Real-world evidence of the impact of adalimumab on work productivity and sleep measures in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

Maria G. Tektonidou (iD), **Gkikas Katsifis, Athanasios Georgountzos, Athina Theodoridou, Eftychia-Maria Koukli, Anna Kandili, Giasna Giokic-Kakavouli and Theofilos-Diamantis Karatsourakis** (iD)

Abstract

Objective: Our aim was to evaluate the effect of adalimumab on work productivity measures, overall activity impairment, and sleep quality in patients with active moderate to severe rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) treated in routine care settings in Greece and determine factors associated with work impairment and sleep disturbance.

Methods: Patients with active moderate to severe RA ($n = 184$), PsA ($n = 166$), and AS ($n = 150$) were enrolled in this 24-month, prospective, observational study at 80 hospital outpatient clinics and private practices throughout Greece. Patients received adalimumab alone or in combination with standard antirheumatic therapies according to routine care. Work productivity and sleep were assessed through two patient-reported outcome measures: the Work Productivity and Activity Impairment–General Health questionnaire and the Medical Outcomes Study Sleep Scale (MOS-SS). Pearson correlation coefficients were estimated to assess the association of work impairment and sleep disturbances with disease activity scores.

Results: In the overall population, adalimumab significantly lowered absenteeism [mean (95% confidence interval) reduction, 18.9% (13.3–24.5%); $n = 100$]; presenteeism [40.0% (33.8–46.3%); $n = 98$], overall work productivity impairment [46.8% (40.4–53.2%); $n = 94$], activity impairment [47.0% (44.3–49.6); $n = 421$], and the MOS-SS sleep problems index [31.6 (29.5–34.1); $n = 421$] after 24-month treatment ($p < 0.001$). Significant improvements were also noted across the RA, PsA, and AS subpopulations ($p < 0.05$). Improvements in overall work impairment and sleep disturbance positively correlated with improvements in disease activity measures.

Conclusion: Adalimumab improves work productivity and sleep problems while lowering disease activity in patients with moderate to severe RA, PsA, and AS managed in real-world settings.

Correspondence to:
Maria G. Tektonidou
1st Department of Propaedeutic and Internal Medicine, Joint Rheumatology Program, Laiko Hospital, Medical School, National and Kapodistrian University of Athens, 17 Agiou Thoma Str., Athens, 11 527, Greece.
mtektonidou@gmail.com

Gkikas Katsifis
Rheumatology Clinic Naval Hospital of Athens, Athens, Greece

Athanasios Georgountzos
Rheumatology Department, G.Gennimatas General Hospital, Athens, Attica, Greece

Athina Theodoridou
Academic Research Fellow Hippokration Hospital Thessaloniki, Thessaloniki, Greece

Eftychia-Maria Koukli
Rheumatologist, Private practice, Kifissia, Athens, Greece

Anna Kandili
Rheumatologist, Metropolitan general Hospital Athens, Cholargos, Athens, Greece

Giasna Giokic-Kakavouli
Rheumatologist, Private practice, Karterini, Greece

Theofilos-Diamantis Karatsourakis
employee of AbbVie Pharmaceuticals S.A., Neo Iraklio, Athens, Greece

Introduction

Chronic rheumatic diseases are characterized by inflammation and joint damage, which may lead to functional loss and impairment of daily living. A large-scale study conducted in Greece found that, among major disease groups, including cardiovascular, respiratory, and endocrine-metabolic diseases, rheumatic diseases were found to be the leading cause of chronic health problems, long- and short-term disability, and physician office visits.[1] The prevalence of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) in Greece have been reported to range between 0.58% and 0.68%,[2,3] 0.17% and 0.35%,[2] and 0.24% and 0.29%,[2] respectively.

In patients with RA, PsA, and AS, impairment of physical function diminishes working ability,[4,5] increasing the economic burden of the diseases. In fact, indirect costs, mainly consisting of costs from work productivity loss, often exceed the direct costs of rheumatic diseases.[6,7] In addition to work productivity impairment, RA, PsA, and AS are associated with sleep disturbances and diminished sleep quality, which in turn affect the patient's cognition, mood, and functional status and intensify physical fatigue.[5,8–13]

Treatment with tumor necrosis factor (TNF) inhibitors has been shown to improve work productivity measures in short- and long-term studies of patients with RA, PsA, and AS,[14–19] and several studies among patients with AS and RA have demonstrated that anti-TNF treatments improve various measures of sleep quality.[20–25] As it specifically pertains to the anti-TNF agent adalimumab, patients with early RA treated with adalimumab plus methotrexate have shown significantly greater improvement in work productivity measures after 26 weeks of treatment[26] and over a 2-year period compared with patients treated with methotrexate alone.[27] Adalimumab has been reported to improve work ability after 6 months,[28] and to improve Work Productivity and Activity Impairment (WPAI) scores after 12, 24, and 48 weeks of treatment among patients with RA.[18] Sustained improvements of all WPAI scores through 3 years of adalimumab treatment have been reported for patients with AS.[29] Studies specifically examining the benefits of adalimumab on sleep measures among patients with RA, PsA, and AS are limited to a single study demonstrating adalimumab-induced improvements in each of the Medical Outcomes Study Sleep Scale (MOS-SS) domains after 12 weeks of treatment

among 1250 patients with AS.[30] To our knowledge, the first data regarding the effects of adalimumab on work productivity among patients with PsA were recently published by Nakagawa *et al.*[31] With this perspective, the present 24-month noninterventional prospective study—AWARE—aimed to bridge this gap by providing real-world evidence on the adalimumab-induced changes in work productivity measures as assessed by the WPAI: General Health (WPAI:GH) questionnaire and in sleep disturbances as estimated by the MOS-SS in patients with moderate to severe RA, PsA, and AS managed in routine clinical care settings in Greece.

Materials and methods

Study design and setting

AWARE was a multicenter, noninterventional, prospective, observational study in patients with moderate to severe RA, PsA, or AS treated with adalimumab. The study took place in hospital outpatient departments and in private practices in Greece by qualified rheumatologists. Data were collected by means of a paper case record form.

