Induction of cure in early arthritis (I CEA) results of a randomised clinical trial to compare three treatment strategies in recent onset undifferentiated arthritis

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ORIGINAL RESEARCH

Induction of Cure in Early Arthritis (I CEA): results of a randomised clinical trial to compare three treatment strategies in recent onset undifferentiated arthritis

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ABSTRACT

Objectives To investigate whether in undifferentiated arthritis (UA) it is beneficial to start early treatment with disease-modifying antirheumatic drugs (DMARDs) compared with symptomatic therapy.

Methods The Induction of Cure in Early Arthritis study is a 3-month multicentre single-blinded randomised controlled trial followed by a 9-month observational period. Patients with early DMARD-naïve UA (arthritis ≥2 joints, not fulfilling American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 Rheumatoid Arthritis criteria) received a glucocorticoid injection (40 mg intra-articular or intramuscular) and were randomised (1:1:1) to a 3-month intervention with (1) non-steroidal anti-inflammatory drugs (NSAIDs) in standard daily dose or (2) methotrexate (MTX) 15 mg/week increased to 25 mg/week or (3) baricitinib 4 mg/day. Primary endpoint was Disease Activity Score (DAS) (44/53 joints) improvement at 3 months. Differences between treatment arms were assessed with analysis of covariance, adjusted for baseline DAS.

Results Patients were randomised to NSAID (n=29), MTX (n=28) or baricitinib (n=28). After 3 months, baricitinib gave a significant improvement in DAS compared with NSAIDs: adjusted mean change in DAS: −0.52 (95% CI −0.93 to −0.11; p=0.01). MTX gave a numerically similar improvement: −0.39 (95% CI −0.84 to 0.06, p=0.09). Although non-significant, at 12 months DAS was lowest in the MTX treatment arm 1.3 (SD 0.7), NSAID 1.6 (SD 0.9), baricitinib 1.7 (SD 0.9), p=0.38. Incidence rates of severe adverse events remained low during the study across all treatment arms.

Conclusions In patients with UA, early DMARD treatment led to greater improvement in disease activity over 3 months compared with NSAIDs, with the improvement for baricitinib reaching statistical significance. Over 12 months, disease activity was not significantly different across treatment arms, with overall favourable outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Undifferentiated arthritis (UA) is a heterogeneous condition: one-third of patients progress to rheumatoid arthritis (RA), but in many patients the disease also resolves spontaneously. Current international guidelines recommend starting early disease-modifying antirheumatic drug (DMARD) treatment in all patients with UA who are considered at risk of progression to persistent arthritis to prevent irreversible joint damage and potentially disrupt disease progression. However, since the introduction of the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) RA classification criteria, contemporary patients with UA are characterised by a milder disease course, in predominantly seronegative patients. Since there are no prognostic factors for persistent disease, balancing overtreatment and undertreatment is challenging and randomised controlled trials in contemporary RA are lacking.

WHAT THIS STUDY ADDS

⇒ In UA, early DMARD treatment with baricitinib or methotrexate (MTX) could provide more rapid symptom relief than symptomatic treatment.

⇒ Long-term UA outcomes are generally favourable, thus DMARD initiation requires careful risk–benefit consideration.

⇒ Incidence rates of severe adverse events remained low during the study across the three treatment arms.

INTRODUCTION

Undifferentiated arthritis (UA) is characterised by clinically evident inflammatory arthritis that does not fulfil classification criteria for a specific rheumatic disease. It is

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Early MTX or baricitinib treatment in contemporary UA can accelerate symptom relief compared with symptomatic treatment with non-steroidal anti-inflammatory drugs and a glucocorticoid injection for symptom relief. However, 12-month outcomes were generally favourable across all treatment arms, highlighting the need to individualise DMARD initiation based on patient goals and risk of adverse events. Future studies should identify which patients benefit most from early treatment.

a heterogeneous entity that may progress to rheumatoid arthritis (RA) or another inflammatory disease, remain undifferentiated or resolve spontaneously.[1]

One-third of UA cases progress to RA, raising concerns about delayed treatment and the risk of irreversible joint damage.[1] International guidelines therefore recommend starting early disease-modifying antirheumatic drug (DMARD) treatment in all patients with UA who are considered at risk of progression to persistent arthritis.[2] This is based on the concept of a therapeutic window in the pre-RA phase to disrupt disease progression and potentially prevent RA development.[3 4]

The introduction of the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) RA classification criteria, emphasising characteristics that emerge early in the disease course, led to the recognition of contemporary UA as a distinct entity within the early arthritis spectrum rather than merely an early stage of RA.[5] In contrast to UA in the era of the 1987 ACR RA classification criteria, contemporary UA is characterised by a generally milder disease course, predominantly seronegative and monoarthritic or oligoarthritic.[6] Known prognostic factors for persistent disease such as radiographic damage and polyarthritis are therefore less prevalent, making treatment decisions challenging.[1] While early aggressive DMARD therapy may benefit some patients, it could lead to overtreatment in others who might achieve spontaneous remission. To date no clinical trials exist in contemporary UA.[7] Trials on DMARD interventions in UA published before 2010 (eg, PROMPT, ADJUST) yielded mixed results and did not prevent RA development.[8–10] Moreover, long-term outcomes in contemporary UA, such as physical functioning and achieving DMARD-free remission, have shown little improvement over the past decades.[11]

Therefore, the objective of starting DMARD treatment in contemporary UA should be to achieve more rapid symptom relief and lasting remission than would occur without DMARD treatment, without significant adverse effects. Methotrexate (MTX) is the first-line DMARD for RA and has also proven effectiveness in other forms of arthritis. However, Janus kinase inhibitors (JAKi), like baricitinib, have a faster onset of action and outperform MTX and some biologics in treating RA.[12–14] In addition, baricitinib blocks the activation of multiple proinflammatory pathways which might make it a potentially effective treatment option for UA, a condition with diverse underlying inflammatory mechanisms.[12–14]

Therefore, this study aims to investigate whether early treatment with baricitinib or MTX is advantageous compared with initial symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and a baseline glucocorticoid (GC) injection for symptom relief. We hypothesise that early DMARD treatment with MTX or baricitinib will result in greater improvement in disease activity than NSAIDs, and that baricitinib will be potentially more effective than MTX in rapidly improving disease activity.

METHODS

Study design and participants

The Induction of Cure in Early Arthritis (I CEA) study is a multicentre, single-blinded (independent assessor), randomised clinical trial conducted in seven (two academic and five peripheral) hospitals in the Netherlands. Patients aged 18–64 years, with early (<1 year symptom duration) DMARD naïve UA in ≥2 joints were eligible. Additional criteria included a Disease Activity Score (DAS, 44/53 joints) >1.6, not fulfilling ACR/EULAR 2010 RA criteria for and no diagnosis of another inflammatory disease.

