CHAPTER 10

Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab

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ABSTRACT

Objectives: To assess the relationship between joint tenderness, swelling and joint damage progression in individual joints and to evaluate the influence of treatment on these relationships.

Methods: First-year data of the Behandel Strategieën (BeSt) study were used, in which patients recently diagnosed as having rheumatoid arthritis (RA) were randomly assigned into four different treatment strategies. Baseline and 1-year x-rays of the hands and feet were assessed using the Sharp-van der Heijde score (SHS). With generalised estimating equations, 3-monthly assessments of tender and swollen joints of year 1 were related to erosion progression, joint space narrowing (JSN) progression and total SHS progression at the individual joint level (definition >0.5 SHS units) in year 1, corrected for potential confounders and within-patient correlation for multiple joints per patient.

Results: During year 1, 59% of all 13959 joints analysed were ever tender and 45% ever swollen, 2.1% showed erosion progression, 1.9% JSN progression and 3.6% SHS progression. Swelling and tenderness were both independently associated with erosion and JSN progression with comparable OR, although with higher OR in the hands than in the feet. Local swelling and tenderness were not associated with local damage progression in patients initially treated with infliximab.

Conclusion: Clinical signs of synovitis are associated with erosion and JSN progression in individual joints after 1 year in RA. A disconnect between synovitis and joint damage progression was observed at joint level in patients who were treated with methotrexate and infliximab as initial treatment, confirming the disconnect between synovitis and the development of joint damage in tumour necrosis factor blockers seen at patient level.

INTRODUCTION

In rheumatoid arthritis (RA) it is well-established that inflammation, joint damage and functional limitations are interrelated.[1-3] Therefore, the treatment of rheumatoid arthritis is aimed at decreasing disease activity as soon as possible in order to restrict limitations in functional ability and to prevent the progression of joint damage. Although the generally accepted concept that inflammation leads to joint damage forms the basis for current treatment approaches, the number of studies assessing this relationship on the individual joint level are limited. There are several earlier studies on the relationship between clinical signs of synovitis and individual joint damage,[4-8] but in these studies no correction was made for the fact that multiple joints per patient were included in the analyses, incorrectly assuming that these measurements all came from different patients. Because of patient characteristics it is likely that within one patient two joints behave more similar than two joints from two different patients, that is within one patient measurements of multiple joints are considered to be correlated. This within-patient correlation needs to be taken into account. In the two studies that did correct for within-patient correlation, foot joints are either not included[9] or not studied separately.[10] Furthermore, the influence of treatment with conventional disease-modifying antirheumatic drugs (DMARDs), corticosteroids and biologicals on the relationship between clinical signs of synovitis and progression of joint damage in individual joints is unclear. Clinical trials with tumour necrosis factor (TNF)-blocking therapies showed a disconnect between inflammation and joint damage progression in patients treated with methotrexate and TNF inhibitors at patient level.[11-14] It can be questioned whether this dissociation exists at joint level.

Therefore, the first objective of our study was to examine the relationship between clinical signs of synovitis (swelling and tenderness) and joint damage progression (erosions, joint space narrowing [JSN], total Sharp-van der Heijde score (SHS)) in the individual joints of the hands and feet of patients with RA. The second aim was to assess the influence of different types of treatment on these relationships.

METHODS

The first year follow-up data from the randomised, single-blind Behandel Strategieën (BeSt) study were used for our analysis. Details of the BeSt study design have been published previously.[15] Briefly, 508 patients with recent-onset RA were randomised into four treatment strategies: sequential monotherapy (group 1, n=126), step-up combination therapy (group 2, n=121), initial combination therapy with prednisone (group 3, n=133) and initial combination therapy with methotrexate (MTX) and the TNF-α inhibitor infliximab (group 4, n=128). Treatment was adjusted based on 3-monthly measurements of disease activity aimed at achieving a disease activity score (DAS) ≤2.4 (ie, the cut-off value for low disease activity).[16,17]

The study was approved by the Medical Ethics Committees of the participating hospitals, and all patients gave written informed consent. The study was designed by the

investigators and supported by a government grant from the Dutch College of Health Insurance Companies, with additional funding from Centocor (Horsham, Pennsylvania, USA) and Schering-Plough Ltd. Data collection, trial management, data collection, data analysis and preparation of the manuscript were performed by the authors.

