Sleep Disturbances and Interleukin 6 Receptor Inhibition in Rheumatoid Arthritis

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ABSTRACT. ***Objective***. Interleukin 6 (IL-6)-mediated interactions have been associated with sleep disturbances in healthy subjects. In this pilot study we examined whether administration of the IL-6 receptor antagonist tocilizumab in patients with rheumatoid arthritis (RA) affects sleep disturbances.

Methods. Fifteen patients (13 women) with sleep disturbances at baseline received 6 monthly infusions of tocilizumab 8 mg/kg for moderately or severely active RA. Sleep quality was assessed by Pittsburgh Sleep Quality Index (PSQI), daytime sleepiness by Epworth Sleepiness Scale, disease activity by the 28-joint Disease Activity Score-erythrocyte sedimentation rate, functional disability by Health Assessment Questionnaire Disability Index (HAQ-DI), and fatigue by the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue Scale; FFS) at baseline and first, second, third, and sixth month of treatment. Medications used before enrollment remained unchanged during followup.

Results. Sleep quality improved and daytime sleepiness decreased significantly at first-month assessment ($p < 0.00001$ and $p < 0.004$, respectively, by repeated measurement analysis) compared to baseline, and these changes became more evident through 6 months. Disease activity decreased, fatigue decreased, and functional status improved significantly. Changes in PSQI score over time were not associated with the corresponding changes in DAS28-ESR ($r = 0.37$, $p = 0.17$), but correlated significantly with HAQ-DI changes ($r = 0.60$, $p = 0.02$) and marginally with changes in FFS scores ($r = –0.46$, $p = 0.08$).

Conclusion. Improvement of sleep quality after tocilizumab treatment in patients with RA does not appear to directly result from decreased disease activity, further suggesting that aberrant IL-6 regulation is associated with sleep disturbances. (First Release Dec 1 2011; J Rheumatol 2012;39:60–2; doi:10.3899/jrheum.110617)

Key Indexing Terms:
SLEEP DISTURBANCES TOCILIZUMAB INTERLEUKIN 6 RHEUMATOID ARTHRITIS

Sleep quality represents a central component of health-related quality of life in patients with rheumatoid arthritis (RA) and correlates with disease activity, pain, and psychological distress. Proinflammatory cytokines have been examined as potential mediators of sleep disturbances in RA[1]. In a pilot study of 6 patients with RA, sleep problems improved after the first infusion of the anti-tumor necrosis factor (TNF) monoclonal antibody infliximab, independently of disease status[2]. Administration of the soluble TNF receptor etanercept in patients with obstructive sleep apnea markedly decreased daytime sleepiness and levels of interleukin 6 (IL-6), suggesting a possible effect of TNF and IL-6 on sleep disturbances[3].

Tocilizumab is a humanized antibody against the IL-6 receptor used for the treatment of RA[4]. In this 6-month pilot study we examined whether sleep disturbances improve after tocilizumab administration in patients with RA, and whether possible changes in sleep quality correlate with changes in disease activity, fatigue, and/or functional status.

MATERIALS AND METHODS

Consecutive patients with sleep disturbances prior to the scheduled tocilizumab administration (8 mg/kg) for moderately or severely active RA [i.e., 28-joint Disease Activity Score-erythrocyte sedimentation rate (DAS28-ESR) > 3.2] were candidates for this 6-month pilot study. Subjective sleep quality over the previous month was evaluated at baseline with the Pittsburgh Sleep Quality Index (PSQI; range 0–21, cutoff score = 5)[5]. Patients receiving antidepressant or antipsychotic drugs were excluded.

The first 15 patients who had completed 6-month treatment of tocilizumab and had PSQI score ≥ 5 at baseline were included in our study. We evaluated PSQI, daytime sleepiness assessed by the Epworth Sleepiness Scale (ESS; range 0–24)[6], disease activity by the DAS28-ESR, functional disability by the Health Assessment Questionnaire Disability Index (HAQ-DI)[7], and fatigue by FACIT-Fatigue Scale (FFS; range 0–52)[7] at baseline and at first, second, third, and sixth month of treatment. All medications used before enrollment remained unchanged during followup.

