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Development of clinically apparent synovitis: a longitudinal study at the joint level during progression to inflammatory arthritis

Robin M ten Brinck,[1] Hanna W van Steenbergen,[1] Annette H M van der Helm-van Mil[1,2]

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[1]Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands
[2]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, The Netherlands

Correspondence to
Robin M ten Brinck;
r.m.ten_brinck@lumc.nl

ABSTRACT

Introduction Subclinical inflammation, detected by MRI, in patients with arthralgia is predictive for development of inflammatory arthritis (IA). However, within patients that develop IA, the course of inflammation at the joint level during this transition is unknown. This longitudinal study assessed progression of inflammation at the joint level.

Methods 350 joints (unilateral metacarpophalangeals (MCPs), wrist, metatarsophalangeal (MTP) joints) of 35 patients presenting with clinically suspect arthralgia (CSA) that progressed to IA were studied at presentation with CSA and subsequently when clinical synovitis was first identified at joint examination (median time interval 17 weeks). At both time points, subclinical inflammation (bone marrow oedema, synovitis, tenosynovitis) was evaluated with MRI and joint examination was performed.

Results At presentation with CSA, 71 joints showed subclinical inflammation. During progression to IA, 20% of these joints had resolution of inflammation, 60% had persistent inflammation and 20% progressed to clinical synovitis. Of all joints that had developed clinical synovitis (n = 45), no prior subclinical inflammation was detected in 69%. Similar results were observed for anticitrullinated protein antibodies (ACPA)-positive and ACPA-negative patients.

Conclusions This longitudinal study demonstrated moderate correlations between joints with subclinical inflammation and joints that developed clinical synovitis. These data imply that IA development is a more systemic rather than a locally outgrowing process.

Key messages

What is already known about this subject?

- Presence of subclinical inflammation in small joints in patients with arthralgia is predictive of rheumatoid arthritis (RA) development.
- Progression to RA is uncommon in patients with arthralgia without MRI-detected subclinical inflammation.

What does this study add?

- This longitudinal study demonstrated moderate correlations between joints with subclinical inflammation and joints that developed clinical synovitis.

How might this impact on clinical practice?

- These data imply that IA development is a more systemic rather than a locally outgrowing process.

INTRODUCTION

During the prearthritis phases of rheumatoid arthritis (RA), subclinical inflammation can already be present.[1–3] Its presence in small joints in patients with arthralgia is predictive of inflammatory arthritis (IA) development.[1–3] Furthermore, at the patient level, progression to IA is uncommon in patients with arthralgia without MRI-detected subclinical inflammation.[1]

Although risk factor studies have made an enormous progress in our comprehension of the development of RA,[4–6] many questions remain unanswered. One of these questions concerns the progression of inflammation at the joint level during development of clinical synovitis. For instance, it is unknown how often joints with subclinical inflammation progress to clinical synovitis in the same joint, and vice versa, how often joints with clinical synovitis had (prolonged) preceding subclinical inflammation at the same location during the phase of arthralgia. Consequently, it is unclear whether IA development is a local outgrowing process where subclinical joint inflammation closely relates to subsequent clinical synovitis, or whether there is a more global deregulation where locations of subclinical inflammation and synovitis development are largely uncoupled. Exploration of these hypotheses necessitates longitudinal studies that start in a prearthritis phase.

This longitudinal study at the joint level in patients with arthralgia that developed IA assessed the course of joint inflammation in this period. In sensitivity analyses, stratification was applied for anticitrullinated protein antibodies (ACPA) status.