Patients

Between March 2000 and August 2002, 508 patients from 20 hospitals in The Netherlands with DMARD-naïve RA according to the 1987 American College of Rheumatology criteria,[18] age ≥18 years, disease duration ≤2 years, active disease with ≥6 of 66 swollen joints and ≥6 of 68 tender joints and either an erythrocyte sedimentation rate (ESR) ≥28 mm/h or a global health score of ≥20 mm on a 100 mm visual analogue scale (VAS; 0, best; 100, worst) were included.

Assessment of radiological damage progression

Radiographs of the hands and feet of each patient taken at baseline and year 1 were scored in one session per patient in random time sequence using the SHS (range 0 to 448 points)[19] by two independent readers blinded to patient identity and treatment allocation. Mean baseline and 1-year follow-up SHS of the two readers were used. Erosion progression in an individual joint was defined as an increase of >0.5 in erosion score, JSN progression for each joint was defined as an increase in JSN score of >0.5 and SHS progression was defined as an increase in SHS score (JSN + erosions) per joint of >0.5 SHS units.

Clinical examination

Clinical joint assessments were performed every 3 months by trained nurses, blinded for treatment allocation. Per joint, swelling was assessed as 0 (absence) or 1 (presence). Joint tenderness was assessed per joint using the Ritchie articular index (RAI)[20] recoded for the current analysis as 0 (absence) or 1 (presence, ie, RAI 1, 2 or 3). In total, five clinical assessments were performed in the first year of the study: one at baseline and four during follow-up. We evaluated whether each joint was never (0 out of 5 assessments), once (1 out of 5 assessments) or twice or more (≥2 out of 5 assessments) swollen and/or tender during year 1.

Statistical analyses

Statistical analyses were performed with the software program SPSS version 16.0 (SPSS, Chicago, Illinois, USA). The current analysis included only clinical data from the joints of fingers and toes that were evaluated using the SHS. Generalized Estimating Equations (GEE) analyses were used to study the association between clinical signs of synovitis and joint damage progression at the joint level. The first outcome used in the GEE was erosion progression defined as yes (>0.5 units) or no (≤0.5 units), based on 32 joints per patient (hands: 10 metacarpophalangeal joints [MCPs], 8 proximal interphalangeal joints [PIPs], 2 interphalangeal joints of the thumbs [IP1s]; feet: 10 metatarsal joints [MTPs], 2 interphalangeal joints of the first toes [IP1s]). The second and third

outcomes used in the GEE were JSN progression and SHS progression (erosion and/or JSN), respectively, both defined as yes (>0.5 units) or no (≤0.5 units), based on 30 joints per patient (same joints as for erosion progression except IP1s of thumbs as these are not assessed for JSN with the SHS method). The GEE corrects for within-patient correlation. The exchangeable correlation matrix was used in all analyses, assuming an equal correlation between all joints. For all three outcomes, the same covariates were added stepwise to the model in the following order: swelling (ever [≥1 out of 5 assessments])/never [0 out of 5 assessments]) alone, than tenderness (ever/never) alone, than swelling and tenderness together and finally swelling, tenderness and the interaction swelling* tenderness together. All analyses were corrected for the following known predictors for joint damage progression and potential confounders: total SHS baseline, erosions at baseline (>0.5 units yes/no per joint for the outcome erosion progression), JSN at baseline (>0.5 units yes/no per joint for the outcome JSN progression), SHS at baseline (>0.5 units yes/no per joint for the outcome SHS progression), age, gender, baseline body mass index, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP)2 status (double positive, RF-positive or CCP2-positive, or double negative), treatment group and baseline ESR. The analyses were repeated for the hands and feet separately to assess whether there was a difference in strength of association. To analyse whether there was a 'dose-response' for swelling and tenderness, a GEE with the outcomes erosion progression, JSN progression, and SHS progression with a categorical variable (never, once and ≥2x swollen/tender during year 1) was performed for swelling and tenderness separately, corrected for the variables described above.

