The impact of rheumatoid arthritis on work and predictors of overall work impairment from three therapeutic scenarios

Aim: To examine the effects of three treatment scenarios in rheumatoid arthritis (RA) on work and to determine potential predictors of work impairment. Materials & methods: Moderate RA patients received etanercept 50 mg weekly plus methotrexate (E50/MTX) for 36 weeks. Those with Disease Activity Score 28 ≤3.2 at week 36 and ≤3.2 from weeks 12–36 were randomized to E50/MTX, etanercept 25 mg weekly/MTX or placebo/MTX for 52 weeks. Results: Work-related components of the Work Productivity Activity Impairment questionnaire significantly improved with E50/MTX, which were maintained at week 88. Age, overall work impairment, disease duration, Health Assessment Questionnaire-Disability Index score >0.5, and pain visual analog scale were significantly predictive of overall work impairment. Conclusion: E50/MTX maintained significant improvements in Work Productivity Activity Impairment:RA. Prediction of potential work impairment may help improve RA work-related issues.

Keywords: anti-TNF • biologic • etanercept • moderate rheumatoid arthritis • quality of life • work impairment • WPAI:RA

Rheumatoid arthritis (RA) is a debilitating autoimmune disease associated with joint inflammation and damage, functional impairment and often disability [1-3]. Impaired physical function has consistently been shown to be related to work disability (the inability to work), a common and costly consequence of active RA, resulting in an increased likelihood of presenteeism, absenteeism, unemployment, income loss and early retirement [4-9]. In the UK and the USA, it has been estimated that 50–85% of patients with RA are of working age at symptom onset and that 30–35% of those initially employed at diagnosis were no longer working 2 and 10 years later, respectively [8,10-12]. Estimates of work disability owing to RA have been shown to vary widely depending on the time frame, geographic location and methodology used but can range from 22–85% between 5 and 10 years after diagnosis in the USA and from 31–42% between 2 and 10 years after diagnosis in Europe [10,12]. However, since intensification of RA treatment in Finland in 2000, the frequency of continuous work disability has declined [13]. Furthermore, in the observational RAPSODIA [14] study assessing health-related quality of life (HRQoL) 15 years after the introduction of biologics in Italy, patients receiving biologic therapy had improved work productivity compared with those receiving conventional treatment. Recently, direct and indirect costs (due to sick leave, disability and workers’ compensation absences) of the total annual incremental burden of RA (costs during the first year as per the Human Capital Management Services research database registry) in the USA have been estimated to be $5.8 billion [15].

The impact of RA on work is a complicated issue because factors such as age, disease duration, disease activity, work requirements, education level, regional/cultural issues and societal and psychological characteristics can all play a part in determining the ability to work [4,16]. Historically, the majority of work-related studies have focused primarily or exclusively on the per-

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permanent cessation of work owing to health [8,11,16–19]. Recently, this narrow view on the impact of RA on work has broadened to include absenteeism and presenteeism [16,20]. Absenteeism, defined as missed work days owing to health, is typically a temporary issue in which the employed use sick days because of their RA with the intention of returning to work [16,21,22]. Absenteeism typically precedes other elements of work disability (e.g., income loss) and has been shown to predict permanent job loss [16,21,22]. Expanding further, presenteeism, defined as a reduction of productivity or diminished work capacity while at work, is considered a critical element in assessing the impact of health on work [6,16]. Although additional research is needed to determine if presenteeism linearly precedes absenteeism and other elements of work disability in RA, its prominence is well established in the work life cycle continuum [21,23,24].

The Work Productivity Activity Impairment Questionnaire for RA (WPAI:RA) is a validated instrument identified by the Outcome Measures in Rheumatology (OMERACT) initiative as a reliable measure of worker productivity [25]. The WPAI:RA assesses four components: absenteeism, presenteeism, overall work impairment and activity impairment [26,27]. These components are capitalized herein to distinguish them from their general use as terms in published literature outside of incorporation in a validated instrument. Each outcome score ranges from 0–100%, with higher scores indicating a worsening outcome.

Absenteeism can be further quantified by extrapolating the value of work absence through wage per time calculations [16]. In the USA, recent estimates report that workers with RA miss an average of 7.9 days/year owing to their disease, which translates into 4 million incremental lost days [15].

