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Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Achieving pain control in early rheumatoid arthritis with baricitinib monotherapy or in combination with methotrexate versus methotrexate monotherapy

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ABSTRACT

Objectives This post hoc analysis assessed speed, magnitude and maintenance of pain improvement in patients with early rheumatoid arthritis (RA) receiving baricitinib, baricitinib and methotrexate (MTX), or MTX over 1 year. Cumulative pain and quality of life benefits were also assessed.

Methods Randomised, double-blind, phase 3 study RA-BEGIN (NCT01711359) compared baricitinib 4 mg (N=159), baricitinib 4 mg +MTX (N=215) and MTX (N=210) in patients with RA who had no or limited prior disease-modifying antirheumatic drug treatment. Pain was assessed on a 0–100 mm Visual Analogue Scale (VAS). Proportion of patients with ≥30%, ≥50% and ≥70% pain improvement from baseline; ≤20 mm and ≤10 mm on the pain VAS; and time to achieve pain improvement thresholds were assessed over 52 weeks, as were Patient Global Assessment (PtGA) and 36-Item Short Form Health Survey Physical Component Score (SF-36 PCS) outcomes.

Results Baricitinib monotherapy or combination with MTX provides greater (least square mean changes (LSM) from baseline −40 mm and −43 mm, respectively) and more rapid (median 12 and 8 weeks to ≥70% improvement, respectively) pain relief than MTX alone (LSM −31 mm, median 20 weeks to ≥70% improvement) over 52 weeks. Baricitinib, alone or combination, provides 9–10 additional weeks of limited to no pain, similar gain in achievable wellness measured through PtGA, and 5–7 additional weeks with change in SF-36 PCS ≥5 vs MTX over 1 year.

Conclusions Patients treated with baricitinib reported significantly greater and more rapid pain relief, more weeks with limited to no pain, and clinically meaningful improvements in physical health than patients treated with MTX alone over 1 year.

Key messages

What is already known about this subject?
► Patient-reported pain is common in rheumatoid arthritis (RA), even in patients who have achieved effective disease control.
► Baricitinib, an oral selective inhibitor of Janus kinase (JAK)1 and JAK2 indicated for the treatment of moderate to severe active RA, has been shown to provide greater improvements in patient-reported pain severity than methotrexate (MTX) or adalimumab.

What does this study add?
► Patients treated with baricitinib, as monotherapy or in combination with MTX, reported greater pain relief and a more rapid attainment of clinically meaningful thresholds of pain improvement than patients who received MTX monotherapy over 1 year of treatment.
► Baricitinib, as monotherapy or in combination with MTX, provided an additional 9–10 weeks of effectively pain-free life, a similarly increased duration of achievable wellness, and 5–7 additional weeks in which clinically meaningful thresholds in physical health were reached compared with MTX monotherapy over 1 year of treatment.

How might this impact on clinical practice or further developments?
► Baricitinib for the treatment of RA can provide greater improvements in patient-reported pain and quality of life than MTX, a first-line standard-of-care in RA.

chronic inflammation. Structural damage generally begins early in the disease course and progression can lead to reduced functional ability.[1]

Patient-reported pain is common in RA, even in patients who have achieved inflammatory remission as assessed through standard metrics used in clinical practice[2 3];

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with progressive and irreversible joint damage caused by

improvements in disease activity may account for only 40% of the reported improvement in pain.[4] This implies that not all of the pain experienced by patients with RA is solely the result of inflammation, and controlling inflammation does not completely eliminate pain in most patients. Furthermore, this points to a patient-focused challenge of overlooking subjectively reported pain by treating to a disease activity target alone.

RA generally has a substantial impact on a patient's perception of their quality of life (QoL)[5] and pain plays a large role in this. Bodily pain is one of the variables of the 36-Item Short Form Health Survey (SF-36), a validated measure of health-related QoL (HRQoL) in many RA clinical investigations.[6–8] There are several studies that have shown a stronger association of reduction in function with pain than with radiographic damage.[9 10]

Many physicians focus on treating the underlying inflammation in RA but pain control is often reported as the main concern for patients, particularly in the early disease stage.[11 12] It is now understood that, even with effective control of inflammation, pain in RA is due to non-inflammatory mechanisms or dysregulation of pain regulatory pathways (ie, peripheral and central sensitisation).[13–15] Janus kinase (JAK) inhibitors are targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), which are effective in limiting inflammation of RA and may additionally have direct action on non-inflammatory pain mechanisms.[16]

