Mortality in Patients with Rheumatoid Arthritis Treated with Low-Dose Oral Glucocorticoids. A Population-Based Cohort Study

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ABSTRACT. ***Objective.*** To evaluate mortality and causes of death in patients with rheumatoid arthritis (RA) treated with low-dose oral glucocorticoids.

Methods. Mortality was analyzed in population-based data of 604 patients with RA. In the original study in 1988, state of general health, severity of RA, and treatment including the use of oral glucocorticoids were recorded. In 1999 vital status and causes of death were evaluated. Mortality in patients with RA who had not received glucocorticoids (Group A, n = 209) was compared to that in patients treated with glucocorticoids for less than 10 years (Group B, n = 276) or for more than 10 years (Group C, n = 119).

Results. From onset of RA to 1999, 395 (65%) patients had been treated with oral glucocorticoids. In 1999 a total of 160 (26%) patients had died, 23% of patients in Group A, 21% in Group B, and 45% in Group C. In multivariate Cox regression analysis, male sex (hazard ratio 2.50; 95% CI 1.74–3.59), impaired functional capacity by Health Assessment Questionnaire (HR 2.11; 95% CI 1.65–2.96), heart failure (HR 1.96; 95% CI 1.36–2.84), and diabetes (HR 1.87; 95% CI 1.17–3.01) predicted increased mortality. In the same analysis glucocorticoid treatment for 1 year increased the mortality risk by 14% (HR 1.14; 95% CI 0.98–1.27, p = 0.057) and treatment over 10 years by 69% (HR 1.69; 95% CI 1.12–2.56, p = 0.011) compared to RA patients without treatment. The major cause of death was cardiovascular disease in all groups, but infections and intestinal perforations due to amyloidosis were more frequent in patients with long-lasting glucocorticoid therapy. Lymphomas were more frequent in all patients treated with glucocorticoids (Groups B and C) than in those not receiving glucocorticoids.

Conclusion. Patients with RA treated with low-dose oral glucocorticoids for more than 10 years had increased mortality compared to those who did not receive glucocorticoids or whose duration of treatment was less than 10 years. The increased mortality was related mainly to infections and complications caused by systemic amyloidosis. (First Release Aug 1 2006; J Rheumatol 2006;33:1740–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS MORTALITY GLUCOCORTICOIDS

Many studies have established increased mortality among patients with rheumatoid arthritis (RA)[1-7], but some recent reports show that mortality is fairly similar to that in the general population[8-10]. In many studies the major cause of death has been cardiovascular diseases[1-4,6,7]. Some observational studies suggest that the increased mortality may be associated with glucocorticoid (GC) therapy, and several large retrospective studies indicate that longterm low-dose GC therapy is a significant independent predictor of numerous, potentially serious adverse events[11]. The potential toxicity of GC is well documented[12]. The risk for GC-induced side effects increases with dose and duration of use[13]. There is also individual variability for development of side effects depending on age and sex of the patient, and on other, less well defined factors[14]. One confounding factor is that GC may be prescribed in severe cases of RA[2], and such patients may be expected to have a higher mortality rate regardless of cause of death[2]. We investigated whether longterm GC treatment is associated with mortality in a population-based study of patients with RA.

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MATERIALS AND METHODS

Study population. In 1987 in the city of Tampere (1987 population 170,511, 3.5% of the population of Finland) 1051 persons (834 women, 217 men) were confirmed to have definite or classic RA according to the diagnostic criteria of the American Rheumatism Association[15]. In 1988, they were invited to participate in a study of renal and urinary tract diseases in RA; altogether, 604 persons (470 women, 134 men) were studied prospectively. The rest were

studied retrospectively by evaluating medical records[16]. In the original study, general state of health, other diseases, and severity and treatments of RA were carefully recorded.

In 1988, the current and previous oral glucocorticoid therapy was carefully recorded, including the generic drug and doses and length of treatment in months. Use of intraarticular GC injections was not recorded. Data on oral GC treatment during the years 1988 to 1999 or at time of death were collected retrospectively from hospital records as accurately as possible (n = 556). We were unable to gather any information about GC treatment of 48 RA patients during the years 1988-99.

