Baricitinib further enhances disease-modifying effects by uncoupling the link between disease activity and joint structural progression in patients with rheumatoid arthritis

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ABSTRACT

Objectives To evaluate if baricitinib, a Janus kinase inhibitor, further enhances disease-modifying effects by uncoupling the link between disease activity and structural damage progression in patients with rheumatoid arthritis (RA) using two phase III randomised, double-blinded trials.

Methods In RA-BEAM, patients with established RA and inadequate response to methotrexate (MTX-IR) received placebo (PBO), baricitinib 4 mg or adalimumab 40 mg on background MTX. In RA-BEGIN, conventional synthetic disease-modifying antirheumatic drug (csDMARD)-naive patients received MTX, baricitinib 4 mg or baricitinib 4 mg plus MTX. Using linear regression analyses, joint damage progression (assessed by change from baseline in van der Heijde modification of the Total Sharp Score) was compared between treatment groups for patients achieving certain disease activity states by the Clinical Disease Activity Index. Time-averaged postbaseline responses were used to week 24 (RA-BEAM) and week 52 (RA-BEGIN).

Results For MTX-IR patients, structural damage progression was reduced regardless of disease activity states in baricitinib-treated patients (p=0.6), whereas in PBO patients there was a clear dependence on disease activity states, being significantly lower in those who achieved remission/low disease activity (REM/LDA) compared with moderate/high disease activity (MDA/HDA) (p=0.02). Furthermore, the baricitinib MDA/HDA group had less damage progression than the PBO MDA/HDA group (p<0.001). For csDMARD-naive patients, progression was lower in REM/LDA versus MDA/HDA within the MTX group (p<0.001). However, for baricitinib+MTX (p=0.5) or baricitinib monotherapy (p=0.07), progression was similar regardless of disease activity. In MDA/HDA groups, progression was lower with baricitinib+MTX (p<0.001) and numerically lower with baricitinib monotherapy (p=0.07) versus MTX. C reactive protein (≤5 mg/L and >5 mg/L) sensitivity analyses supported the primary findings.

Conclusions Baricitinib reduces structural damage progression versus PBO with background MTX and/or MTX, even in patients with MDA/HDA, showing a disease-modifying effect across all disease activity states.

INTRODUCTION

The high propensity to destroy cartilage and bone constitutes a major hallmark of rheumatoid arthritis (RA). While it appears that over the last two decades progression rates of joint damage have declined, patients with established disease entering clinical trials still have high baseline radiographic scores, implying aggressively damaging RA. Indeed, joint damage shows a significant positive association with both swollen joint counts and acute phase reactant levels. Joint swelling or synovitis characterises the local and acute phase reactants reflect the systemic inflammatory response, which usually go
**Key messages**

How might this impact on clinical practice or future developments?

- The uncoupling of disease activity and structural damage progression by baricitinib, a Janus kinase inhibitor, provides evidence which was not previously available for this mechanism of action.
- Preservation of structural progression regardless of disease activity might ensure medium-term to long-term prevention of disability in patients who cannot achieve REM/LDA or require more time to reach this target.
- This may inform treatment decisions in patient groups who have not, or have not yet, achieved sufficient clinical improvement.

hand in hand, but joint swelling is more strongly associated with progression of joint damage than the acute phase response. Effective treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) reduces the rate of structural progression and ultimately halts joint structural damage accrual once stringent remission is achieved and sustained afterwards. However, while joint damage progression is reduced on csDMARDs, structural deterioration still continues to occur in correlation with residual disease activity.

Several years ago, it was observed that the strong relationship between the extent of structural changes and inflammatory disease activity was blunted with infliximab use, a tumour necrosis factor (TNF) inhibitor. In contrast to patients with rheumatoid arthritis, activity was blunted with infliximab use, a tumour necrosis factor inhibitor. Studies have shown that the use of infliximab reduces the rate of structural progression and halts joint structural damage accrual once stringent remission is achieved and sustained. However, while joint damage progression is reduced on csDMARDs, structural deterioration still continues to occur in correlation with residual disease activity.

The uncoupling of disease activity and structural damage progression might be explained by a threshold effect: activation of osteoclasts, which induce bone erosions, requires higher TNF concentrations than induction of the inflammatory response. Therefore, when this cytokine is blocked to a level that still allows an unmitigated perpetuation of the inflammatory response, this reduction may still suffice to not allow continued activation of osteoclasts, a major mediator of joint destruction.

Interestingly, this interference with structural progression despite high disease activity is not confined to TNF inhibitors, but was also found for interleukin 6 (IL-6) inhibition and rituximab, usually combined with MTX. This suggests that biological (b)DMARDs reduce the inflammatory load of cytokines like TNF and IL-6 to a much larger extent than csDMARDs alone and thus downregulate the amplifying activity of these messenger molecules on osteoclastogenesis.