Study data were collected over six visits that took place at enrollment, at 3 and 6 months, and at 6-month intervals thereafter up to 24 months. All assessments were performed based on the clinical judgment and routine practice of the participating physicians. Demographic characteristics, medical history, and comorbidities were captured at enrollment. Adalimumab treatment characteristics, concomitant medications, and physician-assessed disease activity measures [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for all patients; tender and swollen joint counts for patients with RA and PsA; the 28-joint disease activity score (DAS28) for patients with RA; and the physician's global assessment of disease activity (PhGA) for patients with PsA] were recorded at all study visits; adverse events were recorded throughout study participation. The following patient-reported outcome (PRO) instruments were completed at each of the study visits: WPAI:GH, MOS-SS, the patient's global assessment of disease activity (PtGA; for RA and PsA), the Health Assessment Questionnaire Disability Index (HAQ-DI; for RA) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; for AS).

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki

and the International Society for Pharmaco-epidemiology guidelines for Good Pharmacoepidemiology Practice and was in full compliance with all standing regulations. The study was initiated after obtaining approval by the competent institutional review boards of all participating hospital sites. Before the conduct of any study-related procedure each patient signed an informed consent form. The study has been registered at [ClinicalTrials.gov identifier: NCT01282372].

Study population

The study enrolled adult patients with moderate to severe active RA, PsA, or AS for whom the decision to initiate treatment with adalimumab as indicated on the product's label had been taken by the treating physician before their inclusion in the study and who were willing to sign an informed consent. Exclusion criteria included any contraindications to adalimumab according to the Summary of Product Characteristics and participation in other AbbVie-sponsored observational studies. All patients were followed up on an outpatient basis.

Study objectives and endpoints

The study's primary objective was to evaluate the mean change from baseline in activity impairment as measured by the WPAI:GH in adalimumab-treated patients over the 2-year study observation period. The secondary objectives included the assessment of the effect of adalimumab on WPAI:GH outcomes and on the MOS-SS measures in the overall population and the RA, PsA and AS subpopulations; on the DAS28 and HAQ-DI scores among patients with RA, and on the BASDAI score among patients with AS at 3, 6, 12, 18, and 24 months after treatment onset. Furthermore, the study aimed to assess the correlation of the changes in the DAS28, HAQ-DI, and BASDAI from treatment onset to 24 months with respective changes in overall work impairment and sleep disturbance.

Statistical methods

Continuous variables have been summarized as mean, standard deviation (SD), median, and interquartile range (IQR; as applicable), and categorical variables are displayed as absolute and relative frequencies [n (%)]. The normality of the data was examined with the Kolmogorov–Smirnov and the Shapiro–Wilk tests. The paired t test or the Wilcoxon signed rank-test was applied to determine any statistically significant change in continuous variables (WPAI:GH, MOS-SS measures, disease activity measures) from baseline to the postbaseline time points. The McNemar test has been used to assess the significance of any changes in the proportion of patients with tender and swollen joints from baseline to the postbaseline time points. Pearson's correlation coefficients were estimated to assess the association between improvements in disease activity measures and selected PRO measures, as well as for the correlation between DAS28 and HAQ-DI scores at baseline and at 24 months among patients with RA. The chi-square test was used to examine the association between DAS28 disease activity levels (low, $\leqslant 3.2$; moderate, >3.2–5.1; high, >5.1) with the HAQ-DI disability categories (mild to moderate, $\leqslant 1$; moderate to severe, >1–2; severe, >2–3) at baseline and at 24 months among patients with RA. Statistical tests were 2-sided and were performed at a 0.05 significance level. Statistical analyses have been conducted using the statistical software packages IBM SPSS v21.0, R 3.1.2 and R 3.4.0.

Study size estimation

nQuery Advisor v7.0 (Statistical Solutions Ltd, Cork, Ireland) was used for the determination of the sample size required to assess the improvement in disease activity as estimated through the WPAI:GH. Analysis of a univariate single-group repeated-measures analysis of variance using the Greenhouse–Geisser correction with a sample size of $\geqslant 134$ in each group (RA/PsA/AS) and a significance level of 0.050 has a 90% power to detect a difference in the means with "visits" as a factor, with an effect size of 0.0324 (variance of means, 21.086; within group error term, 30) assuming that the "sphericity" epsilon is 1 [the Greenhouse–Geisser correction has an expected bias of about g1/(n–1), g1 = −1.50]. To account for an approximately 20% noneligible/drop-out rate, 168 patients per group (504 in total) were proposed to be enrolled.

Results

Patient characteristics

Patients with RA, PsA, and AS ($n = 500$) were enrolled in the study between March 17, 2011 and July 5, 2012 by five hospital and 75 office-based rheumatologists distributed throughout
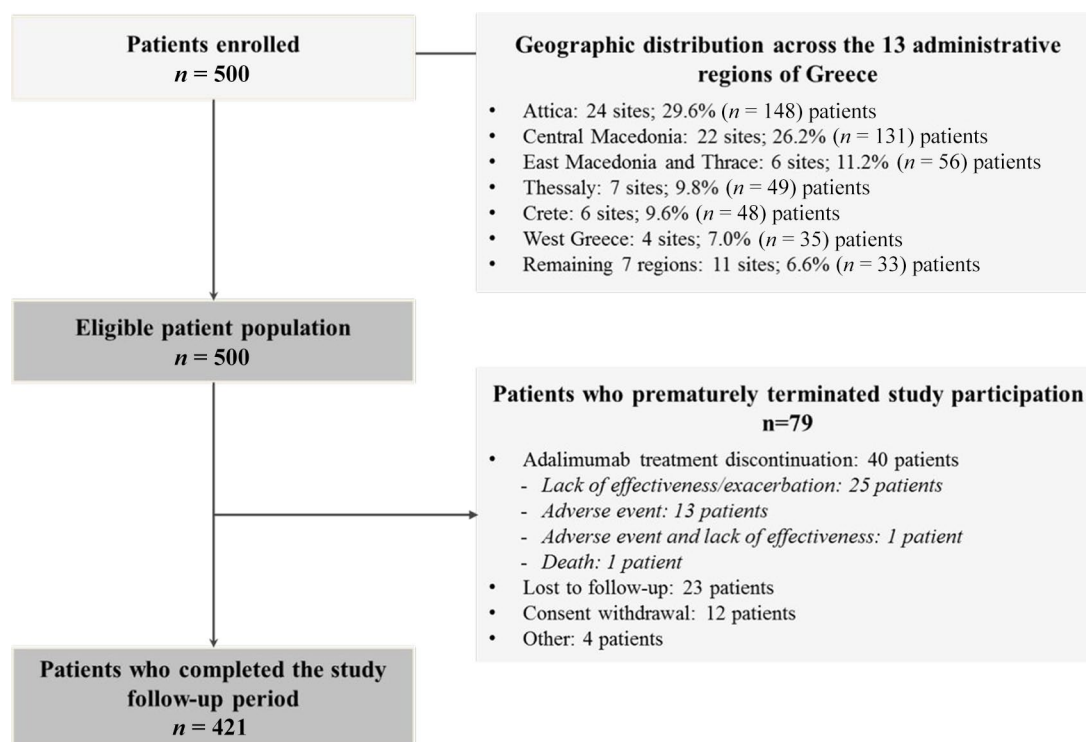
Figure 1. Patient disposition and site and patient distribution throughout the geographic regions of Greece.

