Radiological Progression in Established Rheumatoid Arthritis

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ABSTRACT. Radiographic progression in established rheumatoid arthritis (RA) gives an objective measure of anatomical damage that defines the course of the disease and the longterm effects of treatment. This review defines the rate of joint damage, progression in individual joints, and predictive factors. Six longitudinal prospective studies of 103–378 RA patients followed for up to 20 years show that initially patients had less than 3% maximum possible damage, this rose to 11% maximal damage by 5 years and over 40% by 20 years. The rate of progression changed from an initial rate of 1.6% maximal progression annually to a later rate of 2.0% annually. Between 1977 and 1998 5 prospective studies of 40–147 hospital-based RA cases seen within 12 months of developing RA showed 60–73% of cases developed one or more erosions in the hands and wrists. However a community-based cohort of early RA patients reported, more recently showed 41% of 335 cases developed erosions. There are marked differences between joints. The wrists show most damage and in one series of 103 cases, by 20 years 18% of wrists were completely destroyed and only 25% were non-erosive. The same series showed ankle joints are rarely involved; at 20 years only 7 patients had major abnormalities with minor changes in 17 cases. Rheumatoid factor (RF) positivity is the dominant predictor of erosive damage. In one survey of 439 cases who presented with inflammatory polyarthritis, patients with an initial high RF had over twice the radiographic progression of seronegative cases. A further 8 studies, which enrolled 1395 patients, all show a strong link between radiographic damage and RF status. The other key clinical predictor is disease activity indicated by surrogate measures such as the C-reactive protein (CRP) level. Suppressing disease activity judged by CRP levels not only decreases the progression of joint damage, but also may reduce new joint involvement to a greater extent than progression in already damaged joints. New potential markers of damage such as anticyclic citrullinated peptide ELISA tests may further improve the identification of those RA patients most at risk of erosive damage and, by implication, most in need of suppressive therapy. (J Rheumatol 2004;31 Suppl 69:55–65)

Key Indexing Terms:
RHEUMATOID ARTHRITIS RADIOGRAPHIC PROGRESSION PROGNOSTIC MARKERS

THE VALUE OF RADIOGRAPHIC ASSESSMENT

The place of radiographs

Assessing radiographic progression in established rheumatoid arthritis (RA) provides an objective measure of the extent of anatomical joint damage. This can be used to follow the course of the disease and define the longterm effects of treatment. Once the cascade of radiological damage starts, there is relatively rapid progression in the early years[1]. New techniques such as magnetic resonance imaging and ultrasound are able to visualize the earliest stages of the process, although these techniques require further development and validation. Currently, plain radiographs remain the most appropriate approach to evaluate the progression of damage in established RA. In these circumstances serial measurements of radiological progression are better than a single reading. Rapid radiographic progression suggests patients need aggressive treatment. Radiographic damage increases throughout the course of RA[2,3].

Methods of assessing radiographs

There are many systems for scoring radiographic damage in RA. The dominant methods are those of Sharp, which have been modified by van der Heijde[4], and by Larsen, also modified slightly by Scott, *et al*[5] and substantially by Rau and his colleagues[6]. The balance of current opinion favors the Sharp/van der Heijde system as this is best at detecting meaningful clinical change[7,8]. However, there remains considerable debate about the best method of scoring radiographs[9], and there are complex issues to resolve about the relative weights in the grading systems used and the importance of erosions compared to joint space narrowing. Currently, conventional radiographic films are still used, but it is likely that over the next few years these will be replaced by digital images viewed on simple computing systems[10,11].

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The scope of this review

The literature on radiological progression in RA is vast and cannot be summarized in a single review. The present overview therefore focuses on a limited number of themes. These include the rate of joint damage, progression in individual joints, and predictive factors. It has proved impractical to also include the effects of disease modifying antirheumatic drugs (DMARD) and other imaging methods.

PROGRESSION OF DAMAGE

Rate of progression with disease duration

It is simple to show that joint damage increases with disease duration. Almost any population of RA patients currently attending a specialist clinic confirms this. Figure 1 shows the progression of damage, estimated by changes in the Larsen score, in a convenience sample of 134 patients attending rheumatology outpatients at one UK unit (King's College Hospital). Although these patients show a significant relationship between disease duration and Larsen score (r = 0.47), there are differences between individual cases. Some cases have over 50% maximum possible damage within 5 years of disease onset and others no damage after more than 20 years of RA.

There is doubt whether disease duration influences the rate of progression. Larsen and Thoen[12] followed 200 patients for 12 months, reporting that the rate of increase in the Larsen score fell in late RA. However, this may reflect how the rate of progression is calculated[13]. A subsequent study of 256 RA patients by Wolfe and Sharp[14] found constant progression over 19 years.