Janus kinase (JAK) inhibitors (Jakinibs) belong to the most recent class of targeted synthetic (ts)DMARDs, which have shown at least similar efficacy as bDMARDs. JAKs are needed for signal transduction of various cytokine receptors, including those for IL-6 and interferons, but not TNF or most B cell receptors. Baricitinib, a Jakinib widely approved for treating RA, is a JAK1 and JAK2 inhibitor which has shown efficacy across RA subsets; this efficacy includes structural damage inhibition. However, knowledge on structural damage reduction beyond the decrease in disease activity is limited. Indeed, when patients with poor prognostic factors were assessed for joint damage progression, another Jakinib, tofacitinib, failed to show a significant reduction compared with bDMARD.

This question is the focus of research addressed in the present study.

**METHODS**

**Study design**

In the 52-week RA-BEAM trial, adult patients with active RA (≥6/68 tender joints, ≥6/66 swollen joints and a high-sensitivity serum C reactive protein (hsCRP) ≥6 mg/L) and no previous bDMARD therapy were included. Patients had either ≥3 joint erosions or ≥1 joint erosions plus seropositivity for rheumatoid factor or anticitrullinated peptide antibodies (ACPA). Patients had an inadequate response to MTX (MTX-IR) and received background MTX throughout the study. Randomisation was 3:3:2 to placebo (PBO) (n=488), baricitinib 4 mg (n=487) and adalimumab 40 mg (n=330).

In RA-BEGIN, adult patients with active RA who had received no/limited treatment with csDMARDs (up to 3 weekly doses of MTX allowed) and no treatment with bDMARDs were included. Patients had ≥6/68 tender joints and ≥6/66 swollen joints and serum hsCRP level ≥3.6 mg/L and were seropositive for rheumatoid factor or ACPA. Randomisation was 4:3:4 to MTX (n=210), baricitinib 4 mg (n=159) and baricitinib 4 mg plus MTX (n=215) for 52 weeks.

**Outcome measures**

Joint damage progression was assessed using the van der Heijde modification of the Total Sharp Score (mTSS). Two independent readers, who were unaware of the chronological order, patient identity and treatment group, scored the radiographs and the mean score between the readers was used.

Disease activity was assessed by the Clinical Disease Activity Index (CDAI), stratified by the states of remission/low disease activity (REM/LDA; CDAI ≤10) and moderate/high disease activity (MDA/HDA; CDAI >10). Systemic inflammation was assessed by hsCRP stratified at ≤5 mg/L and >5 mg/L.

**Analyses populations**

In RA-BEAM, analyses were performed for endpoints at week 24 to allow comparison with the PBO group; at week 24 all patients randomised to PBO were switched to baricitinib 4 mg and therefore analyses at week 52 were not done. Analyses in RA-BEGIN were done for endpoints at week 52 because in this study patients who were randomised to MTX were followed up until week 52, unless they were rescued or discontinued from the study, and thus baricitinib could be appropriately compared with this control population in the longer term.

Only completers of the relevant study endpoint were included, excluding patients who switched treatment, were rescued or lost to follow-up before the time point defined for analysis. In RA-BEAM, 329, 427 and 273 patients in the PBO, baricitinib and adalimumab groups, respectively, were defined as completers. Patients with missing structural data and/or missing data on the covariates used in the models were also excluded from the analysis. Thus, 318, 407 and 262 patients, respectively, were included in the CDAI analysis in RA-BEAM. In RA-BEGIN, 142, 129 and 170 patients in the MTX, baricitinib monotherapy and baricitinib+MTX groups, respectively, were defined as completers. After excluding patients with missing data, 134, 125 and 166 patients, respectively, in these groups were included in the CDAI analysis.

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Statistical analysis
Analyses of change from baseline in mTSS in RA-BEAM and RA-BEGIN have been done stratifying by treatment and by postbaseline CDAI response at week 24 and week 52, respectively. Adjusted means for the mTSS change from baseline were estimated using linear regression models adjusted by baseline CDAI. Adjusted means for change from baseline in mTSS responses are displayed as effects plots. The adjusted means were estimated from the multivariable models, with continuous covariates fixed at their mean values and categorical covariates fixed at their proportional distribution in the data. As sensitivity analyses, similar analyses of change from baseline in mTSS were done stratifying by hsCRP. Adjusted means for the mTSS change from baseline, stratified by treatment and by postbaseline hsCRP response at week 24 in RA-BEAM and week 52 in RA-BEGIN, were estimated using linear regression models adjusted by baseline hsCRP. Change from baseline in CDAI at week 24 in RA-BEAM and week 52 in RA-BEGIN in patients with postbaseline CDAI >10 was estimated using linear regression analyses (observed values). Similar analyses were undertaken for hsCRP in patients with elevated postbaseline hsCRP. For both CDAI and hsCRP postbaseline responses, individual time point responses were averaged until the end of the period of analysis (week 24 or week 52) to define the response at the specific time point of analysis. This analytical process tends to diminish the potential influence of extreme values, especially for hsCRP, and also reduces the number of patients with missing data at individual endpoint visits. The definition of disease activity and hsCRP response using a time-averaged CDAI and hsCRP has been used previously.16

