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ORIGINAL RESEARCH

Relative Impact of Pain and Fatigue on Work Productivity in Patients with Rheumatoid Arthritis from the RA-BEAM Baricitinib Trial

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ABSTRACT

Introduction: To explore the relationship of pain and fatigue with daily activity and work productivity in rheumatoid arthritis (RA) patients from the baricitinib clinical trial, RA-BEAM.

Methods: In RA-BEAM, a double-blind phase 3 study, patients were randomized 3:3:2 to placebo (n = 488), baricitinib 4 mg once daily (n = 487), or adalimumab 40 mg biweekly (n = 330) with background methotrexate. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) measured fatigue and the pain visual analog scale (0–100 mm) assessed pain. Work Productivity and Activity Impairment Questionnaire-RA measured daily activity and work productivity. At weeks 12 and 24, pain was assessed using pain reduction (< 30%, 30% to < 50%, ≥ 50%) and overall pain score; clinically relevant FACIT-F changes were assessed by values < 3.56 and ≥ 3.56 and the FACIT-F normative value score (< 40.1, ≥ 40.1). Pairwise comparisons between pain/fatigue reduction groups were assessed using ANCOVA with pooled data on daily activity and work productivity. A mediator analysis with pain, fatigue,

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and disease activity measured their contribution to daily activity and work productivity. Data were pooled from all patients for most analyses, and baricitinib-treated patients were assessed as a sensitivity analysis.

Results: Reductions in pain (≥ 50%) and fatigue (≥ 3.56) had significant ($p \leq 0.001$) effects on daily activity and work productivity improvement at weeks 12 and 24. Reductions in pain, fatigue, and disease activity accounted for most of the improvements in daily activity and work productivity. At the lowest levels of remaining pain (≤ 10 mm) at weeks 12 and 24, however, fatigue did not appear to impact work productivity. Similar trends were observed with baricitinib-treated patients.

Conclusions: Reductions in pain and fatigue were associated with improved daily activity and work productivity for all RA patients and for baricitinib-treated patients in RA-BEAM.

Trial Registration: ClinicalTrials.gov identifier, NCT01710358.

Funding: Incyte Corporation and Eli Lilly and Company.

Keywords: Baricitinib; Health-related quality of life; Patient-reported outcomes; Work impairment

INTRODUCTION

Patients rank ability to work as an important treatment outcome because it affects income, living conditions, quality of life (QOL), and the ability to maintain independence [1, 2]. After the onset of rheumatoid arthritis (RA), a large percentage of patients with RA report impairment in their daily activity and increased issues with presenteeism and absenteeism before their early departure from the work force [3, 4]. It is estimated that work disability for patients with RA is twice that of the general population [4].

With new therapies for RA, there is an increased interest in controlling disease and improving patients' health-related QOL that will enable patients to function in social and work settings [4]. Patients with RA indicate that pain and fatigue are common and burdensome symptoms of their disease [2], yet it is not clear how much pain and fatigue, evaluated individually and together, impact other aspects of life, such as work productivity.

The purpose of our analysis was to explore the relationship between pain and fatigue with daily activity and work productivity, in patients from a randomized, double-blind, phase 3 clinical trial of baricitinib, an oral, selective inhibitor of Janus kinase (JAK)1 and JAK2 [5].

METHODS

Patients

This is a post hoc analysis of the baricitinib clinical trial, RA-BEAM (NCT01710358), in which baricitinib 4 mg plus methotrexate (MTX) was associated with significant clinical improvements, including pain and fatigue, over MTX plus adalimumab [6, 7]. The RA-BEAM study was approved by Quorum Review IRB #27257. Additionally, each participating center's institutional review board or ethics committee approved the study. The list of centers can be found in the first RA-BEAM publication. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. No additional ethical approval was required to conduct the current post hoc analysis. Results from the study have been published previously [6, 7]. Briefly, the trial was a randomized, double-blind, double-dummy, placebo-controlled and active-controlled, parallel-arm, 52-week study. Patients (n = 1,305) on stable background MTX were randomly allocated (3:2:3) to placebo, 40 mg of subcutaneous adalimumab every other week, or 4 mg of baricitinib orally daily. Patients were ≥ 18 years old with active RA [≥ 6/68 tender and ≥ 6/66 swollen joints; C-reactive protein (CRP) ≥ 6 mg/l]. Patients had an inadequate response to MTX and were required to have either ≥ 3 joint erosions (based on radiographs) or > 1 joint erosion and be seropositive for rheumatoid factor or anti-citrullinated peptide antibodies [7].

