A historical perspective concerning population-based and clinical studies of early arthritis and early rheumatoid arthritis

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ABSTRACT

Research concerning early arthritis and early rheumatoid arthritis (RA) may be considered to have begun with population-based studies in the United Kingdom, the United States and Scandinavia, from the late 1950s to the late 1960s. These studies indicated that the majority of people with clinical findings of RA had no evidence of disease 3-5 years later, and that only about 25% to 30% of people in a population who met the criteria for RA had rheumatoid factor. These findings may have contributed to an underestimation of RA until the severity of long-term outcomes of clinical RA were recognized in the 1980s on the basis of clinical cohorts.

The first major early RA clinical cohort was established in 1957-1963 in Bath, England. Although results at 3 and even 11 years were not overly unfavorable, by 15 and 20 years most patients had severe outcomes of functional declines and premature mortality. The Middlesex (UK) early RA cohort established in 1966-1971 indicated that radiographic abnormalities were observed in about 70% of patients by 2 years of disease, and were seen in most patients initially in the feet. The Memphis (Tennessee, USA) early RA cohort established in 1967-1971 suggested that a progressive course of RA is predicted by a higher number of involved joints at baseline. The Lund (Sweden) early RA cohort established in 1985-1989 indicated rather severe long-term outcomes in patients treated according to traditional conservative approaches to use of disease modifying anti-rheumatic drugs (DMARDs). The early RA study (ERAS) involving nine National Health Service trusts in the UK was established in 1987-93, and showed associations of education level and socioeconomic status with clinical status. The movement towards early arthritis clinics was given great impetus following the work by Emery in the early 1990s. These studies and others described elsewhere in this supplement have contributed to the foundations for the clinical approach to early arthritis in the 21st century.

Population-based studies of RA

The historical roots of the study of early arthritis and early RA may be traced to population-based studies in the 1950s and 1960s in the United Kingdom, the United States, and Scandinavia. These studies indicated that a large proportion of individuals who had clinical findings raising the suspicion of RA showed no evidence of disease 3-6 years later (1-4). Furthermore, population-based studies indicated that the prevalence of a positive rheumatoid factor test in people who met American Rheumatism Association criteria for RA (5) ranged from 19% to 33% (Table I): 24% in Wensleydale, United Kingdom (7), 19% in Tecumseh, Michigan, United States (8), 25% in Jerusalem, Israel (9,10), 24% to 33% in Native Americans in the Western United States (11-13), and 21% in Heinola, Finland (14).

In retrospect, these findings suggest that most people with RA identified in populations differ from most patients with established RA observed in the clinical setting, of whom 60-80% had a positive rheumatoid factor test (15) and most had progressive disease (16-18) with radiographic progression (19-21), severe functional declines (16,17), frequent work disability (16,22,23), and pre-mature mortality (16,24,25). These early population studies may explain in part why clinical RA was regarded "in the majority of patients as a disease with a good prognosis" (26),in contrast to the current view of RA as a medical emergency (27,28). The interpretation of these studies is instructive regarding early arthritis and is summarized in this essay.

Table I. Prevalence of rheumatoid factor (RF) in individuals identified in population-based studies as meeting criteria for rheumatoid arthritis (RA).

	Wensleydale UK (1960)	Tecumseh Michigan, USA (1959-1960)	Jerusalem Israel (1962-64)	Blackfeet Indians Montana, USA (1961)	Pima Indians Arizona, USA (1961)	Heinola Finland (1961)
Reference number	(6, 7)	(8)	(9, 10)	(11-13)	(11-13)	(14)
RF test	Latex fixation	Latex fixation	Latex fixation*	Bentonite flocculation	Bentonite flocculation	Waaler-Rose
RF titer	> 1:80	> 1:20	> 1:320	> 1:128	> 1:128	> 1:64
No. of individuals tested	870	6590	1602	1046	959	539
ARA criteria	Definite & probable	Definite, probable & possible	Definite & probable	3-7 Criteria	3-7 Criteria	Definite
RA prevalence by criteria (%)	4.9%	6.1%	2.4%	3.6%	4.5%	3.5%
Prevalence of positive RF test in individuals who met ARA criteria for RA (sensitivity) (%)	24%	19%	25%	24%	33%	21%

*Data also available for Rose-Waaler RF tests, in which only 12% of individuals meeting ARA criteria for RA had positive tests.

