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Relative Impact of Pain and Disease Activity on Improvements in Fatigue

Results From 2 Baricitinib Phase 3 Clinical Trials

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Abstract:

Background/Objective: Fatigue is common in patients with rheumatoid arthritis (RA). We assessed the relative impact of pain and disease activity on improvements in fatigue in 2 phase 3 baricitinib clinical trials.

Methods: RA-BEAM (NCT01710358) and RA-BEACON (NCT01721044) were randomized, double-blind, placebo-controlled studies in adults with moderate to severe RA. RA-BEAM assessed baricitinib + methotrexate (MTX) and adalimumab + MTX in patients with prior inadequate response/intolerance (IR) to MTX (MTX-IR). RA-BEACON assessed patients with IR to ≥ 1 biologic disease-modifying antirheumatic drug (bDMARD-IR). Measures included the Functional Assessment of Chronic Illness Therapy—Fatigue scale, Clinical Disease Activity Index (CDAI) for RA, and pain visual analog scale (VAS). Analyses were implemented separately for each study.

Results: Significant improvements were seen in disease activity and pain, which were greater with baricitinib versus adalimumab. A statistically significant improvement was seen in fatigue with both active treatments versus placebo. Moderate correlations were observed between improvements in disease activity and fatigue and between improvements in pain and fatigue in both MTX-IR and bDMARD-IR patients. Reductions in pain ($\geq 50\%$) and remission or low disease activity (CDAI ≤ 10) had significant associations with fatigue improvement at week 24. In mediation analysis, improvements in fatigue attributable to CDAI and pain VAS in MTX-IR patients were 31% and 52%, respectively, for baricitinib, and 30% and 47%, respectively, for adalimumab. In bDMARD-IR patients, improvement in fatigue was attributed 48% to CDAI and 48% to pain VAS.

Conclusions: In both MTX-IR and bDMARD-IR patients, a large proportion of improvements in fatigue across treatment arms were accounted for by improvements in pain and disease activity.

Key Words: baricitinib, fatigue, mediation analysis

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Fatigue, which broadly manifests as physical or mental tiredness, or exhaustion not relieved by rest, is common among patients with rheumatoid arthritis (RA). Severe fatigue was recently estimated at 41% prevalence among patients with RA alone—4 times the rate observed in the general population—with higher rates among patients with RA and additional rheumatic diseases.¹ Patients rate fatigue as an important and underdiscussed aspect of treatment effectiveness; for example, patients advocated for its measurement in addition to the core set in clinical trials whenever possible at OMERACT 8, and fatigue was included in the final list of Rheumatoid Arthritis Patient Priorities for Pharmacological Interventions outcomes in 2010.^{2,3}

The etiology of fatigue in RA, as in many chronic diseases, is unclear but certainly multidimensional.⁴ One proposed model includes interacting domains for RA disease processes, which include such aspects as deconditioning and inflammatory processes; cognitive/behavioral aspects, including thoughts, feelings, and behaviors related to RA disease; and personal aspects encompassing personal life issues, including work, care, and comorbidities, which can have a major impact on fatigue.⁵ A review by Nikolaus et al⁴ found that the most consistent predictors of fatigue across studies were pain, worse physical functioning, and depression, whereas evidence for the role of other factors, including a direct role for inflammation, was more mixed and either variable or even contradictory between studies. Possibly due in part to such overlapping and interacting domains influencing causality, fatigue has been found to be only moderately responsive to treatment interventions primarily targeting disease activity.^{6–8}

Baricitinib is a selective Janus kinase 1 (JAK1)/JAK2 inhibitor that modulates signaling pathways involved in RA pathogenesis. Baricitinib is widely approved for the treatment of RA across a treatment experience spectrum from patients naive to conventional synthetic disease-modifying antirheumatic drugs (DMARDs) to patients with inadequate response or intolerance (IR) to 1 or more tumor necrosis factor inhibitors (TNFis) or other biologic DMARDs (bDMARDs). The objective of the present study was to assess the relative impact of disease activity, pain, and potential direct effects—those not mediated by pain or disease activity—of baricitinib on fatigue in the RA-BEAM (NCT01710358) study assessing methotrexate-IR (MTX-IR) patients and in the RA-BEACON (NCT01721044) study of patients with bDMARD-IR.

