

processes, independent of joint destruction, resulting in new bone formation³, an aspect that is generally not included in assessment methods for radiographic outcomes⁶. Structural damage of joints in PsA is associated with disability and functional impairment⁷, highlighting the importance of joint integrity in patients with PsA. Treatment recommendations state that in addition to low disease activity, key goals of treatment are to minimize structural damage and optimize patient functioning and quality of life^{4,8}.

Current treatment recommendations for PsA advise conventional synthetic disease-modifying antirheumatic drugs (csDMARD) such as methotrexate (MTX) as initial therapy, followed by biologic DMARD [tumor necrosis factor inhibitors (TNFi), interleukin (IL)-12/23 inhibitors, IL-17 inhibitors] or apremilast for patients with an inadequate response to csDMARD^{4,8}.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. We previously reported primary results of the Oral Psoriatic Arthritis trial (OPAL) Broaden, a phase III study in patients with active PsA and an inadequate response to at least 1 csDMARD. OPAL Broaden evaluated the efficacy and safety of tofacitinib and an active control, adalimumab (ADA), in combination with 1 background csDMARD, in reducing the signs and symptoms of PsA and improving physical function. Progression of structural damage over 12 months was also evaluated⁹. In OPAL Broaden, tofacitinib 5 and 10 mg twice daily (BID) significantly improved American College of Rheumatology (ACR) 20 response rates and change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) compared with placebo at Month 3⁹. Moreover, response rates for ACR50, ACR70, and $\geq 75\%$ improvement in Psoriasis Area and Severity Index with tofacitinib 5 and 10 mg BID were superior to placebo at Month 3. Up to Month 3, more adverse events were reported with active treatments versus placebo.

Given the importance of optimizing joint integrity in patients with PsA, the objective of this posthoc analysis was to examine the relationship between known prognostic factors for radiographic progression in RA and PsA^{10,11,12,13,14} and radiographic outcomes in patients with PsA from OPAL Broaden. We report in-depth analyses of the effect of tofacitinib 5 and 10 mg BID and ADA on radiographic progression at Month 12 in OPAL Broaden, grouped by C-reactive protein (CRP) levels at baseline. In addition, we report linear and logistic regression analyses for baseline risk factors associated with radiographic progression in PsA, including elevated CRP.

MATERIALS AND METHODS

The full study design, patient inclusion and exclusion criteria, statistical analyses, and study results [co-primary endpoints (ACR20 response rates and mean change from baseline in HAQ-DI at Month 3), key secondary endpoints, and safety] for OPAL Broaden have been previously described⁹. In brief, OPAL Broaden (www.ClinicalTrials.gov: NCT01877668) was a randomized, 12-month, placebo-controlled, double-blind, multicenter

phase III study carried out across 126 centers worldwide between January 2014 and December 2015. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol and all documentation were approved by the institutional review boards or independent ethics committees at each investigational site (approval no. for the principal US trial site Quorum was 28306).

Patients. Eligible patients were ≥ 18 years of age, had a diagnosis of PsA for at least 6 months, fulfilled CIASSification criteria for Psoriatic ARthritis (CASPAR)¹⁵, had an inadequate response to at least 1 csDMARD, and had not previously received TNFi. Patients were not required to meet any enrichment criteria for the presence of baseline characteristics associated with radiographic progression. All patients provided written informed consent.

Study treatment. Eligible patients were randomized 2:2:2:1:1 to 1 of 5 parallel treatment sequences: tofacitinib 5 mg BID; tofacitinib 10 mg BID; ADA 40 mg subcutaneous injection once every 2 weeks; placebo switched to tofacitinib 5 mg BID at Month 3; or placebo switched to tofacitinib 10 mg BID at Month 3. All patients received a stable background dose of a single csDMARD (either MTX, sulfasalazine, or leflunomide) throughout the study. Patients were followed through Month 12.

Radiographic assessments. Radiographs of the hands and feet were performed at baseline and at Month 12, or at the early termination visit for any patients who withdrew early.

