A joint evaluation of local and systemic disease activity in treated-to-target rheumatoid arthritis

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Chapter 2

Joint inflammation tends to recur in the same joints during the rheumatoid arthritis disease course

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Abstract

Objectives

We investigated whether local joint swelling recurs in the same joints over time in rheumatoid arthritis (RA) patients who are treated to target.

Methods

Patients with newly diagnosed RA participating in the Behandel-Strategieën, "treatment strategies" (BeSt) study (n=508) were followed for median 10 years while receiving disease activity score (DAS) ≤2.4 steered treatment. Every three months 68 joints were assessed for presence of swelling. We evaluated whether baseline local joint swelling was predictive for swelling in the same joint during follow-up using a multilevel mixed-effects logistic regression model. Different strategies were used to account for missing data. A permutation test was performed to assess if joint swelling was better predicted by baseline swelling of the joint itself than by baseline swelling of randomly selected other joints.

Results

In 46% of the joints that were swollen at baseline, joint swelling later recurred at least once during follow-up. Joint swelling at baseline was statistically significantly associated with swelling in the same joint during follow-up (OR 2.37, 95% CI 2.30 to 2.43, $p<0.001$), and also specifically with recurrent swelling in the same joint (OR 1.73, 95% CI 1.37 to 1.59, $p<0.001$). Local joint swelling was better predicted by baseline swelling of that particular joint than by baseline swelling of other joints ($p<0.001$).

Conclusion

Joint swelling tends to recur locally in the joints swollen at RA onset. This suggests that local factors influence the manifestation of joint inflammation over time.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is primarily characterized by pain, swelling and functional limitations of synovial joints. In addition to systemic inflammatory processes, several local factors have been assumed to play a role in joint inflammation. Location-specific differentiation of fibroblasts, difference in vascularisation and innervation and local differences in exposure to mechanical stress between different types of joints are thought to make individual joints more susceptible for inflammation in RA.[1] For example, different synovial fibroblast phenotypes have been found in the small hand joints compared to other joints of patients with RA.[2] It has also been hypothesized that autoreactive B cells migrate to joints and initiate arthritis locally.[3] Results of in vitro experiments suggest that B cells can survive for months in the synovial compartment and might contribute to joint inflammation becoming chronic.[4]

Insight in joint involvement patterns might provide important clues about local underlying mechanisms of the development of inflammation in RA over time. Therefore, our aim is to investigate whether in RA, despite systemic treatment aimed at suppression of overall disease activity, joint inflammation is more likely to recur in the same joints.

Methods

Patients

This study is a subanalysis of data from the BeSt study. The BeSt study is a multicentre randomized treat-to-target trial, starting in 2000 with a follow-up period of 10 years, in 508 patients with newly diagnosed active RA. All patients fulfilled the American College of Rheumatology 1987 RA criteria[5] and had a symptom duration ≤2 years. Patients were randomized into four different treatment strategies (1. sequential monotherapy, 2. step-up combination therapy starting with methotrexate, 3. initial combination therapy with methotrexate, sulfasalazine and prednisone or 4. initial combination therapy with methotrexate and infliximab). Treatment adjustments were based on three-monthly study visits with a treatment target of disease activity score (DAS) ≤2.4. Details of the BeSt study have been described previously.[6, 7]

Joint assessment

At each study visit 66/68 joint counts were performed, with additional evaluation of the metatarsal joints, totalling 68 individual joints assessed for swelling. For the current analysis we only used swollen joint assessments as representation of joint inflammation. Joints were assessed by trained nurses who were blinded for treatment.

A joint swelling episode was defined as a period of one or multiple subsequent study visits at which a joint was persistently swollen. A joint swelling episode starts with swelling present at baseline, or joint swelling following a study visit without swelling in that joint. Missing assessments were regarded as absence of joint swelling. Joint swelling was considered recurrent if, after local absence of swelling, a second (or third, etc.) joint swelling episode occurred in the same joint. Persistent joint swelling was defined as local joint swelling at two or more consecutive study visits, either from baseline or from a later timepoint. For the statistical analyses baseline joint swelling was used as a reference point for assessment of joint swelling during follow-up.

Statistical analyses

Baseline characteristics were described for all study participants and baseline joint swelling was described at joint level. To study the association between local joint swelling at baseline and later swelling of the same joint we used a multilevel mixed-effects logistic regression model. The model was adjusted for joint location and for time point (study visit) during follow-up, with joints clustered within patients to take into account a possible correlation between multiple joints of the same patient.