Evaluation of mortality and causes of death. Information on the vital status in 1999 and the underlying and immediate causes of death were evaluated as described[3]. Mortality in RA patients who did not receive GC therapy (Group A) was compared to that in patients treated with GC (Groups B and C). In the non-GC group (Group A) patients were treated with oral GC for < 1 month, while in the GC group the treatment had been continued for at least 1 month, but < 10 years in Group B or > 10 years in Group C. Patients with no data on GC treatment from the years 1988-99 (n = 48) were included in Group B. Some of them had been treated with GC for longer than 1 month but < 10 years before 1988. The rest had never received GC before 1988, but data on GC treatment were not available after that. The results did not change when those 48 patients were excluded from the model. Cause of death was not known for 2 patients in the GC Groups B and C and for one patient in Group A, as death certificates were not available. Autopsy was performed in 20 (38%) of the RA patients in Group A, in 17 (37%) in Group B, and in 16 (29%) in Group C.

Ethical approval for the study was obtained from the Finnish Ministry of Social Affairs and Health and from the Ethical Committee of Tampere University Hospital.

Statistical analyses. Kaplan-Meier plots were generated for RA patients in Groups A, B, and C comparing survival for each year of followup. Risk of death was estimated by Cox proportional hazards survival analysis with followup time (time from original study to death) as the response variable, and is expressed as hazard ratio (HR) with 95% confidence intervals. The multivariate Cox proportional hazards model quantifies the predictive values of each variable in the model when all variables are considered together. We used the forward selection method performed in a stepwise manner. Standard statistical methods were employed including Student's paired t test, Kruskal-Wallis test, and chi-square test. Differences were considered significant at p value ≤ 0.05. Data were recorded and calculations performed using SPSS/Win (v 11) software.

RESULTS

Descriptive data in 1988. Descriptive data of patients with RA without GC therapy (Group A) and those treated with GC (Groups B and C) in the original study in 1988 are presented in Table 1. Altogether, 65% of RA patients (total 395: 311 women, 84 men) had been treated with oral GC until 1999, 276 of them for < 10 years (Group B) and 119 for > 10 years (Group C). Age and sex ratio of RA patients in the GC Groups B and C did not differ from those in Group A. However, patients in Groups B and C had more severe disease. Occurrence of other diseases was similar in all groups (Table 1).

Mortality. In 1999 a total of 160 (26%) participating patients with RA had died. Mortality was increased in RA patients treated with GC for more than 10 years (Group C) and they died at younger age than those in Groups A or B (p = 0.003). Forty-eight (23%) patients in Group A, 57 (21%) in Group B, and 53 (45%) in Group C had died (p = 0.001). The mean age at death was 78 ± 8 years in Group A (80 ± 7 for women, 71 ± 8 for men), 77 ± 10 years in Group B (77 ± 7 for women, 75 ± 6 for men), and 73 ± 10 years (74 ± 9 for women, 71 ± 7 for men) in Group C. Figure 1 shows the cumulative survival rate in all groups.

The underlying causes of death noted in death certificates are shown in Table 2. The major cause of death was cardiovascular disease in all groups; mortality from cardiovascular diseases was not higher in the GC Groups B and C than in the non-GC Group A. Underlying causes of death were more frequently classified under the categories of musculoskeletal and urogenital disease in patients with long-lasting GC treatment. Increased mortality in these categories was found to be due to infections or intestinal perforations in all cases according to the immediate cause of death.

Causes of death in detail

Group A. One patient was reported to have died from septicemia and one from esophageal perforation. In 2 cases pneumonia was recorded as cause of death in the category of respiratory diseases. One patient died due to myeloma and 6 due to dementia (Table 2). Infections were quite frequent immediate causes of death, including 11 deaths from pneumonia and one from septicemia (Table 3). Neither RA nor amyloidosis was recorded in any death certificate in patients who had not had GC treatment.

Group B. There was no death due to septicemia, but in 2 cases pneumonia was recorded as cause of death. Altogether, 15 patients had died from malignancies; 3 of these died from lymphoma and one from polycythemia vera. Renal amyloidosis was given as underlying cause of death in 2 patients, and 4 patients died due to dementia (Table 2). Infections were frequent immediate causes of death, including 9 deaths from pneumonia, 2 septicemia, one erysipelas, and one bronchitis (Table 3).

