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Radiographic remission in seropositive rheumatoid arthritis. A 20-year follow-up study

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ABSTRACT

Objective

Rheumatoid arthritis (RA) is in most instances a progressive disease. Very little information is available on halting of the radiographic damage, particularly in later phases of the disease. We studied radiographic remission of RA lasting to the end of follow-up, covering the period 1973-96.

Methods

Radiographs of hands and feet were taken at onset and at 1, 3, 8, 15 and 20 years from entry in 102 cases of recent onset (< 6 months) seropositive and erosive RA. A Larsen score of 0-100 was formed for 20 joints of hands and feet. If the score did not worsen by more than one point between one of the above time points and the end of the study, the patient was considered to be in remission.

Results

Remission was confirmed in 27 (26%) of the patients. In 3 cases the remission was from the 1-year check-up,in 5 from the 3-year check-up, in 6 from the 8-year check-up and in 13 cases from the 15-year check-up. Some of the remission cases had a mild disease from the outset, but there were cases in which the disease process had led to marked joint destruction before slowing down.

Conclusion

This data may serve as a basis for comparison with subsequent cohort studies on new treatments-of-choice.

Introduction

Rheumatoid arthritis (RA) is a chronic and in most instances progressive disease. Its long-term course and outcome are therefore difficult to evaluate (1). Erosions in peripheral joints, as seen on conventional radiographs, represent one of the most characteristic features of RA (2). Information on the radiographic progression of joint damage is derived from prospective and from cross-sectional studies. A number of inception cohorts have been followed for progression of radiographic changes for up to 5-10 years, but only limited data are available covering a period up to 20 years (3-6). Although continuous damage has been noted in most patients, there is great variation in the type of progression (6).

The Heinola Follow-up Survey of Arthritis is one of the very few studies on inception cohorts spanning a period up to 20 years. We have previously reported on the continuous progression of radiographic scores as shown by the mean values of all patients (4). We now studied progression in individual patients, paying special attention to those in whom progression had halted up to the end of follow-up period, i.e. who were in radiographic remission.

Patients and methods

During the years 1973-1975 a total of 117 patients with recent onset (less than 6 months) seropositive RA were recruited for study at the Rheumatism Foundation Hospital in Heinola, Finland. The selection criteria, data collection strategy and details of the patients have been described elsewhere (4,7,8). Follow-up examinations were made at onset and at 1, 3 , 8, 15 and 20 years from entry. The 102 patients (33 men, 69 women) with seropositive and erosive RA seen by KK at their 8- and 20-year check-ups comprise the material described here. One female patient had non-erosive disease; she was excluded from the study because her radiographic damage had neither halted nor progressed. A total of 82 out of the 102 patients attended the 15-year follow-up, and 67 patients the check-up at 20 years during the period 1995-1996; 28 patients had died and 7 could not participate because of severe diseases other than RA. The age at onset ranged from 17 to 70 years, mean 45 years.

Radiographs of the hands and feet were taken in the dorsovolar projection. In the evaluation of radiographs by KK during the years 1982-97 the Larsen score was used (9). Joints with only soft tissue swelling or osteoporosis were assigned Larsen grade 0. Joints with pre-erosive changes or marked joint space narrowing were assigned a Larsen grade of 1 (10). Joints treated by reconstructive surgery were assigned a Larsen grade of 5. Grades for the 1st to 5th MCP joints, wrists and 2nd to 5th MTP joints (20 joints) were sum-

Table I. Comparison of disease characteristics in patients with and without radiographic remission.

	Remission Median (IQR)	Progression Median (IQR)	P value
ESR (mm/h):			
Entry	26 (16, 38)	34 (18, 64)	0.09
8 years	18 (11, 34)	33 (19, 57)	< 0.001
20 years	16 (8, 23)	28 (19, 38)	< 0.001
CRP (mg/l):			
8 years	5 (1, 13)	17 (7, 32)	0.001
20 years	0 (0, 10)	20 (1, 32)	0.002
Number of swollen joints:			
Entry	5 (3, 9)	7 (3, 10)	0.60
8 years	2 (0, 5)	10 (3, 18)	< 0.001
Larsen Score (0 -100):			
Entry	0 (0, 2)	2 (0, 4)	0.02
8 years	8 (4, 29)	28 (17, 45)	< 0.001
20 years	16 (8, 36)	50 (36, 80)	< 0.001

Number of patients: entry and 8 years, remission 27 and progression 75; 20 years, remission 23 and progression 44.
Abbreviations: IQR = interquartile range.