METHODS

RA-BEAM was a phase 3 study that was randomized, double-blind, and placebo- and active-controlled, with a 52-week

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duration. The study evaluated the safety and efficacy of baricitinib in patients with moderately to severely active RA who had previously had an MTX-IR.^{9,10} Briefly, patients enrolled in RA-BEAM were 18 years or older and had 6 or more out of 68 tender joints and 6 or more out of 66 swollen joints, a serum C-reactive protein level 6 mg/L or greater, and prior MTX-IR. Treatment arms included randomization to placebo, baricitinib 4 mg once daily, or biweekly subcutaneous adalimumab 40 mg, added to patients' ongoing background MTX therapy.

RA-BEACON was a phase 3, randomized, double-blind, placebo-controlled, multicenter, study of 24-week duration. The study design and results have been reported previously.^{11,12} In brief, patients enrolled in RA-BEACON were 18 years or older, with 6 or more out of 68 tender joints and 6 or more out of 66 swollen joints, and serum C-reactive protein 3 mg/L or greater. Patients had prior experience with 1 or more TNFis, with treatment discontinuation that resulted from IR (after ≥ 3 months) or intolerance; prior experience with other bDMARDs was permitted. Biological DMARDs were discontinued for 4 weeks or more before randomization (for rituximab, the discontinuation period was ≥ 6 months). Patients had also received 1 or more conventional synthetic DMARDs for at least 12 weeks before entering the study, with the dose stable for 8 weeks or more. Patients were randomized to receive placebo or baricitinib once daily, added on to the therapies with which they were being treated at enrollment.

Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and each was approved by the ethics committee or institutional review board at each study center. All patients provided written informed consent.

Statistical Analyses

Data were assessed from weeks 0 to 24 for the modified intention-to-treat population set (patients who were randomized and received ≥ 1 dose). Missing data were imputed with modified last observation carried forward if needed. Measures of interest included the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scale, on which higher scores represent better functioning/less fatigue¹³; the Clinical Disease Activity Index (CDAI) for RA¹⁴ that incorporates tender joint and swollen joint counts, and both patient and evaluator global assessments of disease activity, on which lower scores represent lower disease activity; and the pain visual analog scale (VAS), on which higher scores represent more patient-reported pain.

Three main types of statistical analyses described in the following were implemented for each study separately.

Correlation analyses were performed using pooled data across treatment arms within each study. Correlations between FACIT-F and CDAI and between FACIT-F and pain VAS were assessed for change from baseline at week 24 using Spearman rank correlation coefficient. The absolute value of the correlation results was evaluated based on Cohen's conventions with a correlation >0.5 defined as large, 0.3 to 0.5 as moderate, and 0.1 to <0.3 as small.¹⁵

Pairwise comparison analyses also used pooled data across treatment arms. We compared fatigue improvement at week 24 between groups based on pain or CDAI using analysis of covariance. Pain subgroups were defined as pain improvement $<30\%$, $30\% \leq$ pain improvement $<50\%$, and pain improvement $\geq 50\%$. The CDAI subgroups were defined using CDAI ≤ 2.8 (remission); $2.8 <$ CDAI ≤ 10 (low disease activity [LDA]); and CDAI >10 (moderate and high disease activity).¹⁴ Change from baseline in FACIT-F at week 24 was the dependent variable. Independent variables included FACIT-F baseline value, pain or CDAI group, and stratification variables (i.e., baseline joint erosion

status and region for RA-BEAM, and bDMARD use history and region for RA-BEACON).

Longitudinal multiple mediator analyses were used to assess whether and to what extent baricitinib 4 mg effects on FACIT-F were mediated via improvement in CDAI and pain VAS.¹⁶ In the mediations analysis, the independent variable was treatment assignment (i.e., baricitinib 4 mg vs placebo and adalimumab vs placebo in RA-BEAM, and baricitinib 4 mg vs placebo in RA-BEACON). The dependent variable was FACIT-F change from baseline to weeks 4, 8, 12, 16, 20, and 24. The multiple mediators included change from baseline in pain VAS and in CDAI at each time point listed above. In mediation analyses, contributions by treatment from improvements in pain and disease activity on those in fatigue represent the overall "indirect effect" or mediation effect; the total remaining effect of treatment on fatigue that is not explained by the mediation effect is referred to as the "direct effect."

