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Treatment with TNF-α inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis

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SUMMARY

Objectives: To investigate the association between systemic and local inflammation and incident and progressive radiographic secondary osteoarthritis (OA) in interphalangeal joints (IPJs) over 3 years in rheumatoid arthritis (RA) patients and the effect of tumor necrosis factor alpha (TNF-α) inhibitor infliximab on secondary OA in IPJs.

Methods: In the present observational longitudinal study baseline and 3-year hand X-rays of 416 recent-onset RA patients were scored for osteophytes and erosions in IPJs, blinded for time, using Osteoarthritis Research Society International atlas and Sharp-van der Heijde score. The associations between inflammatory factors and incident and progressive secondary OA in distal IPJs (DIPJs) and proximal IPJs (PIPJs) and the effect of infliximab compared to disease-modifying anti-rheumatic drug treatment on secondary OA were analyzed by multivariable regression and generalised estimating equations analyses.

Results: Sixty-seven percent of the patients were female with, at baseline, a mean age of 54 years and OA present in DIPJs and PIPJs in 37% and 13%. Three years later, new secondary OA in DIPJs and PIPJs was seen in 11% and 10%, and progressive secondary OA in 36% and 35%. High erythrocyte sedimentation rate over 3 years and progressive erosive damage were risk factors for incident secondary OA in DIPJs, but not in PIPJs. At joint level, progression of erosions was associated with both incident and progressive secondary OA, only in DIPJs. Infliximab treatment was associated with lower incident secondary OA in PIPJs [relative risk 0.5 (95% confidence interval 0.2, 1.0)], independent of decrease in inflammation.

Conclusion: Incident and progressive secondary OA in DIPJs over 3 years was associated with high inflammatory activity in RA. Infliximab treatment reduced incident secondary OA in PIPJs independent of decrease in inflammation, suggesting that anti-TNF-α therapy might be effective against secondary hand OA *via* other pathways than suppression of inflammation. Further studies in populations of primary hand OA are necessary to determine the role of anti-TNF-α in treatment of primary hand OA.

Osteoarthritis (OA) is a heterogenous group of conditions with alterations in articular cartilage, bone and synovium[1]. A frequently involved site is the hand where it leads to considerable loss in function and quality of life[2]. At present, drug therapies used in OA are limited to symptomatic treatment.

The pathogenesis of OA is incompletely understood, but thought to be multifactorial involving degenerative, biomechanical, metabolic, hormonal and genetic factors[3]. Increasing evidence supports the involvement of low-grade systemic and local inflammation in the pathogenesis of OA. A two- to threefold increase in high sensitive C-reactive protein levels is seen in OA patients[4–7]. High resolution magnetic resonance imaging demonstrated subchondral bone edema, synovial enhancement and bone erosions in interphalangeal joints (IPJs) in the majority of OA patients[8,9]. Pro-inflammatory cytokines are found in increased levels in synovial fluid of OA joints[10–12], and heritable differences in cytokine

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production are associated with the development and progression of OA[13,14]. Hence, inhibitors of cytokines might be considered as potential candidates for disease-modifying therapy in OA[15–17].

One of the pro-inflammatory cytokines involved in OA is tumor necrosis factor alpha (TNF-α): increased TNF-α production and increased p55 TNF-α receptor expression on chondrocytes imply the intervention of TNF-α on joint destruction in OA[18–23]. It is shown that TNF-α inhibitors are able to suppress nitric oxide production in human cartilage[24]. Two pilot studies using anti-TNF-α therapy in erosive hand OA reported some improvement in clinical efficacy measures, however the studies were small and therefore inconclusive[25,26].

In the present study we took advantage of the fact that in patients with rheumatoid arthritis (RA) simultaneous development and progression of secondary hand OA exists. In a trial in recent-onset active RA patients who were treated with TNF-α inhibitors and conventional disease-modifying anti-rheumatic drugs (DMARDs) we investigated the associations between systemic and local inflammatory factors and incident and progressive radiographic secondary OA in IPJs over 3 years and the effect of treatment with TNF-α inhibitor infliximab on incident and progression of secondary OA in IPJs in RA patients.

