Declines in Erythrocyte Sedimentation Rates in Patients with Rheumatoid Arthritis Over the Second Half of the 20th Century

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ABSTRACT. *Objective.* To analyze baseline erythrocyte sedimentation rates (ESR) in cohorts of patients with rheumatoid arthritis (RA), which had been included in a review concerning longterm mortality, in reports published between 1973 and 2008, with baseline observations between 1954 and 2000. *Methods.* A computer search and complementary review of the literature had identified 84 unique cohorts with RA for which mortality over 5–40 years was reported. Baseline ESR data were available for 23 of the 84 cohorts. Mean and median ESR, age, disease duration, and rheumatoid factor (RF) status were compiled and analyzed in tertiles according to first year of patient recruitment. *Results.* Among 7 cohorts recruited initially between 1954 and 1980, median ESR at baseline was 47 mm/h (mean 50 mm/h, range 43–66), compared to median 38 mm/h (mean 41 mm/h, range 34–64) among 8 cohorts recruited between 1981 and 1984, and median 36 mm/h (mean 35 mm/h, range 28–42) among 8 cohorts recruited between 1985 and 1996. The lowest mean ESR among 7 cohorts with baseline in 1980 or earlier was 43 mm/h, and the highest reported mean ESR among 8 cohorts recruited after 1985 was 42 mm/h. In 3 cohorts recruited after 1985 from Sweden, Finland, and Spain, mean baseline ESR was < 30 mm/h. *Conclusion.* Mean ESR fell by 30% in cohorts of patients with RA recruited before 1981 compared to cohorts recruited after 1984. This decline may reflect changes in both the natural history and approaches to therapy of RA. (J Rheumatol First Release June 15 2009; doi:10.3899/jrheum.081255)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   ERYTHROCYTE SEDIMENTATION RATE   MILDER DISEASE

An elevated erythrocyte sedimentation rate (ESR) traditionally has been regarded as a primary indicator of inflammation in diagnosis and monitoring of patients with rheumatoid arthritis (RA). Recent textbooks state that "the erythrocyte sedimentation rate is increased in nearly all patients with active RA"[1], and "at least 5% of patients with clinically active disease may have a normal ESR"[2], implying that a normal value is unusual.

One report published in 1994 indicated that mean ESR was 37 mm/h in women and 34 mm/h in men, and about 40% of patients with RA had a normal ESR[3]. This observation suggested that ESR may have declined over the years, concomitant with better clinical status of patients with RA in recent years compared to previous decades[5]. Baseline ESR data were available in 23 of 84 cohorts included in a recent review concerning mortality in RA, with baseline observations from 1954 to 2000, published between 1973 and 2008[6]. These data are analyzed in our report.

MATERIALS AND METHODS
A database of 84 unique RA cohorts for which mortality outcomes had been reported was compiled for a review article concerning mortality in RA[6]. Patients in these cohorts had been recruited initially between 1954 and 1996, with total period of recruitment between 1954 and 2000, and reported between 1973 and 2008. Only one report for each unique cohort was included in the analyses.

Baseline ESR was reported for 23 of the 84 cohorts (Table 1)[7-29], which were grouped in tertiles according to first year of recruitment, 7 initially recruited in 1954–1980, 8 in 1981–1984, and 8 in 1985–1996. Of the 23 cohorts, 22 were clinical cohorts, and one a population-based cohort in the earliest tertile[6]. Seven of the cohorts were inception cohorts, one in each of the first 2 tertiles, and 5 of 8 in the last tertile, while 15 cohorts were non-inception cohorts of consecutive patients who were recruited in clinical settings.

Age at baseline, disease duration, and percentages of patients who had a positive test for rheumatoid factor (RF) were available for 22, 20, and 19 of the 23 cohorts, respectively. Mean and median ESR, age, disease duration, and percentage of RF-positive patients were compiled and calculated in the tertiles defined by first year of recruitment. Spearman rank order correlations of ESR with age, disease duration, and percentage RF-positive were computed for the entire group.

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Table 1. Mean ESR and other baseline characteristics of patients with rheumatoid arthritis in 84 cohorts studied for mortality outcomes[6]. All 23 reports with baseline ESR are included, listed in chronological order based on first year of recruitment.

