Development of rheumatoid arthritis after methotrexate in anticitrullinated protein antibody-negative people with clinically suspect arthralgia at risk of rheumatoid arthritis: 4-year data from the TREAT EARLIER trial

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Summary

Background Prevention of rheumatoid arthritis has become a definitive target. However, whether prevention of anti-citrullinated protein antibody (ACPA)-negative rheumatoid arthritis is possible is still unknown. We aimed to assess the efficacy of a 1-year course of methotrexate on the development of rheumatoid arthritis in ACPA-negative people with clinically suspect arthralgia and predicted increased risk of rheumatoid arthritis.

Methods For this follow-up analysis, we used 4-year data from the TREAT EARLIER trial, a randomised, double-blind, placebo-controlled, proof-of-concept trial conducted in the southwest region of the Netherlands from which we analysed data collected between April 16, 2015, and Sept 11, 2023. ACPA-positive and ACPA-negative adults aged 18 years or older with arthralgia and subclinical joint inflammation who were at risk of developing rheumatoid arthritis were eligible for enrolment. For TREAT EARLIER, participants were randomly assigned (1:1) to active treatment or placebo. Active treatment consisted of a single intramuscular glucocorticoid injection (120 mg of methylprednisolone) upon inclusion, then a 1-year course of methotrexate. Placebo consisted of a single placebo injection followed by a 1-year course of placebo tablets. Trial visits occurred every 4 months during the first 2 years, at which clinical and questionnaire data were collected. Total follow-up was 4 years. For this analysis, participants were stratified via a prediction model into low risk, increased risk, and high risk of developing persistent, clinically apparent inflammatory arthritis. The primary outcome was development of rheumatoid arthritis, defined as the presence of clinically apparent inflammatory arthritis and clinical diagnosis of rheumatoid arthritis, and was assessed in all TREAT EARLIER participants. Severity of subclinical joint inflammation, physical functioning, and grip strength in ACPA-negative participants was studied in each risk group over a period of 2 years.

Findings 901 people with clinically suspect arthralgia were assessed for eligibility and 236 were enrolled in TREAT EARLIER. All 236 participants were included in the intention-to-treat analysis and 217 (92%) completed 4-year follow-up. 154 (65%) of 236 participants were women and 82 (35%) were men, 182 (77%) were ACPA-negative and 54 (23%) were ACPA-positive. Of the 182 randomly assigned ACPA-negative participants, none were predicted to be at high risk of developing persistent, clinically apparent inflammatory arthritis, 66 (36%) at increased risk, and 116 (64%) at low risk. Of the 54 ACPA-positive participants, 24 (44%) were predicted to be at high risk, 30 (56%) at increased risk, and none at low risk. After 4 years, 52 (22%) of 236 participants had developed the primary outcome of rheumatoid arthritis (25 [21%] of 119 in the treatment group and 27 [23%] of 117 in the placebo group). Of the 66 ACPA-negative participants predicted to be at increased risk, three (9%) of 35 in the treatment group developed the primary outcome compared with nine (29%) of 31 in the placebo group (hazard ratio 0·27, 95% CI 0·07–0·99; p=0·034). Of the 116 ACPA-negative participants predicted to be at low risk, four (8%) of 53 in the treatment group met the primary outcome compared with six (10%) of 63 in the placebo group (0·79, 0·22–2·80; p=0·71). Thus, after risk stratification, a 1-year course of methotrexate was associated with a reduced rate of development of ACPA-negative rheumatoid arthritis in participants with predicted increased risk of developing the disease. Subclinical joint inflammation, physical functioning, and grip strength persistently improved upon treatment in ACPA-negative participants with increased risk of developing rheumatoid arthritis, but not in those with low risk.

Interpretation Risk stratification can be helpful in trials of ACPA-negative people with clinically suspect arthralgia to identify participants who could benefit from treatment to prevent development of rheumatoid arthritis.

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Research in context

Evidence before this study

We searched PubMed between database inception and Sept 1, 2023, with no language restrictions, using the search terms "prevention", "rheumatoid arthritis", "arthritis", and "randomized controlled trial". Our search indicated that five interventional studies in the past two decades focused on the possibility of prevention of autoantibody positive rheumatoid arthritis. However, anticitrullinated protein antibody (ACPA)-negative people with rheumatoid arthritis also have a symptomatic period before development of rheumatoid arthritis that entails changes in cytokines, subclinical inflammation, symptoms, and disability. To our knowledge, the TREAT EARLIER trial is the only trial to date that has included autoantibody-negative participants with arthralgia at risk of rheumatoid arthritis. Initial results from this trial showed no treatment effect of methotrexate on development of rheumatoid arthritis in ACPA-negative participants with clinically suspect arthralgia. However, heterogeneity in risk of rheumatoid arthritis development in ACPA-negative participants with clinically suspect arthralgia might have concealed a treatment effect due to dilution. Therefore, risk-stratified analyses are required to adequately assess the possibility of prevention of rheumatoid arthritis in people with clinically suspect arthralgia who are ACPA negative.

Added value of this study

To our knowledge, this is the first time risk stratification has been used to determine which subgroup of ACPA-negative people with varying risk of developing rheumatoid arthritis could benefit from 1-year of methotrexate. We found that a 1-year course of methotrexate was associated with a reduced rate of development of ACPA-negative rheumatoid arthritis in participants with predicted increased risk for developing the disease. This treatment effect is accentuated by improvements of subclinical joint inflammation and physical functioning in ACPA-negative clinically suspect arthralgia with predicted increased risk of rheumatoid arthritis.