METHODS

Patients

Three hundred and fifty small joints of 35 patients that presented withclinically suspect arthralgia (CSA) and progressed to IA were evaluated. Patients that presented at the rheumatology outpatient clinic of the Leiden University Medical Centre were included in a consecutive manner in the Leiden CSA cohort between April 2012 and September 2016. CSA was defined as recent-onset (<1 year) arthralgia of small joints that was clinically considered at risk for IA by the rheumatologists without clinically evident arthritis. Twenty-nine patients (83%) met the EULAR definition of arthralgia suspicious for progression to RA at baseline.[7] Patients included in the CSA cohort were followed until synovitis development (detected at joint examination by an experienced rheumatologist) as described by van Steenbergen *et al*.[8] In this study, patients with CSA that were included between April 2012 and September 2016 and progressed to IA were studied. Regular follow-up visits in the CSA cohort were planned at 4, 12 and 24 months after baseline. If necessary (for instance when the patient experienced more symptoms or noticed a swollen joint) patients were seen in between the scheduled visits by their rheumatologist. This provided early access to rheumatology care if patients developed clinically evident synovitis and thus IA was identified at the first opportunity. When IA was identified at the patient level, individual joints could be in one of these states: clinical synovitis, MRI-detected subclinical inflammation but no clinical synovitis, or no inflammation. Tender joint count (68-TJC) and swollen joint count (66-SJC) for study purposes were performed by one assessor from a pool of six trained research nurses under supervision of an experienced rheumatologist. Regular reliability sessions are held to maintain a high interobserver correlation. All patients provided written informed consent.

Magnetic resonance imaging

Unilateral MRIs of wrist, metacarpophalangeal (MCP)2–5 and metatarsophalangeal (MTP)1–5 were performed at presentation with CSA (most painful side) and at first presentation with clinical synovitis (similar side as scanned at baseline). An ONI MSK Extreme 1.5 T MRI scanner (GE Healthcare, Wisconsin, USA) was used, as described previously[1] and in the Supplementary Methods. Patients were instructed not to use non steroidal anti inflammatory drugs (NSAIDs) 24 hours prior to MRI, with seven patients (20%) reporting daily use of NSAIDs at baseline. MRIs were evaluated for bone marrow oedema (BME; range 0–72)) and synovitis (range 0–33) as described by Østergaard *et al*,[9] and tenosynovitis (range 0–54) as described by Haavardsholm *et al*,[10] by two independent experienced readers who were blind to clinical data and the order in time (all had interclass correlations ≥0.94, see online supplementary table 1). Subclinical inflammation was considered present in clinically non-inflamed joints if the total inflammation score (summing the BME, synovitis and tenosynovitis scores and averaging the score of two readers) was ≥1. In other words: if either the BME, synovitis or tenosynovitis score was ≥1, subclinical inflammation was considered present in a joint. BME scores for the wrist joint were calculated for the bones lining the joint space: proximally the radius and ulna, distally the proximal carpal row (scaphoid, lunate, triquetrum and pisiform). Synovitis scores for the wrist joint were calculated by the radioulnar and radiocarpal compartment and tenosynovitis scores for all wrist flexors and extensors.

Analysis

Percentages were determined by evaluating inflammation in individual joints over time. Generalised estimating equations(GEEs), using an unstructured correlation matrix, were used to investigate differences in the time interval between the paired measurements in joints that did/did not develop clinical synovitis, while holding in account that one patient contributed 10 joints. Sensitivity analyses were performed per inflammatory feature and by stratifying for ACPA status. Finally, a second (more stringent) definition was used for subclinical inflammation: subclinical inflammation was considered present if it occurred in <5% of age-matched symptom-free persons at the same joint and for the same feature (henceforth referred to as 5% corrected definition).

RESULTS

Patient characteristics

Clinical characteristics are demonstrated in online supplementary table 2. Ten patients were ACPA-positive. Thirty-four out of 35 patients (97%) had subclinical inflammation in ≥1 joint that was evaluated with MRI at baseline. Median duration between presentation with CSA and development of IA was 17 weeks (IQR: 6–21). When clinical synovitis was identified at one of the subsequent visits, the median SJC (66-SJC) was 2 (IQR: 1–5), and 23 patients (66%) fulfilled the 2010 ACR/EULAR classification criteria for RA.

Joints with subclinical inflammation during CSA predominantly remain in state of subclinical inflammation

Further analyses were performed at joint level. At presentation with arthralgia, 71 out of 350 joints showed subclinical inflammation on MRI (figure 1). Over time, 14 of these 71 joints (20%) had resolution of subclinical inflammation, 43 joints (60%) had persistent subclinical inflammation and 14 joints (20%) progressed to clinical synovitis. Two hundred and seventy-nine joints (80%) had no subclinical inflammation at baseline imaging.

