Repair of bone erosions in rheumatoid arthritis treated with tumour necrosis factor inhibitors is based on bone apposition at the base of the erosion

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ABSTRACT

Objectives To investigate whether bone erosions in patients with rheumatoid arthritis (RA) show evidence of repair.

Methods 127 erosions were identified in metacarpophalangeal joints 2–4 of the right hands of 30 RA patients treated with tumour necrosis factor inhibitors (TNFi) and 21 sex, age and disease activity–matched patients treated with methotrexate. All erosions were assessed for their exact maximal width and depth by high-resolution μCT imaging at baseline and after 1 year.

Results All erosions detected at baseline could be visualised at follow-up after 1 year. At baseline, the mean width of bone erosions in the TNFi group was 2.0 mm; their mean depth was 2.3 mm, which was not significantly different from the methotrexate-treated group (width 2.4 mm; depth 2.4 mm). Mean depth of erosions significantly decreased after 1 year of treatment with TNFi (−0.1 mm; p=0.016), whereas their width remained unchanged. In contrast, mean depth and width of erosive lesions increased in the methotrexate-treated group. The reduction in the depth of lesions was confined to erosions showing evidence of sclerosis at the base of the lesion. Moreover, deeper lesions in the TNFi group were particularly prone to repair (−0.4 mm; p=0.02) compared with more shallow lesions.

Conclusions Bone erosions in RA patients treated with TNFi show evidence of limited repair in contrast to bone erosions in patients treated with methotrexate. Repair is associated with a decrease in the depth of lesions and sclerosis at the bases of the lesions. Repair thus emerges from the endosteal rather than periosteal bone compartment and probably involves the bone marrow.

Bone erosion is a central pathophysiological process in rheumatoid arthritis (RA). Growth factors such as monocyte colony stimulating factor as well as cytokines such as receptor activator of nuclear factor kappa B ligand, tumour necrosis factor alpha (TNFα) and interleukin-1 expressed in the synovial tissue stimulate the differentiation of monocytes/macrophages into osteoclasts, which initiate the resorption of the periarticular bone.1 2 This resorption process leads to a loss of mineralised tissue along the joints, which can be visualised as bone erosion by conventional radiography. Apart from clinical measurements, the detection and quantification of bone erosion is an important outcome parameter in both clinical studies and clinical practice.3 4 Virtually all currently used drug therapies have been tested for their ability to retard the bone erosive process in RA, which is suggestive of effective disease control and preservation of the joint architecture.

Bone erosion is closely linked to inflammatory disease activity of RA. The better synovial inflammation can be controlled by anti-inflammatory drug therapy, the more likely retardation or arrest of bone erosion is achieved. Despite this link between inflammation and bone erosions, some treatment regimens are particularly effective to retard structural damage.5 Inhibition of tumour necrosis factor alpha inhibitors (TNFi) is widely used in the treatment of RA patients and has shown a consistently strong effect on the retardation of bone erosion.6 Interestingly, this bone-sparing effect of TNFi also applies to patients, which achieve no or only minor improvement of inflammatory symptoms of the disease, suggesting that TNFi exert a favourable effect on the local bone balance in the affected joints.7 Indeed, TNFα fosters osteoclast differentiation and bone resorption and at the same time blocks bone formation leading to a net imbalance of bone homeostasis.5 8 9 These detrimental effects of TNFα on bone homeostasis suggest that the neutralisation of TNFα may not only block the progression of bone damage but may indeed induce repair of existing lesions. In particular, the observation that TNFi might rescue from impaired bone formation in RA could result in new bone formation and repair upon treatment with TNFi. So far, however, evidence for the repair of bone erosions in patients with RA is limited. Occasionally, however, apposition of new bone (‘sclerosis’) in bone erosions is described in radiographs indicating the increased activity of osteoblast-mediated bone formation. Indeed, osteoblasts have been identified in the endosteal space of the periarticular bone of RA patients, and histological examination of animal models of RA and joints explanted from RA patients have revealed enhanced osteoblast activity in the subchondral bone marrow underneath or adjacent to bone erosions.10–13

Hypothesising that the repair of existing bone erosions may indeed occur in RA patients, we aimed to search for further evidence for such repair processes. We therefore sequentially analysed a group of RA patients treated with TNFi and performed an in-depth analysis of the change in the dimension of each single erosion after 1 year of treatment using high-resolution μCT scanning. Also, we sequentially assessed sclerosis of each individual lesion as well as their exact width and depth during TNFi therapy and compared these results with RA patients treated with methotrexate monotherapy.
METHODS