Prospective cohort studies reporting sequential changes in Larsen score

Three readily accessible published studies report longitudinal changes in Larsen scores[15-17]. They evaluated between 103 and 142 patients. These cases were initially seen with disease durations under 3 years and were followed prospectively for up to 20 years. Initially, average Larsen scores were less than 4% of possible maximum damage. By 9 years they were 23% of possible maximum damage, and after 15 years they exceeded 50% of possible maximum damage in the one study in which data were available. The overall average annual increase in Larsen score was approximately 2.0% maximal possible damage.

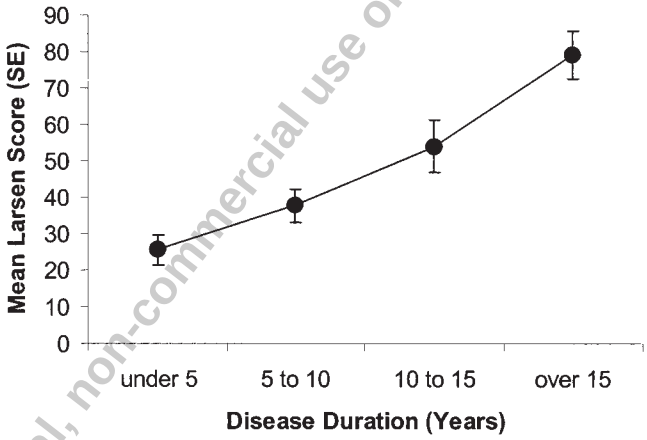

Figure 1. Relationship of disease duration to damage in 134 outpatients with RA. Mean and standard error are shown in relation to 5-year periods.

Prospective cohort studies reporting sequential changes in Sharp score

Another 3 published studies report longitudinal changes in the Sharp score. These evaluated between 123 and 378 patients seen within 2 years of disease onset and followed for up to 19 years[18-20]. Initially, average Sharp scores were less than 4% of possible maximum damage. By 9 years they were 20% of possible maximum damage, and after 15 years they exceeded 28% of possible maximum damage in the one study in which data were available. The overall average annual increase in Larsen score was approximately 1.8% maximal possible damage.

Combining longitudinal studies using Larsen and Sharp scores

The results of these 6 studies are amalgamated in Figure 2. Initially, there was less than 3% maximum possible damage; this rose to 11% maximal damage by 5 years and over 40% by 20 years. The rate of progression changed from an initial rate of 1.6% maximal progression annually to a later rate of 2.0% annually.

Patterns of progression

Plant, *et al*[21] outlined 4 patterns of damage in 114 patients with early RA who were followed for 8 years. These comprised linear progression, which occurred in 51 cases, a lag pattern that was seen in 13 cases, a plateau pattern in 19 cases, and non-erosive RA in 29 cases. Graudal, *et al*[22] studied 109 patients followed for up to 30 years. They identified 5 different patterns of progression. These comprised no progression at all (under 1%), slow onset with a later exponential increase (39%), fast onset with a later stable rate of progression (11%), fast onset with a later slow rate of progression (30%), and slow onset with acceleration and then deceleration in progression (20%). It is likely that these patterns can be reduced to 4 similar patterns of:

- Linear progression
- Rapid onset with a later plateau
- Slow onset with acceleration
- Nonprogressive

The number of patients in these different groups will depend upon patient selection, and is likely to vary substantially between cohorts of RA patients.

Kuper and colleagues[23] suggested a ceiling effect, with many patients reaching maximum scores for erosions, that influences the assessment of radiographic progression. In a

