Supplementary files

Supplementary methods

The TREAT EARLIER trial

The TREAT EARLIER was a randomized placebo-controlled trial, studying the hypothesis that intervention in the symptomatic phase preceding clinical arthritis is more often successful in permanent disease modification, because of less matured underlying disease processes in this early at risk stage.(1)

Participants

A two-level definition was used to identify patients eligible for trial inclusion. Firstly, patients needed to have recent-onset arthralgia (<1 year) that was suspect to progress to rheumatoid arthritis (RA) according to the expertise of the treating rheumatologist (clinically suspect arthralgia; CSA). Secondly, patients needed to have subclinical inflammation of the hand or forefoot joints at 1.5 T MRI, after correction for MRI-findings in healthy controls.(2) 236 patients were included between April 2015 an September 2019.

Intervention

Intervention consisted of a single intramuscular glucocorticoid injection (120 mg methylprednisolone) or corresponding placebo injection, administered by the clinical staff upon inclusion in the trial, followed by a 52-week course of methotrexate or placebo tablets. Follow-up continued for a second year without study medication. All participants and staff involved (including those administering study medication, assessing endpoints, and analyzing the data) were masked to group allocation until after database lock. During follow-up, concomitant treatment with analgesics, such as acetaminophen or non-steroidal anti-inflammatory drugs was allowed. Treatment with any other DMARDs or glucocorticoids (systemic or intra-articular) was prohibited during the trial. Only if participants reached the primary endpoint, they proceeded to open-label DMARD therapy in routine clinical practice.

This trial is registered with EudraCT, 2014-004472-35, and the Netherlands Trial Register, NTR4853-trial-NL4599.

Defining RA-development and symptom resolution

In the current study, we separately studied patients achieving distinct clinical outcomes: RA-development and symptom resolution. RA was defined as clinical arthritis that persisted for at least 2 weeks and fulfilled the 2010 RA-classification criteria or involved two or more joints, both with a

clinical diagnosis of RA. The presence of clinical arthritis was based on the physical evaluation of the patient's joints by two rheumatologists. When clinical arthritis was detected, an additional study visit took place after 2 weeks to determine if the arthritis persisted.(3)

Spontaneous resolution of pain was achieved if a patient did not develop clinical arthritis and indicated a score of 20 or less on a numeric rating scale (0-100) of pain at the last study visit. This cut-off for absence of joint pain was chosen in agreement with the literature.(4) Patients who did not achieve pain resolution and did not develop RA, were characterized as having persistent CSA.

Grip strength measurements

Grip strength was measured using a Jamar dynamometer (in kilograms(kg)). Patients squeezed the dynamometer 3 times per hand as hard as possible, alternating sides after each try. The highest grip strength for each hand was collected, which is less likely to be affected by the number of attempts than the mean.(5). Grip strength was assessed during study visits at baseline and every 4 months afterwards for the 2 years of follow-up. The study visits could take place in the morning or early afternoon (9-16 hours). We cannot rule out that the time of the grip strength assessment differed between patients or within the same patient during follow-up and might have influenced the measurements, but we assumed this variation to be completely at random among all trial participants. In the primary analyses the grip strength of the strongest hand was used. In addition, a sensitivity analyses was performed on grip strength of the weakest hand.

Statistical analyses

To evaluate the natural course of grip strength, linear mixed models with random intercept per individual and random slope for the time variable were used. In addition, the unmodeled (raw) data were depicted. In patients who did not develop RA, time since inclusion was incorporated as the time variable. In patients who developed RA, time before RA-development was used.

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.(6) Interaction between time and treatment was tested to examine if the differences between active treatment and placebo changed over time or sustained during follow-up. In the main analysis time

was included as a continuous variable. In a supplementary analysis (figure 2), time was included as a categorical variable (visit number) to allow depiction of a variable course over time.

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.

Analyses were performed with STATA (version 16).

Supplementary results

Supplementary table 1. Baseline characteristics

	Progressors to RA* (n=21)	Persistent CSA* (n=61)	Pain resolution* group (n=35)	Complete treatment-group (n=119)
Age in years	48 (12)	45 (11)	50 (10)	46 (13)
Female, n (%)	12 (57)	46 (77)	22 (63)	74 (62)
Symptom duration (weeks)	23 (15-27)	29 (18-52)	29 (16-59)	28 (13-45)
Pain (scale 0-100)	50 (30-70)	50 (32-70)	40 (20-60)	28 (13-45)
68-TJC	3 (1-7)	4 (2-10)	2 (1-7)	4 (1-8)
CRP (mg/L)	3 (2.5-11)	3 (3-6)	3 (1-4)	3 (3-6)
CRP increased, (≥5 mg/L), n (%)	7 (33)	18 (30)	7 (20)	36 (30)
RF positive (≥3.5 IU/ml), n (%)	12 (57)	14 (24)	9 (26)	33 (28)
ACPA positive (≥7 mg/L), n (%)	11 (52)	8 (13)	4 (11)	31 (26)
HAQ score	0.5 (0.2-1.1)	0.8 (0.4-1.3)	0.6 (0.1-0.8)	0.6 (0.1-1.1)
Subclinical inflammation score	5.5 (4.0-11.5)	4 (2-8)	4 (3-7)	5 (3-9)

