EXTENDED REPORT

Mortality in patients with rheumatoid arthritis treated actively from the time of diagnosis

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Objectives: To evaluate the mortality rates among patients with early rheumatoid arthritis (RA) treated actively according to the "sawtooth" strategy.

Methods: The study included 150 early, disease modifying antirheumatic drug (DMARD) naive patients with RA from two patient cohorts. The first cohort was assembled between 1986 and 1989 (87 patients, aged 19–65 years at onset) and the second between 1991 and 1993 (63 patients, aged 27–83 years at onset). The mean duration of symptoms at the time of diagnosis was 7.1 months (range 2–24). The clinical data and the use of DMARDs were systematically recorded. The causes of death were obtained from death certificates and medical records, if available. The data were collected up to 1 November 2000.

Results: During a follow up time of 7–14 years, 24 patients died. The standardised mortality ratio was not increased (0.93 in the first cohort and 1.62 in the second cohort). Age adjusted mortality rates did not differ statistically significantly between the two patient cohorts. The causes of death included malignancy (8 patients); cardiovascular diseases (10); respiratory disease (4), including two patients with pneumonia; sepsis (one); and RA (one). High inflammatory activity, disease activity, and poor functional ability at study entry, and the presence of extra-articular features during the follow up were more common among the patients who had died.

Conclusions: No statistically significant increase in mortality rates was seen in these actively treated early RA cohorts during the follow up. High disease activity at the onset and the development of extra-articular features seem to be associated with mortality.

Rheumatoid arthritis (RA) is a chronic disease which has been associated with a shortened life expectancy.[1–7] In most studies mortality rates have been presented by a standardised mortality ratio (SMR), which expresses the observed number of deaths in the study group compared with the expected number of deaths in the general population. Usually the mortality rates have been lower in population based studies than in clinical study settings. The lowest SMR, 0.87, was found by Lindqvist and Eberhardt in 1999 from Sweden[8] and the highest SMR, 3.00, by Prior *et al* in 1984 from the UK.[9] Overall, Wolfe calculated from 10 studies (comprising 8899 patients with RA) a combined SMR of about 2.0 in patients with RA.[10]

Although most studies show increased mortality rates among patients with RA, in some studies no difference in mortality rates compared with general population has been found. In a large population based study by Linos *et al* with 24 years follow up the SMR was only 1.13.[11] Two recent prospective hospital based studies of patients with early RA, disease modifying antirheumatic drug (DMARD) naive at entry, from Sweden[8] and the Netherlands[12] with a mean follow up of 9.8 and 5.8 years, respectively, found no excess mortality among these patient cohorts.

It has been proposed that the disease of RA itself is a cause or a contributing factor in 20%[3] to 50%[13] of all deaths of patients with RA. The disease activity, extent of joint destruction, and disability as consequences of RA may be associated with mortality.[2 3] Higher mortality has also been found in patients with extra-articular features.[14 15] Secondary amyloidosis associated with longstanding active RA contributed to excess mortality among patients with RA at least in Finland.[16 17]

The role of drug treatment as a contributor to mortality among patients with RA has also been evaluated in many studies. The risk of development of malignant diseases after using immunosuppressive treatments, especially azathioprine, has been suspected, but the results are conflicting.[3 18] There is also some evidence that methotrexate, which may be associated with a rise of homocysteine levels, may increase the risk for cardiovascular diseases.[19] A large cross-sectional study from Finland[20] showed that the use of non-steroidal anti-inflammatory drugs (NSAIDs) carried a higher risk of lethal complications than DMARDs. In addition, the role of corticosteroids as a possible predisposing factor to cardiovascular diseases must be remembered.[21]

During the past decade the treatment of RA has become more active. DMARDs are started earlier and new treatments have become available, including the use of combination therapy. Although there is evidence that these new treatments improve short term outcome, including the functional ability of patients with RA, knowledge of the effect of these treatments on long term outcome is scarce. This study aimed at determining whether early, aggressive DMARD treatment started at the time of RA diagnosis has an impact on the mortality rates among patients with RA and whether there are any specific clinical features among the patients at the time of diagnosis which might explain mortality among these patients.