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Statistical analysis. To examine the significance of changes of variables measured longitudinally (PSQI, ESS, DAS28-ESR, HAQ-DI, and FFS) during followup, linear mixed models with random intercept and random slope were applied, in order to take into account the correlation between repeated measurements on the same individual. To analyze whether the rates of change in variable scores (PSQI and ESS) correlated with the corresponding rates of other variables (DAS28-ESR, HAQ-DI, and FFS scores) we first summarized each individual's trajectory by deriving an estimate of the rate of change (slope) through simple linear regressions on his/her measurements over time for each of the aforementioned variables. Having an estimate of the slope for each individual and each variable, we investigated potential associations between each variable's slopes, using Pearson's correlation coefficient. Paired t test was applied for detecting statistically significant changes in PSQI and ESS from baseline to first infusion of tocilizumab. A p value < 0.05 was considered the level of statistical significance.

RESULTS

Fifteen patients (13 women) participated, mean age 48 ± SD 9 years (range 34–65 yrs), with mean disease duration 8.4 ± 6.54 years (range 2–23 yrs). A significant improvement in PSQI was observed from baseline to 6 months (from 7.5 ± 2.3 to 6.8 ± 2.5; p = 0.005 by paired t test), which was evident after the first tocilizumab infusion (Figure 1A). At the first-month assessment, the quality of sleep improved in 8 patients and further progressive improvement was evident up to the sixth month in 4 of them. Of the remaining 7 patients without improved sleep quality after the first tocilizumab infusion, 4 reported improvement through the following months.

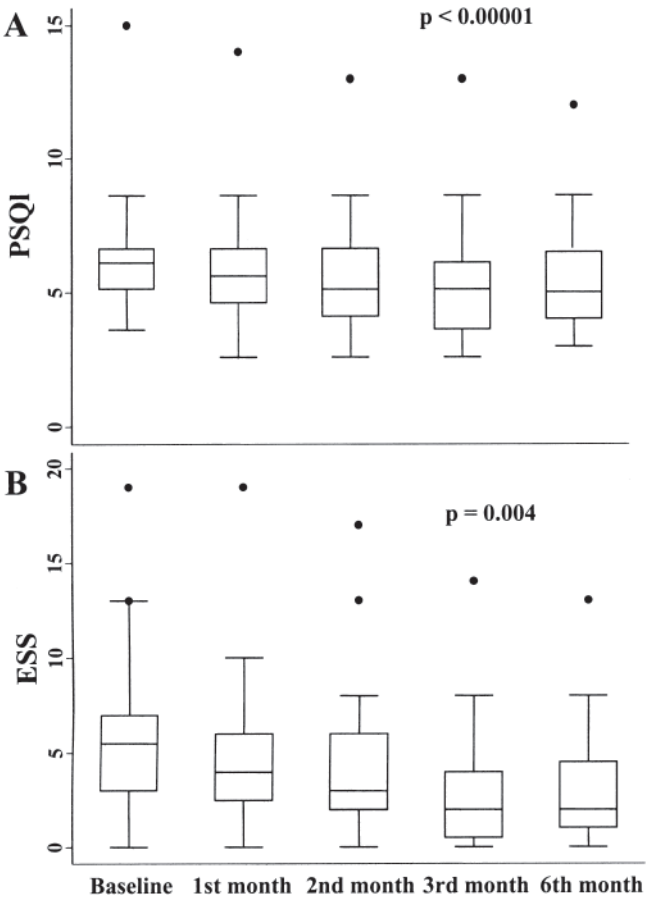

Figure 1. Changes in Pittsburgh Sleep Quality Index (PSQI) scores (A) and Epworth Sleepiness Scale (ESS) scores (B) in 15 patients with RA who received 6 monthly infusions of tocilizumab 8 mg/kg for active disease. Box plots show median values and 25th-75th quantiles. Dots represent outlier values. P values denote significance by linear mixed models.

Compared to baseline, a significant improvement of sleep quality was accompanied by significant decreases in daytime sleepiness (Figure 1B), which became significant at the first-month assessment (ESS from 6.9 ± 4.8 to 5.5 ± 4.5; p = 0.01, paired t test); daytime sleepiness at first month decreased in 10 patients, increased in 1, and remained unchanged in 4 patients. Through the following months, daytime sleepiness was further decreased in 7 of 10 patients who had a favorable response at the first month, whereas improvements were also noted in 3 of those 4 patients with unchanged ESS at first month.