Legend Table 1.
A total of 236 patients participated in the TREAT EARLIER trial and were studied in the current study. Of the 236, 117 participated in the placebo group, 119 participated in the treatment group.
*: these groups were subgroups within the placebo group.
68-TJC, tender joint count including 68 joints; CRP, C-reactive protein; RF, Rheumatoid factor; ACPA, anti-citrullinated peptide antibody; HAQ, Health Assessment Questionnaire.
Data are n (%), mean (SD) or median (IQR). Baseline characteristics as measured at trial inclusion.
Subclinical inflammation score summed the scores of synovitis, tenosynovitis and osteitis on MRI, calculated as the mean of the scores of the two readers.

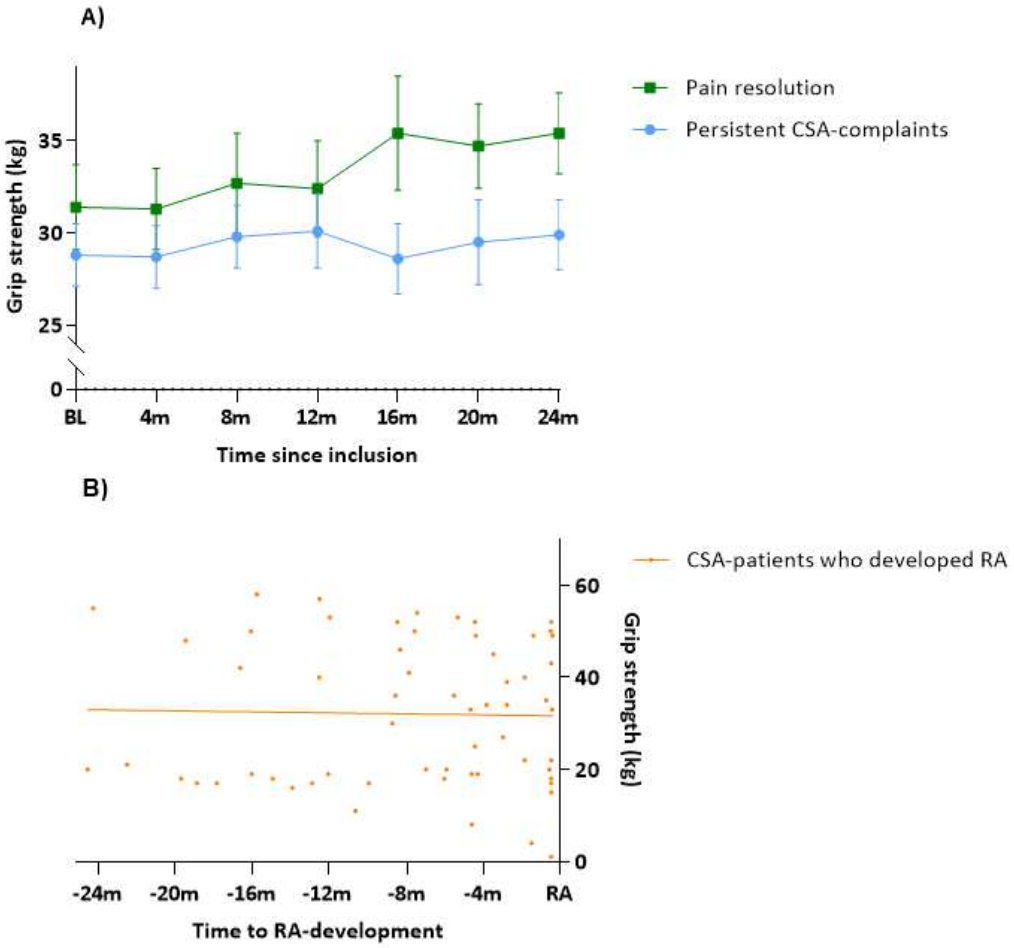
Supplementary table 2. Sensitivity analysis of the GS of the weakest hand

