

Intervention with methotrexate in patients with arthralgia at risk of rheumatoid arthritis to reduce the development of persistent arthritis and its disease burden (TREAT EARLIER): a randomised, double-blind, placebo-controlled, proof-of-concept trial



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Summary

Background Rheumatoid arthritis is the most common autoimmune disease worldwide and requires long-term treatment to suppress inflammation. Currently, treatment is started when arthritis is clinically apparent. We aimed to evaluate whether earlier intervention, in the preceding phase of arthralgia and subclinical joint inflammation, could prevent the development of clinical arthritis or reduce the disease burden.

Methods We conducted a randomised, double-blind, placebo-controlled, proof-of-concept-trial at the Leiden University Medical Centre, Leiden, Netherlands. Adults aged 18 years or older with arthralgia clinically suspected of progressing to rheumatoid arthritis and MRI-detected subclinical joint inflammation were eligible for enrolment across 13 rheumatology outpatient clinics in the southwest region of the Netherlands and randomly assigned (1:1) to a single intramuscular glucocorticoid injection (120 mg) and a 1-year course of oral methotrexate (up to 25 mg/week), or placebo (single injection and tablets for 1 year). Participants and investigators were masked to group assignment. Follow-up continued for 1 year after the end of the 1-year treatment period. The primary endpoint was development of clinical arthritis (fulfilling the 2010 rheumatoid arthritis classification criteria or involving two or more joints) that persisted for at least 2 weeks. Patient-reported physical functioning, symptoms, and work productivity were secondary endpoints, which were measured every 4 months. Additionally, the course of MRI-detected inflammation was studied. All participants entered the intention-to-treat analysis. This trial is registered with EudraCT, 2014-004472-35, and the Netherlands Trial Register, NTR4853-trial-NL4599.

Findings Between April 16, 2015, and Sept 11, 2019, 901 patients were assessed for eligibility and 236 were enrolled and randomly assigned to active treatment (n=119) or placebo (n=117). At 2 years, the frequency of the primary endpoint was similar between the groups (23 [19%] of 119 participants in the treatment group vs 21 [18%] of 117 in the placebo group; hazard ratio 0·81, 95% CI 0·45 to 1·48). Physical functioning improved more in the treatment group during the first 4 months and remained better than in the placebo group (mean between-group difference in Health Assessment Questionnaire disability index over 2 years: -0·09, 95% CI -0·16 to -0·03; p=0·0042). Similarly, pain (on scale 0–100, mean between-group difference: -8, 95% CI -12 to -4; p<0·0001), morning stiffness of joints (-12, -16 to -8; p<0·0001), presenteeism (-8%, -13 to -3; p=0·0007), and MRI-detected joint inflammation (-1·4 points, -2·0 to -0·9; p<0·0001) showed sustained improvement in the treatment group compared with the placebo group. The number of serious adverse events was equal in both groups; adverse events were consistent with the known safety profile for methotrexate.

Interpretation Methotrexate, the cornerstone treatment of rheumatoid arthritis, initiated at the pre-arthritis stage of symptoms and subclinical inflammation, did not prevent the development of clinical arthritis, but modified the disease course as shown by sustained improvement in MRI-detected inflammation, related symptoms, and impairments compared with placebo.

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Introduction

Rheumatoid arthritis is among the most prevalent, disabling, and burdensome autoimmune diseases in high-income countries. It affects 1% of the population and is

characterised by chronic inflammation of joints, resulting in disability, work productivity loss, and high societal costs.¹ The development of treat-to-target strategies and biological disease-modifying antirheumatic drugs

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Research in context

Evidence before this study

Clinical arthritis (joint swelling upon physical examination) is required to identify rheumatoid arthritis. Once clinically diagnosed, rheumatoid arthritis is generally a chronic disease and requires long-term treatment with disease-modifying antirheumatic drugs. Before the development of clinical arthritis, disease processes are less matured and presumably more susceptible to permanent disease modification. We searched MEDLINE (via PubMed), Embase, Cochrane Library, and clinical trial registries, for work published up to Nov 26, 2021, using the terms “prevention”, “(rheumatoid) arthritis”, and “randomized controlled trial”. The first placebo-controlled trial (published in 2009), assessing treatment in people with autoantibody-positive arthralgia at risk of rheumatoid arthritis (n=83), showed that two intramuscular dexamethasone injections decreased autoantibody levels, but did not prevent clinical arthritis or rheumatoid arthritis. The PRAIRI trial (2018) showed that a single infusion of rituximab in people with autoantibody-positive arthralgia (n=81) delayed, but did not prevent, clinical arthritis. Patient-reported outcomes were not assessed in these two trials. The STAPRA trial (2021), on prevention of rheumatoid arthritis with statins, was prematurely stopped due to severe difficulties with recruitment. 6-month interim results of the ARIAA trial showed that anti-citrullinated protein antibody (ACPA)-positive people at risk of rheumatoid arthritis had greater improvement in MRI-detected joint inflammation after 6 months of treatment with abatacept compared with placebo. Whether this difference is sustained after treatment is stopped until the end of follow-up at 18 months is not yet known. Two randomised controlled trials aiming to evaluate rheumatoid arthritis prevention with abatacept (APIPPRA [2013-003413-18]) or hydroxychloroquine (StopRA [NCT02603146]) were identified in trial registries; the results of which are yet to be published.

Added value of this study

This study is, to our knowledge, the first to evaluate the efficacy of the first-line (and inexpensive) therapy for rheumatoid arthritis, methotrexate, when initiated in the pre-arthritis phase. We assessed not only the outcome from the physician's perspective (clinical arthritis development), but also patient-reported outcomes to measure disease burden (physical impairment, symptoms, and work-related problems). By contrast with previous trials, this study was not confined to ACPA-positive or rheumatoid factor-positive patients at risk of rheumatoid arthritis, which is important as the patient-reported disease burden is nowadays similar in ACPA-positive and ACPA-negative rheumatoid arthritis. We showed that a temporary treatment, started in the phase of arthralgia and subclinical joint inflammation, did not prevent clinical arthritis but resulted in sustained disease modification, as measured by a decrease in MRI-detected joint inflammation, disease-related symptoms, physical limitations, and work productivity loss, which persisted after treatment was stopped.

Implications of all the available evidence

Taken together, the evidence to date shows no prevention of the development of clinical arthritis by initiating treatment in the arthralgia (pre-arthritis) phase. However, this study is the first of our knowledge to suggest that patients with arthralgia and increased risk of rheumatoid arthritis might benefit from initiation of methotrexate before the onset of clinical arthritis. Although secondary endpoints should be interpreted with caution, these findings of sustained disease modification might open up a new treatment landscape in the pre-arthritis phase of rheumatoid arthritis, where physical limitations can be just as severe as at the onset of clinical arthritis.