Implications of all the available evidence

Heterogeneity of risk should be considered when conducting and interpreting interventional trials in populations at risk of a disease. Similarly, risk stratification can be helpful in trials of ACPA-negative people with clinically suspect arthralgia to identify participants who could benefit from treatment. The findings of this follow-up analysis suggest unique opportunities to reduce ACPA-negative rheumatoid arthritis and its disease burden.

Introduction

Despite advancing treatment strategies, rheumatoid arthritis remains a chronic disease that has lifelong symptoms and impairments and requires lifelong management. As a result, prevention of rheumatoid arthritis has become a definitive target. Most placebo-controlled trials have studied interventions in autoantibody-positive individuals at risk of rheumatoid arthritis.[1–6] Anticitrullinated protein antibody (ACPA)-negative individuals at risk of rheumatoid arthritis are less frequently studied, possibly because the pathogenesis of ACPA-negative rheumatoid arthritis is barely understood or because ACPA-negative individuals at increased risk of rheumatoid arthritis are considered to be more difficult to recognise than ACPA-positive individuals at increased risk of rheumatoid arthritis. Therefore, whether prevention of ACPA-negative rheumatoid arthritis is possible is still unknown.

False-negative results are a known limitation of trials of populations with high heterogeneity in risk of the outcome. This occurrence was described by Feinstein[7] as the "clinicostatistical tragedy"; if a large group of people has a low risk of a disease or outcome, a small group of people has an increased risk of that disease or outcome, and treatment effects that occur only in the small group might remain undetected when studying the group as a whole. Heterogeneity in risk within a trial population is therefore a reason for risk-stratified subgroup analyses.[8] For example, the PROMPT study[9] investigated the efficacy of methotrexate versus placebo in participants with undifferentiated arthritis. Although the total trial population showed no reduced rate of development of rheumatoid arthritis, participants at high risk of rheumatoid arthritis showed a reduced rate of rheumatoid arthritis development in the treatment group.[10] This effect was initially concealed by a high proportion of participants at low risk of rheumatoid arthritis in the total population. In 2022, the TREAT EARLIER trial[11] examined the efficacy of methotrexate in individuals with clinically suspect arthralgia and subclinical joint inflammation. The results showed no treatment effect on development of rheumatoid arthritis after 2-year follow-up. Although a subgroup analysis that only included participants with a 70% or greater risk of clinical arthritis showed no significant difference in development of rheumatoid arthritis over 2 years overall, it did suggest a possible delay in the treatment group.[11]

Initial results from TREAT EARLIER showed no treatment effect on rheumatoid arthritis development in ACPA-negative people with clinically suspect arthralgia. However, this group contained many participants at low risk of developing rheumatoid arthritis, potentially leading to a false negative result. We hypothesised that heterogeneity in risk within the ACPA-negative group with clinically suspect arthralgia could have diluted a treatment effect and that risk stratification was therefore

required. Stratification for risk of rheumatoid arthritis in people with clinically suspect arthralgia is now possible, unlike in 2014 when the TREAT EARLIER trial was designed.[12] Furthermore, to our knowledge, TREAT EARLIER is the only intervention trial conducted in individuals in the symptomatic risk stage of arthralgia that included ACPA-negative participants, making it uniquely suited to study the prevention of ACPA-negative rheumatoid arthritis now that 4-year follow-up has been completed.

In this follow-up analysis, we aimed to assess the efficacy of a 1-year course of methotrexate on the development of rheumatoid arthritis in ACPA-negative people with clinically suspect arthralgia and predicted increased risk of rheumatoid arthritis.

Methods

Study design and participants

The TREAT EARLIER trial was a randomised, double-blind, placebo-controlled, proof-of-concept trial conducted in the southwest region of the Netherlands from which we analysed data collected between April 16, 2015, and Sept 11, 2023.[11] Trial screening and trial visits occurred at a single centre, the Leiden University Medical Centre (Leiden, Netherlands). For 2 years, outcomes were assessed at this centre also. After 2 years, patients had outcomes assessed by their own rheumatologist. The protocol and amendments were approved by the Leiden University Medical Centre medical ethics committee. The TREAT EARLIER trial is registered with EudraCT (2014–004472–35) and the Netherlands Trial Register (NTR4853-trial-NL4599).

Adults aged 18 years or older with arthralgia who were at risk of developing rheumatoid arthritis were eligible for enrolment across 13 rheumatology outpatient clinics.[11] We used a two-level definition to identify individuals predisposed to develop rheumatoid arthritis.[11] First, participants needed to have recent onset (ie, within the past year) arthralgia that was suspected of progressing to rheumatoid arthritis according to the treating rheumatologist (ie, clinically suspect arthralgia). By definition, clinically suspect arthralgia was not present if participants presented with clinically apparent arthritis or if the symptoms were caused by another more probable explanation (eg, osteoarthritis or fibromyalgia). Establishing clinically suspect arthralgia did not require presence of autoantibodies, so both ACPA-positive and ACPA-negative people were included. Second, people with clinically suspect arthralgia had a contrast-enhanced 1·5T extremity MRI scan of their hands and forefeet that had to show subclinical joint inflammation for inclusion. Subclinical joint inflammation was considered to be present if at least one joint showed synovitis, tenosynovitis, or osteitis according to two independent readers and was present in less than 5% of age-matched, symptom-free volunteers of the same age at the same location (appendix pp 2–4).[13]

Sex data were self-reported, with the options male or female. All participants provided written informed consent for participating in TREAT EARLIER. Patient partners were involved in the design of the TREAT EARLIER trial protocol and the extension of the trial until 5-year follow-up.

