Healing of Radiologic Damage in Rheumatoid Arthritis

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Abstract: Until recently the possibility of healing of erosive changes in RA has been neglected. When evaluating the radiographic course within clinical studies, a reduction of the radiographic score indicating improvement was not allowed since repair of erosions was considered to be impossible. During the last 3 decades several case reports and case series have been published demonstrating convincingly that healing of erosions of RA patients really occurs. In addition, a subcommittee on healing of the OMERACT imaging committee undertook to confirm the existence of repair by performing several studies: different experts had to evaluate erosions on radiographs of the same patients taken at two different time points demonstrating deterioration or improvement. Blinded to the sequence of the films they agreed which film was better or worse and which erosion was greater or smaller. Since 50% of the films showing improvement were taken at the second time point, that study confirmed that healing really exists. Owing to several special features healing could be diagnosed without knowing the sequence of the films in one study, not convincingly so in another study. Among different features indicating healing on radiographs the following can be distinguished with relative certainty: "re-cortication", meaning the re-appearance of a cortical plate that had been destroyed; "filling-in", meaning filling of an erosion with new bone; "restoration", meaning complete normalisation of the shape of the joint and the trabecular structure of the subchondral bone. The best agreement between observers concerns erosion size. Radiographic evaluation blinded to the sequence of the films in trials with biologics resulted in negative scores exceeding the measurement error of the scoring method in a certain percentage of patients, again supporting the existence of healing. As healing only occurs in an individual joint after the inflammatory process has been quiet in that joint for several months, healing could be utilized as an outcome measure in addition to the slowing or arrest of progression. This article gives an overview over the history and present knowledge of radiographic signs of erosion healing.

Keywords: Rheumatoid arthritis, healing of erosions, repair of damage, conventional radiography.

Rheumatoid arthritis (RA) is a chronic inflammatory disease potentially resulting in substantial structural damage in affected joints in a considerable proportion of patients. This review is aimed at demonstrating evidence that damage of joints as seen on conventional radiographs can be reversed which means that erosions may heal. This review is an extension of a previous review [1]. It includes new developments and offers a broader reference of the literature.

Conventional radiography is still considered the gold standard [2] to demonstrate and quantify damage resulting from RA. Although soft tissue inflammation and cartilage destruction can be illustrated better or even exclusively with sonography or magnetic resonance imaging (MRI), conventional radiography offers important advantages to identify bone destruction and it`s change over time: as the local resolution of bone is best with conventional radiography it allows an excellent and anatomically correct portraying of the bone, including the cortical plate, the trabecular structure, bone density etc. Radiographs of hands, wrists and feet demonstrate at the same time all joints that are important in the course of RA. In contrast, MRI and sonography allow an interpretation of a small proportion of these joints only. The amount of bone damage can be estimated on conventional radiographs semiquantitatively by validated scoring methods. The most important outcome of RA for the patient - functional disability - correlates well with the radiographic scores in more progressed and even in early disease [3,3a].

Inhibition of damage progression as documented radiographically is still considered the most important and reliable criterion for disease modification or disease control [4]. At present, radiography is the only imaging method included in the core set of endpoint measures in RA clinical trials [5].

Progression inhibition was accepted as a real outcome of RA treatment characterizing a drug as disease modifying antirheumatic drug (DMARD). However, real improvement of joint damage, i.e. repair or healing of erosions has not been considered to be possible ("erosions never heal"). In contrast, until recently RA was generally regarded as a steadily progressive disease resulting in disability in the majority of patients associated with increased mortality rates [6,7]. This view was the result of the radiographic evaluation in controlled clinical trials and long-term observational studies which always demonstrated progression. The most frequently used scoring systems [8,9] and their multiple modifications [10-19] were designed to quantify progressive destruction and neglect any improvement. When reading films knowing the chronological sequence phenomena of erosion repair, bone reconstruction and remodeling of a joint were usually disregarded, i.e. a reduction of the score was impossible and was prohibited ("once an erosion, always an erosion") [20, personal communications by J.T. Sharp and A. Larsen]. Since radiographs of most clinical trials were scored

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Table 1. Simplified Explanation of Selected Scoring Methods

A Methods with Global Assessment of (Predominantly Erosive) Damage

Larsen Score (9)

grade 0	=	intact bony outlines and normal joint space
grade 1	=	slight change: soft tissue swelling, subchondral osteoporosis or slight joint space narrowing (JSN) may be present
grade 2	=	definitive change: one or several small erosions present
grade 3	=	marked change: marked erosions present
grade 4	=	severe change: large erosions present, only parts of the original joint surface preserved
grade 5	=	mutilating change: the original joint surface has disappeared, severe deformity possible

The following joints are scored: Proximal interphalangeal joints (PIP) II - V, IP I (thumb), metacarpo-phalangeal joint (MCP) I - V, wrist (in one modification divided in 4 quadrants), metatarso-phalangeal joints (MTP) I - V, IP I (great toe), range of the score 0 - 160 (200).