RESULTS
Baseline demographics and patient characteristics
Baseline demographics and patient characteristics have been published previously.24 25 Summaries of these data for the analyses populations are presented in table 1 (CDAI response analyses) and table 2 (hsCRP sensitivity analyses). The characteristics of the different patient populations at baseline were mostly similar. However, reflective of the different patient populations in the two trials, patients in RA-BEGIN (early RA naïve to csDMARDs) had a shorter disease duration and had lower mTSS scores than patients in RA-BEAM (established RA and MTX-IR).

Treatment response in relation to disease activity
In RA-BEAM, 19.2% (n=61), 37.4% (n=98) and 42.0% (n=171) of patients in the analysed population who received PBO, adalimumab and baricitinib, respectively, achieved REM/LDA. Heatmap plots show individual CDAI longitudinal responses at all postbaseline visits for all patients included in the analyses (figure 1), differentiating REM/LDA and MDA/HDA CDAI responses at week 24. In RA-BEGIN, at week 52, the proportion of patients in REM/LDA was 39.6% (n=53), 57.6% (n=72) and 62.7% (n=104), respectively, in the MTX, baricitinib monotherapy and baricitinib+MTX groups. Figure 2 displays the heatmap plots showing individual responses to treatment over time for patients stratified by CDAI responses at week 52.

Structural damage progression in relation to disease activity in RA-BEGIN (csDMARD-naïve patients with early RA)
Among patients who achieved REM/LDA, the adjusted means for mTSS change from baseline to week 52 were 0.31, 0.15 and 0.24, respectively, compared with 0.84, 0.28 and 0.34, respectively, among patients in these groups with MDA/HDA (figure 3A). Thus, in the PBO group, patients achieving REM/LDA had less structural damage progression than patients with MDA/HDA (adjusted mean difference (95% CI): −0.53 (−0.98 to −0.09), p=0.02). In contrast, there was no significant difference in structural damage progression depending on disease activity states within patients receiving baricitinib (−0.09 (−0.41 to 0.22), p=0.6) or adalimumab (−0.13 (−0.53 to 0.26), p=0.5). Given that those with MDA/HDA did not have greater progression than those with REM/LDA, this reveals an uncoupling of disease activity and structural damage progression with baricitinib treatment.

Among patients with MDA/HDA, the adjusted mean difference (95% CI) for adalimumab compared with PBO was −0.56 (−0.87 to −0.25, p<0.001), in line with previous findings on the dissociative capacity of TNF inhibition on the link between disease activity and joint damage progression. The adjusted mean difference for baricitinib versus PBO was −0.50 (−0.78 to −0.23, p<0.001), indicating that, among those with MDA/HDA, there was significantly less structural damage progression in patients receiving baricitinib. This further suggests an uncoupling of disease activity and structural damage progression with baricitinib, which did not occur with PBO. There was no difference in structural damage progression between patients in the baricitinib and adalimumab groups (0.06 (−0.26 to 0.37), p=0.7).

Structural damage progression in relation to disease activity in RA-BEAM (csDMARD-naïve patients with early RA)
Among patients who achieved REM/LDA, the adjusted means for mTSS change from baseline to week 52 were 0.43, 0.39 and 0.28 in the MTX, baricitinib monotherapy and baricitinib+MTX groups, respectively (figure 3B). Patients in the same treatment groups with MDA/HDA had progressed by 1.69, 1.05 and 0.50, respectively. Thus, patients receiving MTX in REM/LDA had significantly less structural damage progression compared with those with MDA/HDA (−1.26 (−1.95 to −0.57), p<0.001). In contrast, there were no significant differences in progression among patients who received baricitinib+MTX (−0.22 (−0.85 to 0.41), p=0.5) or those who received baricitinib in monotherapy (−0.65 (−1.36 to 0.06), p=0.07), although this difference was numerically larger for baricitinib monotherapy.

The magnitude of differences between the MTX (1.69), baricitinib (1.05) and baricitinib+MTX (0.50) groups among patients with MDA/HDA again reveals an effect of both baricitinib monotherapy and combination therapy on structural damage progression inhibition relative to MTX treatment. Compared with MTX, the adjusted mean difference for baricitinib monotherapy was −0.64 (−1.33 to 0.05, p=0.07) and was −1.19 (−1.85 to −0.53, p<0.001) for baricitinib+MTX.

These results indicate an uncoupling of disease activity and structural damage progression with combination therapy and a similar trend with baricitinib monotherapy, which did not occur with MTX monotherapy.