Group C. Two patients had died due to septicemia and in 3 patients pneumonia was recorded as cause of death in the category of respiratory diseases. A total of 10 patients died from malignancies, including 3 from lymphoma (Table 2). There were 11 deaths from pneumonia, 3 septicemia, and one record of pyelonephritis as cause of death (Table 3). Four patients died after intestinal perforation, and 3 of these had histologically confirmed amyloidosis. When RA was recorded as an underlying cause of death, immediate cause of death was renal amyloidosis, pneumonia, and intestinal perforation in 2 cases, respectively, and pyelonephritis in one. Altogether, RA was recorded in 7 and renal amyloidosis in 4 death certificates.

In examining immediate causes of death, RA patients in Group C died more frequently due to infections (p = 0.013; Table 3) and intestinal perforations due to amyloidosis (p < 0.001; Table 3) than patients in Groups A and B. Moreover, deaths due to lymphoma were noted only in patients with GC treatment (Groups B and C; p = 0.039). Only one patient had had cytotoxic treatment at the time of death; cause of death

Table 1. Characteristics of RA patients with or without glucocorticoid treatment at the time of the original study in 1988.

	Glucocorticoid Groups			
	Group A, n = 209	Group B, n = 276	Group C, n = 119	p
Age, yrs, median	58.9	57.7	60.7	0.186
Male, %	24	19	27	0.173
Disease duration, yrs, median	14.0	14.1	15.8	0.929
Severity of RA				
ESR, mm/h, median	23	28	45	< 0.001
Hb, mg/l, median	133	130	121	< 0.001
HAQ (1–3), median	0.38	0.54	1.05	< 0.001
Positive RF, %	43	56	73	< 0.001
Subcutaneous nodules, %	33	36	57	< 0.001
Other diseases, %				
Diabetes	5	7	7	0.661
Coronary artery disease	15	11	15	0.286
Heart failure	12	14	19	0.182
Hypertension	22	20	22	0.809

Group A: no glucocorticoid treatment, Group B: glucocorticoid treatment less than 10 years, Group C: glucocorticoid treatment for more than 10 years. Comparisons between different groups by Kruskal-Wallis test (for continuous variables) and chi-square test (for categorical variables). ESR: erythrocyte sedimentation rate, Hb: hemoglobin, HAQ: Health Assessment Questionnaire, RF: rheumatoid factor.

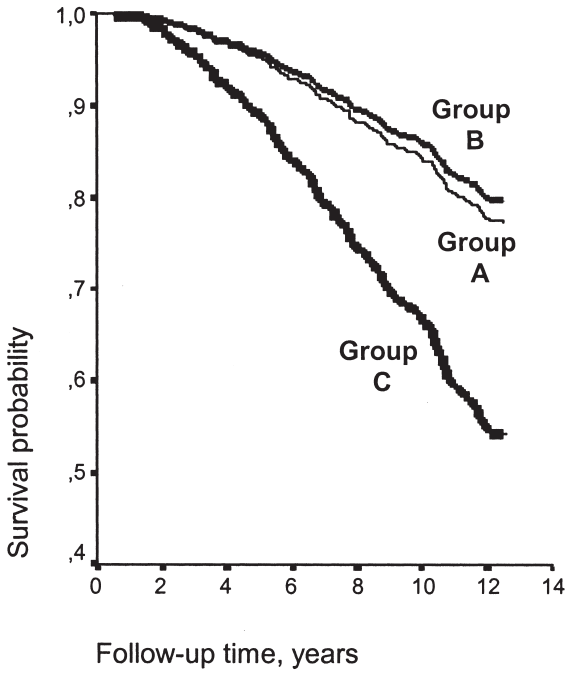

Figure 1. Kaplan-Meier curve illustrates the probability of death during followup time in patients with glucocorticoid treatment (Groups B and C) without treatment (Group A).

was septicemia. However, even if the results are statistically significant, the numbers of the patients with different diagnoses are small, and that must be taken into account when interpreting the causes of death.