Pioneering population-based studies in the UK

The pioneering studies of Lawrence and Kellgren (29, 30) present many important lessons in both the methodology and results of population-based research in rheumatology. An early observation (31) was that only 42% of individuals whose serum was positive for rheumatoid factor were found to have RA, and over a 5-year follow-up another 18% developed clinical or radiographic evidence of the disease. Nonetheless, many rheumatoid factor positive individuals did not develop RA.

Lawrence and Ball also recognized early evidence for a genetic influence on RA, through the examination of 183 relatives of patients with RA compared to a control group (32). In families of seropositive patients the clinical, radiologic and serologic evidence of RA were 4 times more frequent than in control subjects, while no evidence of higher levels of RA was seen in families of seronegative patients.

Kellgren and Lawrence reported that 36 of 380 individuals (9%) in a population-based study described an episode of severe transient arthritis (33). In a follow-up study of 653 males and 690 females (Table II), Lawrence and Bennett found that 5% of males and 7% of females gave a history of one or more attacks of polyarthritis (2). Only 7% of these individuals were rheumatoid factor positive, and very few had radiographic changes of RA. They described this phenomenon as "benign polyarthritis" and suggested that the majority of individuals affected with polyarthritis had a benign syndrome (2).

Early population-based studies in the US

Two classical population-based studies were performed in the United States in the 1960s, in Tecumseh, Michigan (3) and Sudbury, Massachusetts (4). The Tecumseh study conducted baseline examinations during 1959-1960 in a town of about 9,500 residents in the southern Michigan (3). Of those persons who were more than 6 years of age in the population, 7,207 (87%) participated in the study in 1959-1960. A

Table II. Prevalence of past polyarthritis by age and sex in a population based analysis of 653 males and 690 females in the United Kingdom.

	MALES					FEMALES					BOTH	
			Past polyarthritis					Past polyarthritis			Past polyarthritis	
Age (yrs.)	Total in sample	Total examined	Total No.	%	With residual	Total in sample	Total examined	Total No.	%	With residual	Total	% with residual
-24	125	105	6	6%	0	122	106	4	4%	0	10	0%
-34	131	119	4	3%	0	115	106	3	5%	0	9	0%
-44	127	107	4	4%	2	148	124	7	6%	4	11	50%
-54	169	151	6	4%	0	171	152	13	9%	3	19	16%
-64	102	93	10	11%	3	129	112	11	10%	2	21	24%
65+	91	78	4	5%	2	115	90	10	11%	6	14	71%
Total	745	653	34	5%	7	753	690	50	7%	15	84	26%

Source: (2)

Table III. Follow-up study over 3-5 years of 402 subjects in the Tecumseh study in 1959-1960, who were also re-examined in 1962-65.

Diagnostic group in 1959-1960	No. of subjects re-examined in 1962-1965	Diagnostic group in 1962-1965				
		No evidence of disease	Questionable or possible	Probable	Likely	Positive RF test only
Questionable or possible	231	128	48	15	1	39
Probable	47	22	10	6	3	6
Likely	19	4	2	6	4	3
Positive RF test only	105	46	8	2	0	49
Total	402	200	68	29	8	97

Source: (3)

Table IV. Follow-up (3 to 5 years) of American Rheumatism Association (ARA) diagnosed rheumatoid arthritis in the Sudbury Study.

Initial ARA class	Total no. of subjects	No. of subj. re-examined	Final ARA class		
			Probable RA	Definite RA	Probable & definite RA
Probable RA	78	73	7	4	11
Definite RA	40	36	7	12	19
Total	118	109	14	16	30

Source: (4)

re-examination was performed in 1962-1965 (Table III), with special focus on 402 of 563 individuals who had clinical findings suspicious for RA or a positive latex fixation test for rheumatoid factor at the baseline examination.