Measures

Pain was measured on a visual analogue scale (VAS), with responses ranging from 0 mm (no pain) to 100 mm (worst possible pain). The pain VAS was administered at all study visits. Reduction in pain was categorized as < 30%, 30% to < 50%, ≥ 50% pain relief at weeks 12 and 24. These thresholds were chosen based on the recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, a group focusing on improvements of clinical studies in chronic pain conditions [8]. Likewise, remaining pain was assessed and categorized as ≤ 10 mm, > 10 to ≤ 20 mm, > 20 to ≤ 40 mm, > 40 mm. The 10 mm threshold was derived from data by Wells, et al. [9]; the 20 mm threshold reflects when pain does not negatively affect health-related QOL [9, 10]; and the 40 mm threshold was based on cut-off points between the pain VAS and the Patient Acceptable Symptom State (PASS) [11].

Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, with a range from 0 to 52, with higher scores representing less fatigue [12]. A normative score for the FACIT-F is ≥ 40.1 and the minimum clinically important difference (MCID) value of 3.56 was used to assess the clinical relevance of changes in the FACIT-F [12–14]. The FACIT-F was administered at baseline, week 4, and every 4 weeks thereafter until week 32, and then at week 40 and week 52. At weeks 12 and 24, the following were evaluated: the percentage of patients reporting improvement in fatigue (< 3.56, ≥ 3.56) and the percentage of patients reporting FACIT-F normative values (≥ 40.1) or not (< 40.1).

The Work Productivity Impairment Questionnaire-Rheumatoid Arthritis (WPAI-RA) measured work and activity impairments over the past 7 days. The instrument is composed of six questions that are calculated into four scores: normal daily activities (daily activity impairment), work-time missed due to RA (absenteeism), impairment while working due to RA (presenteeism), and overall work impairment due to RA (work productivity impairment). Scores are the percentages of impairment (0–100%), with higher scores denoting greater impairment [15]. The WPAI-RA was administered at baseline, week 2, week 4, and then followed the same schedule as the FACIT-F at later study visits. The current analysis focused on impairment of daily activity and of work productivity. Absenteeism and presenteeism, which are used to calculate work productivity impairment, are presented in the Data Supplement.

Additional Variables

In addition to pain and fatigue, we assessed the relationship between CRP, tender joint count (TJC), and swollen joint count (SJC) with the scores from the WPAI-RA.

Statistical Analyses

Data were pooled across treatment arms for analyses assessing correlation between variables described below and the relationship between pain, fatigue, and the WPAI-RA. Data from baricitinib-treated patients were analyzed alone as a sensitivity analysis and are included in the Data Supplement. Missing values were imputed using the modified last-observation carried forward method.

Spearman correlations were assessed with the change from baseline for pain VAS, FACIT-F, and other variables (CRP, SJC28, TJC28) with the WPAI-RA scores using observed data at weeks 12 and 24. This assessment was conducted to determine which factors were more correlated with impairments in daily activity and work productivity. Spearman correlations ≤ 0.40 were considered low correlation, 0.41 to ≤ 0.75 were moderate correlation, and > 0.75 were strong correlation [16].

Pairwise comparisons of improvement in WPAI-RA scores between pain (< 30%, 30 to < 50%, and ≥ 50%) and between fatigue reduction groups (< 3.56 and ≥ 3.56) at weeks 12 and 24 were assessed by ANCOVA adjusting for geographical region, baseline joint erosion status, and baseline values of WPAI-RA scores.

Because pain, fatigue, and disease activity, defined by Disease Activity Score 28-joint

count-CRP (DAS28-CRP), may impact daily activity and work productivity, we conducted a mediation analysis to assess their relative contribution to improvements in daily activity and work productivity by treatment over placebo at weeks 12 and 24 [17]. In the mediation analysis, the dependent variable was the improvement from baseline to week 12 or 24 for daily activity or work productivity. The treatment (baricitinib vs. placebo or adalimumab vs. placebo) was the independent variable. Changes in pain, fatigue, and DAS28-CRP from baseline to week 12 or week 24 were used as the mediator variables. The total treatment effect on daily activity or work productivity over placebo that can be accounted for by changes in pain, fatigue, and DAS28-CRP is the "indirect" or mediation effect; whereas, the total treatment effect that cannot be accounted for by the mediation effect is the "direct" effect (Figure S1).