Study	Period of Recruitment	Inception Cohort? No/Yes	No. Patients	Age, mean yrs	Disease Duration, mean yrs	RF (% positive)	ESR, mean mm/h
Vandenbroucke 1984[7]	1954–1957	N	209	53.5	8	74	47
Wolfe 1994 (includes Wolfe, 1988 cohort)[8]	1955–1981	N	3501	53.3	9	88	45
Maradit Kremers 2005[9]	1955–1995	N	603	58	—	59	47
Jacoby, 1973[10]	1957–1963	Y	100	51	3 mo	88	47
Gordon, 1973[11]	1965–1966	N	127	55	11.5	93	66
Book 2005[12]	1978–1978	N	152	61	12	85	43
Krause 2000[13]	1980–1987	N	256	64.3	8.5	88	57
Wolfe 1988[14]	1981–1985	N	400	54.8	9.5	80	37
Chehata 2001[15]	1981–1985	N	309	53	2.5*	—	45
Choi 2002[16]	1981–1999	N	1240	—	—	83	34
Wolfe 2003[17]	1981–1999	N	1387	55.5	7.1	85	41
Kremer 1997[18]	1982–1983	N	29	60.6	31.4	—	36
Sokka 1999[19]	1983–1989	Y	135	50.5	6.5 mo	71	38
Maiden 1999[20]	1984–1985	N	200	57*	7*	—	64*
Callahan 1997[21]	1984–1986	N	210	56.6	9.7	—	35
Lindqvist and Eberhardt 1999[22]	1985–1989	Y	183	51	11 mo	75	29*
Kroot 2000[23]	1985–1997	Y	622	53.3	—	82	41
Peltomaa 2002[24]	1986–1993	Y	150	51.8	6.8 mo	65	34*
Soderlin 1998[25]	1989–1991	N	103	59.5	18.4	88	27
Mattey 2007[26]	1991–1991	Y	401	59.4	6 mo	73	38*
Nikolaisen 2008[27]	1993–2000	Y	111	61*	4.5 mo*	78	41*
Gonzalez-Gay 2007[28]	1996–1996	N	182	59.7	10.5	78	28
Escalante 2005[29]	1996–2000	N	779	55.6	11.1	79	42

* Median.

RESULTS

Among 7 cohorts recruited initially between 1954 and 1980, mean ESR ranged from 43 to 66 mm/h (median 47 mm/h, mean 50; Table 2). Among 8 cohorts recruited initially between 1981 and 1984, mean ESR ranged from 34 to 64 mm/h (median 38 mm/h, mean 41). Among 8 cohorts recruited initially between 1985 and 1996, mean ESR ranged from 28 to 42 mm/h (median 36 mm/h, mean 35; Table 2), 30% lower than in the cohorts recruited between 1954 and 1980.

The highest reported mean ESR was 66 mm/h, in patients recruited in Canada between 1965 and 1966[11]. Mean baseline ESR was < 30 mm/h in 3 more recent cohorts of patients from Sweden recruited 1985-1987[22], patients from Finland recruited 1986-1993[25], and patients from Spain recruited in 1996[28]. A decline in ESR was seen in both inception cohorts

Table 2. Mean and median baseline ESR in patients with rheumatoid arthritis in 23 studies that reported ESR[7–29], grouped by years in which patients were recruited.

Tertile	First year of Recruitment	No. of Inception Cohorts/Total no. of cohorts	Total Period of Recruitment	Period of Publication	ESR, mm/h			Percentage of Patients with RF+*		Age, yrs		Disease Duration, yrs*	
					Range	Median (IQR)	Mean ± SD	Median (mean)	n > 75%	Median (mean)	n > 55	Median (mean)	n > 5
1	1954–1980 (7 studies)	1/7	1954–1995	1973–2005	43–66	47 (45–57)	50 ± 8	82 (88)	5/7	55 (56.6)	4/7	8.8 (8.2)	5/6
2	1981–1984 (8 studies)	1/8	1981–1999	1988–2003	34–64	38 (35–45)	41 ± 10	80 (81.5)	3/4	56.1 (55.6)	4/8	7.1 (9.7)	6/7
3	1985–1996 (8 studies)	5/8 5/8	1985–2000	1998–2008	27–42	36 (28–41)	35 ± 6	77 (78)	6/8	57.5 (56.4)	5/8	0.9 (6.1)	3/7
Total	1954–2000 (23 studies)	7/23	1954–2000	1973–2008	27–66	41 (35–47)	42 ± 10	80 (80)	14/19	55.6 (56.2)	13/23	8.3 (8.0)	14/20

* Rheumatoid factor (RF) positivity was reported for 19 of 23 cohorts; duration of disease was reported for 20 of 23 cohorts.

and non-inception cohorts, although there was only a single inception cohort in each of the first 2 tertiles, and only 3 non-inception cohorts in the third tertile.