(DMARDs) has facilitated better suppression of disease activity and reduced joint destruction. However, rheumatoid arthritis remains a chronic, relapsing and remitting disease that impairs physical functioning and requires long-standing immunosuppressive treatment.^{1,2} Therefore, there is an unmet need for a therapy that prevents the development of persistent rheumatoid arthritis or reduces the burden of the disease.

Rheumatoid arthritis is diagnosed once clinical arthritis (eg, joint swelling) is identified upon physical examination.^{2,3} International recommendations advocate a prompt start with methotrexate as first-line therapy, which has a favourable risk-to-benefit profile and low cost, often combined with a short course of low-dose glucocorticoids for a rapid effect.^{2,3} However, disease processes begin long before the manifestation of clinical arthritis, and become clinically recognisable when patients develop symptoms.^{4,5} This pattern of symptoms, including, for example, pain in small joints or morning

stiffness of joints, allows rheumatologists to identify patients at risk of developing rheumatoid arthritis while clinical arthritis is still absent, and is referred to as clinically suspect arthralgia.^{6,7} Clinically suspect arthralgia precedes both autoantibody-positive and autoantibody-negative rheumatoid arthritis. Approximately 32% of people with clinically suspect arthralgia and imaging-detected inflammation develop rheumatoid arthritis.⁶ A study published in 2020 showed that combinations of autoantibody and imaging characteristics in people with clinically suspect arthralgia represent a rheumatoid arthritis risk of greater than 70%.⁸ The ability to identify people with clinically suspect arthralgia and subclinical inflammation who are at risk of developing rheumatoid arthritis provides unique opportunities to study treatment efficacy in inducing sustained disease modification at this stage.

To date, no evidence exists that treatment initiated in the pre-arthritis phase is effective in preventing the

development of clinical arthritis or reducing the disease burden of patients with rheumatoid arthritis. Patients have indicated that physical limitations, pain, fatigue, and work-related problems are most relevant to them.^{9,10} Although autoantibody-positive rheumatoid arthritis was previously regarded as more severe than autoantibody-negative disease, nowadays patients with rheumatoid arthritis with and without autoantibodies have equally severe impairments in physical function and at work,¹¹ presumably because autoantibody-positive patients with rheumatoid arthritis have benefited most from treatment advances over the past few decades.¹² Moreover, physical impairment in the arthralgia (pre-arthritis) phase is almost as severe as at the stage of rheumatoid arthritis diagnosis, and already results in work limitations.^{15,13} We hypothesised that this phase of symptoms and subclinical joint inflammation is a therapeutic window to permanently modify the disease course. We aimed to investigate the efficacy of a single intramuscular injection of glucocorticoids and a 1-year course of methotrexate in the pre-arthritis phase of arthralgia and subclinical joint inflammation to reduce either the progression to clinically apparent persistent arthritis or to modify the disease burden.

Methods

Study design

We conducted a randomised, double-blind, placebo-controlled, proof-of-concept trial (TREAT EARLIER). Trial screening, all study visits, and assessment of endpoints occurred at a single centre, the Leiden University Medical Centre (LUMC), Leiden, Netherlands. The protocol and amendments were approved by the LUMC medical ethics committee and are provided in the appendix (pp 39–71).

Participants

Adults aged 18 years or older with arthralgia at risk of developing rheumatoid arthritis were eligible for enrolment across 13 rheumatology outpatient clinics in the southwest region of the Netherlands. We used a two-level definition to identify patients predisposed to develop rheumatoid arthritis. First, patients needed to have recent-onset (within the past year) arthralgia that was suspected of progressing to rheumatoid arthritis according to the treating rheumatologist (ie, clinically suspect arthralgia). Second, an MRI scan of their hands or forefeet had to show subclinical joint inflammation.

Clinically suspect arthralgia, a complex of clinical symptoms and signs, was identified by rheumatologists using pattern recognition, as no single symptom is sufficiently specific for imminent rheumatoid arthritis.^{6,14} By definition, clinically suspect arthralgia was not present if patients presented with clinical arthritis or if another explanation for the symptoms was more likely to be the cause (eg, osteoarthritis, fibromyalgia, or suspicion of developing psoriatic arthritis or gout). Establishing

clinically suspect arthralgia does not require abnormal results on laboratory investigations (eg, acute phase reactant or autoantibodies). Compliance with the European Alliance of Associations for Rheumatology definition of arthralgia at risk of rheumatoid arthritis was not mandatory, as it was not yet developed at the start of the trial.⁷

To screen for the second inclusion criterion, we invited all patients in the region identified as having clinically suspect arthralgia for a contrast-enhanced 1.5T extremity MRI of the metacarpophalangeal, wrist, and metatarsophalangeal joints. MRIs were assessed by two readers independently for subclinical inflammation (ie, synovitis, tenosynovitis, or osteitis), using the rheumatoid arthritis MRI scoring method (appendix pp 2–4). Subclinical inflammation was defined as present if at least one joint showed one or more inflammatory features scored by both readers and that were present in fewer than 5% of age-matched symptom-free volunteers at the same location. If only one reader identified the presence of such inflammation, the MRI was considered negative (appendix p 4). Readers were masked to any clinical data and showed excellent intrareader and inter-reader reliability (intraclass correlation coefficients >0.90). To speed up screening, immediately after scanning, MRIs were scored and patients were informed on the presence or absence of subclinical inflammation. A detailed MRI and scoring protocol is provided in the appendix (pp 2–4).

We excluded patients with (history of) clinical arthritis, previous or current treatment with DMARDs or glucocorticoids, contraindications for MRI, pregnancy or breastfeeding, bone marrow hypoplasia, elevated hepatic enzyme concentrations (>3 times the upper normal limit), serum creatinine concentration of greater than 150 µmol/L or estimated clearance of less than 60%, serious infections in the past 3 months, or chronic infectious diseases.

Written informed consent for the MRI was obtained from all patients screened. Subsequently, patients who met the inclusion criteria and were willing to participate provided written informed consent for the complete trial.

Randomisation and masking

The hospital trial pharmacist randomly assigned participants (1:1) to active treatment or placebo (using computer-generated block randomisation [block size of ten] without stratification) and issued all study medication, but had no further involvement in the trial. The appearance, packaging, and distribution of the intramuscular glucocorticoid injection and methotrexate tablets were identical to the corresponding placebo products. Neither the participants nor the treating rheumatologist, study team, or staff involved had any knowledge on which treatment participants would receive, ensuring allocation concealment. All participants and staff involved (including those administering study medication, assessing endpoints, and analysing the data)

See Online for appendix

were masked to group allocation until after database lock. MRI results during follow-up were not communicated to participants nor to staff involved with data collection or treatment decisions.