Statistical analyses were performed with SAS (SAS Institute; Cary, NC, version 9.4). A two-sided p value < 0.05 was considered statistically significant. *P*-values were not adjusted for multiple comparisons.

RESULTS

Baseline Patient Characteristics

The baseline patient characteristics were similar across treatment groups [6, 7]. The majority of patients were women with a mean age of approximately 53 years. Most patients included in the trial had long disease duration, with a time from RA diagnosis of approximately 9 years. For the WPAI-RA at baseline, 545 patients (42%) were employed. Across treatment groups, the mean baseline values ranged from 56 to 58% for impairment in daily activities, 12–13% for absenteeism, 42–46% for presenteeism, and 45–49% for work productivity impairment (Table S1, Table 2).

Correlation Analyses

When all the patient data were combined, correlation analyses indicated statistically significant correlations between reductions in pain and fatigue with improvements in daily activity and work productivity at both week 12 and 24 (Table 1). Specifically, the correlation (R values) for pain and fatigue ranged from 0.4 to 0.5 (moderate correlation); whereas the correlation values for CRP, SJC28, and TJC28 ranged from 0.1 to 0.3 (low correlation). Similar results were observed for baricitinib-treated patients (Table S3).

Table 1 Spearman correlation between pain, fatigue, CRP, SJC28, and TJC28 with impairment in daily activity and work productivity

Timepoint	Change in daily activity	Change in work productivity
Change in pain VAS		
Week 12	0.51***	0.43***
Week 24	0.53***	0.41***
Change in FACIT-F total score		
Week 12	− 0.48***	− 0.46***
Week 24	− 0.47***	− 0.38***
Change in CRP		
Week 12	0.20***	0.19***
Week 24	0.15***	0.13*
Change in SJC28		
Week 12	0.23***	0.17***
Week 24	0.19***	0.15**
Change in TJC28		
Week 12	0.32***	0.29***
Week 24	0.26***	0.22***

*$p \leq 0.05$, ***$p \leq 0.001$; Spearman correlation values from approximately 0.4–0.5 indicate moderate correlation; whereas the correlation values from 0.1 to 0.3 indicate low correlation [16]

CRP C-reactive protein, *FACIT-F* functional assessment of chronic illness therapy-fatigue, *SJC28* swollen joint count-28, *TJC28* tender joint count-28, *VAS* visual analog scale

Treatment Effect upon Pain, Fatigue, and WPAI-RA at Weeks 12 and 24

At week 12, patients treated with baricitinib and adalimumab reported statistically significantly greater improvements from baseline for both pain and fatigue compared with placebo-treated patients ($p \leq 0.001$) [6] (Table 2). For pain, the change from baseline was greater for baricitinib-treated compared with adalimumab-treated patients ($p \leq 0.01$). Likewise, at week 12, patients treated with baricitinib or adalimumab reported improvements in their daily activity. Baricitinib-treated patients reported improvement in work productivity compared with placebo; in contrast, there were no statistically significant differences for adalimumab compared with placebo (Table 2). Similar trends were observed at week 24 (Table 2).

Association of Pain and Fatigue with Daily Activity and Work Productivity

For all patients combined at week 12, patients with $\geq 50\%$ reduction in pain from baseline had significantly greater improvements ($p \leq 0.001$) in daily activity and work productivity compared to those with less reduction in pain (Fig. 1). At week 24, patients with $\geq 50\%$ reduction in pain from baseline reported statistically significant improvements ($p \leq 0.001$) only in daily activity compared to those with less pain reduction. Similar findings were observed for baricitinib-treated patients at weeks 12 and 24 (Figure S3).

At weeks 12 and 24, patients who had a clinically relevant change in fatigue, a FACIT-F MCID of ≥ 3.56 from baseline, also experienced significantly greater improvements in daily activity and work productivity compared to those who did not achieve the MCID (Fig. 1). Similar results were observed among baricitinib-treated patients (Fig. 1, Figure S5).