Ratingen Score (19)

grade 0	=	normal joint
grade 1	=	one or more erosions with together < 20% of joint surface destroyed
grade 2	=	21% - 40% of joint surface destroyed, irrespective of the number of erosions
grade 3	=	41% - 60% of joint surface destroyed, irrespective of the number of erosions
grade 4	=	61% - 80% of joint surface destroyed, irrespective of the number of erosions
grade 5	=	> 80% of joint surface destroyed, irrespective of the number of erosions

Joints scored :PIP II - V, IP I (thumb), MCP I - V, 4 bones of the wrist (naviculum, lunatum, distal radius, distal ulna), MTP II - V, IP I (great toe), score range 0-190.

B Methods with Separate Scoring Erosions and Joint Space, Summed Up to a Total Score

Sharp Score (8)

Erosive Changes			Joint Space Narrowing (JSN)		
grade 0	=	no erosion	grade 0	=	normal
grade 1	=	1 erosion	grade 1	=	focal JSN
grade 2	=	2 erosions	grade 2	=	general JSN < 50%
grade 3	=	3 erosions	grade 3	=	general JSN > 50%
grade 4	=	4 erosions	grade 4	=	ankylosis
grade 5	=	> 4 erosions or > 50% of one of the 2 joint surfaces destroyed			

Joints scored for erosions: PIP II - V, IP I, MCP I - V, 7 sites of the wrist.
Joint spaces scored: PIP II - V, IP I, MCP I - V, 7 spaces at the wrist.
Erosion Score 0 -170, JSN Score 0 - 144, total score 0 - 314.
Today, usually the feet are also scored.
If the feet (MTP Joints I - V + IP great toe) are scored, the total score is 0 - 422.

(Table 1) contd…..

Sharp / van de Heijde Score (18)

Erosive Changes			Joint Space Narrowing (JSN)		
grade 0	=	no erosion	grade 0	=	normal
grade 1	=	1 small erosion *	grade 1	=	focal JSN
grade 2	=	2 small erosions, or 1 long erosion*	grade 2	=	general JSN < 50%
grade 3	=	1 erosion crossing the midline, or 3 small erosions, or 1 long + 1small erosion*	grade 3	=	general JSN > 50% or subluxation**
grade 4	=	sum of erosions = 4*	grade 4	=	ankylosis or luxation**
grade 5	=	Sum of erosions = 5 or more*			

*A small erosion is scored 1, a longer erosion is scored 2, an erosion crossing the midline is scored 3.
The joints are nearly identical to those scored with the Sharp method.
**v.d. Heijde scores subluxation and luxation, Sharp does not.

Genant Score (12)

Erosive Changes			Joint Space Narrowing (JSN)		
grade 0	=	no erosion	grade 0	=	normal
grade 0+*	=	questionable or discreet*	grade 0	=	questionable or discreet change
grade 1	=	slight	grade 1	=	focal JSN
grade 1+	=	slight, worse	grade 1+	=	slight, worse
grade 2	=	moderate	grade 2	=	moderate
grade 2+	=	moderate worse	grade 2+	=	moderate worse
grade 3	=	severe	grade 3	=	severe
grade 3+	=	severe, worse	grade 3+	=	severe worse
			grade 4	=	Ankylosis or dislocation

*+ is scored 0.5.
Joints scored for erosions PIP II -V, IP I, MCP I-V, 5 sites at the wrist. Score ranges 0-98.
Joints scored for JSN: PIP II - V, IP I, MCP I-V, 5 sites at the wrist, Score 0-104.
Total score 0-202.

in chronological order, a change of the score could only be documented in the direction of deterioration or - at best - halt of progression.

Previous clinical studies were usually unable to detect improvement also for several other reasons: 1. The duration of most clinical trials is too short to capture healing phenomena. Healing in an individual joint can only occur after the reason for bone destruction in that joint - inflammation - has been stopped completely. Thereafter, the reparative process with formation of new bone can start but usually takes time. As a rule, patients have to be followed many months up to years before radiographic evidence of repair has reached an amount that can be recognized without any doubt. In routine care, healing can be expected to occur in patients with very

low disease activity or in remission, but radiographs are rarely taken in patients who have no clinical signs of active disease. - 2. Most previous clinical trials have been performed in patients with a long disease duration and often severe damage. It is less likely to induce radiographic improvement in joints with severe damage and, if it occurs, to identify it on radiographs since it is often very difficult to assess change in severely damaged joints. - 3. In many instances it is possible to state radiographically if the inflammatory and damaging process in a joint is still active or if it has been inactivated. In conventional scoring methods an "active" erosion is assigned the same score as an "inactivated" erosion. On the other hand the differing quality of radiographs between centers and/or at different time points may obscure the difference between "active" and "inactive".