PATIENTS AND METHODS

The study group comprised 150 patients (35 men, 115 women) from two different patient cohorts taking part in a prospective

Abbreviations: ARA, American Rheumatism Association; CI, confidence interval; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SMR, standardised mortality ratio

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Table 1 Baseline characteristics of two different patient cohorts included in the present study. Data are shown as total number (%) or as median (range)

Patient characteristics	Cohort 1 (n=87)	Cohort 2 (n=63)	p Value
Age (years)	46.5 (19–65)	59.0 (27–83)	<0.001
Duration of symptoms (months)	7.6 (2–12)	5.7 (2–24)	0.3554
Sex, female (No (%))	69 (79)	46 (73)	0.51
Seropositive (No (%))	57 (65)	55 (87)	0.006
Erosive (No (%))	29 (33)	46 (73)	0.02
ESR (mm/1st h)	25 (4–112)	46 (4–130)	0.0019
CRP (mg/l)	13 (1–136)	21 (0–135)	0.4775
Number of tender joints	14 (0–37)	14 (2–40)	0.451
Number of swollen joints	3 (0–32)	7 (0–22)	<0.001
HAQ (0–3)	0.1 (0–1.3)	0.6 (0–2.4)	<0.001

follow up study of early RA in the metropolitan area of Helsinki. The first cohort (87 patients) was assembled between 1986 and 1989 at the Helsinki City Hospital and the Helsinki University Central Hospital and the second (63 patients) between 1991 and 1993 at the Helsinki City Hospital. The patients in the first cohort had to fulfil the American Rheumatism Association (ARA) diagnostic criteria for definite or classical RA[22]; during part of the study they also met the 1987 revised criteria of the ARA.[23] The patients in the second cohort fulfilled the 1987 revised criteria of the ARA from the start. At study entry the duration of symptoms at the time of diagnosis in the first cohort was ⩽12 months and in the second cohort ⩽24 months. In the first cohort only patients aged between 18 and 65 were included, whereas in the second cohort all patients ⩾18 years were admitted to the study. The patients were referred from primary healthcare centres (63/87 (72%) of the patients in the first cohort and 45/63 (71%) of the patients in the latter cohort) or private outpatient clinics. None of the patients had previously been treated with any DMARDs or oral corticosteroids, only with NSAIDs. Intramuscular gold, sulfasalazine, or hydroxychloroquine was started immediately after diagnosis in all except two patients (who refused to start any DMARDs). Oral corticosteroids were given when necessary because of active disease. If the initial DMARD had to be changed either because of inefficacy or side effects, other DMARDs (methotrexate, oral gold, azathioprine, D-penicillamine, cyclosporin, podophyllotoxin, either single or in combinations) were started according to the principle of the so-called "sawtooth" strategy described later.[24]

At entry to the study the following information was collected from each patient: history of comorbidities, duration of symptoms before diagnosis, age at the time of diagnosis, the presence of rheumatoid factor, and erosive changes of radiographs of hands and feet obtained at the diagnostic investigation. The clinical picture, including the number of tender (total 53) and swollen (total 44) joints, erythrocyte sedimentation rate (ESR), C reactive protein, and haemoglobin, was evaluated at entry and every 3–4 months up to three years, and thereafter at 5, 7, and 10 years. Functional ability measured by the Stanford Health Assessment Questionnaire (HAQ) disability index[25] was evaluated at entry and at the three year point. Radiographs of the hands and feet were taken at entry and thereafter at 1, 3, 5, 7, and 10 years and evaluated according to the method of Larsen and coworkers,[26] with a maximum score of 210. Information about every DMARD used (the use of each DMARD, single or in combination, and the reasons for discontinuation of the treatment) was collected for each patient during the prospective follow up.

Every patient lost to follow up was checked and the number of deaths recorded. Death certificates were obtained for all patients who died. Information about the time and causes of death was collected from the death certificates and, when possible, from patient files.