A permutation test[8] was performed for this model to evaluate whether joint swelling during follow-up was specifically predicted by baseline swelling of that particular joint, rather than by baseline swelling in other joints as a representation of general disease activity. Within patient and visit strata, 1000 random permutations were performed, that is, the model was repeated 1000 times with random shuffling between joints of joint swelling scores. In this analysis a p-value <0.05 indicates that joint swelling is better predicted by baseline swelling of that specific joint than by baseline swelling of randomly selected other joints. A 95% confidence interval (CI) for the p-value is provided to address the uncertainty of this estimated p-value since only a selection (that is, 1000 permutations) of all possible permutations is tested.[9]

To investigate whether treatment affected the association between baseline and later joint swelling, the analysis was subsequently stratified for treatment arm.

In a separate model we added an interaction term between each joint and its baseline swelling status to determine whether an observed association between baseline swelling and later local swelling was similar for all individual joints. Metacarpophalangeal (MCP)-2 (right side) was chosen as the reference joint, since it was the joint that was most often affected in the study population.

Since joint swelling during follow-up can either be recurrent (the joint was not swollen at the visit prior to the visit of interest, that is, the start of a new episode) or persistent (the joint was swollen at the visit prior to the visit of interest, that is, continuous swelling within an episode), we subsequently stratified the analysis for recurrent and persistent swelling to assess whether baseline joint swelling was also predictive for recurrent swelling specifically.

The association between baseline joint swelling and the number of joint swelling episodes during follow-up was evaluated using a multilevel Poisson regression model. The model was adjusted for joint location and follow-up duration, with joints clustered within patients to take into account a possible correlation between multiple joints of the same patient. For this model another permutation test with 1000 permutations within patient strata was performed, to assess whether the number of joint swelling episodes was predicted by baseline swelling of that particular joint specifically.

In addition, we assessed the effect of the duration of baseline swelling on swelling during follow-up. For this we used a multilevel mixed-effects logistic regression model as described before, with the number of subsequent visits at which the joint was swollen from baseline as a predictor.

A sensitivity analysis was done for the 25% joints that were most often scored as swollen (MCP joints 1-3, proximal interphalangeal (PIP) joints 2 and 3, the wrists and metatarsophalangeal (MTP) joints 2-4), to rule out a strong contribution of joints that were rarely inflamed to the total observed effect. To assess whether an association between baseline joint swelling and joint swelling during follow-up was more likely to be a result of previous swelling in the same joint rather than a higher susceptibility of joint swelling in general, we performed a permutation test on this model (with only the most susceptible joints included) as well.

Another sensitivity analysis was performed excluding early dropouts (no information available on individual joints after the first 2 years of the BeSt study), since dropout might have been related to the number of times the patients experienced inflammation in the same joints.

All models were repeated to account for missing data in two ways. First, all missing joint evaluations until end of follow-up were regarded as not swollen. Second, last observation was carried forward for one missing time point if the joint evaluation (swelling yes/no) at the time point before a missing evaluation was the same as at a subsequent time point after the missing evaluation.

All analyses were performed in Stata SE16 (StataCorp).

Results

The 508 patients had a median (IQR) follow-up duration of 40 (24-40) study visits, that is, 10 (6-10) years. At baseline, the mean (SD) age was 54 (14) years, median (IQR) symptom duration was 23 (14-53) weeks. Mean DAS (SD) was 4.42 (0.86) and the mean (SD) number of swollen joints was 16 (8) joints.

At baseline, 8,137/34,423 (24%) assessed joints were scored as swollen. Joint swelling was subsequently persistent in 30% of the joints that were swollen at baseline with a median (IQR) duration of 1 (1-2) visit (± 3 months after baseline). In addition, in 46% of the joints that were swollen at baseline, local swelling recurred at least once during follow-up (table 1; figure 1).
The mixed model analysis showed that baseline swelling was predictive for

Table 1. Joint swelling at baseline versus joint swelling during follow-up (persistent joint swelling from baseline disregarded) in all joints assessed at baseline

	Joints with no joint swelling at baseline (n = 26,286)	**Joints with joint swelling at baseline (n = 8,137)**
No joint swelling during follow-up	21,189 (81%)	4,420 (54%)
Joint swelling during follow-up (at least once)	5,097 (19%)	3,717 (46%)

swelling during follow-up with an odds ratio (OR) of 2.37 (95% CI 2.30 to 2.43, p<0.001) for swelling during follow-up if the joint was swollen at baseline. These results were comparable between the treatment arms (OR 2.13, 2.56, 2.25 and 2.52 for treatment arm 1-4 respectively).