More recent trials, where films were scored with unknown sequence [21-24] and where the score change of individual patients was looked at cumulative probability plots have demonstrated that a reduction of the score (negative change score) is possible in a certain percentage of patients and that it may indicate repair. Reporting of mean values may "obscure" improvement because the amount of deterioration usually will be greater than that of improvement. One of the reasons for this is that any joint can deteriorate but only joints having erosions can improve.

When considering if repair has any clinical importance we have to ask what biological meaning healing of damage might have. Bone is a tissue with very active metabolism. Under normal conditions there is a balance between bone resorption by osteoclasts and bone formation by osteoblasts. In a state of active inflammation, bone resorption usually exceeds new bone formation, resulting in loss of bone mass, i.e. destruction. However, as soon as the inflammatory process has been stopped in an individual joint, osteoblastic activity may exceed bone resorption, leading to new bone formation and repair [25]. This is a completely normal process regulated by osteoprotegerin [26,27] which occurs after any kind of bone injury, for example bone fracture. As discussed before, bone formation takes time, and repair may be clearly visible on radiographs only 6-12 months after distinct clinical improvement has occurred. Recent clinical trials indicate that inhibition of radiographic progression occurs earlier and more pronounced with tumornecrosis-factor-alpha-inhibitors [22-24] than with conventional DMARDs. This may be due to direct inhibition of osteoclast activity in addition to earlier (and stronger) inhibition of inflammation. Healing phenomena indicate disease remission, at least in an individual joint. Therefore they could be utilized as an outcome measure in addition to the slowing or arrest of progression. It has to be mentioned, that radiographic healing does not preclude reactivation of joint degradation in the future.

The development or presence of healing or repair can be established on x-rays on the basis of certain morphological features (Figs. **1**-**3**). An active erosion is characterized by a disruption of the cortical plate (which is the definition of an erosion), an unclear edge of the erosion, subchondral osteoporosis with rarefication of the trabecular bone structure, and soft tissue swelling. When following patients over long periods of time in our department we realized that radiographically "active" joints (with signs of inflammation) turned into "inactive" joints (without signs of active inflammation) [28]. Signs of inactivation could be identified as:

1. Recortication, i.e. reappearance of a clear visible cortical plate at a site where it had been destroyed.
2. Partial or complete filling in of erosions or cysts by the formation of new bone.
3. "Restoration", i.e. complete filling-in of an early erosion, regaining a normal shape of the joint, includ-

Fig. (1). Example of recortication and filling in. In July 1988 (left image) there is a long superficial erosion at the tibial surface of the second metatarsal head indicated by an unclear fuzzy edge. There is also a small erosion at the base of the proximal phalanx. One year later, in August 1989, the erosion at the metatarsal head is recorticated, the edge is well defined by a smooth line. The small erosion at the phalanx is (not yet completely) filled in (from [50], with permission).

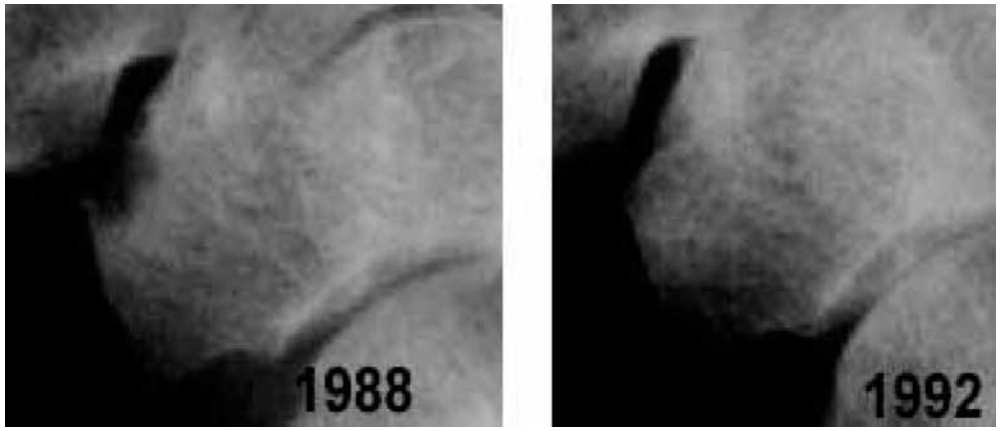

Fig. (2). Filling in and restoration of the bone structure. A large erosion with fuzzy margin of the bone defect at the scaphoid (1988) is completely filled in and recorticated with restoration of a bone structure that appears to be completely normal (from [50], with permission).

ing a normal trabecular structure of the subchondral bone. The joint appears to be normal, there are no signs of previous arthritis.