During the 6 months of tocilizumab treatment, and compared to baseline assessments, fatigue decreased progressively and functional status improved, whereas disease activity decreased (Table 1). Further analysis revealed that individual changes in PSQI scores from baseline to first month, from first to second, from second to third, and from third to sixth month of treatment did not correlate with the corresponding individual changes in DAS28-ESR, but correlated positively with improvement in HAQ-DI and marginally with decreased fatigue (Table 2). No significant correlations were found between decreases of daytime sleepiness and changes in DAS28-ESR, HAQ-DI, and FFS scores. A strong correlation was noted between individual decreases in DAS28-ESR and HAQ-DI scores during the 6 months' treatment (r = 0.75, p = 0.001).

DISCUSSION

Considering the limitations of a pilot study and the small number of patients, our results suggest that tocilizumab treatment is associated with rapid and significant improvement in sleep quality and daytime sleepiness independent of changes in disease activity. Poor sleep quality and related daytime sleepiness are common in RA[1]. Disease activity and depression have been associated with increased risk of sleep disturbances and vice versa[8,9].

Elevated levels of TNF and IL-6 were found in individuals with sleep apnea[10], whereas increased endogenous IL-6 or exogenous IL-6 administration in patients with cancer was associated with daytime sleepiness and fatigue[11]. Proinflammatory cytokines were also elevated in subjects with experimentally induced sleepiness[12]. Cytokines can induce sleepiness by crossing the blood-brain barrier and through peripheral autonomic efferent nerves[13] or links between the immune and endocrine systems[14]. Effects of anticytokine treatment on sleep have been examined only sporadically. Sleep and alertness improved after anti-TNF treatment, independent of disease status, in a study of 6

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Table 1. Changes in scores of disease activity by DAS28-ESR, functional status and disability by Health Assessment Questionnaire (HAQ-DI), and fatigue by FACIT-Fatigue Scale (FFS) in 15 patients with active rheumatoid arthritis from baseline through 6 months of treatment with tocilizumab (8 mg/kg). Data are mean ± SD.

	Baseline	1st Month	2nd Month	3rd Month	6th Month	p*
DAS28	5.77 ± 1.2	4.38 ± 0.88	3.6 ± 0.97	2.7 ± 0.88	2.5 ± 0.9	< 0.00001
HAQ-DI	1.5 ± 0.8	1.1 ± 0.66	1 ± 0.58	0.9 ± 0.6	0.7 ± 0.6	< 0.00001
FFS	20.3 ± 11	28.3 ± 11.3	33.7 ± 12	36.4 ± 10	38 ± 9.93	< 0.00001

* Calculated by linear mixed models. DAS28-ESR: 28-joint Disease Activity Score-erythrocyte sedimentation rate; FACIT: Functional Assessment of Chronic Illness Therapy.

Table 2. Correlation of PSQI and ESS with DAS28-ESR, HAQ-DI, and FFS during tocilizumab treatment. Correlations by Pearson's coefficient (r) between the individual changes in scores of Pittsburgh Sleep Quality Index (PSQI) and of Epworth Sleepiness Scale (ESS) with the corresponding changes of DAS28-ESR, Health Assessment Questionnaire Disability Index (HAQ-DI), and FACIT-Fatigue Scale (FFS), in 15 tocilizumab-treated patients with rheumatoid arthritis from baseline through 6 months.

	DAS28	HAQ-DI	FFS
PSQI	r = 0.37, p = 0.17	r = 0.6, p = 0.02	r = –0.46, p = 0.08
ESS	r = –0.01, p = 0.96	r = –0.05, p = 0.86	r = –0.36, p = 0.2

DAS28-ESR: 28-joint Disability Activity Score-erythrocyte sedimentation rate; FACIT: Functional Assessment of Chronic Illness Therapy.

patients with RA[2]. Randomized trials showed that the costimulation inhibitor abatacept provided significant improvement in multiple sleep variables in patients with RA[15] and idiopathic arthritis[16].

Our results suggest that tocilizumab may improve sleep quality and daytime sleepiness in patients with RA. Whether this effect is directly associated with a central role of IL-6 on sleep regulation or is merely due to improvement in disease activity and functional status warrants further investigation. Sleep disturbance assessment should be included in evaluation of the efficacy of treatments in patients with RA.

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