Patients and methods

Patients

The present study is an exploratory observational longitudinal study analyzing data from the BeSt study, an ongoing multicenter, randomized clinical trial designed to compare the efficacy of four treatment strategies in recent-onset active RA patients, independent of the confirmatory strategy for any of the trial's endpoints[27]. In short, between April 2000 and August 2002, 508 RA patients (American College of Rheumatology [ACR] 1987 revised criteria) with symptom duration less than 2 years and active disease were included. Inclusion and exclusion criteria were reported previously in detail[27]. Rheumatologists participating in the Foundation for Applied Rheumatology Research in 18 peripheral and two university hospitals in the western part of the Netherlands designed and conducted the BeSt study. The medical ethics committee at each participating center approved the study protocol and all patients gave written informed consent prior to participation in the study.

Study design

According to the pharmacoprotocol of each treatment arm, patients could be treated with the TNF-α inhibitor infliximab in combination with methotrexate 25 mg/week, either as initial treatment or as delayed treatment after failing on at least three previous DMARDs ('infliximab group'). Patients started with infliximab 3 mg/kg/8 weeks and in case of insufficient response, a disease activity score (DAS) in 44 joints >2.4, the dose was increased step by step to 6, 7.5, and 10 mg/kg. If the DAS was ≤2.4 for at least six consecutive months, the dose of infliximab was reduced in reverse order to 3 mg/kg and stopped. Patients who did not receive infliximab during the study period ('no infliximab group') were treated with DMARDs (methotrexate, sulphasalazine, leflunomide, hydrochloroquine) and prednisone, either as monotherapy or combination therapy. DAS, including the Ritchie articular index, the 44 swollen joint counts, the erythrocyte sedimentation rate (ESR) and a general health assessment on a visual analogue score, was measured three-monthly during the follow-up period. In all patients, treatment adjustments, previously described in detail, were based on aiming at DAS ≤2.4[27]. Concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDS) and anti-resorptives was permitted.

Radiographic assessment of secondary OA in IPJs

Radiographs of both hands were obtained at baseline and after 3 years. Osteophytes were scored in eight distal IPJs (DIPJs), eight proximal IPJs (PIPJs) and two first IPJs by one reader, blinded for patient characteristics, treatment and chronological order, using the Osteoarthritis Research Society International (OARSI) atlas (scale 0–3 per joint)[28]. The scores of first IPJs were merged with the scores of PIPJs. Intra-reader variability for assessment of osteophytes in DIPJs and PIPJs, depicted by the intra-class correlation coefficient (ICC) based on an at random selection of 30 pairs of hand radiographs, was 0.91 and 0.90 with a smallest detectable change (SDC) of 0.9 units for both joint groups.

OA in IPJs, DIPJs and PIPJs, at baseline was defined as an osteophyte score of at least 1 unit in IPJs, DIPJs and PIPJs, respectively. At patient level, incident and progressive secondary OA in DIPJs and PIPJs was defined as an increase in total osteophyte score ≥SDC (=0.9 units for DIPJs and PIPJs) over 3 years in absence and presence, respectively, of OA at baseline in DIPJs and PIPJs. At joint level, incident and progressive secondary OA was defined as an increase in osteophyte score ≥1 unit in one joint over 3 years in absence and presence of OA in that joint at baseline.

Radiographic assessment of erosions in IPJs

Erosions were scored in 18 IPJs at baseline and after 3 years using the Sharp-van der Heijde score (SHS) method (scale 0–5 per joint) by the same reader in a second session, blinded for all data[29]. According to the SHS method all erosions, whether typical of RA or OA, are scored. The ICC for assessment of erosions in DIPJs and PIPJs was 0.94 and 0.97 with SDCs of 1.3 and 1.1 units.

Erosive disease in DIPJs and PIPJs at baseline was defined as an erosion score ≥1 unit in DIPJs and PIPJs, respectively. At patient level, progressive erosive damage in DIPJs and PIPJs was defined as an increase in erosion score ≥SDC (1.3 units for DIPJs and 1.1 units for PIPJs) over 3 years in DIPJs and PIPJs. At joint level, progressive erosive damage was defined as an increase in erosion score ≥1 unit over 3 years.