CDAI changes in patients with residual disease activity
In RA-BEAM, among all patients with a postbaseline averaged CDAI classed as HDA (n=229), more were in the PBO group than in the baricitinib and adalimumab groups (49.3%, 29.7% and 21%, respectively). The CDAI change from baseline to week 24 among patients with MDA/HDA was significantly greater in the baricitinib (−22.78) and adalimumab (−22.30) groups, compared with PBO (−17.26, both p<0.001; online
### Table 1

Demographic and baseline characteristics of patients in RA-BEAM (MTX-IR patients with established RA) and RA-BEGIN (csDMARD-naive patients with early RA) stratified by averaged CDAI

| CDAI ≤10 | CDAI >10 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **RA-BEAM** | **RA-BEGIN** | **RA-BEAM** | **RA-BEGIN** | **RA-BEAM** | **RA-BEGIN** | **RA-BEAM** | **RA-BEGIN** | **RA-BEAM** | **RA-BEGIN** | **RA-BEAM** | **RA-BEGIN** | **RA-BEAM** | **RA-BEGIN** |
| **PBO (n=61)** | **ADA (n=98)** | **PBO (n=257)** | **CSDMARD (n=164)** | **PBO (n=72)** | **ADA (n=104)** | **MTX (n=53)** | **MTX (n=81)** | **PBO (n=72)** | **ADA (n=104)** | **MTX (n=53)** | **MTX (n=81)** | **PBO (n=72)** | **ADA (n=104)** | **MTX (n=53)** | **MTX (n=81)** |
| **Age, years** | 54.6±12.4 | 53.0±11.8 | 52.5±11.5 | 52.7±12.3 | 52.4±12.2 | 50.9±13.7 | 50.3±13.0 | 51.3±13.0 | 51.3±13.0 | 50.9±13.7 | 50.3±13.0 | 51.3±13.0 | 51.3±13.0 | 51.3±13.0 |
| **Female, n (%)** | 49 (80.3) | 34 (71.4) | 134 (78.4) | 202 (78.6) | 121 (84.7) | 99 (81.3) | 149 (71.6) | 161 (74.5) | 105 (73.5) | 92 (74.0) | 102 (75.1) | 103 (74.7) | 94 (74.7) | 95 (74.7) |
| **BMI, kg/m²** | 28.0±6.2 | 26.3±5.6 | 26.1±5.2 | 26.8±6.6 | 26.8±6.6 | 26.7±6.3 | 25.7±6.6 | 26.3±6.3 | 26.3±6.3 | 25.7±6.6 | 26.3±6.3 | 25.7±6.6 | 26.3±6.3 | 25.7±6.6 |
| **Smoker, yes, n (%)** | 8 (13.1) | 18 (18.4) | 50 (52.6) | 39 (22.8) | 18 (18.4) | 50 (52.6) | 18 (18.4) | 50 (52.6) | 18 (18.4) | 50 (52.6) | 18 (18.4) | 50 (52.6) | 18 (18.4) | 50 (52.6) |
| **Duration of RA from diagnosis, years** | 8.4±7.3 | 9.0±6.8 | 7.8±7.4 | 8.0±6.7 | 7.8±7.4 | 8.0±6.7 | 7.8±7.4 | 8.0±6.7 | 7.8±7.4 | 8.0±6.7 | 7.8±7.4 | 8.0±6.7 | 7.8±7.4 | 8.0±6.7 |
| **hsCRP, mg/L** | 13.7±14.5 | 18.6±16.7 | 17.9±17.2 | 25.0±24.6 | 22.0±20.0 | 17.2±14.6 | 19.8±16.3 | 26.6±28.7 | 25.2±22.6 | 24.2±23.5 | 22.0±21.1 | 24.2±23.5 | 22.0±21.1 | 24.2±23.5 |
| **CDAI** | 28.5±10.6 | 33.2±10.6 | 32.4±13.3 | 38.8±12.4 | 34.0±11.4 | 39.0±13.7 | 38.6±13.3 | 35.3±13.1 | 37.9±12.1 | 38.7±12.6 | 35.3±13.1 | 37.9±12.1 | 38.7±12.6 | 35.3±13.1 |
| **HAQ-DI** | 1.2±0.7 | 1.4±0.7 | 1.3±0.7 | 1.6±0.6 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 | 1.7±0.7 |
| **RF-positive* n (%)** | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) | 55 (90.2) |
| **ACPA-positive† n (%)** | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) | 53 (86.9) |
| **Pain assessment** | 48.6±23.2 | 39.0±23.5 | 43.7±24.0 | 37.4±24.0 | 34.7±24.0 | 37.4±24.0 | 34.7±24.0 | 37.4±24.0 | 34.7±24.0 | 37.4±24.0 | 34.7±24.0 | 37.4±24.0 | 34.7±24.0 | 37.4±24.0 |
| **mTSS** | 34.3±31.5 | 38.9±35.7 | 35.3±33.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 | 34.7±35.7 |

Data are mean±SD or n (%).