Factors predicting mortality. Results of univariate and multivariate Cox regression analysis are shown in Table 4. In the model that included age, sex, duration of RA, functional capacity [by Health Assessment Questionnaire (HAQ)], presence of subcutaneous nodules, other diseases (coronary artery disease, diabetes, heart failure and hypertension), therapy with disease modifying antirheumatic drugs (gold sodium thiomalate, hydroxychloroquine, penicillamine, sulfasalazine) and GC therapy, as forced into the model at the same time, male sex, impaired functional capacity by HAQ, heart failure, diabetes, and oral GC treatment were associated with increased mortality. GC treatment for 1 year increased the mortality risk by 17% (p = 0.002) in the univariate model and by 14% (p = 0.057) in the multivariate model (Table 4). In the multivariate model, patients who had had longterm GC treatment (> 10 years) increased the mortality risk by 69% (p = 0.011) compared to patients without GC treatment.

DISCUSSION

Life expectancy in patients with RA is markedly shortened compared with subjects without RA[1-4,6,7]. Most studies have described an increased mortality from infections and cardiovascular, gastrointestinal, and renal diseases, and in some studies from malignancies[3-5]. There is strong evidence that increased mortality is linked to severity of RA[17,18], but the role of glucocorticoid treatment is not clear. We sought to establish in a population-based investigation whether longterm low-dose GC treatment contributes to the increased mortality.

A limitation of our study is the rather low participation rate in the original study. Only participant patients with RA were included in the present study, because we did not have suffi-

Table 2. Underlying causes of death in death certificates of RA patients without glucocorticoid treatment (Group A) and patients treated with glucocorticoid less than 10 years (Group B) or for more than 10 years (Group C).

International Classification of Diseases Code	Glucocorticoid Groups: Group A, n = 209		Group B, n = 276		Group C, n = 119		p
	n	%	n	%	n	%	
A00-A99 Infections	1	0.5	0		2	2	0.094
Septicemia	1		0		2		
C00-C97 Malignancies	7	3	15	5	10	8	0.144
Lymphoma	0		3		3		
Others	7		12		7		
F00-F98 Mental	6	3	4	1	1	1	0.346
Dementia	6		4		1		
I00-I99 Cardiovascular	26	12	28	10	20	17	0.188
Coronary artery disease	16		18		13		
J00-J99 Respiratory	4	2	3	1	6	5	0.045
Pneumonia	2		2		4		
Pulmonary fibrosis	0		0		2		
Other	2		1		0		
K00-K93 Gastrointestinal	2	1	1	0.4	2	2	0.405
Intestinal perforation	1		0		0		
Other	1		1		2		
M00-M99 Musculoskeletal	0		0		7	6	< 0.001
Rheumatoid arthritis	0		0		7		
N00-N98 Urogenital	0		2	0.7	4	3	0.011
Renal amyloidosis	0		2		4		
V01-Y98 Injuries	1	0.5	3	1	0		0.433
Unknown	1	0.5	1	0.4	1	1	
All categories	48	23	57	21	53	45	< 0.001

n = number of patients in the group, % = number of deaths in the particular disease category/number of patients in the group. Comparisons between groups by chi-square tests.

Table 3. Infections and gastrointestinal perforations as immediate causes of death in RA patients without glucocorticoid treatment (Group A), with glucocorticoid treatment less than 10 years (Group B), or for more than 10 years (Group C).

	Glucocorticoid Groups: Group A, n = 209		Group B, n = 276		Group C, n = 119		p
	n	%	n	%	n	%	
Infections	12	6	13	5	15	13	0.013
Septicemia	1	0.4	2	0.7	3	3	
Pneumonia	11	5	9	0.3	11	9	
Other	0	0	2	0.7	1	0.8	
Gastrointestinal perforations due to amyloidosis	0	0	0	0	4	3	< 0.001

Comparisons between groups by chi-square tests.

ciently detailed data on GC treatment from disease onset to 1988 in the patients studied retrospectively (non-participants) as we had in participants. Non-participant patients were older (64 ± 15 vs 59 ± 13 yrs) and had longer disease duration than participant patients (17 ± 11 vs 15 ± 10 yrs) in 1988. Death rates and causes of death in all patients have been reported[3]. Non-participant RA patients had increased mortality compared with participants, but causes of death were fairly similar. The main causes of death were cardiovascular diseases (over 40%) and about 20% of patients died due to malignancies[3].