RESULTS

Baseline Characteristics

Baseline characteristics by study are shown in the Table. Among the patients enrolled in RA-BEAM and RA-BEACON, mean time since onset of RA symptoms was approximately 10 and 13 years, respectively. Patients in RA-BEACON had higher swollen and tender joint counts, and more disability, than patients in RA-BEAM. Disease activity, based on CDAI, ranged from 37.6 to 38.1 in RA-BEAM and was higher in RA-BEACON (placebo, 40.6; baricitinib 4 mg, 40.3). Similarly, mean pain VAS at baseline ranged from 59.5 to 61.8 in RA-BEAM, and pain was more severe in the RA-BEACON treatment groups (placebo, 64.7; baricitinib 4 mg, 65.8). Mean fatigue at baseline as measured by FACIT-F ranged from 27.6 to 28.6 across treatment groups in RA-BEAM and was also more severe in the 2 RA-BEACON treatment groups (placebo, 22.2; baricitinib 4 mg, 23.4).

Changes From Baseline in FACIT-F, Pain VAS, and CDAI

Statistically significant improvements from baseline to weeks 12, 16, 20, and 24 were seen in the FACIT-F, pain VAS, and CDAI for baricitinib 4 mg in both RA-BEAM and RA-BEACON (Supplemental Table, <http://links.lww.com/RHU/A519>). Similarly, for adalimumab in RA-BEAM, FACIT-F, pain VAS, and CDAI also improved significantly at weeks 12, 16, 20, and 24. Significantly greater improvements were seen with baricitinib versus adalimumab at weeks 12, 16, 20, and 24 for CDAI (all $p < 0.05$) and pain VAS (all $p < 0.01$). Change in FACIT-F was significantly greater with baricitinib (10.1 ± 0.44) versus adalimumab (8.9 ± 0.53) at week 20 ($p = 0.046$).

Correlation Analyses

Correlations between change from baseline to week 24 in FACIT-F versus change in CDAI or change in pain VAS are shown in Figure 1. In RA-BEAM, the Spearman correlation coefficient was -0.38 between change in FACIT-F and change in CDAI and was -0.45 between change in FACIT-F and change in pain VAS. In RA-BEACON, the correlation coefficients between changes at week 24 in FACIT-F versus CDAI and between FACIT-F versus pain VAS were both -0.48 . All of these results represent moderate correlations.

Pairwise Comparisons

Improvements in fatigue are illustrated in Figure 2 for groups of patients with categorical improvements in pain of $<30\%$, 30%

TABLE. Baseline Characteristics by Study

Variable	RA-BEAM			RA-BEACON	
	PBO (n = 488) ^a	BARI 4 mg (n = 487) ^a	ADA (n = 330) ^a	PBO (n = 176) ^a	BARI 4 mg (n = 177) ^a
Age, y	53.4 ± 11.8	53.5 ± 12.2	52.9 ± 12.3	56.0 ± 10.7	55.9 ± 11.3
Female, n (%)	382 (78.3)	375 (77.0)	251 (76.1)	145 (82.4)	149 (84.2)
Duration of RA, y	10.4 ± 8.7	10.3 ± 8.8	9.6 ± 8.5	14.0 ± 9.6	14.3 ± 9.4
TJC68	23.3 ± 13.5	23.4 ± 13.0	23.4 ± 13.7	28.3 ± 16.4	28.1 ± 15.6
SJC66	15.5 ± 9.4	15.0 ± 8.2	15.4 ± 9.1	17.2 ± 10.8	16.3 ± 8.9
HAQ-DI	1.6 ± 0.7	1.6 ± 0.7	1.6 ± 0.7	1.78 ± 0.6	1.74 ± 0.6
CDAI	37.6 ± 12.8	38.1 ± 12.0	38.0 ± 13.0	40.6 ± 12.9	40.3 ± 13.7
Pain VAS	59.5 ± 22.6	61.8 ± 21.8	61.0 ± 22.7	64.7 ± 19.3	65.8 ± 23.4
FACIT-F	28.6 ± 10.7	28.1 ± 10.7	27.6 ± 11.4	22.2 ± 10.6	23.4 ± 11.3

Data shown as mean ± SD unless otherwise noted.