Baricitinib is an oral selective inhibitor of JAK1 and JAK2 indicated for the treatment of moderate to severe active RA in adult patients who do not respond adequately or are intolerant to one or more DMARDs. It can be used as monotherapy or in combination with other conventional synthetic DMARDs (csDMARDs), including methotrexate (MTX). Baricitinib, alone or in combination with MTX, has demonstrated superior efficacy to MTX monotherapy in patients with RA who had no or limited prior DMARD therapy.[17] As well as the effect on inflammation control, baricitinib has been shown to provide greater improvements in pain than MTX or adalimumab.[18–20]

The objective of this study is to comparatively assess the effect size and time to achievement of clinically relevant pain improvement outcomes with baricitinib monotherapy, baricitinib +MTX, and MTX monotherapy and understand the improvement in QoL at the population level by treatment over 1 year. This DMARD-naïve population has the potential to robustly respond to both baricitinib and MTX, facilitating assessment of effect size between these two treatments.

METHODS
Patients and study design
RA-BEGIN (NCT01711359) was a phase 3, 52-week randomised, double-blind active comparator-controlled study investigating the effect of MTX monotherapy, baricitinib monotherapy or the combination of MTX and baricitinib in patients with RA who had no or limited prior DMARD treatment. A detailed description of the study design has been previously published.[17]

Patients were ≥18 years with moderate-to-severely active, adult-onset early RA defined by the ACR/EULAR 2010 criteria,[21] and had no or limited prior treatment with DMARDs or had no more than three prior doses of MTX. Active disease was defined by:≥6/68 tender and ≥6/66 swollen joints, serum high-sensitivity C reactive protein ≥3.6 mg/L (upper limit of normal 3.0 mg/L), and seropositive for rheumatoid factor or anti-citrullinated protein antibody.

Patients in the intention-to-treat population (N=588) were randomised in a ratio of 4:3:4 to receive MTX monotherapy (orally, administered once weekly), baricitinib monotherapy (4 mg administered once daily), or baricitinib and MTX in combination for 52 weeks. Patients receiving MTX were started at 10 mg/week, which was increased to 20 mg by week 8 if tolerated. In patients for whom a lower dose was indicated/required, an initial dose of 7.5 mg/week was available with a maximum dose of 12.5 mg.

From week 24, rescue treatment of baricitinib plus MTX was available for patients whose tender and swollen joint counts did not improve by≥20% from baseline.

Outcomes
Pain was assessed by the patient's assessment of pain Visual Analogue Scale (VAS; 0–100 mm where 0=no pain and 100=worst possible pain) at weeks 1, 2 and 4, every four weeks out to week 24 and weeks 32, 40 and 52. Clinically meaningful thresholds of remaining pain were selected for analysis in this study. Pain VAS ≤10 mm reflects a threshold of limited pain to no pain and is extrapolated from data by Wells *et al.*[22] The ≤20 mm threshold represents a level of pain at which satisfaction with health is not negatively affected,[22 23] and is referred to in this analysis as 'mild pain'. Patients who meet these thresholds of remaining pain have been shown to have an acceptable level of pain which allows them to function relatively normally.

Patient pain is a component of the physical HRQoL which was assessed by the Physical Component Score (PCS) of the SF-36 at baseline, every four weeks out to week 24, and weeks 32, 40 and 52.

Pain also is a component of the Patient's Global Assessment of Disease Activity (PtGA), which was assessed using a VAS (0–100 mm). Patients were asked to give an overall assessment of how their RA was affecting them, with higher scores indicating poorer status or more active disease.

For each scale, the change from baseline to week 12, week 24 and week 52 was assessed, and the change from baseline through week 52 in the summary scores for the PCS of the SF-36 was calculated

Area under the curve (AUC) analysis of responder curves to week 52 was carried out to determine the cumulative duration of clinically relevant thresholds of

improvement in pain, physical HRQoL, and patient-assessed disease activity achieved by study participants.

Statistical analyses

All analyses were conducted on the modified intention-to-treat populations, which included the data from patients who received ≥1 dose of study drug, regardless of whether they completed the trial. Missing values and data after rescue were imputed with last observation carried forward (LOCF) for all analyses where applicable. P values were nominal as they were not adjusted for multiplicity.

