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Concise report

Differing time-orders of inflammation decrease between ACPA subsets in RA patients suggest differences in underlying inflammatory pathways

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Abstract

Objectives. Advanced imaging modalities have shown that not only joints but also bones and tendon sheaths can be inflamed at diagnosis of RA. We aimed to better understand the time-order in which the inflamed tissues respond to DMARD treatment. Also, because ACPA status may reflect a different pathophysiology, differences in time-order of inflammation decrease were hypothesized between these disease types.

Methods. A total of 216 consecutive patients presenting with RA ($n = 176$) or undifferentiated arthritis ($n = 40$), who all started with conventional synthetic DMARD treatment, were studied. 1.5T contrast-enhanced hand and foot MRIs were performed before treatment and after 4, 12 and 24 months. Cross-lagged models evaluated the influence of two time patterns: a simultaneous pattern ('change in one inflammatory feature associated with change in another feature') and a subsequent pattern ('change in one inflammatory feature preceded change in another feature'). ACPA stratification was performed.

Results. The median symptom duration at presentation was 13 weeks. Forty-four percent of patients was ACPA-positive. All pairs of inflammatory features decreased simultaneously in all time intervals (0–4/4–12/12–24 months; $P < 0.05$). Moreover, time-orders were identified: synovitis decrease preceded tenosynovitis decrease (0–4 to >4–12 months; $P = 0.02$ and 4–12 to >12–24 months; $P = 0.03$). Largely similar results were obtained in both ACPA subgroups. Additionally, in ACPA-positive but not ACPA-negative patients, synovitis decrease preceded osteitis decrease (4–12 to >12–24 moths; $P = 0.002$).

Conclusion. This study increased the understanding of the response to treatment on the tissue level. In addition to simultaneous decrease of inflammation, synovitis decrease preceded tenosynovitis decrease. Differences in time-order of inflammation decrease between ACPA subgroups suggest differences in underlying inflammatory pathways.

Key words: imaging, MRI, rheumatoid arthritis, ACPA

CLINICAL SCIENCE

Rheumatology key messages

- This study increased the understanding of the response to RA treatment on the tissue level.
- Additional to simultaneous decrease of inflammation, synovitis decrease preceded tenosynovitis decrease.
- Differences in time-order of inflammation decrease between ACPA subgroups suggest differences in underlying inflammatory pathways.

Introduction

During the last decade, advanced imaging modalities including MRI have refined our understanding of the tissues involved in RA and have shown that not only joints but also bones and adjoining synovial tendon sheaths of small joints are frequently inflamed [1, 2]. These tissues are distinct anatomical structures but

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synovitis, osteitis and tenosynovitis frequently co-occur at diagnosis [1, 3]. Remarkably, previous research suggested time-orders in inflammation development of these tissues during RA development [2, 4]. If time-orders are present in developing RA, we assume that there are also time-orders in inflamed tissue in decrease of inflammation. However, little is known about the mutual influence of inflammation of these tissues when inflammation is resolving due to treatment.

Some studies have investigated inflammation decrease in joints, bones and tendon sheaths after treatment in early RA [5–7]. However, they did not determine whether inflammation decrease is simultaneous in all tissues or whether sequences also play a role, as time-orders were not studied. Also, ACPA subgroups were not studied separately, and these are considered different disease types with differences in underlying pathophysiology [8–10]. Consequently, differences in time-order of inflammation decrease in response to treatment can be expected but, to our knowledge, this has not been explored yet.

Our aim was to achieve a better understanding of the time-orders in which the different inflamed tissues (joint, bone, tendon sheath) respond to DMARD treatment, and whether this differs between ACPA subgroups. In the Leiden Early Arthritis inception cohort, MRIs of undifferentiated arthritis (UA) and RA patients were performed at presentation (before DMARD initiation) and after 4, 12 and 24 months. This allowed for differentiation between simultaneous and subsequent patterns of inflammation decrease of joint, bone and tendon sheath after DMARD initiation in three consecutive time periods.

Methods

Patients

Since 1993, consecutive early arthritis patients (<2 years symptom duration) were included in the Leiden Early Arthritis inception cohort. This inception cohort is extensively described elsewhere [11]. In short, patient characteristics, disease activity and laboratory parameters were obtained at baseline, 4 months and 12 months, and yearly thereafter. From August 2010 until February 2015, MRIs were performed at baseline and 4, 12 and 24 months when the initial clinical diagnosis was UA or RA.