To assess whether the association between clinical signs of synovitis and joint damage progression was different for clinical synovitis at baseline (ie, before the start of treatment) compared with clinical synovitis during follow-up assessments (ie, during treatment), swelling and tenderness in each joint were categorised in: (1) never, (2) only at baseline, (3) only at a follow-up assessment (once), (4) only at follow-up assessments (twice or more) and (5) at baseline and during follow-up assessment(s). A GEE model with this categorical variable as determinant was performed for all three joint damage progression outcomes, again corrected for the variables described above.

Finally, a separate GEE analysis was performed for each treatment strategy to study the influence of the treatment strategies on the relationship between clinical signs of synovitis and joint damage progression, corrected for the potential confounders as described above.

RESULTS

Baseline characteristics between the four groups were comparable, as previously described.[15] At baseline, patients had active disease, with a mean (SD) DAS of 4.4 (0.9) and a mean (SD) HAQ of 1.4 (0.7). The mean (SD) SHS at baseline was 7.1 (10.2), 3.7% of all joints had erosions (>0.5 units), 5.3% had JSN (>0.5 units) and 8.1% of all joints had SHS >0.5 units. During year 1, 45% of the 13959 joints used in the analysis were at least once swollen and 59% were at least once tender. During year 1, 2.1% of all joints showed

erosion progression (295/13959 joints), 1.9% showed JSN progression (251/13084 joints) and 3.6% (477/13084 joints) showed SHS progression.
In total, 3.4%, 3.1% and 5.7% of the joints that were ever swollen and tender during year 1 showed erosion progression, JSN progression and SHS progression, respectively, compared with 1.1%, 0.9% and 1.9% of joints that were never swollen or tender *(figure 1 A)*, indicating that although there was more progression in joints that were swollen or tender, the vast majority of swollen and tender joints did not progress during year 1. However, 30 to 40% of joints with progression of erosion and/or JSN were never recorded as swollen during the 5 assessments during year 1 *(figure 1 B)*. The percentages of joints that were swollen and/or tender during year 1 were similar for joints showing erosion progression, JSN progression or SHS progression. Of the 477 joints with SHS progression >0.5, 87 joints were never recorded as swollen or tender. Of those 87 joints, 23 (26%) had baseline damage, compared to 96 (25%) of the 390 progressive joints with swelling and/or tenderness. Median (IQR) SHS progression in the clinically uninvolved joints with SHS progression was 1.0 (1.0 – 1.6)

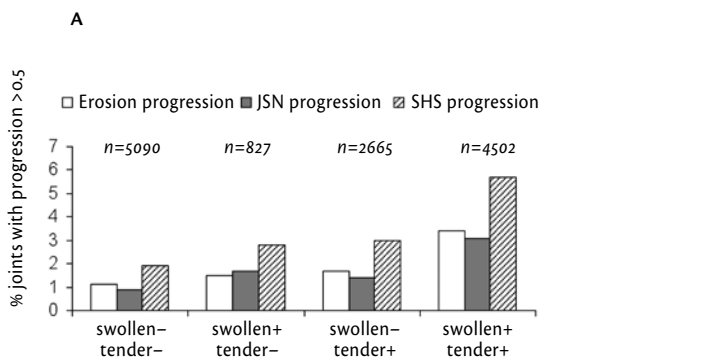

FIGURE 1 Distribution of swollen and tender joints and erosion progression, joint space narrowing progression and SHS progression. (A) The percentage of joints showing erosion progression, joint space narrowing progression and SHS progression depicted among swollen (ever) and tender (ever) joints. (B) The percentage of swollen (ever) and tender (ever) joints among the progressive and non-progressive joints. JSN, joint space narrowing; n, number of joints; SHS, Sharp-van der Heijde Score.