Between-group comparisons were made on the mean change in pain VAS from baseline and the AUC using analysis of covariance. For the comparisons on the proportion of patients achieving pain improvement and remaining pain thresholds at multiple visits, the logistics regression models were applied. Both models adjusted treatment, region, baseline joint erosion status (yes/no), and baseline pain VAS score. The median time needed for patients to achieve pain improvement thresholds were assessed through week 52 using the cumulative incidence estimate with 'competing risks,' which included rescue or discontinuation due to lack of efficacy before reaching the pain improvement threshold. The Cox proportional hazards model with 'competing risks' (proportional subdistribution hazards model) was used to obtain the HR.[24 25]

RESULTS

Patients

A total of 588 adult patients with active RA and no or limited prior DMARD treatment were randomised: 210 received MTX monotherapy, 215 received baricitinib 4 mg plus MTX and 159 received baricitinib 4 mg monotherapy.

Patient characteristics and disease activity at baseline have been previously described in detail.[17] The median duration of RA was 0.2 years across treatment groups and 30%–39% of patients were receiving concomitant corticosteroids. Patients had high disease activity (mean CDAI score of 40 and DAS28-high-sensitivity C reactive protein of 5.9), mean pain of 66 mm on the 100 mm VAS, and reduced physical HRQoL (mean SF-36 PCS of 32) at baseline.

Pain outcomes

A statistically significant improvement in pain from baseline was achieved by patients treated with baricitinib as monotherapy or in combination with MTX as early as week 2 (first measurement) when compared with MTX monotherapy (p<0.001 for both baricitinib treatment groups vs MTX; figure 1). The magnitude of pain improvement with baricitinib observed at week 12 was similar to that at week 52; similar improvement was achieved by both baricitinib monotherapy and baricitinib plus MTX.

As well as a greater change in pain from baseline, a significantly greater number of patients treated with
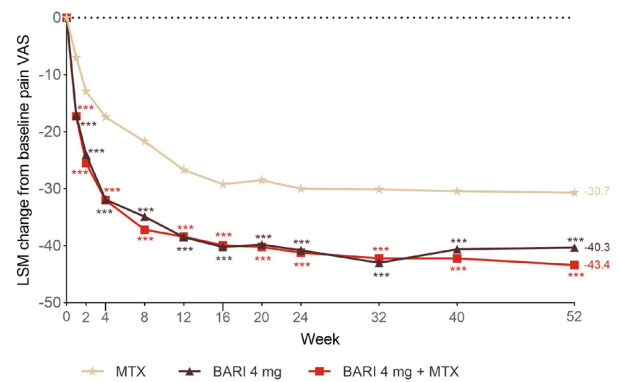

Figure 1 Least squares mean change from baseline in pain VAS over time. ***p<0.001 vs MTX. BARI, baricitinib; LSM, least squares mean; MTX, methotrexate; VAS, Visual Analogue Scale.

baricitinib as monotherapy or in combination with MTX achieved pain improvements that met clinically meaningful thresholds when compared with those who received MTX alone (figure 2A). At week 24, 77.9% (p=0.021 vs MTX) and 80.8% (p<0.001 vs MTX) of patients receiving baricitinib monotherapy and baricitinib plus MTX, respectively, achieved a meaningful improvement[26] of ≥30% in pain from baseline compared with 67.3% of patients receiving MTX monotherapy. A substantial improvement[26] in pain of ≥50% from baseline was seen in 53.5%, 67.7% (p=0.004 vs MTX) and 69.7% (p<0.001 vs MTX) of patients treated with MTX monotherapy, baricitinib monotherapy and baricitinib plus MTX, respectively. Pain relief of ≥70% from baseline was achieved by 32.7%, 50.0% (p<0.001 vs MTX), and 50.5% (p<0.001 vs MTX) of patients treated with MTX monotherapy, baricitinib monotherapy and baricitinib plus MTX, respectively.

The cumulative incidence of patients achieving 30%, 50% and 70% pain improvement are also shown (figure 2B–D, respectively) along with the median time to reach these outcomes (figure 2E). Patients who received either baricitinib monotherapy or baricitinib plus MTX achieved these pain improvement thresholds faster than patients who were treated with MTX monotherapy. The median time to achieve 30% pain improvement was 2 weeks for baricitinib alone and baricitinib plus MTX (p<0.001 vs MTX) compared with 4 weeks for MTX (figure 2E). Median time to achieve 50% pain improvement was 4 weeks for both baricitinib treatment groups (p<0.001 vs MTX) and 12 weeks for MTX monotherapy. Median time to achieve pain improvement of 70% was 8 (p<0.001 vs MTX) and 12 (p<0.001 vs MTX) weeks for baricitinib in combination with MTX and as monotherapy, respectively, and 20 weeks for patients treated with MTX alone.