Scoring was provided by 2 central, blinded assessors independently using the van der Heijde-modified Total Sharp Score (mTSS) for PsA [range 0–528; higher scores indicate greater erosion and/or joint space narrowing (JSN)]⁶; this method is based on the version designed for use in RA, which in addition to evaluating the joints in RA, also assesses the distal interphalangeal joints⁶. The scores of the assessors were averaged for analysis purposes. An independent central and blinded adjudicator provided a third scoring if the difference in the change scores from the 2 primary readers was greater than a predefined margin of 5 points in mTSS; if adjudication was required, the 2 closest change scores among the 3 change scores (2 assessors and 1 independent adjudicator) were used to provide an average score.

Radiographic nonprogression was evaluated posthoc and was predefined as a ≤ 0.5 increase from baseline in mTSS. Additional definitions of nonprogression were assessed posthoc and included an increase from baseline in mTSS of ≤ 0 , and an increase from baseline in mTSS of ≤ 0.66 [the smallest detectable change (SDC) derived from this trial]¹⁶.

Statistical analyses. Full details of the study's statistical plan, including determination of sample size and analysis of the co-primary and key secondary endpoints, have been previously described⁹.

The study was designed to demonstrate the superiority of tofacitinib over placebo in terms of the co-primary endpoints. ADA was used as an active control; the study was not designed or powered to evaluate the noninferiority or superiority of tofacitinib versus ADA, and consequently, unless prespecified, no hypothesis testing was conducted.

Efficacy analyses, including radiographic assessments, and safety analyses were conducted by group using data from all randomized patients who received at least 1 dose of the study drug (full analysis set).

Least squares mean (LSM) changes from baseline in mTSS, erosion, and JSN were produced through an analysis of covariance model, with fixed effects of treatment, geographic location, and baseline values as covariates, and were reported for all patients with measurements. In addition, changes from baseline in mTSS, erosion, and JSN were reported for patients grouped by baseline CRP > 2.87 mg/l or ≤ 2.87 mg/l (measured with a high sensitivity assay), with baseline CRP and its interaction with treatment as additional covariates. This CRP cutoff was chosen because it equates to the upper limit of normal for CRP. LSM changes from baseline in CRP were based on a repeated measures model with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location, and baseline value, using an unstructured covariance matrix without imputation for missing values.

The effects of known baseline risk factors for radiographic progression in PsA, including presence of elevated CRP, swollen joints, dactylitis, PsA

duration, and level of disease activity, were evaluated^{10,12,13,14}. Change from baseline in mTSS and proportion of patients with an increase from baseline mTSS > 0.5 at Month 12 were analyzed using multiple linear and logistic regression, respectively, with the fixed effects baseline CRP, Disease Activity Index for Psoriatic Arthritis, swollen joint counts, dactylitis severity score, Leeds Enthesitis Index, mTSS, and PsA duration. Treatment sequence was used as a classification covariate. Regression coefficient and OR (for logistic regression), and 2-sided 95% CI and p values were calculated. In all the analyses, missing values for mTSS endpoints were imputed by linear extrapolation.

RESULTS

Patients. Of 422 patients who were randomized in OPAL Broaden, all received study treatments, and 373 completed the study⁹. In total, 105 patients were randomized to placebo and switched to tofacitinib at Month 3; in line with the objective of this analysis to focus on patients originally randomized to tofacitinib 5 mg BID, tofacitinib 10 mg BID, or ADA, data for these 105 patients are not included in this analysis.

Of patients randomized to tofacitinib 5 mg BID, tofacitinib 10 mg BID, or ADA at baseline, 98, 99, and 95 patients, respectively, were evaluable for change in mTSS at Month 12. In total, 282/292 (96.6%; n = 95, 95, and 92, respectively) had complete radiographic data at baseline and Month 12, with no imputed data. Reasons for patients not having complete radiographic data included withdrawal of patient consent after discontinuation, radiographic data obtained outside the scheduled time period, quality of radiographs, lack of repeat radiographs, and protocol deviations.

Patient baseline demographic and disease characteristics were generally similar between treatment groups (Table 1), although there were some differences between groups at baseline⁹.