Procedures

A single intramuscular glucocorticoid injection (120 mg methylprednisolone) or corresponding placebo injection was administered by the clinical staff upon inclusion in the trial, followed by a 52-week course of methotrexate or placebo tablets. Dosage was increased over the first 4 weeks up to ten tablets per week (corresponding to 25 mg methotrexate per week), or the highest tolerated dose. From

week 48, tablets were tapered over 4 weeks (six tablets for 2 weeks, followed by three tablets for 2 weeks) and then stopped at week 53. Participants recorded the number of tablets they took each week in their study diary. Folic acid supplementation (5 mg/week) was added to both the active treatment and placebo groups. All participants received oral methotrexate tablets (or placebo tablets); methotrexate injections were not used. After the first year with study medication, participants were followed up for another year without study medication, to ensure that a potential delay in arthritis development was not falsely interpreted as a preventive effect. Study visits occurred every 4 months and included assessment on clinical arthritis development by treating rheumatologists, collection of clinical data (including secondary outcomes), phlebotomy (eg, for safety monitoring, such as complete blood counts, kidney function, and liver panels, and acute phase reactants; except for the safety monitoring, these data were not analysed in the current study), and questionnaires. When a participant had an increase in symptoms between two study visits, an immediate additional visit was scheduled. MRI and radiographs of hands and feet were obtained at baseline and repeated after 4, 12, and 24 months. Anti-citrullinated protein antibody (ACPA)-positivity was defined as ACPA concentration of greater than 7 U/mL (anti-CCP2; Phadia, Netherlands) and rheumatoid factor-positivity was defined as rheumatoid factor concentration of greater than 3.5 IU/mL (in-house ELISA). A full overview of collected data is provided in the appendix (p 30).

During follow-up, concomitant treatment with analgesics, such as acetaminophen or non-steroidal anti-inflammatory drugs was allowed, except for within 24 h before MRI scans. Treatment with any other DMARDs or glucocorticoids (systemic or intra-articular) was prohibited during the trial. Only if participants reached the primary endpoint did they proceed to open-label DMARD therapy in routine clinical practice.

Outcomes

The primary endpoint was development of clinical arthritis that persisted for at least 2 weeks and fulfilled the 2010 rheumatoid arthritis classification criteria or involved two or more joints. The presence of clinical arthritis was based on the physical evaluation of the patient's joints by two rheumatologists. Before the trial started, rheumatologists attended a training session to promote similarity in evaluating the primary endpoint. When clinical arthritis was detected, an additional study visit took place after 2 weeks to determine if the arthritis persisted.

The coprimary endpoint was DMARD-free status after 2 years, defined as the absence of clinical arthritis upon joint examination in the absence of DMARD use (including systemic or intra-articular glucocorticoids).

Secondary endpoints, measured every 4 months, were the assessment of physical functioning, measured with the Health Assessment Questionnaire disability index (HAQ; range 0–3); patient-reported symptoms (joint pain,

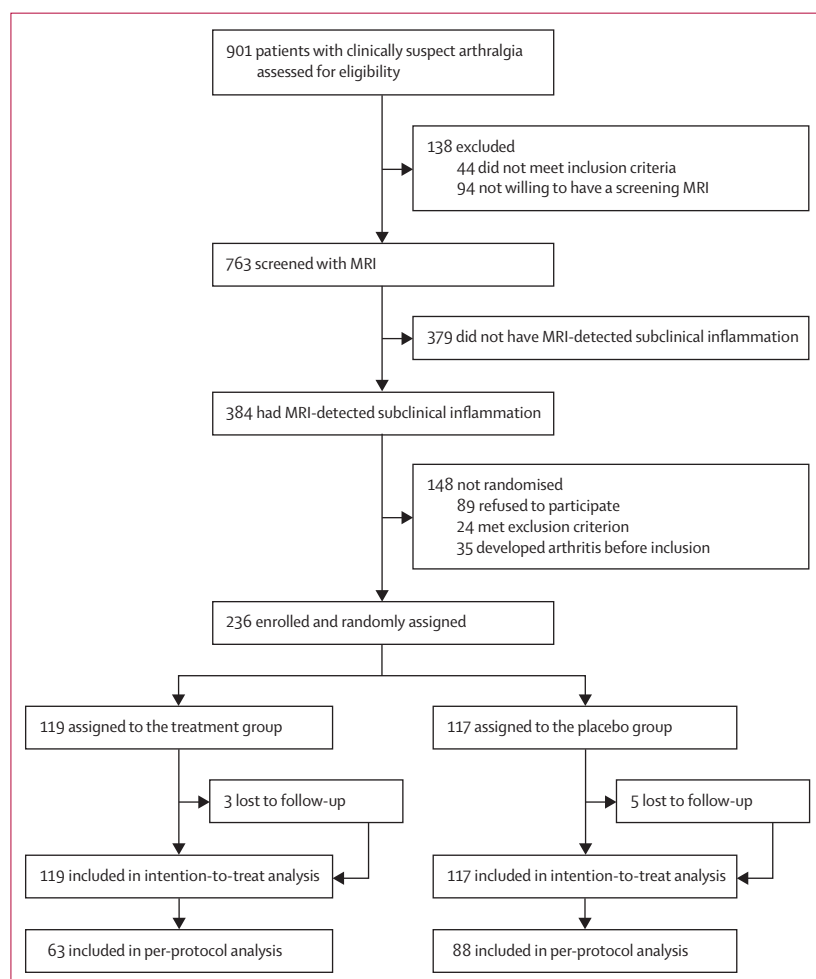


Figure 1: Trial profile

44 patients did not meet the trial inclusion criteria because of contraindication for MRI (n=12), wish to become pregnant (n=25), clinically suspect arthralgia not being the most likely diagnosis (n=1), serious infection (n=2; HIV, chronic viral hepatitis), or language barrier hindering the obtaining of informed consent (n=4). 35 patients developed clinical arthritis before randomisation. The median time between identification of clinically suspect arthralgia and clinical arthritis development was 3 weeks (IQR 1–5). Reasons for loss to follow-up in the treatment group were travel distance (n=1), side-effects of study medication (n=1, nausea), and unknown (n=1), and in the placebo group were development of a diagnosis other than clinical arthritis or rheumatoid arthritis requiring immunosuppressive treatment (n=1), patient-requested evaluation at another hospital where treatment with disease-modifying antirheumatic drugs was started in the absence of clinical arthritis and where treatment was continued without study visits (n=1), immobility due to a vertebral compression fracture (n=1), and unknown reasons (n=2).

morning stiffness of joints, and fatigue), expressed on a scale 0 (no symptoms) to 100 (worst symptoms possible; phrasing of these questions is provided in the appendix [p 7]); and work productivity, measured with the Work Productivity Impairment Scale, expressed as presenteeism (percentage of impairment in productivity due to joint symptoms in the past week) and absenteeism (percentage of time absent from work due to joint symptoms in the past week). Presenteeism has been reported to increase during progression from clinically suspect arthralgia to clinical arthritis, while absenteeism has not.¹³