Presenteeism is more difficult to quantify, albeit a more important measure in determining the economic impact of RA [28]. Productivity loss is not equated to a time value; therefore, extrapolating an economic value for presenteeism is imprecise compared with absenteeism [29]. Although there is no standard for calculating a value, presenteeism has been estimated to account for as much as 35% of total expenses for RA in the USA, and a 2006 systematic review indicated that 66% of employed patients with RA reported productivity loss owing to RA in the previous year [5,24]. The costs associated with presenteeism have been shown to be the largest component of total work productivity losses, greater than absenteeism and several times greater than direct medical costs [5,21,24,29]. A potential reason for this could be that patients with a chronic condition such as RA may have difficulty in taking time off from work, which may result in increased presenteeism.

Publications reporting use of the WPAI:RA to date have emphasized the individual components of absenteeism and presenteeism; however, few publications report on the overall work impairment, calculated using both absenteeism and presenteeism, yielding a comprehensive view of the impact of health-related issues on work. Although published literature on the overall work impairment component is scarce, it has been reported to range from 45.0 to 56.3% at baseline across Asian and Latin American RA populations [30,31]. Currently, the economic impact of overall work impairment in RA has not been estimated, although it is expected to be substantial as it encompasses both absenteeism and presenteeism.

Considering the economic, individual and societal burdens of RA as well as the multifaceted issues surrounding its impact on work, several studies have attempted to identify predictive factors of work-related issues to help determine the value of therapeutic interventions. To date, the majority of analyses of predictors have focused on work disability, followed by absenteeism and presenteeism [11,17–19,31]. Although overall work impairment is a more complete, all-encompassing measure of the impact of health on work, far fewer studies have assessed predictive factors. Nonetheless, overall work impairment measured by the WPAI:RA has been associated with the 28-joint count Disease Activity Score (DAS28), physical function (Health Assessment Questionnaire [HAQ]) and HRQoL, whereas work impairment/productivity assessed by other measures has been associated with structural damage assessed by X-ray, pain and impaired physical function, with inconsistent correlations among studies [11,27,31,32].

Patients with moderate disease activity constitute the majority of the RA population in routine care, seen more frequently in clinical practice than those with high disease activity. The PRESERVE trial (ClinicalTrials.gov identifier, NCT00565409) was the first randomized controlled trial (RCT) in patients with RA with moderate disease activity to assess the effects of three therapeutic scenarios (maintenance or reduction in dose or withdrawal of a biologic agent) after response to initial treatment [33]. This article describes the effects of these three scenarios on work and usual activities using the WPAI:RA and examines potential predictors of the overall work impairment component.

Materials & methods

The PRESERVE trial was a two-period, multicenter investigation into the effects of etanercept plus methotrexate combination therapy in patients with moderate RA. Eligible patients were aged 18–70 years with a diagnosis of active RA based on the American College of Rheumatology (ACR) 1987 revised criteria [34].
Patients were required to have moderate RA disease activity defined by DAS28 erythrocyte sedimentation rate (DAS28-ESR) >3.2 and ≤5.1 at screening and baseline despite taking optimal stable doses of oral methotrexate weekly (≥25 mg/week and ≤25 mg/week) during the previous 8 weeks, as per the investigator.

During the initial open-label period, all patients received treatment with subcutaneous etanercept 50 mg weekly plus methotrexate (E50/MTX) for 36 weeks. In the subsequent double-blind period beginning at week 36, patients with DAS28 ≤3.2 at week 36 who averaged DAS28 ≤3.2 from weeks 12 to 36 were randomized to receive blinded treatment: to either maintain their etanercept dose (E50/MTX), reduce it to etanercept 25 mg weekly plus methotrexate (E25/MTX), or withdraw it to receive placebo plus methotrexate (PBO/MTX) for an additional 52 weeks. In the double-blind period, the modified intent-to-treat (mITT) population comprised all patients who had at least one dose of study drug and one or more DAS28 evaluations. Total study duration of open-label and double-blinded periods was 88 weeks. Inclusion/exclusion criteria and study schema have previously been published in detail [33].

The WPAI:RA is a self-administered validated questionnaire comprising six questions related to RA [27,35,36]. The questionnaire was reproduced for this study. Each question has individual response options with a recall period of the preceding 7 days:

- **Q1** = Are you currently employed (working for pay)?;
- **Q2** = During the past 7 days, how many hours did you miss from work because of your RA?;
- **Q3** = During the past 7 days, how many hours did you miss from work because of any other reason such as vacation, holidays or time off to participate in this study?;
- **Q4** = During the past 7 days, how many hours did you actually work?;
- **Q5** = During the past 7 days, how much did health problems affect your productivity while you were working?; and
- **Q6** = During the past 7 days, how much did health problems affect your ability to do your regular daily activities, other than work at a job?