Randomisation and masking

Participants were randomly assigned (1:1) via computer-generated block randomisation with a block size of 10, without stratification, to the active treatment group or placebo group by the hospital trial pharmacist who issued all trial medication but had no further involvement in the trial. The appearance, packaging, and distribution of the glucocorticoid injection and methotrexate tablets were identical to the corresponding placebo products. Participants, treating rheumatologists, researchers, and other staff involved were masked to group allocation for a minimum of 2 years. After all participants had completed 2-year follow-up, unmasking was done and treatment allocation was communicated to all participants. Database lock was later than the last patient at the last visit. Treating rheumatologists were not actively informed of the group allocation after unmasking.[11] Readers of MRI scans for inclusion in TREAT EARLIER were masked to clinical data and showed strong intra-reader reliability (intraclass correlation coefficient 0·92–0·99) and inter-reader reliability (0·91–0·98).

Procedures

Active treatment consisted of a single intramuscular glucocorticoid injection (120 mg of methylprednisolone) upon inclusion, then a 1-year course of methotrexate in which the dose was increased during the first 4 weeks of the trial up to 25 mg (10 tablets) per week or to the highest tolerated dose. Placebo consisted of a single placebo injection followed by a 1-year course of placebo tablets.

Trial visits occurred every 4 months with treating rheumatologists. In case of increasing symptoms between two trial visits, an immediate additional visit was scheduled. Clinical and questionnaire data were collected at every visit, including physical functioning (via the Health Assessment Questionnaire disability index [HAQ], scored at 0–3) and grip strength (as a measure of hand function; measured with a Jamar dynamometer in kg). For grip strength, participants squeezed three times per hand as hard as possible, alternating sides after each try; the highest grip strength of the strongest hand was used. Contrast-enhanced 1·5T MRIs of metacarpophalangeal joints, metatarsophalangeal joints, and wrist joints were done at baseline, 4 months, 12 months, and 24 months and scored for subclinical inflammation (ie, synovitis, tenosynovitis, and osteitis) via the rheumatoid arthritis MRI scoring system (RAMRIS) by two independent readers.[14,15] Total MRI inflammation score was the sum of

See Online for appendix

synovitis, tenosynovitis, and osteitis scores. ACPA and rheumatoid factor concentrations were measured at every visit. ACPA-positivity was defined as ACPA concentration of 7·0 U/mL or more (anti-CCP2, Phadia, Nieuwegein, Netherlands) at baseline. Rheumatoid factor positivity was defined as rheumatoid factor concentration of more than 3·5 IU/mL (in-house enzyme-linked immunosorbent assay). Participants who developed the primary outcome were thereafter treated in clinical practice without a prespecified treatment protocol.

Follow-up of participants will continue to 5 years.[16] As of Sept 11, 2023, all participants had completed 4 years of follow-up, so we include 4-year follow-up data. The frequency of visits over 2–4 years was not protocolised but scheduled according to the treating rheumatologists. We examined electronic patient files for all participants and extracted joint counts and use of disease-modifying antirheumatic drugs (DMARDs) to verify the primary outcome. To ensure that no information was missed due to participants changing hospitals, all participants were telephoned by the trial physician (QAD) to ask if and where they had visited a rheumatologist. This process ensured completeness of data for the primary outcome. Participant-reported symptoms were not assessed during years 2–4 and were only collected at year 5. MRIs were not conducted during years 2–4.

Outcomes

The primary outcome was development of rheumatoid arthritis, defined as the presence of clinically apparent inflammatory arthritis (established via joint examination by the treating rheumatologist) and clinical diagnosis of rheumatoid arthritis by the treating rheumatologist, assessed in all TREAT EARLIER participants.

During the first 2 years, clinically apparent inflammatory arthritis also had to persist for two outpatient clinic visits that were 2 or more weeks apart. During years 2–4, this 2-week interval was not possible as it differed from usual practice, in which DMARDs are usually initiated at the first visit with clinically apparent arthritis. Instead, during follow-up in years 2–4, DMARD initiation was considered a third criterion for the outcome of rheumatoid arthritis. Treatment with DMARDs, other than the trial medication, including glucocorticoids (eg, systemic or intra-articular), was not allowed before reaching the outcome.

Secondary outcomes were total MRI inflammation score, physical functioning, and grip strength. During years 0–2, the number of adverse events and serious adverse events were collected as safety outcomes.

Risk stratification

To address the hypothesis on the dilution of treatment effect, risk stratification was used to identify people at low risk of developing rheumatoid arthritis. We applied a previously published model for predicting risk of clinically apparent inflammatory arthritis development in people with clinically suspect arthralgia using baseline variables (appendix p 6).[11,12] Predictor variables were ACPA positivity (2 points), rheumatoid factor positivity (1 point), more than two locations of subclinical inflammation on MRI (2 points), and presence of metacarpophalangeal-extensor tenosynovitis on MRI (1 point). Corresponding risks of the cumulative number of points were 8% for 0 points, 9% for 1 point, 30% for 2 points, 54% for 3 points, 73% for 4 points, 79% for 5 points, and 86% for 6 points. Participants with less than 25% predicted risk of developing persistent, clinically apparent inflammatory arthritis were considered to be low risk (ie, 0 or 1 points), participants with 25–70% predicted risk were considered to be at increased risk (ie, 2 or 3 points), and participants with 70% or higher predicted risk were considered to be at high risk (ie, ≥4 points).

Statistical analysis

Analyses were conducted in the intention-to-treat population. To assess time to development of the primary outcome during 4-year follow-up, we plotted Kaplan–Meier graphs and used log-rank tests and Cox regression analyses. We assessed log-minus-log plots to check the proportional-hazard assumption. Participants who did not consent to the extension phase of years 3–5 or who died were censored at 2 years. Participants who started using DMARDs before developing the outcome were censored upon DMARD initiation. All other participants were censored upon development of the primary outcome or at 4 years. We stratified survival analyses by ACPA status and predicted risk (ie, low *vs* increased or high).