Treatment

Patients were treated in routine care and in line with (inter-)national guidelines [12]. Medication data were extracted from the hospital patient information system and quality controlled. Doctors and patients were blinded for MRI data.

Patient selection

From all patients with an initial clinical diagnosis of RA or UA who were consecutively included from August 2010 until February 2015 ($n = 655$), patients starting DMARDs (including glucocorticoids) within 100 days after the first rheumatology outpatient clinic visit were selected ($n = 376$). Some 160 patients did not undergo repeated MRIs (mostly for logistical reasons), resulting in 216 patients being studied. Baseline characteristics of patients who started early with DMARD treatment and who did and did not have repeated MRIs were not statistically significantly different (supplementary Table S1, available at *Rheumatology* online). Ethical approval was provided by 'Commissie Medische Ethiek' of the Leiden University Medical Centre (B19.008). Patient consent was obtained.

MRI

MRI was performed at baseline (before DMARD initiation) and 4, 12 and 24 months. MCP (2–5), wrist and MTP (1–5) joints on the most painful side at baseline (dominant side in case of symmetric symptoms) were imaged with 1.5T MRI (GE, WI, USA). Follow-up MRIs were performed at the side of the baseline MRI. MRIs were scored for synovitis and osteitis in line with RAMRIS (Rheumatoid Arthritis Magnetic Resonance Imaging Score) and tenosynovitis as described by Haavardsholm, by one reader, with known time-order, blinded for any clinical data [13, 14]. Intrareader reliability was excellent (ICC0.98; supplementary Data S1 and Table S2 available at *Rheumatology* online). Scores were summed per inflammatory feature per patient. Supplementary Data S2 (available at *Rheumatology* online) provides a detailed scan and scoring protocol.

Statistical analysis

Data of three time-intervals (0–4/4–12/12–24 months) were studied with cross-lagged models [15]. Cross-lagged models can evaluate the influence of two time-patterns in one model: (i) a simultaneous pattern ('change in one inflammatory feature is associated with change in another feature') and (ii) a subsequent pattern ('change in one inflammatory feature precedes change in another feature') as shown in supplementary Fig. S1, available at R*heumatology* online. Despite these benefits, these models are infrequently used in rheumatology research and most often employed in psychology [15]. Further explanation is presented in supplementary Data S3, available at *Rheumatology* online.

Because of skewness, MRI variables were log-transformed, after addition of 1 point to facilitate transformation of zeroes. This and the complex structure of the cross-lagged models results in estimates that are not easily interpreted. We therefore expressed them in standardized regression coefficients and correlations. Standardized regression coefficients are independent of scale and lie between −1 and 1. A value of −1 (negative) or 1 (positive association) indicates full explanation of the dependent variable by the independent variable, and a value of 0 indicates no association. Congruently,

correlations lie between −1 and 1, and 0 indicates no association.

MRIs at 4, 12 and 24 months were missing in 11, 20 and 47%, respectively (23, 44 and 102 MRIs, respectively). We assumed missing at random (MAR) was not missing completely at random, because patients with a less severe disease presumably had less follow-up with MRI. MAR implies that missingness, not explained by variables included in the model, is random. Since disease activity is correlated with MRI inflammation [16], which is included in the model, and ACPA stratification was performed, no further variables associated with missingness were included in the models to achieve MAR. Also, cross-lagged models were fitted with full-information likelihood, appropriate for MAR [17].

Because ACPA status may reflect a different pathophysiology, analyses were repeated stratified for ACPA status (anti-CCP2).

Additional analyses

To determine sensitivity, analyses were repeated in the subgroup of RA patients (clinical diagnosis plus fulfilment of 1987 or 2010 criteria <1 year). In addition, analyses were repeated in patients that started DMARD treatment within 31 days.

To assess the influence of initial treatment, sensitivity analyses were performed in patients starting MTX as first therapy (as this was the most frequently used first-line DMARD). In addition, analyses were repeated in patients starting MTX without CS bridging.

To assess natural course, decrease of MRI inflammation of UA and RA patients that, in contrast to the guidelines [12], never received DMARD treatment and were therefore excluded, was presented.