At weeks 12 and 24, those patients who reported values that met or exceeded the "normal" value of fatigue (FACIT-F ≥ 40.1) and the lowest levels of remaining pain (pain VAS ≤ 10 mm), reported approximately 30% improvement in daily activities (Fig. 2). For each increasing level of remaining pain, improvement in daily activity decreased. Additionally, patients with less fatigue tended to report greater improvement in daily activity compared to those who reported more fatigue.

At the lowest levels of remaining pain (≤ 10 mm), fatigue did not appear to affect work productivity. For example, at week 12, among patients with minimal remaining pain (≤ 10 mm), the percentage of improvement in work productivity was 26% and 31% for those with low (≥ 40.1) and higher (< 40.1) levels of fatigue, respectively. With increasing levels of pain (> 10 mm), levels of fatigue tended to have a greater relationship with work productivity improvement (Fig. 2, Figure S5).

Mediator Analysis

The total effect of baricitinib over placebo on daily activity or work productivity tended to be greater than that for adalimumab over placebo at both weeks 12 and 24 (Fig. 3). In the mediation analysis, the contributions of pain, fatigue, and disease activity by treatment on daily activity or work productivity represented the combined 'indirect effect' or the mediation effect while the total treatment effect on daily activity or work productivity that is not accounted for by the mediation effect is called 'direct effect'. The mediation effect accounted for the majority of the total effect (indirect and direct effect combined) in improvements in daily activity or work productivity over placebo at weeks 12 or 24 (Fig. 3).

DISCUSSION

The burden of RA for patients in this trial was high in terms of baseline impairments in daily activity and work productivity. Specifically, across all patients at baseline, the daily activity impairment was $> 50\%$. Of the 545 patients who were employed at baseline, the work productivity impairment ranged from 45 to 49%. Treatment with baricitinib or adalimumab resulted in reductions of pain and fatigue and improvements in daily activity and work productivity compared to placebo. In our analyses,

Table 2 Pain, fatigue, and impairment in daily activity and work productivity at baseline and at weeks 12 and 24

	Baseline			Week 12			Week 24		
Pain, mm	**Placebo (N=487)**	**Baricitinib (N=486)**	**Adalimumab (N=329)**	**Placebo (N=484)**	**Baricitinib (N=482)**	**Adalimumab (N=327)**	**Placebo (N=484)**	**Baricitinib (N=482)**	**Adalimumab (N=327)**
Mean ± SD	60 ± 23	62 ± 22	61 ± 23	43 ± 24	29 ± 23***$^{++}$	34 ± 24***	43 ± 25	27 ± 23***$^{++}$	32 ± 25***
Fatigue	**Placebo (N=487)**	**Baricitinib (N=486)**	**Adalimumab (N=329)**	**Placebo (N=475)**	**Baricitinib (N=479)**	**Adalimumab (N=320)**	**Placebo (N=475)**	**Baricitinib (N=479)**	**Adalimumab (N=320)**
Mean ± SD	29 ± 11	28 ± 11	28 ± 11	36 ± 10	38 ± 9***	37 ± 10***	35 ± 11	39 ± 10***	38 ± 10***
WPAI-RA: Impairment in Daily Activity (administered to all patients)	**Placebo (N=487)**	**Baricitinib (N=486)**	**Adalimumab (N=329)**	**Placebo (N=458)**	**Baricitinib (N=474)**	**Adalimumab (N=315)**	**Placebo (N=333)**	**Baricitinib (N=430)**	**Adalimumab (N=272)**
Percent activity impairment due to RA, Mean ± SD	56 ± 25	58 ± 24	58 ± 26	44 ± 25	33 ± 24***$^{++}$	38 ± 24***	40 ± 25	29 ± 23***	32 ± 24***
WPAI-RA: Impairment in Work Productivity (administered to employed patients)									
Number (%) of patients employed	206 (42%)	199 (41%)	140 (43%)	191 (39%)	292 (60%)	138 (42%)	142 (29%)	167 (34%)	127 (38%)
	Placebo (N=183)	**Baricitinib (N=183)**	**Adalimumab (N=124)**	**Placebo (N=147)**	**Baricitinib (N=160)**	**Adalimumab (N=113)**	**Placebo (N=110)**	**Baricitinib (N=134)**	**Adalimumb (N=99)**
Percent overall work impairment due to RA (work productivity loss), Mean ± SD	45 ± 26	49 ± 26	47 ± 26	34 ± 25	26 ± 25***$^{+}$	33 ± 26	35 ± 25	26 ± 25***	25 ± 24**