Statistical analysis

Analyses were performed using SPSS, version 17 (SPSS, Chicago, IL, USA).

To determine the independent demographic [input: age, gender and body mass index (BMI)] and inflammation-related [input: rheumatoid factor (RF), baseline ESR, area under the curve (AUC) of ESR over 3 years, baseline erosion score and progressive erosion score over 3 years ≥2 units] of incident and progressive secondary OA in DIPJs and PIPJs, multivariable logistic regression analyses were performed in which all variables were entered and adjusted for anti-resorptive treatment [bisphosphonates, calcium and vitamin D supplements and hormone replacement therapy (HRT)].

The association between osteophytes and erosions was further explored at joint level by generalised estimating equations (GEE). GEE is a regression technique that allows analyzing longitudinal or clustered data while adjusting for within-patient correlation. GEE requires an *a priori* working correlation structure in order to adjust for the within-patient correlation. Based on the data an exchangeable correlation structure was chosen here. Increase in osteophyte score of ≥1 unit after 3 years was entered as dichotomous dependent variable. Increase in erosion score of ≥1 unit after 3 years, presence of OA at baseline and joint group (categorised in DIP and

Table I
Baseline demographic and disease related characteristics of the total study population and infliximab and no infliximab group

	Total group $n = 416$	Infliximab group $n = 178$	No infliximab group $n = 238$	*P*-value
Demographic variables				
Age, years, mean (SD)	54 (14)	52 (14)	56 (13)	0.001
Women, %	67	70	65	0.280
Postmenopausal, % ($n = 279$)	67	63	71	0.225
BMI, kg/m^2, mean (SD) ($n = 398$)	26 (4)	26 (4)	26 (3)	0.720
Disease related variables				
Inflammatory symptom duration, weeks, median (IQR)	23 (14–53)	27 (15–56)	22 (13–42)	0.040
Positive IgM RF, %	65	68	63	0.345
HAQ score, 0–3, mean (SD)	1.4 (0.7)	1.4 (0.6)	1.3 (0.7)	0.469
ESR, mm/h, median (IQR)	37 (20–56)	34 (18–58)	37 (22–51)	0.987
Erosion score, mean (SD)				
IPJs, 0–90	0.4 (1.9)	0.5 (2.4)	0.3 (1.3)	0.536*
DIPJs, 0–40	0.1 (0.9)	0.1 (0.7)	0.1 (1.0)	0.246*
PIPJs, 0–50	0.3 (1.4)	0.4 (2.0)	0.2 (0.8)	0.842*
≥1 erosion, %				
IPJs	21	18	23	0.317
DIPJs	10	12	9	0.413
PIPJs	16	13	19	0.184
Osteophyte score, mean (SD)				
IPJs, 0–54	1.7 (3.8)	1.2 (3.0)	2.0 (4.3)	0.006*
DIPJs, 0–24	1.3 (2.7)	0.9 (2.2)	1.6 (3.0)	0.009*
PIPJs, 0–30	0.4 (1.5)	0.3 (1.3)	0.5 (1.7)	0.533*
≥1 osteophyte, %				
IPJs	38	30	44	0.004
DIPJs	37	29	42	0.010
PIPJs	13	12	14	0.535

HAQ: health assessment questionnaire.
* *P*-values derived by non-parametric tests.

PIP joint groups) were entered into the model, adjusted for age, gender, BMI and anti-resorptive treatment and additionally for erosion scores at baseline.

The effect of infliximab treatment vs no infliximab, thus DMARD, treatment on incident and progressive secondary OA in DIPJs and PIPJs were analyzed by multivariable logistic regression analyses, adjusted for age, gender, BMI and anti-resorptive treatment and variables differing between the treatment groups at baseline and during study period. These analyses were repeated while additionally adjustments for systemic and local inflammatory factors to study whether the effect of infliximab on secondary OA could be explained by suppression of inflammation.