R3.6.1, RStudio1.2.5001, Onyx 1.0–101 and OpenMx 2.14.11 were used (supplementary Data S3, available at *Rheumatology* online). Two-sided *P*-values <0.05 were considered significant.

Results

Baseline characteristics

Patient baseline characteristics are shown in supplementary Table S3 (available at *Rheumatology* online): mean age was 58 years, 62% were female, 44% ACPA-positive, 74% received initial MTX and the remaining patients started with other conventional synthetic DMARDs (csDMARDs). The median symptom duration at presentation was 13 weeks and the median time to DMARD start was 2.4 weeks. A total of 82% were classified as RA (supplementary Table S4, available at *Rheumatology* online).

Simultaneous and subsequent patterns

Plotting the MRI data over time revealed that synovitis, osteitis and tenosynovitis decreased during follow-up (Fig. 1). For osteitis, this decrease manifested predominantly in decreasing interquartile ranges.

To assess the influence of both the simultaneous and subsequent pattern in one model, cross-lagged models were used. With respect to the simultaneous patterns, all pairs of inflammatory features showed significant simultaneous decrease in all time intervals (0–4/4–12/12–24 months; Table 1).

In addition to simultaneous decrease, time-orders were identified (Table 1). Predominantly, synovitis decrease preceded tenosynovitis decrease. Synovitis decrease 0–4 months preceded tenosynovitis decrease 4–12 months [standardized regression coefficient (β) and 95% CI: 0.28 (0.04; 0.53); Fig. 1] and synovitis decrease 4–12 months preceded tenosynovitis decrease 12–24 m [$\beta = 0.27$ (0.04; 0.50)].

Moreover, early tenosynovitis decrease (0–4 months) significantly preceded osteitis decrease 4–12 months with a smaller effect size [$\beta = 0.15$ (0.00; 0.31)]. However, 'late' tenosynovitis decrease (4–12 months) did not precede osteitis decrease 12–24 months [$\beta = 0.01$ (−0.13; 0.14)]. Taken together, this suggests that this finding with a smaller effect size is less robust than the other findings.

ACPA stratification

Simultaneous decrease was present in both ACPA subsets and similar to that described above (Table 1).

Also, in both ACPA subsets synovitis decrease preceded tenosynovitis decrease with similar estimates, albeit not always reaching statistical significance, which may be due to the smaller sample size (Table 1).

In addition, an ACPA-specific time-order was identified: in ACPA-positive patients synovitis decrease 4–12 months preceded osteitis decrease 12–24 months [$\beta = 0.40$ (0.17; 0.64)]. This was significantly different from ACPA-negative patients ($P < 0.001$), in which the estimate was in the opposite direction [$\beta = -0.23$ (−0.45; −0.01)].

Additional analyses

All analyses were repeated in RA patients ($n = 176$) and in patients that started DMARD treatment within 31 days ($n = 153$); similar results were obtained (supplementary Tables S5 and S6, available at *Rheumatology* online).