Change in CRP at Month 12. Mean changes from baseline in CRP levels with tofacitinib 5 mg BID, tofacitinib 10 mg BID, and ADA are shown in Figure 1. Similar reductions in CRP levels from baseline were observed with tofacitinib 5 and 10 mg BID and ADA at Month 12, with a slower onset in the tofacitinib 5 mg BID group compared with the other groups.

Structural change and nonprogression at Month 12. Mean changes from baseline at Month 12 in mTSS, erosion, and JSN scores were close to 0 (Table 2). At Month 12, 95.9%, 94.9%, and 97.9% of patients receiving tofacitinib 5 mg BID, tofacitinib 10 mg BID, and ADA, respectively, were nonprogressors based on change in mTSS \leq 0.5 and \leq 0.66 (SDC), and 90.8%, 92.9%, and 95.8% of patients were nonprogressors based on change in mTSS \leq 0.0 (Table 2 and Figure 2).

Structural changes at Month 12 according to baseline risk factors. Change from baseline at Month 12 in mTSS and components (erosion and JSN scores), and the proportion of patients with radiographic progression (> 0.5 increase from baseline in mTSS) at Month 12, were similar in patients with baseline CRP levels > 2.87 mg/l or \leq 2.87 mg/l for tofacitinib 10 mg BID and ADA (Figures 3A and 3B). Change from baseline in mTSS and erosion at Month 12 (Figure 3A) and

Table 1. Summary of patient demographics and baseline disease characteristics.

Variables	Tofacitinib 5 mg BID, n = 107	Tofacitinib 10 mg BID, n = 104	ADA 40 mg SC Q2W, n = 106
Age, yrs, mean (SD)	49.4 (12.6)	46.9 (12.4)	47.4 (11.3)
Female, n (%)	57 (53.3)	62 (59.6)	50 (47.2)
White, n (%)	105 (98.1)	97 (93.3)	103 (97.2)
BMI, kg/m ² , mean (SD)	29.0 (5.2)	29.3 (5.5)	28.8 (5.3)
Duration of PsA, yrs, mean (SD)	7.3 (8.2)	5.4 (5.8)	5.3 (5.3)
DAPSA, mean (SD)	45.6 (20.3)	43.7 (19.5)	38.5 (18.2)
Swollen joint count, 66 joints assessed, mean (SD)	12.9 (9.9)	11.7 (7.7)	9.8 (7.9)
Tender/painful joint count, 68 joints assessed, mean (SD)	20.5 (12.6)	20.3 (12.9)	17.1 (11.2)
HAQ-DI score, mean (SD)	1.2 (0.6)	1.1 (0.6)	1.1 (0.6)
Presence of dactylitis, DSS > 0, n (%)	61 (57.0)	60 (57.7)	58 (54.7)
Elevated CRP, n (%) [*]	68 (63.6)	66 (63.5)	64 (60.4)
CRP, mg/l, mean (SD)	10.5 (18.4)	8.1 (11.2)	14.3 (24.7)
CRP, %			
\leq 2.87 mg/l	36.4	36.5	39.6
> 2.87 to \leq 10 mg/l	38.3	38.5	26.4
> 10 mg/l	25.2	25.0	34.0
mTSS > 0, n (%)	96 (89.7)	96 (92.3)	99 (93.4)
mTSS, mean (SD) [#]	17.1 (28.6)	10.4 (18.4)	14.4 (39.2)
Erosion > 0, n (%)	96 (89.7)	96 (92.3)	99 (93.4)
Erosion, mean (SD) [#]	10.8 (16.3)	6.9 (10.5)	9.2 (23.2)
JSN > 0, n (%)	51 (47.7)	39 (37.5)	38 (35.8)
JSN, mean (SD) [#]	11.8 (17.0)	8.6 (11.5)	13.7 (24.3)

* Defined as > 2.87 mg/l (upper limit of normal). # Among patients with baseline score > 0. ADA: adalimumab; BID: twice daily; BMI: body mass index; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DSS: dactylitis severity score; HAQ-DI: Health Assessment Questionnaire–Disability Index; JSN: joint space narrowing; mTSS: modified Total Sharp Score; PsA: psoriatic arthritis; Q2W: once every 2 weeks; SC: subcutaneous.

the proportion of patients with radiographic progression (> 0.5 increase from baseline in mTSS; Figure 3B) at Month 12 were numerically higher in patients with baseline CRP levels > 2.87 mg/l treated with tofacitinib 5 mg BID than in patients with baseline CRP \leq 2.87 mg/l.