Patients
Fifty-one RA patients were included in this study. All patients fulfilled the 1987 American Rheumatism Association revised criteria for the classification of RA as well as the new 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA. Patients were recruited at the Rheumatology Outpatient Clinic of the University Clinic of Erlangen. Twenty-one patients were on methotrexate monotherapy (mean dose 15.5 mg) and continued methotrexate over the entire observation period of 1 year. Thirty RA patients received treatment with TNFi (in combination with methotrexate; mean dose 15.4 mg). Eleven of them were treated with adalimumab, eight received etanercept, six were on infliximab, four patients were treated with certolizumab pegol and one patient received golimumab. All TNFi were used according to the dosages approved for the treatment of RA. Treatment with methotrexate and TNFi was stable for at least 3 months before the baseline μCT examination. Patients receiving methotrexate monotherapy and TNFi were matched for age (methotrexate 51.4±13.5 years; TNFi 54.6±12.9 years; p=0.44), disease duration (methotrexate 3.8±7.0 years; TNFi 5.8±5.6 years; p=0.38) and baseline disease activity (methotrexate disease activity score in 28 joints (DAS28) 3.7±1.4; TNFi DAS28 4.0±1.4; p=0.48). Disease activity dropped in both groups after 1 year (methotrexate DAS28 2.7±1.2; TNFi DAS28 3.4±1.3) with a slightly lower disease activity in the methotrexate-treated group, although not reaching significance (p=0.12). The study was performed in accordance with the Declaration of Helsinki. Approval from the local ethics committee and national radiation safety agency (Bundesamt für Strahlenschutz) and informed consent was obtained for the study.

μCT scanning
All patients received a μCT scan at a resolution of 82×82×82 μm voxel size of the metacarpophalangeal joints 2, 3 and 4 of the right hand using an XtremeCT scanner (SCANCO Medical AG, Brüttisellen, Switzerland). The scan was performed within a region of 80 slices distal and 242 slices proximal of the top of metacarpal head 3. Scan time was 8 min per patient and scan. The scans were performed at baseline and after 1 year. For exact positioning the hand was positioned in a stretched posture and padded. All scans were performed by a single investigator (SF) trained in the technique.

Evaluation of images
Erosions were defined as a break of the juxta-articular cortical bone shell of metacarpophalangeal joints 2–4. Each of the erosions was documented at baseline and after 1 year (follow-up). Assessment included the palmar, ulnar, dorsal as well as the radial sides of each metacarpal head and each phalangeal base investigating overall 322 2D μCT slices in the transversal, sagittal and coronal plane. Individual erosions were characterised by the maximal width of the cortical break as well as the maximal depth of the lesion. In addition, the signs of bone apposition at the base of the erosion were documented. Erosions were defined as sclerosing, if bone apposition was absent at baseline but present at the 1-year follow-up, sclerosed, if present at baseline and at follow-up, and non-sclerosing if absent at both baseline and follow-up. Measurement of the maximal width and depth of the erosion as well as the assessment of bone apposition was done by a single reader (KE), who was unaware of the identity, clinical data and treatment modalities of the patients and also blinded to the sequence of the scans. Intra-observer reproducibility (KE) was 1.0 (both for erosion width and depth), interobserver reproducibility (KE and SS) as determined by intraclass correlation was also very high 0.95 (both for erosion width and depth). The smallest detectable change of erosion depth and erosion width was calculated on the basis of 25 individual erosions as suggested by Bruynesteyn et al.65 and was extremely low (0.002 mm both for erosion width and depth). A definitive change was defined as a change of erosion width or depth above the cut-off of the smallest detectable change.

Statistics
The width and depth of erosions showed a Gaussian distribution at baseline, and follow-up was compared by paired Student’s t test. Calculations were performed using the SPSS program version 17.0. A p value of less than 0.05 was regarded as statistically significant.