Table II. Comparison of treatment with DMARDs and/or predisolone in patients with and without radiographic remission.

Time	Remission		Progression		P value
	No treatment N (%)	Treatment N (%)	No treatment N (%)	Treatment N (%)	
Entry	6 (22)	21 (78)	4 (5)	71 (95)	0.02
8 years	15 (56)	12 (44)	16 (21)	59 (79)	0.001
20 years	10 (43)	13 (57)	3 (7)	41 (93)	< 0.001

*Only NSAID or no treatment at all.

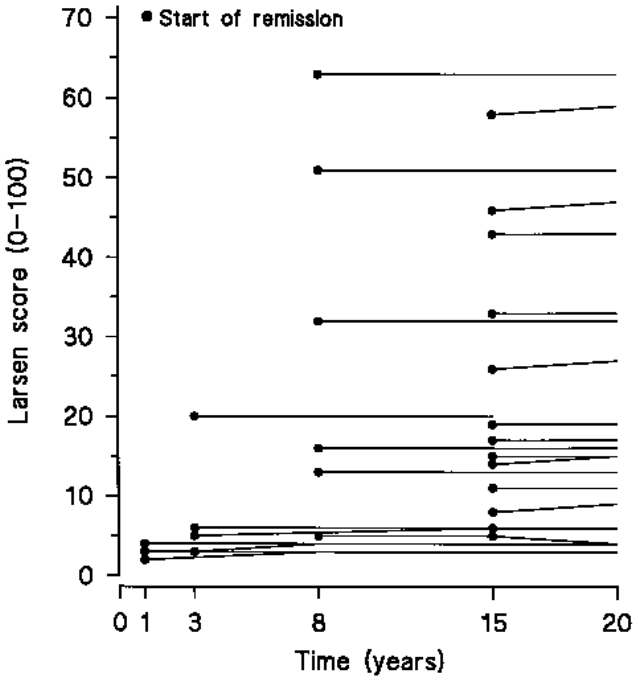

Fig. 1. Larsen scores in 27 patients with rheumatoid arthritis ending in radiographic remission over a 20-year period. Two patients had the same score of 5 at the 3-year check-up.

med to form a Larsen score of 0-100 (1, 4). Additionally, changes in the 1st to 5th PIP joints of hands were recorded. The patient was regarded as being in radiographic remission if the score did not worsen by more than one point between one of the above time points and the end of the study.

The erythrocyte sedimentation rate (ESR) was registered at entry and at the 8- and 20-year check-ups, and quantitive C-reactive protein (CRP) at the 8- and 20-year check-ups. The number of swollen joints was counted at entry and at 8 years. The 72 joints investigated were as follows: DIP, PIP of the hand and foot, MCP, wrist, elbow, shoulder, sternoclavicular, jaw, MTP, subtaloid, ankle and knee. Use of DMARDs and prednisolone was recorded at each check-up.

The results are expressed as the mean or median, and interquartile range (IQR). The Mann-Whitney U test and ^{2} or Fisher's exact test were used to compare patients with and without remission. No adjustment was made for multiple testing.

Results

Remission

One patient had the maximum score of 100 at both the 15- and 20-year follow-ups, but this was considered to be the ceiling effect of the method, especially as at the 20-year follow-up examination she was found to have secondary amyloidosis. One of the Larsen score 0-100 remission patients had a new erosive PIP joint. These two cases were not recorded as remissions. Thus, during the 20 years 27 (26%) of the 102 patients ended in radiographic remission, as shown in Figure 1. The Larsen score of 0-100 remained exactly the same in 20 patients and in 7 patients it increased by one point. In 3 cases the remission was from the 1-year check-up, in 5 from the 3-year check-up, in 6 cases from the 8-year check-up and in the remainder from the 15-year check-up. Four of the remission cases had died or were lost to follow-up prior to the 20-year check-up. Although the Larsen scores in most instances were fairly low, 5 patients had scores over 40.