The statistically significant result of the permutation test (p<0.001, 95% CI 0 to 0.004) indicated that joint swelling is better predicted by baseline swelling of that same joint than by baseline swelling of randomly selected other joints. The association between baseline joint swelling and joint swelling during

follow-up was variable between joints (ORs and p-values for the interaction terms varied, relative to MCP-2 right, online supplemental table 1). The association between baseline and later joint swelling was not affected by whether a joint was weight bearing (as a proxy for mechanical stress) or by symptom duration at baseline (online supplemental table 1).

Baseline joint swelling was not only predictive for joint swelling during follow-up in general, but also for recurrent joint swelling in particular, as was shown by the stratified analysis for recurrent and persistent joint swelling (OR in joints that were swollen at the previous visit: 1.52, 95% CI 1.42 to 1.61, p<0.001, OR in joints that were not swollen at the previous visit (recurrent swelling): 1.73, 95% CI 1.67 to 1.80, p<0.001). Moreover, the number of joint swelling episodes was predicted by the presence of baseline joint swelling in that joint (Incidence Rate Ratio 1.48, 95% CI 1.37 to 1.59, p<0.001). A permutation test showed that the number of swelling episodes in a joint was better predicted by baseline swelling status of that same joint than by baseline swelling status of randomly selected other joints (p<0.001, 95% CI 0 to 0.004).

Not only presence of baseline joint swelling, but also the duration of baseline joint swelling was statistically significantly associated with joint swelling during follow-up (OR 1.20 per 3 months, 95% CI 1.19 to 1.21, p<0.001).

A sensitivity analysis of only the most affected joints (MCP joints 1-3, PIP joints 2-3, the wrists and MTP joints 2-4) showed a similar association between baseline and later joint swelling as in the complete analysis (OR 2.11, 95% CI 2.03 to 2.19, p<0.001). The permutation test showed that also in the most susceptible joints, joint swelling was best predicted by baseline swelling of that particular joint, as opposed to baseline swelling of other joints.

The association was also similar in a sensitivity analysis in which early dropouts were excluded (OR 2.32, 95% CI 2.26 to 2.39, p<0.001). For the other models, these sensitivity analyses showed comparable results too (online supplemental table 2).

Within the available follow-up period for all patients 18% (209,247/1,137,508) of the data points was missing. When accounted for missing data, using the two different methods described before, all models showed similar results (online supplemental table 2).

Joint	Percentage of patients in whom the joint was swollen at baseline	Percentage of patients in whom the joint was recurrently swollen after baseline swelling
Jaw right	2%	0%
Jaw left	1%	14%
Sternoclavicular right	11%	41%
Sternoclavicular left	6%	13%
Acromioclavicular right	5%	8%
Acromioclavicular left	4%	14%
Shoulder right	12%	25%
Shoulder left	11%	14%
Elbow right	19%	41%
Elbow left	19%	48%
Wrist right	61%	60%
Wrist left	60%	61%
MCP 1 right	46%	53%
MCP 1 left	46%	52%
MCP 2 right	64%	63%
MCP 2 left	54%	57%
MCP 3 right	45%	56%
MCP 3 left	43%	44%
MCP 4 right	20%	25%
MCP 4 left	19%	15%
MCP 5 right	29%	34%
MCP 5 left	22%	20%
IP right	33%	35%
IP left	30%	33%
PIP 2 right	63%	53%
PIP 2 left	55%	50%
PIP 3 right	67%	56%
PIP 3 left	57%	50%
PIP 4 right	33%	39%
PIP 4 left	30%	32%
PIP 5 right	33%	32%
PIP 5 left	29%	33%
DIP 2 right	10%	15%
DIP 2 left	11%	13%

Joint	Percentage of patients in whom the joint was swollen at baseline	Percentage of patients in whom the joint was recurrently swollen after baseline swelling
DIP 3 right	9%	11%
DIP 3 left	10%	20%
DIP 4 right	4%	11%
DIP 4 left	4%	10%
DIP 5 right	5%	9%
DIP 5 left	4%	5%
Knee right	35%	58%
Knee left	27%	49%
Ankle right	32%	50%
Ankle left	31%	46%
Subtalar right	23%	39%
Subtalar left	23%	41%
Midtarsal right	7%	16%
Midtarsal left	8%	13%
MTP 1 right	21%	32%
MTP 1 left	21%	29%
MTP 2 right	42%	59%
MTP 2 left	40%	58%
MTP 3 right	45%	62%
MTP 3 left	46%	60%
MTP 4 right	32%	55%
MTP 4 left	34%	53%
MTP 5 right	12%	27%
MTP 5 left	14%	40%
Feet IP right	3%	13%
Feet IP left	5%	4%
Feet IP 2 right	2%	0%
Feet IP 2 left	4%	6%
Feet IP 3 right	2%	0%
Feet IP 3 left	2%	10%
Feet IP 4 right	2%	22%
Feet IP 4 left	2%	0%
Feet IP 5 right	1%	0%
Feet IP 5 left	1%	0%