RESULTS

Baseline characteristics for erosions
We performed a careful examination of metacarpophalangeal joints 2–4 of the right hand in 30 RA patients treated with TNFi using μCT imaging according to previously described protocols. At baseline, we found a total number of 72 erosions at the three metacarpophalangeal joints examined. Their mean (±SEM) width was 2.04 (±0.14) mm with a median width of 1.69 mm. With respect to the baseline depth of erosions a mean (±SEM) depth of 2.30 (±0.25) mm was measured, the median depth of lesions was 1.67 mm. In addition, 21 sex and age-matched RA patients treated with methotrexate were investigated as a control group. At baseline, we could detect 55 erosions in metacarpophalangeal joints 2–4 of the right hand in methotrexate-treated RA patients. The mean (±SEM) width of erosions was 2.41 (±0.24) mm, their median width was 1.77 mm. There was no significant difference in the width of erosions between TNFi and methotrexate-treated patients (p=0.56). The mean (±SEM) depth of erosions in the methotrexate-treated group of RA patients was 2.40 (±0.23) mm with a median of 1.79 mm. Also, the depth of erosions did not significantly differ among TNFi and methotrexate-treated RA patients (p=0.30).

Dynamics in the dimension of bone erosions in TNFi and methotrexate-treated RA patients
To investigate potential evidence for repair of bone erosions we retrieved exactly all 127 bone erosions from baseline examination and re-assessed their width and depth after 1 year. In the TNFi-treated group of RA patients the mean width of erosive lesions (N=75) was unchanged after 1 year (mean±SEM change 0.07±0.05 mm; median 0.01 mm) (figure 1A). With respect to the depth of erosive lesions, however, we observed a significant decrease (−0.10±0.04 mm; median −0.05 mm, paired Student’s t test 0.019) (figure 1B). In contrast, the mean width of the 55 erosive lesions found in methotrexate-treated patients at baseline significantly increased after 1 year (0.17±0.06 mm; median 0.04 mm; paired Student’s t test p=0.005). Furthermore, the depth of erosive lesions substantially increased in methotrexate-treated patients in sharp contrast to patients treated with TNFi (2.16±0.24 mm; median 1.95 mm, paired Student’s t test p<0.001), suggesting an overall progression of erosive lesions in the methotrexate-treated RA patient group (figure 1A, B).
Bone deposition (sclerosis) is associated with decreased depth of bone erosions in TNFi-treated RA patients

We next analysed whether the presence of signs of bone formation (sclerosis) within erosions determines the longitudinal dynamics of individual lesions. Of the 73 lesions, 19 showed no evidence of bone apposition at baseline, but after 1 year ('sclerosing') 40 of them showed evidence of bone apposition at baseline, and in the follow-up ('sclerosed') and 13 lesions did not show bone apposition either at baseline or at follow-up ('non-sclerosing'). Sclerosing erosions showed no change in their width (mean±SEM change 0±0.04 mm; median 0.01 mm) but significantly decreased in depth (−0.16±0.07 mm; median −0.10 mm; p=0.03) (figures 1C and 2). Representative lesions are depicted in figure 3. Similarly, sclerosed lesions showed no change in their width (0.02±0.07 mm; median −0.01 mm), but significantly decreased in their depth (−0.13±0.06 mm; median −0.04 mm; p=0.04) (figures 1C and 2). In contrast, non-sclerosing lesions did not show any significant change in their dimensions.

Figure 1  Change in the width and depth of individual bone erosions in tumour necrosis factor alpha inhibitor (TNFi) and methotrexate (MTX)-treated rheumatoid arthritis (RA) patients. (A,B) Change in the width (A) and depth (B) of individual erosions in RA patients treated with TNFi or methotrexate. X-axis indicates change in width (mm) or depth (mm) of each individual lesion from baseline after 1 year of therapy. (C) Change in the width (upper row) and depth (lower row) of sclerosing (left), sclerosed (middle) and non-sclerosing (right) erosive lesions between baseline and after 1 year of treatment with TNFi. The graphs show the minimum and maximum changes (whiskers), the 25th and 75th percentile (bars) and the means (lines). Asterisks indicate significant differences (p<0.05).
their width and depth after 1 year of TNFi treatment (width 0.34±0.20 mm, median 0.10 mm; depth 0.08±0.05 mm; median 0 mm), although their size tended to increase rather than to decrease (figures 1C and 2). These data suggest that sclerosing and sclerosed bone erosions decrease in depth but not width, suggesting that repair starts from the bottom of the lesion rather than from the bone surface.