Disease characteristics

Table I compares certain disease characteristics in patients with remission and in those with continuing radiographic progression. ESR and CRP were significantly lower in remission patients at both the 8-year and the 20-year check-ups. In respect of the number of swollen joints there was no difference at entry, whereas the number in remission patients was significantly lower at the 8-year check-up. At the end of the follow-up 19 of the 27 patients with radiographic remission had no swollen joints, three had one swollen joint, four had 2-4 swollen joints, and one had 8 swollen joints. The Larsen score was already significantly lower in the patients in remission at entry.

Treatment

The initial plan was to randomize the patients into three groups: gold sodium thiomalate (GST), gold sodium thiomalate and prednisolone, and hydroxychloroquine (CHL). However, the randomization was not complete. In 9 patients the diagnosis of RA had not yet been established at entry and treatment with DMARDs was initiated during the first year. One patient received no specific antirheumatic medication. The proportion of patients receiving prednisolone remained about the same during the whole period, that of patients receiving gold sodium thiomalate and hydroxychloroquine declined and new drugs such as sulphasalazine and methotrexate were added to the armamentarium after the 8-year check-up. At the start of remission treatment was as follows: no treatment in 11 patients, CHL in 4, CHL + prednisolone in 2, GST in 3, GST + prednisolone in 2, prednisolone in 3, azathioprine + prednisolone in 1, sulphasalazine in 1, sulphasalazine + prednisolone in 1.

It will be seen in Table II that the remission patients significantly more often had no specific antirheumatic medication at entry and also at the 8-year and at the 20-year check-ups, compared to patients with radiographic progression.

Discussion

The main finding in the study was that the radiographic destruction in peripheral joints had halted in about a quarter of the study subjects. Half of them had entered remission at the 15-year follow-up and the other half at an earlier stage. The subsequent follow-up period of subjects who had entered remission at 15 years was shorter and, accordingly, the likelihood of a new exacerbation will be greater than in subjects who had entered remission in an earlier phase. Whether the remission was permanent can only be stated with certainty in the case of those who had died.

The only study serving to some degree as a basis for comparison is that by Graudal and co-workers (6). These authors investigated the long-term radiographic course as a mathematical function of disease duration and identified five main types of progression. Looking at individual plots (Fig. 5 in their paper) it is apparent that in a number of patients, particularly among those with sigmoid-type progression, the damage had halted. Since the series in question was a selected group of clinical patients, no detailed comparison with our series is feasible.

Several scoring systems have been devised for the assessment of articular erosions and cartilage loss (2). Two are widely used, the Larsen and the Sharp methods, both in several modifications. We used the Larsen method, which is easy to manage and has good reproducibility. There is nonetheless some evidence that the Sharp score is a more sensitive measure of the progression of joint damage than the Larsen (11,12); it is thus likely that some of our remission cases would have shown progression by more sensitive (and more laborious) scoring methods. Perhaps more importantly, radiographs had been taken in our study series only of hands and feet. Although a good correlation exists in the occurrence of erosions in the small and large joints (13), it is probable that some of our remission patients had had radiographic progression in large joints.

A striking contrast has been observed between improvement in measures of disease activity and simultaneous radiological deterioration (14). On the other hand, virtually nothing is known regarding the presence or absence of clinical and laboratory markers of disease activity in subjects who have entered radiographic remission. The study described here provides some information in this respect, although the relevant data had not been collected in an optimal fashion.

Significant differences in activity measures were noted at the 8-year and 20-year check-ups between patients with radiographic remission and those with evidence of continuing progression; this would strongly suggest that radiographic remission was frequently associated with diminishing activity of clinical disease. There was, however, a considerable overlap between the groups. Underlying reasons for heightened ESR and CRP in remission cases include classification errors, diseases other than RA (for example, cancer), and recent exacerbation of the rheumatoid disease process not yet reflected in radiographic progression. Continuing inflammation without radiographic progression remains in some cases a reasonable possibility.