The odds ratios (OR) with 95% confidence intervals (95% CI) were transformed to relative risks (RR) and corresponding 95% CI using the approximation formula described by Zhang and Yu as OR for common outcomes in a closed cohort are not good approximations of RR[30].

Results

Patient characteristics

In 416 of the 508 RA patients hand radiographs at baseline and after 3 years were available and these patients were included in the present study. Baseline characteristics of these patients are demonstrated in Table I. The baseline characteristics were not significantly different between the patients in the present study and the total study population (data not shown). 67% were female, of whom 67% were postmenopausal at baseline. The mean age was 54 years and 315 patients were over the age of 45. At baseline, OA was present in IPJs in 39% of women and 36% of men. OA occurred more often in DIPJs (37%) than in PIPJs (13%). Only eight patients (7.9%) below the age of 45 [mean standard deviation (SD) 40 (3.9)] had OA in DIPJs and just one of these patients had also OA in PIPJs. Erosive disease was present in IPJs in 21% of the patients. Although erosions were more often seen in PIPJs (16%), a considerable number of patients had also erosions in DIPJs (10%). The patients who were treated with infliximab were significantly younger, had longer inflammatory symptom duration and less osteophytes in DIPJs at baseline. The finding of less osteophytes in the infliximab group was explained by the lower age (data not shown).

Incident and progressive secondary OA in IPJs

The distribution of changes in osteophyte scores in DIPJs and PIPJs over 3 years is shown in Table II. Incident secondary OA occurred in 31 patients (12%) in all IPJs, in 30 patients (11%) in DIPJs and in 35 patients (10%) in PIPJs. Progressive secondary OA was present in 76 patients (48%) in IPJs, in 55 patients (36%) in DIPJs and in 19 patients (35%) in PIPJs.

Table II
Distribution of changes in osteophyte scores, in units, over 3 years in 416 patients with absence and presence of OA in IPJs, DIPJs and PIPJs at baseline

	≤−3	−2	−1	0	1	2	3	4	5	6	7	≥8
No OA at baseline												
All IPJs	0	0	0	226	13	7	5	0	3	1	1	1
DIPJs	0	0	0	233	14	9	4	2	1	0	0	0
PIPJs	0	0	0	327	20	6	6	2	0	0	0	1
OA at baseline												
IPJs	2	10	19	52	33	19	13	4	1	2	0	4
DIPJs	1	7	16	74	27	17	6	1	0	2	1	1
PIPJs	2	3	9	21	11	6	2	0	0	0	0	0

Table III
Associations between demographic and inflammatory factors and incident and progressive secondary OA in DIPJs and PIPJs over 3 years derived by univariable logistic regression analyses

	DIPJs				PIPJs			
	Incident secondary OA $n=263$		Progressive secondary OA $n=153$		Incident secondary OA $n=362$		Progressive secondary OA $n=54$	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Age <50 year	1		1		1		1	
50–60 year	1.8 (1.1, 2.5)	0.023	1.0 (0.4, 2.0)	0.957	1.6 (0.8, 3.0)	0.162	0.2 (0.01, 2.1)	0.290
≥60 year	3.0 (1.5, 4.5)	0.003	1.1 (0.6, 1.4)	0.771	2.8 (1.8, 3.5)	0.000	1.2 (0.5, 1.5)	0.731
Female gender	1.4 (1.1, 1.5)	0.014	1.1 (0.8, 1.2)	0.573	1.1 (0.9, 1.3)	0.312	1.0 (0.6, 1.2)	0.817
BMI <25 kg/m^2	1		1		1		1	
BMI 25–30 kg/m^2	0.9 (0.5, 1.5)	0.813	1.04 (0.7, 1.4)	0.858	0.7 (0.4, 1.3)	0.295	1.1 (0.4, 2.7)	0.898
BMI ≥30 kg/m^2	1.3 (0.5, 2.9)	0.617	1.3 (0.5, 2.7)	0.619	1.1 (0.7, 1.4)	0.754	2.0 (0.3, 9.2)	0.488
Positive RF	1.1 (0.8, 1.3)	0.541	1.2 (0.9, 2.2)	0.260	0.9 (0.6, 1.1)	0.676	1.0 (0.6, 2.4)	0.983
Baseline ESR ≥30 mm/h	1.4 (1.04, 1.6)	0.031	0.9 (0.6, 1.2)	0.599	1.0 (0.7, 1.3)	0.978	1.4 (0.8, 1.8)	0.165
AUC ESR 0–3 year ≥30 mm/h	2.8 (1.5, 5.0)	0.003	1.4 (0.9, 2.0)	0.090	1.4 (0.8, 2.6)	0.255	1.1 (0.5, 1.9)	0.880
Baseline erosion score ≥1 unit	1.4 (0.4, 4.0)	0.599	1.2 (0.9, 1.9)	0.383	2.3 (0.98, 4.7)	0.059	1.2 (0.4, 3.0)	0.729
Delta erosion score 0–3 year ≥2 units	5.5 (1.3, 18.3)	0.023	1.7 (0.4, 7.2)	0.505	1.1 (0.3, 4.0)	0.923	5.5 (0.6, 22.3)	0.121

