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Repair of Erosions in Rheumatoid Arthritis Does Occur. Results from 2 Studies by the OMERACT Subcommittee on Healing of Erosions

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ABSTRACT. The committee was charged with determining whether healing of erosions in rheumatoid arthritis (RA) occurs. Two exercises were performed: The first asked the committee members, as a panel of experts, to express agreement or disagreement with the presence of improvement and features of bone reaction to injury in images submitted by members as examples of healing. The second presented panel members with 28 pairs of serial images, 14 chosen to illustrate progression and 14 chosen to illustrate repair. Agreement was tested on 8 items: global judgment on which image in the pair was better, relative size of the erosion in the 2 images, judgment on which image was first, presence and extent of sclerosis, cortication, filling-in, remodeling, and reconstituting normal structure. Our results showed good agreement, among the 15 respondents, on global assessment of which image was better and which image showed the smaller erosion. Correct assignment of sequence was only slightly better than expected by chance (in 65% of the cases). Agreement was poor regarding the presence of morphologic features of bone repair. A majority of a panel of experts agreed on which 2nd images in a set of paired, serial images represented improvement and which showed progression based on global assessment of which was better and on size of erosion. Features of bone repair were not distinctive and did not enable the panel to deduce the correct sequence of the serial images. This study provides evidence that repair of bone damage in RA does occur, resulting in some degree of improvement, which was recognized by a majority of a panel of experts. (J Rheumatol 2003;30:1102–7)

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EROSIONS HEALING RHEUMATOID ARTHRITIS RADIOGRAPHIC ANALYSIS

Two lines of evidence support the hypothesis that bony erosions in rheumatoid arthritis (RA) may exhibit some degree of healing or repair when treatment effectively controls the inflammatory process. First, a few case reports and small series have presented convincing evidence that improvement in erosions occasionally occurs[1-8]. Second, negative progression scores have been seen in recent controlled trials[9-11], and in some, have been documented to exceed the smallest detectable difference. However, some of the reported cases have not been entirely convincing; artifacts and positioning changes have not always been easily excluded from the published radiographic reproductions and

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at times the reproductions have not been printed with appropriate resolution and hence lack convincing detail. Further, the reported series at times are a mixture of questionable cases along with those that appear to be convincing. It may not be possible for the critical reader to distinguish artifact, poor reproduction, and the natural tendency to overdiagnose newly reported phenomena, in these instances rendering the entire report less than completely convincing.

Several therapeutic agents that have been effective in slowing radiographic progression and that have shown negative progression scores have been introduced[9-11]. The findings renewed interest in healing; therefore, 2 years ago, we started a subcommittee of the OMERACT Imaging Committee to first attempt to confirm whether healing occurs in RA, and if so, to determine how healing should be assessed. Members were chosen to represent multiple imaging modalities including plain film radiography, magnetic resonance imaging, and ultrasound, with the main emphasis on experienced readers of serial plain films. Two individuals with considerable expertise in bone morphogenesis were also appointed to the committee. Although not selected to represent geographic areas, the committee is international. The initial charge to the committee was to determine whether healing occurs in the course of currently available treatment and whether any morphological features distinguish the healing process.

After an initial meeting in which issues related to definitions of healing and radiographic features of healing were discussed, a pilot study was set up to provide hands-on experience examining images of putative healing submitted by several committee members. In carrying out the pilot study committee members evaluated images for the presence of features that had previously been agreed upon as representing the repair process. After the results of the exercise were available and discussed by the committee, a workshop was held in which there was a lengthy discussion of many of the images in the exercise, regarding interpretation of the specific features of repair. During this session the committee reached a consensus on definitions of bone morphology that were considered to represent repair of injury. It was decided that further study to obtain definitive answers to several central questions was feasible. The immediate further objectives were to determine whether a panel of experts presented with pairs of randomly ordered control and putative healing cases would agree on: which of the 2 images of a damaged joint was better by global assessment, whether there was any change in size of erosions in serial films and what the direction of change was, which morphological features of bone repair were present/absent, and which if any of these features were unique to the repair process. The specific morphologic features to be examined included sclerosis, cortication of the eroded region, filling-in of the erosion, and remodeling and reconstitution of normal structure.