4. Increased thickness and density of the trabeculae or sclerosis of the subchondral bone.

5. Re-shaping or re-modeling of a partially damaged joint to restore more normal function, potentially accompanied by osteophyte formation. This state has been termed "secondary osteoarthritis".

HISTORY OF PUBLICATIONS ON HEALING

Despite all difficulties to capture radiographic healing that are mentioned above, this phenomenon has been occasionally reported in the literature. As noted before, the term "secondary osteoarthrosis" has been used in the European literature for decades to refer to degenerative joint disease after the arrest of inflammatory disease.

One of the first publications was that of Morrison and Kuhns [29] who followed 55 patients with "atrophic arthritis" (named "rheumatoid arthritis" in Great Britain) long-term clinically and radiographically. They observed "improvement" in 2 of these patients.

In the first publication of his scoring method [8] Sharp stated that "sclerosis and osteophytes were considered to be secondary changes" (in rheumatoid arthritis).

As early as 1969, Dihlmann [30] described healing of erosions and remodeling of joints without development of deformity as "arthritis reformans". He concluded that the formation of new bone was the consequence of predominance of osteoblast activity over osteoclast activity and the re-modeling of a joint was the result of an adaptation of the shape to increased functional use.

In 1982 Jalava and Reunanen [31] described three cases of erosion healing in several MCP and MTP joints after treatment with gold salts.

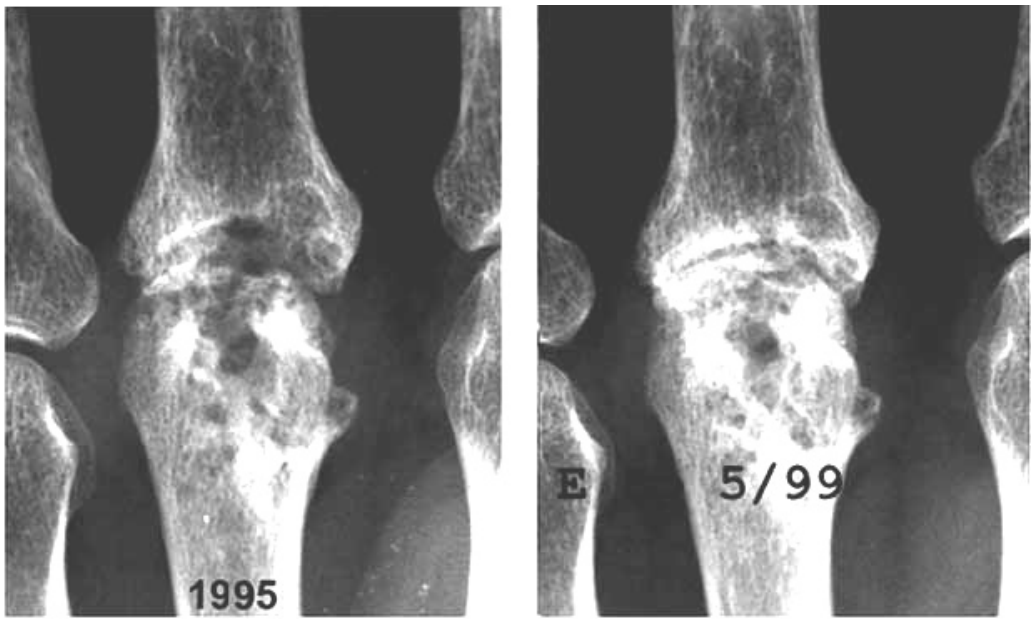

Fig. (3). Filling in and remodelling to regain normal joint function. Multiple lesions of the metacarpal head showing already signs of repair (smooth surface, sclerosis of bone). Four years later the shape of the metacarpal head has further developed towards normality. The base of the phalanx is reconstructed and smoothed (from [50], with permission).

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 antirheumatic drug. Occasionally, pocket erosions may become filled-in with new bone" [32].

Since the early 1980ies we have observed and repeatedly reported radiographic healing in RA patients treated with DMARDs. Images of repair have been included in reports on the inhibition of radiographic progression with MTX [33,36], with parenteral gold [34,35] or with both compounds [36].