Responses to each question are used in basic mathematical formula to derive four outcome scores expressed as percentages by a multiplication of 100. absenteeism = Q2/(Q2+Q4); presenteeism = Q5/10; overall work impairment = Q2/(Q2+Q5)+[1−(Q2/(Q2+Q4)])×(Q5/10)]; and activity impairment = Q6/10 [26,27]. Each outcome score ranges from 0–100%, with higher scores indicating a worsening outcome that is a greater impact of RA on the outcome score [26,27].

Health outcome measures such as the HAQ Disability Index (HAQ-DI), Patient Global Assessment of Disease Activity (PtGA) by visual analog scale (VAS), pain VAS, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) and Physician Global Assessment of Disease Activity (PhGA) VAS were assessed throughout the study.

Potential predictors of work-related issues were assessed by examining relationships between the WPAI:RA overall work impairment component and the patient-reported outcomes (PROs) outlined above as well as PhGA in the employed patients-only population. Comparisons of these relationships during the double-blind period (weeks 36–88) were made between treatment groups. The purpose of these analyses was to assess preservation of treatment effect on the WPAI:RA overall work impairment component after etanercept maintenance, reduction or withdrawal.

**Statistical analyses**

Descriptive statistics were used to summarize baseline demographic and disease characteristics and describe WPAI:RA outcome scores; continuous parameters were analyzed with one-way analysis of variance (ANOVA) and categorical parameters by χ² tests. For the randomized, double-blind period, all analyses of proportions were analyzed for treatment differences using χ² test, stratified by geographic region and DAS28 low-disease activity (LDA)/remission status at week 36. All other post-baseline analyses were based on the last-observation-carried-forward approach. Continuous endpoints were analyzed in analysis of covariance (ANCOVA) models using the week-36 baseline values of endpoints as covariates, geographic region and week-36 DAS28 LDA/remission (except for DAS28).

Statistical analyses determined possible predictive relationships between the WPAI:RA overall work impairment component score and other PROs and PhGA using individual regressions followed by two stepwise regression analyses with overall work impairment at week 36 or 88 as the dependent variable. Independent variables included age, sex and RA duration at baseline and PROs, including HAQ-DI >0.5, PtGA, pain VAS, FACIT-Fatigue and WPAI:RA scores at
baseline or week 36, PhGA and treatment. The level of significance to enter the stepwise model was set at ≤0.15; inclusion in the final model required p ≤ 0.05. Analyses of predictors were conducted in the week 36 randomized employed patient population during the open-label (weeks 0–36) and double-blind periods (weeks 36–88). Treatment response was considered a factor only during the double-blind period. For the three work-related components of the WPAI:RA (absenteeism, presenteeism and overall work impairment), only employed patients (Q1 = yes) were included. Clinical efficacy, safety and additional PRO and HRQoL assessments of the PRESERVE trial have been presented elsewhere [33].

Results
A total of 834 patients met study eligibility criteria and received open-label E50/MTX with 756 (91%) patients completing the initial 36-week treatment period. At week 36, 604 (72%) patients had sustained LDA (DAS28 ≤3.2 at week 36 and an average of DAS28 ≤3.2 from weeks 12–36) and were eligible to enter the double-blind period. A total of 202 patients were randomized to each of the E50/MTX and E25/MTX groups and 200 patients to the PBO/MTX group (randomized population). Of these patients, 107 did not complete the double-blind period (21 E50/MTX, 27 E25/MTX and 59 PBO/MTX), with the most frequent reasons for discontinuation being unsatisfactory response (lack of efficacy, particularly in the dose reduction and PBO/MTX groups), adverse events and ‘other’. A total of 599 patients (201 E50/MTX, 201 E25/MTX and 197 PBO/MTX) were included in the mITT population. Table 1 shows similar demographic and disease characteristics in the three treatment groups at baseline (open-label phase) without statistical differences. The majority of randomized patients at baseline were female (80.8%) and white (75.2%), with a mean age of 47.6 years, disease duration of 6.8 years and DAS28 of 4.3. The percentages of patients employed at the beginning of the double-blind phase (week 36) were 72.4% in the E50/MTX group and 56.8% E50/MTX, 52.5% E25/MTX and 52.5% PBO/MTX (adjusted OR 2.50 [1.6, 3.8] and 2.04 [1.3, 3.1]; versus PBO, respectively; both p ≤ 0.0001). The proportions of patients who achieved improvements in HAQ-DI scores ≥0.5 from baseline (period 1) were 56.8% E50/MTX, 52.5% E25/MTX and 52.5% PBO/MTX (adjusted OR 2.50 [1.6, 3.8] and 2.04 [1.3, 3.1]; versus PBO, respectively; both p ≤ 0.0001). The proportions of patients who achieved improvements in HAQ-DI scores ≥0.22 minimal clinically important differences from baseline (period 1) were 72.4% in the E50/MTX group and 72.5% in the E25/MTX group, significant versus PBO (51.0%, adjusted OR 2.45 [1.6, 3.8] and 2.66 [1.7, 4.1], respectively; both p ≤ 0.0001).