Natural course of GS (within the placebo-group)	Increase per month (in kg):
In patients developing RA	+ 0.001 (-0.007; 0.009, p=0.85)
In patients with persistent arthralgia (who did not develop RA)	+ 0.08 (0.003; 0.16, p=0.04)*
In patients achieving spontaneous pain resolution	+ 0.24 (0.12; 0.37, p<0.001)*

Improvement with treatment (placebo- versus treatment-group)	Mean effect over 2 years follow-up (in kg):
In all participants	+ 1.95 (0.82; 3.08, p=0.001)*
In participants who developed RA	+ 2.70 (-0.37; 5.76, p=0.08)
In participants who did not develop RA	+ 1.92 (0.70; 3.14, p=0.002)*

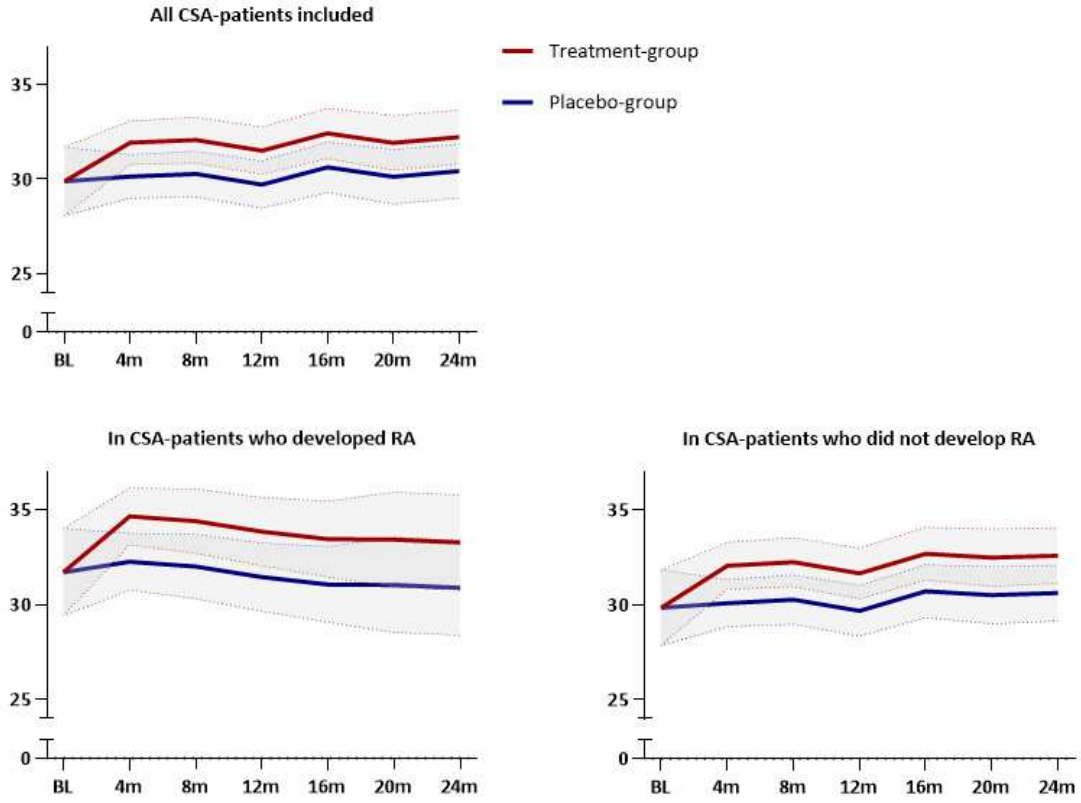
Legend supplementary table 2. In these sensitivity analyses, the minimum GS of the left and right hand was evaluated, in contract to the GS of the strongest hand in the primary analyses.
In the placebo-group, 21 patients developed RA. Of the 96 patients in the placebo-group who did not develop RA, 35 patients achieved resolution of pain. In the lower part of the table, GS of the 119 CSA-patients in the treatment-arm was compared to the 117 CSA-patients in the placebo-arm. 23 CSA-patients developed RA in the treatment-arm. * denotes statistical significance (p<0.05)

Supplementary figure 1. Unmodeled data of the natural course of grip strength in CSA-patients who achieve pain resolution and who have persistent CSA-complaints (A), and in CSA-patients who develop RA (B)



Legend supplementary figure 1. In A, mean GS measurements per study visit are shown. Error bars represent the standard error of the mean. In B, individual measurements are represented by dots, and a interpolation line between these dots was drawn

Supplementary figure 2. Treatment response, using time as a categorical variable in the linear mixed model



Legend supplementary figure 2. In the main analysis on treatment response, time was included in the linear mixed model as a continues variable. In this analysis, we included time as a categorical variable (visit number) to allow depiction of a variable course over time. Grey areas depict the 95% confidence intervals of the estimated mean.

References

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