Data shown are mean ± SD; for pain and fatigue, modified last-observation carried forward was used for missing value imputation. For WPAI daily activity and work productivity, observed values were used

SD standard deviation, *WPAI-RA* Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis

$^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$ versus placebo for change from baseline using ANCOVA

$^{+}p \leq 0.05$, $^{++}p \leq 0.01$, $^{+++}p \leq 0.001$ versus adalimumab change from baseline using ANCOVA

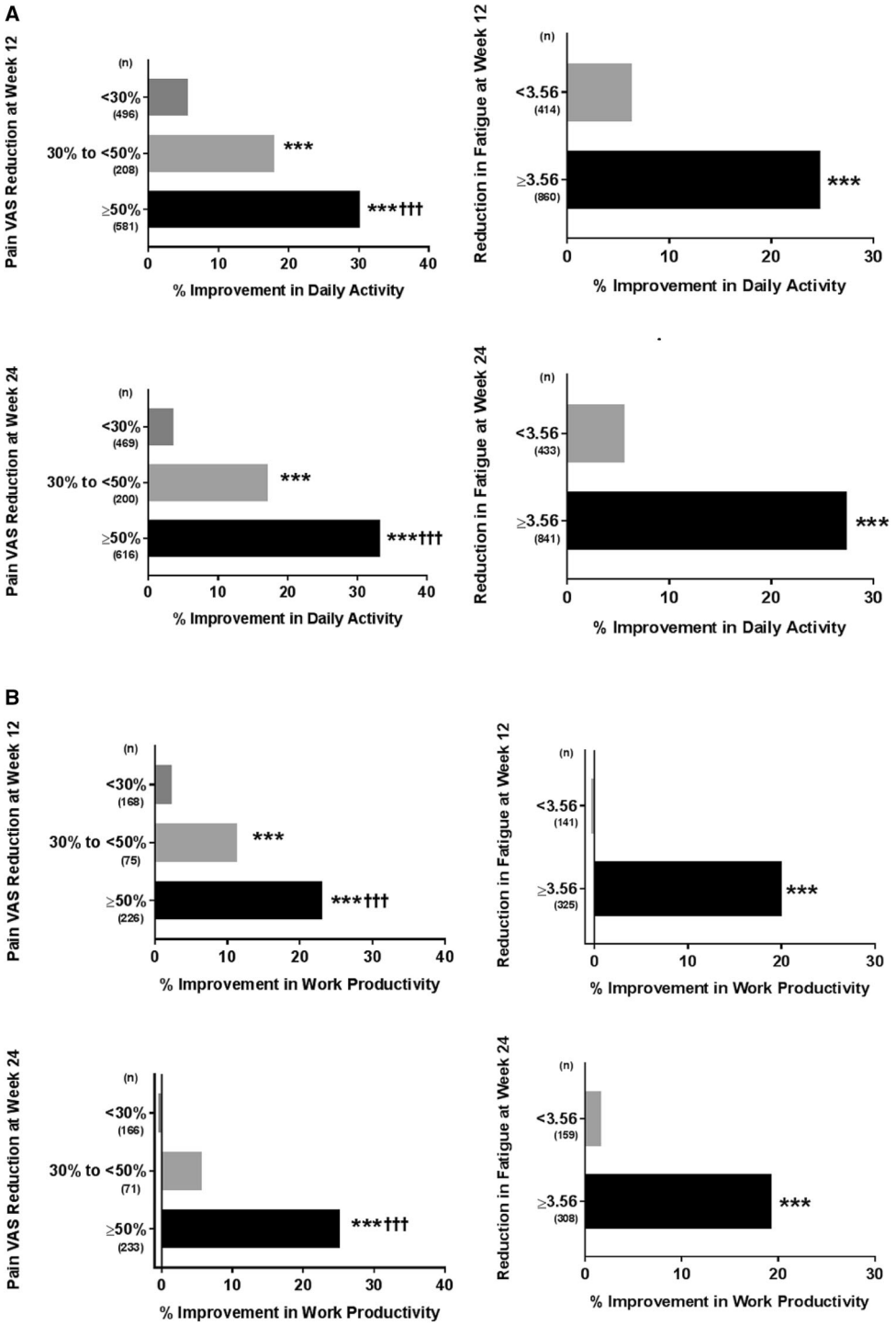

Fig. 1 **a** The relationship of pain and fatigue with improvement in daily activity at weeks 12 and 24. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$ vs. < 30% pain reduction; $^{\dagger}p \leq 0.05$, $^{\dagger\dagger}p \leq 0.01$, $^{\dagger\dagger\dagger}p \leq 0.001$ vs. 30 to < 50% pain reduction. **b** The relationship of pain and fatigue with improvement in work productivity at weeks 12 and 24. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$ vs. < 30% pain reduction; $^{\dagger}p \leq 0.05$, $^{\dagger\dagger}p \leq 0.01$, $^{\dagger\dagger\dagger}p \leq 0.001$ vs. 30 to < 50% pain reduction

