Emerging opportunities in clinically suspect arthalgia: crossing the frontiers of rheumatoid arthritis

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Chapter 9

Grip strength reduction in clinically suspect arthralgia: natural trajectories and improvement after treatment

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Decreased hand function is a major contributor to disease burden in rheumatoid arthritis (RA), and is present in most RA-patients at diagnosis.(1,2) Recent research showed that hand function is reduced in the symptomatic pre-arthritis phase of clinically suspect arthralgia (CSA), and is a reflection of subclinical tenosynovitis.(3) Grip strength (GS) measured with a dynamometer had the highest sensitivity for decreased hand function and underlying tenosynovitis, compared with other assessment methods of hand function.(3) Although this may suggest that the dynamometer could be a practical assessment in CSA to objectify functional impairments originating from subclinical joint-inflammation, it needs to be determined if dynamometer-based GS-assessments in CSA are sensitive to change and mirror the disease course of CSA. To our best knowledge, longitudinal studies on GS in the phases preceding RA-diagnosis are lacking. We hypothesized that GS follows distinct natural trajectories in CSA-patients who have contrasting disease courses (RA-development, persistent CSA-symptoms without RA-development, spontaneous resolution of arthralgia). Secondly, since it was recently shown that a temporary methotrexate-treatment in CSA resulted in sustained improvements of subclinical joint-inflammation, we hypothesized that GS is responsive to treatment in the CSA-phase.(4)

Both hypotheses were evaluated in data from the TREAT-EARLIER trial, in which CSA-patients with subclinical joint-inflammation were randomly assigned to treatment (single intramuscular glucocorticoid-injection and 1-year of methotrexate) or placebo.(4) At 4-monthly visits during 2-years follow-up, patients were assessed for RA-development, symptoms and maximal GS in both hands (explorative trial-endpoint). The natural course of GS was studied in placebo-treated participants, separately in patients who developed RA, had persistent CSA-complaints, or had spontaneous resolution of pain (pain-score ≤20 (scale 0-100) at the last study-visit). To evaluate the treatment-effect, the treatment- and placebo-group were compared. Primarily, GS of the strongest hand was studied; GS of the weakest hand was studied in sensitivity analyses. (Constrained) linear-mixed-models were used. A detailed description of the methods is presented supplementary (p.2-4).

Of the 117 patients in the placebo-group, 21 patients developed RA, 35 patients achieved spontaneous resolution of pain and 61 patients had persistent symptoms. CSA-patients who progressed to RA were more often ACPA-positive: 52% versus 13% and 11% in patients with persistent and resolving complaints respectively, and had a higher median MRI-detected inflammation score on baseline: 5.5 versus 4 in the other two subgroups. The subgroup of patients achieving resolution had somewhat less pain upon inclusion: a median pain score of 40 (versus 50 in the other subgroups) and tender joint count (TJC) of 2 compared to a TJC of 3 and 4 in patients who progressed or had persistent complaints respectively (supplementary table 1). At trial inclusion, mean GS was 31.4 (2.3) in patients achieving resolution, 28.8 (1.7) in patients with persistent symptoms and 31.7 (3.2) in patients who later developed RA (supplementary figure 1). Patients with subclinical joint inflammation on MRI and subclinical tenosynovitis in particular had lower GS: per point increase in tenosynovitis, GS decreased

with −2.63 kg (95% CI −2.26 to −0.33).

Studying the natural course of GS over time in the three patient groups revealed that GS remained stable in CSA-patients who did develop RA (-0.03kg/month; -0.26;0.19,p=0.76) or had persistent CSA-complaints (0.02kg/month; -0.06;0.11,p=0.64). In CSA-patients who achieved pain-resolution, GS increased with 0.16kg/month (0.06;0.27,p=0.002)(Figure 1A). Thus, patients with resolving symptoms had improvement of GS, in contrast to patients who developed RA or had persistent CSA-complaints. In support of these observations, unmodeled data and analysis of treatment response using time as a categorical variable are depicted in the supplementary figure 1 and 2 respectively. Hence, GS followed distinct natural trajectories in CSA-patients with contrasting disease courses.