We conducted two subgroup analyses. First, we re-analysed data for MRI-detected subclinical joint inflammation, physical functioning, and grip strength for years 0–2 in the total ACPA-negative population with clinically suspect arthralgia[11] for treatment effect after risk stratification. For this subgroup analysis, we used constrained linear mixed models (LMMs), similar to the original TREAT EARLIER analysis.[11] The constrained function assumes the baseline mean to be equal between treatment groups, yielding robust estimates of treatment effect. These models included treatment, time in months, a random intercept per individual, and a random slope for the time variable. We checked the interaction–term time×treatment to assess linearity of the treatment effect over time. We graphically inspected residuals to check for model assumptions (ie, constant variance, normality, and independence of errors). As a sensitivity analysis, to check the robustness of the between-group difference, we included time as visit number (categorical) in the model instead of time in months (continuous). Second, we explored the association between methotrexate dose used (tolerated; categorised as mean per week of 0–9 mg, 10–19 mg, 20–25 mg)[17] and reduction of rheumatoid arthritis development at 4-year follow-up.

For the primary outcome, all data up to censoring were included. For subgroup analyses, data were analysed with mixed models under the missing-at-random assumption.

As a sensitivity analysis for the primary outcome, participants were stratified for autoantibody negativity (ie, ACPA negative and rheumatoid factor negative) instead of ACPA negativity. As a second sensitivity analysis, rheumatoid arthritis was defined as clinically apparent arthritis with a clinical diagnosis of rheumatoid arthritis and fulfilment of the 1987 or 2010 rheumatoid arthritis criteria.[18,19] As a final sensitivity analysis, we studied the total trial population without stratification for risk or ACPA status.

We conducted analyses using SPSS version 29 and STATA version 16. We describe subgroup analyses stratified for ACPA positivity or predicted risk of development of rheumatoid arthritis in the statistical analysis plan, which was made for the 2-year follow-up published with the original TREAT EARLIER trial.[11] The hypothesis regarding relevance of risk stratification within the ACPA-negative group was made before analyses of 4-year follow-up data but not described in the published analysis plan for 2-year data.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report.

Results

Between April 16, 2015, and Sept 11, 2019, 901 people with clinically suspect arthralgia were assessed for eligibility and 236 were enrolled in TREAT EARLIER and randomly assigned to a trial group.[11] All 236 participants were included in the intention-to-treat analysis. 154 (65%) of 236 participants were women and 82 (35%) were men, 182 (77%) were ACPA negative and 54 (23%) were ACPA positive. 153 (65%) of 236 participants had completed 4-year follow-up before unmasking in December, 2021. 50 (96%) of 52 rheumatoid arthritis diagnoses occurred before unmasking.

217 (92%) of 236 participants completed years 2–4 of follow-up. 17 (7%) participants did not consent to this follow-up and two (1%) died due to causes unrelated to imminent rheumatoid arthritis, so were censored at 2 years. Of these 19 participants, eight (42%) were initially allocated to the treatment group and 11 (58%) were initially allocated to the placebo group. Four (2%) of 236 participants who started using DMARDs before developing the outcome during years 2–4 were censored at DMARD initiation.

Of the 182 randomly assigned ACPA-negative participants, none were predicted to be at high risk (ie, predicted risk ≥70%) of developing persistent, clinically apparent inflammatory arthritis, 66 (36%) at increased risk (ie, predicted risk 25–70%), and 116 (64%) at low risk (ie, predicted risk <25%; figure 1). Of the 54 ACPA-positive participants, 24 (44%) were predicted to be at high risk, 30 (56%) at increased risk, and none at low risk. Mean age, tender joint count including 68 joints, the proportion with increased C-reactive protein, and rheumatoid factor positivity were similar in both predicted increased-risk and low-risk ACPA-negative participants (table; appendix p 7). In line with the variables in the prediction model, the ACPA-negative increased-risk group had more severe subclinical joint inflammation and worse physical disability than the low-risk group (table).

After 4 years, 52 (22%) of 236 participants had developed the primary outcome of rheumatoid arthritis (25 [21%] of 119 in the treatment group and 27 [23%] of 117 in the placebo group). 22 (12%) of 182 ACPA-negative participants developed the primary outcome during 4-year follow-up. Of ACPA-negative participants predicted to be at increased risk, three (9%) of 35 in the treatment group developed the primary outcome compared with nine (29%) of 31 in the placebo group (hazard ratio [HR] 0·27, 95% CI 0·07–0·99; p=0·034; figure 2A). Of ACPA-negative participants predicted to be at low risk, four (8%) of 53 in the treatment group met the primary outcome compared with six (10%) of 63 in the placebo group (0·79, 0·22–2·80; p=0·71; figure 2B). Thus, after risk stratification, a 1-year course of methotrexate was associated with a reduced rate of development of ACPA-negative rheumatoid arthritis in participants with predicted increased risk for developing the disease. All ACPA-negative participants remained ACPA negative during follow-up (anti-CCP2 ≤7·0 U/mL; measured at baseline, 1-year follow-up, 2-year follow-up, and at time of development of rheumatoid arthritis).