A larger proportion of patients treated with baricitinib achieved thresholds of remaining pain equivalent to limited pain to no pain (≤10 mm)[22] or mild pain
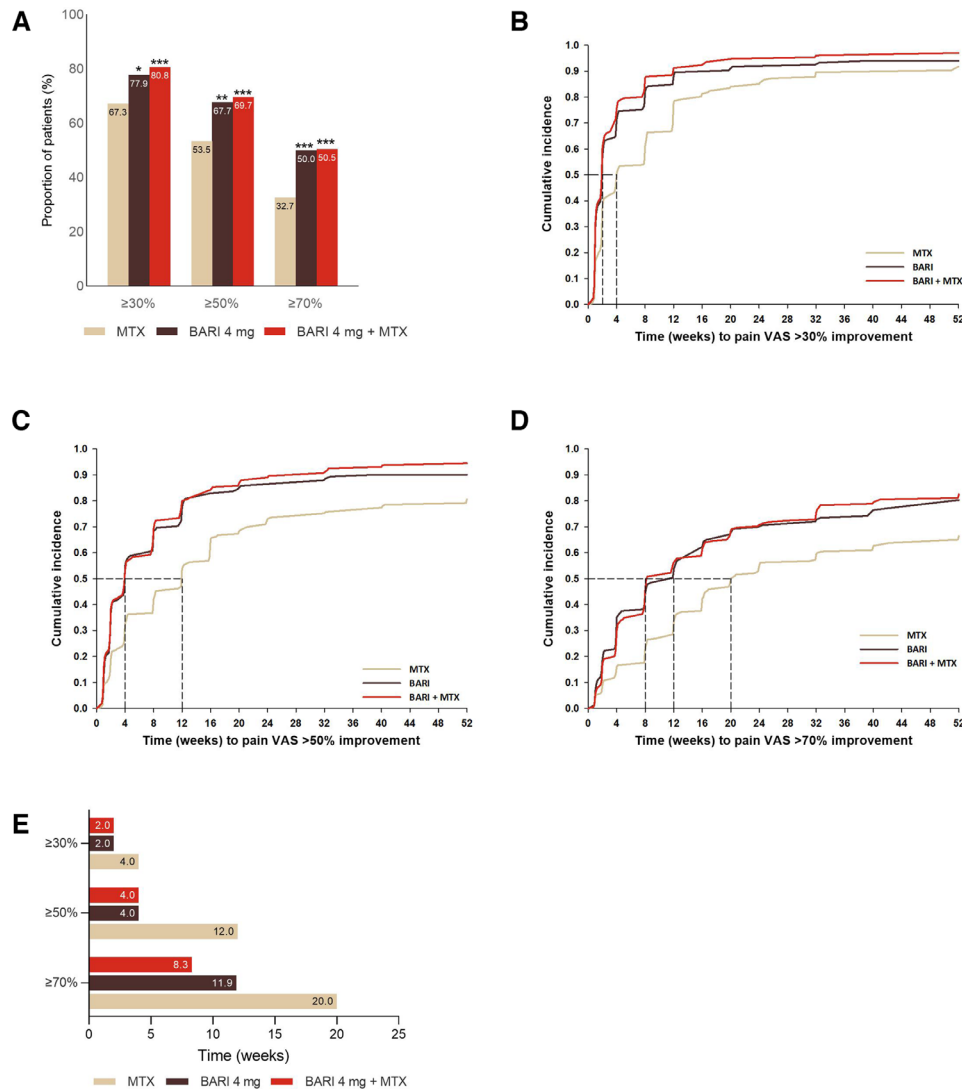
Figure 2 (A) Proportion of patients who achieved thresholds of ≥30%, ≥50% and ≥70% improvement in pain VAS at week 24. (B–D) Time to event analysis depicting the cumulative proportion of patients who achieved ≥30%, ≥50% and ≥70% improvement in pain VAS scores, respectively, over 52 weeks. (E) Median time for patients to achieve ≥30%, ≥50% and ≥70% improvement in pain VAS. *P<0.05, **p<0.01, ***p<0.001 vs MTX. BARI, baricitinib; MTX, methotrexate; VAS, Visual Analogue Scale.