In a series of 6 cases treated with parenteral gold, MTX, or both, we published 3-6 follow-up images of one joint each over a period of 3-11 years demonstrating the gradual development from active erosions to complete filling-in (restoration), partial filling-in, recortication, and, in two cases, the gradual development of a secondary osteoarthritis [37]. Two cases with filling-in and recortication after coming into remission with MTX and gold treatment, respectively, were demonstrated by Socca and Hannonen [38].

A patient who already had severe damage in several joints experienced sustained clinical remission with i.m. MTX treatment and showed clearly visible filling-in of erosions, re-cortication, and densification of the bone structure as early as after one year of treatment with MTX. Over the years, further improvement and re-modeling of the joint structure towards regaining normal function occurred [39].

In a patient treated with anakinra severe active damaging arthritis of the interphalangeal joint of the left great toe healed completely with replacing of lost bone by new bone formation and regaining a new cortex with clear outline of the joint surface [40].

In a long-term trial of low dose methotrexate in 26 patients radiographs of hands and wrists obtained at baseline and after at least 28 months of treatment were available in 14 patients. 5 of these had an improvement in the number and size of the erosions with evidence of healing. The figure of one patient`s hand demonstrated subchondral bone sclerosis, filling-in of an erosion, and re-modeling of bony surfaces. Three of these patients were among those 5 of 26 who exhibited the most "substantial" clinical response to MTX [41].

In a long-term observation of patients on MTX treatment over years we found a decrease in the number of „active" joints and a significant increase in the number of joints with „secondary osteoarthrosis", defined as sclerosis of the subchondral bone and osteophyte formation [33,36].

Cabral *et al.* [42] reviewed hand x-rays of 38 patients with RA whose disease had gone into drug induced remission and found signs of bone remodeling and osteophyte formation at metacarpo-phalangeal (MCP) joints in the "remission" films of 21 patients that had not been present in their "activity" films. In patients who experienced clinical remission the presence of osteoarthritis at the distal-interphalangeal (DIP) joints did not correlate with the development of osteophytes in the MCP-joints. This means that osteoarthritis in the DIP-joints is a different process (primary OA) and has (in most cases) nothing to do with previous inflammatory disease in these joints.

Weissman included "healing of erosions" and "reparative bone formation" in her scoring system that was used in a 36 week trial of methotrexate versus auranofin. No difference between the groups and no signs of repair were detected [43], likely because of the short duration of the trial.

In a macro-radiographic study 29 patients with active RA with a disease duration of < 2 years 13 patients were treated with parenteral gold at presentation, 10 patients received gold only after 6 months and 6 patients did not receive gold at all. Radiographs of hands and wrists were taken at baseline, after 6, 12 and 18 months. The computer-assisted calculation of the erosion area demonstrated an increase during the first half year, no change during the 2nd six months and a decrease in the erosion area during the 3rd half year indicating repair [44].

Menninger *et al.* investigated 27 patients with early RA participating in the controlled trial parenteral gold versus MTX [45]. He compared the results of scoring according to a modification of the Larsen system [15] with those of simply counting all joints which had improved or deteriorated during the observation period. Using the Larsen modification a significant increase of the score indicating deterioration was seen during the first half year, a decreased progression rate during the second half year and nearly no progression during the 2nd and 3rd year. The count of improved or deteriorated joints indicated a significant decrease in the number of deteriorating joints and an increase of improving joints with time. In total, at least one joint improved in 26 of a total of 27 patients. Deterioration was defined as enlargement and/or new development of erosions, improvement was defined as recortication or filling-in of erosions. During the 3rd year the number of improved joints was greater than that of joints that had deteriorated. Correspondingly, the number of "active" joints increased significantly during the first 6 months and thereafter decreased continuously, while the number of "inactive" joints increased continuously. The definition of "active" and "inactive" was similar to that given above. The results demonstrate, that simple counts of active/inactive and deteriorated/improved joints, although prone to measurement error, may demonstrate improvement following treatment better than scoring methods, which also may be exposed to measurement error.

Traditionally scoring of radiographs in clinical trials was performed knowing the time sequence of the films ("paired reading"), a method, which was also found to be more sensitive to detect clinically relevant changes than reading without knowing the chronological order of the films [46]. However, in recent clinical trials investigating the efficacy of leflunomide and biologics, scoring without knowing the chronological order has been preferred [23,47-49], mainly in order to avoid the bias towards progression.

The following study was performed to investigate if repair can be detected without knowing the time sequence of the films [50]: from her outpatient clinic G.H. selected 24 sets of radiographs of hands, wrists and feet taken at two time-points (T0 and T1) 2-8 years (mean 4.8 years) apart. The second radiographs of these sets included 74 joints ("index joints") with clear healing phenomena according to G.H.