We then studied whether GS is responsive to treatment in the CSA-phase by comparing the treatment and placebo arm. Treatment induced a mean GS-improvement of 1.97kg over 2-years (0.86;3.07,p<0.001), which sustained after treatment stop. Treatment-related improvements were present both in CSA-patients who developed RA (total of 44 participants, 23 in treatment-group) (+2.47kg (-0.29;5.24,p=0.08)) and CSA-patients who did not develop RA (+2.04kg (0.83;3.24,p=0.001))(Figure 1B). Sensitivity analysis with GS of the weakest hand showed comparable results, except for a small spontaneous increase in placebo-patients with persistent CSA-complaints (+0.08kg/month; 0.003;0.16,p=0.04)(supplementary table 2).

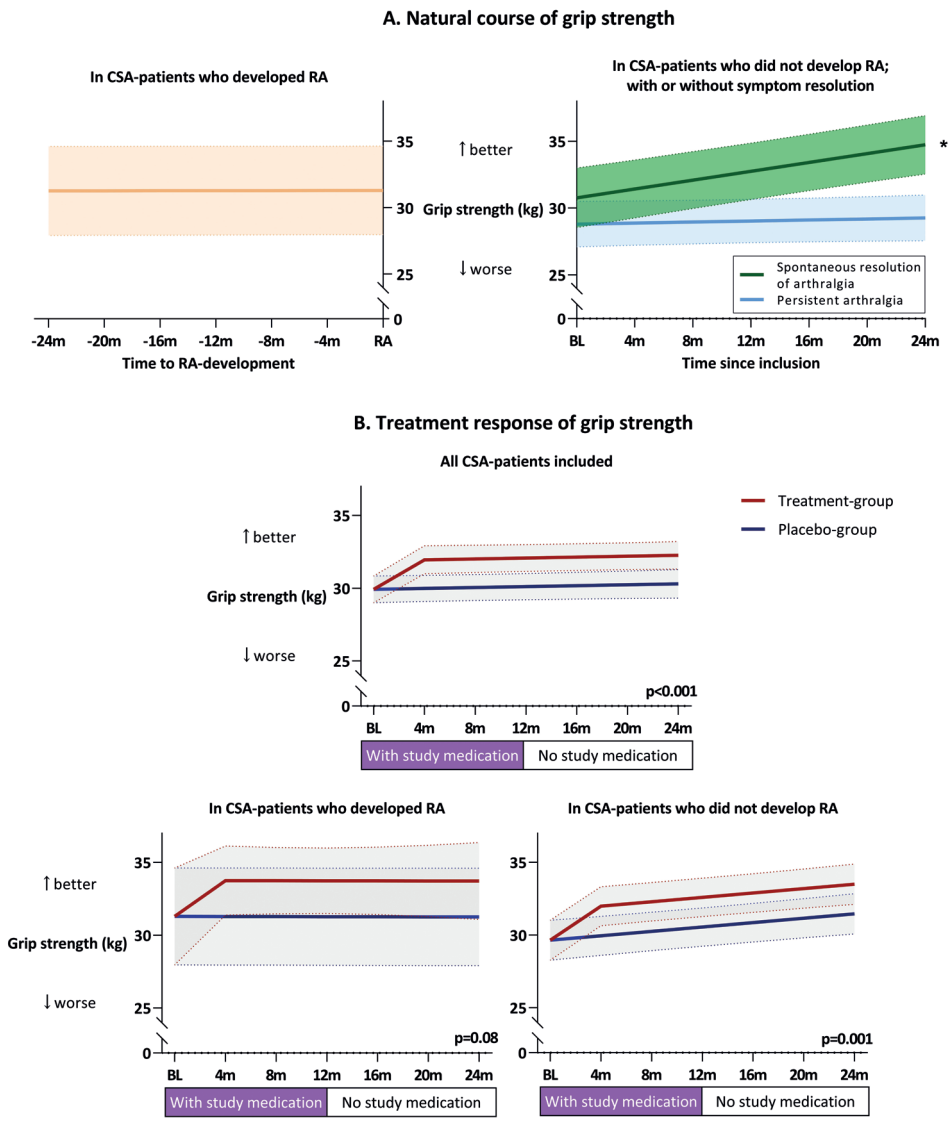
This study provides the first evidence that GS-assessment is sensitive-to-change in CSA-patients with subclinical joint-inflammation. While GS was reduced in CSA and remained so during progression to RA, it improved in CSA-patients with spontaneous resolution. Moreover, it also improved upon treatment.