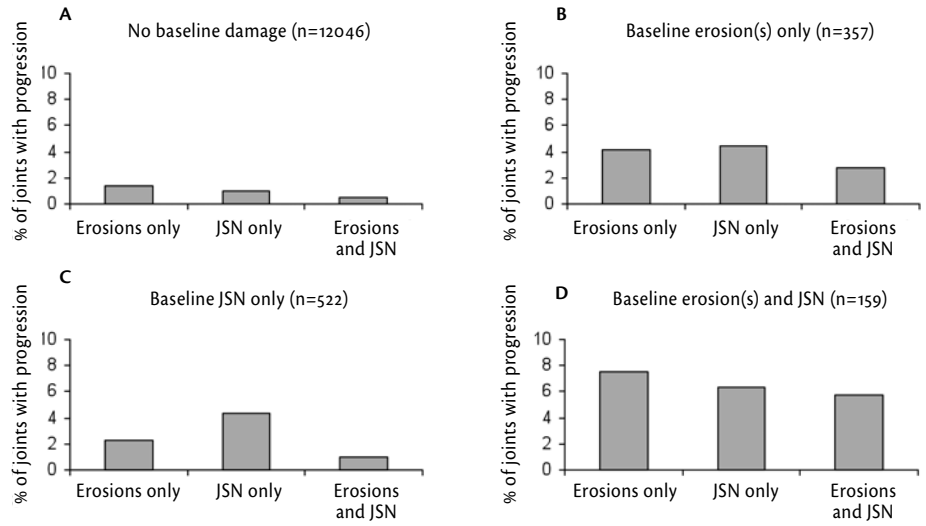

FIGURE 2 The figures show the proportions of patients with erosion progression, joint space narrowing progression, or both, stratified for the absence of baseline damage, baseline erosion(s) only, baseline JSN only, baseline erosion(s) and JSN.

compared to 1.5 (1.0 – 2.5) in the joints that were at least once recorded as swollen and/or tender (p<0.001; Mann Whitney U test). Joints with JSN at baseline had a higher chance to show JSN progression than erosion progression, whereas among the joints with baseline erosions the chance for erosion and JSN progression was comparable *(figure 2)*.

GEE results

The GEE model showed that a joint that was swollen at least once during year 1 had a higher risk for progression than a joint that was never swollen *(table 1: model 1)*. The same was true for joint tenderness *(table 1: model 2)*. Both swelling and tenderness contributed independently to the increased risk for progression *(table 1: model 3)*, but with lower OR than when added separately. The association was comparably strong for swelling and tenderness and as strong for erosion as well as JSN progression. In all models the potential confounders were added. Independent baseline predictors for joint damage progression in the individual joint, that did not influence the association between swelling and tenderness and damage progression (uncorrected data not shown) were: a higher total SHS at baseline, the presence of baseline damage in the same joint, lower age, a higher ESR, presence of anti-CCP2 and RF and initial mono-therapy *(table 1)*. The interaction term swelling*tenderness was not significantly associated with the outcomes erosion progression, JSN progression and SHS progression and was therefore omitted from the analysis. Repeating the GEE analyses in the joints without baseline damage gave comparable results (data not shown).
The association between swelling/tenderness and joint damage progression was stronger in the 18-20 joints scored in the hands than in the 12 joints scored in the feet *(table*

TABLE 1 GEE results (OR (95% CI)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no, with swelling ever (model 1), tenderness ever (model 2), or both (model 3) as determinants.