^aNumber of mITT patients.

ADA, adalimumab; BARI, baricitinib; HAQ-DI, Health Assessment Questionnaire—Disability Index; mITT, modified intention-to-treat; PBO, placebo; SJC66, swollen joint count based on 66 joints; TJC68, tender joint count based on 68 joints.

to 50%, or >50% or by categorical improvements in CDAI corresponding to remission, LDA, or moderate through high levels of disease activity. At week 24, patients with ≥50% pain reduction had significantly greater improvement in FACIT-F score versus those with either a <30% or 30% to 50% reduction in pain in both RA-BEAM and RA-BEACON (Fig. 2A; all *p* < 0.001). Patients who reached target levels for remission or LDA (CDAI ≤10) had significantly greater improvements in FACIT-F versus patients

who continued to have moderate to high levels of disease activity in both RA-BEAM and RA-BEACON (Fig. 2B; all *p* < 0.001).

Mediation Analyses

In MTX-IR patients, the total effect on fatigue relief with baricitinib versus placebo at week 24 was numerically greater than the effect with adalimumab (Fig. 3). Changes in CDAI explained

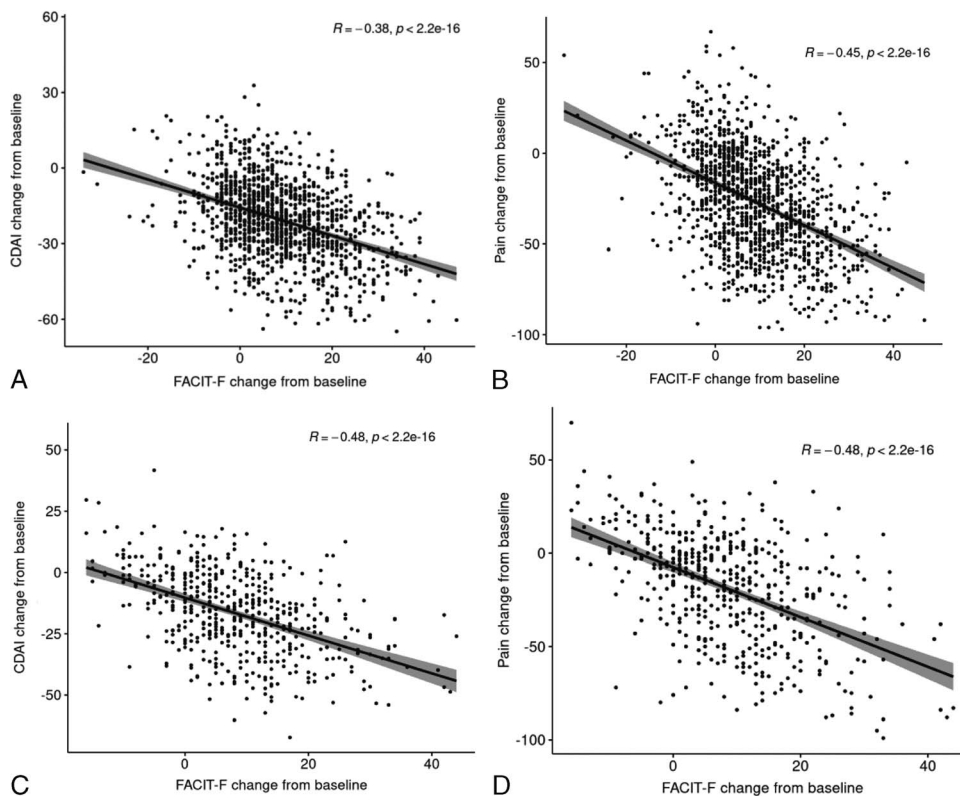


FIGURE 1. Correlation between change from baseline in FACIT-F and (A) CDAI or (B) pain VAS in MTX-IR patients and (C) CDAI or (D) pain VAS in bDMARD-IR patients. *R*, Spearman correlation coefficient. The analysis was performed on pooled data from all treatment arms (including placebo) within each study.