The observed treatment effect is in line with reported findings of sustained improvements in subclinical joint-inflammation and patient-reported outcomes.(4) The 2kg-improvement in GS is clinically relevant and quite comparable to reported improvements during the first year of treatment after RA-diagnosis (+-3.5kg).(2,5) Hence, this study underlines that a temporary treatment in the CSA-phase could improve hand function in the CSA-phase, also in CSA-patients with subclinical inflammation who will not progress to RA.

Once tools for monitoring of disease activity in the CSA-phase will be developed, GS could be of value as a component of a multidimensional/composite score, as it supports the 'sensitivity-to-change' and 'longitudinal construct validity' items in the OMERACT filter for instrument-selection.(6)

Concluding, GS is easily assessed in practice, responds to treatment in CSA, and its course could be of value for monitoring disease activity in the at risk phase of CSA.

Figure 1. The natural course of grip strength in CSA (A) and improvement on a temporary treatment in CSA (B)



*Legend figure 1A. Of the 117 patients in the placebo-group, 21 patients developed RA, 35 patients achieved spontaneous resolution of pain and 61 had persistent CSA-symptoms. Figure 1B. GS of CSA-patients in the treatment-group (N=119) was compared to the placebo-group (N=117). Within the treatment-group 23 CSA-patients developed RA and 96 did not; in the placebo-group these numbers were 21 and 96 respectively. The bands represents the 95% confidence interval of the estimated mean. * p=0.002.*

Supplementary methods

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.(7)

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.(8) 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.(9). 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.(10) 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 data

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.

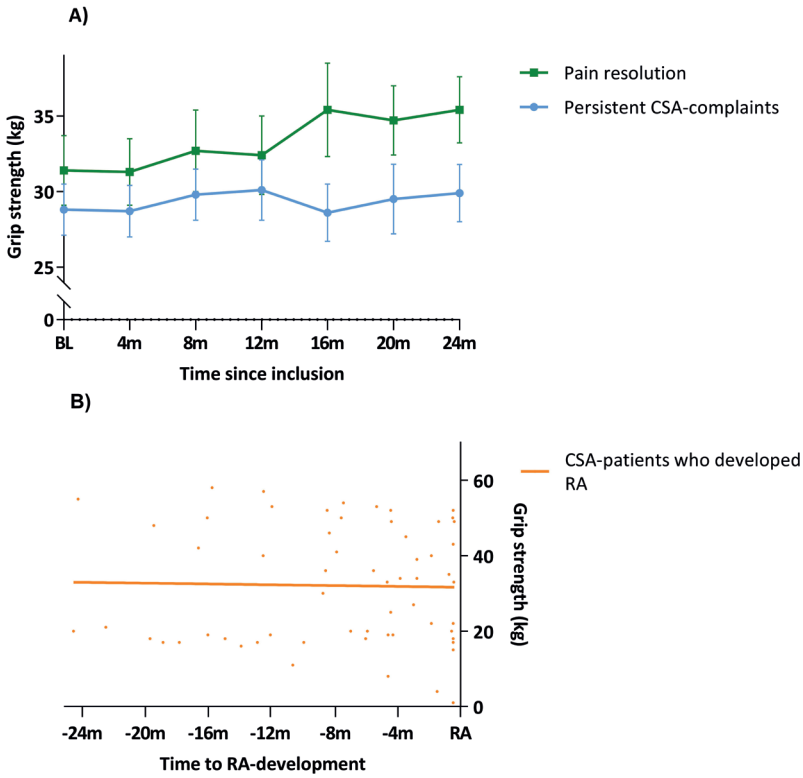
Supplementary table 2. Sensitivity analysis of the grip strength of the weakest hand