The 3-5 year review indicated that only 19 of 66 individuals (29%) who met the definition of likely or "probable RA" at baseline met the same definitions at re-examination 3-6 years later, while 12 of the 66 (18%) met the definition of possible RA,9 (14%) had positive rheumatoid factor only, and 26 (39%) had no signs of the disease (3) (Table III). The status of 161 subjects (29%) who did not participate in the re-examination was not known, although the baseline characteristics of these subjects were similar to those who participated in the re-examination (3).

In the Sudbury study, the adult population of Sudbury, Massachusetts was invited to participate in a medical examination in 1964, in order to determine the prevalence of RA and to compare the clinical value of two sets of criteria – the preliminary ARA criteria being used at that time (34) and the New York Criteria (35). 77% of the population (n = 4,552) participated in the study. Subjects who initially met 1 or more of the New York Criteria or 3 or more of the preliminary ARA criteria were re-examined 3-5 years later (4).

Initially, 40 subjects met the ARA criteria for definite RA; 19 of 36 (53%) who were re-examined 3-5 years later did not meet the ARA criteria for probable or definite RA (Table IV). Of 73 subjects who initially met criteria for probable RA at baseline, only 11 (15%) met criteria for probable or definite RA during the re-examination (4).

These population-based studies provided data concerning the prevalence of RA and rheumatoid factor. The findings were correct in concluding that self-limited polyarthritis was more common than progressive RA in general populations. However, it is now recognized that RA in the clinical setting differs from RA in population studies, in that a far higher proportion of patients have progressive disease. These differences were not widely recognized until the 1980s, when the severity of long-term outcomes of clinical RA were reported from several sites.

Clinical cohorts of early RA

The population-based studies were followed by the establishment of a few cohorts of patients with early RA in clinical settings in the United Kingdom and other European countries, as well as in the United States; some of these cohort studies are briefly described here.

The Bath Cohort: The first hospital-based cohort of patients with early RA

An early hospital-based cohort was established in 1957-1963 in Bath, UK (36), which included 100 patients who met the ARA criteria (5) for definite or classical RA and who had a baseline visit within one year of their first arthritis symptoms. The outcomes of this cohort were reported after 3 and 11 years (36), 15 years (18), 18 years (37), 20 years (38), 25 years (39), and 40 years (40).

A significant decline in functional capacity was seen over 3, 11, and 15 years (Table V). The greater change was seen between year 11 and year 15, rather than between year 3 and year 11, in that the proportion of patients in functional capacity grades 1 and 2 declined from 95% to 75% from year 3 to year 11, but to 49% at year 15, while the proportion in grades 3 and 4 was 5%, 25% and 51% in years 3, 11 and 15. Only 28% of the patients remained in the same

Table V. Bath series: Functional capacity in 65 survivors in reviews at 3, 11 and 15 years.

Functional capacity	Year 3		Year 11		Year 15	
Grade 1	43	(66%)	27	(42%)	9	(14%)
Grade 2	19	(29%)	22	(34%)	23	(35%)
Grade 3	2	(3%)	14	(22%)	25	(39%)
Grade 4	1	(2%)	2	(3%)	8	(12%)
Total	65	(100%)	65	(100%)	65	(100%)

Source: (18)

functional grade between 3 and 15 years, and the others deteriorated by 1, 2 or 3 grades (18). These results indicated that studies which do not include observations for 15 years would be likely to underestimate outcomes of RA.

At the 20-year review, the number of affected joints increased further than was seen at the 11-year review (38), with marked radiographic damage of the hands and cervical spine (41). The investigators concluded that at least 59% of patients with classical or definite RA seen in a hospital setting will become severely disabled over the long-term (42).