RR (95% CI): relative risk (95% CI).

Incident and progressive secondary OA in IPJs and demographic and inflammatory factors

The association between various demographic and inflammation-related factors and incident and progressive secondary OA were analyzed by univariable logistic regression analyses (Table III). To determine the independent risk factors of incident and progressive secondary OA multivariable analyses were performed (Table IV). Higher age was independently associated with incident secondary OA in DIPJs and PIPJs and female gender only with incident secondary OA in DIPJs. High AUC of ESR and progressive erosion score over 3 years were associated with incident secondary OA in DIPJs, however these associations were not statistically significant. Progression of erosions over 3 years was associated with progressive secondary OA in PIPJs but not independently. None of the other demographic and inflammation-related factors were related to progressive secondary OA in DIPJs and PIPJs.

Table V summarizes the results of the GEE analyses. The presence of an osteophyte in an interphalangeal hand joint at baseline increased the chance of having an increase in the osteophyte score in the same joint during the study period with a RR (95% CI) of 1.6 (1.2, 1.9) and increase of osteophyte score was more often seen in DIPJs than in PIPJs with a RR (95% CI) of 1.7 (1.1, 1.5). Progressive erosion score in an interphalangeal hand joint was associated with an increase in the osteophyte score in the same joint with a RR (95% CI) of 2.5 (0.9, 6.4). Interaction and *post hoc* analyses showed that progressive erosive damage in a single joint was significantly associated with both incident and progressive OA only in DIPJs ($P=0.036$ and 0.045, respectively), not in PIPJs.

Effect of infliximab on incident and progressive secondary OA in IPJs

During the study period 178 (43%) patients were treated with infliximab. The median interquartile range (IQR) cumulative infliximab dose was 40 (24–61) mg/kg during a median (IQR) period of 13 (9–21) months. The patients from the 'no infliximab group' were treated with conventional DMARDs: 60% with combination therapy, mostly methotrexate and sulphasalazine with prednisone and/or hydrochloroquine. After 3 years, 58% still received monotherapy (60% methotrexate, 31% sulphasalazine monotherapy, 9% other), and 13% had discontinued all treatment due to clinical remission. Patients in the infliximab group received less bisphosphonates (12% vs 22%, $P=0.013$) due to lower corticosteroid use, but more HRT (21% vs 11%, $P=0.005$) due to more perimenopausal women. There were no significant differences in the use of NSAIDS and specific cyclooxygenase 2 (COX 2) inhibitors between the treatment groups (data not shown). None of these treatments had effect on incident or progressive secondary OA over 3 years (data not shown).