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)*

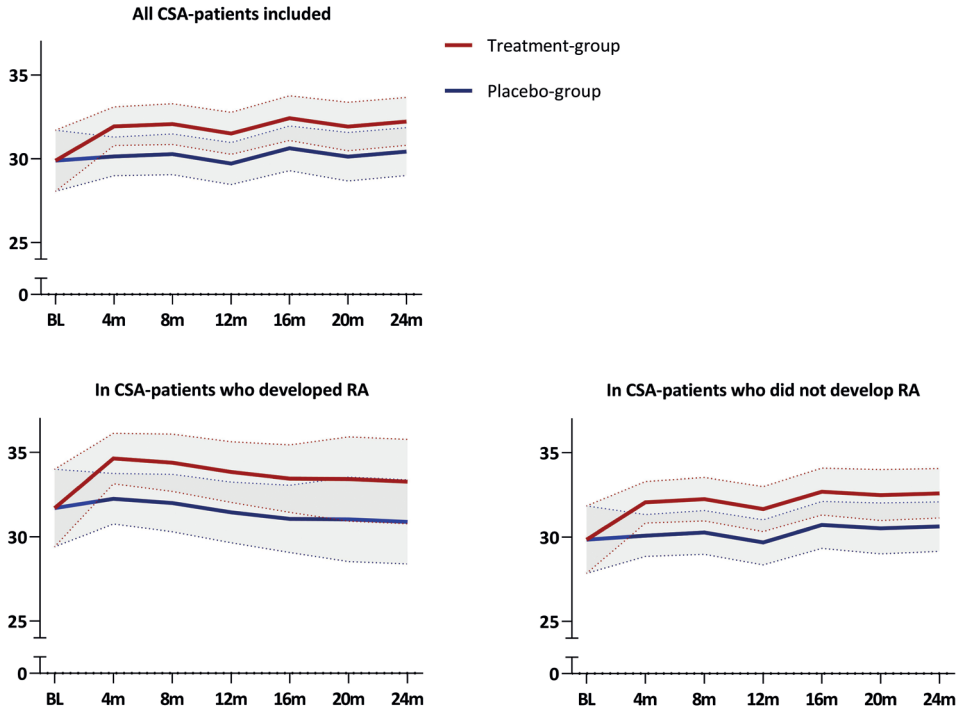
*Legend supplementary table 2. In these sensitivity analyses, the minimum GS of the left and right hand was evaluated, in contract to the GS of the strongest hand in the primary analyses. In the placebo-group, 21 patients developed RA. Of the 96 patients in the placebo-group who did not develop RA, 35 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.

Additional supplementary materials are published online on the website of RMD open

References

1. Björk MA, Thyberg IS, Skogh T, Gerdle BU. Hand function and activity limitation according to health assessment questionnaire in patients with rheumatoid arthritis and healthy referents: 5-year followup of predictors of activity limitation (The Swedish TIRA Project). The Journal of rheumatology. 2007;34(2):296-302.

2. Rydholm M, Book C, Wikström I, Jacobsson L, Turesson C. Course of Grip Force Impairment in Patients With Early Rheumatoid Arthritis Over the First Five Years After Diagnosis. Arthritis care & research. 2018;70(4):491-8.

3. Krijbolder DI, Khidir SJH, Matthijssen XME, Ten Brinck RM, van Aken J, Speyer I, et al. Hand function is already reduced before RA development and reflects subclinical tenosynovitis. RMD open. 2023;9(1).

4. Krijbolder DI, Verstappen M, van Dijk BT, Dakkak YJ, Burgers LE, Boer AC, et al. 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. Lancet (London, England). 2022;400(10348):283-94.

5. Villafañe JH, Valdes K, Bertozzi L, Negrini S. Minimal Clinically Important Difference of Grip and Pinch Strength in Women With Thumb Carpometacarpal Osteoarthritis When Compared to Healthy Subjects. Rehabil Nurs. 2017;42(3):139-45.

6. Beaton DE, Maxwell LJ, Shea BJ, Wells GA, Boers M, Grosskleg S, et al. Instrument Selection Using the OMERACT Filter 2.1: The OMERACT Methodology. The Journal of rheumatology. 2019;46(8):1028-35.

7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the rheumatic diseases. 2010;69(9):1580-8.

8. Wolfe F, Michaud K. Assessment of pain in rheumatoid arthritis: minimal clinically significant difference, predictors, and the effect of anti-tumor necrosis factor therapy. The Journal of rheumatology. 2007;34(8):1674-83.

9. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age and ageing. 2011;40(4):423-9.

10. Coffman CJ, Edelman D, Woolson RF. To condition or not condition? Analysing 'change' in longitudinal randomised controlled trials. BMJ open. 2016;6(12):e013096.