Of the 100 patients at baseline, 46 had died by the 20-year review, 35% of whom had been classified as grade IV, i.e., wheelchair-bound or bedridden, and an additional 24% were classified as grade III at the last report of functional capacity. By the 25-year review, 63 patients had died; RA was regarded as either having directly caused or contributed to death in one-third of these patients. Mortality was again predicted by poor functional capacity and higher disease activity at presentation (39).

Therapies were reviewed in detail at the 15-year review. Of the 65 survivors, 55 had taken hydroxychloroquine, 35 intramuscular gold, 8 D-penicillamine, 5 azathioprine, and 29 corticosteroids, usually prednisolone for some time. Twenty-nine of 65 survivors had undergone a total of 69 surgical procedures on their joints (18).

At the 20-year review of 54 survivors, three patterns regarding the course of the disease were described: (i) 12 patients had remitting RA, initially active RA for up to 5 years, but with no sustained return of active disease thereafter; (ii) 12 had chronic remitting and relapsing RA, with periods of remission lasting 12 months or more, but with intermittent return to active disease; and (iii) 25 had chronic persistent RA with sustained disease activity and no remission lasting for as long as 12 months. Five patients had an atypical course (38).

The Bath study was the first conducted in a clinical setting over a period of 20 years and it indicated that RA was a severe disease, a very different conclusion from that of the population-based studies. About 60% of the patients become disabled over 20 years, and mortality rates were higher than in the general population (42). The severe course of clinical RA in most patients in the Bath study – with progression of joint damage, functional losses, and premature mortality – has been confirmed in cross-sectional and longitudinal observational studies of RA over the decades from many countries in Western Europe and the United States, including in patients with early RA, as reviewed in (43).

The Middlesex cohort

A prospective study of patients with RA who had symptoms for less than one year was established between 1966 and 1971 at Middlesex Hospital, London, UK (44, 45). Again, all patients met the ARA criteria (5) for RA. The aim was initially to gather detailed information on the characteristics of the disease onset. The disease began more often in the colder months and was usually insidious, symmetrical, and involved the upper limbs (44).

The patients were followed prospectively and outcome was assessed after a mean of 4.5 years. There was a trend for a poorer prognosis in older patients, patients with an insidious onset, and patients with early progression to symmetrical involvement (44). The joints most commonly affected were the metacarpophalangeal joints, the proximal interphalangeal joints, and wrists, followed by the metatarsophalangeal joints and shoulders (46). More severe disease was associated with a pattern of large joint involvement (shoulder, elbow, wrist, knee) and a pattern based on metatarsophalangeal joints I and III (47). Extra-articular manifestations that were common in the early stages included hand-muscle wasting, carpal tunnel syndrome, lymphadenopathy, non-specific ankle swelling, and rheumatoid nodules (48).

Radiographic changes appeared very early and occurred in 71% of patients over 5 years (49) (Table VI). Overall, 29 of 94 patients (31%) developed erosions in the first year of disease, 31 patients (33%) developed erosions in the second year, 5 patients (6%) between the second and third year, and 2 patients (2%) between the third and fifth year of disease. Therefore, 60 of 67 patients (90%) who developed erosions, developed them during the first 2 years of disease, although some patients developed erosions after the first 2 years. Erosive changes occurred initially in the feet more commonly than in the hands, and often preceded radiographic joint-space narrowing. It was suggested that frequent x-ray examination of the feet and hands in the first 2 years after presentation is needed to identify patients at risk for serious joint damage (49) (Table VII). The severity of peripheral radiographic damage was associated with the presence of rheumatoid factor (50). In some patients, erosive changes become stable at an early stage in the disease (51).

During the first 10 years, 54 patients developed rheumatoid changes of the cervical spine, of whom 34 (63%) had subluxations. The severity of rheumatoid neck damage, including cervical subluxation, was associated with the severity of peripheral erosions (52). Subluxation of the cervical spine was

Table VI. Middlesex early RA cohort: Number of patients developing "diagnostic" erosive change among 94 patients with early rheumatoid arthritis.