Averaged CDAI responses in RA-BEAM calculated as the mean of postbaseline measurements at weeks 4, 12, 16, 20 and 24 and in RA-BEGIN as the mean of postbaseline measurements at weeks 4, 12, 16, 20, 24, 32, 40 and 52.

*RF-positive >14 units/mL (ULN).

†ACPA-positive >10 units/mL (ULN).

ACPA, anticyclic citrullinated peptide antibody; ADA, adalimumab; Bari, baricitinib; BMI, body mass index; CDAI, Clinical Disease Activity Index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C reactive protein; mITT, modified intent-to-treat; mTSS, modified Total Sharp Score; MTX-IR, inadequate response to methotrexate; n, number of mITT completers; PBO, placebo; RA, rheumatoid arthritis; RF, rheumatoid factor; ULN, upper limit of normal.
Table 2  Demographic and baseline characteristics of patients in RA- BEAM (MTX- IR patients with established RA) and RA- BEGIN (csDMARD-naïve patients with early RA) stratified by averaged hsCRP

|                  | RA- BEAM  |                  |                  | RA- BEGIN |                  |                  |                  |
|------------------|----------|------------------|------------------|----------|------------------|------------------|------------------|
|                  | hsCRP ≤5 mg/L |                  |                  | hsCRP >5 mg/L |                  |                  |                  |
|                  | PBO (n=63) | Bari 4 mg (n=262) | ADA (n=158) | PBO (n=257) | Bari 4 mg (n=149) | ADA (n=107) |                  |
|                  | hsCRP ≤5 mg/L |                  |                  | hsCRP >5 mg/L |                  |                  |                  |
|                  | MTX (n=56) | Bari 4 mg ± MTX (n=120) | MTX (n=54) | MTX (n=81) |                  |                  |                  |
|                  | Bari 4 mg |                  |                  | Bari 4 mg |                  |                  |                  |
| Age, years       | 52.9±10.6 | 52.3±12.2 | 52.2±12.6 | 52.2±12.2 | 53.2±11.1 | 49.8±12.5 | 51.4±12.5 | 47.7±14.4 | 50.7±14.0 | 47.7±11.4 | 49.5±13.3 |
| Female, n (%)    | 50 (79.4) | 202 (77.1) | 121 (76.6) | 202 (78.6) | 113 (75.8) | 78 (72.9) | 89 (74.2) | 55 (67.9) | 44 (81.5) | 34 (72.3) |
| BMI, kg/m²       | 26.2±5.1 | 25.8±5.2 | 25.3±4.5 | 27.3±6.8 | 29.0±6.5 | 28.1±5.9 | 24.9±4.4 | 26.0±5.9 | 23.1±5.6 | 28.1±7.3 | 27.5±7.2 | 29.0±5.6 |
| Smoker, yes, n (%) | 13 (20.6) | 56 (21.4) | 28 (17.7) | 54 (21.0) | 36 (24.2) | 30 (20.0) | 6 (10.7) | 15 (20.5) | 30 (21.3) | 20 (24.7) | 16 (29.6) | 6 (12.6) |
| Duration of RA from diagnosis, years | 7.6±7.0 | 8.4±8.1 | 6.9±6.6 | 9.2±7.8 | 8.9±9.3 | 10.0±9.3 | 0.8±1.9 | 2.0±4.4 | 1.0±2.1 | 1.2±3.8 | 1.2±2.6 | 2.3±4.1 |
| hsCRP, mg/L      | 6.3±5.9 | 17.9±18.6 | 17.0±16.2 | 20.1±18.3 | 30.1±26.8 | 26.5±21.8 | 14.8±13.9 | 19.2±17.9 | 17.5±18.6 | 27.0±22.0 | 24.6±21.4 | 43.3±39.1 |
| HAQ-DI           | 1.4±0.7 | 1.4±0.7 | 1.5±0.7 | 1.5±0.7 | 1.8±0.7 | 1.7±0.7 | 1.5±0.7 | 1.6±0.8 | 1.5±0.7 | 1.7±0.7 | 1.6±0.7 | 1.9±0.7 |
| RF-positive*     | 57 (90.5) | 238 (90.8) | 144 (91.1) | 238 (92.6) | 134 (91.9) | 99 (92.5) | 56 (100) | 73 (100) | 113 (94.2) | 76 (93.8) | 53 (98.1) | 45 (95.7) |
| ACPA-positive†   | 53 (84.1) | 233 (89.2) | 141 (89.2) | 223 (86.8) | 133 (89.3) | 96 (89.7) | 53 (94.6) | 67 (91.8) | 110 (91.7) | 74 (91.4) | 49 (90.7) | 42 (89.4) |
| Pain assessment  | 55.2±22.1 | 60.0±21.7 | 57.7±22.1 | 58.8±22.1 | 63.6±22.2 | 62.9±24.3 | 60.4±25.0 | 62.0±23.3 | 61.4±23.9 | 67.1±24.2 | 60.9±20.7 | 69.5±15.3 |
| mTSS             | 34.4±43.2 | 40.4±50.1 | 41.4±47.5 | 44.7±50.2 | 40.5±51.6 | 49.5±8.5 | 11.4±24.5 | 10.3±20.1 | 11.4±20.7 | 11.0±14.2 | 12.9±29.9 | 13.2±21.8 |