Greece (Figure 1). More than half of the patients were enrolled from the two most populous regions of Greece: Attica (29.6%) and Central Macedonia (26.2%). The overall study duration was 40 months (March 17, 2011 to July 28, 2014). The median length of patient follow-up was 24.0 (IQR, 23.3–24.2) months. Of the 500 patients, 421 (84.2%) completed the planned 24-month observation period; 79 (15.80%) were prematurely withdrawn after a median follow-up of 6.0 (IQR, 0.0–31.0) months. The main reasons for early termination were study treatment discontinuation (*n* = 40), loss of follow-up (*n* = 23), and consent withdrawal (*n* = 12; Figure 1).

The median age of the study population at enrollment was 52.0 (IQR, 41.0–63.0) years, and 57.8% were female. A total of 74.6% experienced ≥1 comorbidity, with arterial hypertension (24.8%), dyslipidemia (15.0%), and osteoporosis (13.4%) being the non-disease related comorbidities reported at a frequency >10% of the overall population (Table 1).

Adalimumab treatment

A total of 85.6% of the overall population were biologic treatment-naive; the remaining 14.4% had been exposed to biologics before adalimumab treatment onset. Of the overall population, 93.2% received their first adalimumab dose on the day of enrollment, and 5.8% and 1.0% received their first dose 1–7 and 8–15 days before enrollment, respectively. The median exposure to adalimumab during the study was 23.7 (IQR, 23.0–24.0) months.

Patient disposition per rheumatic disease type and disease management throughout the study

Of the overall study population, 36.8% (184/500) were diagnosed with RA, 33.2% (166/500) with PsA, and 30.0% (150/500) with AS. Among those with available data, RA, PsA, and AS diagnoses occurred a median of 1.4 (IQR, 0.4–4.1), 0.9 (IQR, 0.3–3.1), and 2.2 (IQR, 0.3–9.5) years before enrollment, respectively (Table 1).

A total of 8.2% (15/184) of RA, 24.7% (41/166) of PsA, and 37.3% (56/150) of AS patients were initially prescribed adalimumab as monotherapy. Treatments co-administered in >10% of patients at adalimumab onset included methotrexate (59.8%), steroids (52.7%), and leflunomide (19.0%) in the RA group (Figure 2A); methotrexate (48.8%), cyclosporine (15.7%), steroids

Table 1. Baseline sociodemographic, anthropometric, and clinical characteristics in the overall eligible population and subpopulations diagnosed with RA, PsA, and AS.

	Overall population (n = 500)	RA (n = 184)	PsA (n = 166)	AS (n = 150)
Sex, n (%)				
Male	211 (42.2)	39 (21.2)	73 (44.0)	99 (66.0)
Female	289 (57.8)	145 (78.8)	93 (56.0)	51 (34.0)
White race, n (%)	498 (99.6)	184 (100)	166 (100)	148 (98.7)
Age at enrollment, n (%)				
<65 years	391 (78.2)	118 (64.1)	136 (81.9)	137 (91.3)
≥65 years	109 (21.8)	66 (35.9)	30 (18.1)	13 (8.7)
Age at enrollment, years, median (IQR)	52.0 (41.0–63.0)	60.0 (50.8–69.0)	51.0 (41.0–60.8)	45.0 (34.3–56.0)
BMI, mean (SD)	26.7 (4.3)	27.4 (4.5)	27.4 (4.3)	25.7 (3.9)
Employment status, n (%)				
Employed	116 (23.2)	25 (13.6)	44 (26.5)	47 (31.3)
Self-employed	95 (19.0)	28 (15.2)	33 (19.9)	34 (22.7)
Retired	118 (23.6)	57 (31.0)	35 (21.1)	26 (17.3)
Household duties, student, unemployed	171 (34.2)	74 (40.2)	54 (32.5)	43 (28.7)
Smoking status, n (%)				
Current smoker	133 (26.6)	27 (14.7)	56 (33.7)	50 (33.3)
Ex-smoker	27 (5.4)	6 (3.3)	10 (6.0)	11 (7.3)
Never smoked	340 (68.0)	151 (82.1)	100 (60.2)	89 (59.3)
Alcohol consumption, n (%)*				
Current drinker	67 (13.5)	12 (6.6)	24 (14.6)	31 (20.7)
Ex-drinker	9 (1.8)	1 (0.5)	4 (2.4)	4 (2.7)
Age at diagnosis, years, median (IQR)†	47.5 (45.8–49.4)	56.0 (53.2–58.9)	45.5 (43.4–49.2)	39.4 (36.7–42.3)
Time elapsed from diagnosis to enrollment, years, median (IQR)†	1.4 (0.3–4.2)	1.4 (0.4–4.1)	0.9 (0.3–3.1)	2.2 (0.3–9.5)
Patients with ≥1 comorbidity, n (%)‡	373 (74.6)	128 (69.6)	138 (83.1)	107 (71.3)
Arterial hypertension	124 (24.8)	60 (32.6)	43 (25.9)	21 (14.0)
Dyslipidemia	75 (15.0)	33 (17.9)	29 (17.5)	13 (8.7)
Osteoporosis	67 (13.4)	46 (25.0)	14 (8.4)	7 (4.7)