METHODS

In the initial pilot study 3 members of the committee contributed digitized images that they considered demonstrated some degree of bony repair. The images were cropped to include one joint of interest and one or 2 adjacent joints to allow evaluation of whether hand or foot position changed between films. The cropped images were randomly ordered within sets that consisted of 2 to 6 serial examinations. A report form was constructed. Eleven members of the committee submitted results. The contributors of the image sets and the organizer were included in the review of results. Since all members of the panel had already seen most or all of the images used in the exercise and no control images were included, it was not considered that clear answers would be obtained to many of the questions; rather, the study would give an indication of how well the members of the panel agreed on radiographic features of putative healing cases and would provide some indication of whether further pursuit of the issues by these methods was likely to provide useful information. After the initial review of the contributed images and the workshop, 2 images per patient were selected for further review. These were randomized again for sequence of images, given new record numbers, and circulated to the panel a second time with the request that the panel not refer to the previous distribution. The full hand or foot view was provided to the panel to review for their interest and study after completing the exercise.

After completing the first exercise and deciding that additional study could provide answers to the questions posed, a randomized, controlled study was carried out. One member of the committee set up the exercise and was subsequently barred from including data on reading of images. No image had been seen previously by 14 of the 15 members of the panel. The exception was one member of the panel who had participated in a randomized controlled trial in which some of the images were included but had not seen any of the images presented in the way the study was set up. Multiple examples that were judged to demonstrate either definite progression or improvement in an erosion in the hands or feet were selected. Examples of erosion improvement were solicited from a number of sources, but the poor response suggested that such cases are infrequent. Examples were successfully found by reviewing those film sets with negative progression scores in 3 extensive databases with baseline and 3–5 year followup films, having altogether 900 or more cases. No attempt was made to examine all the films in these sets. In this search 30–40 pairs of films showing improvement were selected initially. A similar number of cases exhibiting progression were found easily in the same databases. Fourteen pairs of films showing improvement and a similar number showing progression were finally selected as the most definite examples and the best quality of digital images without features in adjacent joints that would serve to identify the sequence within the pair. Images

were cropped to include only the joint of interest and one or 2 adjacent joints, to allow the reviewer sufficient image to evaluate rotation and positioning of the hand or foot. Images were presented to the panel as pairs that had been randomized within pairs for sequence, and between pairs for progression or improvement. Reviewers were told that the exercise contained cases of both progression and repair, but were not informed of the number of each type. The average interval between films for the entire set was 2.6 years, for progressor and repair groups 2.5 and 2.6 years; the minimum interval was 0.5 years (0.5 and 1); the maximum was 4 years (4.1 and 3.2).

A report form was developed as an EXCEL worksheet for reviewers to record their judgments regarding 8 items as follows: global evaluation of erosion in image A as better, worse, or the same as in B; the erosion size as smaller, larger, or the same in image A compared with B; the sequence of the 2 images as first, second, or unable to determine; findings of sclerosis, cortication, and filling-in of the erosion and remodeling as absent (0), minimal (1), moderate (2), or extensive (3); and reconstitution of normal architecture reported as absent or present. Respondents were instructed to fill out all items in the report form leaving no blanks. Scales for judging items were not defined; instead, reviewers were instructed to use the scale to indicate the relative extent of the items within pairs in case a feature — for example sclerosis — was found in both images. Analysis of data was carried out using an EXCEL spreadsheet (Microsoft Corp., Redmond, WA, USA) and STATA statistical programs (Stata Corp., College Station, TX, USA). The accuracy of determining the sequence within each pair was examined by determining the average accuracy for each respondent and the average for all respondents. The unweighted kappa statistic was calculated to assess agreement between the panel members for 7 of the items reported, excluding only sequence. In the initial analysis of the morphological features of repair (all items excluding global appraisal, size, and sequence) data from all respondents were included. In further analysis, data were stratified in 2 ways: First, respondents were assigned to one of 3 groups: (A) members of the panel who had reported cases of healing erosions, (B) members who regularly scored therapeutic trials and observational studies or reviewed diagnostic bone and joint films on a full-time basis, and (C) members who had less extensive experience. Second, data were stratified according to whether the case had been selected originally to demonstrate progression or repair.

RESULTS

In the pilot study there was a trend for agreement (kappa 0.36) on which image was better when the exercise was repeated using only 2 images per patient and thus providing a more limited comparison. Agreement on morphologic features of bone repair was not impressive (kappa values ranging from 0.10 to 0.26). After completing the exercise and workshop it was agreed that more clear definitions for the morphologic features were needed for the next study. A consensus on definitions for the morphologic features of repair was achieved as follows:

Sclerosis: Increased density of morphologically normal bone within or on the edge of an existing or previous erosion.