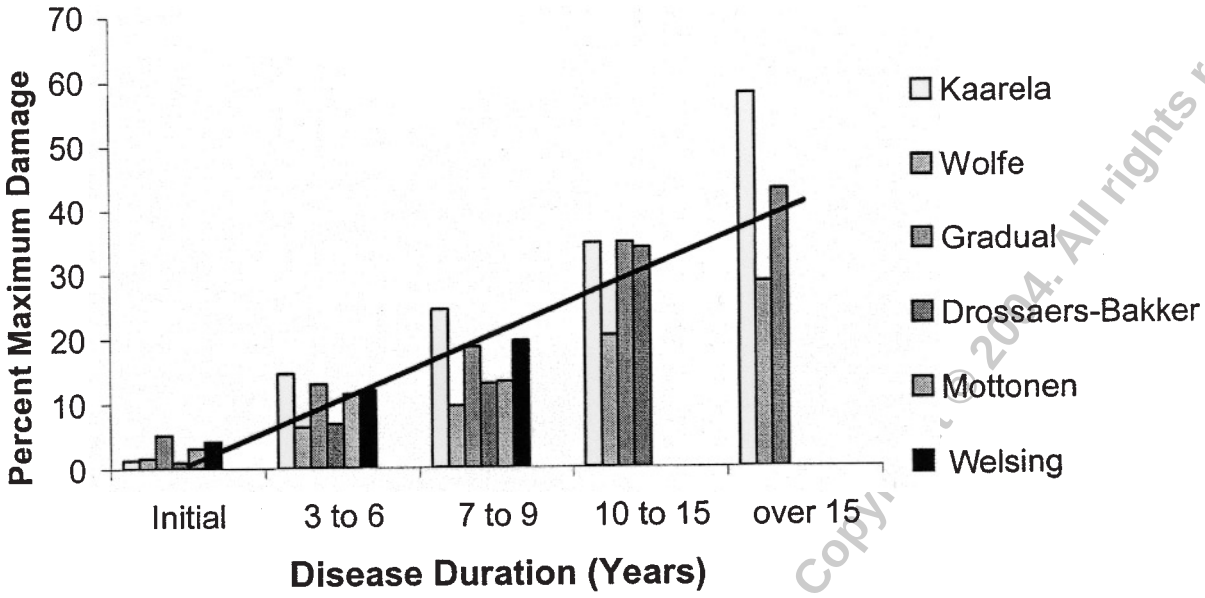

Figure 2. Progression of joint damage in longterm observational studies. Data are shown from 6 studies using Larsen and Sharp scores[16-20,22]. The results are shown as percentage of maximum damage.

prospective followup study of 87 RA patients followed for 6 years they found that the maximum scores were distributed over 50% of the patients, and 20% of the patients had maximum scores in more than 10 joints, although there was no preference for specific sites.

DEVELOPING NEW EROSIONS

Initial observational studies

Five prospective studies of hospital-based cases[21-27], reported between 1977 and 1998, which included 40–147 patients seen within 12 months of the onset of their RA, described results after 3–8 years of prospective followup. They showed 60–73% of cases developed one or more erosions in the hands and wrists.

Recent observational studies

Subsequent studies show the situation is complex. First, many patients have erosions when they are first seen in the clinic. One study to highlight this is the report by Jansen and colleagues[28]. This describes 130 patients with early RA followed for 12 months. At the end of this period, 98 (86%) cases were erosive. However, when first seen, many patients already had erosions, and the extent of joint damage was related to the duration of symptoms before patients were initially seen. Those patients whose symptoms had lasted for 34 weeks or longer had higher Sharp-van der Heijde scores than all other cases, indicating a higher number of erosions (Figure 3).

Second, there is growing evidence that the development of erosions is influenced by ceiling effects. Hulsmans and colleagues[29] described radiological outcome at 6 years in a longitudinal study of 502 patients with recent-onset RA, who were seen with disease durations under 1 year. They reported stable rates of progression of the Sharp-van der Heijde score and erosion score. The rate of progression of newly, not previously, damaged joints declined. However, the rate of progression of already damaged joints that became more damaged increased during followup. The joints of the feet, especially the fifth metatarsophalangeal (MTP) joint, generally became eroded earlier, and more of them became eroded compared with the joints of the hands. There was a pronounced ceiling effect in the percentage of patients who developed more than one erosion. After 6 years, 95% of the patients had already developed more than one erosive joint. This is shown in Figure 4.

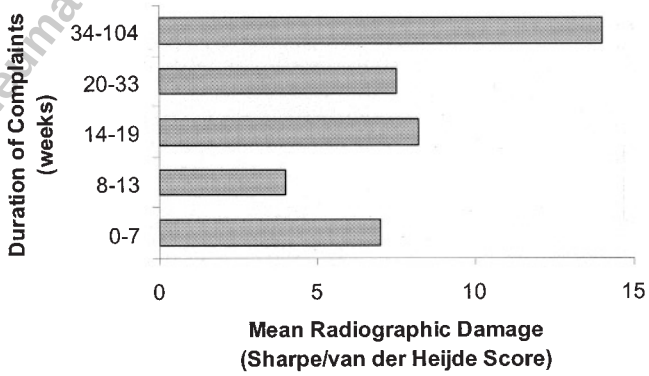

Figure 3. Radiological damage at baseline in 130 patients with early RA. Results are shown in 5 centile groups by duration of complaints. From Jansen, *et al*[28].

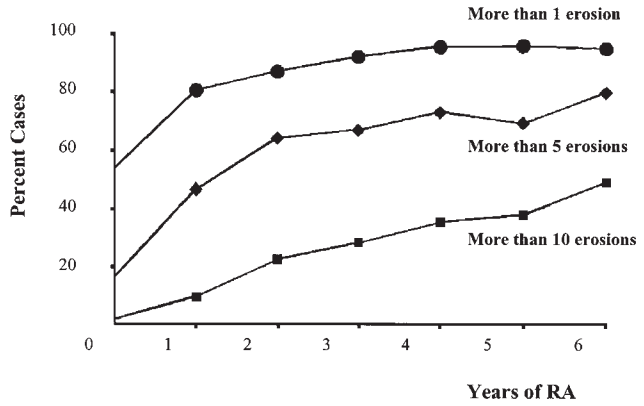

Figure 4. Development of erosions at different cutoff points in a 6 year study of 520 early RA patients[29]. Erosion score cutoffs were > 1, > 5, and > 20.