	Treatment group (n=119)	Placebo group (n=117)
Age, years	46 (13)	47 (11)
Sex		
Female	74 (62%)	80 (68%)
Male	45 (38%)	37 (32%)
First-degree relative with rheumatoid arthritis	31 (27%)	32 (28%)
Symptom duration, weeks	28 (13–45)	27 (16–51)
Morning stiffness of joints for ≥ 60 min	40 (34%)	41 (35%)
Positive squeeze test of MCP joints	53 (45%)	52 (45%)
68-TJC	4 (1–8)	3 (1–9)
Body-mass index, kg/m ²	28 (6)	28 (5)
CRP concentration, mg/L	3 (3–6)	3 (3–6)
CRP concentration increase ≥ 5 mg/L	36 (30%)	32 (27%)
Rheumatoid factor positive (≥ 3.5 IU/mL)	33 (28%)	35 (30%)
ACPA positive (≥ 7 mg/L)	31 (26%)	23 (20%)
Rheumatoid factor or ACPA positive	39 (33%)	38 (32%)
HAQ score	0.6 (0.1–1.1)	0.6 (0.3–1.0)
Pain, scale 0–100	50 (30–70)	50 (30–70)
Morning stiffness of joints, scale 0–100	55 (30–80)	60 (30–80)
Fatigue, scale 0–100	60 (30–70)	50 (20–70)
Presenteeism	40% (0–60)	30% (0–70)
Absenteeism	0% (0–0)	0% (0–0)
MRI total inflammation score	5 (3–9)	5 (3–8)
Tenosynovitis score	1.0 (0.0–2.5)	1.0 (0.0–2.0)
Synovitis score	2.5 (1.0–4.0)	1.5 (1.0–3.5)
Osteitis score	1.5 (0.5–2.5)	1.5 (0.5–2.5)
Erosion score	2.0 (1.0–3.5)	1.5 (0.5–3.0)

Data are n (%), mean (SD), or median (IQR). Baseline characteristics as measured at trial inclusion. MRI scores were calculated as the mean of the scores of the two readers. Total inflammation score on MRI summed the scores of tenosynovitis, synovitis, and osteitis. MCP=metacarpophalangeal. 68-TJC=tender joint count including 68 joints. CRP=C-reactive protein. ACPA=anti-citrullinated protein antibody. HAQ=Health Assessment Questionnaire disability index.

Table 1: Baseline characteristics

The course of MRI-detected joint inflammation (measured as the sum of synovitis, osteitis, and tenosynovitis) and radiographical progression (using the Sharp–van der Heijde scoring methodology) were explorative endpoints. MRI scans were scored by two readers independently, masked to any clinical data and with known time order (appendix pp 2–5).

Safety endpoints were the number of adverse events and serious adverse events, whether considered treatment-related or not.

Statistical analysis

On the basis of an estimated risk of 35% of developing rheumatoid arthritis and the assumption that treatment would result in a 50% reduction in risk, we computed a sample size of 182 participants for 80% power of a logistic regression analysis with success rates of 35.0% in the placebo group and 17.5% in the active treatment group and a two-sided α level of 0.05. Accounting for 20% dropout resulted in a total sample size of 230 participants (115 per group).

The intention-to-treat population consisted of all randomly assigned participants. The randomisation groups were used in this analysis, irrespective of any protocol violations. This primary analysis population was used for primary and secondary efficacy endpoints and safety analyses. The per-protocol population consisted of participants who met the study entry criteria, completed follow-up, did not discontinue study medication within the first 2 months after randomisation, used at least eight study tablets per week (corresponding to at least 20 mg methotrexate per week) for more than 80% of the first year or up to the primary endpoint, and used no other DMARDs or (systemic or intra-articular) glucocorticoids prescribed by rheumatologists during the complete follow-up. All primary and secondary endpoints were also analysed in the per-protocol population.

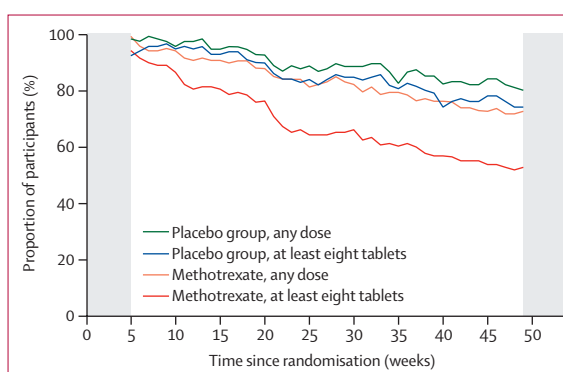


Figure 2: Adherence to study medication

The proportion of non-censored participants adhering to any dose of study medication or at least eight tablets per week (corresponding to ≥ 20 mg/week of methotrexate) in the first study year. The grey shaded areas depict the 4 weeks of dose increase at the start and 4 weeks of dose tapering at the end of the treatment period.

Time to development of the primary endpoint was analysed using Kaplan-Meier estimators and Cox regression. Origin of this time was the inclusion visit

(start of the study), and participants were censored upon the detection of persisting clinical arthritis or at the final study visit at 24 months. Participants who discontinued the study were censored at the point of withdrawal. Adjustment for ACPA status (positive [>7 U/mL] or negative) was predetermined because of the known strong association between ACPA status and clinical arthritis development.^{6,8} The proportional-hazards assumption was checked graphically (log-log plot). The coprimary endpoint was only tested when analysis of the key primary endpoint showed significant results (gatekeeping strategy). To evaluate the mean treatment difference between the groups during 2 years in secondary endpoints and MRI-detected joint inflammation, constrained linear mixed models, including time in months and treatment, and incorporating a random intercept per individual and random slope for the time variable were used. Constrained longitudinal data analysis is a well established unconditional technique that constrains means of baseline to be equal between groups.¹⁵ Interaction between time and treatment was tested to examine if the difference between active treatment and placebo changed over time (since inclusion in months). Model assumptions (constant variance, normality, and independence of the errors) were checked graphically by inspection of residuals. Random effects were assumed to be normally distributed with mean zero and unknown variance and to be independent of residuals.

We performed two prespecified subgroup analyses for the primary and secondary endpoints. First, to mitigate any effects due to heterogeneity in risk of rheumatoid arthritis,¹⁶ analyses were restricted to participants with high risk of clinical arthritis development (positive predictive value $\geq 70\%$). This risk stratification was based on a prediction model developed previously in an independent population with clinically suspect arthralgia and combined autoantibody and imaging characteristics (appendix p 6).⁸ Secondly, analyses were stratified by ACPA status, because of accumulating evidence that patients with ACPA-positive rheumatoid arthritis and those with ACPA-negative rheumatoid arthritis have differences in underlying pathology.¹⁷ The subgroup treatment effect interactions were quantified.