Statistical analyses

The ratio between observed and expected numbers—that is, the SMR, was calculated with 95% confidence intervals (95% CI), assuming a Poisson distribution. The expected number of deaths was calculated on the basis of person-years of observation within five years of the study period, multiplied by the calendar year and age-specific death rates for Finnish men and women.[27] Statistical comparison between groups was made with the *t* test, Mann-Whitney test, χ^2 test, or Fisher's exact test. Normality of variables was evaluated by the Shapiro-Wilk test. The Kaplan-Meier method was used to calculate the cumulative probability of survival. The prognostic factors predicting the duration of survival time were analysed using univariate and multivariate proportional hazard regression models with robust variance estimate, called Cox's regression models. No adjustment was made for multiple testing, but this information can be obtained by multiplying the actual p value by the number of comparisons made.

RESULTS

Table 1 shows the baseline characteristics of the 150 patients entering the study. None of the patients had previously been treated with DMARDs. Fifty four patients (36%) had a positive family history of RA. Seventy two patients (48%) had a history of one or more comorbidities at the time of RA onset: hypertension in 14 patients (9%), degenerative joint disease or other musculoskeletal diseases in 13 patients (9%), ischaemic heart disease in nine patient (6%), diabetes and asthma in five patients each (3%), psychiatric disorder in five patients (3%), hypothyroidism in three patients (2%). Three patients had a

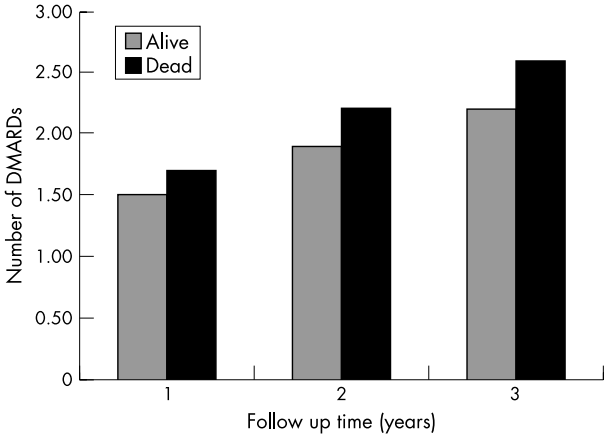

Figure 1 Mean cumulative number of DMARDs used during the first three years in patients who are still alive and those who died during the follow up. The differences between the two groups are not statistically significant.

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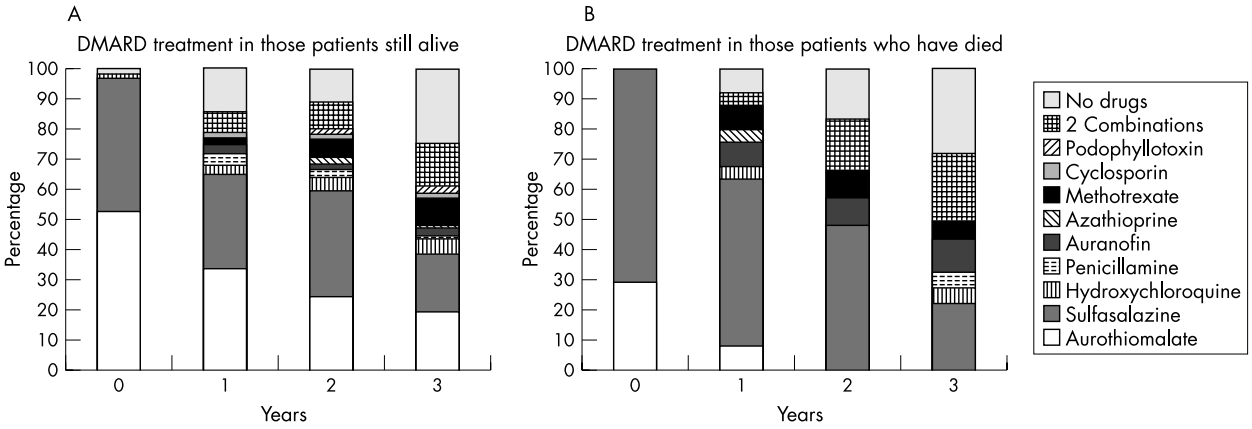

Figure 2 Antirheumatic treatment at different times in (A) patients still alive at the end of follow up and (B) patients who died during the follow up.

positive history of tuberculosis and another three patients had a history of malignancy: ovarian, uterus, or rectal cancer.

