Is remission in rheumatoid arthritis associated with radiographic healing?

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ABSTRACT

The precondition for joint damage in rheumatoid arthritis (RA) is inflammation, and the precondition for healing is absence of inflammation. A systematic search for healing phenomena in RA patients in remission has not yet been undertaken. In reports of patients in whom healing was observed, clinical and laboratory data have not been published in part due to space restrictions. However, this preliminary review of the existing literature about repair supports the thesis that a strong association may exist between remission and repair. Several reports indicate that patients in whom radiographic repair was seen were in clinical remission. In most reports clinical response to treatment was very good, and in groups of patients in which scoring was done, evidence of repair was seen in patients with strong inhibition or halt of radiographic progression. In contrast, healing is unlikely to be detected in patients with persistent clinically active disease and/or moderate or strong radiographic progression.

No systematic investigations are available yet to answer the question of whether remission is associated with radiographic healing in rheumatoid arthritis (RA). However, there are strong indications that radiographic healing occurs predominantly in patients in remission or in a state of low disease activity. This article is a brief and preliminary review of published data indicating a relationship between control of disease activity and repair of joint damage.

Many studies have documented that rheumatoid inflammation is the precondition and the main cause for joint damage in RA. As a rule, inflammatory disease activity is well correlated with subsequent damage progression. Clinically very active disease as well as strong elevation of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the best predictors of progressive disease (1, 2). Therefore, suppression of inflammation, generally by disease-modifying antirheumatic drugs (DMARDs), leads to slowing or halt of damage progression. Conversely, groups of joints (3) or single joints (4) that never were swollen do not develop erosions, and patients with persistently low disease activity rarely get considerable joint damage.

A joint that has not been and is not affected by rheumatoid inflammation therefore remains normal in its clinical and radiographic appearance. A joint that had developed erosions during an inflammatory phase of the disease but becomes and remains inactive will – in the absence of inflammation – start a process of repair that can be detected on X-rays as soon as repair has reached a state that is visible radiographically. Repair is a completely normal process comparable to healing of a fracture. As the absence of inflammation is the precondition for healing, the correlation between clinical remission and radiographic repair should be strong.

Clinical experience and published data underscore this relationship (although clinical and laboratory data frequently have not been published in case reports due to space restrictions).

In the 11th edition of his textbook, published in 1989, McCarty wrote:

> Little has been written about healing of erosions. In most instances, the bony cortex re-forms within the contour of a pocket erosion. This often accompanies clinical remission, nearly always induced by a slow acting anti-rheumatic drug. Occasionally, pocket erosions may become filled-in with new bone (5).

Already in 1982, McCarty and Carrera (6) reported 17 patients with progressive erosive seropositive RA refractory

to conventional therapy, who had been treated with a combination of cyclophosphamide, azathioprine, and hydroxychloroquine for an average of 27 months. Five patients achieved a complete remission, 2 had activity in a single joint only, 7 had partial disease suppression, and 3 showed no response. Serial hand radiographs demonstrated recortication of erosions in 9 patients with "filling-in" of some erosions in 3 of these, no change in 5 patients, and progressive damage in 3. In this series, improvement (repair) occurred only in patients who had no radiographic progression.

The term "secondary osteoarthrosis" has been used in the European literature for decades, and refers to degenerative joint disease that develops secondary to injury of cartilage and bone due to inflammatory joint disease. This term is based on the clear understanding of all clinicians that bony sclerosis and osteophyte formation can occur only if the inflammatory process has come to an end. Therefore, inactivation of RA, or "burnt out" RA, is a precondition for the development of secondary degenerative disease. Bony sclerosis and new bone formation (i.e. osteophytes) are special features that indicate inactivity of inflammation and repair at the same time. (A joint with repair or degenerative changes is no longer actively inflamed.) Interestingly, in his first publication concerning his scoring method (7), Sharp stated that "sclerosis and osteophytes were considered to be secondary changes" [in RA].

As a special variant of the "usual" development of secondary osteoarthrosis, Dihlmann (8), as early as 1969, described healing of erosions and remodelling of joints without development of deformity as "arthritis reformans."

Cabral *et al*. (9) reviewed hand X-rays of 38 patients with RA whose disease had gone into drug-induced remission for a mean duration of 2.5 years. Metacarpophalangeal (MCP) joints and distal interphalangeal (DIP) joints of good quality radiographs taken during active disease and after a mean of 2.5 years in remission were scored according to the method of Sharp (7); in addition, osteophytes were identified. In 21 patients, signs of bone remodelling and osteophyte formation at MCP joints in the "remission" films were seen that had not been present in their "activity" films. Remodelling and osteophyte formation are indicators of "secondary" osteoarthritis (OA) in joints in which inflammatory disease had been found previously. The presence of OA at the DIP joints did not correlate with the development of osteophytes in the MCP joints. That means that the "primary" OA in the DIP joints is a different process from the "secondary" OA seen in the MCP joints in these patients whose RA had been controlled to remission.