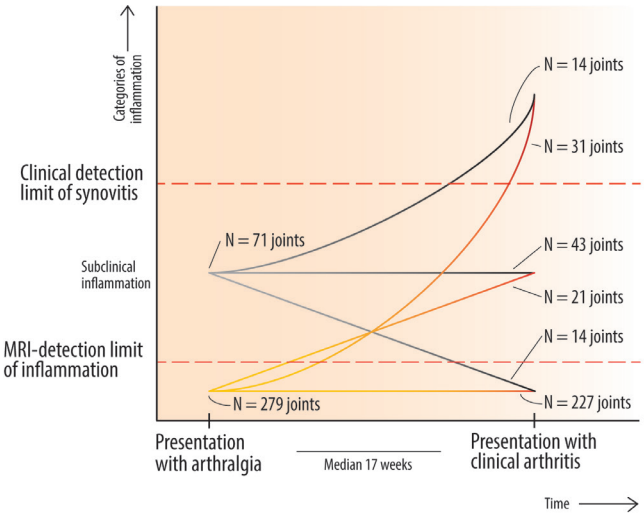

Figure 1 Schematic depiction of categories of inflammation in 350 small joints during progression from clinically suspect arthralgiato inflammatory arthritis. Presence of subclinical joint inflammation was detected by MRI. An MR inflammation score ≥1 (sum of bone marrow oedema, synovitis or tenosynovitis in one joint, average of two readers) was defined as subclinical inflammation. At the time of IA development, individual joints could show clinically detectable joint swelling at physical examination, while this was per definition not possible at presentation with arthralgia. Please note that the y-axis indicates categories of inflammation (below MRI-detection limit of inflammation/ above MRI-detection limit but under clinical detection limit of synovitis at physical examination/above clinical detection limit of synovitis at physical examination (ie, clinically detectable joint swelling)), not absolute MRI-inflammation scores.

Next, the absolute total inflammation scores were evaluated. The mean change in total inflammation score for all patients was 2.0 points (p=0.008). Summing BME, synovitis, tenosynovitis scores (yielding the total inflammation score) of the 43 joints that had subclinical inflammation at both time points revealed that 16 joints (37%) had increasing inflammation scores (mean increase 1.8 points), 21 joints (49%) had identical inflammation scores and 6 joints (14%) with subclinical inflammation had decreasing scores (mean decrease 1.4 points) despite still having scores >0 for subclinical inflammation.

Most joints developing clinical synovitis had no preceding subclinical inflammation at presentation with CSA

In total, 45 MCP, wrist or MTP joints developed clinically apparent synovitis in 21 patients; 20 joints in the feet (MTP) were swollen, whereas 25 joints in the hand (MCP or wrist) were swollen. The other 14 patients had synovitis in ≥1 joint, but these joints were not evaluated on MRI. Of these 45 swollen joints, 31 joints (69%) had no preceding subclinical inflammation at presentation with arthralgia (figure 1). A GEE investigating if swollen joints with or without preceding subclinical inflammation could have dissimilar times to arthritis revealed no difference in time intervals (β=1.3; p=0.71). Hence, the absence of preceding subclinical inflammation in joints with clinically apparent synovitis was not associated with a longer time interval. An MRI example of a joint developing clinical synovitis whereas it showed no subclinical inflammation in the CSA phase is presented in figure 2A.

Analyses were repeated per inflammatory feature, revealing that 9% of joints (4 out of 45) with clinical synovitis had preceding BMO in the CSA-phase. Similarly, 24% (11 out of 45 joints) had prior MRI-detected synovitis. For tenosynovitis, only the MCP and wrist joints were evaluated: 36% of joints (9 out of 25) had preceding tenosynovitis (online supplementary figure 1A-C).

Resolution of subclinical inflammation was observed despite progression to IA

Fourteen joints (in 11 different patients) had subclinical inflammation in the CSA phase which resolved over time, despite progression to IA at the patient level: an MRI example is provided in figure 2B.

However, the majority of joints assessed (N=227/350; 65%) had no inflammation at either point in time (figure 1).