	Model 1			Model 2			Model 3		
	Erosion progression	JSN progression	SHS progression	Erosion progression	JSN progression	SHS progression	Erosion progression	JSN progression	SHS progression
Swollen, ever	2.2* (1.6 – 3.2)	2.4* (1.7 – 3.3)	2.1* (1.6 – 2.7)	-	-	-	1.6* (1.2 – 2.2)	1.9* (1.4 – 2.6)	1.6* (1.2 – 2.0)
Tender, ever	-	-	-	2.7* (1.8 – 3.9)	2.4* (1.6 – 3.5)	2.4* (1.8 – 3.2)	2.0* (1.4 – 2.9)	1.7* (1.2 – 2.4)	1.9* (1.4 – 2.5)
Total SHS baseline	1.02 (0.99 – 1.04)	1.02* (1.00 – 1.04)	1.02* (1.01 – 1.04)	1.02 (0.99 – 1.04)	1.02* (1.00 – 1.04)	1.02* (1.01 – 1.04)	1.02 (0.99 – 1.04)	1.02* (1.00 – 1.04)	1.02* (1.01 – 1.02)
Erosions baseline in individual joint	3.5* (1.9 – 6.3)	-	-	3.2* (1.8 – 5.7)	-	-	3.3* (1.9 – 6.0)	-	-
JSN baseline in individual joint	-	2.7* (1.8 – 4.2)	-	-	2.8* (1.8 – 4.3)	-	-	2.7* (1.7 – 4.2)	-
SHS baseline in individual joint	-	-	2.9* (2.0 – 4.1)	-	-	2.8* (2.0 – 4.0)	-	-	2.8* (2.0 – 4.0)
Age, years	0.98* (0.96 – 0.99)	0.98* (0.97 – 0.99)	0.98* (0.97 – 0.99)	0.98* (0.96 – 0.99)	0.98* (0.96 – 0.99)	0.98* (0.97 – 0.99)	0.98* (0.96 – 0.99)	0.98* (0.96 – 0.99)	0.98* (0.96 – 0.99)
Female gender	0.74 (0.42 – 1.31)	0.99 (0.50 – 1.63)	0.78 (0.48 – 1.28)	0.74 (0.42 – 1.29)	0.89 (0.49 – 1.61)	0.78 (0.48 – 1.27)	0.73 (0.41 – 1.27)	0.89 (0.49 – 1.62)	0.77 (0.48 – 1.25)
Body mass index, kg/m2	0.96 (0.90 – 1.03)	0.99 (0.92 – 1.06)	0.99 (0.94 – 1.05)	0.96 (0.90 – 1.02)	0.98 (0.91 – 1.05)	0.99 (0.93 – 1.04)	0.96 (0.90 – 1.02)	0.98 (0.92 – 1.06)	0.99 (0.94 – 1.05)
ESR, mm/hour	1.01* (1.00 – 1.02)	1.02 (1.01 – 1.03)	1.01* (1.01 – 1.02)	1.01* (1.01 – 1.02)	1.02* (1.01 – 1.03)	1.01* (1.01 – 1.02)	1.01* (1.00 – 1.02)	1.02* (1.01 – 1.03)	1.01* (1.01 – 1.02)
RF+ and CCP+	6.0* (2.8 – 12.6)	6.2* (3.1 – 12.4)	6.6* (3.6 – 11.8)	5.7* (2.7 – 12.0)	5.6* (2.7 – 11.4)	5.7* (3.1 – 10.4)	5.9* (2.8 – 12.3)	5.9* (2.9 – 12.0)	6.1* (3.4 – 11.0)
RF+ or CCP+	5.1* (2.1 – 12.5)	3.1* (1.2 – 8.2)	5.2* (2.6 – 10.4)	4.9* (2.0 – 11.7)	2.9* (1.1 – 7.7)	4.6* (2.3 – 9.2)	5.2* (2.2 – 12.6)	3.0* (1.1 – 8.0)	5.0* (2.5 – 9.9)
RF- and CCP-	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Sequential monotherapy	4.5* (2.3 – 8.7)	3.4* (1.9 – 6.3)	3.6* (2.1 – 6.2)	4.1* (2.1 – 8.0)	3.1* (1.7 – 5.6)	3.2* (1.9 – 5.5)	4.4* (2.3 – 8.6)	3.3* (1.8 – 6.1)	3.5* (2.1 – 5.9)
Step up combination therapy	3.4* (1.8 – 6.5)	3.1* (1.6 – 6.3)	3.6* (2.2 – 6.2)	3.2* (1.6 – 6.2)	2.9* (1.5 – 5.9)	3.4* (2.0 – 5.7)	3.3* (1.7 – 6.3)	3.0* (1.5 – 6.1)	3.5* (2.1 – 5.9)
Initial combination with prednisone	0.91 (0.40 – 2.1)	2.2* (1.1 – 4.6)	1.5 (0.84 – 2.7)	0.79 (0.34 – 1.8)	2.0 (0.99 – 4.0)	1.3 (0.72 – 2.3)	0.86 (0.37 – 1.9)	2.2* (1.1 – 4.4)	1.4 (0.79 – 2.5)
Initial combination with infliximab	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

