A 10 Year Prospective Followup of Patients with Rheumatoid Arthritis 1986–96

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ABSTRACT. ***Objective.*** To determine the 10 year outcome of hospital patients with established rheumatoid arthritis (RA) treated with disease modifying drugs (DMARD).

Methods. All patients with RA of at least a year duration and attending a single clinician were followed prospectively for 10 years. DMARD treatments changed with time but were continued throughout. Measurements of joint tenderness (Ritchie Index), morning stiffness, grip, and disability (Health Assessment Questionnaire, HAQ) and radiographs of hands and feet were documented. A record of joint surgery was maintained. Patients who stopped attending the clinic were traced and an accurate record of deaths was obtained from the National Registry of Deaths. Paired clinical indices were compared where available between 0, 5, and 10 years.

Results. At entry there were 289 patients of variable disease duration. Within 10 years, 71 had died (standardized mortality ratio 1.3) and 92 were alive but unavailable. Median joint tenderness, morning stiffness, grip strength, and hemoglobin were not significantly different at 0, 5, and 10 years. Erythrocyte sedimentation rate (ESR) declined but not significantly. By contrast, HAQ scores and radiographs worsened between 0 and 10 years ($p = 0.0004$, $p = 0.0001$, respectively). There was a trend toward lower ESR values and less disability and the lower radiographic scores in those with 10–15 years' disease duration in 1996 compared with those of similar duration in 1986. However, worsening of radiographs occurred in patients with short, medium, and long histories of RA. Correlations between disability, radiographic scores, and joint tenderness were apparent at the start and conclusion of the study. At 10 years, 54 (19%) of the original cohort had undergone at least one large joint replacement. Significantly more women required joint replacement surgery (chi-square 5.44, $p = 0.02$).

Conclusion. Over a 10 year period patients with RA exhibited an excess of deaths and a deterioration of radiographs and function despite regular DMARD treatment and apparent clinical containment. Worsening of radiographs occurred in both relatively early and late disease. There was a steady requirement for surgical large joint replacement with time. This study suggests that in the long term, the effect of DMARD treatments may be less than the expectations derived from short term studies. (J Rheumatol 2001;28:2409–15)

Key Indexing Terms:
PAIN DISABILITY RADIOGRAPHS JOINT SURGERY TREATMENT

It is axiomatic that rheumatoid arthritis (RA) causes disability and premature death[1,2]. This apocalyptic vision is commonly expressed in the preamble to articles that advocate more aggressive treatment of early disease[3,4]. The notion that prognosis is influenced by the early introduction of disease modifying treatments (DMARD) has steadily gained ground[5-9]. The rationale for this approach derives from studies indicating that radiographic progression is most rapid in the early years of disease[10]. DMARD have been established for several decades and many units, including our own, have used these treatments as a conventional first-line approach for a generation or more[11-13].

The popularity of available agents has changed with time and few would now dispute the primacy of methotrexate (MTX), a drug whose superiority can be ascribed to its tolerability[14,15]. However, as far as efficacy is concerned the clinical response to sodium aurothiomalate, D-penicillamine, sulfasalazine, and azathioprine is similar to that of MTX[16,17]. The regular application of these drugs to RA over the last 2 decades should by now be reflected in an improving outlook if their short term effect confers longterm benefits. However, the results of such treatment may not, over time, realize this promise[18]. We have determined, as far as possible, the 10 year outcome of a series of patients with RA who were already receiving DMARD in 1986. These comprised patients with a wide spectrum of disease duration and severity. They were under the care of a single physician and were followed prospectively until 1996. This report outlines the course of their illness over that period.

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MATERIALS AND METHODS

All patients with RA of at least one year duration attending a single physician and who satisfied the American Rheumatology Association (ARA) revised criteria for RA[19] were admitted to a prospective study of outcome in 1986. Many had been undergoing similar surveillance for several years. All had embarked on DMARD treatment for a variable period before entering the study in 1986. The choice of DMARD at that time was arbitrary and followed no specific sequence. Seven patients were taking doses of prednisolone not exceeding 10 mg daily and this was continued at this or a lower dose if clinically indicated. The majority of patients received occasional intraarticular or intramuscular depot methyl prednisolone at intervals during the 10 years of survey[20]. No record of this was maintained.