Third, case selection is very important in determining whether or not patients will develop erosions. Thus the Norfolk Arthritis Register (NOAR), which seeks to enrol all patients with inflammatory polyarthritis from a community near Norwich in the UK, has reported less erosive disease in these patients. Three hundred and ninety (80%) of the 486 patients in the NOAR study satisfied the criteria for radiography and 335 patients had available radiographs[30]. Due to the selection criteria, the patients who were radiographed had slightly more severe disease than the whole cohort. One hundred and thirty-seven (41%) of the patients examined radiographically had developed erosions. The prevalence of erosions was also higher in patients with a longer symptom duration before initial presentation.

Randomized clinical trials using erosions as outcome measures

A review of the literature until 2001 identified 9 randomized controlled trials that used radiographic damage as an outcome measure in early RA[31-39] (Table 1). Four enrolled patients were within one year of diagnosis, 3 within 2 years of diagnosis, one within 3 years, and one did not specify an exact time frame. These 9 trials, which randomized 81 to 632 patients, showed marked variations in the presence of erosions at entry. Two had very low damage scores at entry, in one 30% had erosions at entry, and the others showed varied numbers up to all cases having erosions at entry. Although DMARD and steroid treatment reduced the rate of radiographic progression in all these studies, there was considerable diversity in the rate of progression, with some evidence that patients with no initial erosions were unlikely to develop new erosions.

It has been possible to evaluate the effect of existing erosions on subsequent progression in more detail using data from the trial by Choy and colleagues. This compared sulfasalazine with diclofenac in early RA[40]. The key erosion data from this study are shown in Table 2. Initially, there

Table 1. Early RA studies with erosions as outcome measures. MTX: methotrexate; SZP: sulfasalazine; HCQ: hydroxychloroquine; Pred: prednisolone.

Study	Kirwan	Bathon	Van Everdingen	Dougados	Van Jaarsveld	Boers	Rau	Mottonen	Proudman
Year	1995	2000	2002	1999	2000	1997	1998	1999	2000
Number	128	632	81	205	313	155	174	199	82
Duration, yrs	< 2	< 3	< 1	< 1	< 1	< 2	Unclear	< 2	< 1
Drugs	DMARD vs DMARD/ oral steroids	MTX vs Etanercept	Pred vs Placebo (no DMARD for 6 months)	MTX vs SZP vs MTX/SZP	HCQ vs Gold vs MTX	SZP vs SZP/MTX/ Pred	HCQ vs Gold	Monotherapy (SZP & MTX) vs Combination (SZP/MTX/ HCQ/Pred)	SZP vs MTX/ cyclosporine/ steroids
Study, yrs	2	1	2	1	2	1	1	2	1
X-rays	Hands	Hands and feet	Hands and feet	Hands and feet	Hands and feet	Hands and feet	Hands and feet	Hands and feet	Hands and feet
Initial Erosions, %	30	87	38	Very low initial damage scores	Very low initial damage scores	74	All had erosions	50	62
Outcome	• 22% of non-eroded hands developed erosions with steroids • 46% of non-eroded hands developed erosions without steroids	• 28% had increase in erosion score with high dose Etanercept • 40% had increase in erosion score with MTX	• Mean erosion score 19 with steroids • Mean erosion score 29 with placebo	• Erosion score increased in 13% with SZP • Erosion score increased in 10% with MTX • Erosion score increased in 7% with MTX/SZP	• Median joint damage increased by 12 with HCQ • Median joint damage increased by 9 with gold • Median joint damage increased by 8 with MTX	• Median erosion score 2 with combination • Median erosion score 5 with SZP	• Mean erosion score 12 with MTX • Mean erosion score 94 with gold	• Median Larsen score 4 with combination • Median Larsen score 12 with monotherapy	• Median erosion score 1.5 with combination • Median erosion score 2.5 with SZP

Table 2. Data from early RA trial by Choy, *et al* [40] evaluating the numbers of patients with erosions.

Visit	Erosion Scores	Sulfasalazine		Diclofenac		Difference
		N	%	N	%	
Baseline	0 to < 1	25	61	23	55	3.20*
	1 to < 10	15	37	17	40	DF = 3
	10 to < 20	0	0	2	5	p = 0.36
	≥ 20	1	2	0	0	
1 year	0 to < 1	20	49	17	40	10.69*
	1 to < 10	17	41	9	21	DF = 3
	10 to < 20	3	7	7	17	p = 0.013
	≥ 20	1	2	9	21	

* Chi-square.

was no difference between groups, but after 12 months' treatment there were significantly more erosions in the diclofenac group than in the sulfasalazine group. This is an expected outcome based on existing knowledge of DMARD. However, the data have been further evaluated to examine the effect of DMARD treatment in cases with existing erosions and those without. The revised erosion data (Table 3) show that in both sulfasalazine- and diclofenac-treated cases most patients who initially have erosions develop further erosions, and that cases who have no initial erosions are unlikely to develop new erosions.