*p<0.05; CCP, cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; GEE, generalised estimating equations; JSN, joint space narrowing; RF, rheumatoid factor; SHS, Sharp-van der Heijde score

2), with the strongest association between swelling and erosion progression . In the feet, swelling and tenderness were not independently associated with the outcome erosion progression, although swelling was still independently associated with JSN progression and SHS progression.

In the hands and feet combined, a 'dose-response' was observed (*table 3*), indicating that a joint that was swollen or tender twice or more had a higher risk for progression than if it was swollen or tender only once, that is, a more persistent synovitis carried a higher risk for local damage progression.

The development of swelling and tenderness during follow-up despite treatment (even if present during only 1 assessment) was associated with a higher chance for erosion progression, but not for JSN progression, than the presence of swelling and tenderness at the baseline assessment, that is, before treatment (*table 4*).

Table 5 displays the GEE results for the four treatment strategies separately. In patients treated with sequential monotherapy (group 1), step-up combination therapy (group 2) or initial combination with prednisone (group 3), swelling and tenderness were significantly related to the outcomes erosion progression, JSN progression and SHS progres-

TABLE 2 GEE results (OR (95% CI)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no, for hands and feet separately

	Erosion progression	JSN progression	SHS progression
Hands			
Swollen, ever	10.0 (4.0 – 24.7)	2.4 (1.4 – 3.8)	3.5 (2.2 – 5.3)
Tender, ever	2.9 (1.4 – 6.1)	2.1 (1.1 – 4.2)	2.5 (1.5 – 4.1)
Feet			
Swollen, ever	1.4 (0.95 – 2.1)	2.3 (1.4 – 3.7)	1.5 (1.1 – 2.1)
Tender, ever	1.02 (0.7 – 1.6)	0.9 (0.6 – 1.4)	0.99 (0.69 – 1.4)

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and erythrocyte sedimentation rate.
CCP, cyclic citrullinated peptide; GEE, generalised estimating equations; JSN, joint space narrowing; SHS, Sharp-van der Heijde score.

TABLE 3 GEE results (OR (95% CI)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no, showing a dose response for both swelling and tenderness

	Erosion progression	JSN progression	SHS progression
Swollen never	Reference	Reference	Reference
Swollen, 1x	1.4 (1.00 – 2.3)	1.7 (1.2 – 2.4)	1.5 (1.2 – 2.0)
Swollen, ≥2x	3.0 (2.0 – 4.5)	3.2 (2.1 – 4.8)	2.7 (2.0 – 3.7)
Tender never	Reference	Reference	Reference
Tender, 1x	1.6 (1.03 – 2.4)	1.4 (0.94 – 2.1)	1.5 (1.1 – 2.1)
Tender, ≥2x	3.9 (2.6 – 5.9)	3.7 (2.2 – 5.2)	3.3 (2.4 – 4.5)