Patients were reviewed at regular intervals by clinicians of our team but the annual clinical measurements were performed by the same observer throughout. Early morning stiffness estimates, Ritchie joint tenderness score[21], grip strength using an inflated bag attached to a sphygmomanometer pressure gauge[22], and Health Assessment Questionnaire (HAQ) scores were estimated[23]. A summated raw score (maximum score 60) was used for the HAQ results because this approach resembled an assessment of disability previously devised and used by us. The summated scores correlate well with the conventional mean calculation ($n = 25$, $r = 0.92$, $p = 0.0001$) and has been successfully deployed by us in the past[24]. At 5 and 10 years, radiographs of hands and feet were obtained. These were evaluated toward the end of the study in batches of 6 to 10 films by a single observer using the Larsen scoring method[25]. There was a good correlation between results of the same films scored after a 4 week interval ($n = 25$, $r = 0.93$, $p = 0.0001$). The films of patients who had undergone finger or toe joint surgery were excluded. A record of joint surgery was maintained.

Those who failed to attend successive clinics were contacted directly or information was sought about their welfare and whereabouts from next of kin and primary care physicians. Where possible, those who had moved out of area were encouraged to attend for assessments. Reported deaths were recorded and at 10 years, a search of the Register of Deaths was undertaken to determine whether any of those on whom information could not be obtained had died. Causes of death were not ascertained. Inevitably, all data were not collected at each time point. Some radiographs obtained at entry to the study had been destroyed. The incompleteness of measurements and scores made multivariate analysis difficult. Where information for a measurement was complete, paired data for years 0, 5, and 10 were compared using the 2 tailed Wilcoxon signed-rank test. The Wilcoxon rank-sum test was used for comparing the unpaired data of patients with 10–15 years' disease in 1986 and 1996. Subgroups arranged according to disease duration at entry to the study were compared in the same way. Spearman's correlation coefficient was calculated for some data sets.

RESULTS

At entry there were 289 patients (210 women, 79 men), median (range) age 59 (19–82) years, with a median disease duration of 10 (1–61) years.

There were 71 deaths over 10 years with standardized mortality rate (95% CI) of 1.302 (1.076–1.564). A Kaplan-Meier survival curve is shown in Figure 1.

At 10 years, 92 were known to be alive but for whom no further information was available. These had either moved out of London and were unwilling to return for assessment or their latest address was unknown to the initial primary care clinicians. At 5 years, assessment was possible for 194 and at 10 years for 126 patients. The 92 patients lost to followup were not significantly different to the remainder in sex, age at initial assessment, age of disease onset, initial erythrocyte sedimentation rate (ESR), HAQ, and radiographic score (data not shown).

The use and doses of DMARD over the study period are expressed in Table 1. No patient in this study received combination DMARD therapy, and the trends over 10 years reflected common usage. Failure to improve, symptomatic relapse, or toxicity were indications for changing from one DMARD to another. Improvement and relapse were not defined by specific clinical and laboratory criteria. Thirty-one (25%) patients reviewed at 10 years had continued with a single DMARD for the duration of the study. The remainder underwent one or more changes of DMARD during this time.