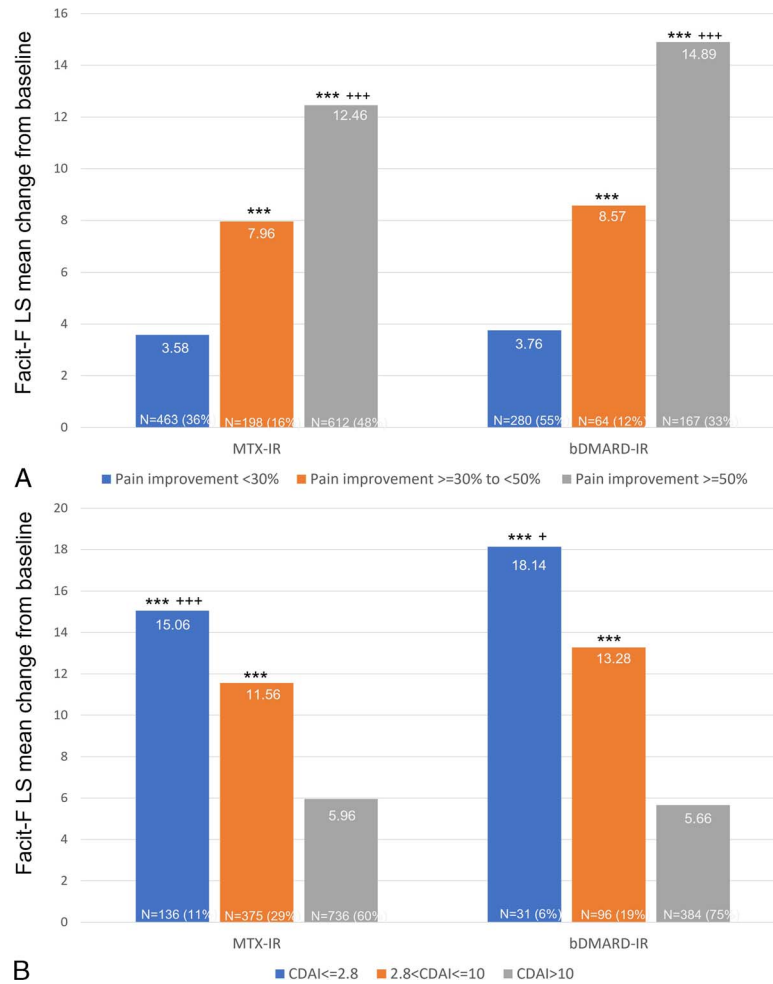


FIGURE 2. Pairwise comparison between fatigue and categorical change at week 24 in MTX-IR and bDMARD-IR patients for (A) pain VAS and (B) CDAI. LS, least squares. The analysis was performed on pooled data from all treatment arms (including placebo) within each study. In A, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ versus <30% pain improvement; + $p \leq 0.05$, ++ $p \leq 0.01$, +++ $p \leq 0.001$ versus 30% to <50% pain improvement. In B, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ versus CDAI >10; + $p \leq 0.05$, ++ $p \leq 0.01$, +++ $p \leq 0.001$ versus 2.8 < CDAI ≤10.

approximately 30% of the reductions in fatigue in both the baricitinib and adalimumab groups, whereas changes in pain accounted for 52% of the reduction in fatigue among patients receiving baricitinib and 47% of the reduction in fatigue with adalimumab (Fig. 3A). Among the bDMARD-IR population assessed in RA-BEACON (Fig. 3B), the change in fatigue was largely explained by indirect effects mediated by the improvements in disease activity (48%) and pain (48%).

DISCUSSION

In the present analysis, baricitinib demonstrated significant improvements in disease activity and pain by week 12 and through 24 weeks in both MTX-IR and bDMARD-IR patients, as previously reported in part for these populations.^{10,12} A statistically significant improvement in fatigue was also observed, although residual fatigue remained following treatment. Mediation analyses demonstrated that a large proportion of the improvements in fatigue were explained by improvements in disease activity or pain.