Patients were excluded in case of current alcohol or substance abuse, smoking or long history of smoking, pregnancy or breastfeeding, contraindications for study medication, laboratory abnormalities that were considered an unacceptable risk for participation, an immunocompromised state, renal insufficiency with estimated creatinine clearance <60%, interstitial lung disease as seen on chest radiograph, maintenance treatment with GCs exceeding 10 mg daily, serious infections in the past 4 months or chronic infectious diseases, an increased risk of major cardiovascular events (cardiovascular SCORE), arterial or venous thrombosis, or an increased risk of malignancy.[15]

Randomisation and blinding

Participants were randomised (1:1:1) to a 3-month intervention period in one of three treatment arms, followed by a 9-month observational period. Initially, the study had a more complex design. However, European Medicines Agency (EMA) safety warnings concerning treatment with JAKi required adjustments to the treatment protocol and exclusion criteria, as has been extensively described previously.[15] In short, patients with an increased risk for adverse events (AEs) following JAKi treatment had to stop treatment with baricitinib and continue observational follow-up. High-risk patients were no longer included in the trial. The initial complex strategy trial design was simplified to a 3-month interventional and 9-month observational design, with an adjusted primary outcome and consequently also an updated sample size calculation.

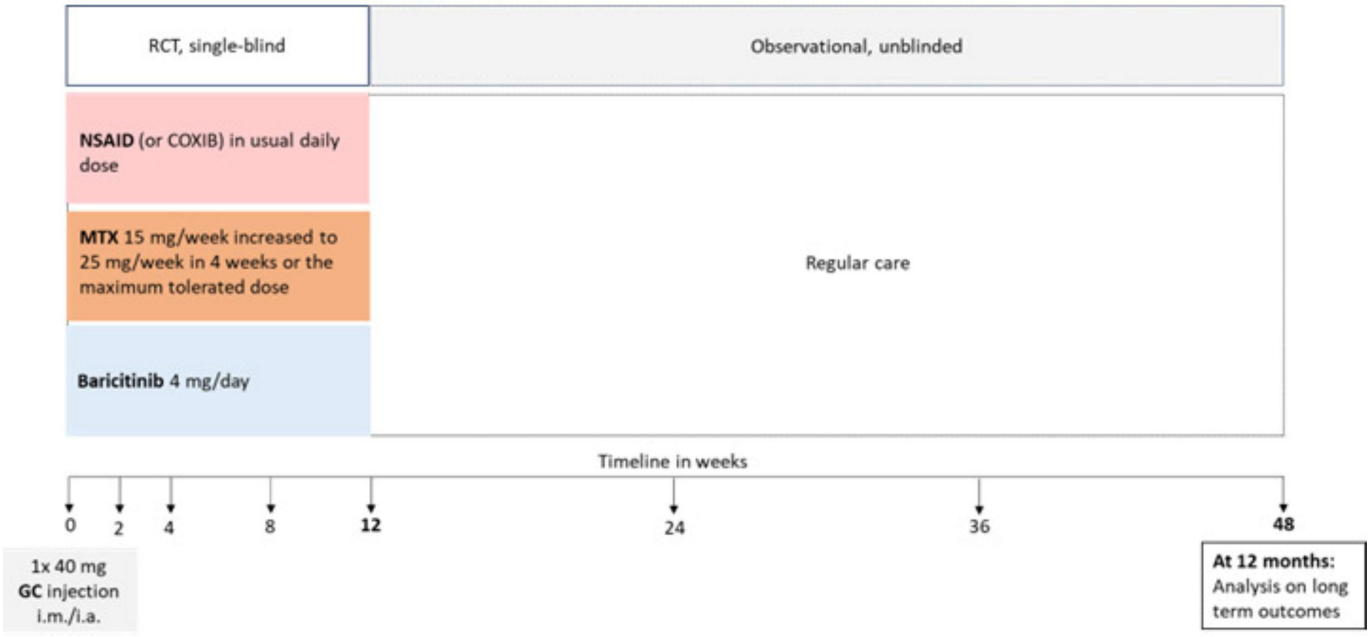

Figure 1 Schematic overview of the trial design.
COXIB, cyclo-oxygenase-2 inhibitor; GC, glucocorticoid; i.a., intra-articular; i.m., intramuscular; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial.

Treatment was allocated by a computer-generated variable block randomisation (block sizes 6, 12, 18) stratified by centre. The randomisation and allocation sequence was generated by an external staff member using the programme Castor. Enrolment was performed by study doctors, research nurses or local study coordinators who were blinded to randomisation outcomes. After enrolment, randomisation was de-blinded to enrolling personnel and patients were informed of their treatment allocation. The independent assessor remained blinded until the end of the intervention period.

Procedures

The three treatment strategy groups consisted of (figure 1a): (1) NSAIDs or COX-2 selective NSAIDs (cyclo-oxygenase-2 inhibitor) in a standard daily dose, choice left to the shared decision between rheumatologist and participant. This could be, for example, naproxen 500 mg twice daily or an equivalent NSAID at the appropriate therapeutic dose, such as ibuprofen 600 mg twice daily (maximum 800 mg twice daily) or diclofenac 75 mg twice daily, or celecoxib 100 mg twice daily. Paracetamol, with a maximum dose of 1000 mg three times daily, was optional. (2) MTX 15 mg/week increased to 25 mg/week within 4 weeks or the maximum tolerated dose, orally or subcutaneously. In case MTX was contraindicated, sulfasalazine (500 mg/day, increased within 4 weeks to 1000 mg two times per day) or leflunomide (20 mg/day or 10 mg/day depending on tolerance) were alternatives. (3) Baricitinib 4 mg/day. In arms 2 and 3, cotreatment with an NSAIDs or cyclo-oxygenase-2 inhibitor with or without paracetamol was allowed. All participants received a single dose of intramuscular or intra-articular GCs (40 mg methylprednisolone or alternative in an equivalent dose) at the start of treatment. In case of a disease flare, a single additional intra-articular or intramuscular GC injection was allowed, provided the next study visit was more than 1 month in the future. During the 9-month observational period participants received treatment in shared decision with the treating physician, including all available treatment options. Study visits occurred every 3 months, with additional visits at week 2, 4 and 8. All study visits included a full joint assessment by the independent assessor, collection of clinical data (including secondary outcomes), laboratory testing for safety monitoring and acute phase reactants, and questionnaires (full overview online supplemental table S1). Anticitrullinated protein antibody (ACPA)-positivity and rheumatoid factor (RF)-positivity were defined according to local reference levels. Radiographs of hands and feet were obtained at baseline and repeated after 6 and 12 months. Additional radiographs of inflamed joints were made at baseline and 12 months.