Cumulative probability of change from baseline in mTSS to Month 12 by baseline CRP level (\leq 2.87 vs > 2.87 mg/l) is shown in Figure 3C.

Results of the linear and logistic regression analysis of the effects of baseline risk factors on change in mTSS score, and the proportion of patients with > 0.5 increase from baseline in mTSS, respectively, at Month 12 are shown in Table 3. In the linear regression analysis, no significant relationship ($p > 0.05$) was observed between any risk factor at baseline and change in mTSS score at Month 12. In the logistic regression analysis of the proportion of patients with > 0.5 increase in mTSS from baseline, a significant relationship ($p \leq 0.05$) was observed between baseline CRP level and

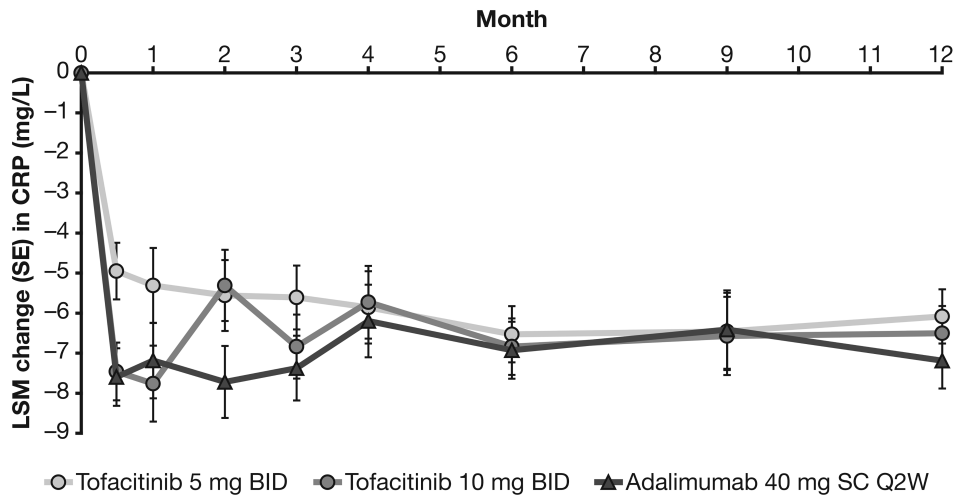


Figure 1. LSM change from baseline in CRP levels through Month 12 (FAS). Results are based on a repeated measures model with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location, and baseline value, using an unstructured covariance matrix. No imputation for missing values. BID: twice daily; FAS: full analysis set; CRP: C-reactive protein; LSM: least squares mean; Q2W: once every 2 weeks; SC: subcutaneous; SE: standard error.

Table 2. Structural changes at Month 12.*

Variables	Tofacitinib 5 mg BID, N = 98	Tofacitinib 10 mg BID, N = 99	ADA 40 mg SC Q2W, N = 95
mTSS nonprogression (change ≤ 0.5), n (%)	94 (95.9)	94 (94.9)	93 (97.9)
mTSS nonprogression (change ≤ 0), n (%)	89 (90.8)	92 (92.9)	91 (95.8)
mTSS nonprogression (SDC, change ≤ 0.66), n (%)	94 (95.9)	94 (94.9)	93 (97.9)
LSM change from BL mTSS (SE)	0.01 (0.067)	-0.01 (0.067)	-0.07 (0.069)
LSM change from BL erosion score (SE)	0.02 (0.059)	-0.00 (0.059)	-0.06 (0.062)
LSM change from BL JSN score (SE)	-0.01 (0.021)	-0.01 (0.021)	-0.01 (0.021)

* Linear extrapolation applied at Month 12. No. patients with imputed values at Month 12 by linear extrapolation: tofacitinib 5 mg BID (n = 3); tofacitinib 10 mg BID (n = 4); adalimumab (n = 3). LSM were based on an ANCOVA model. ADA: adalimumab; BID: twice daily; BL: baseline; JSN: joint space narrowing; LSM: least squares mean; mTSS: modified Total Sharp Score; N: no. patients with data available at Month 12 after linear extrapolation; n: no. patients with nonprogression; Q2W: once every 2 weeks; SC: subcutaneous; SDC: smallest detectable change; SE: standard error.

increases from baseline in mTSS > 0.5 at Month 12, but not for other baseline risk factors ($p > 0.05$).