Time, months	X-ray of hands	X-ray of feet	Hands and feet	Total
0-12 months	5	12	12	29
13-24 months	6	8	17	31
25-36 months		2	3	5
36 months		2		2
Total	11	24	32	67

Source: (49)

Table VII. Middlesex early RA cohort: Site of first diagnostic erosions (67 patients).

Site	Involved alone	Involved with another site	Total
Ulnar styloid	2	12	14
Radiocarpal joint	2	6	8
Remainder of carpus	2	9	11
Metacarpophalangeal	1	14	15
Proximal interphalangeal	2	10	12
Distal interphalangeal		5	5
Metatarsophalangeal	26	26	52
Interphalangeal hallux		6	6

Source: (49)

also associated with the presence of HLA-Dw2 and HLA-B7 cross-reacting groups (50).

Sixty-four survivors were assessed again at a mean of 15.2 years from presentation, and were compared to 29 patients who had died (45). As expected, those who died were older. Over the first year of disease, they had lower haemoglobin levels, a lower body mass, higher sedimentation rates and higher levels of blood urea. One-fifth at entry to the study and two-fifths by the time of death, had poor functional capacity. Of 64 survivors, 6 had poor functional capacity at entry and 9 after 15 years. A combination of early erosive change, seropositivity, poor grip strength and cervical subluxation predicted the outcome correctly in 73% of survivors (45). The pattern of disease progression was chronic-persistent in 26%, relapsing and remitting in 40%, and non-recurrent in 34% of patients (53).

Data reported on this cohort were important to establish evidence for radiographic changes within the first 2 years of disease, which was confirmed and extended by others (54, 55). This study provided an important component of the change in the approach to RA from long-term observation in a "pyramid" approach to aggressive early intervention. Secondly, the findings illustrated that radiographic data are critical to evaluate the progression of RA, as functional status may improve over the first few years of treatment, but radiographic progression was common in most patients using traditional treatment approaches.

The University of Tennessee (UT) Early Rheumatoid Arthritis (RA) Cohort (The UT Memphis Cohort)

In 1967-1971, 50 young adults (16-44 years) with early arthritis who met American Rheumatism Association (ARA) criteria (5) for at least probable RA, and had a physician diagnosis within 6 months of symptom onset, were enrolled in the University of Tennessee (UT) Memphis Cohort (56, 57). Patients were examined clinically at baseline and twice yearly for 5 years; radiographs of the hands and wrist, and blood samples for comprehensive laboratory tests were taken annually.

The goals of the study were to define the patterns of onset and disease course in early arthritis. The median interval from onset of the first symptoms of arthritis until entry into the study was 5 months. At study entry, joint manifestations were similar in rheumatoid factor positive and negative patients, but during the follow-up, rheumatoid factor positivity was associated with development of subcutaneous nodules and bone erosions (56). Predictors for more favorable outcomes over the first 3-4 years included male sex, acute onset, age less than 30 years, fewer swollen upper extremity joints, and negative rheumatoid factor (56). In retrospect, this clinical picture appears to characterize patients with a self-limited reactive arthritis, although a positive HLA B27 test was an exclusion criterion for this study.

At 5 years after study entry, 18 (36%) patients had no swollen joints and no erosions (Category I), 22 (44%) had swollen joints but no erosions (Category II), and 10 patients (20%) had erosions (Category III) (53). An index of 6 entry items was created including positive rheumatoid factor; 2 or more swollen upper extremity joints on examination (2 points each joint); history of Raynaud-like symptoms; malaise or weakness at the onset of arthritis; white race; and female sex. Zero to 2 points on entry predicted category I, 3 to 5 points category II, and 6 to 8 points category III at 5 years (58), with 80% accuracy in classifying patients in the 3 categories in a multivariable model.

The mean level of painful or tender joints at baseline was 26 in 6 patients who had progressive RA, compared to 13.5 in 26 patients with polycyclic-continuing disease, 8.2 in 14 patients with a polycyclic intermittent course, and 7.0 in 4 patients with monocyclic arthritis (Table VIII) (59). Similar results were seen for swollen joints (Table VIII), indicating that patients who were destined to have a progres-

Table VIII. Memphis early rheumatoid arthritis cohort: Mean levels of painful-tender and swollen joints at entry according to various course patterns of arthritis over 6 years.