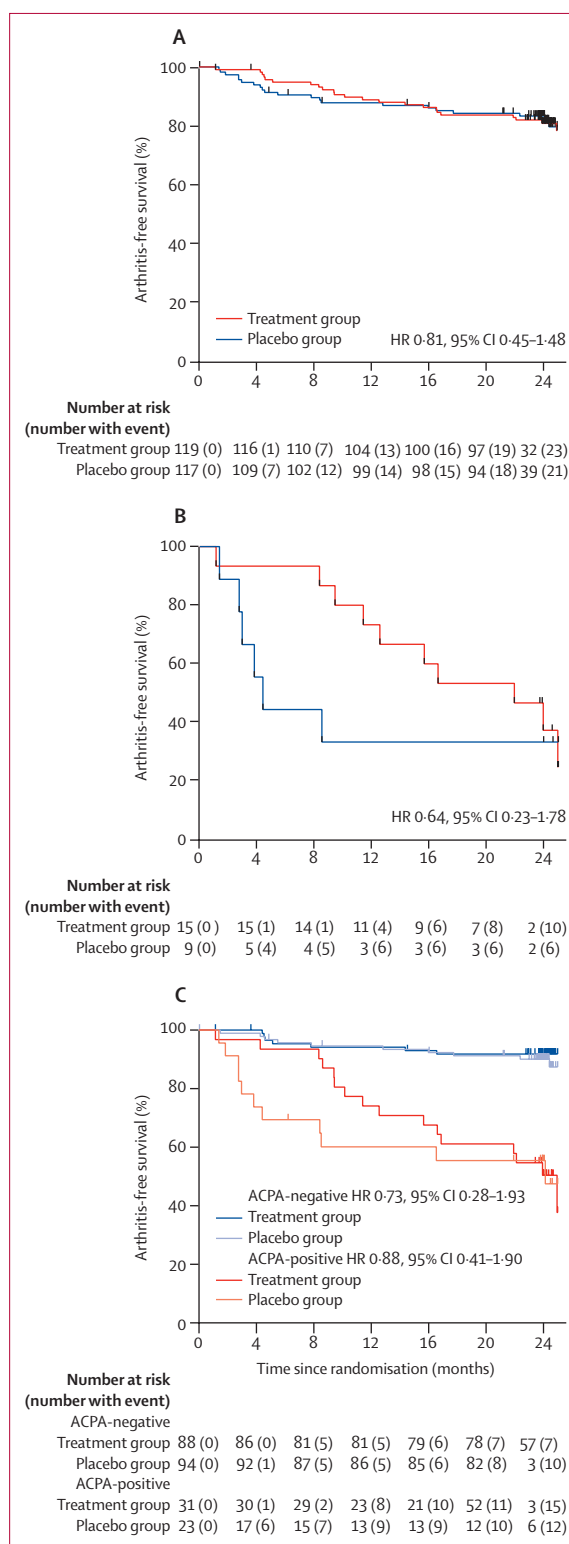
Analyses were performed with SPSS (version 25) and STATA (version 16). *p* values of less than 0.05 were considered significant. The statistical analysis plan was written and submitted to the medical ethics committee before breaking the randomisation code (appendix pp 24–38). This trial is registered with EudraCT, 2014-004472-35, and the Netherlands Trial Register, NTR4853-trial-NL4599.

Role of the funding source

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

Figure 3: Arthritis-free survival

Arthritis-free survival in all participants (A), participants with an estimated high risk ($\geq 70\%$; based on autoantibody-positivity and extensiveness of subclinical joint inflammation) of rheumatoid arthritis (B), and stratified by ACPA status (C). HRs in the figure are at 24 months. HRs at intermediate timepoints were 0.10 (95% CI 0.01–0.86; $p=0.036$) at 6 months, 0.26 (0.07–0.93; $p=0.037$) at 12 months, and 0.43 (0.14–1.30; $p=0.14$) at 18 months in participants at high risk of rheumatoid arthritis, and 0.19 (0.04–0.92; $p=0.038$) at 6 months, 0.52 (0.20–1.35; $p=0.18$) at 12 months, and 0.70 (0.34–1.63; $p=0.41$) at 18 months in ACPA-positive participants. ACPA=anti-citrullinated protein antibody. HR=hazard ratio.



Results

Between April 16, 2015, and Sept 11, 2019, 901 patients with clinically suspect arthralgia were identified and informed about the trial; 763 patients were willing to have a screening MRI, which showed subclinical joint inflammation in 384. Of these patients, 148 were not enrolled as they refused to participate ($n=89$), met an exclusion criterion ($n=24$), or developed clinical arthritis before inclusion ($n=35$; figure 1; appendix p 8). 236 patients were enrolled and randomly assigned to receive a single intramuscular glucocorticoid injection and a 52-week course of oral methotrexate (treatment group; $n=119$ [50%]) or placebo (injection and tablets; $n=117$ [50%]). All 236 participants were included in the intention-to-treat analysis. The last study visit occurred on Sept 27, 2021.

Baseline characteristics are shown in table 1. There was a higher proportion of ACPA-positive participants in the treatment group than in the placebo group (31 [26%] vs 23 [20%]).

Three (3%) of 119 participants in the treatment group and five (4%) of 117 in the placebo group were lost to follow-up. 72 participants (65% of non-censored participants at that moment) in the treatment group used eight or more tablets per week (corresponding to ≥ 20 mg methotrexate per week) at 6 months, and 56 (53%) at week 49; in the placebo group, 86 (83%) used eight or more tablets per week at 6 months and 74 (75%) at week 49. At 6 months, 19 (17%) participants in the treatment group and 13 (13%) in the placebo group had discontinued all study tablets. At 12 months, 28 (27%) participants in the treatment group and 19 (19%) in the placebo group had discontinued all study tablets (figure 2).

In the intention-to-treat population, 44 (19%) of 236 participants developed the primary endpoint (27 ACPA-positive participants and 17 ACPA-negative participants). The frequency of the primary endpoint at 2 years was similar between the groups (23 [19%; of whom 16 (70%) fulfilled the 2010 classification criteria] of 119 participants in the treatment group vs 21 [18%; of whom 14 (67%) fulfilled the 2010 classification criteria] of 117 in the placebo group; hazard ratio [HR] 0.81, 95% CI 0.45–1.48; figure 3; appendix p 9). All participants who developed the primary endpoint were clinically diagnosed with rheumatoid arthritis. In the treatment group, one ACPA-negative participant developed persisting clinical arthritis of one joint. In five participants in the treatment group and nine participants in the placebo group, clinical arthritis was detected that did not persist for 2 weeks; therefore, these patients did not reach the primary endpoint. DMARD-free status at 2 years (the coprimary endpoint) was infrequent after developing clinical arthritis (two participants in the treatment group and one in the placebo group) and was not statistically tested (gatekeeping principle).