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and erythrocyte sedimentation rate.
CCP, cyclic citrullinated peptide; GEE, generalised estimating equations; JSN, joint space narrowing; SHS, Sharp-van der Heijde score.

sion, with the exception of swelling versus erosion progression and JSN progression in group 2 and tenderness versus erosion progression in group 3. In patients treated with the initial combination methotrexate and infliximab (group 4) neither swelling nor tenderness were significantly associated with progression of erosions, JSN and SHS in the individual joint, with the exception of tenderness and SHS progression, indicating a disconnect between clinical signs of synovitis and radiological damage progression.

DISCUSSION

We found that clinical signs of synovitis in hands and feet are associated with the development of joint damage progression at the individual joint level. The association is as strong for swelling as for tenderness and similarly strong for the outcomes erosion progression, JSN progression and SHS progression.

We showed a dose-response relationship, indicating that a persistent synovitis, that is, the presence of clinical synovitis during two or more out of five clinical assessments, was associated with a higher risk for progression compared with clinical synovitis at only one assessment. The association is probably even stronger for joints that show signs of inflammation during three to five visits, however, due to a dynamic treatment strategy aiming at low disease activity in the BeSt study, the number of joints with synovitis during more than two visits is limited, and therefore we had insufficient power to assess a stronger dose-response effect. Furthermore, our results suggest that a joint with clinical signs of synovitis despite treatment has a worse prognosis than a joint with clinical synovitis before the start of treatment.

The relationship between clinical signs of synovitis and joint damage progression is stronger in hands than in feet. Although there was a significant association between

TABLE 4 GEE results (OR (95% CI)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no, showing the association between swelling, tenderness and joint damage progression split for baseline and follow-up clinical assessments

	Erosion progression	JSN progression	SHS progression
Swollen never	Reference	Reference	Reference
Only swollen at baseline	1.2 (0.77 – 1.9)	1.6 (1.1 – 2.4)	1.3 (0.98 – 1.8)
Only swollen during follow-up, 1x	2.0 (1.1 – 3.4)	1.5 (0.91 – 2.7)	1.8 (1.2 – 2.8)
Only swollen during follow-up, ≥2x	2.7 (1.5 – 4.6)	2.4 (1.1 – 5.4)	2.0 (1.2 – 3.3)
Swollen at baseline and during follow-up	3.2 (2.1 – 4.9)	3.3 (2.2 – 4.9)	3.0 (2.2 – 4.0)
Tender never	Reference	Reference	Reference
Only tender at baseline	1.2 (0.77 – 2.0)	1.3 (0.83 – 2.1)	1.4 (0.99 – 2.0)
Only tender during follow-up, 1x	2.0 (1.1 – 3.4)	1.4 (0.86 – 2.3)	1.7 (1.1 – 2.5)
Only tender during follow-up, ≥2x	3.8 (2.3 – 6.3)	3.3 (1.9 – 5.7)	3.4 (2.2 – 5.2)
Tender at baseline and during follow-up	3.6 (2.5 – 5.4)	3.2 (2.1 – 4.8)	3.3 (2.4 – 4.5)

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and erythrocyte sedimentation rate.
CCP, cyclic citrullinated peptide; GEE, generalised estimating equations; JSN, joint space narrowing; SHS, Sharp-van der Heijde score.