Figure 1. Joint swelling at baseline and local recurrence of swelling following baseline joint swelling, for each assessed joint

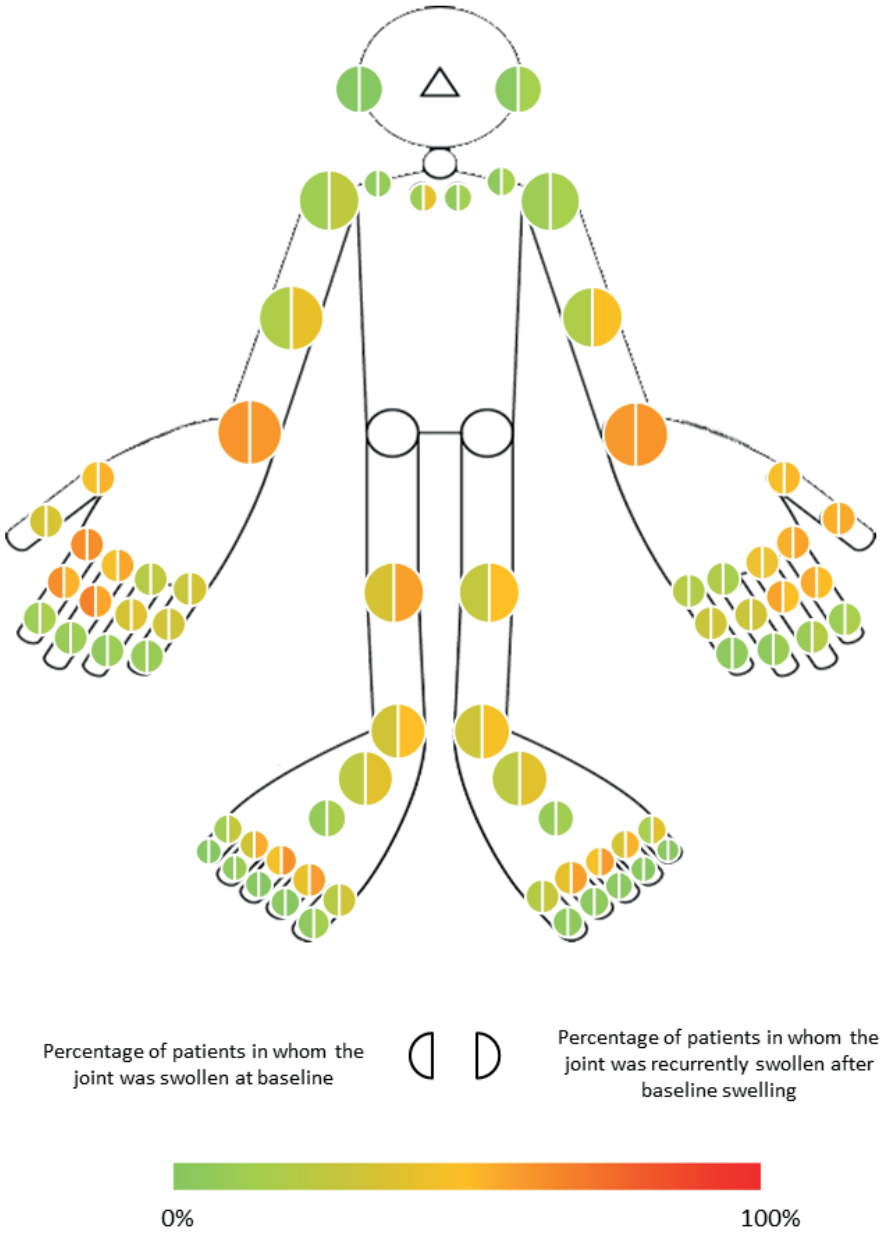

Figure 1. *Continued*

Discussion

In this sub analysis of the BeSt study we evaluated if joint inflammation tends to recur locally in the same joints over time. Joint swelling was assessed in 508 patients with newly diagnosed active RA who were treated to target (DAS ≤2.4) during up till 10 years. We observed that local joint swelling during the follow-up period recurred at least once in 46% of the joints that were swollen at baseline. We found that baseline local joint swelling was predictive for both the occurrence of swelling in that same joint during follow-up and the number of recurrent swelling episodes in that joint. This effect was stronger for joints with a longer duration of swelling. Moreover, the association between baseline and later local joint swelling was stronger within the same joint than between different joints. This joint-specific association may suggest that apart from systemic effects of systemic inflammatory processes in RA, local conditions in individual joints affect the course of inflammation in these joints.