The development of rheumatoid arthritis at 4-year follow-up in ACPA-positive people with clinically suspect arthralgia was evaluated for comparison. Of 54 ACPA-positive participants, 30 (56%) developed rheumatoid arthritis during 4-year follow-up. The analysis showed no effect of treatment on development of

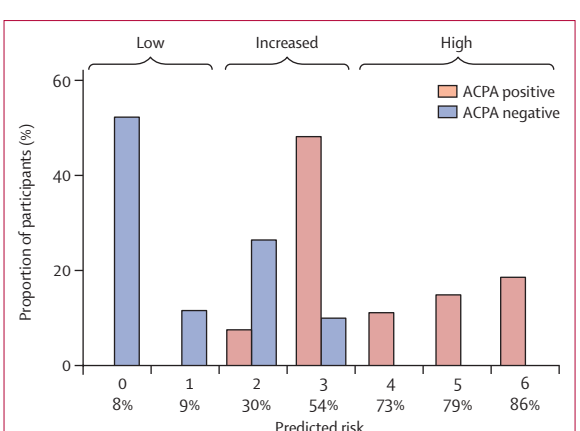

Figure 1: **Predicted risk of developing persistent, clinically apparent inflammatory arthritis among participants with subclinical joint inflammation[12]**
ACPA=anticitrullinated protein antibody.

rheumatoid arthritis (HR 0·93, 95% CI 0·45–1·93; p=0·84; figure 3).

Previously published results of 2-year data from TREAT EARLIER showed a sustained beneficial effect of treatment on severity of MRI-detected subclinical joint inflammation in ACPA-negative participants with clinically suspect arthralgia (appendix p 10).[11] On the basis of these results, we analysed treatment effect on severity of subclinical joint inflammation separately in ACPA-negative participants at low risk and increased risk of developing persistent, clinically apparent inflammatory arthritis. Overall decrease in subclinical joint inflammation was greater in the increased-risk group than in the low-risk group (–2·8 total MRI-inflammation score, 95% CI –4·0 to –1·5 *vs* –0·7, –1·3 to –0·2; figure 4). Median inflammation score of ACPA-negative participants with increased risk who developed rheumatoid arthritis at the time of rheumatoid arthritis development was 13 (IQR 10–15) in the placebo group and 7 (7–7) in the treatment group.

Previous research in people with clinically suspect arthralgia has shown that impairments in physical functioning and grip strength are associated with subclinical inflammation,[20,21] so we also assessed these data in the two ACPA-negative risk groups. The increased-risk group showed improvement after treatment regarding physical functioning (mean difference in HAQ between treatment group and placebo group during 2 years –0·14, 95% CI –0·27 to –0·01) but the low-risk group did not (0·02, –0·06 to 0·10). Results were similar for grip strength; the increased-risk group had a 3·00 kg (95% CI 0·85 to 5·15) predicted mean improvement with treatment versus placebo during 2 years whereas the low-risk group had a 1·28 kg (–0·32 to 2·87) predicted mean improvement with treatment versus placebo during 2 years (appendix p 12). Sensitivity analysis with time as visit number showed similar between-group differences (appendix p 13).

As sensitivity analyses, we assessed rheumatoid arthritis development in autoantibody-negative people with clinically suspect arthralgia (ie, negative for ACPA and rheumatoid factor) for increased-risk and low-risk groups separately, which gave similar results as for the ACPA-negative group (appendix p 8). We then excluded three ACPA-negative participants who did not fulfil the classification criteria for rheumatoid arthritis despite clinical diagnosis of rheumatoid arthritis and treatment as rheumatoid arthritis, which provided similar results (appendix p 9). We evaluated the total trial population without stratification for ACPA and risk, which showed no effect of treatment after 4 years (HR 0·88, 95% CI 0·51–1·51; p=0·64; figure 5), which showed no prevention. Finally, we explored the association between methotrexate dose and effect, expressed as the percentage reduction of development of rheumatoid arthritis at year 4. Participants taking 10–19 mg per week and 20–25 mg per week both did better than participants taking 0–9 mg per week (appendix p 14). Numbers of adverse events and serious adverse events have been published previously and were consistent with the known safety profile of methotrexate.[11]

	Increased risk (n=66)*	Low risk (n=116)†
Age, years	47 (13)	46 (12)
Sex		
Female	41 (62%)	82 (71%)
Male	25 (38%)	34 (29%)
Symptom duration, weeks	22 (14–42)	29 (17–54)
Tender joint count including 68 joints	4 (1–10)	4 (1–9)
BMI, kg/m²	28 (6)	29 (6)
Increased C-reactive protein (ie, ≥5 mg/L)	18 (27%)	30 (26%)
Health Assessment Questionnaire disability index	0·8 (0·4–1·4)	0·5 (0·1–1·0)
Grip strength, kg	28 (14)	29 (14)
MRI total inflammation score‡	9 (6–14)	4 (2–5)
Prediction model variables		
Rheumatoid-factor positive (ie, ≥3·5 IU/mL)	8 (12%)	15 (13%)
More than two locations of subclinical inflammation on MRI	65 (99%)	0
Presence of metacarpophalangeal-extensor tenosynovitis	12 (18%)	6 (5%)

Data are n (%), mean (SD), or median (IQR). ACPA=anticitrullinated protein antibody. *ACPA-negative participants with 25–70% risk of developing persistent, clinically apparent inflammatory arthritis. †ACPA-negative participants with <25% risk of developing persistent, clinically apparent inflammatory arthritis. ‡Sum of subclinical tenosynovitis, synovitis, and osteitis rheumatoid arthritis MRI scoring system scores, each consisting of the mean of the score of two independent readers.