Cortication: The generation of a continuous and smooth white edge on the surface of an erosion.

Filling-in: Diminishing of the volume of the erosion.

Remodeling: New bone formation in a previous or existing erosion resulting in a revised, smooth shape of the bone that more nearly approaches the normal shape.

Restoration: The return to radiographically normal architecture.

It was also agreed that in a future study the panel should be asked to make a judgment on whether the size of the erosion changed between the serial images.

In the controlled study — exercise 2 — there was substantial agreement on global assessment as to which joint image was better (kappa 0.47) and on the relative size of the erosion (kappa 0.56; Table 1A). When the data were examined for differences among readers with different experience, group A, with the most experience reviewing images exhibiting putative healing, showed better agreement for size difference and for better/worse assignment; however, the groups are all small and there was no scaling among the

Table 1A. Kappa statistic for reported variables, all readers

Variable	Kappa
Size difference	0.56
Better/worse assignment	0.47
Sclerosis	0.12
Cortication	0.08
Filling in of erosion	0.17
Remodeling	0.10
Reconstitution normal	0.05

Table 1B. Kappa statistic for reported variables, readers by new groups.

Variable	Kappa Group A	Kappa Group B	Kappa Group C
Size difference	0.79	0.45	0.47
Better/worse assignment	0.77	0.22	0.62
Sclerosis	0.09	0.20	0.07
Cortication	0.09	0.07	0.05
Filling in of erosion	0.26	0.17	0.05
Remodeling	0.22	0.22	0.04
Reconstitution normal	0.06	–0.04	0.13

Group A: experts familiar with reading films for healing; Group B: experts reading films regularly for clinical trials or observational studies; Group C: less extensive experience

3 groups with different levels of experience. Agreement on presence of morphologic features of bone repair was poor (Table 1B).

Assignment of sequence by the respondents (Table 2) agreed poorly with the correct sequence, although the average correct assignment of 18.2 of the 28 pairs was slightly better than 14 correct responses expected by chance alone. When the level of experience was considered, the 5 readers in group A (experts) accurately assigned sequence more often than the other groups, and the agreement with the correct assignment scaled parallel with experience. However, the difference in the 3 groups was not significant. When the cases were divided according to whether they were chosen for exhibiting progression or repair, the cases chosen for progression were more frequently assigned the correct sequence and the difference between the 2 subsets was significant.

When correct sequence of images was used in combination with the majority view of the panel as to which image was better, there was 100% agreement on whether the case was selected to represent progression or repair. For example, if image A was the image taken at an earlier date and it was also judged by the majority as better, then the pair of images had originally been selected to show progression; moreover, with all the possible combinations of judging better/worse and correct sequence, the combination corresponded to the selection category of progression or repair. Thus, per case, between 53% and 93% of panel members agreed on the better/worse choice, so that in all cases there was agreement by a majority of the panel on the selected category. By applying a stricter rule that two-thirds of the panel needed to agree, 27 out of 28 pairs were still in agreement. If 80% of the panel were required to agree, 19 of 28 cases had the same better/worse agreement. Per-panel member correct assignment of sequence for the 28 pairs varied from a low of 8 to a high of 25. Three individuals correctly assigned 14 or fewer pairs; 3 assigned 22 or more.

Since scoring of morphological features was included in the exercise primarily to enable the readers to indicate changes in features between serial films, the change in scores was examined. Change in score was calculated by subtracting the score for the first image from that of the second. The change in score was averaged across all readers for all image pairs in each subset, i.e., pairs selected to illustrate progression or repair. Except for sclerosis the average score was greater for all paired images selected for illustrating repair if the image's true date indicated it was the later of the 2, while it was greater in the first image by true date if the pair had been selected as illustrating progression (Table 3A).

Thus, on average, the better image was judged to show morphological features of repair. However, in all but 2 instances a majority of scores showed no change between the images (Table 3B). When the average score of all readers for the morphologic features was tabulated by the majority of respondent judgment of erosion size, the scores were higher for the image considered to be the smaller, except for sclerosis (Table 4). Tabulating scores by respondent assign-

Table 2. Accuracy in assigning sequence to 28 pairs of images.