Course patterns	Painful or tender joints			Swollen joints		
	Cases	Entry mean	Slope*	Cases	Entry mean	Slope*
Monocyclic	4	7.0	-4.7	17	2.8	-1.7
Polycyclic						
Intermittent	14	8.2	-0.6	18	4.7	-0.4
Continuing	26	13.5	-0.8	13	6.8	-0.3
Progressive	6	26.0	+2.3	2	12.0	+2.9
All patients	50	13.2	-0.6	50	4.5	-0.3

*Mean annual slope of each patient's linear regression.
Source: (59)

Table IX. Early Rheumatoid Arthritis Study (ERAS). Patient characteristics and clinical markers according to educational attainment.

	n	Median (interquartile range) or count (percentage)		Percentage above median or positive for characteristic: University/ National diploma (n=74)	A level/ vocational training (n=210)	"O" level/ CSE (n=127)	None/no CSEs (n=274)	P value for trend
Age (years)	685	56	(44-65)	29.7%	42.4%	33.9%	52.2%	-
Female (%)	685	442	(64.5%)	47.3%	54.8%	82.7%	68.3%	-
Clinical markers at presentation visit								
HAQ	685	0.5	(0.125-1.625)	29.7%	39.1%	44.1%	53.7%	0.002
ESR	572	34	(17-58)	45.1%	49.7%	44.7%	47.6%	> 0.2
Joint score	684	14	(7-25)	40.5%	47.1%	33.9%	55.3%	0.13
Pain score	660	41	(22-61)	40.3%	45.4%	50.4%	54.9%	0.04
Grip strength	684	140	(95-210)	64.4%	54.3%	44.9%	43.1%	0.06
Clinical markers at 3 years								
HAQ	649	0.75	(0.25-1.375)	35.2%	40.3%	53.7%	53.5%	0.002
ESR	535	20	(10-41)	48.5%	40.4%	56.9%	50.5%	> 0.2
Joint score	646	7	(2-16.5)	26.8%	45.3%	43.0%	51.4%	0.006
Pain score	644	27	(7-50)	40.9%	46.2%	58.5%	54.7%	0.006
Grip strength	648	170	(115-260)	65.2%	53.2%	39.7%	42.8%	0.003

CSE: Certificate of Secondary Education; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate.
Source: (71)

sive course had a higher number of active joints at presentation.

The outcomes in the Memphis cohort appear considerably more favorable than those in the Bath and Middlesex UK cohorts, but are consistent with the observations from population-based studies presented above (3, 4). In retrospect, three important differences can be pointed out between the UK and Memphis cohorts. First, the UK cohorts allowed patients whose symptoms may have begun as many as 12 months earlier, while the Memphis cohort included only patients with a symptom onset of less than 6 months, which may select for more patients with self-limited disease or a diagnosis other than RA. Secondly, the Memphis cohort was monitored for 5 years, while the UK cohorts were monitored for 15-25 years and higher rates of joint damage and mortality were seen after 15 years. Thirdly, functional losses and mortality were not analyzed in the Memphis cohort. Nonetheless, this series represents one of the first efforts to monitor an inception cohort over an extended period of time, and established that high levels of joint involvement were associated with a more progressive course of disease.

The Lund Early Rheumatoid Arthritis Cohort

The Lund Early Rheumatoid Arthritis Cohort consisted of 183 patients with symptoms of less than 24 months at enrollment in 1985-89 (60), all of whom had definite RA (5). A 2-year review included the first 89 patients (60). Radiographic damage increased steadily in the hands and feet; 82% of the patients had erosions after 2 years, and one-third developed hand deformities. Six patients developed rapidly progressive damage in large joints, 5 in the hip joints and 1 in the shoulder joint, all requiring joint replacement. The median HAQ score at 2 years was 0.9 with an interquartile range of 0.4 to 1.3. Fourteen (16%) patients were considered to be in remission (61), but 3 of them had nodules and 4 had hand deformities.