Table: **Baseline characteristics of ACPA-negative participants with clinically suspect arthralgia**

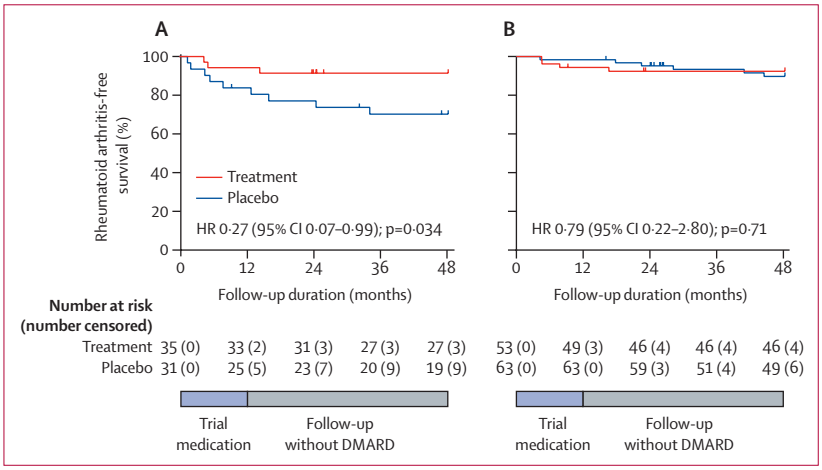

Figure 2: **Rheumatoid arthritis-free survival at 4-year follow-up in ACPA-negative participants with clinically suspect arthralgia**

(A) Participants with increased risk of developing persistent, clinically apparent inflammatory arthritis. (B) Participants with low risk of developing persistent, clinically apparent inflammatory arthritis. ACPA=anticitrullinated protein antibody. DMARD=disease-modifying antirheumatic drug. HR=hazard ratio.

Discussion

We found that a single intramuscular glucocorticoid injection and a 1-year course of methotrexate was associated with a reduced rate of development of ACPA-negative rheumatoid arthritis in participants with clinically suspect arthralgia at increased risk of rheumatoid arthritis, but not in those with low risk of rheumatoid

arthritis. This finding indicates that prevention of developing ACPA-negative rheumatoid arthritis is possible with methotrexate in the phase of clinically suspect arthralgia.

ACPA-negative disease has received relatively little attention in the research field of so-called pre-rheumatoid arthritis, and most interventional trials in people with arthralgia at risk for rheumatoid arthritis have only included participants with autoantibodies, possibly due to perceived difficulties in identifying ACPA-negative people who are at risk of rheumatoid arthritis. However, ACPA-negative rheumatoid arthritis also has a symptomatic pre-rheumatoid arthritis period, in which people have joint symptoms, disability, subclinical inflammation, and differentially expressed inflammatory cytokines.[22,23] ACPA-positive rheumatoid arthritis, which is traditionally more severe, has benefitted the most from improved treatment strategies, but the current disease burden of ACPA-negative rheumatoid arthritis is similar to that of ACPA-positive rheumatoid arthritis.[24,25] Progress has been made in risk stratification of people with clinically suspect arthralgia. Although many ACPA-negative individuals with clinically suspect arthralgia have a low risk of developing rheumatoid arthritis, about a third of ACPA-negative people with clinically suspect arthralgia have an increased risk. A 1-year course of methotrexate in these participants was associated with a reduced rate of development of ACPA-negative rheumatoid arthritis, which was sustained for 3 years after methotrexate was stopped, which contrasts with findings of some trials in ACPA-positive individuals with arthralgia.[1,2] Furthermore, the effect remained and was more pronounced during 2–4 years of follow-up, indicating sustained prevention of development of ACPA-negative rheumatoid arthritis.

Of all ACPA-positive participants with subclinical joint inflammation included in the TREAT EARLIER trial, we observed that 30 (56%) of 54 developed rheumatoid arthritis during 4-year follow-up in line with their predicted risk. Data from 4-year follow-up showed delayed rheumatoid arthritis development during the treatment year, but no sustained difference during the subsequent 3 years. As such, 4-year follow-up data from the ACPA-positive group are in line with their 2-year follow-up data.[11]

Comparing data from ACPA-positive and ACPA-negative participants with clinically suspect arthralgia showed that methotrexate has a sustained effect in ACPA-negative people with clinically suspect arthralgia but not in ACPA-positive people with clinically suspect arthralgia. There are various possible explanations for this finding. For example, the pathophysiology of ACPA-negative people with rheumatoid arthritis is not well understood and developing ACPA-negative rheumatoid arthritis could be more sensitive to methotrexate than developing ACPA-positive rheumatoid arthritis. Although there are no known differences in methotrexate efficacy between ACPA-negative and ACPA-positive rheumatoid arthritis in

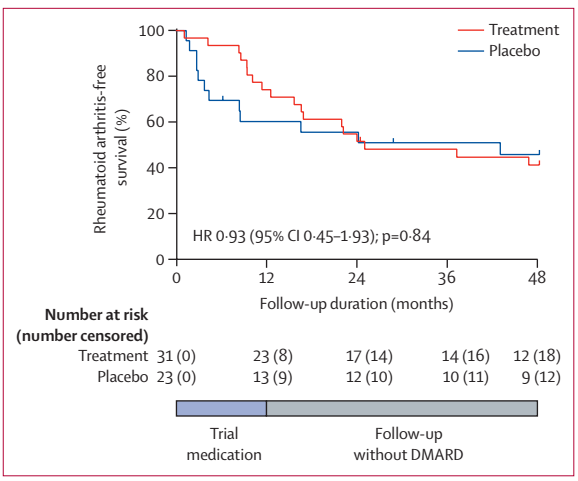

Figure 3: **Rheumatoid arthritis-free survival at 4-year follow-up in ACPA-positive participants with clinically suspect arthralgia**
ACPA=anticitrullinated protein antibody. DMARD=disease-modifying antirheumatic drug. HR=hazard ratio.