	Accurately Assigned
All readers, all cases	18.2 (65%)*
Group A (5 readers), all cases	20.8 (74%)**
Group B (6 readers), all cases	18.3 (65%)**
Group C (4 readers), all cases	14.8 (53%)**
All readers, 14 pairs selected for showing progression	10.7 (77%)***
All readers, 14 pairs selected for showing improvement	7.5 (53%)***

Group A: experts familiar with reading films for healing. Group B: experts reading films regularly for clinical trials or observational studies. Group C: less extensive experience. * Significantly different from chance alone (i.e., 14 (50%) accurately assigned); ** not significantly different (ANOVA); *** significantly different between progression and improvement sets; progression set significantly different from expected; repair set not significantly different from expected.

Table 3A. Average change in repair features score between image a and b.

Repair Feature	Image Pair Selected to Show: Progression	Repair
Sclerosis	0.24*	0.30*
Cortication	–0.24	0.58
Filling in	–0.57	1.03
Remodeling	–0.28	0.58
Restoring normal	–0.28	0.22

* Average difference in feature scores subtracting the 1st from 2nd image score using the true date of the images. A positive number indicates that there was a higher average score in the 2nd image than in the 1st, a negative number indicates the opposite.

Table 3B. Change in score for features of repair.

	No çhange*	Negative*	Positive*
Sclerosis			
Progression	122	22	66
Repair	107	28	75
Cortication			
Progression	138	45	27
Repair	93	21	96
Filling in			
Progression	138	64	8
Repair	64	14	132
Remodeling			
Progression	163	41	6
Repair	112	9	89
Restoration			
Progression	162	45	3
Repair	167	9	34

* 15 readers scored 14 paired images chosen to demonstrate progression and 14 pairs chosen to demonstrate repair for each of the features. Data are numbers showing no change, a decrease in score between the earlier and followup films (Negative), or an increase in score (Positive).

ment of better or worse also resulted in a higher score in images judged to be better, with the exception of sclerosis.

DISCUSSION

The data demonstrate good agreement among a panel of experts on which image is better and on the size of erosions when comparing 2 images chosen to show a definite difference. The panel as a group was not able to determine which was the first image by true date. Correct assignment of sequence for the 28 pairs varied from a low of 8 to a high of 25. When sequence assignment was examined by panel subgroups, the 5 individuals with the most experience in reporting healing phenomena did better than those with less experience, but the difference was not significant. Because there were such small numbers in each group of readers, it cannot be determined whether this represents random variation or reflects the greater experience of the expert group (group A). If this is a result of the greater experience, then more training is indicated for individuals selected to evaluate films for evidence of repair. However, all members of both groups A and B had extensive experience reading films for erosions and all members of group C regularly used films in case evaluations in practice, in clinics, or on consulting rounds. In a report with observations similar to this study 3 observers from the same clinic agreed 89% of the time in judging which of 2 index joints was better when presented with images of the entire hands, wrists, and feet blinded for sequence by a colleague[11]. The image set consisted of 24 cases selected as demonstrating improvement in 74 joints and 10 cases selected for progression by the same colleague.

When the morphological features of bone repair (which hypothetically might be specific for repair) were examined, there was poor agreement among panel members, with no indication that greater experience enabled better recognition of these features. Further, if any radiographic feature were specific for repair and the experts regularly recognized that feature, experts should have been able to identify which pairs were selected to represent progression of erosions and which to represent repair. Recognizing such a feature would have enabled them to easily deduce the correct sequence. Performance in assigning correct sequence was only somewhat better than would be expected by chance, although the findings were statistically significant and did scale for the 3 groups of experts based on experience.

Table 4. Average change in features scores according to respondents judgment of size*.

	Image A Judged by Respondents to Be: Smaller**	Larger
Sclerosis	0.05	0.15
Cortication	–0.33	0.53**
Filling in	–1.36	1.82**
Remodeling	–1.13	1.41**
Restoration	–0.26	0.23**

*Smaller and better were completely concordant using the majority rankings for each pair. **Average difference in feature scores subtracting the 1st from 2nd image score by true date of images. A positive number indicates that there was a higher average score in the 2nd image than in the 1st, a negative number indicates the opposite. ***Significantly different compared with smaller.

Because of the small numbers it is not certain whether the lack of significance between the 3 groups of respondents is due to variation in responses or whether lack of significance would be confirmed in surveying a larger number of readers. Perhaps this finding is an indication that more training would improve performance.

The score of the panel as a group was higher for judging the morphologic features, except sclerosis, in the image judged to be smaller and better, regardless of whether this image was presented as image A or B. Sclerosis was found almost as frequently in each image of the pairs. When image pairs were segregated for whether they had been selected to illustrate progression or repair, the morphological feature scores reflected finding more of each feature in the smaller or better image, except for sclerosis.