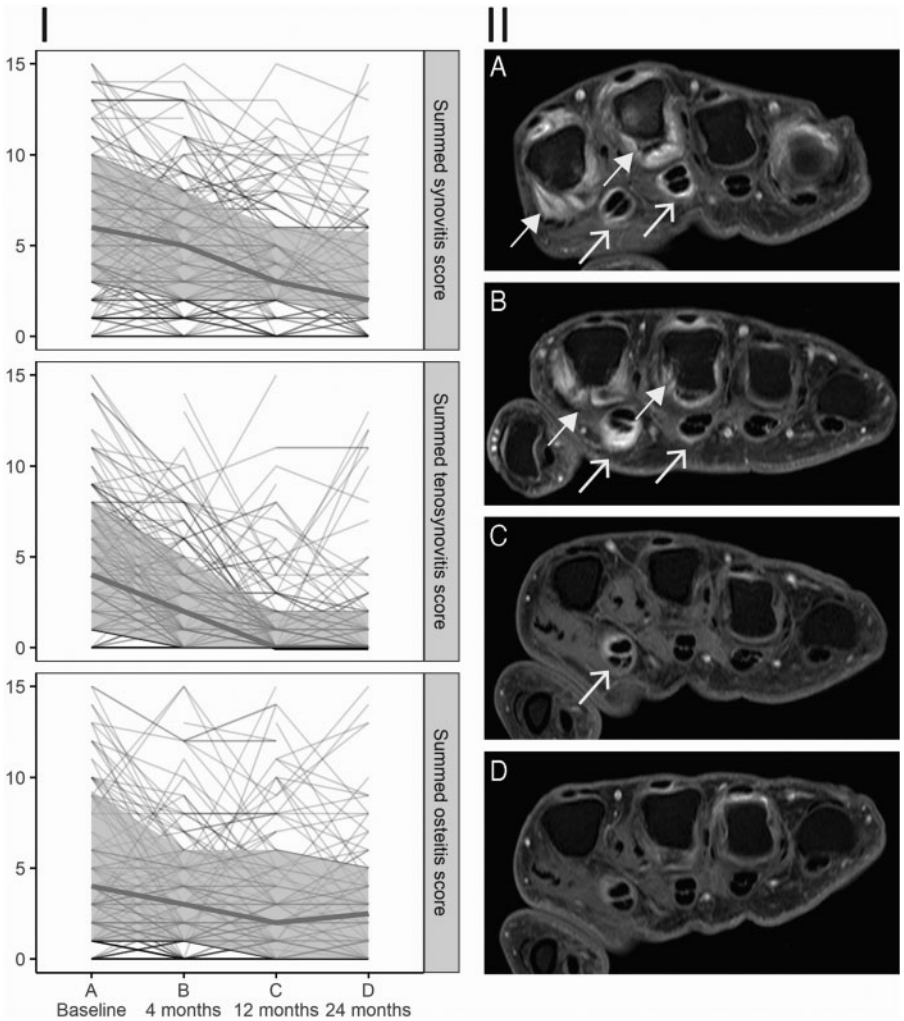
In patients starting with MTX, similar results were obtained, and also when excluding patients receiving CS bridging (supplementary Table S7, available at *Rheumatology* online).

Finally, the natural course of subgroup of UA and RA patients that never received DMARD treatment (and were therefore excluded from the analyses) was plotted, and showed little decrease (supplementary Fig. S2, available at *Rheumatology* online).

Discussion

We aimed to better understand the time-order of the response of different inflamed tissues (joint, bones and adjoining tendon sheaths of small joints) to DMARD

FIG. 1 All individual courses of synovitis, tenosynovitis and osteitis, and an example of serial MCP joint MRIs



(**I**) Lines represent individual patient trajectories. The bold line represents the median and the grey area the interquartile range. For readability, summed RAMRIS (Rheumatoid Arthritis Magnetic Resonance Imaging Score) above 15 were omitted from the graph. (**II**) These MRIs show synovitis (closed arrows) decrease between 0 and 4 months preceding tenosynovitis (open arrows) decrease between 4 and 12 months; A = 0 months, B = 4 months, C = 12 months, D = 24 months.

treatment. Using cross-lagged models, we found not only that the inflammatory features decrease simultaneously, but also that decrease in synovitis preceded decrease in tenosynovitis.

Over the last decade, advanced imaging studies have revealed that inflammation in RA is not only synovitis but also comprises osteitis and tenosynovitis. Information on time-orders of inflammation decrease provide insight into the sensitivity to treatment of these different inflamed tissues. Previous research on RA development suggested that tenosynovitis presents early in the pre-arthritis phase and is followed by synovitis [2, 4]. Our research suggests that a decrease of synovitis is followed by a decrease in tenosynovitis; these findings together possibly suggest that the inflammation that begins the earliest (e.g. tenosynovitis), resolves more slowly. Further research is needed to elucidate the molecular mechanism of this relationship.

Previous studies have shown that osteitis is more often present in ACPA-positive RA and is strongly associated with erosion development, and is therefore an important feature in ACPA-positive RA [18, 19]. In our data, ACPA-positive patients at baseline had slightly higher osteitis scores (supplementary Table S3, available at *Rheumatology* online). Moreover, our data further support that osteitis is an important feature in ACPA-positive RA by showing that synovitis decrease 4–12 months preceded subsequent osteitis decrease 12–24 months only in ACPA-positive patients. In contrast to this late subsequent decrease, no significant effect of synovitis decrease 0–4 months on osteitis decrease 4–12 months was observed in ACPA-positive patients.