(≤20 mm)[27 28] at week 24 and week 52 (figure 3). By week 52 of the study, more than half of the patients who were treated with baricitinib monotherapy (56.6%, p=0.001 vs MTX) or baricitinib plus MTX (58.9%, p<0.001 vs MTX) achieved pain VAS scores of ≤20 mm compared with 38.8% of patients who received MTX monotherapy. A pain VAS score of ≤10 mm was achieved by 40.9% (p<0.001 vs MTX) and 42.1% (p<0.001 vs MTX) of patients treated with baricitinib monotherapy and baricitinib plus MTX, respectively, at week 52 compared with 23.0% of patients treated with MTX alone.

Cumulative assessment of patient-reported outcomes

The proportion of patients who reached the ≤10 mm (limited pain to no pain) and ≤20 mm (mild pain) remaining pain thresholds over the duration of the 52-week study is shown in figure 4A,C. A higher proportion of patients who were treated with baricitinib alone or in combination with MTX achieved these meaningful improvements in pain when compared with patients who were treated with MTX monotherapy. To determine the cumulative effects of treatment on pain relief throughout the study duration, the area under the pain response curve was calculated to represent the average number of weeks the study population spent below these pain thresholds. By analysing the AUC, it was determined that patients treated with baricitinib monotherapy or baricitinib plus MTX had more cumulative time spent with pain scores below these clinically meaningful thresholds of ≤10 mm (8.9 additional weeks vs MTX over the 52-week treatment period, p<0.001, and 9.8 additional weeks vs MTX, p<0.001, respectively; figure 4B) and ≤20 mm (8.9 additional weeks vs MTX, p<0.001, and 10.4 additional weeks vs MTX, p<0.001, respectively; figure 4D) than patients
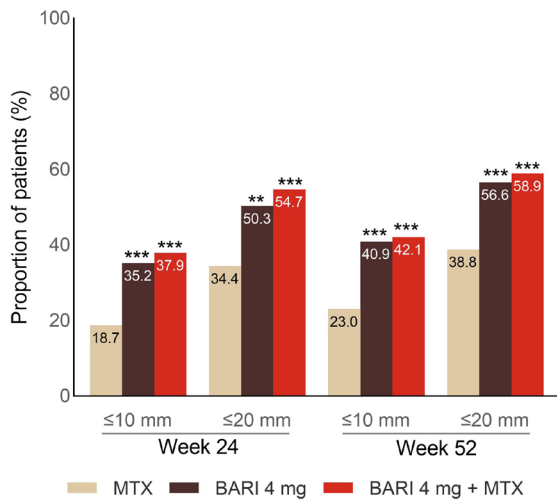
Figure 3 Percentage of patients meeting thresholds of remaining pain (VAS) at week 24 and week 52 by treatment group. **p<0.01, ***p<0.001 vs MTX. BARI, baricitinib; MTX, methotrexate; VAS, Visual Analogue Scale.

who received MTX monotherapy over the course of the 52-week treatment period.

Another important patient-reported outcome (PRO) in RA is PtGA, which assesses the patient's perceptions of disease activity. Pain is one of the main drivers of

PtGA, accounting for approximately 76% of variability, with physical function and fatigue also contributing.[29 30] When the AUC is analysed for the proportion of patients achieving ≤10 mm PtGA scores (figure 5A), it was determined that patients who received baricitinib monotherapy or baricitinib plus MTX had more cumulative time with PtGA below this threshold (17.7 weeks, p<0.001 vs MTX for both groups) than patients treated with MTX monotherapy (9.6 weeks; figure 5B) over the 52-week treatment duration. Similarly, when considering participants who achieved a PtGA score of ≤20 mm (figure 5C), a threshold that is considered to be representative of low disease activity,[28] AUC analysis shows that patients treated with baricitinib plus MTX or baricitinib monotherapy had on average 26.9 weeks (p<0.001 vs MTX) and 25.3 weeks (p<0.001 vs MTX), respectively, with scores below this threshold, compared with 16.6 weeks achieved by patients who received MTX alone (figure 5D).