We have demonstrated cases with healing of erosions since the early 1980s and included images of such cases in reports on the inhibition of radiographic progression with methotrexate (MTX) (10), with parenteral gold (11, 12), or with both compounds (12). From that experience we concluded that "the precondition for erosion healing seems to be at least a sharp decrease in disease activity or a remission-like situation that lasts for several months", since healing of erosion takes time.

In a series of 6 cases, 3 to 8 follow-up images of one joint each over periods of 3 to 11 years (mean 7 years) were published, that demonstrated the gradual development from an active erosion to recortication, partial filling-in, complete filling-in, and restoration. In two cases, the development of a secondary osteoarthrosis was seen (13). All these patients had responded very well to DMARD treatment and had reached a state of remission, near remission, or at least very low disease activity.

In a long-term trial of low dose MTX in 26 patients, radiographs of hands and wrists obtained at baseline and after at least 28 months of treatment were available in 14 patients. Five of these patients had an improvement in the number and size of erosions with evidence of healing. The image of one patient's hand demonstrated a subchondral bone sclerosis, filling-in of an erosion, and remodelling of bony surfaces. Three of the 5 patients with evidence of healing were among those 5 of 26 patients who exhibited the most "substantial" clinical response to MTX (14). "Substantial" clinical response was defined as > 50% improvement of both swollen and tender joint counts and of physician's and patient's assessment of disease activity. A remission as defined by American College of Rheumatology (ACR) criteria (15) was not observed.

Weisman included "healing of erosions" and "reparative bone formation" in her scoring system that was used in a 36-week trial of MTX versus auranofin. No differences regarding radiographic progression between the groups and no signs of repair were detected (16), likely because of the short duration of the trial. The majority of patients in both groups had radiographic progression. It is known from other studies that in patients treated with conventional DMARDs the second radiograph (taken after 6 or 12 months) usually continues to indicate progression and that proof of radiographic progression inhibition can be seen only after significant clinical response has occurred.

This view has been confirmed in a macro-radiographic study in 29 patients: 13 patients treated with parenteral gold at presentation, 10 patients treated with gold after a delay of 6 months, and 6 patients who received no gold at all (17). The computer-assisted calculation of the erosion area demonstrated an increase during the first half year, no change during the second 6 months, and a decrease in the erosion area, indicating repair during the third half year. This was true for gold-treated patients, while patients who were treated only with nonsteroidal anti-inflammatory drugs demonstrated continuous progression. With gold, the number of clinically "active joints" had decreased from 6 to 2 during the first half year and to 1 after the second half year; the ESR decreased from 28 to 14 mm/h during the first half year and was 15 after 1 year, indicating that some of the patients may have been in clinical remission (17). The study demonstrates clearly that clinical improvement with reduction in disease activity precedes new bone formation with reduction of erosion size indicating repair.

A similar result was obtained by Menninger *et al*. (18) when investigating 27

patients with early RA who participated in a controlled trial of gold/MTX, in which radiographs were scored according to a modification of the Larsen system (19). A significant increase of the radiographic score indicating progression was seen during the first half year, a reduced progression rate during the second half year, and nearly no progression during the second and third year. In addition, the investigators simply counted all joints that had improved or progressed during the observation period. With time (radiographs had been taken at baseline and after 6, 12, 24, and 36 months), a significant decrease in the number of deteriorating joints was found, along with an increase in the number of improving joints. Deterioration was defined as enlargement and/or new development of erosions; improvement was defined as recortication or filling-in of erosions. During the third year, the number of joints with repair phenomena (9.3% of joints) was greater than the number of joints that had deteriorated (7.1%) (18). (Active joints were defined as having lesions with blurred outlines, indistinct margins of erosions, and/or unsharp or diminished trabecular structure. Inactive joints had to exhibit clear articular outlines, have sharp demarcation of erosions and cysts, and normal trabecular structure) (18). The number of "active" joints increased significantly during the first 6 months and thereafter decreased continuously, while the number of "inactive" joints increased continuously after month 6. No clinical data were given (18), however, these 27 patients were part of the study population of a study comparing parenteral gold with parenteral MTX (20) in which approximately 35% of patients had achieved "clinical remission" (defined as no swollen and tender joints, ESR <20 mm/h in males and <30 mm/h in females, and no corticosteroids within the last 4 weeks). The mean ESR had decreased to about 17 mm/h after 12 and 36 months. Therefore, in this study, most of the patients in the cohort had a state of low disease activity or even remission.

In a study including 31 RA patients, we documented progression of radiographic damage during clinically ineffective gold treatment and after switching treatment to MTX. The change in medication in these cases had been necessary because of persistent clinically active disease and rapid radiographic progression under gold treatment. After switching to MTX, patients showed significant improvement in disease activity. Six of the 31 patients achieved clinical remission according to American Rheumatism Association (ARA) criteria (15), and 12 patients had an ESR <15 mm/h. Serial radiographs of hands, wrists, and feet had been taken after 1 to 5 years (mean 2.2 years) of prior treatment and 2 to 6 years (mean 3.9) after switching to MTX. The films were scored using a modification of the Larsen scoring system (19); in addition, all joints were checked for the presence or absence of radiologic signs of active disease indicated as defined above.