AS, ankylosing spondylitis; BMI, body-mass index; IQR, interquartile range; PsA, psoriatic arthritis; RA, rheumatoid arthritis.
*Overall population, n = 497; RA, n = 183; PsA, n = 164; AS, n = 150.
†Overall population, n = 286; RA, n = 103; PsA, n = 90; AS, n = 93.
‡Non-disease related comorbidities present in ≥10% of the overall population.
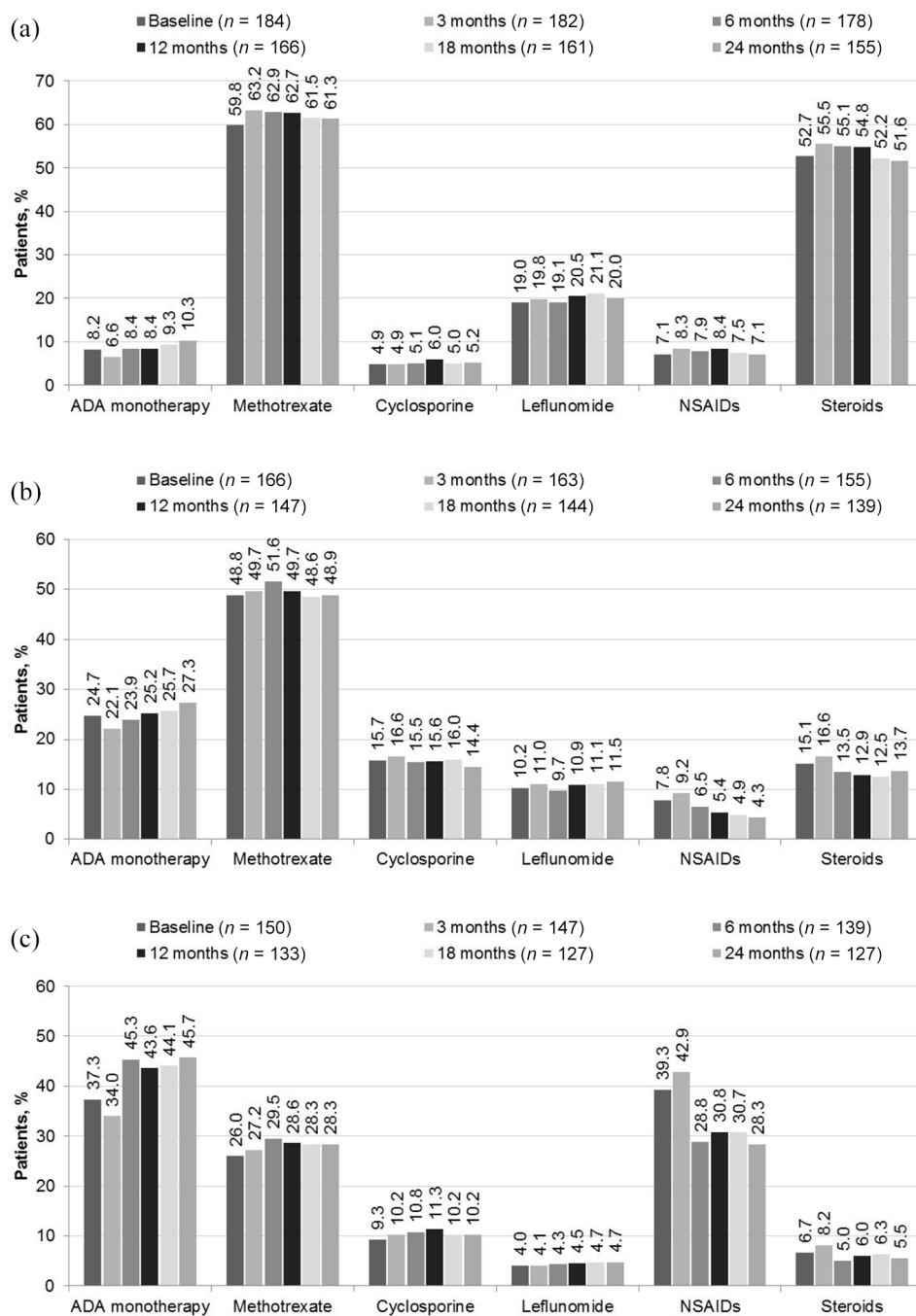
Figure 2. Adalimumab monotherapy and antirheumatic treatments co-administered with adalimumab throughout the study among patients with (A) rheumatoid arthritis, (B) psoriatic arthritis and (C) ankylosing spondylitis. In addition to the medications depicted in the bar graphs, 4.9–6.2% of patients with rheumatoid arthritis, 1.2–1.4% of those with psoriatic arthritis, and 4.0–4.7% of those with ankylosing spondylitis were receiving hydroxychloroquine, and 0.–1.3%, 0.6–1.4%, and 3.9–4.8%, respectively, were receiving sulfasalazine at the study time points.
ADA, adalimumab; NSAIDs, nonsteroidal anti-inflammatory drugs.

(15.1%), and leflunomide (10.2%) in the PsA group (Figure 2B); and nonsteroidal anti-inflammatory drugs (NSAIDs; 39.3%) and methotrexate (26.0%) in the AS group (Figure 2C). A substantial number of the AS patients used classic disease modifying anti-rheumatic drugs (DMARDs) although this is, in fact, an out of label use. Treatment decision for each patient was made

according to the treating physician's judgment and the reasons for using DMARDs were not recorded. The proportion of patients treated with adalimumab alone increased at 24 months in all three subpopulations, whereas frequencies of co-administered treatments among patients with RA, PsA, and AS remained fairly stable throughout the study observation period, except for the frequency of NSAIDs, which decreased among patients with PsA and AS (Figure 2).

