

## Effect of Adalimumab on Work Ability Assessed in Rheumatoid Arthritis Disease Patients in Saudi Arabia (AWARDS)

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**Abstract:** *Objectives:* Rheumatoid arthritis (RA) is a chronic disabling disease that can jeopardize the ability of affected individuals to participate in paid work. Our objective was to evaluate the effectiveness of a 6-month course of tumor necrosis factor (TNF) antagonist (adalimumab) on work ability, overall health, and fatigue in RA patients.

*Methods:* Between October 2012 and February 2014, this prospective, observational study enrolled 63 consecutive patients with established adult RA at outpatient clinics in Makkah, Jeddah, Riyadh and Abha (Saudi Arabia). Patients received subcutaneous injections of adalimumab (40 mg every 2 weeks). Outcomes were measured at baseline and 6 months using the following tools: Work Productivity and Activity Impairment (WPAI), Health Assessment Questionnaire Disability Index (HAQ-DI), Fatigue Severity Scale (FSS), Visual Analog Scale for Fatigue (VAS-F), and work disability self-assessment.

*Results:* All outcomes showed improvements after 6 months of adalimumab therapy. Significant improvements from baseline were observed in absenteeism ( $64\% \pm 11.62$  to  $11.60\% \pm 11.17$  [ $p < 0.0001$ ]), presenteeism ( $62.15\% \pm 20.11$  to  $34.92\% \pm 20.61$  [ $p < 0.0001$ ]), overall work impairment ( $69.08\% \pm 18.86$  to  $40.73\% \pm 22.29$  [ $p < 0.0001$ ]), overall activity impairment ( $68.46\% \pm 18.58$  to  $36.46\% \pm 20.79$  [ $p < 0.0001$ ]), HAQ score ( $1.69 \pm 0.57$  to  $0.81 \pm 0.61$  [ $p < 0.0001$ ]), and FSS score ( $47.08 \pm 9.55$  to  $27.86 \pm 13.43$  [ $p < 0.0001$ ]).

*Conclusion:* A 6-month course of adalimumab improved work ability, fatigue, and overall health assessments in patients with established RA. Our findings encourage randomized controlled trials investigating the cost-effectiveness and long-term effects of TNF inhibitors on work disability.

**Keywords:** Adalimumab, health assessment, rheumatoid arthritis, tumor necrosis factor (TNF) inhibitor, work ability.

### INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disabling disease that threatens the ability of affected individuals to participate in paid work [1]. RA patients not only suffer from pain when disease activity is high, but also experience an impaired quality of life (QoL) and increased prevalence of fatigue [2,3]. Therefore, both newly diagnosed and longstanding RA patients have a high prevalence of work disability, which is associated with a significant socioeconomic burden [4,5].

Indeed, it was demonstrated that approximately 40% of new and 60% of established RA patients are unable to work [6,7].

In order to reduce the pain and suffering of RA patients, several novel treatment strategies have been developed. In this regard, tumor necrosis factor (TNF)-blocking agents were shown to be effective in reducing disease activity, slowing disease progression, and improving QoL [8,9]. In fact, a recent study reported considerably longer periods of work and continuous employment in RA patients receiving adalimumab in comparison to those receiving conventional treatment with disease-modifying anti-rheumatic drugs (DMARDs) [10]. However, even though recent emphasis has been placed on improving work-related outcomes in RA

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patients [11], work ability in those receiving TNF agonists has not been fully investigated.

Recently, progress has been made in measuring work ability in RA patients. Indeed, the Work Productivity and Activity Impairment (WPAI) questionnaire is a validated tool for measuring the effect of RA on both work and non-work activities [12]. This assessment tool consists of six items that are used to produce percentage scores in four distinct domains (i.e., absenteeism, presenteeism, overall work impairment, and non-work activity impairment). Prior use of this questionnaire has demonstrated that a > 7% change in the WPAI score constitutes a minimally important difference (MID) [13]. In addition, work efficiency of RA patients might be affected by fatigue, which can be measured using various self-report assessment tools, including the Fatigue Severity Score (FSS) and the Visual Analog Scale for Fatigue (VAS-F) [14,15]. Moreover, functional disability can be examined using the well-known Health Assessment Questionnaire-Disability Index (HAQ-DI) [16].