Outcomes

The primary endpoint was clinical improvement measured as the change in DAS (44/53 joints) at 3 months compared with baseline. Secondary endpoints were the proportion of participants achieving clinical remission (DAS <1.6) at 3, 6, 9 and 12 months. Remission was based on the DAS assessed by the independent assessor. An additional assessment by the treating physician was performed to prevent treatment escalation for high DAS based on pain without clinical arthritis (see online supplemental S2). Other secondary endpoints, measured at each study visit, included progression to classifiable (ACR/EULAR 2010) RA using ACPA, RF and symptom duration at baseline; patient-reported outcomes (PROs)

including joint pain, morning stiffness, fatigue and functional impairment and physician global assessment (MDGA), expressed on a Visual Analogue Scale (VAS) from 0 (no symptoms) to 100 (worst symptoms possible).

Safety endpoints were the number and severity of (severe) AEs ((S)AEs), whether treatment-related or not.

Statistical analysis

EMA safety guidelines regarding the use of JAKi required recalculation of the primary sample size calculation compared with the original protocol, as previously described.[15] The new sample size calculation was performed based on (blinded interim analysis) an observed difference in DAS between two treatment arms of 0.5 at 3 months, providing 90% power with a two-sided α-level of 0.05 and a correlation between baseline DAS and DAS at 3 months of 0.8. This resulted in a sample size of 30 participants per treatment arm. An expected dropout rate of 10% and the addition of 10 patients with monoarthritis already included in the trial at the time of the blinded interim analysis, resulted in the anticipated requirement of 109 patients.

Participants were analysed using their randomised treatment arm (intention-to-treat, ITT). Participants with DAS <1.6 (remission) at treatment initiation were excluded from the main analysis. All analyses were performed using Stata (StataCorp LLC, release V.16.1).

Analysis at 3 and 12 months

The number of (participants with) (S)AEs were presented by treatment arm and calculated per 100 patient years (incidence rate). Improvement in DAS, MDGA, PRO and number of (S)AEs were compared between treatment arms at 3 and 12 months. Visual assessment of box plots was used to compare similarity of variability across trial sites (homoscedasticity). In case of homoscedasticity across trial sites, an analysis of covariance (ANCOVA) analysis was performed with treatment arm as independent variable and baseline DAS/VAS as covariate.

Before assessing overall differences between treatment arms, it was assessed whether baseline symptom duration and ACPA status were prognostic for the outcome and improved model fit. In case of a significant improvement in model fit or association with the outcome they were added as covariates to the final model.

A gatekeeping strategy was employed to control the type I error by performing statistical testing in a predefined sequence and stopping testing at the first non-rejection. The sequence started with a test for overall treatment arm differences (ANCOVA for factor treatment).[16] In case of a significant overall difference, the treatment arms with the largest expected differences were compared: first baricitinib compared with the NSAID treatment arm, then the MTX and NSAID treatment arms and finally the MTX and baricitinib treatment arms. All tests were performed at an α-level of 0.05. Because the analyses of secondary endpoints were exploratory, corrections for multiple testing were not performed.

GEE analysis over time

To evaluate mean treatment differences in DAS, PROs and MDGA (VAS) over 12 months follow-up we performed generalised estimation equations (GEEs). This model included time in months and treatment as predictor, taking into account repeated measurement within individuals over time. Linearity was graphically assessed and the interaction between time and treatment was tested (at $p<0.05$) to examine whether the difference between treatment arms changed over time. No gatekeeping procedure was employed.

Time to remission and progression to RA

Kaplan-Meier estimators and Cox regression analyses were used to compare time to progression to classifiable RA (ACR/EULAR 2010 criteria) and time to first clinical remission. Time to remission was adjusted for baseline DAS. The proportional-hazards assumption was checked using the log-rank test. ACPA status and/or symptom duration were added to the final model in case they were prognostic for the outcome or further improved model fit (likelihood ratio test).

Missingness

To account for missing data, multiple imputation was performed if ≥5% data was missing for a variable. Multiple imputation was performed using chained equations with predictive mean matching (with five observations to draw from) creating 80 imputed data sets. Data were assumed to be missing at random. Since missingness of the primary endpoint was 6%, analyses on imputed datasets were performed as a sensitivity analysis. For secondary endpoints, ANCOVA analyses were performed with imputed datasets. All GEE analyses were performed on non-imputed data since GEE was considered robust for missingness. A list of variables used for imputation and the amount of missingness per variable is included as online supplemental S3 and online supplemental tables S2 and S3.

Sensitivity analyses

To check the robustness of GEE estimates, time was included as a categorical variable (visit number) and all analyses were repeated including the patients in remission at baseline. Additionally, the prognostic value of differing baseline characteristics between treatment arms, including RF positivity, sex, age and smoking status, was assessed.

RESULTS

Between 14 December 2020 and 27 November 2023, 283 patients with UA were screened. Of these, 113 patients were enrolled and randomised; 39 to NSAIDs, 37 to baricitinib and 37 to MTX treatment (figure 1b). 28 participants underwent delayed exclusion after randomisation. Of these, 21 had a DAS <1.6 at baseline. These patients were eligible for inclusion at the time of enrolment. Ultimately, 85 participants were included in the ITT analysis:

Table 1 Baseline characteristics stratified by treatment arm

	NSAID (n=29)	MTX (n=28)	Baricitinib (n=28)
Female, n (%)	15 (52)	20 (71)	17(61)
Age, mean (SD)	52 (15)	48 (16)	57 (13)
Symptom duration in months, median (IQR)	4.2 (2.2–8.4)	5.0 (2.9–11.2)	3.6 (1.9–12.5)
DAS, mean (SD)	2.4 (0.6)	2.4 (0.6)	2.5 (0.8)
TJC, median (IQR)	5 (2–8)	3 (1–4)	3 (2–5)
SJC, median (IQR)	3 (1–5)	2 (1–7)	2 (1–4)
VAS, mean (SD)	42 (19)	41 (21)	49 (25)
Smoking status, n (%)			
Current	6 (21)	7 (25)	4 (14)
Never	14 (48)	15 (54)	16 (57)
In the past	8 (28)	4 (18)	8 (29)
BMI (kg/m^2), median (IQR)	27.3 (25.3–29.9)	25.8 (23.5–29.1)	27.8 (25.5–29.7)
CRP concentration, (mg/L), median (IQR)	2.8 (1.3–8.9)	3.2 (1.2–10.5)	4.3 (1–14.2)
ESR concentration, (mg/L), median (IQR)	9 (4–23.5)	13.5 (6.5–30)	16 (9.5–33)
RF +, n (%)	6 (21)	3 (11)	8 (29)
ACPA +, n (%)	5 (17)	2 (7)	1 (4)
Functional impairment (VAS), median (IQR)	64 (37–70)	50 (32–74)	50 (25–70)
Fatigue (VAS), median (IQR)	60 (50–72)	60 (30–75)	62 (25–80)
Joint pain (VAS), median (IQR)	60 (38.5–62.5)	50 (35–70)	50 (32–65)
Morning stiffness (VAS), median (IQR)	69 (50–80)	58 (35–80)	50 (30–65)

ACPA +, anticitrullinated antibody positive; BMI, body mass index; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RF +, rheumatoid factor positive; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale of 0–100.