One figure in that report illustrates the change from an "active" to an "inactive" joint with sharply demarcated and sclerosed outline of the erosions, sclerosis of the subchondral bone, and partial filling-in of some erosions and cysts. Mean radiographic progression was significantly reduced during MTX treatment when compared to the preceding gold treatment, accompanied by "a sharp decrease in the proportion of radiologically active joints," from approximately 45% of all finger-, wrist-, and MTP joints at start of MTX treatment to approximately 27% of all joints 2 years later. This observation implies that slowing of progression in the context of clinical improvement may be accompanied by "inactivation" (in other words: healing) of radiographically "active" joints, as seen in the study by Menninger (18).

In two cases published by Sokka and Hannonen (21), erosion healing could be documented on radiographs 2 and 4 years after clinical remission; complete normalisation of the ESR had occurred in these patients. In case 2, the patient was in remission in January 1990 and 3 months later erosions were seen in proximal interphalangeal (PIP) joints. This does not mean that erosions develop in spite of and during remission: we do not know when the last previous radiograph had been taken, and it is likely that the erosion had developed before the patient went into remission. But in rare occurrences, the inflammatory process may lead to a rarification and weakening of the subchondral trabecular bone structure without an apparent erosion, and the mechanical breakdown of the cortical plate might occur after the patient has achieved clinical remission. To answer the question of whether erosions also develop during clinical remission, radiographs have to be taken as soon as the patient has achieved remission and be repeated 6 or 12 months thereafter.

A case report (22) describes a patient who already had severe damage in several joints when starting intramuscular MTX treatment (15 mg/wk), which was later switched to oral medication (20 mg/wk) without folate supplementation. After 1 year of treatment with MTX, she demonstrated clearly visible filling-in of erosions, recortication, and densification of the bone structure in a number of different joints. Over the years, further improvement and remodelling of the joint structure toward regaining normal function occurred. Within 6 months, the ESR had improved from 39 mm/h to 25 mm/h and CRP from 4.1 mg/dL to 2.4 mg/dL. After 1 year, the patient was in complete remission with no joint swelling or tenderness, normal mobility of all joints, ESR 19 mm/h, and CRP 0.5 mg/dL. The patient remained in remission after 4.5 years. In this case, clearly visible repair could already be seen 1 year after start of MTX treatment, at the same time at which clinical remission was observed.

A patient with very active disease who had failed to respond to parenteral gold, MTX, and sulfasalazine had severe radiographic progression in the forefeet, active disease with a CRP of 4.3 mg/dL when starting anakinra (22). She went into remission (ESR 10 mm/h, CRP <0.5 mg/dL) after 1 year, and at the same time, demonstrated recortication, new bone formation, and filling-in of small bone defects in the interphalangeal joint of the left great toe. Three years later, she demonstrated

a remodelled joint with completely restored proximal and distal joint surfaces and a well-defined normal wide joint space while still treated with anakinra and still in clinical remission (22). Since healing phenomena had been detected only in sets of radiographs that were investigated with known time sequence of the films, we tried to answer the question of whether repair could be identified also when radiographs were read in random order. For this purpose, 24 sets of radiographs containing healing phenomena were mixed with 10 sets without healing and read blinded and in random order.

The group of patients with healing were found to have a slight mean decrease of the Ratingen score (24) (indicating improvement) when all joints of hands, wrists and feet were scored. The group of patients without healing demonstrated moderate progression. Laboratory data have not been published. However, since 13 of the 24 patients with healing had participated in the parenteral gold/parenteral MTX study (20) with long-term follow-up, their clinical data were easily available. In 12 of these 13 patients, the ESR had decreased to values ≤20 mm/h; the mean value had decreased from 34 mm/h to 10 mm/h. Eight patients had no tender joints, 5 had no swollen joints, and 4 had ≤2 swollen joints. These data indicate that many of the patients with healing were in remission or at least in a state of low disease activity.

Molenaar *et al*. (25) followed 187 patients clinically and radiographically for 2 years; these patients were in clinical remission according to a modification (omitting fatigue) of the ACR criteria (15). In patients with persistent remission (n = 93), they found a median increase of the radiographic score (Sharp/van der Heijde) of 0 and in patients with an exacerbation of RA (n = 86), a change score of + 1.0 (which is less than 0.25% of the maximum score). In patients with persistent remission, clinically relevant progression (Sharp score increase >5 units/2 years) occurred in only 7% of patients compared with 23% of patients who experienced an exacerbation. These results indicate that in cases with persistent remission (small) damage progression is quite unusual. It might occur only in those patients who still have some active disease despite fulfilling existing remission criteria. The radiographs of this study population would be ideal to search for healing phenomena, since a number of radiographically "inactivated" joints – joints with signs of repair –should be detectable in patients with persistent remission.

In conclusion, we can state that although a systematic study has not yet been undertaken, data from reports on healing strongly indicate that remission and radiographic repair are associated phenomena. It is likely that in patients in remission, healing phenomena can be detected – and the presence of healing phenomena may indicate remission.

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