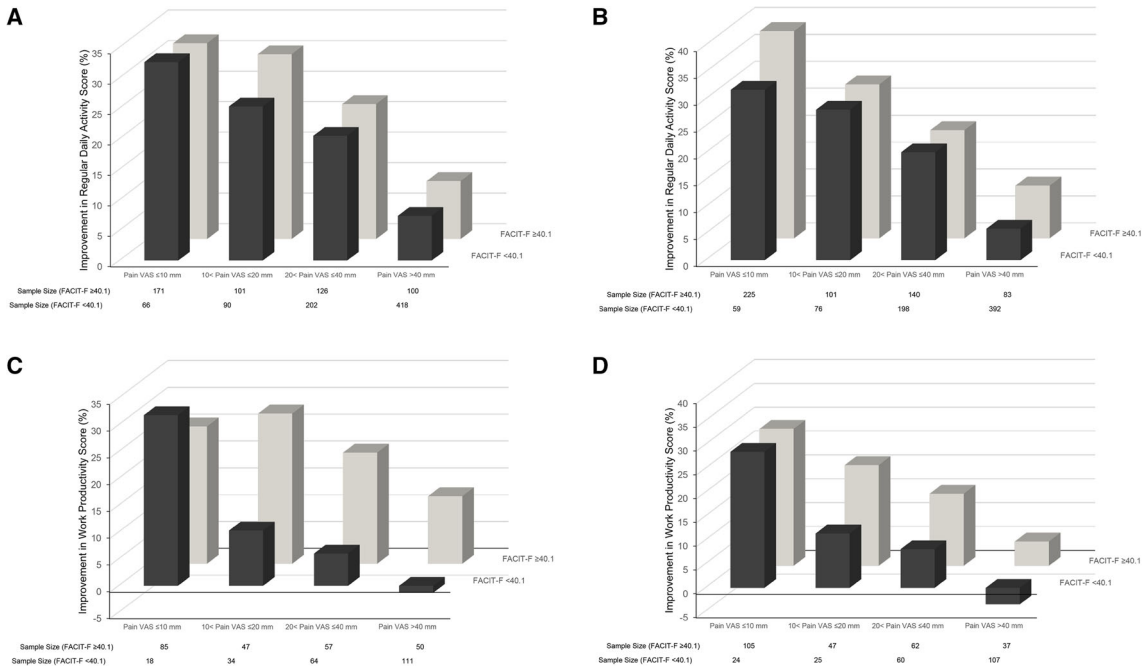

Fig. 2 **a** Pain, fatigue, and improvement in daily activity at week 12. **b** Pain, fatigue, and improvement in daily activity at week 24. **c** Pain, fatigue, and improvement in work productivity at week 12. **d** Pain, fatigue, and improvement in work productivity at week 24

we observed that pain and fatigue tended to be more correlated with daily activity and work productivity, compared to other measures, such as CRP, TJC, and SJC, thus confirming the feasibility of focusing on pain and fatigue as factors for impairments in daily activity and work productivity. Pain and fatigue had significant independent effects on daily activity and work productivity over 24 weeks of treatment. When pain and fatigue were evaluated together, we observed that at the lowest level of remaining pain, work productivity improvement was not influenced by fatigue. At higher levels of remaining pain, however, the data suggested that both pain and fatigue have an impact on patient's work productivity. Reductions in pain and fatigue, along with low disease activity, accounted for most of the improvements in daily activity and work productivity with treatment.