Significant differences were observed in PtGA, pain VAS and FACIT-Fatigue after randomization at weeks 36 to 88 in the E50/MTX and E25/MTX groups compared with PBO. The adjusted mean (SE) change in PtGA was 0.29 (0.14) and 0.59 (0.14) in the E50/MTX and E25/MTX groups, respectively, compared with 1.84 (0.14) in the PBO/MTX group (p < 0.0001). Adjusted mean (SE) changes in pain VAS scores for the three treatment groups were 3.9 (1.4), 6.3 (1.4) and 18.6 (1.4; p < 0.0001), respectively. Statistically significant differences in the adjusted mean (SE) changes of FACIT-Fatigue were -1.3 (0.6) and -2.3 (0.6) in favor of the E50/MTX and E25/MTX groups, respectively, compared with -5.8 (0.6) in the PBO/MTX group (p < 0.0001).

Patients’ ability to perform work and general activities was highly affected by their disease as indicated by the WPAI:RA components at baseline. In the open-label population at baseline, mean (95% CI) activity impairment was 44.4% (43.0, 45.8); absenteeism was 13.1% (10.3, 15.9); presenteeism was 36.2% (34.0, 38.5); and overall work impairment was 40.7% (38.2, 43.2). After 36 weeks of open-label treatment with E50/MTX, all four components significantly improved
(decreased) by 22.2 (20.6, 23.8), 9.0 (6.2, 11.7), 19.4 (16.8, 21.9) and 22.2 (19.4, 25.0), respectively, and exceeded a minimal clinically important difference of 7% (p < 0.0001 vs baseline) (Figure 1) [37]. At week 36, after open-label E50 treatment in the randomized population, activity impairment was improved (decreased) by mean (95% CI) 27.7 (24.7, 30.7) significantly worsened (increased) in the E25/MTX group, versus week 36 (p < 0.001). In patients who received PBO/MTX, absenteeism (8.1, [3.6, 12.6]), presenteeism (11.9 [7.2, 16.5]) and overall work impairment (13.0 [7.8, 18.2]) significantly worsened (increased) versus week 36 (p < 0.001).

Across treatment groups, activity impairment, presenteeism and overall work impairment were statistically significant for the E50/MTX group compared with PBO/MTX at week 88 (p < 0.05), whereas absenteeism was borderline significant (p = 0.051). Adjusted mean treatment differences (95% CI) were: 10.28 (-14.2, -6.3), -10.57 (-15.8, -5.4), -6.23 (-12.5, 0.0) and -12.45 (-18.5, -6.4) for activity impairment, presenteeism, absenteeism and overall work impairment, respectively. Activity impairment and presenteeism were significant at week 88 in the E25/MTX group versus PBO/MTX (p < 0.0001; adjusted mean treatment difference [95% CI] -10.28 [-14.2, -6.3] and p < 0.05; -5.31 [-10.3, -0.3], respectively) but not for absenteeism or work impairment (p = 0.27; -3.40 [-9.4, 2.6]) and p = 0.12; -4.53 [-10.3, 1.2], respectively. No significant differences were observed between the two etanercept dose groups for activity impairment or absenteeism (p = 0.72; adjusted mean treatment difference [95% CI] -0.72 [-4.7, 3.2] and p = 0.37; -2.8 [-9.1,