TABLE 5 GEE results (odds ratios (95% confidence intervals)) for the outcomes erosion progression, joint space narrowing progression and Sharp-van der Heijde progression yes/no in the four treatment strategies

	Erosion progression	JSN progression	SHS progression
Sequential monotherapy			
Swollen, ever	3.0 (1.8 – 4.9)	4.5 (2.5 – 8.0)	2.9 (1.9 – 4.3)
Tender, ever	3.5 (1.9 – 6.7)	2.2 (1.02 – 4.8)	2.5 (1.4 – 4.3)
Step-up combination therapy			
Swollen, ever	1.6 (0.9 – 3.1)	1.7 (0.98 – 3.1)	1.6 (1.0 – 2.5)
Tender, ever	2.7 (1.1 – 6.8)	3.1 (1.5 – 6.5)	2.9 (1.6 – 5.0)
Initial combination with prednisone			
Swollen, ever	3.8 (1.5 – 9.4)	2.9 (1.5 – 5.9)	3.2 (1.7 – 6.3)
Tender, ever	1.8 (0.7 – 4.6)	2.4 (1.2 – 5.1)	2.1 (1.2 – 3.6)
Initial combination with infliximab			
Swollen, ever	0.9 (0.4 – 2.0)	1.2 (0.8 – 2.8)	1.2 (0.7 – 2.1)
Tender, ever	1.4 (0.8 – 2.5)	2.0 (0.8 – 4.9)	2.0 (1.1 – 3.5)

All corrected for: total SHS baseline, erosions at baseline yes/no per joint (for outcome erosion progression), JSN at baseline yes/no per joint (for outcome JSN progression), SHS at baseline yes/no per joint (for outcome SHS progression), age, gender, body mass index, rheumatoid factor (RF)/anti-CCP2 status (double positive, RF-positive or CCP2-positive, double negative), treatment group and erythrocyte sedimentation rate.
CCP, cyclic citrullinated peptide; GEE, generalised estimating equations; JSN, joint space narrowing; SHS, Sharp-van der Heijde score.

joint swelling and JSN progression in the feet, we did not find a statistically significant association between joint swelling or tenderness and erosion progression. This may be due to less accurate joint assessments of the feet, and a fewer number of assessable joints in the feet than in the hands (10 MTPs + 2 IP1s joints vs 18-20 MCPs, PIPs, IP1s joints). To the best of our knowledge, there are no mechanisms proposing that local inflammation affects local joint damage differently in the hands and feet.

The presence of tenderness might be seen as less specific for local inflammatory activity than the presence of swelling.[21] Our analysis showed, however, that joint tenderness contributes independently of swelling to an increased risk for progression in the individual joint. Therefore, to identify joints at risk for damage progression, separate clinical assessments of swelling and tenderness are warranted, as is required when calculating the DAS.

As expected, the association between clinical signs of synovitis and joint damage progression explains only part of the total variability of joint damage progression in patients with RA. The risk for damage progression in an individual joint depends on patient characteristics, local joint circumstances, as well as treatment. Age, the baseline presence of erosions or JSN in the joint, total baseline joint damage, presence of anti-CCP and RF, high ESR, and initial monotherapy were observed to be independent predictors for joint damage progression in the individual joint. In addition, the clinical presence of swelling and tenderness multiplies the absolute risk for progression by its OR.

Previous data suggested a disconnect between inflammation and joint damage in patients treated with TNF blockers at patient level, that is, even when there is little clinical response, treatment with TNF inhibitors can inhibit the progression of joint damage[11,12,14,22]. This dissociation was present at the individual joint level in patients treated with an initial combination of methotrexate and infliximab as well. The exact pathogenic mechanism of the

dissociation between synovitis and joint damage in patients treated with TNF inhibitors is unclear. Altering of the receptor activator for nuclear factor κβ ligand (RANKL)/osteoprotegerin (OPG) ratio by TNF blockade and thereby inhibiting osteoclast activation probably plays a role. [14,23-25] The disconnect again emphasises the important role of TNFα in the development and progression of joint damage.

A limitation of this study might be that there were no ultrasound or MRI data available, which might have given insight in subclinical synovitis. However, the clinical associations we observed are accurate. With ultrasound or MRI a stronger association between synovitis and progression might be observed. Another drawback might be that the percentage of joints with progression was limited, as a result of the effective treatment approach.

In conclusion, swelling and tenderness are independently associated with erosion and JSN progression, but not in patients treated initially with MTX and infliximab combination treatment.

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