Treatment with infliximab was associated with less incident secondary OA in PIPJs, however not statistically significant [6% vs 13%, $P=0.059$, Table VI, Fig. 1(A)]. Five patients treated with infliximab (24%) had progressive secondary OA in PIPJs vs 14 (42%) of the patients not treated with infliximab [$P=0.163$, Table VI, Fig. 1 (B)]. In multivariable analyses, adjusted for age, gender, menopausal status, BMI, inflammatory symptom duration, OA at baseline and the use of anti-resorptive treatment during the study period, treatment with infliximab showed a trend towards less incident secondary OA in PIPJs with a RR (95% CI) of 0.5 (0.2, 1.1) ($P=0.087$,

Table IV
Independent associations between demographic and inflammatory factors and incident and progressive secondary OA in DIP and PIP joints over 3 years derived by multivariable logistic regression analyses

	DIPJs				PIPJs			
	Incident secondary OA $n=263$		Progressive secondary OA $n=153$		Incident secondary OA $n=362$		Progressive secondary OA $n=54$	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Age <50 year	1				1			
50–60 year	1.7 (0.9, 2.5)	0.073	–	–	1.6 (0.8, 2.4)	0.191	–	–
≥60 year	3.5 (1.8, 5.2)	0.002	–	–	2.9 (1.8, 3.6)	0.001	–	–
Female gender	1.5 (1.2, 1.6)	0.003	–	–	–	–	–	–
AUC ESR 0–3 year ≥30 mm/h	1.6 (0.9, 2.1)	0.081	–	–	–	–	–	–
Delta erosion score 0–3 year ≥2 units	5.1 (0.9, 15.6)	0.068	–	–	–	–	–	–

Following variables were entered in the multivariable analyses: age, gender, BMI, presence of RF, baseline ESR, AUC ESR 0–3 year, baseline erosion score and progressive erosion score 0–3 year, adjusted for anti-resorptive treatment during study period.

Table V
Associations between presence of hand OA at baseline, distribution over the joints (DIPJs and PIPJs) and progressive erosive damage and changes in osteophyte scores over 3 years at joint level in IPJs derived by GEE

Variables	Delta osteophyte score ≥1 unit per joint	
	RR (95% CI)	Overall *P*-value
Presence hand OA at baseline	1.6 (1.2, 1.9)	0.003
DIPJs vs PIPJs	1.7 (1.1, 1.5)	0.006
Delta erosion score ≥1 unit per joint	2.5 (0.9, 6.4)	0.078

All data are adjusted for age, gender, BMI and anti-resorptive treatment and delta erosion score ≥1 unit is additionally adjusted for erosive damage at baseline.

Table VI). Extra adjustments for changes in systemic and local inflammatory factors over 3 years did not change the association between infliximab treatment and incident secondary OA in PIPJs, which suggests that the effect of infliximab on incident secondary OA in PIPJs is independent of suppression of inflammatory activity over 3 years (Table VI). After adjustment for inflammatory activity during 3 years, the effect of infliximab on incident secondary OA in DIPJs was also getting more substantial, but not significant, with a RR (95% CI) of 0.6 (0.2, 1.3) compared to 1.0 (0.5, 1.9) in the unadjusted analysis. Infliximab did not have an effect on progressive secondary OA in DIPJs and PIPJs.

Discussion

The present study showed, by an alternative approach evaluating secondary OA outcome in patients with RA, two important findings: (1) there is a link between inflammation, measured by high ESR and progressive erosive damage over 3 years, and incident and progressive secondary OA in DIPJs but not in PIPJs; and (2) there is a clear trend towards an inhibitory effect of treatment with infliximab on incident secondary OA in PIPJs, not in DIPJs, independent of the effect of infliximab on inflammatory activity during 3 years.

There has been increasing evidence that both low-grade systemic and local inflammation are playing a role in the pathogenesis of primary OA[4–9]. We found that high systemic and local inflammation during 3 years, measured by high AUC of ESR (at patient level) and progressive erosive damage (at joint level), were significantly associated with incident and/or progressive secondary OA in DIPJs in RA patients, suggesting that systemic inflammation might play a role in the development of secondary hand OA. The differences in association between inflammation and the development of secondary OA in DIPJs and PIPJs in RA patients could be due to differences in the level of inflammation at the different joint levels in RA patients and in differences in the role of inflammation with regard to the pathophysiological mechanisms of secondary OA between DIPJs and PIPJs.