### Table 1. Demographic and baseline disease characteristics at baseline of the open-label phase.

<table>
<thead>
<tr>
<th>Demographic and disease characteristics</th>
<th>Overall population in open-label period (n = 834; week 0)</th>
<th>Total randomized population (n = 604)</th>
<th>Randomized to the double-blind phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.4 (11.9)</td>
<td>47.6 (12.1)</td>
<td>E50/MTX (n = 202)† E25/MTX (n = 202)† PBO/MTX (n = 200)‡</td>
</tr>
<tr>
<td>Female; n (%)</td>
<td>694 (83.2)</td>
<td>488 (80.8)</td>
<td>164 (81.2) 157 (77.7) 167 (83.5)</td>
</tr>
<tr>
<td>White; n (%)</td>
<td>619 (74.2)</td>
<td>454 (75.2)</td>
<td>158 (78.2) 145 (71.8) 151 (75.5)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.9 (7.0)</td>
<td>6.8 (7.0)</td>
<td>6.8 (7.2) 6.4 (7.1) 7.3 (6.7)</td>
</tr>
<tr>
<td>Employed WPAI; n (%)</td>
<td>338 (40.5)</td>
<td>283 (47.4)</td>
<td>85 (42.7) 101 (50.5) 97 (49.0)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>22.2 (13.1)</td>
<td>21.4 (12.8)</td>
<td>22.2 (12.9) 21.7 (13.4) 20.4 (12.0)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>12.3 (16.4)</td>
<td>11.7 (15.1)</td>
<td>11.9 (13.9) 12.8 (18.0) 10.3 (13.0)</td>
</tr>
<tr>
<td>RF+; n (%)</td>
<td>603 (72.7)</td>
<td>436 (72.7)</td>
<td>147 (73.1) 142 (70.7) 147 (74.2)</td>
</tr>
<tr>
<td>aCCP+; n (%)</td>
<td>642 (77.6)</td>
<td>473 (78.8)</td>
<td>161 (80.1) 156 (77.6) 156 (78.8)</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.4 (0.5)</td>
<td>4.3 (0.4)</td>
<td>4.3 (0.5) 4.4 (0.4) 4.3 (0.4)</td>
</tr>
</tbody>
</table>

**Observed cases. Data are mean (standard deviation) or n (%).**

†n = 756/834 patients completed the open-label period.

‡n = 497/604 patients in the total randomized population completed the double-blind phase of the study; n = 181 E50/MTX, n = 175 E25/MTX, n = 141 PBO/MTX.

aCCP+: Anticyclic citrullinated peptide antibody positive; CRP: C-reactive protein; DAS28: 28-joint count Disease Activity Score; E: Etanercept; ESR: Erythrocyte sedimentation rate; MTX: Methotrexate; RF+: Rheumatoid factor positive; WPAI: Work Productivity Activity Impairment.

![Figure 1](https://futuremedicine.com/)

The percentage of patients employed (increased) significantly at week 88 by mean (95% CI) 3.9 (1.3, 6.6) and 3.0 (0.5, 5.5), respectively (p ≤ 0.05 vs week 36). Week 36 improvements in absenteeism (0.89 [-2.9, 4.7]), presenteeism (1.6 [-1.2, 4.4]) and overall work impairment (0.6 [-2.8, 4.0]) were maintained at week 88 in the E50/MTX group (none of the mean changes were significant vs week 36). Absenteeism (4.2 [-0.7, 9.1]), presenteeism (3.9 [2.2, 7.7]) and overall work impairment (8.1 [3.7, 12.5]) worsened (increased) in the E25/MTX group, significant for presenteeism and overall work impairment (p < 0.01 vs week 36). In patients who received PBO/MTX, absenteeism (8.1, [3.6, 12.6]), presenteeism (11.9 [7.2, 16.5]) and overall work impairment (13.0 [7.8, 18.2]) significantly worsened (increased) versus week 36 (p < 0.001).
### Table 2. Characteristics at baseline of the overall modified intent-to-treat population in the open-label period and at baseline, weeks 36 and 88 in the modified intent-to-treat population of the double-blind period.