Allebeck, *et al*[19] and Mitchell, *et al*[17] found no significant differences in RA mortality rates associated with GC treatment. Pincus, *et al*[18] and Leigh, *et al*[20] reported increased mortality with prednisone use in patients with RA, but both studies conceded that prednisone use may simply have been a marker of increased disease activity. Scott, *et al*[21] noted 35% mortality by 20 years in the followup study of 112 RA patients assigned to a standard regimen that included prednisone. The investigators attributed at least some of these deaths to use of GC[21]. Wolfe, *et al*[5] showed that the use of prednisone was

Table 4. Indicators predicting mortality; results of univariate Cox regression analysis and multivariate model by forward stepwise method.

Variables	Univariate Model			Multivariate Model		
	HR	95% CI	p	HR	95% CI	p
Age (yrs)	1.09	1.07–1.11	< 0.001	1.08	1.06–1.10	< 0.001
Sex (male)	1.89	1.36–2.64	< 0.001	2.50	1.74–3.59	< 0.001
RA severity						
Duration of RA (yrs)	1.01	0.99–1.03	0.062	0.95	0.93–0.97	< 0.001
Subcutaneous nodules	2.15	1.56–2.94	< 0.001			NS
HAQ (1–3)	2.15	1.75–2.63	< 0.001	2.11	1.65–2.96	< 0.001
Other diseases						
Coronary artery disease	2.29	1.57–3.34	< 0.001			NS
Diabetes	3.81	2.46–5.88	< 0.001	1.87	1.17–3.01	0.009
Heart failure	4.61	3.31–6.41	< 0.001	1.96	1.36–2.84	0.001
Hypertension	2.33	1.68–3.23	< 0.001			NS
Medication						
Gold sodium thiomalate (yes/no)	0.61	0.44–0.85	0.004			NS
Hydroxychloroquine (yes/no)	0.72	0.48–1.07	0.107			NS
Penicillamine (yes/no)	1.01	0.67–1.52	0.946			NS
Sulfasalazine (yes/no)	0.73	0.46–1.15	0.177			NS
Glucocorticoid (yrs)	1.17	1.06–1.31	0.002	1.14	0.98–1.27	0.057

HR: Hazard ratio, HAQ: Health Assessment Questionnaire score 1–3, NS: nonsignificant.

clearly a risk factor for higher mortality in RA regardless of age, sex, or disease severity. They also showed that cardiovascular diseases were the leading cause of death[5]. However, Wållberg-Johnsson, *et al*[22] found no relationship connecting mortality from cardiovascular diseases to the use of GC in their cohort of 606 patients with RA.

We observed that patients with RA treated with GC (Groups B and C) had a more severe disease than those in the non-GC Group A at the screening in 1988. However, in the multivariate model including medication and variables describing disease severity, longterm oral GC therapy still predicted an increased risk of death. In these patients' death certificates, RA and amyloidosis were recorded more often as underlying cause of death, and the immediate causes of death were infections or intestinal perforations due to amyloidosis in all cases.

We also noted increased mortality from infections in other disease categories, especially from pneumonia, in RA patients with GC treatment of more than 10 years. The propensity of GC to predispose to infections is controversial[23]. It has been suggested that the risk of infection is dependent on the dose and duration of GC therapy[13]. The use of low-dose GC does not seem to impair host resistance to infection. Several studies demonstrate that prednisone dosages < 10 mg/day do not suppress macrophage function sufficiently to allow opportunistic infection, and even large doses are required to inhibit other defence mechanisms such as neutrophil function[24,25]. The relative risk of infection across a number of clinical settings was roughly 2-fold compared to that in controls in a metaanalysis of 71 trials involving more than 2000 GC-treated patients[25]. The risk varied according to type of disease treated. Doran, *et al*[26] analyzed risk factors for infections in 609 patients with RA; they noted that the relative risk was 1.70 in RA patients compared to controls, with increasing age, extraarticular manifestations, leukopenia, and GC use as independent risk factors.