In the present study, we have evaluated the impact of adalimumab therapy on work disability among RA patients in Saudi Arabia using assessment tools. We examined the burden of RA with respect to work outcomes and QoL at baseline and after six months of adalimumab treatment. Our findings are of particular interest in the Middle East where there is a lack of data on work disability among those with RA. Thus, our investigation contributes valuable knowledge for improving the outcomes of RA patients in Saudi Arabia and around the world.

## METHODS

### Study Design and Patients

Between October 2012 and February 2014, this prospective, observational study consecutively enrolled 65 established RA patients. The subjects were recruited from rheumatology outpatient clinics at various hospitals in Makkah, Jeddah, Riyadh and Abha (Saudi Arabia). Patients were eligible if they were working aged (i.e., >18 and <60 years old), fulfilled the revised 2010 American College of Rheumatology (ACR) criteria for RA [17], displayed inadequate responses to at least two DMARDs, had no history of biological treatment during the preceding 6 months, showed negative results for tuberculosis (i.e., chest x-ray and skin test), and were willing to receive subcutaneous adalimumab injections (40 mg every 2 weeks) for 6 months (i.e., either self-administered or given by a qualified person). Patients with any contraindication to adalimumab treatment as outlined in the latest version of the adalimumab product label and patients with a history of using biologic treatment during the preceding 6 months were excluded from the study. All patients gave written informed consent in accordance with the Declaration of Helsinki, and the local medical ethics committees of the participating sites approved the study.

Adalimumab was prescribed according to the product label. Patients were assessed at baseline (namely, study enrollment) and at approximately 8, 16, and 24 weeks

thereafter. Up to 3 follow-up visits were scheduled for each patient. The timing of these visits occurred at the discretion of the physician, and failure to adhere to the suggested follow-up schedule did not constitute a breach of the protocol. Data regarding concomitant RA medications or other diseases were recorded in the case report form at enrollment and at each follow-up. Adherence to treatment was assessed through direct interviews with patients during these visits. If treatment with adalimumab was interrupted, then the patient was treated and followed as per standard care. When patients withdrew at > 3 months but < 6 months after initiating treatment, missing follow-up data was imputed using the last observation carried forward. If the physician decided to permanently discontinue adalimumab before the end of the follow-up period, then the reason(s) for discontinuation and the new RA regimen were documented.

### Assessment Tools and Outcomes

We assessed work disability in RA patients at baseline and after 6 months of adalimumab therapy using the WPAI questionnaire [12]. The questionnaire was adapted for use in the Arabic language as was done in other studies among Saudi population by our group [18]. In addition, we determined the following: 1) percentage of patients achieving an improvement of  $\geq 7\%$  in the overall WPAI score; 2) mean 6-month changes in scores for WPAI absenteeism, presenteeism, and activity impairment; 3) mean 6-month changes in HAQ-DI scores [16]; and 4) mean 6-month changes in FSS and VAS-F outcomes [14,15]. We also analyzed the percentage of patients who considered themselves to be work disabled due to RA before and after adalimumab treatment based on affirmative responses to the following question: "do you consider yourself work disabled due to RA?"

### Statistical Analysis

Data were summarized using the mean, median, standard deviation, maximum, and minimum for continuous variables, whereas categorical variables were presented as frequencies and percentages. Mean 6-month changes in continuous outcomes, including the WPAI overall work impairment domain score, were analyzed using a paired student's t-test when normally distributed, or a Wilcoxon test otherwise. The 6-month change in the percentage of patients who considered themselves as work disabled due to RA was assessed using McNemar's test.

## RESULTS

### Patient Characteristics

A total of 65 RA patients were enrolled in the study, and the characteristics of these subjects are presented in Table 1. The majority of these patients were Saudi females. They had a mean age of  $45.96 \pm 14.42$  years old and displayed a mean RA disease duration of approximately 5 years. Moreover, the average body mass index (BMI) of the study participants was  $28.98 \pm 7.27$ , with over one-third of them considered to be overweight or obese. In addition, we found that 9% of the

patients showed extra-articular manifestations of RA and that almost half presented co-morbidities, including hypertension, osteoarthritis, diabetes mellitus, osteoporosis, and dyslipidemia (19%, 12%, 10%, 7%, and 6%, respectively). Furthermore, these individuals received a mean HAQ-DI score of  $1.69 \pm 0.57$  at baseline, which is consistent with the functional disability experienced by this population.