DISCUSSION

The objective of this posthoc analysis was to examine the rates of radiographic progression according to baseline CRP levels and other risk factors in patients with PsA treated with tofacitinib or ADA in OPAL Broaden. Understanding which patients may be at increased risk for radiographic progression is important for achieving treatment goals to minimize structural damage. Risk factors for radiographic progression in patients with PsA have been identified and include elevated CRP, number of tender and swollen joints, longer disease duration, and a greater current level of damage^{10,11,12,13,14}.

Radiographic assessments in OPAL Broaden were

included at baseline and Month 12 to assess radiographic progression at Month 12. Minimal mean changes from baseline in mTSS erosion score and JSN at Month 12 were observed for tofacitinib- and ADA -treated patients. Across the treatment groups, $> 90\%$ of patients were nonprogressors based on several cutoffs, including change from baseline in mTSS ≤ 0.5 , ≤ 0.66 (SDC), and ≤ 0.0 at Month 12. Tofacitinib did not differ in a numerical sense from ADA in its effect on radiographic outcomes.

Analysis of structural progression by baseline CRP levels and the regression analysis suggest that elevated CRP at baseline was associated with greater structural progression in the OPAL Broaden study population. This observation is consistent with a previous study in which elevated baseline CRP was shown to be a strong independent predictor of

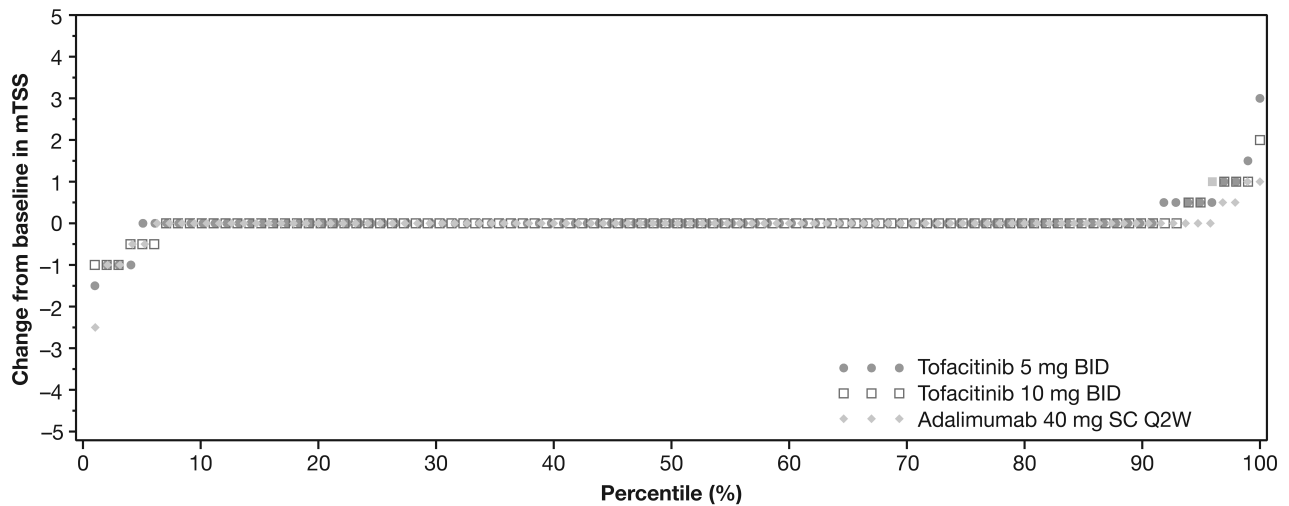


Figure 2. Cumulative probability of change from baseline in mTSS at Month 12⁹. mTSS reported for evaluable patients in the FAS. Missing values imputed by linear extrapolation. From Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017;377:1537-50. Copyright 2017. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. BID: twice daily; FAS: full analysis set; mTSS: modified Total Sharp Score; Q2W: once every 2 weeks; SC: subcutaneous.