The patients were treated actively after RA was diagnosed. Figure 1 shows the mean cumulative number of DMARDs used in the two different patient groups (those alive and those who subsequently died) at various times. During the follow up all patients except one received DMARD treatment at some point. Fifty eight patients (39%) received combination therapy at some point during the follow up. The most popular combination during the first years included intramuscular gold with either sulfasalazine or hydroxychloroquine. Sixty nine patients (46%) received methotrexate at some point either alone or in combination with other DMARDs. When each DMARD (single, each combination of two different DMARDs, or any combination of three or more DMARDs) was evaluated separately, no difference between the two patient groups in the use of different DMARDs was seen. Figure 2 shows the DMARD treatments used at different times points by the two patient groups.

One patient was lost to follow up after two years. His data are included in the baseline data, but otherwise he has been excluded from the analysis. The mean (range) follow up time of the patients in the first cohort (87 patients) was 12.2 years (1.8–14.0) and in the second cohort (63 patients) 7.7 years (2.1–9.6). Twenty four patients died between the time of RA diagnosis and 1 November 2000. Death certificates were obtained for all of the 24 patients. For seven patients who died in hospital the medical records were also reviewed.

The SMR in the total study group with 95% CI was 1.33 (95% CI 0.85 to 1.98). Figure 3 shows the cumulative survival curve. The patients from the first cohort did better than the patients from the second cohort. The SMR with 95% CI in the first cohort was 0.93 (95% CI 0.37 to 1.92) and in the second cohort 1.62 (95% CI 0.95 to 2.60). Although the mortality rate in the second cohort was increased, the difference between either of these groups and the Finnish population did not differ statistically significantly. There was no statistically

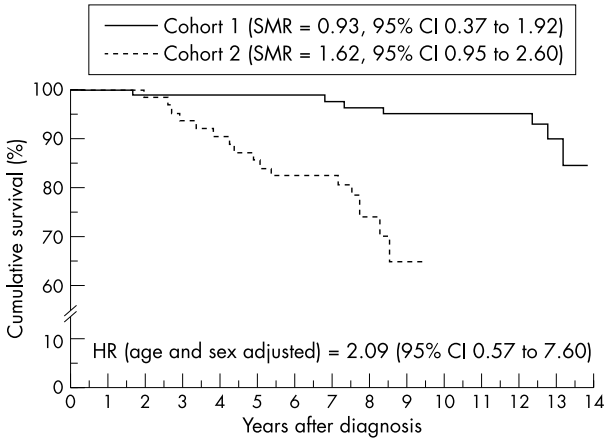

Figure 3 Cumulative survival curve of the patients of the two different cohorts. The SMR (95% CI) of the first cohort was 0.93 (0.37 to 1.92) and of the second cohort 1.62 (0.95 to 2.60).