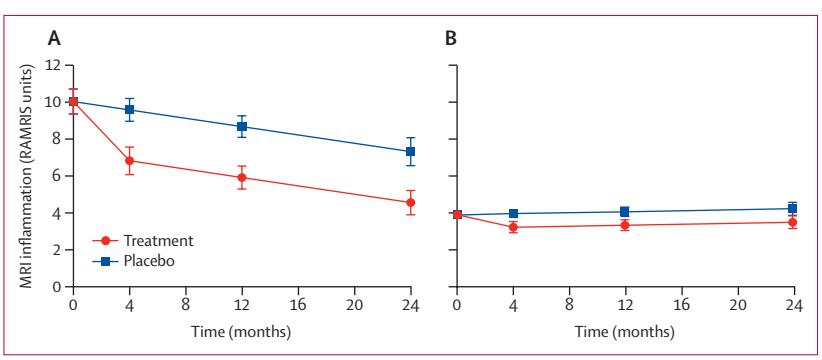

Figure 4: **Severity of subclinical joint inflammation for 2 years in ACPA-negative participants**
(A) Participants with increased risk of developing persistent, clinically apparent inflammatory arthritis. (B) Participants with low risk of developing persistent, clinically apparent inflammatory arthritis. Total predicted MRI inflammation score is shown (ie, sum of synovitis, tenosynovitis, and osteitis RAMRIS scores), with predicted means calculated via linear mixed models per treatment group. Error bars show SE of the mean.
ACPA=anticitrullinated protein antibody. RAMRIS=rheumatoid arthritis MRI scoring system.

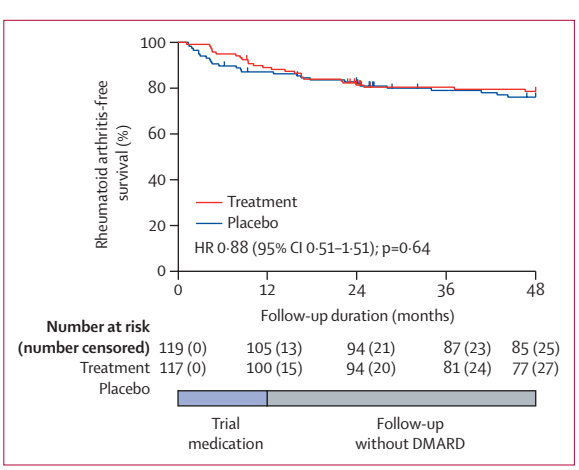

Figure 5: **Rheumatoid arthritis-free survival at 4-year follow-up in all participants with clinically suspect arthralgia**
DMARD=disease-modifying antirheumatic drug. HR=hazard ratio.

the phase of classified disease, the phase of disease development could be different.[26,27] Another explanation could be timing of the intervention, implying that maturation of autoimmune response differs and, hypothetically, the point of no return has already been passed in ACPA-positive people with clinically suspect arthralgia and subclinical inflammation upon symptom onset, whereas this is not yet the case in APCA-negative people with clinically suspect arthralgia and subclinical inflammation. Some trials of different DMARDs in ACPA-positive people with arthralgia showing no sustained difference in development of rheumatoid arthritis could support this notion.[1,2,4] Therefore, the opportunity for prevention could extend to a later point in time during the course of ACPA-negative rheumatoid arthritis development, compared with ACPA-positive rheumatoid arthritis.

The relevance of risk stratification when interpreting the trial results was supported by our findings of subclinical joint inflammation. Although all participants with clinically suspect arthralgia had a sustained improvement of subclinical joint inflammation during 2-year follow-up, it now appears that this effect might have been mainly attributed to improvement in ACPA-negative participants at predicted increased risk of developing persistent, clinically apparent inflammatory arthritis. Treatment effects on physical functioning and grip strength were also present in this group. MRI and questionnaires were not repeated during years 2–4 of follow-up, so no 4-year data were available. Nevertheless, our data on subclinical inflammation indicate that ACPA-negative participants with predicted increased risk of rheumatoid arthritis benefitted from treatment in the clinically suspect arthralgia phase.

The population of people with arthralgia who are at risk of rheumatoid arthritis is heterogeneous. When studying more homogeneous groups, nuanced conclusions about the effects of treatment during the clinically suspect arthralgia phase can be made, which would not be possible by studying the total heterogeneous population. Further validation studies are needed to substantiate our findings.

ACPA negativity is not the same as autoantibody negativity. Eight (12%) of 66 of ACPA-negative participants at predicted increased risk of rheumatoid arthritis included in this analysis were rheumatoid factor positive. The frequency of rheumatoid factor positivity was similar in both ACPA-negative risk groups, suggesting that this risk was not related to a difference in rheumatoid factor positivity. Furthermore, survival data for rheumatoid arthritis development in autoantibody-negative participants showed similar findings. In 2022, several other autoantibody reactivities were described, such as anti-carbamylated protein antibodies (anti-CarP) and anti-acetylated protein antibodies.[27] These autoantibody reactivities were not measured in TREAT EARLIER participants, but previous studies of people with rheumatoid arthritis have shown low proportions (8–14%) of anti-CarP positivity and anti-acetylated protein antibody levels in ACPA-negative or rheumatoid factor negative participants with rheumatoid arthritis.[29–31] Similarly, in a 2017 study of patients with clinically suspect arthralgia, only nine (4%) of 209 ACPA-negative patients were positive for anti-CarP.[32] That the majority of ACPA-negative participants with an increased risk (66 [36%] of 182 ACPA-negative participants) were positive for unmeasured autoantibodies is unlikely. Therefore, that the treatment effect is based on unmeasured autoantibody positivity is improbable.