Of the 55 erosions in the methotrexate-treated patient group, eight were sclerosing, 39 were sclerosed and eight were non-sclerosing lesions. Sclerosing erosions showed no change in their width (−0.05±0.08 mm; median 0.01 mm) and also did not significantly increase in their depth, although there was a trend towards increased depth (0.25±0.16 mm; median 0.12 mm) (see supplementary figures 1 and 2, available online only). Sclerosed lesions in methotrexate-treated patients showed no change in width (0.15±0.06 mm; median 0.02 mm) or depth (0.07±0.05 mm; median 0 mm) (see supplementary figures 1C,D and 2C,D, available online only). In contrast, the width and depth of non-sclerosing lesions strongly increased after 1 year of methotrexate treatment (width 0.43±0.17 mm, median 0.30 mm; depth 1.05±0.47 mm; median 0.50 mm; both p=0.04) (see supplementary figures 1 and 2, available online only), indicating an overall progression of erosive lesions in RA patients treated with methotrexate.

Deeper lesions show more evidence of repair than more shallow erosions

We next aimed to identify which subgroup of the sclerosing/sclerosed lesions shows the highest potential for repair. We therefore stratified bone erosions according to their depth into quartiles. For sclerosing lesions the quartiles for depth of erosions were as follows: quartile 1 less than 0.85 mm, quartile 2 0.85–1.55 mm, quartile 3 1.56–2.6 mm and quartile 4 more than 2.6 mm in depth (figure 4A). Surprisingly, lesions in the highest quartile showed the most evidence for repair as detected by a significant reduction of erosion depth (−0.49±0.16 mm; median −0.38 mm; p=0.04). Lesions in quartiles 2 and 3 showed a tendency for repair, which however, did not reach significance. Small lesions in quartile 1 did not show evidence of repair. Analysis of sclerosed erosions was very consistent and an even more pronounced association between repair and depth of erosive lesions was noted (figure 4B). Quartiles for depth of sclerosed lesions were comparable to sclerosing lesions (quartile 1 less than 0.94 mm, quartile 2 0.94–1.53 mm, quartile 3 1.54–2.2 mm and quartile 4 more than 2.2 mm). Erosions in quartile 4 showed a very pronounced reduction in depth (−0.42±0.15 mm; median −0.22 mm; p=0.02), whereas smaller lesions in quartiles 1 and 2
Repair of existing bone lesions and restoration of joint architecture is an ambitious treatment goal in patients with RA. Our hypothesis in this study was to maximise the chances to depict repair by: (1) using a high-resolution imaging technique for bone; (2) performing direct quantitative measurement of erosion size; and (3) including patients with a therapy such as TNFi, which is considered to be highly effective in blocking bone erosions. We observed that repair of bone erosions starts from the base of the lesion, where bone apposition (sclerosis) is observed leading to a reduction in the depth of the erosion (figure 5). In contrast, there was no evidence for repair processes emerging from the periosseous adjacent to the erosions and this observation was in accordance with no change in the width of the cortical breaks. Interestingly, repair processes were almost exclusively seen in the deeper but in shallow lesions. This observation suggests that repair in RA emerges from the periarticular endosteal lining of the bone marrow but not along the outer parts of the bone erosions. Very similar results were obtained when quantifying bone resorption and bone formation simultaneously in arthritis models. Bone formation was

DISCUSSION

Our investigation aimed to evaluate the prevalence of joint repair in patients with RA. We used sequential μCT to measure the width and depth of individual bone erosions at the second, third and forth metacarpophalangeal joints at baseline and at follow-up after 1 year. Indeed, limited signs of repair were found in bone erosions of RA patients treated with TNFi, but not in patients treated with methotrexate. Repair was based on a decrease in the depth of the lesions and was exclusively found in erosions, which showed evidence of bone apposition (sclerosis) at baseline or at follow-up. Importantly, evidence of repair was most pronounced in deeper lesions and virtually absent in more shallow bone erosions.