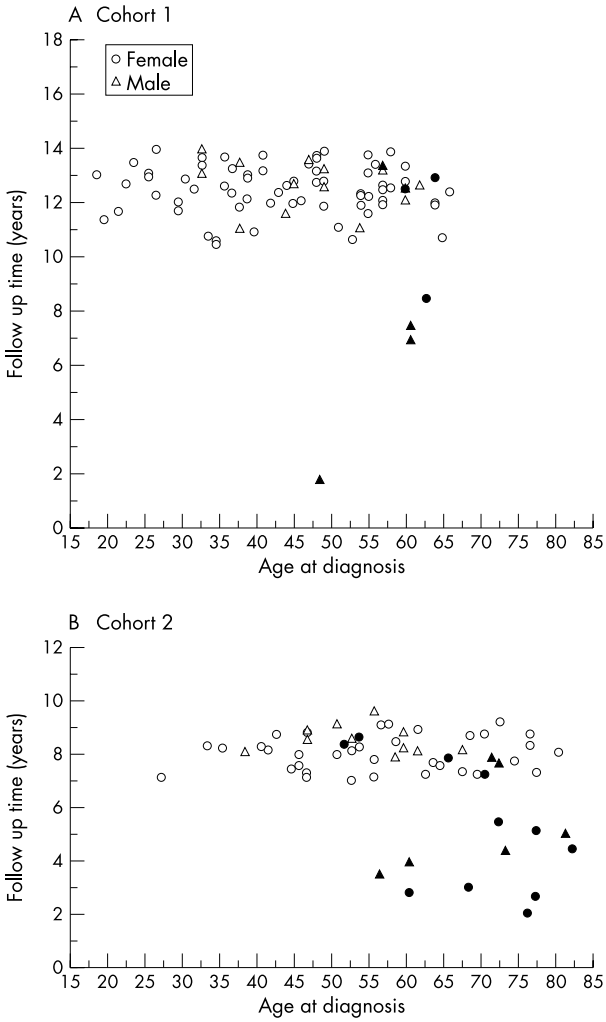

Figure 4 Follow up time and age at the time of diagnosis of each patient in the first (A) and the second cohort (B). Solid symbols represent those who died.

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Table 2 Causes of death of patients who died during the follow up

Cause of death	Number of patients (n=24)
Cardiovascular	10
Acute myocardial infarction	6
Rupture of aortic aneurysm	2
Intracerebral haemorrhage	1
Universal arteriosclerosis and ischaemic heart disease	1
Malignancies	8
Lung cancer	3
Brain lymphoma	1
Oesophagus cancer	1
Liver cancer	1
Hypernephroma	1
Mediastinal tumour	1
Infection	3
Pneumonia	2
Sepsis	1
Lung disease	2
Chronic obstructive pulmonary disease	1
Bronchiolitis obliterans	1
Rheumatoid arthritis	1

significant difference between the cohorts (age and sex adjusted hazard ratio 2.09 (95% CI 0.57 to 7.60)). Figure 4 shows the follow up time of each patient and age at the time of diagnosis. Most of the patients from the second cohort who died were over 65 years of age at the time of diagnosis of RA.

Cardiovascular diseases were the main cause of death in 10 patients (42%). Six patients (25% of all deaths) died of myocardial infarction: of these six, three had diabetes and two had a previous history of coronary heart disease. Table 2 presents all the causes of death. In only one patient was RA considered to be the cause of death. This patient was female, 77 at the time of diagnosis, developed amyloidosis, and died after only five years of RA. In two other death certificates RA was mentioned as comorbidity. None of the deaths were related to the use of DMARDs or NSAIDs, despite extensive use of DMARDs especially.

Age at onset was significantly higher among those patients who died (mean (SD)) 65.9 (9.7) *v* 48.3 (13.6) years ($p<0.001$). Ten of 35 men (29%) and 14/114 (12%) women died ($p<0.05$). Of the baseline variables, age, male sex, ESR, the number of swollen joints, and HAQ predicted mortality in univariate analysis. However, in multivariate analysis only age at onset and male sex were significant prognostic factors (table 3). During the first year there was a significant improvement ($p<0.05$) in all clinical variables in both groups except the number of tender joints in those patients who died ($p=0.1$).

Table 4 Extra-articular features at entry or during the follow up of the 24 patients who died and the 125 patients still alive

Extra-articular symptom	Patients alive No (%)	Dead No (%)	p Value
Sicca syndrome	27 (21.6)	10 (41.7)	0.068
Rheumatoid nodules	14 (11.2)	8 (33.3)	0.01
Neuropathy	2 (1.6)	5 (20.8)	0.001
Vasculitis	4 (3.2)	2 (8.3)	0.25
Episcleritis	2 (1.6)	0 (0)	0.99
Pleuritis	3 (2.4)	1 (4.2)	0.61
Lung fibrosis	2 (1.6)	1 (4.2)	0.41
Amyloidosis	0 (0)	1 (4.2)	0.16
Pericarditis	1 (0.8)	0 (0)	0.99
Venous ulcer	1 (0.8)	0 (0)	0.99
Total	45 (36.0)	18 (75.0)	<0.001

Sixty three patients (42%) had extra-articular manifestations at entry or developed them during the follow up. The presence of an extra-articular feature was much more common among those patients who died (table 4), and significant differences were also found when different manifestations were analysed separately.

Sixteen of the 24 patients who died during the follow up (67%) had some comorbidities at entry compared with 56/125 patients (45%) who were alive at the end of follow up, but this difference was not statistically significant.