### Patient Therapies

All patients participating in the study were on non-biological medications for RA prior to the start of adalimumab therapy (Table 1). Indeed, over half were taking a combination of methotrexate (MTX) and steroids, whereas fewer patients were on DMARDs other than MTX plus steroids or MTX alone (16.4% each). Notably, the mean duration of these non-biological treatments was almost 5 years.

After excluding the possibility of infection, all 65 patients started adalimumab therapy (40 mg subcutaneously, every two weeks for 6 months, pre-filled syringe). However, two patients were prematurely discontinued from adalimumab therapy: one subject lacked efficacy and the other developed a lower respiratory tract infection. Nevertheless, results of their last assessment were included in the results presented here. Thus, the overall adherence of the adalimumab-treated patients in the present study was 96.4%.

**Table 1. Baseline characteristics of patients.**

Characteristic	All Patients (n=65)
Female (%)	80.3
Saudi (%)	73.4
Mean Age (years $\pm$ SD)	45.96 $\pm$ 14.42
Mean disease duration (months $\pm$ SD)	64 $\pm$ 61.71
Mean BMI (score $\pm$ SD)	28.98 $\pm$ 7.27
Overweight or obese (%)	37.3
Extra-articular RA manifestations (%)	9.2
Hypertension (%)	20.0
Osteoarthritis (%)	12.3
Diabetes (%)	10.8
Osteoporosis (%)	7.7
Mean HAQ-DI (score $\pm$ SD)	1.69 $\pm$ 0.57
Baseline therapies:	
Prednisone use (%)	70.1
MTX and steroids (%)	53.7
DMARDs other than MTX plus steroids (%)	16.4
MTX monotherapy (%)	16.4
DMARDs combination (not including MTX) (%)	13.5
Duration of non-biological therapy (years $\pm$ SD)	4.63 (5.42)

Legend: SD, standard deviation, BMI, body mass index; RA, rheumatoid arthritis; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs.

### Work Ability and Fatigue Assessments in RA Patients

Outcomes of the various assessment tools employed in this study are presented in Table 2. The WPAI questionnaire revealed that absenteeism was almost halved following 6 months of adalimumab treatment in our patients ( $p < 0.0001$ ). In this regard, work hours missed due to RA or other reasons also decreased significantly (Table 2). Moreover, there was a significant improvement in presenteeism after therapy ( $p < 0.0001$ ), with RA patients showing reductions in the degree to which their disease impacted both work and non-work activities. Indeed, overall work impairment improved substantially from baseline ( $p < 0.0001$ ), with 79.1% of patients achieving clinically meaningful progress. Also, the percentage of overall activity impairment was significantly reduced following adalimumab treatment ( $p < 0.0001$ ). Additionally, the degree of functional disability (HAQ-DI) and fatigue (FSS) were found to improve significantly from baseline (both  $p < 0.0001$ ). Notably, 81.5% of patients achieved clinically meaningful decreases in fatigue, while 73.8% of them displayed a status of minimal or no fatigue. Finally, we observed no significant changes in VAS-F scores.

### DISCUSSION

Patient-reported outcomes for evaluating the treatment of chronic conditions, such as RA, are gaining importance, as these evaluations are increasingly required by regulatory agencies [19-21]. Thus, we have used various patient assessment tools to demonstrate that a 6-month course of adalimumab significantly improved work ability, fatigue, and overall functional disability in patients with established RA in Saudi Arabia. Importantly, we observed high adherence rates in our patient cohort, which was probably driven by the positive outcomes and the short duration of follow-up. In this regard, the 6-month study duration was decided based on previous data, which indicated that the largest improvement for all outcome measurements was gained in the first 6 months of adalimumab treatment and was sustained in later follow-ups [22].