29 in the NSAID (27 completer, 2 lost to follow-up), 28 in the MTX (24 completer, 4 lost to follow-up) and 28 in the baricitinib (25 completer, 3 lost to follow-up) treatment arms. The last study visit occurred on 12 December 2024. The ITT population (n=85) was smaller than the anticipated sample size of 109 participants.

In the ITT population, at baseline (table 1) the average age was 52 (SD 15) years, 61% were female and 21% were ACPA and/or RF positive, with median symptom duration of 4.4 (IQ 2.1–9.9) months and mean baseline DAS of 2.4 (SD 0.6). Participants in the MTX treatment arm had, on average, a lower age (48 years), longer symptom duration (5 months) and a greater proportion were female (71%) compared with the other two treatment arms. In the baricitinib treatment arm, participants were on average older (57 years) and a lower proportion of participants were people who smoke currently (14%). Baseline characteristics of participants not included in the ITT population are described in online supplemental table S4.

Three and 9 out of 85 participants were lost to follow-up before 3 and 12 months, respectively. At 3 months, 1 participant from each treatment arm was lost to follow-up, while at 12 months, 2 (7%) of 29 participants in the NSAID, 4 (14%) of 28 participants in the MTX and 3 (11%) of 28 participants in the baricitinib treatment arm were lost to follow-up (online supplemental figure S1). At baseline two participants in the MTX treatment arm had not initiated the assigned treatment (protocol violation) but instead initiated NSAID treatment due to spontaneous improvement in concerns and fear of side effects from MTX. Before 3 months follow-up, of the participants who initiated treatment per protocol, 31% in the NSAID, 20% in the MTX and 26% in the

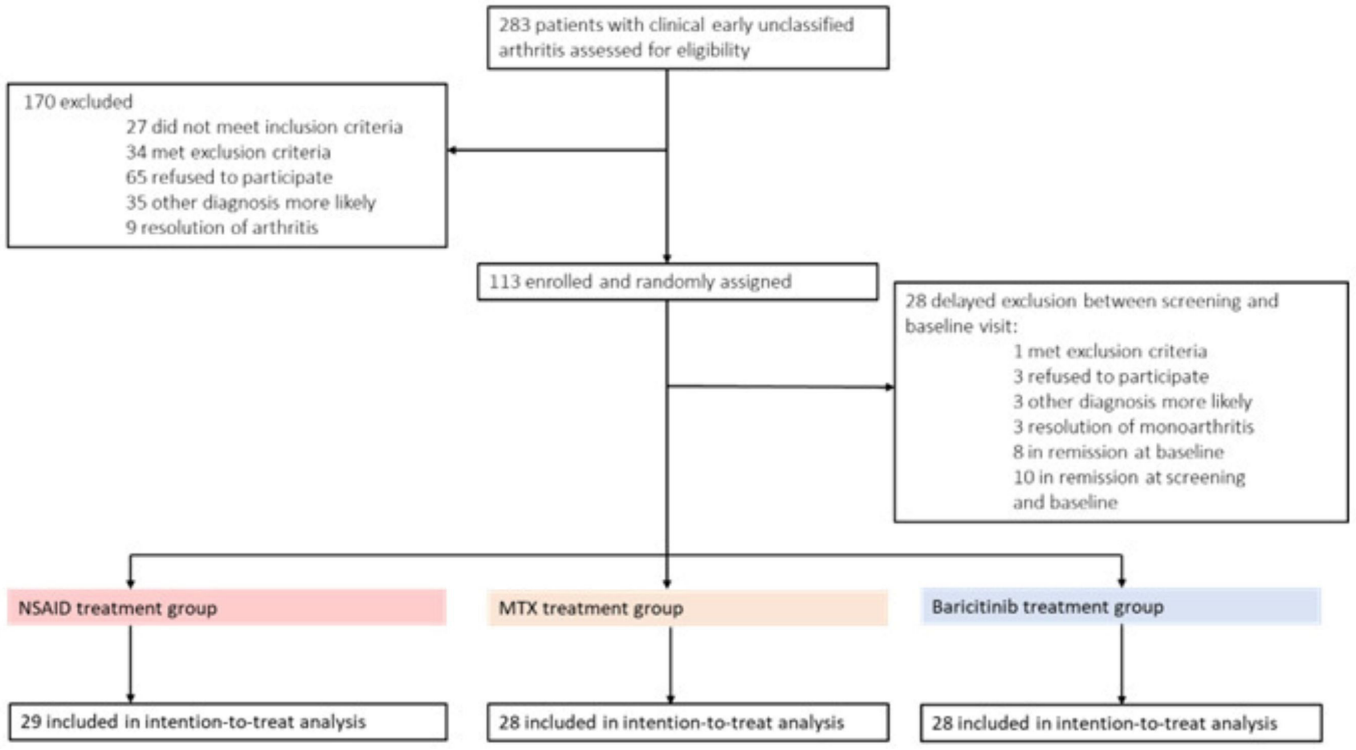

Figure 2 Flow chart of patient inclusion
MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug.

baricitinib treatment arm had discontinued the assigned treatment. Reasons for discontinuation were remission (NSAID n=2, MTX n=1), an AE (NSAID n=2, MTX n=2, baricitinib n=2), ineffectiveness (NSAID n=4, MTX n=2, baricitinib n=1) or the EMA safety warning (baricitinib n=3) resulting in a switch to/addition of hydroxychloroquine (NSAID n=1, MTX n=1), leflunomide (MTX n=1), MTX (NSAID n=2, baricitinib n=3) or GC use (NSAID n=1). Other reasons included drop-out (NSAID n=1, baricitinib n=1) and living abroad (baricitinib n=1). The proportion of participants adhering to the assigned treatment strategy and alternative prescribed treatments at 3 and 12 months are displayed in figure 2. During the observational study period, treatment strategies varied considerably across treatment arms. At 12 months, the proportion of participants remaining on the original treatment strategy was 19%, 9% and 0% in the NSAID, MTX and baricitinib treatment arm, respectively. The proportion of participants who had ever used MTX, a biological (adalimumab) or baricitinib at some time between 3 and 12 months was 64%, 4% and 39% in the NSAID treatment group, 60%, 12% and 32% in the MTX treatment group and 56%, 15% and 15% in the baricitinib treatment group. The prescribed GC, including its baseline dose and the frequency of rescue GC therapy during follow-up are described per treatment arm in online supplemental tables S5 and S6. The proportion of participants receiving rescue GCs before and after 3 months follow-up was 21% (6/29) and 32% (9/28) in the NSAID, 0% and 19% (5/26) in the MTX and 7% (2/28) and 33% (9/27) in the baricitinib treatment arm. The proportion of participants receiving a rescue GC prescription for a flare (DAS >1.6), after achieving remission, before and after 3 months was 0% and 11% (3/28) in the NSAID, 0% and 8% (2/26) in the MTX and 0% and 11% (3/27) in the baricitinib treatment arm.