Some studies have suggested that GC treatment is associated with accelerated arteriosclerosis[27,28]. In a study of 647 patients with RA the investigators reported that GC exposure was associated with increased carotid plaques, independent of known cardiovascular risk factors[29]. Wållberg-Johnsson, *et al*[30] reported that GC increased mortality due to cardiovascular diseases if given early in RA, but not when given extensively during the course of the disease. They suggested that GC treatment early in disease may possibly indicate an active, aggressive RA, in agreement with high erythrocyte sedimentation rate, rather than indicating a risk of GC treatment per se. In the large prospective study by Solomon, *et al*[31], patients with RA had 2-fold higher risk for myocardial infarction than the general population even after adjusting for known and potential cardiovascular risk factors. Unfortunately they did not have detailed information about GC treatment or inflammatory markers. On the other hand, GC could also reduce the risk of atherosclerosis by controlling inflammation[32]. In our study RA patients treated with GC (Groups B and C) did not have increased mortality from cardiovascular diseases compared to those without GC therapy (Group A).

Peptic ulcers have long been considered a complication of GC therapy. A prospective study of 1400 patients receiving GC therapy showed an overall 2-fold higher risk of peptic ulcers[33]. However, multivariate analysis showed that concomitant use of nonsteroidal antiinflammatory drugs (NSAID) explained the increased risk of ulcers[33]. Myllykangas-Luosujärvi, *et al*[34] noted that nearly two-thirds of the putative treatment-related

deaths in their series were attributed to the use of NSAID, and a considerable proportion of deaths were due to perforation or bleeding of the lower small or large intestine. We found 4 deaths from intestinal perforation in RA patients treated with GC over 10 years compared to one among patients who did not receive GC. Three out of 4 patients who died from intestinal perforation used both GC and NSAID medications, and all of them also suffered from amyloidosis.

One interesting finding in our study was that 6 patients in the GC groups had died from lymphoma. Many studies have reported an association of RA with lymphoproliferative malignancies[35-37]. Cytotoxic drugs such as azathioprine and cyclophosphamide have been associated with increased incidence of lymphomas[38], but there is also evidence that the lymphoma risk is associated with the severity of RA[36,37] or immunologic alterations accompanying RA, such as chronic immune stimulation[36] or Epstein-Barr virus infection[38,39]. In our study patients who died from lymphoma had not received any cytotoxic drugs up to the screening in 1988 or after that, but they had more severe RA at study entry.

We found that patients with RA treated with low-dose oral glucocorticoids for more than 10 years had increased mortality compared to those who did not receive glucocorticoids or whose duration of treatment was less than 10 years. Increased mortality was related mainly to infections and complications caused by systemic amyloidosis.