The SF-36 scale is a validated PRO to evaluate HRQoL, and the PCS summary scale was used in this analysis to measure the patient's perception of overall physical health alongside the improvements in other PROs. As with pain and PtGA, a statistically greater proportion of patients treated with baricitinib as monotherapy or in combination with MTX achieved the minimal clinically important differences of change from baseline ≥5 in SF-36 PCS when compared with patients who received MTX only
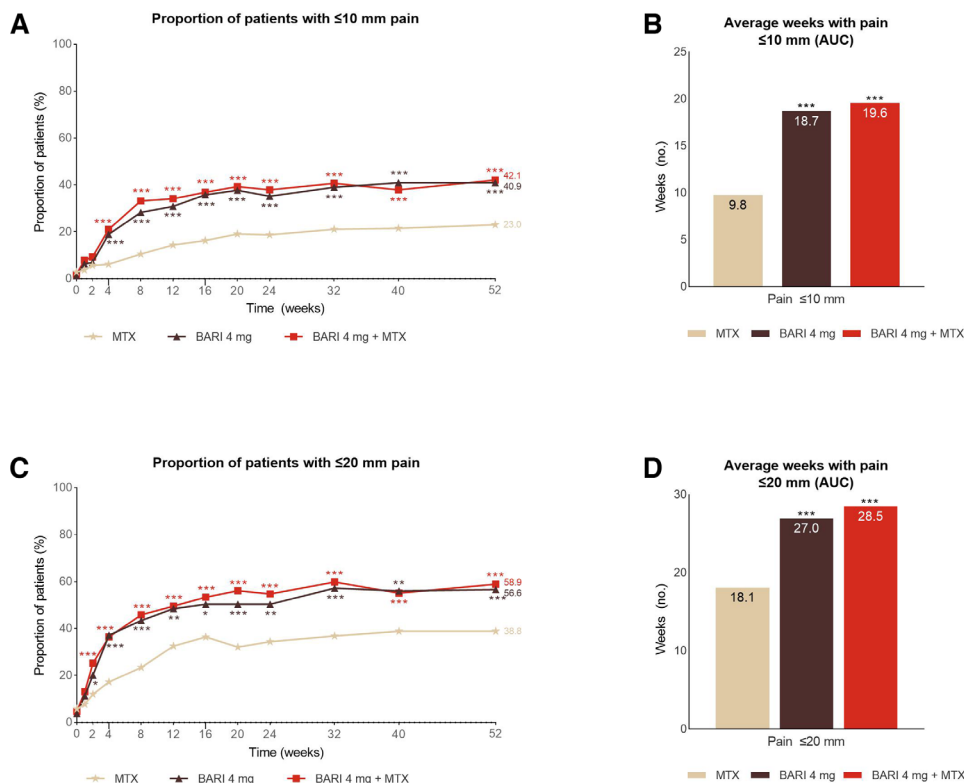

Figure 4 (A) The proportion (%) of patients with ≤10 mm pain, and (B) average number of weeks with pain Visual Analogue Scale (VAS) ≤10 mm per treatment group over 52 weeks calculated by area under the curve (AUC) analysis of the curve in (A). (C) The proportion (%) of patients with ≤20 mm pain and (D) average number of weeks with pain VAS ≤20 mm per treatment group over 52 weeks calculated by AUC analysis of the curve in (C). *P<0.05, **p<0.01, ***p<0.001 vs MTX. BARI, baricitinib; MTX, methotrexate.
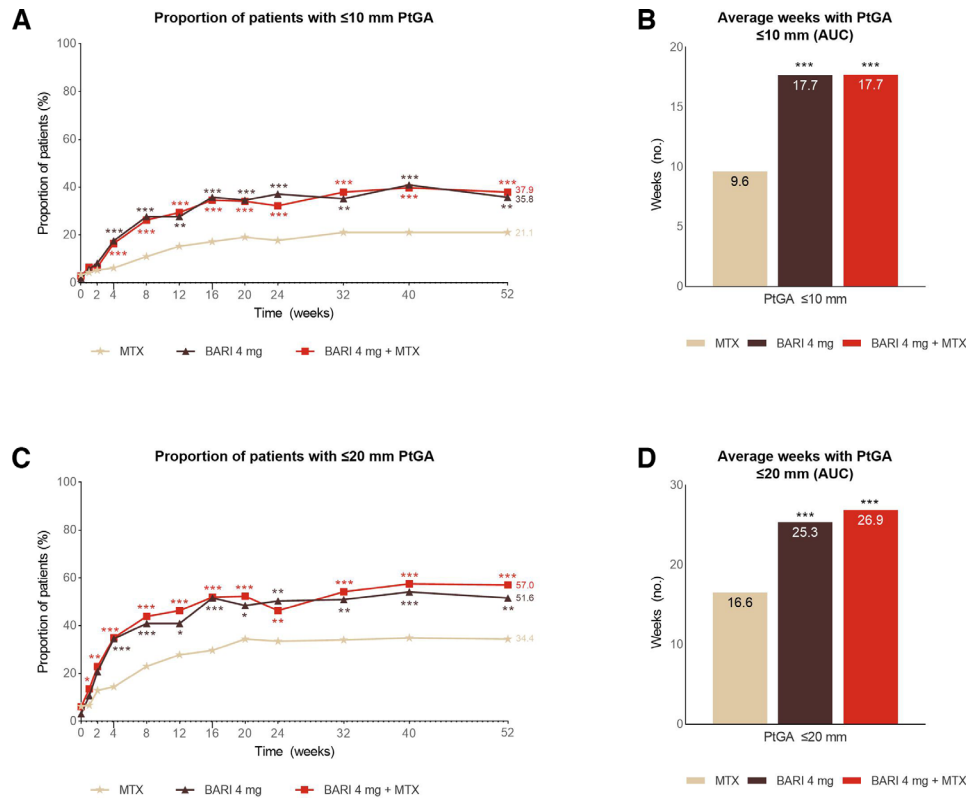
Figure 5 (A) The proportion (%) of patients with ≤10 mm PtGA and (B) average number of weeks with PtGA ≤10 mm per treatment group over 52 weeks calculated by AUC analysis of the curve in (A). (C) The proportion (%) of patients with ≤20 mm PtGA and (D) average number of weeks with PtGA ≤20 mm per treatment group over 52 weeks calculated by AUC analysis of the curve in (C). *P<0.05, **p<0.01, ***p<0.001 vs MTX. AUC, area under the curve; BARI, baricitinib; MTX, methotrexate; PtGA, Patient Global Assessment.