Disease activity throughout the study
Among patients with RA, the mean (SD) DAS28, HAQ-DI, and PtGA scores were 6.0 (1.2), 1.6 (0.6), and 67.6 (18.5), respectively, at baseline, noting statistically significant decreases at month 24 ($p < 0.001$; Table 2). The HAQ-DI score positively correlated with the DAS28 score at baseline (Pearson's rho, 0.283; $p < 0.001$) and at month 24 (Pearson's rho, 0.590; $p < 0.001$). Similarly, a significant association was observed between DAS28 categories (low, moderate, and high) and the HAQ-DI categories (mild to moderate, moderate to severe, and severe) at baseline ($p = 0.003$) and at month 24 ($p < 0.001$), with the frequency of patients with moderate to severe and severe HAQ-DI being higher among patients with moderate and high than those with low DAS28. Regarding PsA, the mean (SD) baseline PhGA and PtGA scores were 62.6 (16.7) and 65.8 (16.9), respectively, noting significant decreases at month 24 among patients with PsA with available data ($p < 0.001$; Table 2). Similarly, among patients with AS, the mean (SD) BASDAI score was 5.8 (1.7) at baseline, denoting a significant decrease at month 24 ($p < 0.001$; Table 2). Significant reductions from baseline to month 24 were also observed in the levels of acute phase reactants (ESR and CRP) among patients with RA, PsA and AS (Table 2).

Work productivity throughout the study
The mean (SD) baseline percentage of absenteeism, (work time missed due to health), presenteeism (impairment while working due to health), and overall work productivity impairment and activity impairment due to health among the overall population with available data were 21.0% (27.4%), 52.8% (26.2%), 57.8% (26.9%), and 62.1% (24.2%), respectively. All four measures gradually decreased throughout the study (Figure 3A). Specifically, among patients with paired data, the mean [95% confidence interval (CI)] decreases from baseline to month 24 for absenteeism, presenteeism, overall work impairment, and activity impairment were 18.9% (13.3–24.5%; $n = 100$), 40.0% (33.8–46.3%; $n = 98$), 46.8% (40.4–53.2%; $n = 94$), and 47.0% (44.3–49.6%; $n = 421$), respectively ($p < 0.001$). WPAI:GH domain scores did not differ between the three subpopulations at baseline nor at month 24. Significant improvements from baseline to month 24 in all WPAI:GH domain scores were observed for RA, PsA, and AS (Table 3). Improvements in the percentage of overall work impairment from baseline to month 24 positively correlated with respective improvements in disease activity measures (Table 2).

MOS-SS measures throughout the study
Among patients of the overall population with available data, the mean (SD) sleep disturbance score and sleep problems index score were 50.9 (23.6) and 47.7 (19.4) at baseline, respectively, noting gradual decreases throughout the study (Figure 3B). Specifically, among patients with paired data, the mean (95% CI) decreases from baseline to month 24 for sleep disturbance and sleep problems index were 34.7 (32.2–37.3; $n = 421$) and 31.6 (29.5–34.1; $n = 421$; $p < 0.001$). Similarly, significant decreases from baseline to Month 24 among patients with paired assessments were noted for somnolence [mean decrease: 23.1 (95% CI: 20.8–25.5); $n = 421$], snoring [21.3 (95% CI: 18.6–23.9); $n = 417$], and awakening short of breath [23.1 (95% CI: 20.3–25.8); $n = 420$], while significant increases were noted for sleep adequacy [35.9 (95% CI: 33.0–38.5); $n = 421$] and sleep quantity [1.3 (95% CI: 1.2–1.5); $n = 415$] ($p < 0.001$) (Figure 3B). Snoring significantly differed between RA [mean (SD), 50.5 (18.8); $n = 184$], PsA [43.3 (18.7); $n = 166$], and AS [49.1 (20.3); $n = 150$] at baseline ($p = 0.001$) but not at month 24 ($p = 0.215$), by which time significant decreases had occurred in all three subpopulations ($p < 0.001$). In addition, improvements in the sleep disturbance score from baseline to month 24 were shown to positively correlate with improvements in disease activity measures for all three subpopulations from baseline to month 24 (Table 2).

Safety assessment
During the study observation period, 12.0% of patients experienced 121 adverse events assessed by the physicians as causally related to the study

Table 2. Disease activity throughout the study and correlations with patient-reported outcome measures in the RA, PsA, and AS subpopulations.