Data are mean±SD or n (%).
Averaged hsCRP in RA- BEAM calculated as the mean of postbaseline measurements at weeks 4, 12, 16, 20 and 24 and in RA- BEGIN as the mean of postbaseline measurements at weeks 4, 12, 16, 20, 24, 32, 40 and 52.
*RF-positive >14 units/mL (ULN).
†ACP-A-positive >10 units/mL (ULN).
ACPA, anticyclic citrullinated peptide antibody; ADA, adalimumab; Bari, baricitinib; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C reactive protein; mITT, modified intent-to-treat; mTSS, modified Total Sharp Score; MTX-IR, inadequate response to methotrexate; n, number of mITT completers; PBO, placebo; RA, rheumatoid arthritis; RF, rheumatoid factor; ULN, upper limit of normal.
supplemental table 1A). This indicates that even in patients who do not achieve REM/LDA, baricitinib conveys more clinical improvement and radiographic control than PBO, which is evidenced by the dissociation seen in this study (figure 3A).

Similarly, among all patients with HDA (n=40) in RA-BEGIN, more were on de novo MTX (57.5%) than on baricitinib (15.0%) and baricitinib+MTX (27.5%). Interestingly, in contrast to RA-BEAM, among patients classed as having MDA/HDA in RA-BEGIN, the CDAI change from baseline on MTX (−24.8) was not significantly lower than on baricitinib monotherapy (−26.4) or combination therapy (−27.0) (both p>0.05; online supplemental table 1B). Nevertheless, structural progression was higher, suggesting that the capacity of baricitinib to dissociate the tight link between activity and damage goes beyond the mere association with change in disease activity or disease activity states (figure 3B).

Structural damage progression in relation to systemic inflammation

Regarding systemic inflammation, as reflected by hsCRP levels, 80.3% (n=257), 40.4% (n=107) and 36.3% (n=149) of patients receiving PBO, adalimumab and baricitinib, respectively, had a postbaseline averaged hsCRP >5 mg/L up to 24 weeks in RA-BEAM.

The impact of the systemic inflammatory response on structural damage progression within each treatment group differed (figure 4A). Among patients receiving PBO, those with hsCRP >5 mg/L had significantly greater structural damage progression compared with those with hsCRP ≤5 mg/L (0.48 (0.04 to 0.91), p=0.03). However, there were no significant differences among patients receiving baricitinib (0.18 (−0.14 to 0.50), p=0.3) or adalimumab (0.12 (−0.26 to 0.51), p=0.5).

Across treatment groups, among patients with hsCRP >5 mg/L, structural damage progression was lower in those receiving baricitinib compared with PBO (−0.45 (−0.77 to −0.13), p=0.006). Structural damage progression was also lower in patients who received adalimumab versus PBO (−0.55 (−0.90 to −0.20), p<0.01). As in the clinical assessment analyses, there was no essential difference between the baricitinib and adalimumab groups (0.10 (−0.29 to 0.49), p=0.6).

These results indicate that structural damage progression was uncoupled from inflammation in patients receiving baricitinib and show that, even with high systemic inflammation, structural damage progression was inhibited by baricitinib.
In RA-BEGIN, at week 52, 59.1% (n=81), 42.5% (n=54) and 28.1% (n=47) of patients in the MTX, baricitinib and baricitinib+MTX groups, respectively, had hsCRP >5 mg/L. These patients had progressed by 1.51, 1.20 and −0.15, respectively (figure 4B). Structural damage progression was significantly lower in the baricitinib+MTX group compared with the MTX group (−1.66 (−2.36 to –0.95), p<0.001). Damage progression in patients who received baricitinib monotherapy was also numerically lower compared with those who received MTX, but this was not significant (−0.31 (−0.97 to 0.36), p=0.4).

Within treatment groups stratified by acute phase response, structural damage progression was significantly greater in patients with hsCRP >5 mg/L in the MTX (0.73 (0.07 to 1.40), p=0.03) and baricitinib monotherapy (0.89 (0.21 to 1.57), p=0.01) groups, but did not significantly differ in the baricitinib+MTX group (−0.67 (−1.35 to 0.02), p=0.06).