<table>
<thead>
<tr>
<th>Health outcome measures</th>
<th>Overall population</th>
<th>mITT population (n = 599)</th>
<th>E25/MTX (n = 201) ‡</th>
<th>PBO/MTX (n = 197) ‡</th>
<th>E50/MTX (n = 201) ‡</th>
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<tr>
<td></td>
<td>(n = 834†; week 0)</td>
<td>Week 0</td>
<td>Week 36</td>
<td>Week 88</td>
<td>Week 0</td>
</tr>
<tr>
<td>FACIT-Fatigue (0–52 scale ¶)</td>
<td>32.5 (9.7)</td>
<td>32.8 (9.5)</td>
<td>42.0 (8.7)</td>
<td>40.8 (8.9)</td>
<td>34.5 (8.8)</td>
</tr>
<tr>
<td>Pain VAS (0–100 mm)</td>
<td>45.5 (17.4)</td>
<td>16.9 (18.3)</td>
<td>4.8 (1.7)</td>
<td>2.1 (1.8)</td>
<td>4.9 (1.77)</td>
</tr>
<tr>
<td>PtGA of disease activity</td>
<td>4.9 (1.7)</td>
<td>1.8 (1.7)</td>
<td>2.1 (1.8)</td>
<td>2.1 (1.8)</td>
<td>4.8 (1.7)</td>
</tr>
<tr>
<td>HAQ-DI (0–3 scale)</td>
<td>1.1 (0.58)</td>
<td>3.2 (0.58)</td>
<td>4.6 (0.57)</td>
<td>4.0 (0.52)</td>
<td>4.0 (0.52)</td>
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<tr>
<td>FACIT-Fatigue (0–52 scale)</td>
<td>1.1 (0.6)</td>
<td>3.2 (0.6)</td>
<td>3.2 (0.6)</td>
<td>3.0 (0.6)</td>
<td>3.0 (0.6)</td>
</tr>
<tr>
<td>Pain VAS (0–100 mm)</td>
<td>4.6 (1.78)</td>
<td>4.3 (1.61)</td>
<td>4.3 (1.59)</td>
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<td>4.0 (0.52)</td>
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</table>

*Last observation carried forward analysis. †Data are mean (standard deviation). ‡n = 756/834 patients completed the double-blind phase of the study, n = 181 E50/MTX, n = 175 E25/MTX, n = 141 PBO/MTX.

#### Discussion

The relationship between impaired physical function and work disability in RA is well established, as is the increased likelihood of patients with RA experiencing unemployment, income loss and early retirement [2,4,6,20,21,24,28,38,39]. The impact of RA on work is multifactorial and complicated, with no gold standards for measuring it or equating its economic values. Nonetheless, all work-related instruments and economic models are in agreement that RA poses a significant burden on patients, healthcare resources, payers, patients’ workplace and society [2,4,6,20,21,24,28,38,39]. Therefore, it is important to identify relationships between work-related measures and other health outcome measures to enhance therapeutic interventions. Several publications have examined predictive factors associated with work disability, absenteeism and presenteeism; however, this analysis is the first examining predictors of the overall work impairment component of the WPAI:RA that encompasses both absenteeism and presenteeism, giving a more unified viewpoint of patients with moderate disease.

This analysis of the PRESERVE trial has demonstrated that work and activity levels worsened after dose reduction or withdrawal of etanercept in patients with RA with sustained LDA. Activity impairment, presenteeism, absenteeism and overall work impairment increased (worsened) in those who received PBO/MTX versus those who continued to receive E50/MTX, indicating a potential benefit of contin-
Work impairment in rheumatoid arthritis

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...used biologic treatment in those with persistently active RA, albeit LDA. Combination etanercept plus methotrexate treatment provided sustainability in work and activity levels as well as health outcome scores over 88 weeks of treatment.

Patients with moderate disease activity constitute the majority of the RA population in routine care and are seen more frequently in clinical practice [40–42]. The unique study design of the PRESERVE trial allowed for analysis of the moderate RA population despite methotrexate’s use after LDA was achieved and sustained by a conventional dose of E50/MTX. The subsequent maintenance or reduction in dose or withdrawal of etanercept after sustained LDA is in concert with three of four recommended RCT design elements by the ACR Rheumatoid Arthritis Clinical Trial Investigators Ad Hoc Task Force [43].

Determining if dose reduction is beneficial after sustained LDA is achieved is important to maximize the benefit of costly biologics. A previous publication of this RCT determined that a reduction in etanercept dose was associated with continued good clinical responses; however, presenteeism, overall work impairment and activity impairment significantly increased in the E25/MTX group at week 88 compared with week 36. It is possible that the relatively short follow-up...
period precludes showing an impact of dose modification on clinical and structural changes over the longer time period and that more subtle changes are represented by the work outcomes. Longer-term controlled trial data are needed to better clarify this point. Interestingly, activity impairment significantly increased after randomization regardless of whether the etanercept dose was maintained, reduced or withdrawn, although the degree of increase was less in the E50/MTX and E25/MTX groups, similar to observations with HAQ-DI, pain VAS and PtGA, as well as PhGA. Patients’ age, pain VAS and overall work impairment at baseline were significant predictors of overall work impairment at week 36 in these patients with moderate RA, noting that treatment can only be a relevant parameter for prediction during the double-blind period (weeks 36–88). Baseline disease duration and week 36 HAQ score >0.5 and overall work impairment were significant predictors of overall work impairment at week 88. These findings are similar to previously reported predictive factors for work disability [11,17,32]. However, this model is exploratory and needs to be validated in other populations.