DISCUSSION

We evaluated mortality rates and causes of death in this prospective follow up study of 150 DMARD naive patients with early RA. The patients were treated actively according to the "sawtooth" strategy. During the follow up 24 patients died. Mortality among these patients was not increased: SMR 1.33 (95% CI 0.85 to 1.98). Among those patients who died, the clinical picture at onset was more active and they also had more extra-articular manifestations. However, the patients who died did not have significantly more comorbidities than those patients still alive. Cardiovascular diseases (42%) and malignancies (33%) were the most common causes of death.

Because this study consists of two different patient cohorts that were assembled at different times and the inclusion criteria differed, the mortality rates were analysed separately. In the first cohort with patients under 66 years at the time of diagnosis of RA, the mortality rates were lower than in the second cohort. However, the mortality rates were not statistically significantly higher in either of these cohorts than in the

Table 3 Univariate and multivariate analysis of demographic factors and baseline characteristics on mortality

	Univariate model		Multivariate model	
Variables at entry	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Sex (male)	2.49 (1.12 to 5.57)	0.026	2.33 (1.03 to 5.27)	0.043
Age (years)	1.13 (1.08 to 1.17)	<0.001	1.15 (1.09 to 1.21)	<0.001
Duration of symptoms (months)	0.93 (0.81 to 1.07)	0.33	0.98 (0.84 to 1.15)	0.82
Rheumatoid factor present	2.79 (0.83 to 9.44)	0.099	2.31 (0.70 to 7.65)	0.17
ESR per 10 mm/h	1.26 (1.14 to 1.39)	<0.001	1.00 (0.86 to 1.16)	0.97
Swollen joint count	1.08 (1.02 to 1.14)	0.004	1.08 (1.00 to 1.17)	0.050
Erosions present	1.12 (0.49 to 2.54)	0.80	0.64 (0.27 to 1.54)	0.32
HAQ	3.45 (1.83 to 6.48)	<0.001	0.66 (0.29 to 1.51)	0.33

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normal population. When only patients aged ≤65 years at the onset were considered, the mortality rates were equal in both cohorts.

The study group was not large enough for conclusions to be drawn about the effect of different DMARDs on the mortality rates. One study from Germany showed the beneficial effect of active treatment (methotrexate) on mortality of patients with RA,[28] but this study included patients with longlasting RA. The treatments in this study were analysed for up to three years. Because the patients of the first cohort were assembled between 1986 and 1989, the use of, for example, methotrexate and combination treatments was not very common during the early years of this follow up and therefore the use of different DMARDs does not represent the present treatment strategy of early RA in Finland. However, the number of different DMARDs used in both cohorts was equal, showing that both groups were treated actively and as early as possible. Older patients with recent onset RA were excluded from the first study and therefore the results of this study may be biased by patient selection. Owing to the small size of this study group, it is not possible to draw any conclusions about the causes of death. However, although this study has its limits, it shows the trends in the causes of mortality among patients with early, actively treated RA.

In most previous studies the mortality among patients with RA is higher than that of the control population. Usually in hospital based studies the mortality rates are higher than in community based studies. In a large clinically based study by Wolfe *et al*,[3] in which 3501 patients with RA (four different centres with follow up varying between nine and 35 years) were evaluated, the SMR in the study group was 2.26. In another hospital based study from Sweden over 1000 patients with RA were followed up for seven years.[29] In this study an increase in mortality of almost 2.5 was found among patients with RA compared with the general Stockholm population. In a population based study from Arizona, where a cohort of Pima Indians was followed up between 1965 and 1989, Jacobsson *et al* observed significantly lower, although still increased, mortality rates among patients with RA, with an SMR of 1.28 (95% CI 1.01 to 1.62).[30]

Two recent studies from Norway showed lower figures than previous hospital based studies, although increased mortality was found in both of them. In a study by Kvalvik *et al* 149 patients with early RA were followed up for 15 years and the observed SMR was 1.49 (95% CI 1.15 to 1.88).[5] Another Norwegian study by Riise *et al* showed similar figures with an SMR of 2.0 (95% CI 1.6 to 2.5) among 187 patients.[31] Although both of these studies were based on hospital patients, they can be considered as community based studies, because in practice every RA patient in both of the study areas was treated in a hospital. In our study the mortality rates were slightly lower than those of the Norwegian studies, although the study setting was similar. However, the follow up period was shorter in our study and only the study by Kvalvik *et al* was performed among patients with early RA.[5]