**hsCRP changes in patients with residual inflammation**  
In RA-BEAM, in patients with averaged hsCRP >5 mg/L, the change from baseline in hsCRP was significantly greater in the baricitinib group (−6.61, p<0.001), but not in the adalimumab group (−0.75, p=0.64), compared with PBO (online supplemental table 2A). This might be in line with the direct effect of baricitinib on IL-6 signalling and thus on C reactive protein (CRP). However, the fact that the change of hsCRP on adalimumab was not different from that in PBO again reveals that the dissociation is largely independent of changes of acute phase reactant levels in non-responders, confirmed by the similar inhibitory effect of baricitinib on progression of damage as that of adalimumab (figure 4A). This is further exemplified in RA-BEGIN. The difference in change from baseline in participants with averaged hsCRP >5 mg/L was −1.71 (p=0.35) for baricitinib and −3.94 (p=0.045) for baricitinib+MTX, compared with MTX alone (online supplemental table 2B), although MTX did not inhibit structural damage progression to the same extent as baricitinib, particularly when in combination with MTX (figure 4B).

**DISCUSSION**  
The research presented here originates from observations that in csDMARD-naïve patients with RA, MTX alone might not halt the progression of joint damage if there is ongoing residual disease activity. Early in the disease, as part of the window of opportunity, this is not acceptable, and patients should
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optimise treatments; thus far, tsDMARDs and bDMARDs are approved and recommended options. Later in the disease, in MTX-csDMARD insufficient responders who receive PBO, damage accrual is high, in line with their continued active established disease; in patients who receive either tsDMARDs or bDMARDs (with/without background MTX, but more so with combination therapy), damage could be halted or dramatically reduced even if they continue to have MDA/
HDA. These analyses confirmed this hypothesis for baricitinib.

The results presented reveal that baricitinib, with/without de novo MTX or with background MTX, enhances disease-modifying effects by blunting the tight link that is usually seen between disease activity and progression of joint damage in csDMARD naïve and MTX-IR patients, being more evident when baricitinib is combined with MTX. Thus, baricitinib and baricitinib+MTX exert efficacy in structural terms even in patients who remain in MDA/HDA on this treatment, being significant for baricitinib+MTX. This was also evident when changes from baseline in disease activity were examined in those with residual active disease.

These data are very robust on several grounds. First, they are independent of disease duration and prior treatment. They pertain to patients with early disease who are MTX naïve, as exemplified in the RA-BEGIN trial analyses, and to patients with established disease who had an insufficient response to MTX, as evaluated in RA-BEAM. Second, the analyses are consistent and confirmatory irrespective of the type of inflammatory marker used. When subgroups for the definition of disease activity are formed according to clinical assessment (CDAI), which is primarily driven by joint counts and thus local inflammation, damage progression is not larger in higher versus lower disease activity states on baricitinib+MTX in contrast to control (MTX in RA-BEGIN and PBO with background MTX in RA-BEAM). These data are confirmed when employing CRP, a systemic inflammatory marker induced by proinflammatory cytokines in the liver, to distinguish patients with higher and lower disease activity.

In RA-BEGIN baricitinib monotherapy was also studied. While there was a trend towards better structural efficacy in patients with higher disease activity states also with baricitinib monotherapy compared with MTX monotherapy, this did not reach statistical significance. It should be considered that in early disease if up titration of MTX does not control inflammation, structural progression would be higher than with use of a bDMARD or Jakinib, such as baricitinib, as indicated by mTSS progression over time. However, other studies of bDMARDs and tsDMARDs on csDMARD/MTX naïve patients with early RA have not compared monotherapy, MTX combination therapy and MTX up titration.

One of the strengths of the present study is the use of time-averaged disease activity, for both CDAI and CRI, so that the effects of extreme values and missing data are mitigated. Interestingly, when following disease activity in individual patients over time, in patients in whom REM/LDA is achieved at endpoint, a drop in activity is already discernible within 4–12 weeks, in line with the treat-to-target recommendations and independent of whether patients have established or early RA. In contrast, those who remain in MDA/HDA never achieve any better status.

The visualisation as ‘heatmaps’ allowed us to show these data for individual patients very clearly. Another strength is the use of CDAI for clinical disease activity assessment rather than a single measure. Composite scores capture RA better than individual variables. Because the CDAI does not include an acute phase reactant, we could validate the clinical findings by using a serological marker.

Our study has some limitations. First, we used different time points for analysis of the early csDMARD naïve and established MTX-IR RA populations. While the ideal time frame for comparative assessment of radiographic progression is 1 year, as done in the RA-BEGIN analysis, assessments of RA-BEAM data were restricted to the 24-week time point. However, it was more important to have a valid active comparator, and in RA-BEAM all patients in the PBO group received baricitinib after at most 6 months; analyses at 1 year would then have confounded the value of the data. Interestingly though, significant differences between the groups could already be seen at 6 months, which may even increase the importance of the data. Another limitation is our focus on baricitinib and therefore we cannot be sure that our findings can be translated to other JAKinibs. While it is likely this will be the case, there might be some differences based on the different selectivity of the compounds.