radiographic progression in patients with PsA who were treated with ADA¹⁰. No other baseline risk factor evaluated was associated with structural progression; however, certain risk factors known to be associated with structural progression were not present for all patients at baseline, and therefore it was not feasible to analyze these. Overall, minimal radiographic progression was observed in tofacitinib- or ADA-treated patients regardless of baseline CRP level. There was no difference observed for patients with baseline CRP > 2.87 mg/l and ≤ 2.87 mg/l in mean change from baseline in mTSS, or in the proportion of patients with progression (mTSS increase > 0.5 from baseline) for tofacitinib 10 mg BID or ADA; however, a numerical difference was observed for tofacitinib 5 mg BID.

In OPAL Broaden, no specific inclusion criteria were included to enroll a PsA patient population at high risk of structural progression. Despite this, most patients in OPAL Broaden were likely to be at some risk of structural progression based upon baseline characteristics previously described^{10,11}. This included about 90% of patients with baseline mTSS and erosion scores > 0, and > 60% of patients with elevated CRP (exceeding the upper limit of normal of 2.87 mg/l). The magnitude of several risk factors at baseline, including mean CRP values, mTSS, erosion, and JSN scores was, however, generally lower in the OPAL Broaden patient population relative to other published randomized controlled trials that were designed to demonstrate superiority of active treatment relative to placebo, and in which structural progression was evaluated^{17,18,19,20,21,22}.

CRP, which is an acute-phase protein, reflects the systemic inflammation state and is believed to correlate with joint destruction in PsA²³. Here, we show that tofacitinib and ADA substantially reduce mean levels of CRP in patients with PsA.

The identification of a significant relationship between baseline CRP levels and structural progression in patients with PsA who were treated with tofacitinib or ADA suggests an important role for CRP and inflammation in radiographic progression. Of note, the onset of CRP reduction was slower with tofacitinib 5 mg BID than tofacitinib 10 mg BID or ADA, and in this treatment group a numerical difference was observed in radiographic progression between patients with baseline CRP > 2.87 mg/l and ≤ 2.87 mg/l.

The lack of an association between other baseline risk factors and progressing patients in OPAL Broaden may be due to the low number of progressors in the study, which is a limitation of this analysis. OPAL Broaden was not designed to compare active treatment versus placebo for assessment of radiographic outcomes, and all patients in this posthoc analysis were receiving an active treatment (either tofacitinib or ADA) for the duration of the study. Moreover, it should be noted that new bone formation is a specific component of PsA; however, this phenotype is not assessed by the mTSS method of scoring radiographs; therefore, the effect of tofacitinib or ADA on bone proliferation could not be evaluated in this analysis.

In this analysis of 12-month radiographic progression data from OPAL Broaden in patients with active PsA who had an inadequate response to csDMARD and were treated with tofacitinib or ADA, elevated CRP levels at baseline were shown to be associated with greater structural progression. Treatment with tofacitinib or ADA rapidly reduced the mean concentration of CRP in patients with PsA, although the onset of CRP reduction was slower with tofacitinib 5 mg BID than with tofacitinib 10 mg BID or ADA. Overall, changes in radiographic outcomes were minimal regardless of CRP levels, though a small difference was seen with tofacitinib 5 mg BID.