Similar results observed for joints of ACPA-positive and ACPA-negative patients

As the pathogenesis of IA development presumably differs between ACPA-positive and ACPA-negative disease, analyses were stratified for ACPA status. At the patient level, the interval between presentation with CSA and IA development was shorter for ACPA-positive disease (median 7 weeks, compared with 18 weeks in ACPA-negative disease). However, at the joint level the percentages of joints that progressed from subclinical inflammation to clinical synovitis were similar (online supplementary figure 2B). Likewise, analyses within ACPA-positive disease showed that 62% of joints with clinically apparent synovitis had no prior subclinical inflammation in the same joint, whereas in ACPA-negative disease this percentage was 72%.

Inflammation corrected for age-matched symptom-free persons yielded similar results (5% corrected definition)

Finally, a second definition of presence of MRI-detected subclinical inflammation was used. The values of normality of MRI-detected joint inflammation depends on age and should take into account the occurrence of inflammation in symptom-free persons. Therefore, in this second definition (5% corrected definition), subclinical inflammation was considered present after correction for the level of inflammation occurring in <5% of age-matched symptom-free persons at the same joint and for the same feature (a definition used previously[1 11]). With the 5% corrected definition, similar findings were obtained (online supplementary figure 3),[3] with the majority of small joints (84%) that developed clinical synovitis having no preceding phase lasting for weeks with subclinical inflammation in the same joint.