(figure 6A). AUC analysis shows that patients receiving baricitinib treatment met this threshold for an average of 39.1 weeks (baricitinib plus MTX, p<0.001 vs MTX) and 36.7 weeks (baricitinib monotherapy, p=0.008 vs MTX), compared with an average of 31.8 weeks for patients treated with MTX only (figure 6B).

DISCUSSION

The aim of this study was to determine whether treatment of patients who had limited to no prior treatment

with DMARDs with baricitinib 4 mg, as monotherapy or in combination with MTX, early in the disease course of RA resulted in more rapid, greater, and sustained improvements in patient-reported pain than MTX treatment alone. The importance of the patient population under study is that this population has the potential to robustly respond to all active treatments, allowing for a proper assessment of the effect size between the active treatments. Further, roughly one-third of the patients across the treatment arms were being treated
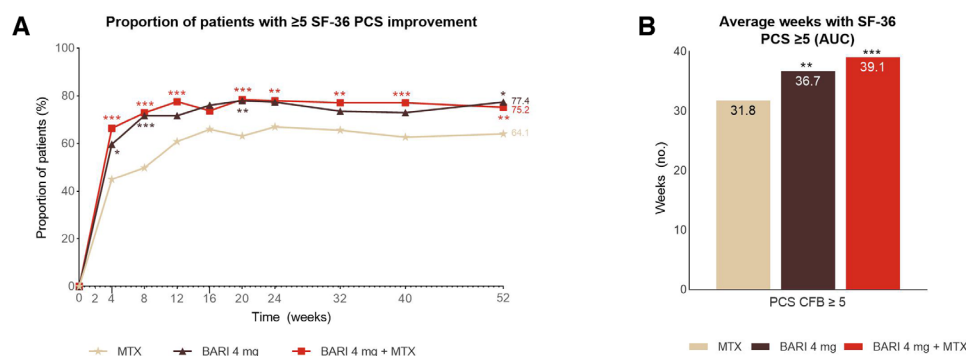

Figure 6 (A) The proportion (%) of patients with ≥5 points SF-36 PCS improvement and (B) average number of weeks spent with ≥5 points improvement in SF-36 PCS per treatment group over 52 weeks calculated by AUC analysis of the curve in (A). *P<0.05, **p<0.01, ***p<0.001 vs MTX. AUC, area under the curve; BARI, baricitinib; CFB, change from baseline; MTX, methotrexate; PCS, Physical Component Score; SF-36, Short Form-36.

concomitantly with corticosteroids, reflecting a common 'corticosteroid-bridging' clinical practice in early RA and that MTX treatment, and associated outcomes, was aided by corticosteroids in a subset of the cohort.[31]

Patients who received baricitinib as monotherapy or in combination with MTX showed greater and more rapid pain improvements than patients who received MTX alone, with higher proportions of patients achieving clinically meaningful thresholds of pain improvement and fewer patients with remaining pain after 52 weeks of treatment. Across PRO outcomes, the responses observed with baricitinib monotherapy were similar to baricitinib plus MTX combination. Results show that MTX monotherapy does provide pain relief for patients; however, the improvements in pain are not as profound in magnitude or speed as those achieved in the baricitinib treatment arms over 24–52 weeks of observation.