Change in DAS at 3 and 12 months

ANCOVA analyses demonstrated overall differences between treatment arms in DAS improvement at 3 months (p=0.04, figure 3A). Early treatment with baricitinib gave a significantly greater improvement in DAS at 3 months compared with NSAIDs: −0.52, 95% CI −0.93 to −0.11; p=0.01. The difference between MTX and NSAIDs was numerically similar, but non-significant: −0.39, 95% CI −0.84 to 0.06; p=0.09.

At 12 months, the mean predicted DAS was lowest in the MTX treatment arm (mean DAS 1.3 (SD 0.7) compared with 1.7 (SD 0.8) in the baricitinib and 1.6 (SD 0.9) in the NSAID treatment arm), this difference was non-significant (p=0.4, figure 4B). Median swollen joint count (SJC) and tender joint count ranged between 0 and 1 across all treatment arms at 12 months (table 2).

A sensitivity analysis after multiple imputation showed a mean DAS at 3 months of 2.2 (SE 0.2), 1.8 (SE 0.2) and 1.9 (SE 0.2) in the NSAID, MTX and baricitinib treatment arm. At 12 months mean DAS was 1.6 (SE 0.2), 1.2 (SE 0.1) and 1.6 (SE 0.2) in the NSAID, MTX and baricitinib treatment arms. ANCOVA analyses on the imputed dataset demonstrated no significant overall differences between treatment arms in DAS improvement at 3 and 12 months (online supplemental figure S2).

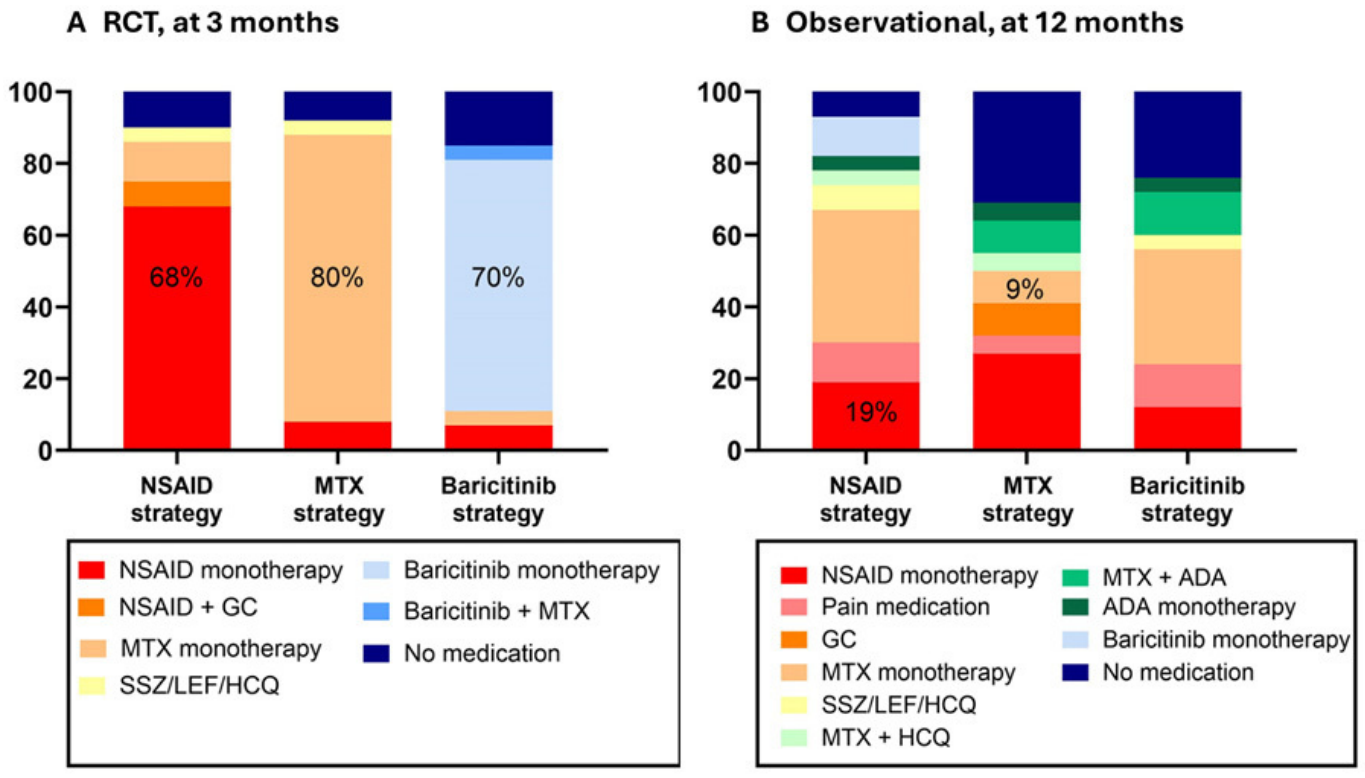

Figure 3 ADA, adalimumab; GC, glucocorticoid; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial; SSZ, sulfasalazine.