Repair of existing bone lesions and restoration of joint architecture is an ambitious treatment goal in patients with RA. Based on the improvement of therapeutic regimens during the past decade allowing more RA patients to enjoy a state of low disease activity or even remission, the question arises as to whether effective control of inflammation allows the repair of existing bone erosions. In contrast to the vast evidence for retardation of structural damage by anti-inflammatory drug therapy in RA, however, the evidence for repair of existing bone erosions is limited. Exercises with experts blindly reading conventional radiographs assessing them for the evidence of repair of erosions consistently indicated that repair of individual lesions can indeed occur. Small radiographic case series from Rau and Herborn, McCarty and Carrera, Jalava and Reunanen and Sokka and Hannonen also suggested the principal possibility of the repair of individual bone erosions. As virtually all of these patients were either treated with gold salts or disease-modifying anti-rheumatic drug (DMARD) combinations the authors concluded that effective control of inflammation is a prerequisite for inducing repair. Some additional evidence for repair also comes from a case series of three patients treated with bucillamine and a case report on treatment with adalimumab. Larger cohorts of RA patients treated with conventional DMARD in Japan and The Netherlands showed that repair of erosions is indeed limited and confined to a rather small (<10%) number of RA patients analysed. Rigorous assessment of repair in the Leiden Early Arthritis Cohort comprising 250 patients identified a total number of 32 joints with evidence of repair of bone erosions. Interestingly, the analysis of this latter cohort showed that a higher level of joint destruction is more like being associated with repair, which is in accordance with our finding that deeper lesions are more likely to show evidence of repair. Two radiographic studies recently addressed whether repair occurs in patients treated with TNFi. One study by Lukas et al was based on a post-hoc analysis of a clinical study on etanercept, which showed that TNFi treatment is more likely to be associated with signs of repair in conventional radiographs. Moreover, Möller Døhn and colleagues compared radiography, MRI and conventional CT and suggested that repair is rare even in patients undergoing TNFi. In particular, these latter and other comparative studies using high-quality imaging techniques such as MRI and CT have created new possibilities to assess the dimensions of individual bone erosions in a more accurate way, which is of essential importance for assessing repair.

Despite these previous studies, the process and extent of repair of bone erosions in RA is still poorly defined but of seminal importance to allow an improved protection of the joint architecture. Our hypothesis in this study was to maximise the chances to depict repair by: (1) using a high-resolution imaging technique for bone; (2) performing direct quantitative measurement of erosion size; and (3) including patients with a therapy such as TNFi, which is considered to be highly effective in blocking bone erosions. We observed that repair of bone erosions starts from the base of the lesion, where bone apposition (sclerosis) is observed leading to a reduction in the depth of the erosion (figure 5). In contrast, there was no evidence for repair processes emerging from the periosseous adjacent to the erosions and this observation was in accordance with no change in the width of the cortical breaks. Interestingly, repair processes were almost exclusively seen in the deeper but in shallow lesions. This observation suggests that repair in RA emerges from the bone marrow and the endosteal lining rather than the periosseous compartment. Indeed, histological evaluations of human joints affected by RA and joints from mice induced for inflammatory arthritis clearly indicated that new bone apposition is preferentially, if not exclusively, found in the endosteum. Furthermore, studies on animal models of arthritis also support this notion. Walsh et al have shown that bone apposition, as detected by calcein labelling preferentially occurs at the periarticular endosteal lining of the bone marrow but not along the outer parts of the bone erosions. Very similar results were obtained when quantifying bone resorption and bone formation simultaneously in arthritis models. Bone formation was

Figure 4

Depth of bone erosions as an indicator for repair. (A) Change in the depth of sclerosing erosive lesions between baseline and after 1 year of treatment with tumour necrosis factor alpha inhibitors in the different quartiles according to baseline erosion depth; (B) Change in the depth of sclerosed erosive lesions between baseline and follow-up in the different quartiles according to baseline erosion depth. Asterisks indicate significant differences (p<0.05).
virtually absent in the erosion itself but was elevated in the endosteal compartment in the vicinity of the lesions.

Evidence of repair was almost exclusively confined to patients treated with TNFi, but was barely present in patients treated with methotrexate monotherapy. This observation highlights the skeletal effects of TNF and its pharmacological inhibition. TNF is considered as a potent downregulator of osteoblast differentiation and an inducer of bone resorption thus creating a local imbalance between bone formation and resorption. This negative influence of TNF on bone is of key relevance for synovial tissue to elicit bone resorption. TNF blockade may restore bone balance in addition to blocking synovitis and may thus facilitate repair. TNF has consistently been shown to halt the progression of bone erosions in radiographs and this effect has even been observed in patients not achieving a clinical response, highlighting a specific effect of TNF on bone, which exceeds its anti-inflammatory potential. These data support the concept that TNF have profound beneficial effects on joint structure and function. Refilling of erosions as evident by a decrease in their depth is incomplete after 1 year of treatment. This observation suggests that repair processes in RA start from the base of a bone erosion and are seen with deep erosions having gained access to the bone marrow. Repair of erosions in RA thus emerges from the endosteum but not the periosteum. TNFi are facilitating the repair of bone erosions; however, repair is incomplete and lacks sufficient anabolic response to fill the lesion completely within 1 year of follow-up.

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Competing interests None.

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Radiologic observation: repair of focal bone erosions


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