Previous studies showed that joint tissues in primary OA are the site of active production of TNF-α enhancing joint destruction[18–23]. Two pilot studies and one case report showed positive results of anti-TNF-α treatment in primary OA patients[25,26,31]. The first pilot study was an open-label study and showed in 12 patients with inflammatory erosive hand OA treated with adalimumab 40 mg/2 weeks for 3 months significant improvement in the number of swollen joints and similar trends in other outcome measures[25]. The second pilot study was a 1-year placebo-controlled double-blind study and showed in 10 female patients with erosive hand OA treated with monthly intra-articular injections of infliximab 0.1 mg/ml or physiological saline for 1 year significant improvement in pain scores and non-significant reduction of radiographic score in IPJs in the infliximab group[26]. However, these studies were small and therefore inconclusive. We found a clear trend towards an inhibitory effect of infliximab on incident secondary OA: infliximab treatment resulted in a twofold decrease in incident secondary OA in PIPJs in RA patients, independent of the effect of infliximab on suppression of inflammation. This suggests that treatment with TNF-α inhibitors might be effective against development of secondary OA, however not by inflammatory pathways, but by other bone linked pathways. This corresponds with the absence of an association between inflammation and secondary OA in PIPJs and the observed increasing trend towards a more protective effect of infliximab against incident secondary OA in DIPJs after adjusted for cumulative systemic and local inflammatory activity during 3 years. Osteophytes are thought to be formed by mesenchymal stem cells present in the periosteum or synovial lining undergoing chondrogenesis, followed by endochondral ossification and deposition of bone[32]. The process is not fully understood, but key factors appear to be transforming growth factor beta and insuline-like growth factor-I[32]. We speculate that TNF-α might also play a role in the process of osteophyte formation, since inhibition of TNF-α appears to suppress it. Therefore we think that our data on secondary hand OA might also be relevant for primary hand OA, suggesting that treatment with TNF-α inhibitors might reduce the development or progression of primary hand OA and this might be possibly *via* other mechanisms than suppression of inflammation. Large randomized, placebo-controlled, clinical trials in primary hand OA are needed to confirm this.

Table VI
Incident and progressive secondary OA in DIPJs and PIPJs over 3 years between the infliximab and 'no infliximab group' derived by chi-square tests and univariable and multivariable logistic regression analyses

Chi-square analyses	DIPJs				PIPJs			
	Incident secondary OA		Progressive secondary OA		Incident secondary OA		Progressive secondary OA	
	No. patients/ total no. (%)	*P*-value	No. patients/ total no. (%)	*P*-value	No. patients/ total no. (%)	*P*-value	No. patients/ total no. (%)	*P*-value
Infliximab group	14/125 (11)	0.920	20/53 (38)	0.737	9/157 (6)	0.059	5/21 (24)	0.163
No infliximab group	16/138 (12)		35/100 (35)		26/205 (13)		14/33 (42)	
Logistis regression analyses	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Infliximab group, unadjusted	1.0 (0.5, 1.9)	0.920	1.1 (0.7, 1.7)	0.737	0.5 (0.2, 0.9)	0.027	0.6 (0.2, 1.3)	0.163
Infliximab group, adjusted for demographics*	0.8 (0.4, 1.7)	0.578	1.2 (0.7, 1.8)	0.490	0.5 (0.2, 1.1)	0.087	0.6 (0.2, 1.5)	0.477
Infliximab group, adjusted for demographics and cumulative inflammatory activity†	0.6 (0.2, 1.3)	0.182	1.1 (0.6, 1.7)	0.682	0.5 (0.2, 1.0)	0.059	0.5 (0.1, 1.6)	0.332

* Adjusted for age, gender, BMI and anti-resorptive treatment.
† Adjusted for age, gender, BMI, and anti-resorptive treatment, presence of RF, baseline ESR, AUC ESR 0–3 years, baseline erosion score and progressive erosion score over 3 years.