One limitation to this study is the small number of randomized patients who were employed (E50/MTX = 96/201 [47.8%], E25/MTX = 108/201 [53.7%] and PBO/MTX = 103/197 [52.3%] at week 88) and eligible to answer work-related questions of the WPAI:RA. In contrast, all patients could respond to questions pertaining to activity impairment (n = 604), which may account for the differing trends between weeks 36 and 88. The WPAI:RA has a recall period of 7 days, which may leave gaps in the work life cycle continuum and ebb and flow of the disease when administered episodically. More frequent administration or a continuous measure may provide additional insight into outcome trends and work impairment relationships. In addition, no normative values for the WPAI:RA currently exist for comparison with a general population or other chronic conditions. Other limitations include limited access within a clinical trial design to a broader range of variables, which may influence work-related outcomes, including economic status, education, access to insurance/payer programs and persistence on treatment.

### Table 3. Individual and stepwise-selected predictors of Work Productivity Activity Impairment Questionnaire for rheumatoid arthritis overall work impairment in employed patients.

<table>
<thead>
<tr>
<th></th>
<th>Predictors of week 36 overall work impairment</th>
<th>Predictors of week 88 overall work impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient (SE) p-value</td>
<td>Regression coefficient† (SE) p-value</td>
</tr>
<tr>
<td><strong>Individual predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.24 (0.11)‡ 0.0245</td>
<td>0.22 (0.13)‡ 0.1039</td>
</tr>
<tr>
<td>Female</td>
<td>1.71 (2.92)‡ 0.5597</td>
<td>-3.35 (3.42)† 0.3286</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.03 (0.18)‡ 0.8700</td>
<td>0.53 (0.21)‡ 0.0119</td>
</tr>
<tr>
<td>HAQ-DI (score &gt;0.5)</td>
<td>5.42 (2.83)‡ 0.0565</td>
<td>14.51 (3.04)§ &lt;0.0001</td>
</tr>
<tr>
<td>PtGA</td>
<td>2.82 (0.64)‡ 0.0001</td>
<td>5.56 (0.98)§ 0.0001</td>
</tr>
<tr>
<td>WPAI:RA: Overall work impairment</td>
<td>0.30 (0.05)‡ 0.0001</td>
<td>0.61 (0.08)‡ &lt;0.0001</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>0.30 (0.06)‡ 0.0001</td>
<td>0.57 (0.12)§ 0.0001</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>-0.41 (0.12)‡ 0.0005</td>
<td>-0.52 (0.19)§ 0.0059</td>
</tr>
<tr>
<td><strong>Stepwise-selected predictors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.26 (0.10)‡ 0.0089</td>
<td>–</td>
</tr>
<tr>
<td>Disease duration</td>
<td>–</td>
<td>0.49 (0.19) 0.0110</td>
</tr>
<tr>
<td>HAQ-DI (score &gt;0.5)</td>
<td>–</td>
<td>7.05 (3.01) 0.0199</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>0.16 (0.06)‡ 0.0120</td>
<td>–</td>
</tr>
<tr>
<td>WPAI overall work impairment</td>
<td>0.25 (0.05)‡ 0.0001</td>
<td>0.54 (0.09) &lt;0.0001</td>
</tr>
</tbody>
</table>

† Treatment is a covariate for the regression model.
‡ Baseline values as predictors.
§ Week 36 values as predictors.
Conclusion
In conclusion, E50/MTX maintained significant improvements in absenteeism, presenteeism and overall work impairment to week 88 in the first RCT in patients with RA to assess the effects of maintenance, dose reduction or withdrawal of a biologic agent after sustained LDA. Predictors of overall work impairment were age, disease duration, HAQ-DI score >0.5, pain VAS and overall work impairment, consistent with previously published findings.