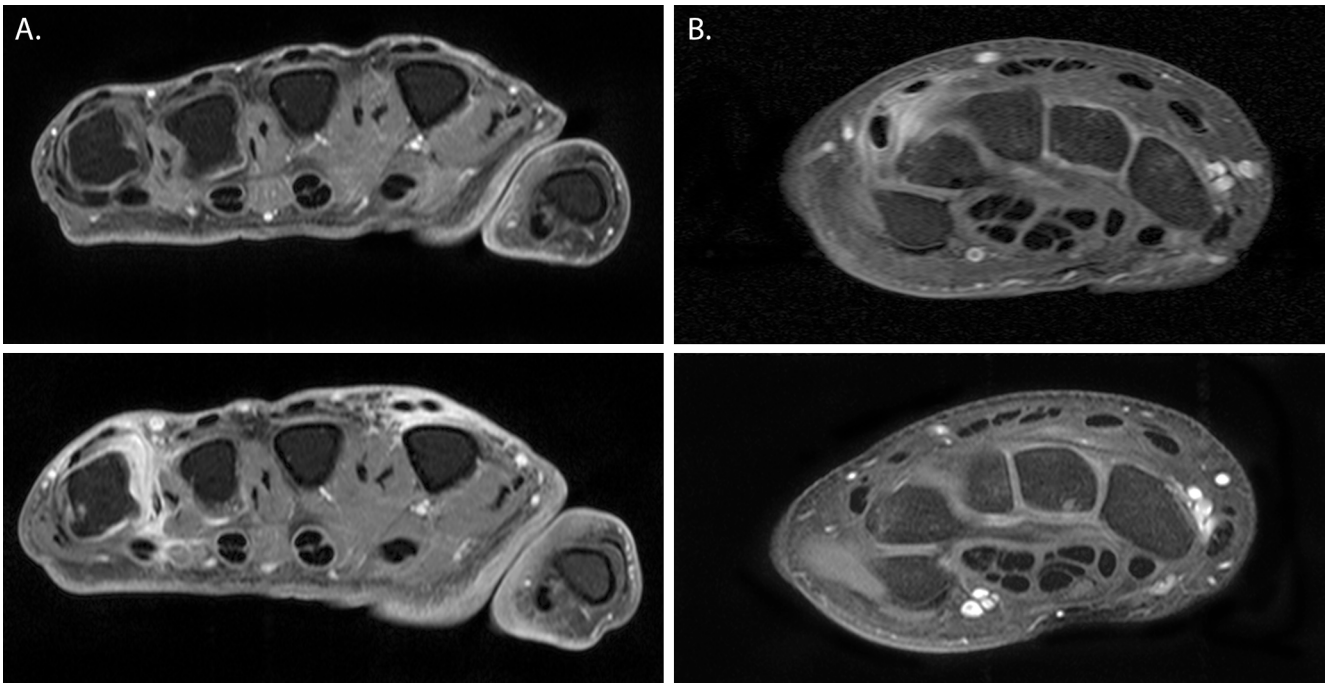

Figure 2 Examples of MRI at presentation with clinically suspect arthralgia (CSA) (top panel) and at IA development (bottom panel), showing joints (A) from no inflammation to clinical synovitis and (B) resolution of subclinical inflammation. Presented in (A) are: (top panel) left MCP joints with no subclinical inflammation as detected by MRI, and (bottom panel) left MCP joints of the same patient with synovitis in MCP5 and tenosynovitis in MCP2 and 5. According to clinical examination the patient developed clinical synovitis in the left MCP2 (depicted), left MCP5 (depicted), left proximal interphalangeal (PIP)2 and right PIP5 joints (both not imaged). From a different patient (B) are presented: (top panel) right wrist joint with tenosynovitis in the extensor carpi ulnaris tendon, and (bottom panel) right wrist joint of the same patient without MRI-detected subclinical inflammation despite progression to inflammatory arthritis at the patient level. The patient developed clinically apparent synovitis in the left PIP3 joint (not imaged). All images were made in T1-weighted fast spin echo (FSE) sequence with frequency selective fat saturation in the axial plane after gadolinium contrast injection.

DISCUSSION

To our knowledge, this study was the first to perform longitudinal joint-level analyses in order to investigate progression of inflammation in patients converting from CSA to the earliest clinical phase of IA. At the joint level, only moderate correlations were observed between presence of subclinical inflammation and subsequent development of clinical synovitis. The majority of joints with clinical synovitis had no subclinical inflammation in the same joint at the baseline observation.

The present joint-level observations on inflammatory progression fit best with the hypothesis of 'global deregulation', rather than that of a localised exacerbating process. Previous observations of increased markers of systemic inflammation in prearthritis phases may support this.[12] Additionally, our study showed only moderate correlations between inflammation on MRI and progression of synovitis as assessed by physical examination, with BME showing the lowest proportion of prior subclinical inflammation in the joints progressing to synovitis. Another study found that MRI-detected subclinical inflammation is present in clinically swollen joints and in non-swollen joints; in particular, BME frequently occurred in clinically non-inflamed joints.[13]

Our results should be interpreted within the context of some methodological limitations. Considering that 10 joints (unilateral MCP, wrist and MTP joints) per patient were studied, many synovial joints were not assessed. Furthermore, the total sample size was limited despite large availability of data on joint level. However, this study offers the first and largest longitudinal scrutiny of data on joint inflammation in patients with arthralgia that progress to IA. Finally, the time interval between presentation with CSA and IA differed between individual patients, posing the possibility of dissimilarities in time intervals for joints with or without preceding subclinical inflammation. Nonetheless, a GEE model incorporating each patient contributing 10 joints suggested no differences in time to arthritis for joints with or without preceding subclinical inflammation, indicating that results were not based on a few patients with longer time intervals.

An elementary, but sensitive, definition of subclinical inflammation (summed inflammation score ≥1 per joint) was used. Reference values of normality for MRI-detected joint inflammation depending on age, inflammatory feature and joint were not included in this definition. When subclinical inflammation was defined as inflammation present in <5% of age-matched symptom-free persons at the same joint and for the same feature (5% corrected definition), similar findings were obtained.

ACPA-positive and ACPA-negative disease have different risk factors, presumed differences in pathogenesis and

known dissimilarities in speed in progressing from CSA to IA.[14] However despite these differences, the observations on joint level on the relation between subclinical inflammation in the CSA phase and clinical synovitis in the IA phase were roughly similar in both groups. Larger studies validating these findings are required.

MRI depicts inflammation of different tissues around the joint. Stratified analyses showed that clinical synovitis was most often preceded by MRI-detected tenosynovitis. This fits previous observations that tenosynovitis had the highest predictive accuracy for RA development,[1] and that tenosynovitis was an initial preclinical change in mouse models of arthritis development.[15] Although further studies are needed to explore this thoroughly, the combination of these findings suggests that tenosynovitis is a very early phenomenon.