In conclusion, the JAKinib baricitinib has shown to have significant inhibitory effects on the progression of structural joint damage even in patients who continue to have MDA/HDA states. This quality has hitherto been described only for bDMARDs and has important clinical value. Adherence to treat-to-target principles calls for a rapid change of treatment with insufficient improvement. However, when a patient improves clinically on baricitinib but not yet to the desired extent, the decision to change treatment could be delayed for a short while in accordance with the patient because joint damage progression and thus irreversible disability need not be feared.

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Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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REFERENCES

1. Rahman MI, Buchanan J, Doyle MK, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. *Ann Rheum Dis* 2011;70:1631–40.
2. Smolen JS. Treat to target in rheumatology: a historical account on occasion of the 10th anniversary. *Rheum Dis Clin North Am* 2019;45:477–85.
3. van der Heije DM, van Riel PL, van Leeuwen MA, et al. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. *Ann Rheum Dis* 2010;69:2107–13.
4. Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the disease activity score in 28 joints and is driven by residual swollen joints. *Arthritis Rheum* 2011;63:3702–11.
5. van Leeuwen MA, van der Heije DM, van Rijswijk MH, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. *J Rheumatol* 1994;21:425–9.
6. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Rheum Dis Clin North Am* 1998;1:1571–82.
7. Aletaha D, Alasti F, Smolen JS. Rheumatoid arthritis near remission: clinical rather than laboratory inflammation is associated with radiographic progression. *Ann Rheum Dis* 2011;70:1975–80.
8. van der Heije DM, van Riel PL, Nuijten-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036–8.
9. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. *Lancet* 1999;353:259–66.
10. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide rheumatoid arthritis Investigators group. *Arch Intern Med* 1999;159:2542–50.
11. Aletaha D, Funovits J, Breedveld FC, et al. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. *Arthritis Rheum* 2009;60:1242–9.
12. Smolen JS, Han C, Cella M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;52:1020–30.
13. Smolen JS, van der Heijde DMFM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 2009;68:823–7.
14. Landewé R, van der Heijde D, Klarskov L, et al. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results of the trial of etanercept and methotrexate with radiographic and patient outcomes. *Arthritis Rheum* 2006;54:3119–25.
15. Emery P, Genovese MC, van Vollenhoven R, et al. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J Rheumatol* 2009;36:1429–41.
16. Binder NB, Puchner A, Niedereiter B, et al. Tumor necrosis factor-inhibiting therapy preferentially targets bone destruction but not synovial inflammation in a tumor necrosis factor-driven model of rheumatoid arthritis. *Arthritis Rheum* 2013;65:608–17.
17. Smolen JS, Avilia JCM, Aletaha D. Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects; disassociation of the link between inflammation and destruction. *Ann Rheum Dis* 2012;71:687–93.
18. Aletaha D, Alasti F, Smolen JS. Rituximab dissociates the tight link between disease activity and joint damage in rheumatoid arthritis patients. *Ann Rheum Dis* 2013;72:7–12.
19. Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat Rev Drug Discov* 2012;11:234–50.
20. Nash P, Korschbaumer A, Dömer T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2021;80:71–87.
21. O’Shea JI, Schwartz DM, Villarino AV, et al. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med* 2015;66:311–28.
22. Fleischmann R, Schiff M, van der Heije D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol* 2017;69:506–17.
23. Taylor PC, Keystone EC, van der Heije D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376:652–62.
24. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374:1243–52.
25. Landewé RBM, Connell CA, Bradley JD, et al. Is radiographic progression in modern rheumatoid arthritis trials still a robust outcome? experience from tofacitinib clinical trials. *Arthritis Res Ther* 2016;18:212.
26. van der Heije D, Boers M, Lassere M. Methodological issues in radiographic scoring methods in rheumatoid arthritis. *J Rheumatol* 1999;26:726–30.
27. van der Heije D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 1999;26:743–5.
28. Ten Klooster PM, Versteeg LGA, Oude Voshaar MAH, et al. Radiographic progression can still occur in individual patients with low or moderate disease activity in the current treat-to-target paradigm: real-world data from the Dutch rheumatoid arthritis monitoring (DREAM) registry. *Arthritis Res Ther* 2019;21:237.
29. van der Heije DM, van’t Hof MA, van Riel PL, et al. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. *Ann Rheum Dis* 1992;51:177–81.
30. Goldsmith CH, Boers M, Bombardier C, et al. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. *J Rheumatol* 1993;20:561–5.
31. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.