In the prespecified subgroup analysis that only included participants with a 70% or greater risk of clinical

arthritis, six (67%) of nine patients in the placebo group developed persisting clinical arthritis in the first year. The treatment group showed a delay, but ten (67%) of 15 patients had developed persisting clinical arthritis at 2 years (figure 3B). In the prespecified subgroup analysis stratified by ACPA status, ACPA-positive participants in the treatment group also initially developed the endpoint less often during treatment than those in the placebo group, but arthritis development was similar at 2 years (15 [48%] of 31 vs 12 [52%] of 23; figure 3C).

The key secondary endpoint of physical functioning was improved at the 4-month study visit in the treatment group compared with the placebo group and this difference persisted during follow-up; the mean between-group difference in HAQ during the 2-year follow-up was -0.09 (95% CI -0.16 to -0.03 ; $p=0.0042$) in the intention-to-treat population (figure 4, table 2; appendix p 10). Given the small time-by-treatment interaction-effect estimates (eg, HAQ 0.04, 95% CI -0.09 to 0.18) and non-significant p values, the data suggest a stable treatment difference over time (appendix p 11). To check the robustness of a linearity of the time effect, we included time as visit number (categorical time) instead of continuous or calendar time per months in the model, which yielded a similar between-group difference over time (appendix p 12).

Pain and morning stiffness of joints showed a similar effect, with a sustained improvement in the treatment group compared with the placebo group. The mean 2-year difference between the groups for pain was -8 (95% CI -12 to -4 ; $p<0.0001$), and for morning stiffness was -12 (-16 to -8 ; $p<0.0001$; table 2; appendix pp 13–14). Presenteeism also showed significantly greater improvement in the treatment group than in the placebo group (mean difference -8% , 95% CI -13 to -3 ; $p=0.0007$; table 2; appendix pp 13–14). Fatigue and absenteeism were similar between the two groups (appendix p 15). For HAQ, pain, and presenteeism, similar effects were observed

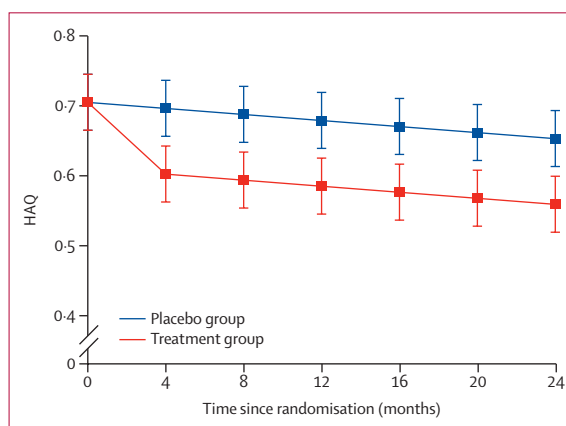


Figure 4: Key secondary endpoint, physical functioning measured by HAQ, estimated over 24 months in all participants
Predicted means are depicted. Error bars are SE of the mean. HAQ=Health Assessment Questionnaire disability index.

	All participants		Participants at high risk of rheumatoid arthritis		ACPA-positive participants		ACPA-negative participants	
	Mean difference	p value	Mean difference	p value	Mean difference	p value	Mean difference	p value
Key secondary endpoint								
HAQ	-0.09 (-0.16 to -0.03)	0.0042	-0.33 (-0.56 to -0.11)	0.0037	-0.27 (-0.41 to -0.12)	0.0004	-0.04 (-0.12 to 0.03)	0.23
Other secondary endpoints								
Pain, scale 0–100	-8 (-12 to -4)	<0.0001	-23 (-37 to -10)	0.0008	-12 (-21 to -4)	0.0039	-7 (-11 to -2)	0.0022
Morning stiffness of joints, scale 0–100	-12 (-16 to -8)	<0.0001	-10 (-24 to 5)	0.21	-6 (-15 to 2)	0.16	-14 (-18 to -9)	<0.0001
Presenteeism	-8% (-13 to -3)	0.0007	-20% (-33 to -8)	0.0019	-18% (-28 to -9)	0.0002	-6% (-11 to -1)	0.029
Exploratory endpoint								
MRI-detected joint inflammation	-1.4 (-2.0 to -0.9)	<0.0001	-2.7 (-5.6 to 0.2)	0.067	-1.7 (-3.2 to -0.2)	0.029	-1.5 (-2.1 to -0.9)	<0.0001

Mean estimated differences over 2 years of follow-up between the treatment group and placebo group are denoted. For MRI inflammation, the total MRI inflammation score (sum of scores of osteitis, synovitis, and tenosynovitis) was studied. ACPA=anti-citrullinated protein antibody. HAQ=Health Assessment Questionnaire disability index.

Table 2: Mean between-group treatment difference for secondary endpoints and MRI-detected joint inflammation in all participants, participants at high risk of rheumatoid arthritis, and stratified by ACPA status

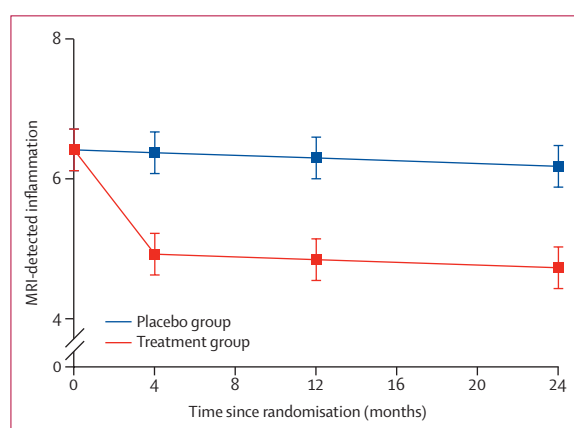


Figure 5: MRI-detected joint inflammation over 24 months in all participants MRI-detected joint inflammation was measured as the sum of synovitis, osteitis, and tenosynovitis scores. Predicted means are depicted. Error bars are SE of the mean.

within the subgroup at high risk of developing rheumatoid arthritis compared with the overall study population, albeit with somewhat larger effect sizes. Effects were present in both the ACPA-positive and ACPA-negative subgroups (appendix pp 10, 13; interaction terms between treatment and the studied subgroups are shown in the appendix [p 16]).

The severity of MRI-detected joint inflammation decreased more in the treatment group than in the placebo group and remained lower over 2 years of follow-up (mean difference -1.4 points, 95% CI -2.0 to -0.9; $p < 0.0001$; figure 5; appendix p 14). The course of MRI-detected joint inflammation in the subgroups is shown in the appendix (p 17). Radiographical progression was infrequent in both groups (appendix p 18).

Analysis in the per-protocol population showed similar results as the primary analysis (appendix pp 19–20).

In the intention-to-treat population, 13 (11%) of 119 participants in the treatment group and 13 (11%) of

117 in the placebo group reported a serious adverse event. These were mostly protocolised hospital admissions after elective surgery; a relation with the studied treatment was not presumed. Rates of adverse events were mostly similar between the two groups, except for a higher incidence of raised liver enzymes and a two-times higher incidence of symptoms indicating gastointolerance (nausea, vomiting, reflux, and diarrhoea) in the treatment group, as was expected from methotrexate (table 3). No deaths occurred during follow-up.