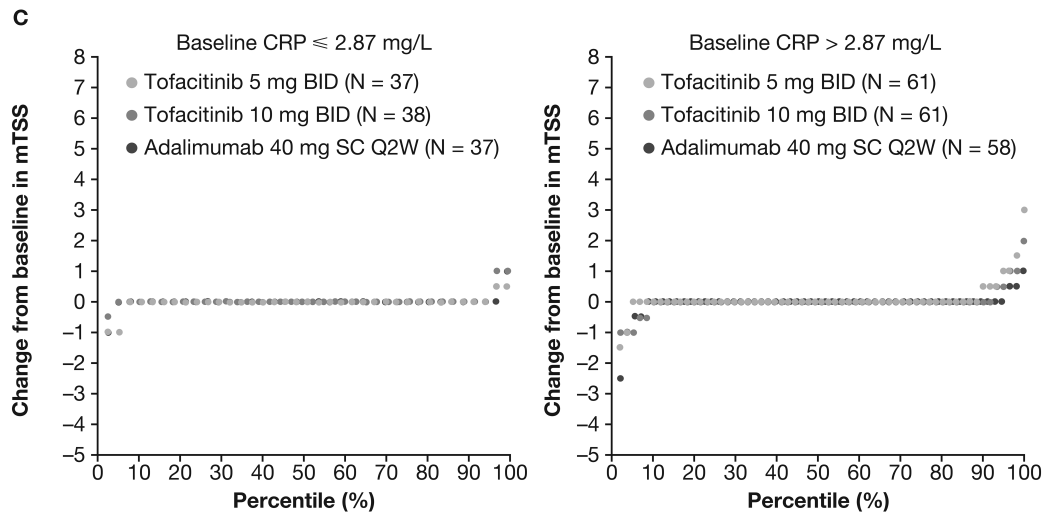
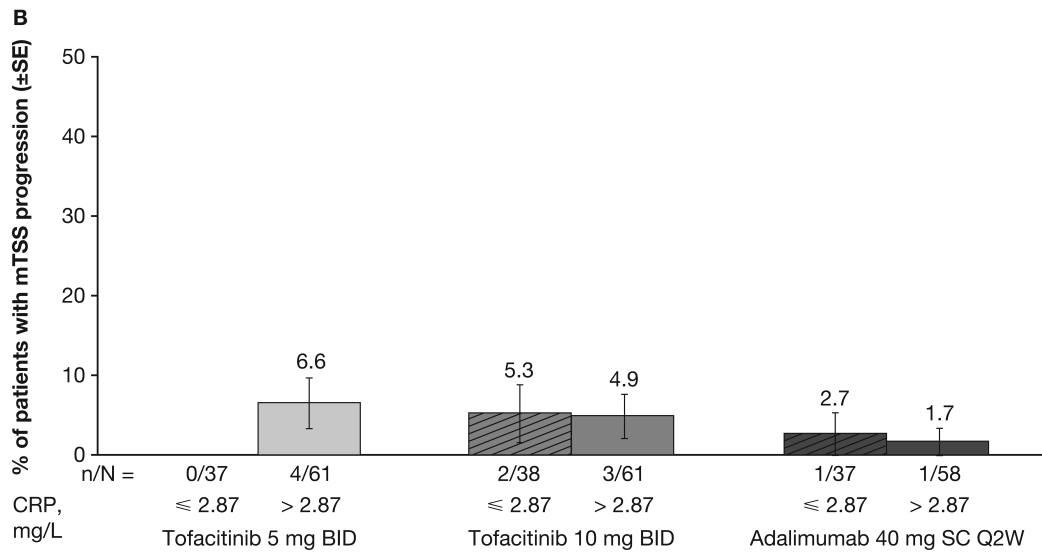
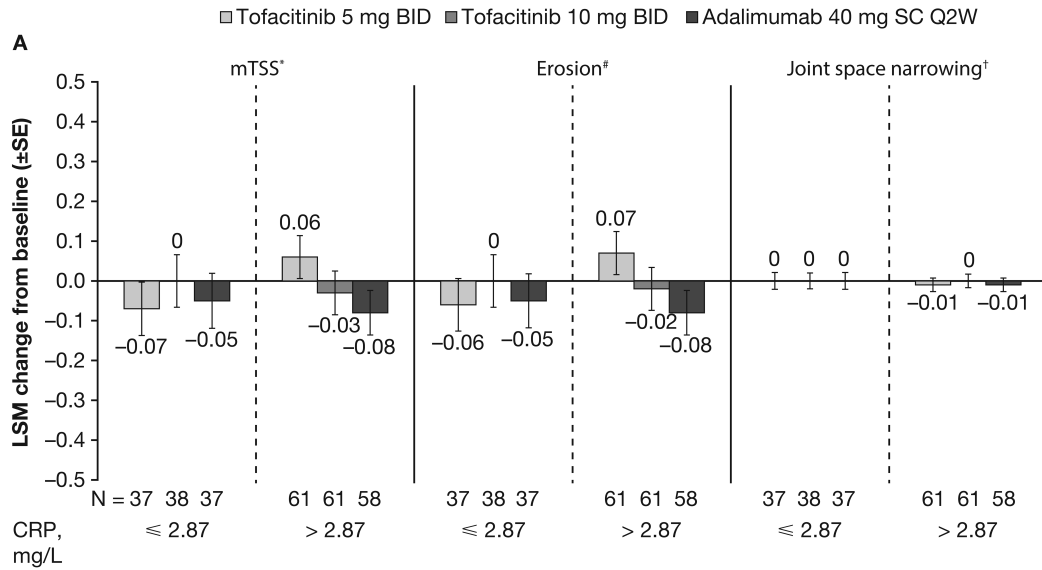


