Prognosis of 5-year Radiographic Erosions of the Wrist According to Early, Late, and Persistent Wrist Swelling or Tenderness in Patients with Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether early inflammatory activity in the first year of disease compared to persistent or later occurrence of swelling or tenderness in the wrist joints is associated with 5-year erosions in the same joint in patients with early rheumatoid arthritis (RA).

Methods. A cohort of 195 patients with early active RA was enrolled in the Finnish RA Combination Trial. Swelling and tenderness of wrists were assessed at baseline and at 3, 6, 12, 24, 36, and 48 months. Radiographs of the wrists were taken at the baseline and at 5 years. The 237 wrist joints of 125 patients without erosions at baseline were classified according to wrist swelling, i.e., I: never swollen; II: swollen during first year only; III: swollen during the second to fourth year only; and IV: swollen during the first year and followup, and similarly according to tenderness.

Results. Thirty percent of the wrists were never swollen in all clinical examinations; 43% were swollen only during the first year; 11% were not swollen in the first year, but were swollen at some time during 24–48 months; and 16% of wrists were swollen during the first year and at some time during 24–48 months. At 5 years, 64% of 237 wrists remained free of erosions. Erosions developed in 82% of wrists that were swollen during both the first year and 24–48 months, versus 56% of wrists that were not swollen at first year but were swollen during 24–48 months, 31% of wrists that were swollen during the first year only, and 11% of wrists that were never swollen. Similar results were seen for joint tenderness.

Conclusion. Wrist swelling during the first year only is associated with less future wrist radiographic damage than persistent swelling or swelling only during the followup. Our results emphasize the value of early and continuous suppression of inflammatory activity in early RA. (First Release Nov 1 2006; J Rheumatol 2007;34:50–3)

Key Indexing Terms:
RHEUMATOID ARTHRITIS RADIOGRAPHIC EROSIONS
JOINT COUNT SWELLING TENDERNESS

Joint swelling is the most characteristic feature of rheumatoid arthritis (RA), and persistent joint swelling is associated with subsequent development of joint destruction[1-4]. Rheumatologists agree that the inflammatory process leads to joint destruction and that suppression of inflammation in individual joints slows or prevents cartilage loss and joint erosions[4-6]. However, certain recent studies suggest that inflammation and destruction might be uncoupled[6-8], and that clinical inflammation and joint destruction result from at least partly different mechanisms.

Our previous studies indicate a dose-response relationship between inflammation and subsequent erosions in wrists of patients with RA[3,4]. However, relatively few data are available on whether early or later occurrence of clinically detectable joint swelling may be associated differently with development of future erosions. Therefore, we compared erosions in the wrists 5 years after baseline in patients with early RA according to prior evidence of wrist inflammation. We were particularly interested in comparisons of patients with early inflammatory activity in the first year of disease whose inflammation was controlled after the first year with patients who had persistent inflammation or control of inflammation during the first year but not 2–4 years after baseline.

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MATERIALS AND METHODS

From April 1993 to May 1995, a total of 195 patients with early RA (symptoms < 2 yrs; mean 8 mo) were enrolled in the Finnish RA Combination study (FIN-RACo) and randomized to receive combination therapy of disease modifying antirheumatic drugs (DMARD) including sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone or monotherapy, initially with sulfasalazine, with or without prednisolone[9]. Adjustments of the treatments were performed according to the protocol with a goal of remission. After 2 years, the treatment strategy was no longer restricted. The details of the study have been described previously[9].

The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and ethics committees in all participating hospitals. All patients gave written informed consent.

Clinical examinations were performed at the baseline and at 3, 6, 12, 24, 36, and 48 months, and included assessment of joint swelling and tenderness according to a 66/68 joint count. To analyze whether early compared to later inflammation of a single joint is more meaningful concerning future erosion, we divided clinical observations of inflammation of the wrist into 4 groups: I: never swollen; II: swelling during first year only; III: no swelling during the first year but swelling in the second to fourth year; and IV: swelling during the first year and during the followup. Observations of wrist tenderness were classified similarly.

Radiographs of the wrist joints were taken at baseline and at 5 years, and were scored by an experienced radiologist (LL) according to the Larsen method[10], with a score of 2 to 5 indicating erosions. This analysis included 125 patients who had 237 wrist joints without erosions at baseline.

Statistical analysis. Comparison of the presence of erosions at 5 years in different groups was analyzed using generalized estimating equations models with an exchangeable correlation structure. This model deals with the issue of a patient having 2 wrists. We did not include any other adjustments in the analyses.

RESULTS

One hundred twenty-five patients had 1 or 2 wrists with no erosions at baseline and were included in the analyses. The mean (SD) age of the patients was 48 (9) years, 62% were female, and 71% had positive rheumatoid factor.

At baseline, 43% of the wrists were swollen and 35% were tender. At 3, 6, 12, 24, 36, and 48 months, 22%, 12%, 16%, 18%, 17%, and 15% of the wrists were swollen, and 35%, 22%, 23%, 20%, 19%, and 20% of wrists were tender, respectively.

Swelling was never seen in 71 of 237 wrists (30%), and was seen at some time during the first year in 102 (43%) wrists. Further, swelling was not seen during the first year, but was seen at some time during 24–48 months in 25 (11%) wrists, while 39 wrists (16%) were swollen at some time during the first year and during 24–48 months. The corresponding figures for tenderness of the wrists were 45 (19%), 109 (46%), 22 (9%), and 61 (26%), respectively.