ACPA-negative rheumatoid arthritis is a disease for which classification is sometimes questioned. Because characteristic autoantibodies (ie, objective features) are missing, classification is largely based on a combination of clinical features. We attempted to avoid misclassification at time of inclusion (ie, identification of clinically suspect arthralgia) and when establishing the outcome (ie, identification of rheumatoid arthritis). People with pain for which other diagnoses were more likely than imminent rheumatoid arthritis (eg, presence of osteoarthritis or fibromyalgia) were not diagnosed as having clinically suspect arthralgia and were not included in the analysis. Moreover, to meet the outcome, participants had to have clinically apparent inflammatory arthritis with a clinical diagnosis of rheumatoid arthritis that persisted for 2 weeks (during years 0–2) or were treated with DMARDs after reaching the endpoint (during years 2–4). As a sensitivity analysis, rheumatoid arthritis was also defined as fulfilment of 1987 or 2010 classification criteria. The similarity in findings with the primary outcome in this sensitivity analysis shows robustness. Furthermore, of participants who developed rheumatoid arthritis, 30 (58%) of 52 were ACPA positive and 22 (42%) of 52 were ACPA negative; this distribution is similar to that observed in early arthritis cohorts, in which also approximately half of patients with classified rheumatoid arthritis were ACPA negative at diagnosis.[33,34]

The risk stratification method we used was derived from observational data of people with clinically suspect arthralgia.[12] The prediction model for people with arthralgia that we used was built including data from autoantibody-negative, individuals at risk of rheumatoid arthritis.[12] The risks we observed during this analysis were in line with predicted risks. Nevertheless, the choice of risk-stratification method is secondary to the importance of risk stratification in a heterogeneous group. When another risk stratification model is published that specifically applies to ACPA-negative individuals with clinically suspect arthralgia, it can also be used. The prediction method we used balances the presence of autoantibodies (ie, ACPA and rheumatoid factor) and subclinical joint inflammation. We observed that ACPA-negative participants with low and increased predicted risk of developing persistent, clinically apparent inflammatory arthritis had similar prevalence

of rheumatoid factor positivity but differed in the extent of subclinical joint inflammation. Therefore, for ACPA-negative individuals with more extensive subclinical joint inflammation, the treatment was effective in reducing development of rheumatoid arthritis, severity of joint inflammation, and physical disability.

Treatment after having developed rheumatoid arthritis (primary outcome) and trial visits during years 2–4 were not protocolised and were established by treating rheumatologists according to European Alliance of Associations for Rheumatology recommendations.[35] However, this process did not hinder data collection for the primary outcome as all data could be accurately derived from electronic patient files. Furthermore, DMARD initiation before rheumatoid arthritis development was absent during years 0–2 and infrequent during years 2–4, and these participants were censored at this time point.

Unmasking of treatment group allocation was done after database lock. Group allocation was only actively communicated to participants, not to rheumatologists. 153 (65%) of 236 participants had already completed 4-year follow-up at the time of unmasking. As rheumatologists were not directly informed, and because 50 (96%) of 52 rheumatoid arthritis diagnoses occurred before unmasking during the first follow-up years, we believe that unmasking of participants during the final part of follow-up did not majorly influence our findings.

The TREAT EARLIER trial was not powered to analyse subgroups. Subsequent trials in ACPA-negative people with clinically suspect arthralgia at increased risk of rheumatoid arthritis development should be conducted to substantiate treatment efficacy and establish optimal treatment duration and dose. We explored the association between methotrexate dose and treatment effects, which suggested that both the highest methotrexate dose (20–25 mg) and a slightly lower dose (15 mg) might be valuable. Nonetheless, future trials are required to establish the optimal treatment strategy.

Overtreatment is important to consider when treating people who are at risk of a disease. A 20% reduction in development of rheumatoid arthritis corresponds with a number needed to treat of five, which is much lower than generally accepted for treatments such as statin therapies to reduce cardiovascular events or anti-coagulant treatment for atrial fibrillation.[36,37] Moreover, ACPA-negative participants with clinically suspect arthralgia and increased predicted risk who did not progress to rheumatoid arthritis still benefitted from treatment. Their physical functioning improved and the severity of subclinical inflammation returned close to levels found in symptom-free volunteers.[13] Resolution can also be an important treatment goal. Thus, on the basis of our data, overtreatment of ACPA-negative individuals at increased risk of rheumatoid arthritis is not a concern.

Future research should assess the cost-effectiveness of treatment with methotrexate during the clinically suspect arthralgia phase. As methotrexate is relatively inexpensive, assessing health benefits in proportion to societal costs could be interesting.

Overall, our 4-year follow-up analysis of the TREAT EARLIER trial suggests that the development of ACPA-negative rheumatoid arthritis can be prevented by a 1-year course of methotrexate in people with clinically suspect arthralgia at increased risk of developing rheumatoid arthritis, which provides promising prospects for ACPA-negative people at risk of rheumatoid arthritis.

Contributors

AHMvdH-vM designed the original TREAT EARLIER trial and this follow-up analysis. QAD, DIK, KV, and LRL collected the data. QAD and DIK accessed and verified the data. QAD analysed the data. AHMvdH-vM was the principal investigator. All authors had full access to all data in the analysis, interpreted the data, wrote the report, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Requests for data collected in the TREAT EARLIER trial, such as deidentified participant data, can be made to the corresponding author of this Article on publication. Requests will be considered on an individual basis. The statistical analysis plan and study protocol of the 2-year follow-up analyses have been published previously.[11]

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