Discussion

In this randomised, double-blind, placebo-controlled trial in patients with arthralgia that was clinically suspected to progress to rheumatoid arthritis, and subclinical joint inflammation, we found that a single intramuscular glucocorticoid injection and a 1-year course of methotrexate did not prevent development of clinical arthritis. Two previous trials in ACPA-positive patients at risk of rheumatoid arthritis showed a delay in arthritis development with a temporary treatment of intramuscular glucocorticoids or rituximab, but neither found a lasting difference in clinical arthritis onset after treatment was stopped.^{18,19} To our knowledge, this study is the first to assess the efficacy of a course of methotrexate initiated in the pre-arthritis phase and to evaluate the effect on the disease burden. This very early treatment improved physical function, pain, morning stiffness of joints, and work productivity, and improvements were sustained over the 2 years of follow-up. The definition of a clinically relevant difference in improvements in pre-arthritis stages is unknown. In rheumatoid arthritis, differences between early and advanced disease were observed and a 0.09 change in HAQ has been defined as clinically relevant in early rheumatoid arthritis;^{20,21} for visual analogue scale pain assessment, a 10-point reduction is considered relevant.²² Data and discussions on clinically relevant effects in the at-risk disease phase are awaited. Importantly,

MRI-detected joint inflammation remained consistently reduced after treatment stop in the treatment group compared with the placebo group, and most effects occurred in both autoantibody-positive and autoantibody-negative participants. Therefore, these findings could provide new possibilities for improving the disease burden of rheumatoid arthritis for patients.

Selecting the right individuals is an important challenge in secondary prevention. The sample size calculation with 35% risk was based on data from our observational cohort study. However, the proportion of participants in the placebo group who developed the primary endpoint was lower than expected (19%). The process of referral by regional hospitals and trial screening might have contributed to a symptom duration at inclusion of about 10 weeks longer than previously reported in our observational cohort. During the time lag, 35 eligible individuals developed clinical arthritis before randomisation. Adding these to the 44 participants who developed clinical arthritis during follow-up, the rate of arthritis development would be as expected. Risk prediction has considerably advanced since the trial was designed in 2014, and risk as high as greater than 70% for developing clinical arthritis can now be identified in clinically suspect arthralgia when autoantibodies and more severe subclinical inflammation are present.⁸ Heterogeneity in prognostication is known for the risk of leaving a therapeutic trial defective.¹⁶ To overcome this risk, a prespecified subgroup analysis was performed in patients with high risk of developing rheumatoid arthritis. Results from this subgroup analysis might also be relevant to clinical practice, as evidence suggests that treatment with methotrexate is increasingly considered in patients without clinical arthritis, but who are ACPA-positive and have subclinical inflammation.²³

The willingness to participate in our prevention study (295 [75%] of 384 patients who fulfilled the inclusion criteria) was higher than was estimated in studies of preferences of patients at risk (50%).²⁴ Additionally, loss to follow-up was low (3%). These findings might illustrate the perceived importance of rheumatoid arthritis prevention. However, treatment adherence to the target dose of eight tablets (corresponding with methotrexate 20 mg/week) was moderate: 53% in the treatment group and 75% in the placebo group. Similar adherence frequencies have been described for methotrexate in classified rheumatoid arthritis.²⁵ Adverse events were similar to those in earlier research that systematically investigated side-effects of methotrexate.²⁶ Side-effects were a main reason for low adherence in both treatment groups (appendix p 21). Among participants that did not adhere to the target dose, 27% in the treatment group and 19% in the placebo group had completely stopped taking study medication by the end of the first year. Presumably, people at risk, but without a diagnosed chronic disease, are likely to stop taking medication, whether or not related to side-effects. Interestingly, a large meta-analysis

on the prevention of cardiovascular disease found that approximately 50% of participants did not adhere to medication and that non-adherence was not greatly influenced by the class of drug prescribed.²⁷

	Treatment group (n=119)		Placebo group (n=117)		p value
	Number of events	Incidence rate per 100 person-years (95% CI)	Number of events	Incidence rate per 100 person-years (95% CI)	
Serious adverse events					
Total	14	6.5 (3.6–11.0)	14	6.9 (3.8–11.6)	>0.99
Admission after elective surgery	6	..	7
Infection*	1	..	2
Cardiovascular event†	2	..	1
Trauma	1	..	1
Depression	1	..	1
Malignancy	1	..	0
Acute kidney injury	1	..	0
Other‡	1	..	2
Adverse events possibly related to study medication§					
Gastrointestinal (any)	34	15.0 (11.0–22.2)	25	12.3 (8.0–18.2)	0.40
Nausea, vomiting, reflux, or diarrhoea	23	10.8 (6.8–16.1)	12	5.9 (3.1–10.3)	0.12
Abdominal pain or constipation	8	..	13
Mouth sores	2	..	0
Malaise after study medication	4	1.9 (0.5–4.8)	1	0.5 (0.0–2.7)	0.41
Infections (any)	136	63.6 (53.3–75.2)	134	66.0 (55.3–78.2)	0.80
Upper respiratory tract infection or influenza	97	..	104
Lower respiratory tract infection or pneumonia	3	..	4
Skin or soft tissue infection	8	..	12
Urinary tract infection	7	..	4
Pulmonary (any)	9	4.2 (1.9–8.0)	5	2.5 (0.9–5.7)	0.48
Laboratory adverse events¶					
Leukopenia	2	0.9 (0.1–3.4)	3	1.5 (0.3–4.3)	0.95
Thrombocytopenia	0	0	1	0.5 (0.6–2.7)	0.97
AST or ALT >ULN	42¶	19.6 (14.1–26.5)	8	3.9 (1.7–7.8)	<0.0001
AST or ALT >3 × ULN	13	6.1 (3.2–10.4)	1	0.5 (0.0–27.4)	0.0025

Data are n unless otherwise stated. 13 (11%) of 119 patients in the treatment group and 13 (11%) of 117 in the placebo group had a serious adverse event; 106 (89%) patients in the treatment group and 92 (79%) in the placebo group had any adverse event (whether possibly treatment-related or not). AST=aspartate aminotransferase. ALT=alanine aminotransferase. ULN=upper normal limit. *Pyelonephritis (n=1 in placebo group), pneumonia (n=1 in placebo group), and viral pericarditis (n=1 in treatment group). †(Suspicion of a) cerebrovascular event (n=1 in treatment group and n=1 in placebo group), and hypertensive crisis (n=1 in treatment group). ‡Hospital admission for observation of abdominal pain (n=1 in treatment group), for pain after inguinal hernia surgery (n=1 in placebo group), or for emergency surgery of acute appendicitis (n=1 in placebo group). §Adverse events described here are the most common side-effects of methotrexate as reported by previous studies. ¶Raised liver panels to greater than the upper limit of normality were found 42 times: in five cases this did not have any consequences on the continuation of study medication, in 13 cases the dose was lowered, in eight cases medication was temporarily discontinued (1–4 weeks), and in 15 cases participants temporarily discontinued their medication (1–4 weeks) and restarted at a lower dose; one participant temporarily stopped the study medication, after which AST and ALT levels normalised, but this patient did not want to restart treatment.