After 5 years, 89% of patients had erosions and radiographic damage was 26% of the maximum (62). It was recognized that many variables suggested improved status, including the Ritchie Index of tender joints, functional scores, and pain scores, but radiographs showed progression (62). At the 10-year review, all but 4% of the patients had erosions and median radiographic damage was 34% of maximum (63). By 10 years, 30 patients (17%) had large joint replacement.

Functional capacity according to the HAQ increased from a median of 0.8 at the study start to 1.1 after 10 years ($p = 0.001$), while the median pain score remained stable. Sixteen patients (10%) were severely disabled at 10 years (64).

At the 2-year follow-up, 23 of the 62 initially employed patients (37%) had stopped working due to RA, and 10 other patients had changed work tasks or reduced their working time due to RA (65, 66). Mortality over 8-13 years was not statistically significantly increased compared to the general population (67).

During the first 2 years of observation, 33 patients (31%) had been treated with DMARDs for at least 6 months, including penicillamine in 18 and chloroquine in 12 patients (60). Over 10 years, 137 (75%) of patients had been treated with any DMARDs and 84 (46%) with low dose oral glucocorticoids. At the 10-year visit,23% of patients were taking methotrexate (64).

The outcomes in this cohort included a high work disability rate early in the disease course and substantial radio-

graphic progression in most patients. The cohort may be regarded as documenting the "natural history" of early RA using traditional DMARDs in traditional strategies, and showed that radiographic damage may progress even though clinical measures appear to have improved. That observation was made in other clinical settings as well (68).

The ERAS (Early Rheumatoid Arthritis Study) Cohort

An inception cohort of RA patients was recruited from the rheumatology outpatient departments of 9 National Health Service (NHS) hospital trusts in England beginning in 1987 (69, 70). All consecutive patients with RA of less than 2 years' duration, and who had no prior DMARDs, were recruited and followed up for 5 years. Standard clinical, laboratory and radiological assessments, and all hospital-based treatments were recorded prospectively at presentation and annually. Outcome measures included clinical remission, joint and pain scores, grip strength, radiological evidence of bony erosions, functional ability [functional grades I-IV and Health Assessment Questionnaire (HAQ)], extra-articular features, use of aids, appliances and home adaptations, loss of paid work, and medical/surgical interventions (69, 70).

A 3-year review of 869 patients indicated that socioeconomic deprivation was associated with a more severe clinical course of rheumatoid disease, and these associations were already apparent at presentation (71) (Table IX). These observations confirmed previous reports from the United States of associations of poor outcomes with low socioeconomic status in RA (72-74), as well as associations of low socioeconomic status and cardiovascular disease (75, 76) and poor general health (77,78). The data suggest that assessment of socioeconomic deprivation might help to identify patients with early RA who may need more intensive interventions at an early stage, including more intensive drug treatment.

At the 5-year review, 84% of 732 patients had received second-line drugs. Overall, 113 patients (16%) had marked functional loss as compared to 64 (9.4%) at presentation, while 296 patients (40%) had normal function compared to 243 (33%) at baseline. Home adaptations and/or wheelchair use were seen in 74 (10%) by 5 years. One hundred and seventeen (17%) patients underwent orthopaedic surgery for RA, 55 (8%) for major joint replacements. Marked functional loss at 5 years was more likely in women [odds ratio (OR) 1.63, 95% confidence interval (CI) 1.04 – 2.5], patients older than 60 years of age (OR 1.94, 95% CI 1.3 – 2.9), and patients with health assessment questionnaire (HAQ) scores higher than 1.0 at presentation (OR 4.4, 95% CI 2.8-7.0) (69).