The erosion data in this trial are comparable to the risk of erosions developing during methotrexate therapy for early RA reported in an observational study by Rich, *et al*[41]. This study evaluated 24 RA patients receiving methotrexate as their first DMARD. Baseline radiographs showed erosions (one or more) in 11 and none in 13. Half the patients showed no progression; 73% of patients with erosions at baseline but only 31% without erosions at baseline progressed.

HEALING OF EROSIONS

Identifying healing on plain radiographs

Athough healing of erosive damage is rarely reported, it can occur. Reports of healing include 2 cases reported by Sokka and Hannonen[42], 3 cases reported by Jalava and Reunanen[43], and 6 cases reported by Rau and Herborn[44]. Healing phenomena include recortication of erosions, filling in of erosions with new bone, and secondary osteoarthrosis with bone sclerosis and osteophyte formation. Menninger and colleagues[45] examined radiographs of hands and forefeet over 3 years at 34 joints based on the modified Larsen index and found repair in 9% of the joints compared with 7% of deteriorating joints.

Methods of assessing healing

Rau and his colleagues addressed this in a detailed evaluation[46]. They studied 24 cases with possible healing phenomena from longterm treatment studies, and compared these to 10 cases with progressive disease. Out of 1292 joints scored, 74 had healing phenomena, with agreement between readers in 89% of these cases. The 24 patients with healing had slight reductions in their radiographic score, while 10 patients without healing showed moderate progression.

PROGRESSION IN DIFFERENT JOINTS

The Finnish series

The most comprehensive assessment of changes in different joints is the Finnish series reported in many studies by Kaarela and his colleagues. These reports describe findings in 103 patients with seropositive RA followed for 15–25 years. The cases were first seen within one year of diagnosis and were followed prospectively while receiving standard treatment with DMARD[47].

Large joint replacements. Large joint replacement was evaluated in 83 patients who attended for a 15-year review and 68 patients who attended for a 20-year review[48]. During up to 25 years of followup, 22 of these patients had received 41 large joint replacements. These comprised:

• 17 total hip joint replacements in 13 patients after 14 years from diagnosis (median)

Table 3. Further analysis of data from early RA study by Choy, *et al* [40] looking at the development of new erosions in relation to the presence or absence of erosions at entry.

Results at 12 mo	Sulfasalazine				Diclofenac			
	Initial Erosions (n = 17)		No Initial Erosions (n = 28)		Initial Erosions (n = 19)		No Initial Erosions (n = 24)	
	Patients	Percent	Patients	Percent	Patients	Percent	Patients	Percent
No new erosions	5	29	22	79	2	11	17	71
New erosions	12	71	6	21	17	89	7	29

• 14 total knee replacements in 11 patients after 17 years
• 3 total shoulder replacements on 3 patients after 18 years
• 7 total elbow replacements on 4 patients after 21 years.

Wrist joints. These joints had the most destruction and the greatest need for reconstructive surgery[49]. At 15-year followup, mean Larsen scores showed 50% of maximal damage and reconstructive surgery had been performed in 33 of 83 patients. After 20 years 18% of wrists were completely destroyed (Larsen scores of 5) and 23% had needed total or partial fusions. Only 25% of wrists were non-erosive.

MTP joints. After 20 years, 62% of these joints had erosions and 24% were severely damaged, with Larsen scores of grade 4–5[50]. The first MTP joints showed the least damage and the fifth MTP greatest destruction. Erosive changes occur early in the MTP joints.

Elbow joints. After 15 years, 51% of elbow joints had erosive involvement, with 30 of 74 patients showing bilateral changes and 15 unilateral involvement[51]. The 13 most severely involved elbow joints (Larsen grade 4–5) were seen in 8 patients.

Ankle joints. After 20 years' duration of RA, only 7 patients had major abnormalities in their ankle joints, with minor changes in 17 patients[52].

Hip joints. After 15 years, severe radiological changes in the hips (Larsen grade 3–5) were seen in 31 cases and acetabular protrusion in 5[53].

Shoulder joints. After 15 year followup, erosive involvement was seen in 96 of 148 shoulders evaluated[54]. Both glenohumeral and acromial clavicular joints were affected in 62 shoulders, the glenohumeral joint alone was involved in 9 shoulders and the acromioclavicular joint alone was affected in 25 shoulders. There was a close relationship between damage to the glenohumeral and acromioclavicular joints, though the acromioclavicular joint was affected more often.