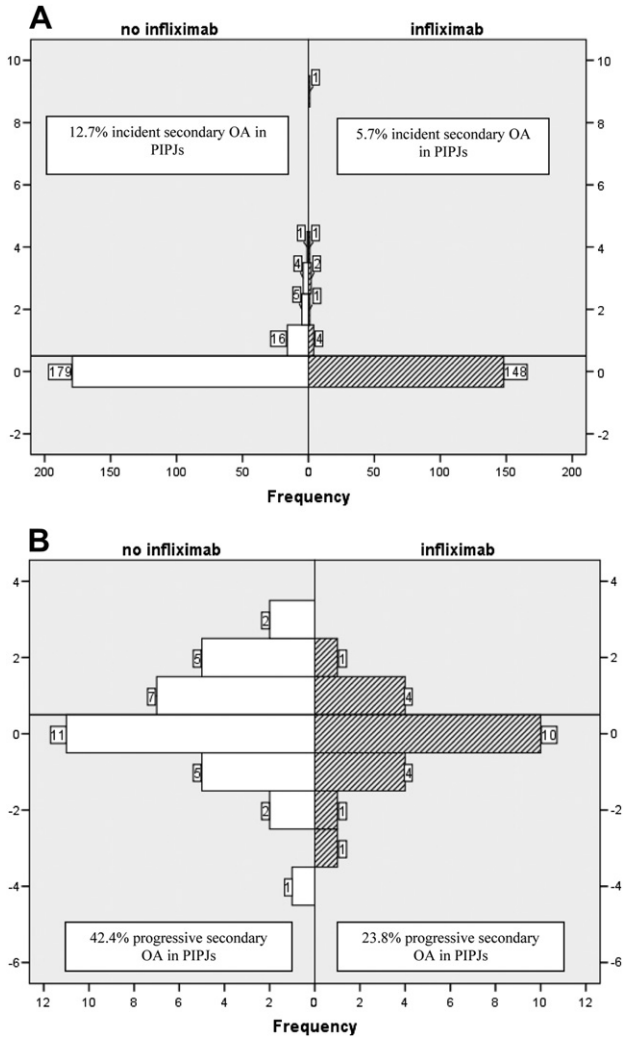

Fig. 1. Incident (A) and progressive (B) secondary OA in PIPJs over 3 years in the infliximab and no infliximab group. Incident secondary OA is defined as an increase in osteophyte score $\geq$1 unit in absence of OA at baseline, thus 26/205 = 12.7% incident secondary OA in PIPJs in the no infliximab group compared to 9/157 = 5.7% in the infliximab group. Progressive secondary OA is defined as an increase in osteophyte score $\geq$1 unit in presence of OA at baseline, thus 14/33 = 42.4% progressive secondary OA in PIPJs in the no infliximab group compared to 5/21 = 23.8% in the infliximab group.

A limitation of the present study is that the development and progression of secondary OA is studied in a RA cohort. First, in this setting the evaluation of two diseases in a single joint might be less reliable. Second, the value of radiographic evaluation by the presence of osteophytes, in stead of the much wider used joint space narrowing, might be argued, however the evaluation of cartilage degradation was not preferred in this study due to high occurrence in both diseases. The focus on osteophytes might introduce the possibility of underestimation of incident and progressive secondary OA, however any possible misclassification of OA is non-differential with regard to treatment because the radiographic changes were assessed blinded for the treatment group. Furthermore changes in bone and cartilage seem to be tightly coupled in OA[33], emphasized by the protective effect of alendronate on both cartilage degradation and osteophyte formation in a rat model[34]. Third, a minority of the patients had OA at baseline and a 3-year follow-up period is relatively short for OA processes, hence the numbers of patients who had incident and progressive secondary OA in IPJs over 3 years were rather small, especially progressive secondary OA in PIPJs was only seen in 19 patients. A longer follow-up period might reveal more incident and progressive secondary OA and therefore add power to find associations between inflammation and TNF-α inhibition and incident and progressive secondary OA.

In conclusion, our study showed that high systemic and local inflammation is linked to incident and progressive secondary OA in DIPJs over 3 years in recent-onset active RA patients. Treatment with a TNF-α inhibitor might decrease incident secondary OA in PIPJs, independent of the suppression of inflammation. The value of anti-TNF-α in treatment of primary hand OA is still unknown and needs further research.

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Conflict of interest

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