In the MTX-IR population in which baricitinib and adalimumab were compared, the reduction in pain and disease activity observed with baricitinib was significantly greater than with adalimumab.

These findings are consistent with a meta-analysis assessing a range of outcomes for JAK inhibitors versus placebo, MTX, or bDMARDs in RA, which demonstrated significant improvements in pain VAS and in measures of disease activity including CDAI, for JAK inhibitors versus placebo and in pain VAS and some measures of disease activity versus TNFi.¹⁷ At some time points in the present study, greater improvement in fatigue was observed with baricitinib than with adalimumab; however, those differences were relatively limited.

Fatigue is a multifactorial symptom. When assessed across treatment arms within each study population, patients with higher pain reduction or with more disease activity improvement also experienced higher fatigue improvement compared with those with less reduction in pain or improvement in disease activity. In addition, correlation analysis demonstrated correlations that were statistically significant between improvements in pain and fatigue and between improvements in disease activity and fatigue in both MTX-IR and bDMARD-IR patients. Consistent with these findings, pain is one of the factors most consistently linked to fatigue in RA, including correlations between improvements in pain and fatigue during treatment.^{4,6,8,18,19} Following successful treatment of RA, improvements in disease activity measures are generally

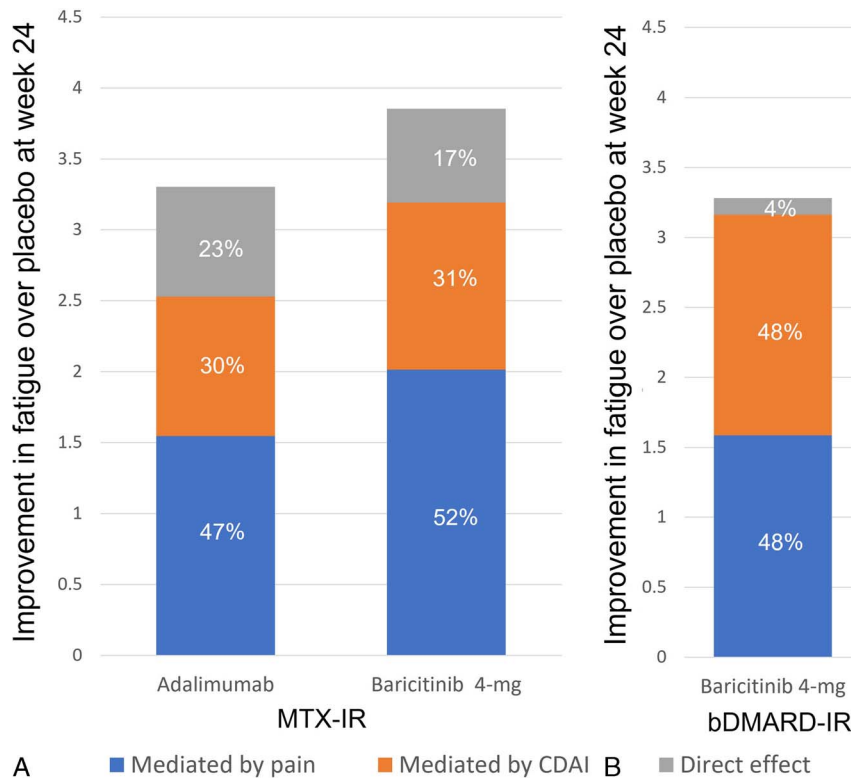


FIGURE 3. Mediation analyses showing the proportion of direct effect and indirect effects mediated by pain and CDAI in (A) MTX-IR patients or (B) TNFi-IR patients. Direct effect = the treatment effect that cannot be accounted for by the indirect/mediation effect from improvement in CDAI and pain.