Joint replacement in an observational cohort from Wichita

Joint replacement is one method of defining the existence of severe joint damage and joint failure independently of radiography. Wolfe and Zwillich[55] reported the likelihood of RA patients needing total joint arthroplasty based on 34,040 patient visits in 1600 consecutive RA patients observed for 23 years. Kaplan-Meier life table estimates showed that 25% would undergo a total joint arthroplasty after they have had their diseases for 22 years. Of those patients who received one total joint replacement, 25% had a second total joint replacement in a different joint within 1 year and 50% within 7 years. Ten years after total joint replacement about 6% of knees and 4% of hips required revision surgery.

Joint replacement in Rochester

Massardo and colleagues[56] reported a retrospective medical record review of RA cases in Rochester, Minnesota, between 1955 and 1985. These patients were followed until 1998 and all joint surgeries recorded. There were 424 RA incident cases, and 148 (35%) patients had one or more surgical procedures involving joints during a median of 15 years' followup. The estimated cumulative incidence at 30 years was 53%. The most frequent procedure performed was total joint arthroplasty, and this had an estimated cumulative incidence at 30 years of 32%. Surgery of the knee for RA related disease was more frequent than any other joint or group of joints. The frequency of surgery to different joints is shown in Figure 5.

PREDICTING EROSIVE DAMAGE

Rheumatoid factor

The data from NOAR suggest rheumatoid factor (RF) is the dominant predictor of erosive damage. The most recent publication from this register[57] analyzed 439 cases who presented with inflammatory polyarthritis. All cases had paired radiographs, the first obtained within 2 years of presentation and the second years after presentation. The effect of baseline clinical and laboratory variables in predicting radiological severity judged by the Larsen score was assessed at both time points and adjusted for baseline severity. RF status, CRP levels, nodules, and the number of swollen joints at baseline predicted radiographic damage (Table 4). After adjusting for baseline severity, a high RF titer was an independent predictor of deterioration over 5 years: patients with an initial high RF showed more than twice the progression in their Larsen score than seronegative cases.

Many other studies suggest there is a strong link between radiographic damage and RF status. Bukhari and colleagues identified 12 such studies. These enrolled 1395 patients with disease duration between 1 and 10 years. Five looked at a single time point[58-62] and 7 looked at changes with time[21,63-69]. They included assessments of new erosions, total damage, progression, the Sharp score, and the Larsen score. The balance of evidence suggests strongly that RF posi-

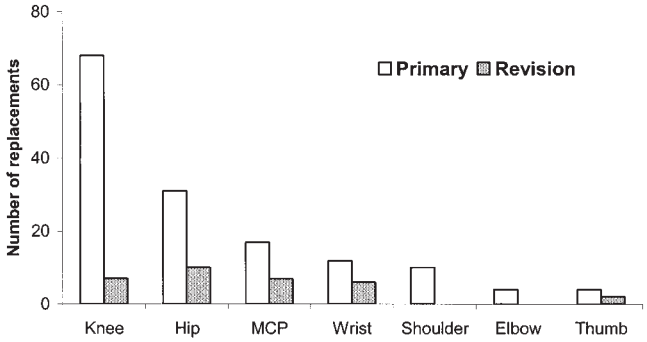

Figure 5. Types and frequencies of orthopedic procedures for RA-related joint disease, including primary and revision procedures. This is based on the population-based assessment from Rochester, Minnesota[56].

Table 4. Rheumatoid factor and the prediction of erosions.