To our knowledge, this is the first study in which location-specific recurrence of joint involvement in RA was investigated. Previous studies have compared patterns of joint involvement in an RA study population at several time points, but no intra-individual comparisons were made.[10, 11]

We also found that the strength of the association between baseline joint swelling and joint swelling during follow-up was different for individual joints. This difference is probably related to variable susceptibility for swelling between joints. Therefore, we performed a sensitivity analysis in the 25% joints that were most often scored as swollen. In these joints too we observed an association between baseline swelling and later swelling in the same joint. This finding supports the idea that local factors, rather than systemic inflammation only, play a role in joint swelling.

The major strength of our study is that joint assessment was performed systematically over a long time period of 10 years. All 68 joints were assessed for swelling every three months in a large patient cohort (508 patients). Joint assessment was done according to the EULAR handbook by professionals who were trained and retrained by the same rheumatologist, and most assessors followed up the same patients for many years. This allowed us to do a longitudinal analysis within an extensive and reliable data set. Because of the treat-to-target design of the BeSt study we were able to investigate recurrence of joint swelling in patients who are intensively treated. Furthermore, the various sensitivity analyses and permutation tests substantiate the robustness of the obtained results.

Nevertheless, there are also some limitations to our study. As swelling of joints is more strongly associated with inflammation than tenderness, for our analysis we only considered scores for joint swelling.[12, 13] However, inflammation may have been present in tender joints that were not swollen.[12, 13] Thus inflammation may have been persistent where we have called swelling 'recurrent'. Joint swelling assessments were also not always available. During the 10 years follow-up of the BeSt study, patients missed study visits and we found that 18% of the data for our analyses was missing. It is possible that both loss to follow-up and missing joint assessments within the follow-up time are non-random. Nevertheless, different methods of dealing with missing data yielded comparable results. Both conservative analyses in which a joint was regarded as not swollen if the joint swelling status was missing and analyses in which presence or absence of swelling was assumed based on the previous and following study visit showed similar outcomes as the analyses based on complete data. We did not have information on joint swelling between two consecutive study visits and assumed that the swelling status of a joint did not change in between two consecutive study visits. Although this assumption might not always be true, the time between two study visits was relatively short (3 months) and it is probably as unlikely that joints were swollen in between two visits in which no swelling was observed as it is that joints are not swollen in between two visits when swelling was observed. In addition, since radiographic data was not available for each joint included in the analysis, we cannot exclude that some local joint swelling was due to local joint damage caused by either RA or other diseases such as osteoarthritis. However, this misclassification would probably lead to joints consistently being assessed as swollen at every study visit, which would not affect the analyses of recurrent swelling. Another limitation of this study is that, since we chose to analyse only baseline swelling as a predictor for later swelling, we were not able to show an association between swelling after baseline and later swelling.

Local recurrence of joint swelling might be a result of inflammatory tissue priming as described in rodent models, in which it was shown that synovial fibroblasts of joints that were previously exposed to inflammatory triggers were sensitized, leading to a higher susceptibility to inflammation of the joint tissue.[14] More research is needed to uncover the underlying local mechanisms of recurrence of joint swelling.

The finding that joint swelling tends to recur in the same joints might support more intensive local monitoring, including imaging techniques if joints appear clinically no longer swollen. Subclinical inflammation has been found to be associated with radiographic progression.[15] Moreover, it

has been shown that, despite treatment to target, the risk of radiographic joint damage progression is higher in joints with previous clinical signs of synovitis.[16, 17] Therefore, local treatment, combined with systemic treatment, may be necessary to avoid local damage progression. However, in previous studies the effects of intra-articular corticosteroids on radiographic damage remain uncertain, although they can provide short- and sometimes long-term reduction of signs and symptoms of local arthritis.[18-20] The recurrence of signs and symptoms after injections may indicate that more effective local therapies need to be investigated or developed. So far, previously investigated local therapies, potentially with the exception of surgical synovectomy for refractory symptoms, did not show convenient results.[21-26]

To conclude, this is to our knowledge the first study to investigate joint-specific recurrence of swelling in RA. We found that, even in patients who are intensively treated, joint swelling tends to recur in the same joints, suggesting that local factors play a role in the occurrence of clinical joint inflammation during the disease course. More research is needed to investigate the consequences of recurrence of joint swelling, and potentially find the mechanisms behind it. This might lead to advances in personalized monitoring and treatment of RA patients.

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