However, there could be other joints with healing as well. 10 sets of radiographs with moderate disease progression but without any healing phenomena were randomly added to the other sets. Three readers performing four readings scored the radiographs according to the Ratingen score [17, 19] without knowing the identity of the patients or the chronological order of the films. In addition, the readers had to identify the time sequence of the films and the joints with healing.

Within the 1292 joints scored at the 2nd time point (T1) the 74 joints with healing were correctly identified at a mean level of 89% (95%, 89%, 88% and 82%, respectively) in the four readings. All observers agreed that 1090 joints showed no healing phenomena, the 10 patients without healing were correctly identified by all observers. These patients showed a moderate progression in the Ratingen score. In contrast, the 24 patients with healing had a slight mean decrease in the Ratingen score.

In our view, the results of this study indicate that different observers can agree on the existence of healing even without knowing the time sequence of the radiographs and that healing in individual joints is usually associated with no or minimal progression in the other joints.

The question is which morphological signs can help us to distinguish between healing and deterioration. If we see two images of a joint with unknown sequence, one of them (A - better with a smaller erosion) than the other (B - with a larger erosion) we cannot say if this pair of radiographs represents progression (A → B) or healing (B → A). Some criteria can help us to identify improvement. For example, an active erosion is characterized by an indistinct fuzzy margin of the erosion, juxta-articular osteoporosis, irregularity and unclear delineation of the trabecular structure, occasionally soft tissue swelling etc. In contrast, an inactivated (healed) erosion is characterized, as discussed before, by the reappearance of a distinct cortical plate (re-cortication), disappearance of subchondral osteoporosis, increased density or sclerosis of the subchondral bone or complete normalization of the trabecular structure. If the size of an eroded area has been reduced by visible formation of new bone leading to partial or complete filling-in of the erosion, this is also a reliable sign of repair. These phenomena can help to distinguish a healed lesion from an active lesion, even without knowing the chronological sequence of the radiographs. Usually, a healed joint can also be distinguished from a completely unaffected joint.

It should be noted, however, that in most cases a time interval of at least one or two years is necessary to clearly distinguish between an active and a healed erosion. Furthermore, discrimination may be impossible if the quality of the films has changed. A search for healing will always increase the time requirements for scoring significantly because the reader has to compare all pairs of joints looking for signs of healing.

In the real situation of scoring the observer sees all joints of hands and feet which can help to distinguish if time-point A or B is the first or the second film. If there are irreversible signs of progression in one film, i.e. subluxation, degenerative changes that cannot be seen on the other film, it must be the second radiograph. This analysis, however, is also time consuming.

The question is if and to what extent healing can be captured by existing scoring methods; if this is not the case we have to consider if healing adds so much important information in addition to scoring that it has to be evaluated separately or the scoring methods be changed to capture healing. A decrease in the size of an erosion may be the most important criterion for repair. If this occurs, a change in the score should be possible with the van der Heijde modification of Sharp's method [18] and with the Ratingen score [19]. With both methods the size of the erosions [18] or the percentage of the eroded joint surface [19] is taken into account. But the decrease in size of the erosion must be large enough to change the score on the ordinal scale. With the original Sharp system [8] where only the number of erosions is counted, the score can only decrease if the erosion is completely filled in and does not exist anymore. Healing phenomena without changing the size of the erosions - recortication, normalization of the subchondral bone structure, sclerosis, osteophyte formation - will not be captured by scoring systems, because assessment of these phenomena is not part of the scoring systems.

Negative change scores have been reported in a certain proportion of patients after one year of treatment with infliximab [23], etanercept [22,48], adalimumab [49]. Negative change scores may be the result of measurement error. However, if the negative change score is greater than the minimal detectable change representing the measurement error of the method it is likely that negative change scores indicate true healing.

So far, the radiographic results of clinical trials were presented as mean values. Even if repair occurred, the amount of progression (positive change scores) may have over-weighted the amount of improvement (negative change scores) resulting in positive mean scores indicating progression on a group level. The results of recent trials with biologics [22-24] demonstrated very little or even no increase in the mean score. In addition, most study reports indicated which proportion of patients had no progression or even a decrease in the score. The recently introduced probability plot [51] (Fig. **4**) where the change scores of all individual patients are plotted allows to see immediately how many patients show what amount of progression and what amount of improvement. Recently, the first trial was published where the mean progression rate was negative with the confidence interval also being below zero [52]. This is the first evidence of repair overweighting progression in a clinical trial. It is an astonishing result since we have to keep in mind that repair is still underestimated with the scoring methods currently available. Moreover, only joints having erosions can demonstrate repair, while essentially every joint of a patient can be the subject of progression.