Disease activity	Baseline		Month 3		Month 6		Month 12		Month 18		Month 24	
	n		*n*		*n*		*n*		*n*		*n*	
RA subpopulation												
DAS28, mean (SD)	184	6.0 (1.2)	179	4.1 (1.4)	175	3.4 (1.3)	164	3.1 (1.3)	160	2.9 (1.2)	153	2.7 (1.3)*
HAQ-DI, mean (SD)	181	1.6 (0.6)	179	1.0 (0.6)	176	0.8 (0.6)	164	0.7 (0.5)	159	0.6 (0.6)	153	0.5 (0.5)*
PtGA of disease activity mm, mean (SD)	184	67.6 (18.5)	181	37.1 (19.0)	178	26.9 (17.6)	166	20.7 (16.0)	161	18.1 (14.9)	155	17.3 (16.7)*
Tender joints, *n* (%)	184	181 (98.4)	182	145 (79.7)	178	117 (65.7)	166	85 (51.2)	161	73 (45.3)	155	65 (41.9)*
Swollen joints, *n* (%)	184	172 (93.5)	182	117 (64.3)	178	88 (49.4)	166	66 (39.8)	161	58 (36.0)	155	53 (34.2)*
ESR, mm/h, mean (SD)	182	49.3 (21.7)	177	30.4 (16.4)	174	25.0 (14.1)	163	22.4 (12.8)	160	21.3 (14.1)	153	18.8 (12.5)*
CRP, mg/L, mean (SD)	167	14.5 (20.2)	156	6.7 (10.6)	158	4.2 (6.2)	156	2.9 (4.6)	152	2.9 (4.6)	148	2.4 (3.3)*
PsA subpopulation												
PhGA of disease activity, mm, mean (SD)	166	62.6 (16.7)	163	29.3 (19.4)	155	19.7 (17.4)	147	14.2 (15.1)	144	12.8 (12.1)	139	11.3 (13.9)*
PtGA of disease activity, mm, mean (SD)	166	65.8 (16.9)	163	32.0 (19.4)	155	21.9 (18.2)	147	15.1 (13.9)	144	14.1 (13.2)	139	12.0 (13.6)*
Tender joints, *n* (%)	166	164 (98.8)	163	118 (72.4)	155	75 (48.4)	147	50 (34.0)	144	47 (32.6)	139	39 (28.1)*
Swollen joints, *n* (%)	166	151 (91.0)	163	86 (52.8)	155	50 (32.3)	147	39 (26.5)	144	41 (28.5)	139	24 (17.3)*
ESR, mm/h, mean (SD)	158	40.2 (22.1)	157	25.3 (15.4)	150	21.7 (16.3)	146	18.5 (13.3)	140	17.6 (12.6)	137	16.2 (11.5)*
CRP, mg/L, mean (SD)	150	9.9 (13.9)	144	5.1 (9.5)	140	3.3 (6.5)	141	1.9 (3.1)	137	2.0 (3.6)	133	1.9 (4.2)*
AS subpopulation												
BASDAI, mean (SD)	146	5.8 (1.7)	146	3.3 (1.7)	138	2.5 (1.6)	130	2.0 (1.5)	125	1.7 (1.2)	125	1.5 (1.3)*
ESR, mm/h, mean (SD)	147	41.1 (23.5)	140	24.5 (16.2)	130	19.3 (10.6)	125	18.6 (11.8)	120	16.6 (9.7)	122	15.6 (11.2)*
CRP, mg/L, mean (SD)	139	11.2 (13.5)	130	5.1 (7.5)	120	3.6 (8.3)	117	2.9 (5.1)	111	2.4 (4.3)	116	1.9 (2.7)*

Correlations between improvement in disease activity and patient-reported outcome measures	WPAI:GH overall work impairment		MOS-SS sleep disturbance score	
	Pearson's rho (95% CI)	*p* Value	Pearson's rho (95% CI)	*p* Value
RA subpopulation				
DAS28 improvement	0.47 (0.11–0.72)	0.013	0.32 (0.18–0.45)	<0.001
HAQ-DI improvement	0.57 (0.23–0.78)	0.003	0.44 (0.30–0.56)	<0.001
PtGA of disease activity improvement	0.42 (0.05–0.69)	0.028	0.40 (0.27–0.52)	<0.001
PsA subpopulation				
PtGA of disease activity improvement	0.59 (0.33–0.77)	<0.001	0.52 (0.39–0.63)	<0.001
PhGA of disease activity improvement	0.54 (0.26–0.73)	<0.001	0.56 (0.44–0.66)	<0.001
AS subpopulation				
BASDAI improvement	0.69 (0.49–0.82)	<0.001	0.64 (0.52–0.73)	<0.001

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; MOS-SS, Medical Outcomes Study Sleep Scale; PhGA, physician's global assessment of disease activity; PsA, psoriatic arthritis; PtGA, patient's global assessment of disease activity; RA, rheumatoid arthritis; WPAI:GH, Work Productivity and Activity Impairment–General Health; CI, Confidence Interval.
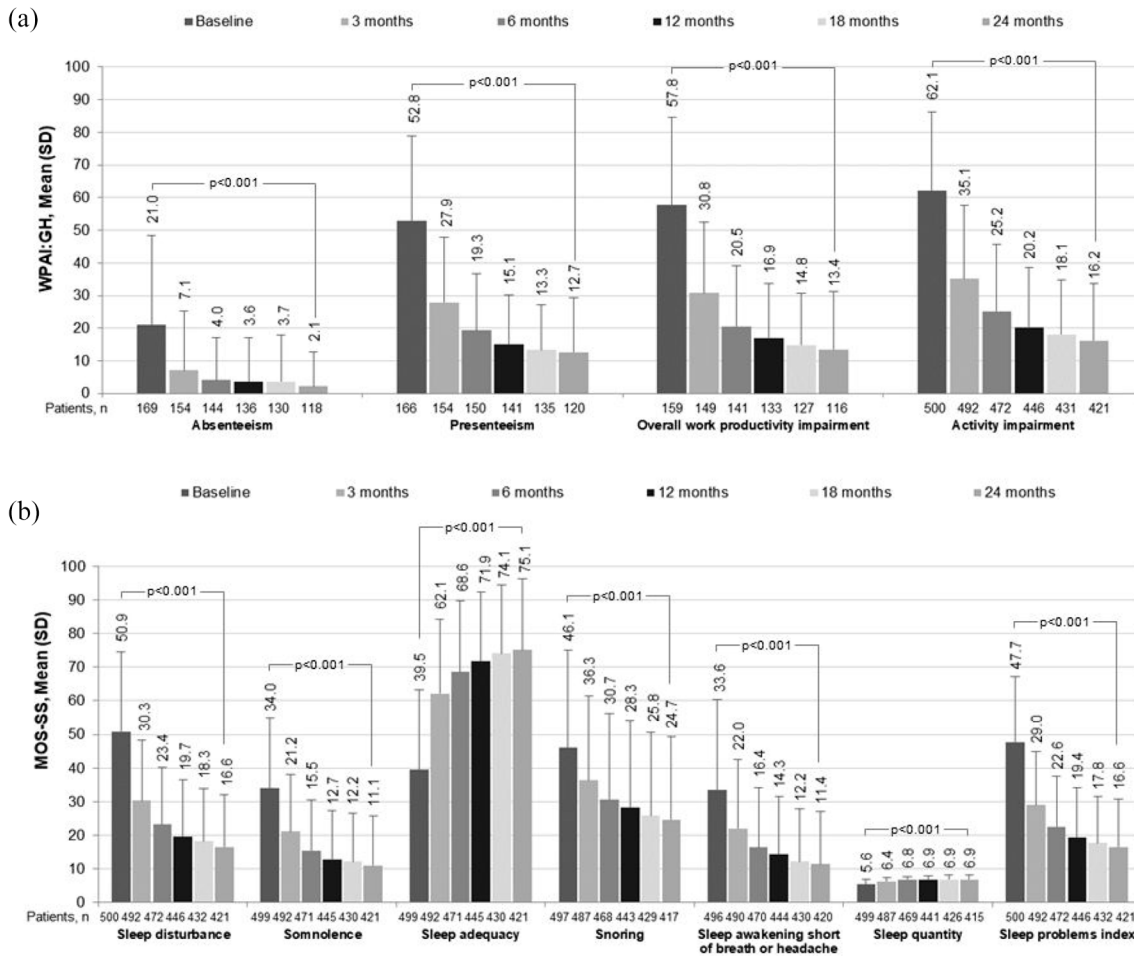*Statistically significant change from baseline, *p* < 0.001.