Table 1 Estimates of simultaneous and subsequent change of three inflammatory features

Simultaneous change	All patients	ACPA-positive	ACPA-negative
Synovitis with tenosynovitis			
0–4 months	0.20 (0.14; 0.26)*	0.21 (0.12; 0.31)*	0.20 (0.12; 0.28)*
4–12 months	0.20 (0.13; 0.28)*	0.19 (0.09; 0.30)*	0.22 (0.11; 0.33)*
12–24 months	0.29 (0.20; 0.38)*	0.27 (0.15; 0.39)*	0.31 (0.18; 0.45)*
Synovitis with osteitis			
0–4 months	0.13 (0.08; 0.19)*	0.19 (0.10; 0.28)*	0.10 (0.02; 0.17)*
4–12 months	0.16 (0.09; 0.22)*	0.14 (0.05; 0.23)*	0.17 (0.07; 0.26)*
12–24 months	0.11 (0.04; 0.19)*	0.20 (0.10; 0.30)*	0.00 (−0.09; 0.09)
Tenosynovitis with osteitis			
0–4 months	0.07 (0.01; 0.14)*	0.06 (−0.03; 0.16)	0.08 (−0.01; 0.17)
4–12 months	0.13 (0.05; 0.22)*	0.11 (0.01; 0.22)*	0.21 (0.09; 0.33)*
12–24 months	0.12 (0.04; 0.21)*	0.14 (0.03; 0.25)*	0.07 (−0.05; 0.19)
Subsequent change	**All patients**	**ACPA-positive**	**ACPA-negative**
Synovitis precedes tenosynovitis			
0–4 to >4–12 months	0.28 (0.04; 0.53)*	0.23 (−0.11; 0.56)	0.35 (0.01; 0.68)*
4–12 to >12–24 months	0.27 (0.04; 0.50)*	0.38 (0.10; 0.66)*	0.18 (−0.17; 0.54)
Tenosynovitis precedes synovitis			
0–4 to >4–12 months	0.04 (−0.11; 0.19)	0.08 (−0.13; 0.29)	0.02 (−0.20; 0.23)
4–12 to >12–24 months	0.04 (−0.13; 0.20)	0.08 (−0.18; 0.34)	−0.03 (−0.23; 0.17)
Synovitis precedes osteitis			
0–4 to >4 − 12 months	0.11 (−0.09; 0.32)	0.13 (−0.16; 0.42)	0.07 (−0.22; 0.36)
4–12 to >12–24 months	0.09 (−0.09; 0.27)	0.40 (0.17; 0.64)*	−0.23 (−0.45; −0.01)*
Osteitis precedes synovitis			
0–4 to >4–12 months	0.12 (−0.04; 0.27)	0.08 (−0.15; 0.32)	0.13 (−0.08; 0.33)
4–12 to >12–24 months	0.17 (−0.05; 0.38)	0.24 (−0.05; 0.53)	0.16 (−0.14; 0.47)
Tenosynovitis precedes osteitis			
0–4 to >4–12 months	0.15 (0.00; 0.31)*	0.04 (−0.18; 0.25)	0.19 (−0.02; 0.40)
4–12 to >12–24 months	0.01 (−0.13; 0.14)	0.12 (−0.11; 0.35)	−0.11 (−0.27; 0.04)
Osteitis precedes tenosynovitis			
0–4 to >4–12 months	−0.02 (−0.23; 0.19)	−0.02 (−0.31; 0.26)	−0.04 (−0.33; 0.25)
4–12 to >12–24 months	0.14 (−0.10; 0.39)	0.23 (−0.07; 0.54)	0.09 (−0.30; 0.49)

Estimates of simultaneous change represent correlation of proportion of change of two inflammatory features that is not explained by the subsequent pattern and previous values of those inflammatory features, with 95% CIs. Estimates of subsequent change represent standardized regression coefficients of change of one inflammatory feature to subsequent change in another inflammatory feature, corrected for the simultaneous pattern and previous values of those inflammatory features, with 95% CIs. Standardized regression coefficients are independent of scale and lie between −1 and 1. A value of −1 or 1 indicates full explanation of change in one inflammatory feature by change in the previous period of another inflammatory feature, and a value of 0 indicates no explanation. Values −1 and 0 (negative estimate) indicate that a decrease in the first period is associated with less decrease in the subsequent period; in addition values between 0 and 1 indicate that a decrease in the first period is associated with more decrease in the subsequent period. *$P < 0.05$ (significant estimate).