Table 3: Adverse events

The primary endpoint was development of clinical arthritis, which is mandatory for traditional and current rheumatoid arthritis diagnosis. A limitation of physical joint examination in the early stages of clinical arthritis is that its sensitivity might be lessened by interobserver and time-dependent variation. To overcome this limitation, clinical arthritis had to persist for at least 2 weeks and be diagnosed twice by two rheumatologists for the primary endpoint to be reached. Longer evaluation of persistence was considered unethical, as guidelines advocate a prompt start of treatment upon occurrence of clinical arthritis.³ Participants who developed clinical arthritis in this trial, including those who did not meet the 2010 rheumatoid arthritis classification criteria, were clinically diagnosed with rheumatoid arthritis.

As is customary, secondary endpoints were not corrected for multiple testing. Reassuringly, if a Bonferroni correction had been used to account for the analysis of all primary and secondary endpoints in the intention-to-treat-population ($n=8$), our findings would have remained significant.

A strength of this study is the additional 12-month follow-up after treatment stop, which ensured that a potential delay in clinical arthritis development was not falsely interpreted as a preventive effect. The ARIAA study in ACPA-positive patients with arthralgia reported a difference in clinical arthritis incidence after 6 months of treatment with abatacept compared with placebo.²⁸ Our data from ACPA-positive participants show a similar effect: two (6%) of 31 participants in the treatment group reached the primary endpoint within 6 months, compared with seven (30%) of 23 in the placebo group (HR 0.19, 95% CI 0.04–0.92). Although at 12 months and 18 months a difference was still present, it was lost at 24 months. This underlines the relevance of sufficient follow-up to evaluate the sustainability of the effect of a temporary treatment.

To prevent selection bias, all consecutive patients presenting to rheumatology outpatient clinics in the region with clinically suspect arthralgia were approached and informed about the study. Baseline characteristics of enrolled and non-enrolled patients were similar. This suggests that our results are generalisable to people with clinically suspect arthralgia and subclinical inflammation on MRI. Additionally, among the participants who were randomly assigned, the low proportion who were lost to follow-up, the fact that these participants were censored upon withdrawal, and the inclusion of relevant covariates, makes it unlikely that selection bias due to censoring might have influenced the results.

Our finding that treatment did not prevent the development of clinical arthritis in ACPA-positive clinically suspect arthralgia can be understood in the context of recent research showing that the number and concentrations of autoantibodies and their isotypes were already matured at first presentation with arthralgia and similar in those who did and did not progress to

rheumatoid arthritis.²⁹ By contrast, only a subset of ACPA-positive participants with arthralgia and subclinical inflammation who received placebo progressed to clinical arthritis, a finding that is consistent with previous work. Unfortunately, little is known regarding the mechanisms that contribute to or prevent the transformation of subclinical joint inflammation into persistent clinical arthritis. Methotrexate presumably has a pleiotropic effect on inflammatory processes. A deeper understanding of the final stage of the multiple-hit process, especially in the joint, would allow the design of preventive interventions that specifically interrupt the final steps towards clinical arthritis and rheumatoid arthritis.

A therapeutic window of opportunity in the pre-arthritis stage of rheumatoid arthritis, in which the disease is more susceptible to disease-modifying treatment and biological processes can be halted, is presumed but has not yet been proven. Clinical arthritis was at most delayed in patients who progressed, but it was not prevented. MRI-detected joint inflammation, physical functioning, and inflammatory symptoms showed improvement that persisted after treatment discontinuation in the overall study population. Several outcomes can be used to assess disease modification. The clinical arthritis endpoint is often leading from a rheumatologist's perspective and reflects current treatment guidelines. The secondary endpoint, physical functioning, focuses on both patients' and rheumatologists' perspectives.^{9,10,30} The lasting improvement in both indicators we used for increased risk for rheumatoid arthritis (inflammatory symptoms and MRI-detected joint-inflammation) might suggest a therapeutic window in the pre-arthritis period. Interestingly, sustained treatment effects for both indicators were present in participants who did not progress, as well as in participants who did develop persistent clinical arthritis. Participants who did not progress to clinical arthritis in the treatment group had reduction of pain and MRI-detected joint inflammation to almost normal levels. Participants who developed clinical arthritis in the treatment group had less pain and MRI-detected joint inflammation at that time than those in the placebo group (appendix p 22). This finding in participants at high risk of developing rheumatoid arthritis might also explain the apparent paradox between a non-sustained effect in the primary endpoint and sustained effects for the secondary endpoints. The value of treatment initiation in the at-risk phase could be expressed in the ability to obtain reduction of symptoms and physical impairments, or to maintain normal activities of daily living, including work. Therefore, this study could open a new treatment landscape for the rheumatoid arthritis field.

Methotrexate is the gold standard for established rheumatoid arthritis, because it is effective and cheap. Future research is needed to assess whether initiation of methotrexate in clinically suspect arthralgia and

subclinical joint inflammation leads to a milder long-term disease course, lowers disease activity, reduces the need for biological DMARDs, and increases DMARD-free remission in those who develop clinical arthritis.³⁰ An observational extension to 5 years of follow-up is in progress to evaluate this. Whether the effects can be attributed to either methotrexate or the glucocorticoid injection cannot be deduced from these data, and would require a trial in participants at risk of developing rheumatoid arthritis with a study visit after 2–4 weeks after glucocorticoid injection at baseline. The cost-effectiveness of a methotrexate course in the pre-arthritis phase also needs to be established, in the context of increasing pressure from society to spend less on health care.

In conclusion, this trial showed that a single intramuscular glucocorticoid injection and a 1-year course of methotrexate did not prevent the development of detectable clinical arthritis, but could offer new perspectives on lowering the burden of disease.

Contributors

AHMvdH-vM designed the study. DIK, MV, BTvD, YJD, LEB, ACB, MEdW-L, YJP, KV, MRK, ETHM, PHPdJ, and EN collected the data. DIK, MV, SB, and EN accessed and verified the data. DIK and SB analysed the data. All authors interpreted the data and wrote the report. AHMvdH-vM was the principal investigator. All authors approved the final version of the manuscript and were responsible for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Requests for data collected in the TREAT EARLIER study (such as deidentified participant data) can be made to the corresponding author following publication, and requests will be considered on an individual basis. The statistical analysis plan and study protocol are available in the appendix (pp 24–71).

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