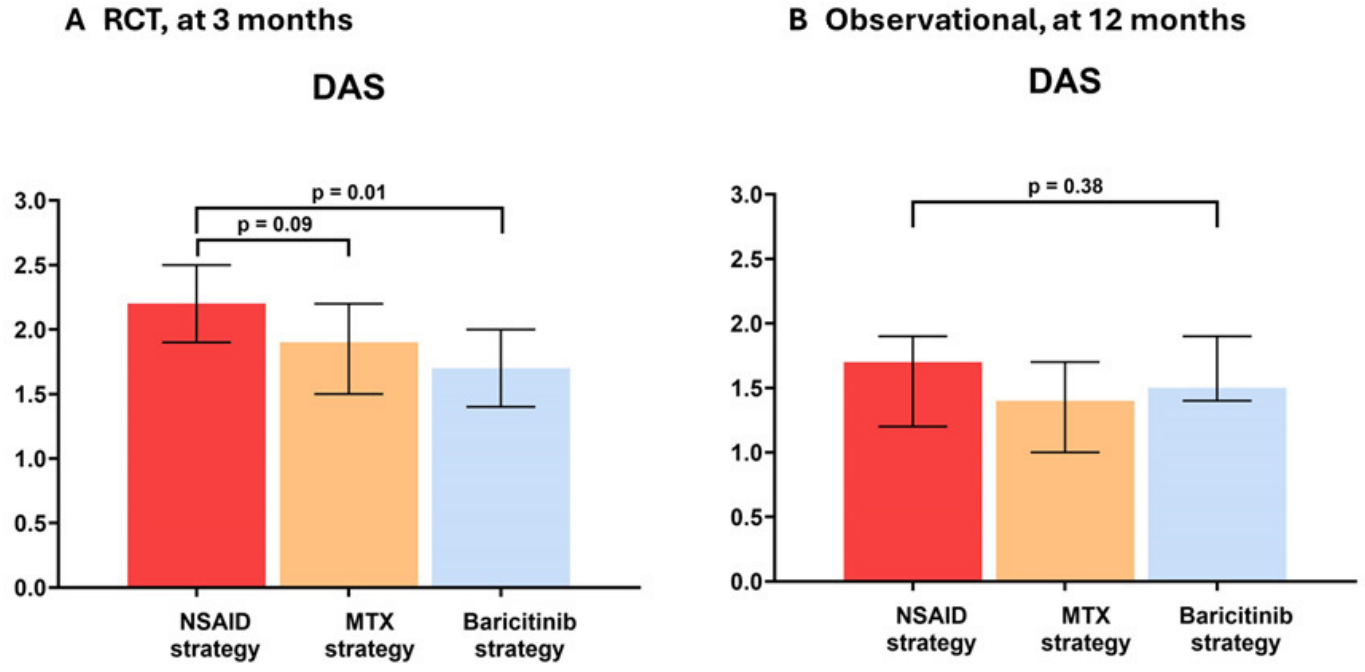

Figure 4 DAS at 3 and 12 months per treatment strategy arm.
DAS, Disease Activity Score; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial.

Table 2 DAS and its components at 3 and 12 months stratified by treatment arm

	NSAID (n=29)	MTX (n=28)	Baricitinib (n=28)
DAS at 3 months, mean (SD)	2.2 (0.9)	1.8 (0.7)	1.9 (0.9)
Components			
SJC, median (IQR)	1 (0–3)	1 (0–2)	1 (0–2)
TJC, median (IQR)	4 (2–7)	2 (1–4)	1 (1–3)
VAS, median (IQR)	40 (30–61)	30 (14–50)	28 (11–50)
DAS at 12 months, mean (SD)	1.6 (0.9)	1.3 (0.7)	1.7 (0.8)
Components			
SJC, median (IQR)	0 (0–1)	0 (0–0)	0 (0–1)
TJC, median (IQR)	1 (0–5)	0 (0–1)	1 (0–3)
VAS, median (IQR)	33 (19–60)	20 (10–30)	20 (10–45)

DAS, Disease Activity Score assessed using 44/53 joints; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale (0-100).

Change in DAS over time

A persistent greater improvement in DAS for both early treatment with baricitinib and MTX, compared with NSAIDs was observed: adjusted mean DAS improvement per week, over 12 months for baricitinib and MTX compared with NSAIDs was −0.28, 95% CI −0.50 to −0.06 (p=0.01) and −0.27, 95% CI −0.49 to −0.04 (p=0.02), respectively. Graphical inspection revealed a linear trend and no significant time-by-treatment interactions were observed, suggesting a stable treatment effect over time (online supplemental table S7). To check the robustness of the observed effect, time was also included as a categorical variable into the model (as visit numbers), which yielded similar results (online supplemental figure S3).

Time to remission and RA diagnosis

In the ITT population, 36% of 28 participants treated with NSAIDs, 41% of 27 participants treated with MTX and 44% of 27 participants treated with baricitinib achieved clinical remission (DAS <1.6) at 3 months. After the open label observation period, at 12 months, 56% in the NSAID, 67% in the MTX and 40% in the baricitinib treatment arm achieved remission. The median time to achieve remission was 12, 8 and 4 weeks in the NSAID, MTX and baricitinib treatment arms, respectively (online supplemental figure S4A). No difference in remission rates was observed when comparing baricitinib to NSAID treatment at 12 months: adjusted HR (aHR) 1.4, 95% CI 0.8 to 2.5; p=0.3. However, compared with NSAIDs, initial treatment with MTX resulted in a higher chance of achieving remission at 12 months: aHR 1.9, 95% CI 1.0 to 3.3; p=0.04.

At 3 and 12 months, respectively, 10% and 26% of 20 participants in the NSAID treatment arm, 8% and 13% of 24 participants in the MTX treatment arm and 15% and 15% of participants in the baricitinib treatment arm fulfilled the ACR/EULAR 2010 RA classification criteria. These percentages did not differ significantly at 12 months (online supplemental figure S4B).

Proportional hazard assumption test on the basis of Schoenfeld residuals and log minus log plots are depicted in online supplemental figure S5.

Change in PRO at 3 and 12 months

After multiple imputation, ANCOVA analyses showed no statistically significant differences in functional impairment, joint pain, morning stiffness or MDGA at either 3 or 12 months for baricitinib or MTX compared with NSAIDs. Nevertheless, numerically greater improvements were observed with both treatments. At 3 months, estimated improvements ranged from −7.4 (MDGA) to −13.4 (morning stiffness) for baricitinib and from −8.2 to −16.6 for MTX. At 12 months, estimated improvements with baricitinib ranged from −1.5 (morning stiffness) to −4.6 (functional impairment) and from −7.4 to −13.5 for MTX. For MTX, improvements in functional impairment, joint pain, morning stiffness and MDGA were considered clinically meaningful (online supplemental figures S7 and S10).[17–19]

Change in PRO over time

When comparing the baricitinib with the NSAIDs strategy, there were no significant differences in mean improvement of functional impairment (−5.05, 95% CI −13.2 to 3.1; p=0.2), joint pain (−6.0, 95% CI −14.6 to 2.5; p=0.2), morning stiffness (−6.5, 95% CI −15.8 to 2.9; p=0.2) and MDGA (−4.5, 95% CI −12.6 to 3.6; p=0.3) per week over 12 months (online supplemental table S11).

However, a persistent greater improvement in functional impairment (−11.2, 95% CI −20.7 to −1.6; p=0.02), joint pain (−9.6, 95% CI −17.3 to −1.9; p=0.01), morning stiffness (−9.3, 95% CI −16.9 to −1.8; p=0.02) and MDGA (−7.2, 95% CI −13.8 to −0.6; p=0.03) per week was observed over 12 months for the MTX compared with the NSAIDs strategy. Improvement in fatigue over 12 months was similar across treatment arms (online supplemental table S11).

No significant time-by-treatment effects were observed suggesting a stable treatment effect over time (online supplemental table S7) including time as a categorical variable to the model yielded similar results (online supplemental figures S8 and S11).