Mean age in the 23 cohorts ranged from 51 to 64.3 years, with an overall mean of 55.6 years (median 56.2 yrs). ESR and age were not correlated significantly (rho = –0.02, p > 0.05). Median duration of disease was 8.0 years, with median durations in the tertiles of 8.8, 7.1, and 0.9 years, respectively, reflecting that 5 of the 8 cohorts in the most recent tertile were inception cohorts, compared to only one cohort each in the earlier tertiles. However, mean disease duration was 8.2, 9.7, and 6.1 years in the respective tertiles, and 5/6, 6/7, and 3/7 cohorts had mean disease duration > 5 years. ESR and disease duration were not correlated significantly (rho = –0.12, p > 0.05). The median proportion of RF-positive patients was 80% overall, including 82%, 80%, and 77% in the respective tertiles (mean 88%, 82%, and 78%). ESR and the percentage of patients with positive RF were correlated at rho = 0.31 (p > 0.05).

DISCUSSION

These data indicate a decline of 30% in mean ESR, from 50 mm/h in cohorts recruited in 1980 or earlier, to 41 mm/h in cohorts recruited 1981-1984, to 35 mm/h in cohorts recruited after 1985. The lowest mean ESR of 7 cohorts with baseline in 1980 or earlier was 43 mm/h, and the highest reported mean ESR of 8 cohorts recruited after 1985 was 42 mm/h. Three cohorts recruited after 1985 had mean ESR < 30 mm/h (Table 1). A relatively similar pattern was seen in inception and non-inception cohorts, suggesting that these findings may result from milder disease at presentation[30] as well as effects of more aggressive treatment strategies[31].

We considered whether the trend to lower ESR data in recent years might be explained by age, duration of disease, or RF status. No meaningful differences among the 23 cohorts were seen according to age, and no correlation of ESR with age was seen. This phenomenon reflects that the mean age of the cohorts was quite similar, and is independent of the recognized association of higher ESR with higher age. With respect to duration of disease, 5 of the 8 cohorts in the most recent tertile were inception cohorts, compared to only 1 in the each of the earlier tertiles. Nonetheless, an inception cohort would be anticipated to have a higher ESR than a cohort after treatment, albeit that treatments available in the past may not have reduced the ESR to the extent of currently available treatments. The correlation of ESR with duration of disease, rho = –0.12, was also essentially meaningless.

The correlation of ESR with RF of rho = 0.31 was expected, but not statistically significant with low numbers of cohorts in this study. The proportion of patients who were positive for RF, 80%, is higher than 69% in an extensive metaanalysis of 50 studies[32] and 74% in the QUEST-RA (Questionnaires in Standard Monitoring of RA) database of

4363 patients from 48 sites in 15 countries available when that report was prepared[33]. This finding may reflect a goal of the investigators who assembled the included cohorts to have a high level of diagnostic certainty for RA. Nonetheless, the cohort with the lowest mean ESR of 27 mm/h included 88% of patients with positive RF[25], the second highest level of any cohort (Table 1). The ESR results cannot be explained according to differences in RF positivity, age, or duration of disease.

A number of limitations are seen in this study. First, the data may be viewed as based on a "convenience sample" of cohorts from another study, rather than on a systematic review of all published cohorts. However, no selection for ESR (or any other variable) was apparent in the reported studies. A search revealed about 86,000 possible additional reports to be considered for inclusion in a systematic review. Many of these studies are clinical trials, which should not be included in an analysis of ESR data in unselected cohorts of patients diagnosed with RA. Clinical trial inclusion criteria generally select for individuals with elevated ESR, and it is recognized that many patients with RA seen in usual care at this time do not meet inclusion criteria for clinical trials[34]. Further, screening all 86,000 identified reports at a rate of 100 per day would require 2.4 years — and would appear unlikely to change the results.

Second, many of the cited reports may have included missing ESR values in some patients. Again, there appears no evidence of selection. Third, ESR values in most studies may reflect treatment differences between inception and non-inception cohorts. However, results were similar for both types of cohorts, although only 1 inception cohort was available in each of the first 2 tertiles. Fourth, these patients generally were recruited from advanced rheumatology centers in North America and Western Europe, who are not necessarily representative of all patients with RA in other areas[35].

It is possible that the mean ESR may be an overestimate, resulting from "spectrum bias"[36], as patients with normal laboratory tests may be less likely to be referred to rheumatology treatment centers for possible RA. The details of mean ESR data appear less important in care of individual patients with RA than recognition that ESR may not be elevated in a large proportion of patients with RA at this time.

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