturbance, sleep adequacy, sleep quantity, and sleep problems, while small or moderate ES were reported for shortness of breath, somnolence, and snoring following treatment with gabapentin or pregabalin[15,16]. Similar results were found in the current study; ES were small for snoring and shortness of breath and greater for disturbance, adequacy, and sleep problems. Dissimilarly, the ES for quantity of sleep was small and the ES for somnolence was moderate in the RHAPSODY study population.

Cole, *et al*[32] evaluated the available patient-reported measures of sleep disturbance in patients with chronic pain and found the MOS-SS to be the best option. Advantages of the MOS-SS include that it has been validated to measure sleep disturbance alone and compared to other well-used sleep measures and it is shorter and may be less cumbersome for patients to complete. Of the available patient-reported sleep measure tools, the MOS-SS appears to possess the best psychometric properties for measuring sleep issues in patients with chronic pain[32]. Of note, the MOS-SS reflects the patient's perception of sleep quality and quantity and should not be taken as a measure of sleep physiology. Indeed, our results support further investigations of sleep physiology in patients with AS using polysomnographic methods. Possibly because of restrictions in thoracic and spinal mobility, patients with AS are more likely to have obstructive sleep apnea syndrome compared with the general population[33].

Sleep may have a considerable effect on function, pain, mood, and other health variables. Sleep integrity has been correlated with an overnight increase in psychomotor performance in patients with AS[7]. Although Taheri, *et al*[34] determined that there was no relationship between CRP concentration and sleep duration, Meier-Ewert, *et al*[35] demonstrated that CRP concentrations in healthy individuals increased during both total deprivation and partial deprivation conditions, but was stable in the control group. In our study, the association between sleep and CRP concentrations was low (Table 5). In their evaluation of the effect of 12 days of sleep restriction on subjective ratings of mood and physical symptoms in healthy patients, Haack and Mullington[36] observed a decrease in optimism-sociability and increases in discomfort and pain; they suggested that chronic insufficient sleep may compromise optimistic outlook and psychosocial functioning. Thus, improved sleep quality and reduction in fatigue may ultimately result in improved health status, work productivity, daily activity, and psychosocial functioning. Consistent with these findings, the results of our current study show that adalimumab-treated patients with active AS had improvement in clinical symptoms, work productivity, and QOL. Interestingly, nocturnal pain was among the variables that showed the greatest correlation in the Sleep Problem Index II (0.463; Table 5).

Knowledge regarding the efficacy of adalimumab in patients with Stage V spinal ankylosis is quite limited because most AS clinical trials exclude these severely impaired patients. RHAPSODY allowed the inclusion of patients with Stages IV and V AS and represents a large cohort of patients with complete spinal fusion (Stage V AS). Patients with Stage V spinal ankylosis reported greater sleep adequacy and lesser

scores on the sleep problems indices at screening compared with patients with nonadvanced AS. Through Week 12, treatment with adalimumab improved MOS-SS items to the same extent in patients with Stage V spinal ankylosis compared with patients with nonadvanced AS.

Multiple linear regression analyses were performed to identify independent associations between the change in MOS-SS and age, AS duration, BASDAI at baseline, and prior TNF antagonist use. These analyses demonstrated that more severe AS (determined by baseline BASDAI scores) was associated with greater improvement in 6 of the 8 sleep domains and indices, excluding snoring and adequacy. Duration of AS was associated only with more improvement in somnolence. Older age was associated with significantly less improvement in sleep disturbance, adequacy, somnolence, and overall sleep problems. Previous TNF antagonist use was associated with less improvement in sleep disturbance, adequacy, quantity, optimal sleep, and overall sleep problems (Sleep Problem Index II).

As these analyses did not stem from a randomized controlled study, it is difficult to know the precise cause for sleep improvement. The sleep changes observed here may have been affected by variables unrelated to AS. For example, environmental or other health issues may have influenced sleep in the perception of the patients. However, the correlation of patient-reported sleep improvements with other QOL outcomes in the study help suggest that the findings were a result, at least in part, of adalimumab exposure. Nevertheless, our study did not measure sleep physiology and thus, the correlations observed in the statistical analysis do not prove a causal relationship. In addition, ours was an open-label uncontrolled study, which could have introduced bias into it. However, to our knowledge, based on a search of the literature, this is the largest study of a TNF antagonist assessing sleep in patients with active AS to date, and the results reflect consistent improvements in sleep for these patients throughout the 12-week study. Similar results in sleep improvement have been reported in patients with RA treated with the TNF antagonist infliximab[11].

Patients treated with adalimumab for active AS reported positive, significant improvements in sleep and sleep quality. Our results suggest that further investigations of sleep physiology in patients with AS during anti-TNF therapy are warranted.

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