Of 732 patients, 353 (49%) were gainfully employed at the onset of RA. Among these 353 patients, 211 (60%) were still working at 5 years, 104 patients (29%) had stopped because of the disease, and 31 (9%) had retired for reasons other than RA. Work disability at 5 years was more likely in manual workers (OR 2.3, 95% CI 1.4 to 3.8) and in those with poorer baseline HAQ scores (HAQ > 1.5, OR 2.26, 95% CI 1.38 to 3.7). In combination with other baseline variables [erythrocyte sedimentation rate (ESR), sex, age of onset, and radiological erosions], employment outcome was predicted in 78% using multivariate analysis.

The movement toward early arthritis clinics

Emery and Gough (79) pointed out that RA is the most common cause of potentially treatable disability in western countries, based on recognition of the long-term severity of clinical RA since the mid-1980's (16, 18, 19). At that time, general practitioners were advised to give patients a non-steroidal drug for up to 2 years before the use of DMARDs (80). During that interval however the optimal window of opportunity to treat RA inflammation may be lost, as is discussed elsewhere in this supplement. The establishment of early arthritis clinics was advocated, with the characteristics of a large referral population, knowledgeable and cooperative primary care physicians and an enthusiastic organizer (79).

The early arthritis cohorts described in this supplement have provided much valuable data over the past decade. However, more data are needed from special early arthritis clinics supplemented with data which are collected on consecutive patients in rheumatology clinics.

Discrepancies in outcomes of early arthritis in population-based versus clinic-based studies

It is now apparent that most patients classified with early arthritis in the general population have good outcomes with frequent spontaneous remissions, while most patients seen in clinics have poor outcomes with radiographic progression, severe functional declines, work disability, and premature mortality. The most obvious basis for this discrepancy is patient selection. Although subjects in the population may meet the criteria for RA, symptoms may resolve completely over a short period of time, and many subjects identified in population studies never seek medical help, including patients with reactive arthritis or hand osteoarthritis. In contrast, patients who seek care in a medical setting are more likely to have persistent and progressive disease.

Although evidence of greater severity at baseline may ironically predict remission, sustained high joint counts and functional disability predict poor outcomes, as was demonstrated in the analysis of prediction markers for premature mortality in RA (81). However, at this time no single marker or set of markers can be used to predict with certainty whether early arthritis will resolve in some patients and not in others. Further research conducted in early arthritis clinics described in this supplement are designed to address this matter.

Overall, patients with RA appear to have a better clinical status at this time compared to previous decades (82, 83), including improved mortality rates in patients who respond to methotrexate (84, 85). It has been suggested that RA is becoming milder (86). Furthermore, treatment strategies have become more aggressive, and the efficacy of DMARDs has increased over the last 15 years.

While the course of RA in most patients appears improved, this phenomenon remains poorly documented in most rheumatology treatment settings.

Quantitative data collection in routine rheumatology care

It would be ideal to document long-term improvements in patient status in RA over 10-20 years through randomized controlled clinical trials to analyze treatment results. However, long-term clinical trials cannot be conducted in patients with RA because of logistic and ethical considerations (87). Furthermore, even if long-term trials were possible, the inclusion criteria for clinical trials in RA have not changed substantially over the last two decades (88), and the majority of patients seen in standard clinical care do not meet the eligibility criteria used for most of the RA clinical trials conducted over the last decade (89).

One approach to analyze whether patients with RA have better clinical status in recent years compared to the past would be to compare patient status according to quantitative measures in consecutive patients seen in standard clinical care. Quantitative data collection in routine clinical care in all consecutive patients has been unusual in the past, other than laboratory data in some settings. However, the ESR may be normal in up to 40% of patients at presentation (90), and the most significant clinical predictor of work disability, costs, and premature mortality is functional status (91, 92). Therefore, quantitative data collection in consecutive patients with RA might focus on patient self-report questionnaires to assess functional status, as well as pain, and global status (92,93). Of course, documentation may include quantitative joint counts, radiographic scores, and laboratory data. However, patient questionnaire data alone would facilitate documentation of the possible improved outcomes of RA, compared to earlier periods, with new approaches to therapy.

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