accompanied by improvements in fatigue; however, it should be noted that several studies have demonstrated a strong relationship between results for the subjective portions of measures such as the CDAI, Simplified Disease Activity Index, or Disease Activity Score with 28-joint counts—the Patient Global Assessment and to a lesser degree tender joint count—and improvements in fatigue (and other patient reported outcomes), but more limited associations with objective indicators of inflammation such as erythrocyte sedimentation rate, C-reactive protein, swollen joint counts, or ultrasound assessments of swollen joints.^{20–23} Therefore, composite measures of disease activity are not necessarily fully distinct from measures of pain²⁴ or from other psychosocial or other factors that might impact patient global assessments of health. On the other hand, an observation linking C-reactive protein normalization with fatigue improvement has also been reported, suggesting a link between fatigue and inflammation, although potentially mediated at least in part by improvements in pain.¹⁹ Fatigue due to reasons other than pain or disease activity does not seem to be substantially modified by DMARDs, suggesting that combined pharmacological and nonpharmacological therapies may be needed to achieve the best outcomes for fatigue. In the present study, we applied mediation analysis to quantify the contribution/impact of reductions in pain and in disease activity on fatigue. In MTX-IR patients, the improvement in pain contributed more than half of the total improvement in fatigue. Consistent with this finding, a pathway analysis showed that a large part of the improvement in fatigue following initial TNFi therapy was mediated by pain, either directly or through impact on mental health,²⁵ and pain is among the factors most commonly linked with fatigue in RA.^{4,26,27}

In this analysis, we found that the change in CDAI accounted for approximately 30% of the improvement in fatigue in both the

baricitinib and adalimumab groups. Previous reports on the impact of changes in disease activity on fatigue have been inconsistent.^{4,6,8,25} As noted, improvements in disease activity measures such as the CDAI, Simplified Disease Activity Index, and Disease Activity Score with 28-joint counts have shown associations with improvements in fatigue in some studies; however, this may be due in substantial part to the subjective components of these measures, as inflammation per se has not regularly been correlated with improvements in fatigue.^{4,20}

This study has several strengths and limitations. First, the data were obtained from 2 phase 3 clinical studies of patients with persistent RA and substantial residual disease activity, and the results may not be readily generalizable to other patients seeking treatment for RA. Notably, these and other registrational drug trials generally exclude patients with fibromyalgia, which is relatively common in RA; results may therefore not be comparable to real-life cohorts, which are likely to include a substantial group of patients in whom a potential linkage between the degree of pain experienced and the extent of disease activity is altered. In addition, the use of modified last observation carried forward data handling may have reduced the sensitivity of the correlation and pairwise analyses somewhat due to the inclusion of data from patients experiencing limited response. We also expect this could result in limited numerical differences in the mediation analysis, but it should not change the conclusions. However, the assessment of a population with persistent RA and high disease activity, including both MTX-IR and bDMARD-IR patients, is a strength, as patients in these populations are relatively likely to experience high levels of fatigue. In addition to disease activity and pain, other factors such as depression and cognitive function may be involved in the mechanisms of fatigue and were not captured and studied in

this analysis. Such factors may contribute to unexplained variance and residual confounding that were observed in the model.

In summary, in both MTX-IR and bDMARD-IR RA patients from randomized clinical trials, reductions in disease activity and pain explained the majority of the observed improvements in fatigue. For clinicians who are seeking to improve fatigue related to RA, additional benefits may potentially be obtained from nonpharmacological interventions, in addition to improving disease activity and pain through pharmacological therapies. Further studies would be helpful to evaluate factors in addition to disease activity and pain contributing to improvements in fatigue seen in patients with active RA.

KEY POINTS

- Significant improvements were seen in CDAI, pain VAS, and FACIT-F with baricitinib in MTX-IR and bDMARD-IR patients and with adalimumab in MTX-IR patients at weeks 12 through 24; improvements were consistently greater with baricitinib than adalimumab for CDAI and pain VAS.
- In the pooled treatment arms, correlations of moderate strength were seen between change from baseline to week 24 in FACIT-F versus change in CDAI and versus change in pain VAS; the correlation was somewhat stronger in bDMARD than in MTX-IR patients.
- Mediation analysis showed that the large majority of the improvement in FACIT-F was explained by changes in pain and disease activity for both baricitinib and adalimumab in MTX-IR patients, and these factors explained almost all of the improvements in FACIT-F in the bDMARD experienced population.