Supplementary data
To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/ijr.15.40

Executive summary

Background
• The impact of rheumatoid arthritis (RA) on work is a complicated issue because factors such as age, disease duration, disease activity, work requirements, education level, regional/cultural issues, societal and psychological characteristics can all play a part in determining the ability to work.
• Considering the economic, individual and societal burdens of RA as well as the multifaceted issues surrounding its impact on work, several studies have attempted to identify predictive factors of work-related issues to help determine the value of therapeutic interventions.
• The PRESERVE trial (NCT00565409) was the first randomized controlled trial in patients with RA with moderate disease activity to assess the effects of three therapeutic scenarios (maintenance or reduction in dose or withdrawal of a biologic agent) after response to initial treatment.
• This article describes the effects of these three scenarios on work and usual activities using the WPAI:RA and examines potential predictors of the overall work impairment component.

Materials & methods
• Patients with moderate RA received open-label etanercept 50 mg weekly plus methotrexate (E50/M) for 36 weeks.
• Those who had disease activity score $\leq 3.2$ at week 36 and averaged $\leq 3.2$ from weeks 12–36 were randomized at week 36 to double-blind treatment to E50/M, etanercept 25 mg weekly plus methotrexate or placebo plus methotrexate for 52 weeks.
• WPAI:RA was used to assess absenteeism, presenteeism, overall work impairment, and activity impairment. Relationships were analyzed between overall work impairment and demographic and other quality-of-life variables in the randomized population by stepwise regression analyses.

Results
• All four Work Productivity Activity Impairment:RA components improved after 36 weeks of open-label treatment with E50/M after randomization; improvements in absenteeism, presenteeism and overall work impairment were maintained at week 88 in the E50/M group versus those with a dose reduction or discontinuation of etanercept.
• Age, pain VAS and overall work impairment at baseline were significantly predictive of week 36 overall work impairment ($p < 0.05$).
• Week 36 Health Assessment Questionnaire-Disability Index (HAQ-DI) score >0.5, overall work impairment and baseline disease duration were predictive of week 88 overall work impairment ($p < 0.05$).

Discussion
• All work-related instruments and economic models are in agreement that RA poses a significant burden on patients, healthcare resources, payers, patients’ workplace and society. Therefore, it is important to identify relationships between work-related measures and other health outcome measures to enhance therapeutic interventions.
• This analysis is the first to examine predictors of the overall work impairment component of the Work Productivity Activity Impairment:RA that encompasses both absenteeism and presenteeism, giving a more unified viewpoint of patients with moderate disease.
• This analysis of the PRESERVE trial has demonstrated that work and activity levels worsened after dose reduction or withdrawal of etanercept in patients with RA with sustained low-disease activity.
• Patients’ age, pain VAS and overall work impairment at baseline were significant predictors of overall work impairment at week 36 in these patients with moderate RA, noting that treatment can only be a relevant parameter for prediction during the double-blind period (weeks 36–88).
• Baseline disease duration and week 36 HAQ score $>0.5$ and overall work impairment were significant predictors of overall work impairment at week 88. These findings are similar to previously reported predictive factors for work disability.
Acknowledgements
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Author contributions
All of the authors have participated in the acquisition of data, analysis and/or interpretation of the data and development of the submitted manuscript, providing their approvals of the final version to be published in accordance with the International Committee of Medical Journal Editors criteria.

Financial & competing interests disclosure
V Strand has received consulting fees from Pfizer unrelated to the development of this manuscript. TV Jones, AS Koenig and SK Kotak are employees of Pfizer. W Li was an employee of Quintiles, Inc. during the development of this manuscript and was a paid contractor to Pfizer in the statistical analysis of data. V Strand states that he was the guarantor for the content of the paper. All authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research
This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable local/ country-specific regulations. Before the start of the study, independent ethics committees or institutional review boards in each country/region reviewed and approved this study, and written and informed consent was received from all patients.

References
Papers of special note have been highlighted as:
• of interest; ** of considerable interest.

• Demonstrates that disease severity is associated with the presence of absenteeism, presenteeism and activity impairment.


• Provides strong evidence that physical job demands, low-functional capacity, old age and low education predict work disability in rheumatoid arthritis.


• Demonstrates that manual work and high-baseline Health Assessment Questionnaire scores are important predictors of work disability.


• Demonstrates that Health Assessment Questionnaire-A and Rheumatoid Arthritis Quality of Life measures are associated with reduction of total work productivity.


Phase IV clinical trial demonstrating that reduced doses of etanercept are effective at maintaining low-disease activity in patients with rheumatoid arthritis than methotrexate monotherapy after withdrawal of etanercept.


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