Table 2 shows the median clinical, radiological, and laboratory measurements at 0, 5, and 10 years. It is notable that although the trend for ESR was downward except for a small number with disease duration of 10–15 years at outset (Table 3) and the clinical indices of joint inflammation did not worsen, there was significant deterioration of radiographs and function after 10 years. When the population was examined in relation to disease duration at the time of entry to the study, the same trends were apparent for those with short, medium, and long histories of disease (Tables 3 and 4). It is noteworthy that the HAQ and radiographic scores of those with 10–15 year disease at entry in 1986 were higher than those with 11–14 year disease in 1996 (Tables 3 and 4), suggesting some effect of contemporary DMARD on the cohort presenting later. This was pursued by comparing all the available data for patients with RA of 10–15 year disease duration in 1986 with those of similar disease duration in 1996. This analysis also incorporated subjects excluded from the main analysis because of missing sequential paired observations. The median (range) results of those with disease duration of 10–15 years in 1986 were compared to those of patients with similar disease duration in 1996 (Table 5). They were well matched and the major change of DMARD was of more frequent use of MTX in 1996. Higher median values for ESR, HAQ, and radiographic scores were apparent in the 1986 cohort, but none of these differences reached statistical significance.

There was no correlation between either the initial or the 10 year ESR and change of radiograph, nor between ESR

Table 1. DMARD treatment (%) given to study patients over 10 years 1986-1996.

Time	Time, yrs 0	5	10
No. of patients	289	194	126
Methotrexate, 10–25 mg/wk	2	19	36
Sulfasalazine, 2.0 g daily	11	15	15
IM sodium aurothiomalate, 50/mg weekly then monthly	18	19	18
D-penicillamine, 750/mg daily	47	24	3
Azathioprine, 100–150 mg daily	22	18	5
Chloroquine, 200 mg daily	0	4	12
Cyclosporine, 100–200 mg daily	0	1	0

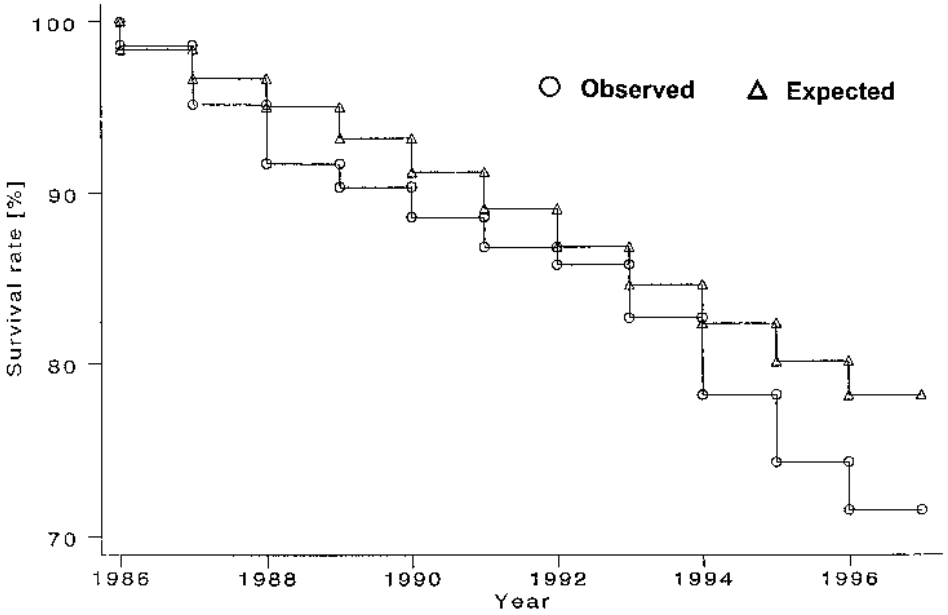

Figure 1. Kaplan-Meier curve of deaths of patients with RA over 10 years of the study.

Table 2. Clinical, laboratory, and radiological measurements (median and range) of study patients over 10 years. Complete sets of observations were unavailable for each patient at each time point. Number of paired observations available for analysis is indicated.