Our results are consistent with prior studies that have found that pain and fatigue are contributors to productivity-related outcomes [18–22]. Our analysis, however, expands upon prior research by demonstrating the relative contributions of pain and fatigue.

The current analysis has limitations. Because the data are derived from a clinical trial in which patients initially had long disease duration and high disease activity, the results may not be generalizable to other RA patients. Additionally, we did not capture the type of employment for the patients, which may influence patient reporting. For example, patients with RA working in an office setting may more easily adjust their work day to accommodate their symptoms compared with patients in more physically demanding work. Similarly, we may not have captured other factors that influence daily activity and work productivity.

CONCLUSIONS

Results from this analysis indicate that reductions in pain and fatigue were associated with improved daily activity and work productivity in RA regardless of treatment, and greater

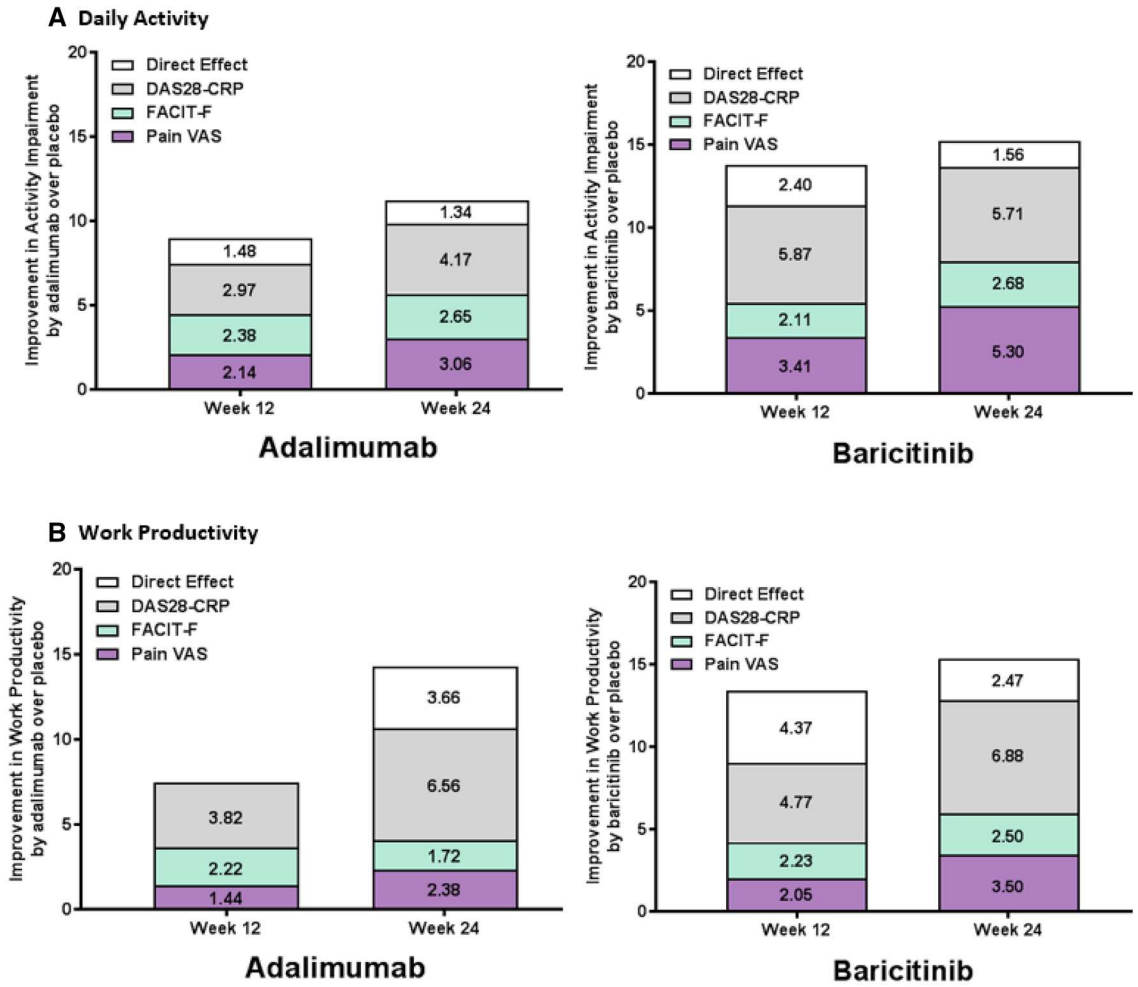

Fig. 3 Mediator analysis to assess the contribution of pain, fatigue, and disease activity on daily activity and work productivity by treatment at weeks 12 and 24

reductions resulted in more productivity. If remaining pain was minimal, however, similar levels of improvement in work productivity were observed regardless of fatigue level. These trends were also observed among baricitinib-treated patients.

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Compliance with Ethics Guidelines. The RA-BEAM study was approved by Quorum Review IRB #27257. Additionally, each participating center's institutional review board or ethics committee approved the study. The list of centers can be found in the first RA-BEAM publication. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. No additional ethical approval was required to conduct the current post hoc analysis.

Data Availability. Lilly provides access to relevant anonymized patient level data from studies on approved medicines and indications as defined by the sponsor specific information on clinicalstudydatarequest.com. For details on submitting a request, see the instructions provided at clinicalstudydatarequest.com.

REFERENCES

1. Tillett W, Bojke L. Work disability and the cost-effectiveness of drugs to treat rheumatic diseases—time for a new dialogue? J Rheumatol. 2018;45(8):1075–7.

2. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int. 2016;36(5):685–95.

3. Burton W, Morrison A, Maclean R, Ruderman E. Systematic review of studies of productivity loss due to rheumatoid arthritis. Occup Med (Lond). 2006;56(1):18–27.