It is not yet clear if and how healing could be integrated into existing scoring methods. Until now, healing can only be reported in addition to scoring; for example, we could count the number of joints with healing in relation to the total number of joints with erosions. We even don`t know if healing should be regarded as an important independent outcome measure indicating an active process towards normalization of joint structure or if halt of progression is a sufficient outcome information.

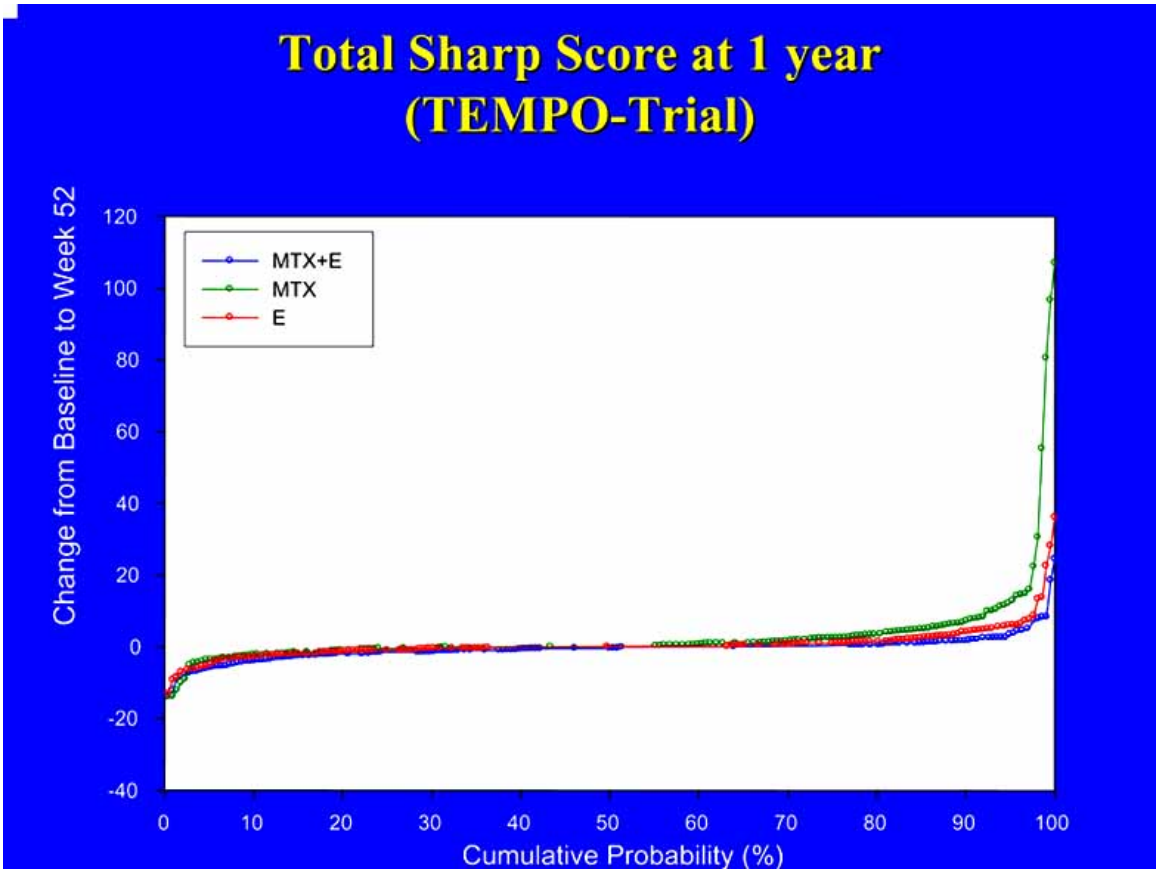

Fig. (4). Probability plot of change scores of the 3 treatment groups of the TEMPO trial (52): Most patients demonstrate no or only minor change while approximately 5-10% show improvement (negative change scores) and up to 20% show progression, more so in the MTX group (from the Wyeth Enbrel™ slid kit).

Until recently there were doubts of internationally leading experts if healing or repair really exists. It was of great merit, therefore, that John Sharp and Desiree van der Heijde initiated a subcommittee of the OMERACT (Outcome measures in rheumatoid arthritis clinical trials) imaging committee. It includes international experts interested in this field and started to perform several exercises as an "attempt to confirm whether healing occurs in rheumatoid arthritis, and if so, to determine how healing should be assessed" [53].

After general discussions about the implications of healing the committee members evaluated 28 pairs of images of single joints, 14 cases showing progression and 14 showing improvement in a randomized double blind study. Most committee members were able to determine correctly which joint was better. There was also a good agreement concerning the relative size of the erosion. Since the second films were always judged to be better in the cases demonstrated as examples of improvement, it was concluded that healing or repair of erosions really exists [53].