	No. of Patients	Time 0	5 yrs	p (0–5 yrs)	10 yrs	p (0–10 yrs)
Joint tenderness, Ritchie index	116	5.0 (0–23)	4.0 (0–26)	0.37	5.0 (0–28)	0.59
Early morning stiffness, min	94	30 (0–480)	30 (0–480)	0.83	30 (0–480)	0.34
Grip strength, mm Hg	115	220 (60–600)	220 (60–600)	0.75	220 (0–600)	0.96
HAQ	115	13 (0–60)	13 (0–60)	0.29	23 (0–60)	0.0004
Hemoglobin, g/l	95	12.9 (8.7–17.9)	12.8 (9.0–17.7)	0.5	12.5 (8.2–15.8)	0.7
ESR, mm/h	70	32 (1–107)	25 (1–126)	0.9	24 (1–127)	0.25
Larsen radiographic score	88	21 (0–135)	—	—	42 (1–136)	0.0001

HAQ: Health Assessment Questionnaire

values at 0 and 10 years with respective radiographic scores. There were strong correlations between ESR and HAQ at 0 and 10 years (n = 100, r = 0.44, p = 0.0001 and n = 73, r = 0.37, p = 0.0008, respectively), but not between ESR values at these times and the change of HAQ over 10 years.

There were correlations between the radiographic scores at 0 time and the change of score over 10 years (n = 85, r = 0.24, p = 0.025) and between the change of radiographs and change of HAQ (n = 78, r = 0.35, p = 0.007). There was an association between HAQ and radiographic scores at 0 time (n = 70, r = 0.465, p = 0.001) and at 10 years (n = 81, r = 0.31, p = 0.004), but the relationship was stronger between HAQ and joint tenderness at both time points (r = 0.63, p = 0.0001 and r = 0.38, p = 0.002, respectively).

At 10 years, at least 54 (19%) of 289 patients had undergone some form of joint surgery and 44 (15%) had received at least one large joint replacement. In ten patients 3–4 different joints had been replaced and in 4 patients as many as 5–6. Significantly more women required large joint replacement (chi-square 5.44, p = 0.02). The median (range) of disease duration at the time of the first prosthesis was 14 (2–38) years. The need for large joint replacement increased with time and 52% had at least one prosthesis after 20 years of RA. Those requiring prosthetic surgery had at the outset a higher ESR, more disability, and more erosive damage on hand and foot radiographs. They also had a longer history of disease (Table 6).

DISCUSSION

This study describes a cohort of patients with RA treated

Table 3. Comparison of clinical measurements over 10 years. Patients distributed according to their RA disease duration at entry to study. Numbers of patients paired for each analysis as shown.

	No. of Patients	Disease Duration, yrs	Time 0	5 yrs	p (0–5)	10 yrs	p (0–10)
Joint tenderness, Ritchie Index	45	1–4	4 (0–27)	5 (0–26)	0.38	6 (0–28)	0.07
	26	5–9	4 (0–21)	3 (0–26)	0.97	4 (0–17)	0.93
	19	10–15	6 (0–30)	4 (0–24)	0.02	5 (1–21)	0.93
	26	> 15	4 (0–23)	5 (0–28)	0.7	3 (0–28)	0.44
Grip strength, mm Hg	43	1–4	225 (100–600)	245 (125–600)	0.79	240 (120–600)	0.39
	17	5–9	270 (100–600)	240 (70–530)	0.87	240 (110–420)	0.24
	35	10–15	215 (100–500)	230 (70–550)	0.48	200 (100–500)	0.72
	20	> 15	190 (60–560)	170 (60–510)	0.28	205 (120–340)	0.24
HAQ	37	1–4	12 (0–58)	12 (0–59)	0.89	15 (0–60)	0.27
	24	5–9	13 (2–60)	18 (5–51)	0.52	22 (2–60)	0.84
	18	10–15	23 (1–60)	30 (16–60)	0.68	22 (1–57)	0.47
	26	> 15	28 (0–60)	31 (3–58)	0.38	30 (1–60)	0.95

HAQ: Health Assessment Questionnaire

Table 4. Comparison of median (range) ESR and radiological scores over 10 years. Patients distributed according to their RA disease duration at the entry to the study.