This could indicate that suppression of inflammation in ACPA-positive patients affects synovitis first, but that a prolonged suppression of inflammation is needed to attain osteitis decrease in these patients.

In ACPA-negative patients, the effect of synovitis decrease 4–12 months on subsequent osteitis decrease 12–24 months was negative, meaning that more decrease in synovitis 4–12 months is associated with less decrease in osteitis 12–24 months. In addition, synovitis and osteitis showed high simultaneous decrease in 4–12 months. Together, this can imply that more inflammation suppression and resulting synovitis and osteitis decrease between 4–12 months results in a plateau in osteitis 12–24 months in ACPA-negative patients.

To our knowledge, our study is the first to show a differential disease course after treatment at the tissue level in ACPA subgroups. While this might not have any direct clinical implications, important improvements in treatment are often fuelled by a better understanding of the pathophysiology of a disease. By increasing knowledge of the effect of treatment of RA on tissue level, stratified for autoantibody status, we ultimately hope to contribute to improved treatment in RA, which might differ between ACPA subgroups.

This study is, to our knowledge, the first observational MRI study in DMARD-naïve patients that includes both early (<6 months) and late (>1 year) MRIs. Timing of MRIs was set at fixed timepoints after inclusion and therefore not dependent on date of DMARD initiation. Reassuringly, in patients treated within 31 days, and therefore having similar time periods between treatment and MRIs, results were comparable. The second MRI was performed after 4 months, the time when the efficacy of the initiated csDMARD is generally evaluated. Therefore, we could not perform analyses on very fast inflammation decrease due to CS, as this was beyond the scope of this study.

Limitations include that MRI scans were scored by a single reader. Encouragingly, intrareader reliability was excellent (supplementary Data S1, available at *Rheumatology* online). Moreover, two different MRI protocols were used for the MTP joints. Reassuringly, previous studies have shown that these protocols perform equally in depicting osteitis, and sensitivity analyses omitting the MTPs showed similar results (supplementary Data S2, available at *Rheumatology* online) [20]. The number of patients with missing MRI increased over time, especially in patients with less severe disease, resulting in missingness depending on measured covariates (MAR). Hence, we used statistical techniques appropriate for MAR.

Numbers became smaller after ACPA stratification. Therefore, the main analyses were performed in all patients with both definite RA and UA that required, according to the rheumatologist, early DMARD treatment. Several sensitivity analyses were performed to assess robustness of results, all showing similar results. Additionally, data were insufficient to perform analyses on the joint level. Therefore, validation of our findings in larger longitudinal MRI studies in both ACPA subgroups is warranted.

Our analyses were conducted in longitudinal cohort data, not in randomized placebo-controlled trial data. While treatment was not randomized, it was protocolized, indicated by >80% of RA patients starting with initial MTX. Analyses in patients starting with MTX showed similar results. Analyses for patients that started with other first-line csDMARDs were not performed due to low numbers. Biologics were only allowed if patients failed on two or more csDMARDs, and biologic use during the study's 2-year follow-up was infrequent (3% in ACPA-negative and 14% in ACPA-positive patients at year 2), impeding sensitivity analyses in this group. Therefore, whether different DMARDs (including biologics) have differential influence on the tissue level remains an interesting question for future research.

Importantly, both patients and rheumatologists were blinded for MRI data, limiting the influence of MRI inflammation on treatment decisions. Still, inflammation decrease can be partly due to natural course or bias due to reading MRIs in chronological order. To evaluate this, MRIs of UA and RA patients that, in contrast to the guidelines [12], never received DMARD treatment, were scored simultaneously with the MRIs of our study, blinded for clinical data. This revealed that MRI inflammation decreased little in untreated patients (supplementary Fig. S2, available at *Rheumatology* online). Therefore, the decrease observed in the treated patients most likely represents a treatment effect.

In conclusion, this study increased the understanding of treatment response in RA on the tissue level. In addition to simultaneous decrease of synovitis, osteitis and tenosynovitis, time-orders of response in inflamed tissues were identified, which were partly different in the ACPA subgroups. This suggests different inflammatory pathways underlie MRI inflammation in ACPA-positive and ACPA-negative disease.

Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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