At 5 years, 64% of wrists remained free of erosions. Erosions developed in 82% of wrists that were swollen during the first year and the followup, versus 56% of wrists that were not swollen during the first year but were swollen at 24–48 months, 31% of wrists that were swollen during the first year only and not swollen at 24–48 months, and 11% of wrists that were never swollen ($p < 0.001$; Figure 1A). Similarly, erosions developed in 66% of wrists that were tender during the first year and the followup, versus 55% of wrists that were tender only during 24–48 months, 28% of wrists that were tender only during the first year, and 7% of wrists that were never tender ($p < 0.001$; Figure 1B).

DISCUSSION

Our results confirm and extend observations in the previous reports that persistent clinical activity is associated with development of erosions in previously unaffected joints[3,4,11]. Our results also indicate that control of inflammation during the first year of disease does not necessarily prevent later erosions if swelling is seen during the second to fourth year after baseline. Indeed, there was a higher likelihood of subsequent erosions in such patients, compared to patients who had swelling in the first year that was controlled thereafter. Thus, a strategy to control inflammation as completely as possible over the course of RA appears to have value to slow or prevent longterm development of radiographic erosions.

It was documented many years ago that joint swelling and tenderness are only weakly associated with radiographic damage in cross-sectional studies[12]. Evidence of "uncoupling" of inflammation and radiographic damage may be seen in our present report, as 18% of patients whose wrists were swollen in both periods did not develop erosions. Further, 11% of patients who had no swelling at any evaluation developed erosions, echoing the observations of Molenaar, *et al*[13], who showed that progression of joint damage may occur in patients with RA who are in prolonged remission in clinical examinations. Although clinical examination is the most feasible tool to assess inflammatory activity in individual joints, it may not be sufficiently accurate, especially in long-standing disease, as a guide to clinical therapy. Indeed, there is evidence that asymptomatic synovitis without clinical signs of joint inflammation may exist in some patients with RA[14]. In long-standing disease, asymptomatic synovitis may have been present longer with higher likelihood of joint destruction compared to early RA. In the study by Molenaar, *et al*[13], the mean duration of disease at baseline was 7 years. Further, it may also be possible that the mediators of inflammation may be more active in clinically silent joints that already have some destruction compared to joints without destruction.

A further possible explanation for the finding that erosions developed in 11% of wrists that never showed swelling and 18% of wrists that never showed tenderness after baseline is that the activity of RA may fluctuate. These fluctuations may have a significant effect on the relationship between clinical joint inflammation and radiological progression[15]. At the time of examinations a joint may have no signs of inflammation, although between the visits there can be flares, or vice versa, although in general an association of inflammation with later erosions was seen, as found in previous studies[3,4].

Clinical examination is the most pragmatic assessment of joint inflammation, but is not the "gold standard." A clinical examination may not detect joint effusion that can be detect-

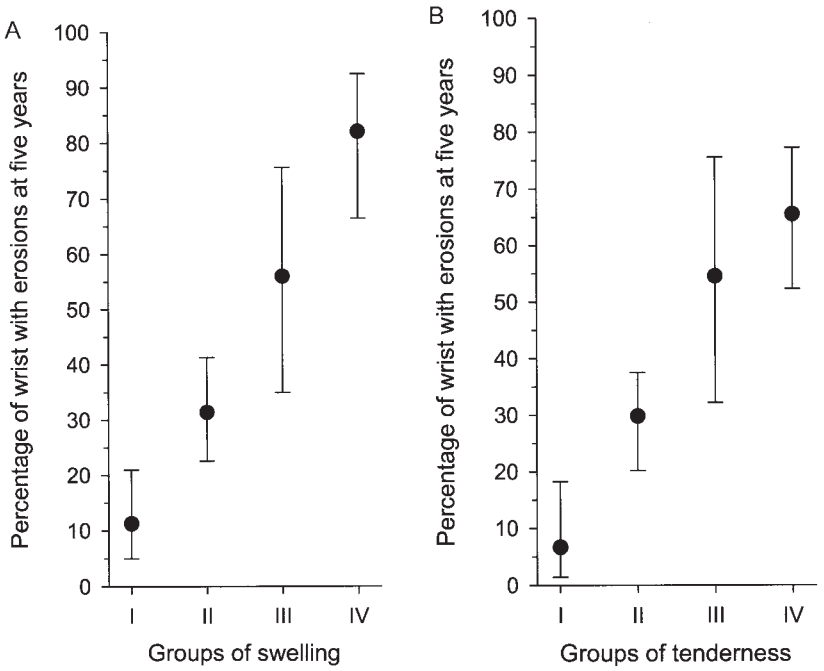

Figure 1. Percentage of wrists (95% CI) that developed erosions within 5 years in early active RA, according to the timing of inflammation: I: never, II: during the first year only, III: during second to fourth year only, and IV: during the first year and the followup.

ed by ultrasonography[16] and/or magnetic resonance imaging (MRI). These techniques are significantly superior to radiography of the hands, wrists, and forefeet to detect joint destruction in RA[17]. However, ultrasonography and MRI cannot generally be included in standard clinical care because of availability and costs. Therefore, careful examination of joints remains the most available tool to recognize joint inflammation in individual joints.

Historical RA cohorts indicated that the progression of joint damage is most rapid during the first years of disease[18-20]. Further, radiographic damage is progressive in most patients, with 30–50% of maximal erosion score over 20 years[19]. A lower rate of damage has been observed in recently reported RA cohorts[21,22]. In the Fin-RACo trial, only one-third of wrists developed any erosions over 5 years. These observations indicate better outcomes compared to previous decades, and confirm benefits of a combination of traditional DMARD in the treatment of early RA[23]. Further, our observations suggest that the value of a transient remission is questionable and is not a reason to reduce therapies.

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