	No. of Patients	Disease Duration	Time 0	10 yrs	p (0–10 yrs)
ESR, mm/h	30	1–4	17 (1–120)	19 (2–57)	0.26
	19	5–9	34 (3–108)	21 (1–52)	0.11
	9	10–15	20 (3–81)	49 (18–85)	0.004
	12	> 15	21 (2–70)	24 (1–75)	0.7
Larsen radiographic score	27	1–4	8 (0–59)	21 (1–104)	0.0001
	22	5–9	22 (1–78)	38 (4–93)	0.0001
	15	10–15	55 (0–135)	60 (11–130)	0.0001
	24	> 15	51 (4–132)	76 (8–136)	0.006

with DMARD over a 10 year period. About a quarter of those reviewed at the end of the study were taking the same agent they had been taking at the outset. The pattern of drug usage over this time accords with the experience of others in the UK[26], and the inability to sustain treatment with a single DMARD over time echoes observations elsewhere in the world[14,15]. It is estimated that after 5 years of treatment the only DMARD likely to be continued is methotrexate[15].

This study indicates that regular DMARD treatment over a 10 year period 1986–96 did not abolish the excess of deaths in RA nor the average progression toward disability and worsening of radiographic damage for paired observations. These seemed independent of the clinical features that we measured, although a strong correlation between joint pain and functional ability was a consistent feature. Lower but statistically insignificant scores for disability and radiographic damage in those with 10–15 year disease in 1996 compared with 1986 may suggest that modern management and especially MTX has altered the outlook, but this did not detract from the prospective paired data, which pointed strongly to deterioration of these variables no matter how long the illness had been present. The relatively large number of patients alive but lost to followup were indistinguishable from those who either died or completed 10 years. This suggests that our data were not skewed by missing patients, although their absence does diminish the value of our observations.

The standardized mortality rate of 1.3 seen in our series is substantially less than that of 2.26 reported by Wolfe, *et al* in 1994, but similar to many series published before that time[27]. Premature death is more likely in those with the most severe disease and the longest histories of RA[28,29]. The apparently better survival prospects among patients referred to hospital early in the course of their disease suggest that effective treatment of the arthritis may reduce mortality[30]. We did not attempt ascertainment of the causes of death, but

Table 5. Details of patients with disease duration of 10–15 years in 1986 compared with those patients who had similar disease duration in 1996.

	1986	1996	p*
Total	62	60	—
Sex	F 42, M 20	F 41, M 19	—
Age	61 (40–82)	59 (30–86)	0.49
Disease duration, yrs	12 (10–15)	12 (10–15)	0.74
DMARD (%)			
D–penicillamine	28 (45)	2 (3)	
IM sodium aurothiomalate	12 (19)	11 (18)	
Sulfasalazine	6 (10)	10 (17)	
Azathioprine	15 (24)	6 (10)	
Chloroquine	0	5 (8)	
Methotrexate	1 (2)	26 (44)	
Joint tenderness, Ritchie index	5 (0–30), n = 59	6 (0–28), n = 34	0.93
ESR, mm/h	27 (2–91), n = 44	20 (2–87), n = 31	0.18
Larsen radiographic score	44 (0–135), n = 14	28 (4–106), n = 31	0.17
HAQ	23 (0–60), n = 47	17 (0–60), n = 31	0.04

*Wilcoxon rank sum test

Table 6. Details at start of study of patients who underwent large joint replacement compared with those who did not. Results expressed as median (range).

	Joint Replacement	No Joint Replacement	p
Men	5	72	—
Women	39	171	0.02
Age of RA onset, yrs	38 (16–59)	43 (16–79)	NS
Disease duration, yrs	14 (1–44)	7 (1–48)	0.002
Joint tenderness, Ritchie Index	4 (0–23)	3 (0–30)	NS
HAQ	29 (1–60)	7 (0–55)	0.0004
ESR, mm/h	36 (5–100)	20 (1–98)	0.0003
Larsen radiographic score	37 (0–135)	17 (0–132)	0.006

NS: Not significant.

cardiovascular disease is perceived as the most common, with infection and lymphoproliferative diseases also being excessive[30,31]. The optimism of some reports suggesting a fall in mortality is not borne out by a recent study that found no secular decline when RA cohorts were studies at 10 year intervals from 1950 to 1996[32].