Subjects	Predictors at first film*		Predictors at second film*		Predictors of severity at 2nd film adjusted for severity at 1st film	
	All	With erosions	All	With erosions	All	With erosions at 1st film
Sex						
Female	1 (referent)	1 (reverent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Male	1.2 (0.8–1.7)	0.9 (0.7–1.1)	1.0 (0.8–1.4)	0.9 (0.7–1.1)	1.1 (0.8–1.4)	0.9 (0.7–1.1)
Age at onset, per decade	1.2 (1.1–1.4)	1.1 (1.0–1.2)	1.2 (1.1–1.3)	1.0 (0.9–1.7)	1.2 (1.1–1.3)	1.0 (0.9–1.05)
No. of swollen joints						
Lowest third	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Middle third	1.1 (0.7–1.6)	1.1 (0.8–1.4)	0.8 (0.6–1.2)	1.0 (0.8–1.4)	1.0 (0.8–1.4)	1.2 (0.9–1.5)
Highest third	1.7 (1.1–2.5)	1.2 (0.9–1.7)	0.8 (0.6–1.1)	1.1 (0.9–1.7)	1.1 (0.8–1.5)	1.1 (0.9–1.4)
No. of swollen and tender joints						
Lowest third	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Middle third	1.1 (0.7–1.6)	1.0 (0.8–1.4)	1.1 (0.7–1.5)	1.0 (0.8–1.2)	0.9 (0.7–1.3)	1.0 (0.8–1.3)
Highest third	1.1 (0.7–1.6)	1.0 (0.7–1.5)	1.1 (0.7–1.5)	0.9 (0.7–1.3)	1.0 (0.7–1.3)	1.0 (0.8–1.8)
Nodules						
Absent	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Present	1.7 (0.9–3.1)	1.3 (1.1–2.0)	1.8 (1.1–3.0)	1.3 (1.0–1.8)	1.5 (1.0–2.3)	1.1 (0.8–1.5)
CRP concentration						
Lowest third	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Middle third	2.5 (1.4–4.6)	1.1 (0.8–1.5)	1.9 (1.2–3.1)	1.0 (0.8–1.4)	1.5 (1.0–2.3)	1.0 (0.7–1.3)
Highest third	4.3 (2.3–7.7)	1.8 (1.2–2.5)	2.5 (1.5–4.0)	1.4 (1.1–1.9)	1.1 (0.7–1.6)	1.1 (0.8–1.5)
Rheumatoid factor titer						
< 1:40	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
1:40–1:160	1.7 (1.0–2.8)	1.0 (0.7–1.5)	1.7 (1.1–2.7)	1.2 (0.9–1.6)	1.5 (1.0–2.3)	1.1 (0.9–1.4)
> 1:160	2.0 (1.2–3.2)	0.9 (0.7–1.2)	2.8 (1.9–4.1)	1.6 (1.2–2.0)	2.3 (1.7–3.2)	1.5 (1.2–1.8)
DRB1 shared epitope						
–/–	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
–/+	1.0 (0.6–1.5)	1.0 (0.7–1.5)	1.2 (0.8–1.8)	1.0 (0.8–1.3)	1.4 (1.0–1.9)	1.2 (0.7–1.0)
+/+	1.6 (0.9–3.2)	1.1 (0.8–1.7)	2.0 (1.1–3.4)	1.2 (0.9–1.7)	1.5 (0.9–2.3)	1.0 (0.8–1.8)

tivity, especially high levels of RF when patients first attend, is a powerful predictor of deteriorating radiographic damage in RA patients who were receiving conventional therapy. Seropositive patients are the key group on which to target the most powerful anti-erosive treatments.

Antikeratin antibodies and anticyclic citrullinated peptide (anti-CCP) ELISA tests

Antikeratin antibodies are strongly associated with RA, but because they can only be detected by immunofluorescence they have little value in routine practice. Identifying filaggrin as the antigen involved led to specific tests. Using these, Aho and collaborators[70] showed pre-illness serum antifilaggrin antibody levels are directly proportional to the risk of developing RF positive RA. The subsequent development of synthetic peptides containing citrulline, an amino acid present in filaggrin, enabled the introduction of an accurate ELISA. Initial reports suggested anti-CCP ELISA[71] tests have high specificity for RA. Combining anti-CCP and IgM RF ELISA gave a high positive predictive value for RA and predicted erosive disease at 2 years[72]. Kroot and colleagues[73] reported almost 70% of RA patients were positive for anti-CCP in early RA and these cases had more radiological damage. However, multiple regression analyses suggested the additional predictive value of anti-CCP ELISA was only moderate. Further, Van Jaarsveld, *et al*[74], who evaluated the clinical value of the anti-CCP ELISA in combination with RF status in 249 patients with early RA, concluded the prognostic value of combining both tests lies in their ability to predict mild disease. A further recent report by Visser and colleagues[75] looked at 524 consecutive, newly referred patients with early arthritis. The combination of 7 variables — symptom duration at first visit, morning stiffness over 60 minutes, arthritis in 3 or more joints, bilateral compression pain in the MTP joints, RF positivity, anti-CCP positivity, and the presence of erosions — predicted the likelihood of developing self-limiting arthritis, persistent nonerosive arthritis, and persistent erosive arthritis. For the present, the value of the anti-CCP ELISA remains unclear, although it has much potential.

Disease activity

It is generally agreed that patients with active RA have most erosive damage. The probable relationship of the processes has been illustrated by Kirwan[76] (Figure 6). His theoretical view that sustained disease activity is seen throughout the course of RA, with temporal fluctuations, and that this is reflected in a gradual increase in joint damage, matches data

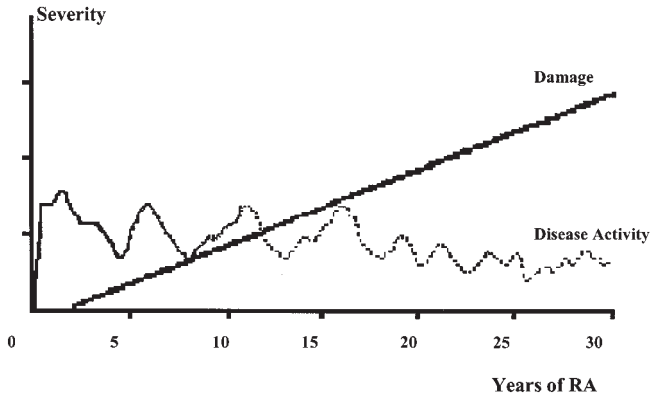

Figure 6. The theoretical progression of damage and disease activity.

from clinical practice. An example is given by the Nijmegen series that was reported by Welsing and colleagues[20] and is illustrated in Figure 7.