The ability of a clinician to detect swollen joints may be dissimilar between different joint groups (MCP, wrist and MTP joints) analysed in this paper. Nevertheless, the number of swollen joints in the feet (MTP: 20 joints) was similar to the number of swollen joints in the hand (MCP and wrist: 25 joints). Future studies could investigate the correlation between MRI-detected subclinical inflammation in clinically swollen and non-swollen joints in the feet versus joints of the hand.

This study evaluated inflammation on MRI scans in individual joints over time. Future studies with serial MRI at more frequent time points (and thus shorter intervals) in patients progressing from arthralgia to RA might further increase the understanding of inflammatory processes in small joints during IA development.

In conclusion, this first longitudinal MRI study on joint level during progression from CSA to IA indicates that the course of subclinical inflammation is variable and showed that the majority of small joints that developed clinical synovitis had no subclinical inflammation in the same joint at the baseline observation.

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Contributors RMtB and AHMvdHvM contributed to the conception and study design. RMtB analyzed the data. RMtB, HWvS and AHMvdHvM contributed to interpretation of the data. RMtB and AHMvdHvM wrote the first version of the manuscript and RMtB, HWvS and AHMvdHvM revised it critically. MtB, HWvS and AHMvdHvM read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the medical ethics committee of the Leiden University Medical Centre, which is named Commissie Medische Ethiek (CME), under Ethics Approval Number NL38832.058.11.

Data statement No additional data are available.

REFERENCES

1. van Steenbergen HW, Mangnus L, Reijnierse M, *et al*. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. *Ann Rheum Dis* 2016;75:1824–30.
2. van de Stadt LA, Bos WH, Meursinge Reynders M, *et al*. The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. *Arthritis Res Ther* 2010;12:R98.
3. Nam JL, Hensor EM, Hunt L, *et al*. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. *Ann Rheum Dis* 2016;75:2060–7.
4. Mankia K, Emery P. Preclinical rheumatoid arthritis: progress toward prevention. *Arthritis Rheumatol* 2016;68:779–88.
5. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011;365:2205–19.
6. van Steenbergen HW, Huizinga TW, van der Helm-van Mil AH. The preclinical phase of rheumatoid arthritis: what is acknowledged and what needs to be assessed? *Arthritis Rheum* 2013;65:2219–32.
7. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, *et al*. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. *Ann Rheum Dis* 2017;76:491–6.
8. van Steenbergen HW, van Nies JA, Huizinga TW, *et al*. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. *Ann Rheum Dis* 2015;74:1225–32.
9. Østergaard M, Edmonds J, McQueen F, *et al*. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. *Ann Rheum Dis* 2005;64 Suppl 1:i3–i7.
10. Haavardsholm EA, Østergaard M, Ejbjerg BJ, *et al*. Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. *Ann Rheum Dis* 2007;66:1216–20.
11. Boer AC, Burgers LE, Mangnus L, *et al*. Using a reference when defining an abnormal MRI reduces false-positive MRI results-a longitudinal study in two cohorts at risk for rheumatoid arthritis. *Rheumatology* 2017;56:1700–6.
12. Nielen MM, van Schaardenburg D, Reesink HW, *et al*. Simultaneous development of acute phase response and autoantibodies in preclinical rheumatoid arthritis. *Ann Rheum Dis* 2006;65:535–7.
13. Krabben A, Stomp W, Huizinga TW, *et al*. Concordance between inflammation at physical examination and on MRI in patients with early arthritis. *Ann Rheum Dis* 2015;74:506–12.
14. Burgers LE, van Steenbergen HW, Ten Brinck RM, *et al*. Differences in the symptomatic phase preceding ACPA-positive and ACPA-negative RA: a longitudinal study in arthralgia during progression to clinical arthritis. *Ann Rheum Dis* 2017;76:1751–4.
15. Hayer S, Redlich K, Korb A, *et al*. Tenosynovitis and osteoclast formation as the initial preclinical changes in a murine model of inflammatory arthritis. *Arthritis Rheum* 2007;56:79–88.