A disparity between the seemingly stable clinical status of our patients and their radiological deterioration is similar to observations by others[33]. Predictors of radiographic erosions in early RA include a high ESR or C-reactive protein[6,34]. We could not confirm the prognostic value of ESR among our population with established disease followed over a relatively long period. This may imply that the acute phase response may be less predictive of radiological progression in longstanding disease, although fluctuations with time may escape detection and it is unrealistic to anticipate a relationship between radiographic change and a single ESR measurement[35].

Progression of radiographic damage was observed in our patients with short and long histories, suggesting that this process continues steadily throughout the course of the disease despite DMARD treatment. Similar observations have been made by others[36,37], although the rate of erosive damage may be most rapid in the first 2 years[38]. Whether this indicates an inadequacy of DMARD treatments or their inappropriate application or some other phenomenon we cannot say.

If the ESR measurements in our series carried little prognostic value for radiographs and disability over 10 years, they were most certainly indicative of the degree of disability at the time of measurement. These data accord with short term studies in which acute phase response measures have correlated with disability scores[39]. In other words, function is as much a reflection of contemporaneous disease activity as cumulative joint damage. The close relationship between joint tenderness and disability has been emphasized by others[40]. However, the correlations of overall disability with the extent of peripheral joint radiological damage seen in our study have also been well documented[41,42]. Our results suggest that pain is the stronger determinant of functional incapacity in earlier disease. These unremarkable conclusions were proposed in 1987 by Sherrer, *et al*, who, in a study of 2448 patients, suggested that disability was more closely linked to radiological change in late as opposed to early RA[43]. Given the confounding factors on disability of unrecorded comorbidity and the frailty of advancing age, it is testimony to the robustness of the measurements devised by rheumatologists that relationships between active arthritis and disability are so strongly demonstrable in this and other studies. Nevertheless, it has been estimated that socioeconomic, ethnic, psychological, and additional factors account for about 60% of the measurable disability in RA[44].

One feature that must predictably have a beneficial influence on disability in RA is joint surgery. Our results indicate that after 20 years of disease, half of hospital outpatients may have undergone at least one large joint replacement. Few attempts have been made to assess the influence of orthopedic surgery on the longterm outcome of RA. Arguably, large joint replacement has done more to improve the welfare of RA patients than any other treatment including DMARD. However, the very need for surgery could also be seen as a failure of treatment.

One previous series illustrated a similar steady increase with time in the requirement for joint surgery and the necessity of multiple joint replacements[45]. Like us, these authors showed that the likelihood of surgery is greatest for those with the longest histories, the highest ESR values, and the worst disability. Our observation that those undergoing large

joint replacement surgery had more severe hand and foot damage on radiographs reflected the chronicity of their disease and supported the reported relationship between small and large joint disease involvement[41]. We found that women were more likely to undergo joint replacement and this is in accord with the more severe radiological joint damage seen in women[42].

Our study of established disease in 289 patients receiving continuous DMARD treatment is probably representative of worldwide experience. Our patients had an excess death rate between 1986 and 1996, progression of hand and foot radiographic damage even in those with the lengthiest disease duration, worsening of disability, and a requirement for large joint replacement that increased with time. These results occurred despite no worsening of ESR and other clinical indices.

It is possible that more aggressive attempts to treat our patients and to suppress the acute phase response may have resulted in a different outcome. Whether more liberal use of corticosteroids or of combination DMARD would have achieved this, we cannot say[46,47]. Alternatively, it remains possible that joint inflammation and joint destruction are partially or wholly separate processes[48]. In one recent longterm study of patients given a DMARD over 12 years, striking reductions of ESR were accompanied by worsening of function[49]. There is a need to determine whether longterm benefits accrue from a strategic therapeutic emphasis on eradicating the acute phase response. It was in 1988 that Pincus suggested that short term studies may give rise to false expectations, and that radiological and laboratory values are overemphasized at the expense of the longterm outcomes of functional status and death[50]. Perhaps our study serves to reinforce this message.

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