Sensitivity analyses

The sensitivity analysis including 20 participants who were in remission at baseline showed a similar significant improvement in DAS at 3 months for early baricitinib treatment compared with NSAIDs. No significant differences were observed for improvement in DAS and all PRO at 12 months. Furthermore, GEE analysis demonstrated a significant improvement in mean DAS difference per week over 12 months for baricitinib compared with NSAIDs (−0.23, 95% CI −0.42 to −0.04; p=−0.02) (online supplemental tables S13-20).

Additionally, baseline characteristics which differed between treatment arms were tested for predictive value: sex, age, RF and smoking status (current/never/in the past). After multiple imputation, only smoking status was predictive for the outcome time to RA diagnosis. Adjusted HR are displayed in online supplemental table S21, and were similar to unadjusted models. After EMA warnings on the use of baricitinib, which necessitated adjusted exclusion criteria, three participants with a low cardiovascular risk (people who do not smoke/no history of smoking, age ≤65) were randomised to baricitinib treatment. Before the EMA warnings 8 participants with a low cardiovascular risk and 17 participants with a high cardiovascular risk were randomised to baricitinib treatment. These numbers were considered too low to perform additional sensitivity analyses.

Safety endpoints

The number of (S)AEs per treatment group, whether or not related to the treatment, are reported in table 3. In the ITT population, 0, 1 (4%) and 4 (14%) of participants in the NSAID, MTX and baricitinib treatment arms reported an SAE after 12 months follow-up. These included one acute myocardial infarction in the MTX treatment arm and three hospital admissions (acute appendicitis, post-traumatic subdural haematoma, complicated urinary tract infection with delirium) and one case of confirmed melanoma (signs present before study entry) in the baricitinib treatment arm. One participant in the baricitinib treatment arm, who was in remission at baseline and therefore not included in the ITT analysis, suffered a sudden death. In all treatment arms, all participants experienced an AE at some time during follow-up. In the first 3 months, incidence rates of AEs were higher with baricitinib and MTX compared with NSAID treatment: the incidence rate ratio (IRR) for baricitinib treatment compared with NSAIDs was 1.2, 95% CI 1.1 to 1.2; p<0.001 and the IRR for MTX treatment compared with NSAIDs was 1.2, 95% CI 1.1 to 1.3; p<0.001 (online supplemental table S23). Over 12 months the incidence rate of reported AEs remained higher in the baricitinib treatment arm (IRR compared with NSAIDs (1.1, 95% CI 1.1 to 1.2; p<0.001) while no difference in the incidence rate of reported AEs was observed for the MTX treatment arm (IRR compared with NSAIDs 1.0, 95% CI 0.9 to 1.1; p=0.2, table 3).

DISCUSSION

In this first randomised controlled trial (RCT) in patients with contemporary UA, early treatment with MTX or baricitinib led to improved outcomes at 3 months compared with initial symptomatic treatment with NSAIDs and a baseline GC injection without DMARD therapy. Although the change in DAS at 3 months, the primary outcome, was only significantly improved for baricitinib compared with NSAIDs, absolute DAS improvements were similar for both the MTX (−0.4) and baricitinib (−0.5) treatment arms. Findings were consistent across secondary outcomes, including PROs and MDGA. Despite non-significant between-group differences, clinically relevant improvements were observed for all PROs besides fatigue, with VAS improvements ranging from −8.2 for MDGA to −16.6 for morning stiffness with MTX treatment and from −7.4 for MDGA to −13.4 for morning stiffness for baricitinib treatment.[17–19]

The ultimate goal of UA treatment, next to prevention of progression to destructive RA, is to induce rapid and lasting symptom relief or even permanent remission. Therefore, this trial included a 9-month observational follow-up period during which treatment was no longer protocolised. Although we had hypothesised that baricitinib, with its broader mechanism of action, might show advantages compared with MTX in this heterogeneous patient population, at 12 months we only observed long-term advantages for early MTX treatment. This was reflected in improved PROs compared with the NSAID and baricitinib treatment arms (all non-significant). Although participants in the MTX treatment arm seemed to be on milder treatment regimens at 12 months (more often medication free or NSAIDs only compared with the baricitinib treatment arm), differences in treatment regimens may have been influenced by baricitinib discontinuation in response to EMA safety warnings, with MTX initiated as substitute. The duration of baricitinib use in this study may have been too short to allow meaningful differences in treatment outcomes to be detected over time when compared with MTX. Furthermore, the proportion of patients receiving a GC dose >40 mg at baseline was higher in the MTX treatment arm (23% vs 17% in the NSAID and 8% in the baricitinib treatment arm), with subsequently less rescue GC prescriptions given over 12 months follow-up compared with the NSAID and baricitinib treatment arms. On the other hand MTX, with its slow mechanism of action, may not have reached its full therapeutic effect in all patients at the initial 3-month single-blinded trial evaluation point. It is unsure whether small differences between MTX and baricitinib would have remained similar if the initial trial phase would have been extended to 4–6 months.

At 12 months, approximately 10% fewer participants in the baricitinib and MTX treatment arms fulfilled the 2010 EULAR/ACR RA classification criteria compared with the NSAID treatment arm (non-significant difference). However, at baseline approximately 10% more participants in the NSAID treatment arm were ACPA

Table 3 The number of (S)AEs reported per treatment group over 12 months follow-up

	NSAID (29)		MTX (28)		Baricitinib (28)	
	Number of events	**Incidence rate per 100 person-years (95% CI)**	**Number of events**	**Incidence rate per 100 person-years (95% CI)**	**Number of events**	**Incidence rate per 100 person-years (95% CI)**
(S)AE						
Total	0		1	4 (1 to 28)	**4**	**15 (6 to 41)**
Cardiovascular*	0		1		0	
Infectious†	0		0		2	
Malignancy‡	0		0		1	
Trauma and fractures§	0		0		1	
AE						
Total	96	566 (464 to 692)	93	516 (421 to 632)	**112**	**568 (472 to 684)**
Cardiovascular	3		2		2	
Pulmonary	2		2		2	
Gastrointestinal	13		16		19	
Central nervous system	8		6		13	
Metabolic	3		1		2	
Haematological	2		1		5	
Urogenital	1		4		2	
Skin/soft tissue	7		9		6	
Infectious	36		37		35	
Autoimmune	1		0		0	
Trauma and fractures	3		1		3	
Malaise	8		6		5	
Other	9		8		17	

Other included: three problems of hot flushes in the NSAID treatment arm; five elective procedures in the MTX treatment arm; nine elective procedures baricitinib treatment arm.
*Myocardial infarction.
†Acute appendicitis and urinary tract infection.
‡Melanoma.
§Subdural haematoma after fall.
AE, adverse event; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; (S)AEs, (serious) adverse events.