Our findings have indicated that significant improvement was achieved in all work ability domains after relatively short-term use of biological therapy, which is in agreement with published clinical trial data [22]. Combination therapy with DMARDs may have added benefit on our findings as shown in other studies [23]. Nevertheless, it is difficult to demonstrate an increased rate of paid employment following short-term treatment. Indeed, obtaining work can be influenced by various contributing factors (individual, environmental, and social) as well as work-related characteristics (nature of work, the workplace, and work policies) [24]. In addition, it was found that patients with longstanding RA were less likely to improve employability after effective treatment than those with early disease [7]. This fact could have influenced our results since our patients exhibited mean disease duration of approximately 5 years prior to adalimumab therapy. Indeed, such an effect on work disability could result from increased structural damage and comorbidity in late disease, whereas the role of disease activity on work disability could be reversed in early disease [23, 25, 26]. For this reason, the current objective of RA

**Table 2. WPAI, HAQ-DI, FSS, and VAS-F outcomes before and after adalimumab therapy.**

Parameter	Baseline (Mean ± SD)	6-Months Therapy (Mean ± SD)	p-Value
Absenteeism (%)	21.64 ± 11.62	11.60 ± 11.17	<0.0001
Hours missed due to RA	24.35 ± 12.31	11.01 ± 10.63	<0.0001
Hours missed for other reasons	3.03 ± 1.55	2.65 ± 1.47	0.008
Presenteeism (%)	62.15 ± 20.11	34.92 ± 20.61	<0.0001
Degree of RA-affected productivity at work	6.31 ± 1.89	3.49 ± 2.078	<0.0001
Degree of RA-affected non-work activities	6.95 ± 1.68	3.65 ± 2.095	<0.0001
Overall work impairment (%)	69.08 ± 18.86	40.73 ± 22.29	<0.0001
Overall activity impairment (%)	68.46 ± 18.58	36.46 ± 20.79	<0.0001
HAQ-DI score	1.69 ± 0.57	0.81 ± 0.61	<0.0001
FSS score	47.08 ± 9.55	27.86 ± 13.43	<0.0001
VAS-F score	5.35 ± 1.86	4.52 ± 2.62	0.079

Legend: WPAI, Work Productivity and Activity Impairment; HAQ-DI, Health Assessment Questionnaire-Disability Index; RA, rheumatoid arthritis; FSS, Fatigue Severity Score; VAS-F, Visual Analog Scale for Fatigue.

treatment is to induce remission as soon as possible in order to prevent any structural damage and disability. In this respect, a previous 2-year study revealed that patients receiving adalimumab worked for a longer duration than did those treated with DMARDs [10]. Therefore, our study, along with others, highlights the importance of early and comprehensive control of RA to maintain work ability. Notably, effective early treatment, which is becoming increasingly feasible, can avoid the need for later initiatives to facilitate re-employment of RA patients.

Our results also demonstrated that adalimumab had a beneficial effect on general fatigue. However, even though the FSS questionnaire revealed a clinically relevant improvement in the fatigue of adalimumab-treated RA patients, the VAS-F assessment did not. While the reason for this discrepancy remains unclear, our positive findings obtained with the FSS questionnaire are in agreement with results from a randomized clinical trial using the Functional Assessment of Chronic Illness Therapy fatigue scale [27].

This study presented some limitations. Indeed, the small sample size may not have been adequate for drawing significant conclusions. Moreover, this study did not include a control arm in order to confirm the specificity of the adalimumab effect. In addition, longer follow-up may be needed to confirm the long-term effects of this treatment strategy on work ability and fatigue. In this regard, controlled studies evaluating more patients with a longer follow-up are needed to demonstrate the long-term effects of adalimumab on work disability, as well as the potential cost-effectiveness of TNF inhibitors.

## CONCLUSION

In this study, we have shown that work ability, functional disability, and fatigue improved after 6 months of adalimumab therapy in patients with established RA. To translate work ability into actual employment, there is a need to apply early and comprehensive disease control measures in order to maintain work ability and avoid the need for re-employment. Given the importance of improving work

ability in patients with RA, and the results of this study, new trials on TNF inhibitors should consider including work ability assessments and fatigue scales as relevant outcomes for RA patients.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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