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REFERENCES

- Overman CL, Kool MB, Da Silva JA, et al. The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol*. 2016;35:409–415.
- Sanderson T, Morris M, Calnan M, et al. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res (Hoboken)*. 2010;62:647–656.
- Kirwan JR, Minnock P, Adebajo A, et al. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol*. 2007;34:1174–1177.
- Nikolaus S, Bode C, Taal E, et al. Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res (Hoboken)*. 2013;65:1128–1146.
- Hewlett S, Chalder T, Choy E, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology (Oxford)*. 2011;50:1004–1006.
- Pope JE. Management of fatigue in rheumatoid arthritis. *RMD Open*. 2020;6:e001084.
- Almeida C, Choy EH, Hewlett S, et al. Biologic interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2016;CD008334.
- Druce KL, Basu N. Predictors of fatigue in rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58:v29–v34.
- Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376:652–662.
- Keystone EC, Taylor PC, Tanaka Y, 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;76:1853–1861.
- Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374:1243–1252.
- Smolen JS, Kremer JM, Gaich CL, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis*. 2017;76:694–700.
- Cella D, Yount S, Sorensen M, et al. Validation of the functional assessment of chronic illness therapy fatigue scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol*. 2005;32:811–819.
- Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005;7:R796–R806.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
- Burns RA, Crisp DA, Burns RB. Re-examining the reciprocal effects model of self-concept, self-efficacy, and academic achievement in a comparison of the cross-lagged panel and random-intercept cross-lagged panel frameworks. *Br J Educ Psychol*. 2020;90:77–91.
- Tóth L, Juhász MF, Szabó L, et al. Janus kinase inhibitors improve disease activity and patient-reported outcomes in rheumatoid arthritis: a systematic review and meta-analysis of 24,135 patients. *Int J Mol Sci*. 2022;23:1246.
- Katz P. Fatigue in rheumatoid arthritis. *Curr Rheumatol Rep*. 2017;19:25.
- Madsen SG, Danneskiold-Samsøe B, Stockmarr A, et al. Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. *Scand J Rheumatol*. 2016;45:255–261.
- Bergman MJ, Shahouri SH, Shaver TS, et al. Is fatigue an inflammatory variable in rheumatoid arthritis (RA)? Analyses of fatigue in RA, osteoarthritis, and fibromyalgia. *J Rheumatol*. 2009;36:2788–2794.
- Versteeg GA, Ten Klooster PM, van de Laar MAFJ. Fatigue is associated with disease activity in some, but not all, patients living with rheumatoid arthritis: disentangling “between-person” and “within-person” associations. *BMC Rheumatol*. 2022;6:3.
- Hammer HB, Michelsen B, Sexton J, et al. Fatigue is cross-sectionally not associated with objective assessments of inflammation, but changes in fatigue are associated with changes of disease activity assessments during biologic treatment of patients with established rheumatoid arthritis. *Clin Rheumatol*. 2021;40:1739–1749.
- Hammer HB, Agular B, Terslev L. Fatigue is not associated with objective assessments of inflammation during tocilizumab treatment of patients with rheumatoid arthritis. *ACR Open Rheumatol*. 2022;4:202–208.
- Strand V, Kaine J, Alten R, et al. Associations between patient global assessment scores and pain, physical function, and fatigue in rheumatoid arthritis: a post hoc analysis of data from phase 3 trials of tofacitinib. *Arthritis Res Ther*. 2020;22:243.
- Druce KL, Jones GT, Macfarlane GJ, et al. Determining pathways to improvements in fatigue in rheumatoid arthritis: results from the British Society for Rheumatology biologics register for rheumatoid arthritis. *Arthritis Rheumatol*. 2015;67:2303–2310.
- Minnock P, Veale DJ, Bresnihan B, et al. Factors that influence fatigue status in patients with severe rheumatoid arthritis (RA) and good disease outcome following 6 months of TNF inhibitor therapy: a comparative analysis. *Clin Rheumatol*. 2015;34:1857–1865.
- Huyser BA, Parker JC, Thoreson R, et al. Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum*. 1998;41:2230–2237.