When the study described here was commenced in 1973, gold sodium thiomalate, hydroxychloroquine, glucocorticoids and a limited number of different NSAIDs were the only agents available for the treatment of RA. After the 8-year follow-up examination, additional DMARDs were gradually taken into use. There was some evidence recorded at entry that some of the remission cases had a mild disease from the beginning (lower Larsen scores and a higher proportion of cases without specific antirheumatic medication). On the other hand, there were cases in which the disease process had led to marked joint destruction prior to slowing down. The role of drug treatment in inducing remission remains elusive. However, comparison over an 8-year period of the radiographic outcomes in the present study cohort and in a later inception cohort treated more actively with a "sawtooth" strategy support a role of DMARDs in preventing joint destruction (15). Our 20-year study may serve as a basis for comparison with later long-term cohort studies using better treatment possibilities.

References

1. DONELLY S, SCOTT DL,EMERY P: The long-term outcome and justification for early treatment. *Baillière's Clin Rheumatol* 1992; 2: 251-60.
2. SCOTT DL, LAASONEN L, PRIOLO F, HOUSSIEN DA, BACARINI L, CERASE A, CAMMISA M: The radiological assessment of rheumatoid arthritis. *Clin Exp Rheumatol* 1997; 15 (Suppl. 17): 53-61.
3. SCOTT DL, SYMMONS DPM, COULTON BL, PROPERT AJ: Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987; 11: 1108-11.
4. KAARELA K, KAUTIAINEN H: Continuous progression of radiological destruction in seropositive rheumatoid arthritis. *J Rheuma - tol* 1997; 24: 1285-7.
5. WOLFE F, SHARP JT: Radiographic outcome of recent-onset rheumatoid arthritis. A 19-year study of radiographic progression. *Arth - ritis Rheum* 1998; 41: 1571-82.
6. GRAUDAL NA, JURIK AG, DE CARVALHO A, GRAUDAL HK: Radiographic progression in rheumatoid arthritis. A long-term prospective study of 109 patients. *Arthritis Rheum* 1998; 41: 1470-80.
7. KAARELA K: Prognostic factors and diagnostic criteria in early rheumatoid arthritis. *Scand J Rheumatol* 1985; 14 (Suppl. 57): 1-54.
8. KAARELA K, LUUKKAINEN R, KOSKIMIES S: How often is seropositive rheumatoid arthritis an erosive disease? A 17-year follow-up study. *J Rheumatol* 1993; 20: 1670-73.
9. LARSEN A, DALE K, EEK M: Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diagn* 1977; 18: 481-91.
10. LARSEN A: How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in longterm studies? *J Rheumatol* 1995; 22: 1974-5.
11. CUCHACOVICH M, COURET M, PERCY P, GATICA H, SAURY J: Precision of the Larsen and the Sharp methods of assessing radiological change in patients with rheumatoid arthritis. *Arthritis Rheum* 1992; 35: 736-9.
12. PLANT MJ, SAKLATVALA J, BORG AA, JONES PW, DAWES PT: Measurement and prediction of radiological progression in early rheumatoid arthritis. *J Rheumatol* 1994; 21: 1808-13.
13. DROSSAER-BAKKES KW, KROON HM, ZWINDERMAN AH, BREEDVELD FC, HAZES JMW: Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function. *Rheumatology* 2000; 39: 998-1003.
14. MULHERIN D, FITZGERALD O, BRESNIHAN B: Clinical improvement and radiological deterioration in rheumatoid arthritis: Evidence that pathogenesis of synovial inflammation and articular erosion may differ. *Br J Rheumatol* 1996; 35: 126-8.
15. SOKKA TM, KAARELA K, MÖTTÖNEN TT, HANNONEN PJ: Conventional monotherapy compared to a "sawtooth" treatment strategy in radiographic progression of rheumatoid arthritis over the first eight years. *Clin Exp Rheumatol* 1999; 17: 527-32.