positive. Since ACPA positivity strongly contributes to classification, these baseline differences may explain the 12-month difference. Moreover, it should be noted that classification criteria cannot be used as a diagnostic tool.[20]

To our knowledge, this is the first RCT to assess the efficacy of early DMARD initiation in patients with early contemporary UA with suppression of disease activity as main outcome. It includes the novel use of baricitinib, which is not currently registered as treatment for UA. A previous trial in patients with conventional UA, the PROMPT trial, compared early initiation of MTX with placebo. In this trial, DAS also decreased in the MTX group, whereas it remained unchanged in the placebo group at 3 months. However, the PROMPT trial included more ACPA positive patients than the current trial and, by current standards, most patients would fulfil the 2010 RA classification criteria. In this heterogeneous patient population, in the absence of well-defined prognostic factors to predict spontaneous remission, it is equally important to prevent overtreatment. From the patients that were initially randomised, 10/113 (9%) participants who were not in remission at the time of screening achieved spontaneous remission before treatment start (median duration 9 days). Therefore, it may be considered reasonable to introduce a short waiting

period before starting treatment, since some patients seem to experience rapid resolution of symptoms in the first weeks after diagnosis. The majority of these participants (>60%) remained in remission at 3 and 12 months follow-up. Since participants who were in remission at baseline were not included in the ITT analysis, our study remained underpowered compared with the eventual sample size calculations. This may explain why most of our results were non-significant, although numerical effects seem clinically relevant and consistent across outcomes. A serial gatekeeping procedure was employed to efficiently control the type I error rate in our main analyses. However, this also implied that subsequent comparisons were purely exploratory if the primary analysis was non-significant. To reflect routine clinical practice and enhance the external validity of the trial, patients in the MTX and baricitinib treatment arms were allowed the use of NSAIDs or cyclo-oxygenase-2 inhibitors as needed, which may have attenuated between-group differences. However, all patients received a GC injection at baseline, providing rapid suppression of inflammatory symptoms which likely reduced the need for additional symptomatic treatment. This limited potential effects on early DMARD response. Moreover, NSAIDs primarily affect pain-related outcomes and PROs, whereas DAS, our main outcome, is strongly influenced by objective inflammatory components such as SJCs and acute-phase reactants. The observed differences in DAS are therefore more likely explained by the effects of DMARD treatment than by differential NSAID use.

As described previously, changes to the design and exclusion criteria were necessitated during the trial, after the EMA warning about the use of JAKi in patients with chronic inflammatory disorders.[21] This also led to updated power calculations, which were lower than the original power calculation that matched the originally more complex study design. To reduce the risk of (S)AEs for treatment with baricitinib, we excluded patients at a high risk of these AEs (eg, smoking, increased cardiovascular risk) and we used baricitinib for a relatively short time. Nevertheless, when these changes were implemented, some participants had already received baricitinib beyond the 3 months timepoint, including some high-risk participants. These groups were too small for additional sensitivity analyses. The I CEA trial was originally designed as a complex adaptive treatment strategy trial with multiple conditional treatment pathways, which precluded double blinding. Following a protocol amendment after the EMA safety warning regarding JAKi, the study was simplified to a 3-month randomised treatment phase followed by observational follow-up. Although the simplified design could in principle have allowed for double blinding during this phase, this could not be implemented in already enrolled patients after the mid-trial redesign. Outcomes were assessed by blinded independent assessors; however, lack of patient blinding may have influenced (patient-reported) outcomes. Over 12 months, we observed more (S)AEs in participants in the baricitinib than in the MTX or NSAIDs treatment arms, although drop-out rates were similar across treatment arms. Nevertheless, safety endpoints should be interpreted with caution, since similar to most clinical trials, this study was not powered to detect safety outcomes. Moreover, all patients in the baricitinib treatment arm had switched treatment during the 9-month observational follow-up period, often to MTX.

The first 3 months of the trial protocol did not change, which allowed us to simultaneously analyse participants that were included before and after the EMA warning. Nevertheless, protocol changes may have influenced outcomes. We observed a reduced willingness to participate after the EMA warning, also in patients without an increased risk for (S)AEs. Moreover, high-risk participants who were already randomised to receive baricitinib had to stop trial medication and continue with observational follow-up. This may be reflected in differences in baseline characteristics, with a lower proportion of people who smoke currently in the baricitinib treatment arm. Potentially relevant baseline differences were evaluated for prognostic relevance, with adjusted analyses performed when appropriate. Another limitation was the proportion of missingness, especially in secondary outcomes. As prespecified in the protocol, we performed multiple imputation of missing data to reduce the risk of bias. Also, approximately 25% of patients did not adhere to the assigned treatment strategy within the first 3 months, which may dilute observed differences between treatment arms. In conclusion, this trial showed that early DMARD treatment with MTX or baricitinib in patients with contemporary UA led to greater improvement in disease outcomes over 3 months compared with awaiting spontaneous remission with NSAID treatment, with the improvement for baricitinib being statistically significant. However, long-term disease outcomes for UA were favourable across all treatment arms, up to 12 months. Thus, DMARD initiation should be weighed against the wishes and treatment goals of the patient and the risk of (S)AEs. Studies with more extensive follow-up are needed to determine factors that identify patients with UA who would benefit most from early DMARD treatment, and to weigh costs and benefits of different treatments compared with symptomatic treatment.

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Contributors SAB and FAVG were the principal investigators. SAB designed the statistical analyses. TWJH was the independent physician related to the study. LVO, JAVDP, GSH and ISN were involved with data collection. JAVDP, SAB and ISN assessed and verified the data. SAB and ISN analysed the data. SB advised on the study protocol and statistical analysis plan. IH and AV contributed as patient partners. RB, SMVDK, HEV, TWJH and FAVG included patients. All authors commented on drafts and approved the final version of the manuscript. All authors approved the final version of the manuscript and were responsible for the decision to submit the manuscript for publication. SAB was guarantor.

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Competing interests We declare that SAB reports having received funding from Pfizer (payments made to the LUMC) and speaker fees from Benecke. FAVG reports having received consulting fees from AbbVie, ASAS, BMS, Galapagos, Janssen, Lilly, Novartis, Pfizer, UCB with all payments made to the LUMC. RB reports having received research grants from Galapagos, Sanofi and consulting fees from AbbVie, Galapagos, Janssen, Pfizer and UCB. HEV reports having received research grants from Galapagos and Boehringer Ingelheim and personal fees or honouraria from AbbVie, Novartis, Pfizer, UCB, Janssen and Lilly.

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Patient consent for publication Not applicable.

Ethics approval All participants provided written, informed consent before screening. The I CEA trial is registered with EudraCT (2019–0 04 359-35) and the Netherlands Trial Register (NL73202.058.20) and approved by the Leiden, The Hague and Delft medical ethics committee (P20.027).

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