(a)

(b)

Figure 3. (A) WPAI:GH scores and (B) MOS-SS domain scores throughout the study in the overall population.
MOS-SS, Medical Outcomes Study Sleep Scale; WPAI:GH, Work Productivity and Activity Impairment–General Health.

medication (i.e. adverse drug reactions); 97 reactions experienced by 11.0% of patients were nonserious, and 24 reactions experienced by 1.4% were serious. The adverse reactions reported at a frequency >1% were "general disorders and administration site conditions" (36 events by 5.8% of patients, including 22 events of drug ineffective/incomplete effect, and six events of pyrexia), "infections and infestations" (28 events by 4.0% of patients, including 16 events of respiratory tract infection, four events of urinary tract infections, and two events each of herpes zoster and tooth abscesses), "musculoskeletal and connective tissue disorder" (17 events by 3.2% of patients) and "skin and subcutaneous tissue disorder" (12 events by 1.8% of patients). Serious adverse reactions were mainly "general disorders and administration site conditions" (eight events by 0.8% of the patients, including three events of pyrexia and two events of asthenia). All other

serious adverse reactions had only a single occurrence. During the study, a case of "spontaneous abortion" and of "fetal exposure during pregnancy" with a normal neonatal outcome were reported. Furthermore, a case of death due to gastric cancer was reported, which according to the physicians' assessment was not causally related to adalimumab per the investigators assessment.

Discussion
AWARE represents the largest study to have collected real-world data relating to work productivity and sleep disturbance measures of moderate to severe RA, PsA, and AS in patients treated with adalimumab in routine care settings in Greece. Adalimumab yielded statistically significant decreases among all WPAI:GH domain scores, including percentage of work missed, of work

Table 3. Changes in WPAI:GH absenteeism, presenteeism, overall work impairment, and activity impairment due to health and the MOS-SS sleep problems index from baseline to month 24 among patients with RA, PsA, and AS with paired assessments.

| | Median (IQR) | | | | | | | | | | | |
| | RA | | | | PsA | | | | AS | | | |
	n	Baseline	Month 24	Change	n	Baseline	Month 24	Change	n	Baseline	Month 24	Change
WPAI:GH, %												
Absenteeism	22	21.0 (0.0–43.5)	0.0 (0.0–0.0)	−21.0 (−43.5 to 0.0)*	34	12.0 (2.0–24.0)	0.0 (0.0–0.0)	−12.0 (−24.0 to −1.0)*	44	9.5 (0.0–22.5)	0.0 (0.0–0.0)	−7.0 (−22.5 to 0.0)†
Presenteeism	21	60.0 (40.0–80.0)	10.0 (0.0–15.0)	−50.0 (−65.0 to −30.0)*	34	50.0 (30.0–62.5)	10.0 (0.0–20.0)	−40.0 (−60.0 to −10.0)*	43	60.0 (30.0–80.0)	10.0 (0.0–20.0)	−40.0 (−70.0 to 20.0)*
Overall work impairment due to health	21	61.0 (50.5–89.0)	10.0 (0.0–20.0)	−59.0 (−74.5 to −38.5)*	31	61.5 (36.0–80.0)	10.0 (0.0–20.0)	−49.0 (−72.8 to −21.8)*	42	66.0 (35.8–84.0)	10.0 (0.0–20.0)	−49.0 (−73.0 to −20.0)*
Activity impairment due to health	155	70.0 (50.0–80.0)	10.0 (0.0–20.0)	−50.0 (−70.0 to −30.0)*	139	70.0 (50.0–70.0)	10.0 (0.0–20.0)	−50.0 (−60.0 to −30.0)*	127	70.0 (50.0–80.0)	10.0 (0.0–20.0)	−50.0 (−70.0 to −30.0)*
MOS-SS, sleep problems index												
Overall subpopulation	149	52.2 (40.3–66.1)	15.6 (4.4–27.2)	−31.1 (−50.6 to −20.3)*	133	42.2 (29.2–57.5)	13.3 (4.4–20.8)	−29.4 (−43.3 to −11.4)*	125	49.4 (35.3–64.7)	16.1 (4.4–24.4)	−30.0 (−51.1 to −15.6)*
Biologic-naive patients	133	52.2 (40.0–66.7)	15.6 (4.4–27.2)	−32.2 (−53.1 to −21.7)*	117	45.0 (29.4–59.4)	15.6 (5.6–21.7)	−30.0 (−45.0 to 11.4)*	104	50.0 (35.7–63.8)	15.0 (2.2–24.4)	−31.7 (−52.6 to −15.7)*
Biologic-experienced patients	16	47.5 (40.7–59.0)	16.9 (3.2–44.6)	−24.2 (−40.6 to −3.9)*	16	32.2 (27.8–47.2)	6.7 (4.4–18.3)	−22.8 (−28.9 to −11.1)*	21	42.8 (29.4–66.9)	22.8 (13.6–3.1)	−20.0 (−34.2 to −10.3)*

AS, ankylosing spondylitis; MOS-SS, Medical Outcomes Study Sleep Scale; PsA, psoriatic arthritis; RA, rheumatoid arthritis; WPAI:GH, Work Productivity and Activity Impairment–General Health.
*Statistically significant change from baseline, $p < 0.001$.
†Statistically significant change from baseline, $p = 0.002$.