REFERENCES

1. Allebeck P, Ahlbom A, Allander E. Increased mortality among persons with rheumatoid arthritis, but why RA does not appear on death certificate: eleven year follow-up of epidemiological study. Scand J Rheumatol 1981;10:301-6.
2. Symmons D, Prior P, Scott D, Brown R, Hawkins C. Factors influencing mortality in rheumatoid arthritis. J Chron Dis 1986;39:137-45.
3. Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis. A population based study. Scand J Rheumatol 2004;33:1-7.
4. Jacobsson L, Knowler W, Pillemer S, et al. Rheumatoid arthritis and mortality. A longitudinal study of Pima Indians. Arthritis Rheum 1993;36:1045-53.
5. Wolfe F, Mitchell D, Sibley J, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481-94.
6. Myllykangas-Luosujarvi R. Mortality and causes of death in rheumatoid arthritis in Finland in 1989 — An epidemiological, population-based study on mortality in RA [thesis]. Tampere: Acta Universitatis Tamperensis 1995 Ser A vol. 461:63p.
7. Kvalvik A, Jones M, Symmons D. Mortality in a cohort of Norwegian patients with rheumatoid arthritis followed from 1977-1992. Scand J Rheumatol 2000;29:29-37.
8. Linqvist E, Eberhard K. Mortality in rheumatoid arthritis patients with disease onset in the 1980s. Ann Rheum Dis 1999;58:11-4.
9. Bjornadal L, Baecklund E, Yin L, Granath F, Klareskog L, Ekbom A. Decreasing mortality in patients with rheumatoid arthritis: result from a large population based cohort in Sweden, 1964-95. J Rheumatol 2002;29:806-12.
10. Peltomaa R, Paimela L, Kautiainen H, Leirisalo-Repo M. Mortality in patients with rheumatoid arthritis treated actively from the time of diagnosis. Ann Rheum Dis 2002;61:889-94.
11. Saag K, Koehnke R, Caldwell J. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115-23.
12. Caldwell J, Furst D. The efficiency and safety of low-dose corticosteroids for rheumatoid arthritis. Semin Arthritis Rheum 1991;21:1-11.
13. Dale D, Petersdorf R. Corticosteroids and infectious diseases. Med Clin N Am 1973;57:1277-87.
14. Cohen M, Conn D. Benefits of low-dose corticosteroids in rheumatoid arthritis. Bull Rheum Dis 1987;46:4-7.
15. Ropes MW, Bennet GA, Cobb S, Jacox R, Jessar RA. Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9:175-6.
16. Korpela M. Rheumatoid arthritis and the kidneys — cross sectional study of prevalence, clinical significance and risk of renal and urinary tract diseases in patients with rheumatoid arthritis. Helsinki, Finland: Publications of the Social Insurance Institution: 1993, ML:122.
17. Allebeck P, Rodvall Y, Allender E. Mortality in rheumatoid arthritis, particularly as regards drug use. Scand J Rheumatol 1985;14:102-8.
18. Mitchell DM, Spitz PW, Young D, Bloch D, McShane D, Fries J. Survival prognosis and cause of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706-14.
19. Pincus T, Callahan LF, Vaughn WK. Questionnaire, walking time and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. J Rheumatol 1987;14:250-1.
20. Leigh JP, Fries JF. Mortality predictors among 263 patients with rheumatoid arthritis. J Rheumatol 1991;18:1307-12.
21. Scott D, Symmons P, Coulton B, Popert A. Long-term outcome of treating rheumatoid arthritis: result after 20 years. Lancet 1987;1:1108-11.
22. Wallberg-Jonsson S, Öhman ML, Rantapää-Dahlqvist S. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in northern Sweden. J Rheumatol 1997:24;445-51.
23. Boumpas D, Chrousos G, Wilder R, Cupps T, Balow J. Glucocorticoid therapy for immune diseases: basic and clinical correlates. Ann Intern Med 1993;119:1198-208.
24. Schaffner A. Therapeutic concentrations of glucocorticoids suppress the antimicrobial activity of human macrophages without impairing their responsiveness to gamma interferon. J Clin Invest 1985;76:1755-64.
25. Stuck A, Minder C, Frey F. Risk of infectious complications in patients taking corticosteroids. Rev Infect Dis 1989;2:954-61.
26. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294-300.
27. Nashel D. Is atherosclerosis a complication of long-term corticosteroid treatment? Am J Med 1986;80:925-9.
28. Maxwell S, Moots R, Kendall M. Corticosteroids. Do they damage the cardiovascular system? Postgrad Med J 1994;70:863-70.
29. del Rincon I, O'Leary DH, Haas RW, Escalante A. Effect of glucocorticoids on the arteries in rheumatoid arthritis. Arthritis Rheum 2004;50:3813-22.
30. Wallberg-Jonsson S, Johansson H, Öhman ML, Rantapää-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol 1999;26:12:2562-71.
31. Solomon D, Karlson E, Rimm E, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-7.
32. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis — An extra-articular feature of rheumatoid arthritis? Arthritis

Rheum 2002;46:862-73.
33. Piper J, Ray W, Daugherty J, Griffin M. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;114:735-40.
34. Myllykangas-Luosujarvi R, Aho K, Isomäki H. Deaths attributed to anti-rheumatic medication in a nationwide series of 1666 patients with rheumatoid arthritis who had died. J Rheumatol 1995;22:2214-7.
35. Isomaki HA, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chron Dis 1978;31:691-6.
36. Prior P, Symmons DP, Hawkins CF, Scott D, Brown R. Cancer morbidity in rheumatoid arthritis. Ann Rheum Dis 1984;54:128-31.
37. Gridley G, Mclaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. J Nat Cancer Inst 1993;85:307-11.
38. Pedersen-Bjergaard J, Philip P. Therapy related malignancies: A review. Eur J Haematol 1989;42:39-47.
39. Kamel OW, van de Rijn M, Weiss LM. Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 1993;328:1317-21.