While baricitinib and MTX are both effective at controlling clinical signs of RA,[17] patients treated with baricitinib as monotherapy or combination, due to its rapid and sustained improvement in pain, experience longer cumulative durations with pain below clinically significant thresholds over the course of the study. The thresholds of ≤10 mm and ≤20 mm on the pain VAS were chosen as patients who meet these thresholds are considered to be living an effectively pain-free life, with a score of 10 mm on the pain VAS determined to be a cut-off point for minimal pain in patients with RA.[22] These patients also experience greater cumulative durations with outcomes below clinically significant thresholds of perceived physical health and disease activity, as measured by SF-36 PCS and PtGA. The similarity between the outcomes for pain and PtGA emphasises the importance of perceived pain in an individual's subjective evaluation of their disease status and supports the known correlation between pain and patient assessment of disease activity, which has previously been reported in other studies.[28 30 32]

This research builds on analysis of data from RA-BEAM, which demonstrated the effect of baricitinib on patient-reported pain in participants who have previously had an inadequate response to MTX.[18 20] In RA-BEGIN, a population of patients early in the RA disease course were treated. These patients had limited to no prior DMARD treatment, therefore a full response to MTX would be expected in many of these patients. Further, one-third of the MTX-treated patients were treated concomitantly with corticosteroids which may have contributed to a more rapid and robust clinical response, both in terms of improvement in disease activity and PRO (pain, physical function, other), in this cohort. As these patients were enrolled early in the RA disease course, they may also be more responsive to changes in the outcomes of this study as they are unlikely to have significant irreversible consequences of longstanding disease. Patients who received baricitinib, alone or in combination with MTX, showed greater reduction in measures of pain than patients who received MTX monotherapy. This suggests that baricitinib has a greater impact on pain relief than

MTX, which is consistent with evidence supporting the overarching involvement of the JAK/signal transducer and activator of transcription (STAT) pathway in physiological pain mechanisms.[16]

Many cytokines involved in the pathogenesis of RA signal through the JAK/STAT pathway, including interleukin (IL)-4, IL-6, IL-10, IL-17, and granulocyte-macrophage colony-stimulating factor (GM-CSF). These signalling molecules may also be involved in pain signalling and central sensitisation, where they can mitigate pain (IL-4, IL-10) or enhance pain sensitivity (IL-6, IL-17, GM-CSF).[16] Other cytokines that have been implicated in pain, such as tumour necrosis factor-α and IL-1β, do not signal directly though the JAK/STAT pathway but may have their signalling effects modulated by its inhibition.[16]

The similarity of results in the baricitinib monotherapy and baricitinib plus MTX treatment arms suggests that baricitinib itself is responsible for the majority of the effect, as there was no significant additional benefit specific to pain relief provided by the addition of MTX. This rapid onset of efficacy with regards to management of pain could reduce the need for corticosteroid bridging with MTX treatment and the associated challenges with short- and long-term toxicity/safety of this practice in patients with early disease when initiating treatment.[31] Though MTX with corticosteroid bridging is a common and effective clinical practice in early RA,[31] this study is unable to address a comparative efficacy question, including with pain outcomes, between baricitinib monotherapy, MTX monotherapy and MTX plus corticosteroids.

This analysis has several limitations. Post hoc analyses are exploratory in nature and are aimed towards hypothesis generation rather than demonstration of fact. Each end point was only assessed using a single measure. LOCF imputation was prespecified in this trial as the method for handling missing data, however, current approaches use multiple imputation methods. There is a high correlation reported between two outcomes assessed, pain and PtGA. Patient-reported symptoms may not be reported consistently and should be interpreted with caution. In clinical practice, patients typically begin treatment with MTX as monotherapy or in combination with other csDMARDs or biological DMARDs prior to the use of tsDMARDs such as baricitinib. However, to investigate the true effect size between active treatments, a patient population with no or limited prior treatment is most suitable. The dosage of MTX was limited to 20 mg once weekly and was not adjusted in patients with an inadequate response to treatment. Additional benefits of a higher dose of MTX cannot be excluded.

In conclusion, baricitinib showed rapid and sustained improvements for pain, PtGA and SF-36 PCS compared with MTX monotherapy during this 52-week study. Baricitinib as monotherapy or in combination with MTX showed significantly greater cumulative pain relief than MTX alone with more weeks of low/mild pain status over 52 weeks.

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