4. Kim D, Kaneko Y, Takeuchi T. Importance of obtaining remission for work productivity and activity of patients with rheumatoid arthritis. J Rheumatol. 2017;44(8):1112–7.

5. Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010;184(9):5298–307.

6. Keystone EC, Taylor PC, Tanaka Y, Gaich C, DeLozier AM, Dudek A, et al. Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or

adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study. Ann Rheum Dis. 2017;76(11):1853–61.

7. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376(7):652–62.

8. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9(2):105–21.

9. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol. 2005;32(10):2016–24.

10. Wolfe F, Michaud K. Assessment of pain in rheumatoid arthritis: minimal clinically significant difference, predictors, and the effect of anti-tumor necrosis factor therapy. J Rheumatol. 2007;34(8):1674–83.

11. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. Arthritis Care Res (Hoboken). 2012;64(11):1699–707.

12. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the functional assessment of chronic illness therapy fatigue scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32(5):811–9.

13. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59(6):785–93.

14. Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes. 2003;1:79.

15. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353–65.

16. Fleiss JL. Reliability of measurement. The design and analysis of clinical experiments. New York: Wiley; 1986.

17. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879–91.

18. Bansback N, Zhang W, Walsh D, Kiely P, Williams R, Guh D, et al. Factors associated with absenteeism, presenteeism and activity impairment in patients in the first years of RA. Rheumatology (Oxford). 2012;51(2):375–84.

19. Druce KL, Aikman L, Dilleen M, Burden A, Szczypa P, Basu N. Fatigue independently predicts different work disability dimensions in etanercept-treated rheumatoid arthritis and ankylosing spondylitis patients. Arthritis Res Ther. 2018;20(1):96.

20. Enns MW, Bernstein CN, Kroeker K, Graff L, Walker JR, Lix LM, et al. The association of fatigue, pain, depression and anxiety with work and activity impairment in immune mediated inflammatory diseases. PLoS ONE. 2018;13(6):e0198975.

21. Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. Rheumatology (Oxford). 2010;49(10):1900–10.

22. Hone D, Cheng A, Watson C, Huang B, Bitman B, Huang XY, et al. Impact of etanercept on work and activity impairment in employed moderate to severe rheumatoid arthritis patients in the United States. Arthritis Care Res (Hoboken). 2013;65(10):1564–72.