As patients who have active disease are more likely to be seropositive for RF, it can be difficult to distinguish the effects of these different variables. Combe and colleagues[77] attempted to do so in a study of 191 patients with early RA prospectively followed for 3 years. Radiological progression, seen in 71 of the 172 patients, closely correlated with baseline erythrocyte sedimentation rate, CRP level, and RF positivity. However, this study only evaluated baseline values and in routine practice the control of disease activity seems most important.

CRP is a good surrogate measure of disease activity and, since the early work of McConkey[78], it has been known to predict erosive damage. The time lag between synovial inflammation and joint damage has been shown by Matsuda, *et al*[79] in a study of 98 patients. This study showed that increases in the number of erosive joints after 12 months correlated with the CRP and other inflammatory markers at

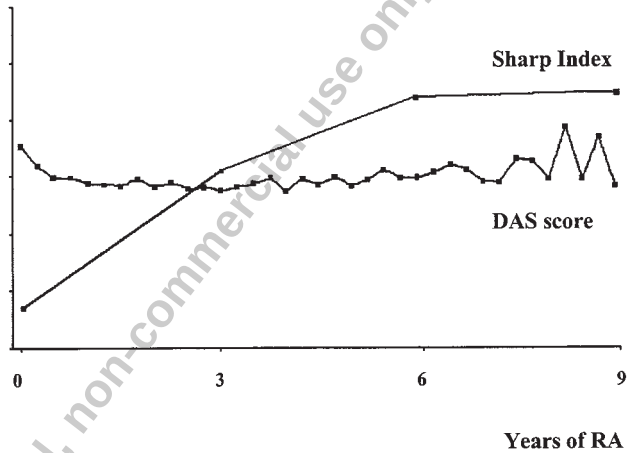

Figure 7. The observed progression of damage and Disease Activity (DAS) and Sharp scores over 9 years in the Nijmegen inception cohort[20].

6 months. Further, the number of erosive joints was high in patients whose levels of CRP were high at 6 months and suppressed by 12 months, and was much less in patients whose levels of CRP were successfully suppressed by 6 months.

The work of van Leeuwen and her colleagues[80] has established there are individual relationships between CRP and the progression of radiological damage. They modelled this relationship mathematically using adjustments for discontinuity in the radiographic scoring system in 149 patients with early RA followed prospectively for 3 years. Time-integrated CRP values correlated closely with radiological progression in each patient, but there was considerable variation between individuals with similar radiographic scores.

Subsequent research by the same group[81] provided evidence that early "aggressive" drug treatment to control the CRP reduces radiographic progression. They undertook a prospective followup study with an experimental group and historical controls divided into high-risk and low-risk subgroups based on prognostic factors. Overall, they investigated 228 consecutive patients with recent-onset RA. After 2 year followup, comparing the 2 high-risk subgroups showed radiographic progression in the aggressively treated cases was significantly lower than in controls. Cumulative CRP values were also significantly lower than in the control group.

Another study by Plant and his colleagues[82] confirmed the link between high CRP levels and joint damage. It showed that suppressing disease activity judged by CRP levels reduced new joint involvement to a greater extent than progression in already damaged joints. This conclusion was based on a secondary analysis of 359 patients with active RA enrolled in a 5-year randomized, prospective, open-label study of DMARD therapy. Time-averaged CRP correlated with increases in Larsen score, and the percentage of new joint involvement over 5 years, varied markedly with time-integrated CRP. Radiographic progession was 7% with low CRP values and 39% with high CRP levels, a 5-fold increase.

Despite these studies, variations in CRP levels between patients with similar radiographic scores make it difficult to generalize from initial single CRP values in individual cases. Further, not all investigations show a similar relationship. For example, one study from Leeds in the UK, in which 63 patients with early RA were followed up for 6 months, found that high initial CRP levels did not predict the persistence of arthritis at 6 months[83]. The conventional view that high CRP levels indicate a poor prognosis does not necessarily apply in very early RA.

CONCLUSIONS

Radiographic damage progresses throughout the course of RA. It is worse in patients with initial erosions, who are seropositive for RF and have a persistently high CRP. The

average increase in damage is in the region of 2% maximal damage annually. Some patients never develop erosions and the numbers of such patients depend on how cases are selected, with a higher number identified in community studies and less in hospital studies of severe disease.

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