The poor agreement on the morphological features of bone repair is an indication that these features were not sufficiently clear on these images to be recognized regularly by the panel. This is supported in that a majority of the panel found no change between images in the pairs for all features, except cortication and filling-in, among image pairs selected for illustrating repair. The linkage to the better and smaller image suggests that judging the extent of these features is strongly influenced by the size of the erosion and respondent's global assessment. Cortication, filling-in, normal structure, and perhaps some aspects of remodeling are present in the normal joint, so there would be more of these features in the first image in pairs of images representing progression. That was the case in our study. The respondents were unable to distinguish the normally corticated margin from the recovery of cortication in a previous erosion. Similarly, filling-in, remodeling, and normalization were not distinctive features of bone repair. Thus there are no radiographic features in this set that were identified by a majority of readers as distinguishing progression of erosion damage from repair. That result does not diminish the significance of agreement within the panel on which image was better. More relevant is the question, how significant is that agreement? Does agreement by a majority of a panel of experts rule out the possibility that technical factors that are not discernible in the image pairs account for the differences read as improvement? At this point we simply do not know, but clearly the majority opinion of the panel is the best standard available. If we apply a stricter rule than the requirement of a simple majority of the panel and require a two-thirds majority, there is still agreement in 27/28 cases. Confirmatory examination by 2 or more modalities, including at least one 3-dimensional imaging technique,

would greatly strengthen the conclusion, but at the present time this is not available on an appropriate set of patients. One small step has been taken in this direction; many more are needed[10].

Since the beginning of the deliberations of the Subcommittee on Healing there has clearly been irreconcilable disagreement on the definition of healing. Some considered that healing means complete restoration of normal contour and structure, even in severely damaged joints. Others argued that healing of other kinds of wounds and injury regularly leaves a scar and in that context healing does not indicate restoring pristine normality. Without agreement on a definition of healing the committee recommends using the term "repair" to indicate improvement in an erosion. Since no case reports support complete restitution of a severely damaged joint, it is postulated at this time, with current therapy and incomplete knowledge of bone growth and repair, that complete restoration of normal structure of severely damage joints does not occur. The findings in our study provide strong evidence that repair of bone damage in RA does occur, with effective treatment resulting in some degree of improvement that is recognized by a majority of a panel of experts.

The finding of improvement, even though limited, has implications for future observational studies and therapeutic trials. First, it should be emphasized that this set of study pairs was selected for demonstrating definite progression or definite improvement from an unknown number of cases. A large number of serial radiographic films were reviewed to select the 14 cases of improvement used. However, the review process did not systematically evaluate all films to exclude improvement in those cases not selected, so that the actual denominator for the 14 cases is unknown. However, with the favorable effects of today's therapy, only a small proportion of patients in the usual clinic setting show radiographic progression during a one year interval[9,11], and the non-systematic search of films found the number of examples showing improvement to be much lower than those showing progression. In spite of this expected low frequency of improvement, as rheumatologists study new agents and new combinations of existing ones in order to find therapeutic regimens that will induce better responses and more remissions, it is important to be prepared to evaluate radiographic images for evidence of erosion repair when it does occur, in a reproducible manner.

As conclusive as this study appears to be, it does not follow that a simple recording of extent of improvement, recognized in serial films read blinded for sequence when combined with the correct sequence, will produce useful data. If films are read with sequence known to the reader, bias could influence the scores favoring progression, since progression is far more common than improvement with current therapy. Progression is expected in patients who are not in complete remission, in whom remission is infrequent and improvement in erosions occurs at an unknown rate — presumably only with complete remission. Moreover, agreement by the panel on improvement and on relative erosion size was not 100% when assessing this set of images selected as definite cases. Although there was complete agreement between the majority of reviewers on global assessment (better/worse) and on the category the image pair was selected to represent (progression or repair), a significant number of judgments would not have agreed with the majority opinion found here if only one, 2, or 3 readers had evaluated the images. Although better agreement among readers might have resulted if the images had been selected by unanimous opinion of a panel of experts, this would only have eliminated cases that fall in the "gray" area. Given that in future trials and in clinical practice many cases will fall into a gray area, a reliable method for scoring erosion repair in therapeutic trials and longterm observational studies is a large challenge now facing the rheumatological world.

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