Figure 3. Structural changes (mTSS and components) at Month 12 by baseline CRP (FAS). A. * Score range: 0–528. # Score range: 0–320. † Score range: 0–208. Linear extrapolation applied at Month 12. No. patients with imputed values at Month 12 by linear extrapolation: tofacitinib 5 mg BID, n = 3; tofacitinib 10 mg BID, n = 4; adalimumab, n = 3. LSM were based on an analysis of covariance model. B. Data reported for evaluable patients in the FAS. Missing values imputed by linear extrapolation at Month 12. C. mTSS reported for evaluable patients in the FAS. Missing values imputed by linear extrapolation. BID: twice daily; FAS: full analysis set; CRP: C-reactive protein; LSM: least squares mean; mTSS: modified Total Sharp Score; N: no. patients with data available at Month 12 after linear extrapolation; n: no. patients with progression; Q2W: once every 2 weeks; SC: subcutaneous; SE: standard error.

Table 3. Regression analysis* of change in mTSS from baseline at Month 12 by baseline risk factors.

Baseline Risk Factor	Linear Regression of Change from Baseline		Logistic Regression of Proportion of Patients with > 0.5 Increase from Baseline		
	Regression Coefficient (SE) [95% CI]	p	Regression Coefficient (SE) [95% CI]	OR (95% CI) [#]	p
CRP, mg/l	0.0014 (0.002) [–0.002 to 0.005]	0.411	0.023 (0.01) [0.003–0.042]	1.02 (1.00–1.04)	0.023
DAPSA	–0.0004 (0.003) [–0.006 to 0.005]	0.881	0.014 (0.023) [–0.031 to 0.059]	1.01 (0.97–1.06)	0.548
SJC	0.0081 (0.007) [–0.005 to 0.021]	0.217	0.028 (0.054) [–0.078 to 0.135]	1.03 (0.92–1.14)	0.602
DSS	–0.0090 (0.005) [–0.019 to 0.001]	0.079	–0.067 (0.049) [–0.163 to 0.028]	0.93 (0.85–1.03)	0.165
LEI	0.0108 (0.020) [–0.029 to 0.051]	0.596	–0.089 (0.181) [–0.443 to 0.266]	0.92 (0.64–1.30)	0.624
mTSS	–0.0003 (0.001) [–0.002 to 0.002]	0.767	0.005 (0.005) [–0.004 to 0.015]	1.01 (1.00–1.02)	0.274
PsA duration, yrs	0.0054 (0.005) [–0.004 to 0.015]	0.274	0.019 (0.038) [–0.056 to 0.094]	1.02 (0.95–1.10)	0.617

* The linear or logistic regression analysis included fixed effects of baseline CRP, DAPSA, SJC, DSS, LEI, mTSS, PsA duration, and treatment sequences (tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo switched to tofacitinib 5 mg BID, placebo switched to tofacitinib 10 mg BID, and adalimumab) as covariates. A total of 380 patients were included in each analysis. Missing mTSS was imputed by linear extrapolation. [#] The OR of progression is for 1 unit increase in the baseline risk factor. BID: twice daily; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DSS: dactylitis severity score; LEI: Leeds Enthesitis Index; mTSS: modified Total Sharp Score; PsA: psoriatic arthritis; SE: standard error; SJC: swollen joint count.

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