Two studies with no increased mortality among patients with early RA have been published recently. In a study from Sweden[8] the SMR value was 0.87 (95% CI 0.53 to 1.36). This result is clearly better than previously reported. The follow up time in the Swedish study was 8–13 years and the clinical picture at the onset was comparable with that of the present study. In another study from the Netherlands by Kroot *et al* the mortality rates were not increased, but although some patients were followed up for 10 years, the mean follow up time was 5.8 years.[12] The effect of disease duration on mortality rates has been shown in a study from Canada,[3 7] where the SMR increased from 1.50 to 2.24 when the follow up period was continued for eight years. The excess of deaths due to infections and renal diseases has been shown to increase with time in at least in two different studies.[32 33]

In our study, age and male sex seemed to be poor prognostic factors. Also, factors indicating active disease at the onset (ESR, number of swollen joints, and functional status) predicted mortality. These results are in accordance with most previous reports.[2 34–36] Old age at the onset of RA, especially, is a strong predictor of increased mortality in many studies.[7 37 38] Contrary to the present study and a recent report by Riise *et al*,[31] the presence of rheumatoid factor has also been considered to be a poor prognostic factor in some studies.[3 30 39] Other studies, in agreement with ours, have shown that poor functional ability[2 36 39 40] and the development of extra-articular features[3 14 15] indicate an increased mortality risk.

Patients with a shorter duration of disease at the time of diagnosis and in whom active treatment is started early seem to have a better outcome, as was observed in 1998 by Symmons and coworkers.[33] In agreement with this, mortality rates in our study and also in another study from Finland by Sokka *et al*,[37] where all patients with early RA (duration of symptoms <2 years) were also treated according to the "sawtooth" strategy, were not significantly increased.

Death from RA in the general population is rare. In a large study from France between 1970 and 1990 only 0.22% of all deaths were related to RA.[41] When the causes of death among patients with RA are evaluated separately, RA may be underreported in death certificates. Despite the limitations, death certificates are the best available source of information about the causes of death. In a study from Finland published in 1986[42] RA was mentioned in 206 (58%) of all death certificates of 356 patients with RA, but in only nine (11%) of 84 death certificates of patients with RA in Sweden published in 1981.[39] In the present study RA was mentioned as a cause of death in one patient (4%) and as a contributory cause in two other cases.

Cardiovascular diseases (42%), malignancies (33%), and diseases of the respiratory system, including pneumonia (17%), were the main groups of causes of death in this study. The corresponding prevalences in the total Finnish population were 44% for cardiovascular diseases, 21% for malignancies, and 8% for diseases of the respiratory system (Official Statistics of Finland 1998). In a study from Finland by Koota *et al*, cardiovascular diseases were clearly the main cause of death among patients with RA.[43] Patients with RA were also more prone to die of cardiovascular diseases than the control population.[43] In several previous studies with higher mortality rates among patients with RA, the excess of deaths has been due to cardiovascular diseases[1 5 30 33] or infections.[1 31] Also, in two studies with mortality rates equal to those of the whole population,[8 12] cardiovascular diseases were the largest causes of death followed by malignancies. Cardiovascular diseases were the main cause of death in this study and also in the recent study by Sokka *et al*.[37] Except for the study by Prior *et al*,[9] increased mortality due to malignancies (especially when lymphoproliferative malignancies are excluded) has not usually been found.[3 29 31 43] Patients with RA have a slightly increased incidence of lymphoproliferative malignancies,[34 44] which is not, however, reflected in the mortality rates. In our study the most common malignancy was lung cancer, only one patient with lymphoma was observed. An association between RA and lung cancer among men has been found also previously by Isomäki,[34] and this might be explained by the fact that smoking predisposes to both of these conditions.[45]

In conclusion, the mortality rate among patients with early RA treated actively according to the "sawtooth" strategy was not significantly increased compared with the whole Finnish population. Activity of the disease at the onset, evaluated by the number of swollen joints, functional ability or ESR, and the development of extra-articular features, was associated with increased mortality. However, by multivariate analysis, only male sex and age at onset predicted mortality. Longer follow up and larger patient groups are needed to evaluate the effect of individual DMARDs on the mortality rates.

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