While there was a good agreement concerning the relative size of erosions, agreement regarding the morphologic features of bone repair (re-cortication, filling-in, sclerosis, restoration, re-modeling) was not impressive. This was - in part - due to a lack of agreement on the meaning or definition of these terms. The correct sequence of the films could be determined only by 65% of the committee members, more frequently, however, by committee members with greater experience in scoring. In images representing examples of healing, morphological features presumably indicating bone repair were much more pronounced than in images representing examples of progression [54].

In March 2004 John Sharp organized another workshop of the subcommittee at Bioimaging in Newtown/Pennsylvania. A small number of experts experienced in scoring and evaluating healing discussed the morphologic features of repair and their definitions agreed upon at the OMERACT conference in 2002 (Omeract 6). Thereafter, 64 pairs of single joints taken at 2 time-points showing improvement, no change or deterioration were evaluated in a randomized double blind exercise by seven readers. The readers had to score which film was worse, which erosion was larger, which film was first and if there were specific features of repair in one or both images, i.e. filling-in, re-cortication, sclerosis, re-modeling, reconstitution of a normal joint, trabeculation. This was a very complicated exercise, since a large number of questions had to be answered at the same time and, somewhat confusingly, for both time points. For example, cortication or trabeculation or restoration had to be stated even if it was clear to the observer that this was a completely normal joint seen at baseline. This exercise was repeated the next day after a new randomization displaying not only the index joint but the whole hand or foot to assess whether the determination of the time sequence of the films was facilitated by considering the other joints.

Later, the pairs of images of whole hands and feet were scored independently by two other investigators using the van der Heijde modification of the Sharp score [18]. This exercise has been done to answer the question what proportion of healing in single joints is captured by regular scoring and to what extent negative scores represent healing. The exercises also hopefully will answer the question how much agreement exists between the investigators regarding the morphological features of healing and if these are reliable indicators of repair.

Although healing has been described and still is primarily a morphological feature as seen on conventional radiographs (CR), some readers might wish to get a (very brief) statement in this review about the relation of "healing" to the modern imaging techniques, MRI and sonography. Final statements about these methods are not possible yet, since both methods are still developing. Both are different imaging techniques, and some features indicating healing with CR cannot be identified. For example, with MRI the cortical plate gives no signal and the structure of the subchondral bone cannot be analyzed. An advantage of MRI as a multiple planar method is the possibility of a 3-dimensional assessment with an estimation of the erosion volume. The number of (small) MRI erosions - whose relevance is not yet completely established - is larger than that seen on CR, especially in the wrist. In part this has to do with the fact that MRI is a tomographic method and evaluation of erosions on CR is especially difficult in the wrist because of the large volume of the bones and overlapping of different bones. It might be difficult in follow-up studies to reproduce exactly the same planes and to compare the erosion size at different time points. Progression in the number (not the size) of erosions could be documented [55-57]. Several cases have been shown where erosions appear to have "filled in", but it is not known for sure if this is simply fat or true bone (**Peterfy**, Personal communication 2006). CT of the same region may be helpful for clarification. So far, systematic studies on "healing" have not been performed with MRI (**Charles Peterfy** - Personal communication).

The advantage of sonography is that joints can be examined in multiple planes enabling the investigator to detect more and smaller erosions earlier (as with MRI) than with CR [55,58,59]. Small disruptions of the cortical plate (which is the definition of an erosion) may also be identified. The disadvantage of sonography is the user dependence of the method, the lack of standardization, the difficulty to reproduce the same plane at follow up investigation and to be able to really compare the same erosion at different points in time. As with MRI, an evaluation of the bone structure is impossible. In long-term studies up to 7 years` duration a steadily increase of erosions was counted although disease activity could be substantially suppressed. I suspect that many of the erosions seen with time were already inactivated, that means they were meaningless "scars". I am not aware of follow-up studies looking especially for repair in RA.

In comparison to conventional radiography the main advantage of both, MRI and sonography, is the far better portrayal of soft tissue changes representing inflammatory disease activity, the main disadvantage is the insufficient portrayal of bone structure.

CONCLUSION

Healing or repair in RA detected on radiographs is a reality. Different observers agree in the identification of healing. They also agree in the identification of improvement if radiographs are seen in random order. Healing could be diagnosed without knowing the sequence of the films in one study, not convincingly so in another study. With getting more familiar with signs of repair experts hopefully will agree better in detecting features of improvement. Since healing in an individual joint can be observed only after active inflammation has discontinued for several months, it might be regarded as a good additional outcome measure in RA clinical trials.

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Received: March 30, 2006 Revised: June 23, 2006 Accepted: August 23, 2006