impairment while working, of overall work impairment, and of activity impairment from baseline to month 24. The decreases were significant among the overall study population as well as the RA, PsA, and AS subpopulations. The evidence concurs with previous reports of adalimumab-induced improvements in WPAI domains[18,31] and in the Work Ability Index[28] after about 6 months of treatment among patients with RA and in WPAI domains through 3 years of exposure among those with AS.[29] Improvements in the WPAI:GH scores noted here were accompanied by statistically significant improvements in patient disease activity measures. In fact, changes in overall work impairment were found to be significantly correlated with all disease activity measures examined (i.e. DAS28, HAQ-DI, and PtGA for RA; PtGA and PhGA for PsA; and BASDAI for AS). The strongest correlation was observed with the BASDAI score, followed by disease activity measures for patients with PsA and lastly those for patients with RA. Similar to our observations, correlations between improvements in the WPAI:GH scores and improvements in the DAS28 and HAQ-DI scores among patients with RA,[18] and between the WPAI spondyloarthritis questionnaire scores and the BASDAI score among AS patients,[32] have been reported elsewhere.

In addition to improvements in work productivity measures, in the present study adalimumab demonstrated significant improvements in all domains of the MOS-SS at 24 months after treatment onset in the overall population. Significant decreases in the baseline MOS-SS sleep problems index after 24 months of treatment were also noted in the RA, PsA, and AS subpopulations. This finding complements the results of a study demonstrating sleep measure improvements among patients with AS 12 weeks after onset of adalimumab treatment.[30] Improvements in the MOS-SS sleep disturbance score were found to correlate with improvements in disease activity measures across all three study subpopulations, matching previous reports of a correlation of sleep quality improvement with improvements in the BASDAI (patients with AS)[33] and HAQ-DI (patients with RA) scores.[34] Herein, the strongest correlation was observed with the BASDAI score among the AS subpopulation, followed by disease activity measures of the PsA and lastly of the RA subpopulations. Interestingly, the correlation of poor sleep with disability among patients with RA

has been suggested to be mediated *via* pain severity and fatigue.[35]

In alignment with published literature, AS was more commonly diagnosed among male than female patients,[36,37] whereas the reverse was true for RA.[38,39] In addition, age at diagnosis was the lowest among those with AS, followed by PsA and RA. Employment (including self-employment) rate was 29% among those with RA, but 46% among those with PsA and 54% among those with AS. This is likely related to the fact that 36% of enrolled patients with RA but only 18% of those with PsA and 9% of those with AS were ⩾65 years of age at enrollment, and thus of retirement age. WPAI:GH domain scores did not differ between the three subpopulations at baseline nor at month 24. On the other hand, the MOS-SS sleep problems index at baseline was higher for those with RA and AS than those with PsA, suggesting greater sleep impairment among those with RA and AS. Nonetheless, this score significantly decreased at treatment month 24 to levels that did not differ between the three subpopulations, indicating the effectiveness of adalimumab across all three subpopulations in improving sleep quality.

Limitations of this study stem from the fact that employment rates were rather low, especially among patients with RA, limiting the size of the population that provided data regarding the WPAI:GH outcome measures and lowering the statistical power of the detected changes in the WPAI:GH absenteeism, presenteeism, and overall work impairment scores. In addition, the study premature withdrawal rate was 16%, limiting the number of observations at month 24. Interview bias has been avoided by completion of the questionnaires before the performance of any study-related activities. Recall bias has been controlled by the use of validated standardized instruments, widely used in studies of rheumatic diseases that employ a short recall period of 1 week, except for the MOS-SS, for which there is a 4-week recall period. Moreover, although PROs completed at enrollment served as baseline data, the effect of this limitation seems minimal considering that only about 7% of the patients had initiated adalimumab before study enrollment, and only 1% of these patients initiated adalimumab >1 week before enrollment. Study limitations are outweighed by the observational design of the study, which yields outcomes that

are more representative of the population under study compared with those derived from the strictly controlled randomized clinical trials.

In conclusion, AWARE has captured data from 500 patients with rheumatic diseases distributed throughout all geographic regions of Greece, facilitating generalization of study outcomes to patients with moderate to severe RA, PsA, and AS who are candidates to receive treatment with adalimumab, are mainly biologic treatment-naive, reside in urban, semi-urban, and rural areas, and have disease that is managed in routine outpatient hospital and private practice settings. Patients were nearly equally distributed among the RA, PsA, and AS diagnoses. Adalimumab lowered disease activity and reduced the work time missed and overall work impairment while also improving sleep problems across patients with RA, PsA and AS through 2 years of treatment, during which no new safety signals arose.

Author contributions
MGT contributed to the design, and the acquisition, analysis, and interpretation of data. TK contributed to the design, and the collection, analysis, and interpretation of data. GK, AG, AT, EK, AK and GG-K contributed to the acquisition, analysis, and interpretation of data. All authors participated in the writing and critical revision of the article for important intellectual content and gave their approval for this version to be published.

Conflict of interest statement
MGT has received consultant fees and unrestricted grants from AbbVie, GlaxoSmitheKline (GSK), Merck Sharp & Dohme (MSD), Novartis, Pfizer and Union Chimique Belge (UCB) Pharma deposited to the Special Account for Research Funding (ELKE) of the National and Kapodistrian University of Athens Medical School. GK: Honoraria for educational activities and consultancy payments from UCB Pharma, Janssen, Abbvie, Novartis, MSD, Aenorasis, Genesis Pharma, Pfizer, Roche. AG: no conflicts declared. AT: no conflicts declared. EK: no conflicts declared. AK: Honoraria for educational activities and consultancy payments from Novartis and UCB Pharma, GG-K: no conflicts declared. TK: employee of AbbVie Pharmaceuticals S.A.

ORCID iDs
Maria G Tektonidou iD https://orcid.org/0000-0003-2238-0975

Theofilos-Diamantis Karatsourakis iD https://orcid.org/0000-0003-4928-8853

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