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NO INCREASED RISK OF MALIGNANCIES AND MORTALITY IN CYCLOSPORIN A–TREATED PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective. **To evaluate the cyclosporin A (CSA)–attributed risk of developing malignancies in general and malignant lymphoproliferative diseases (LPDs) and skin cancers in particular, as well as the CSA-attributed incidence of mortality in patients with rheumatoid arthritis (RA).**

Methods. **In a retrospective, controlled cohort study, the incidence of malignancies and mortality was evaluated in 208 CSA-treated patients with RA compared with 415 matched control patients with RA between 1984 and 1995. Patients were followed up for a median of 5.0 years (range 1.4–12.0).**

Results. **Forty-eight cases of malignancy (8 in the CSA group and 40 in the control group; relative risk [RR] 0.40, 95% confidence interval [95% CI] 0.19–0.84) were identified, of which 8 were malignant LPDs (2 CSA versus 6 control; RR 0.67, 95% CI 0.14–3.27) and 14 were skin cancers (2 CSA versus 12 control; RR 0.33, 95% CI 0.08–1.47). Seventy-three patients died (16 CSA versus 57 control; RR 0.56, 95% CI 0.33–0.95) due primarily to cardiovascular diseases (4 CSA versus 22 control; RR 0.36, 95% CI 0.13–1.04) or a malignancy (3 CSA versus 8 control; RR 0.67, 95% CI 0.18–2.43). Proportional hazards regression analysis with correction for potential confounding factors did not significantly change the results.**

Conclusion. **The study findings suggest that CSA treatment in RA patients does not increase the risk of malignancies in general or the risk of malignant LPDs or skin cancers in particular. Moreover, the incidence of mortality in CSA-treated RA patients was comparable to that in matched control RA patients.**

Cyclosporin A (CSA) is an immunosuppressive drug that has been used in transplantation medicine and in the treatment of autoimmune diseases (1). In organ transplant recipients, the use of CSA has been associated with an increased risk of malignant lymphoproliferative diseases (LPDs) (2,3) and skin cancers (4,5). In patients with rheumatoid arthritis (RA), the contribution of a particular drug to the development of malignancies is difficult to estimate, since both RA itself and the immunosuppressive drugs used in the treatment of RA confer additional risks (6–10). The relative risk of malignant LPDs in RA patients when compared with the general population varies from 5 to 20 (6–10). In an uncontrolled cohort study of CSA-treated RA patients, it was suggested that the CSA-related risk of developing malignancies was comparable to that associated with other disease-modifying antirheumatic drugs (DMARDs) (11).

The incidence of mortality has been reported to be increased in patients with RA compared with the general population (12,13), and the primary cause of death in patients with RA is cardiovascular disease (13). The use of CSA has been associated with kidney dysfunction (14), sympathetic activation (15), and hypertension (16), which can result in end-stage renal failure (14) and cardiovascular-related mortality in the long term.

In order to evaluate the risk of developing ma-

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lignancies and the incidence of mortality attributed to CSA treatment in patients with RA, we performed a retrospective, matched cohort study of 208 RA patients who were derived from 4 Dutch studies of CSA. Consistent with findings reported in the available literature, our hypothesis was that RA patients who have ever been treated with CSA have a higher risk of malignancies and a higher cardiovascular- and malignancy-related mortality than RA patients who have never been treated with CSA.

PATIENTS AND METHODS

Study design. The study was designed as a retrospective, matched cohort study.

Index patients. The index group consisted of all RA patients who had participated in 3 randomized controlled trials (RCTs) (17–19) and in 1 uncontrolled observational study (20), all of whom had been treated with CSA for various lengths of time.

In the first study, CSA was compared with placebo (17). Patients were selected for inclusion in this trial between January 1984 and January 1986. The CSA group consisted of 17 patients whose RA was considered intractable. In the second study, CSA was compared with D-penicillamine (18). Enrollment in this trial took place between October 1986 and November 1988. The CSA group consisted of 46 patients with advanced RA. In the third study, CSA was compared with chloroquine (19). The inclusion period for this trial was between February 1991 and December 1992. The CSA group consisted of 22 patients with early RA. In each of these 3 RCTs, the study duration was 6 months. In the fourth study, CSA was evaluated in an uncontrolled manner (20). Patients were enrolled between September 1990 and October 1993. The study group consisted of 115 patients with advanced RA, and the results were reported for 102 of the 115 patients. The duration of this uncontrolled observational study was 12 months.

Seven patients, who had been primarily allocated to the control group (3 from the first study, 1 from the second study, and 3 from the third study), were subsequently treated with CSA after other treatments were unsuccessful. For the purpose of this study, these 7 patients were considered index patients. Five of the 102 CSA-treated patients in the fourth study had been control patients in either the second study (n = 3) or the third study (n = 2). Furthermore, 1 patient who was treated with CSA in the same time period as the fourth study but not involved in the study protocol was considered an index patient. This extra index patient fulfilled the same inclusion and exclusion criteria as the other patients participating in the fourth study.

The index patients were recruited from 11 rheumatology departments in hospitals that are geographically distributed throughout The Netherlands. Most index patients (≥80%) were recruited from the rheumatology departments in 3 rural hospitals (De Wever Hospital, Heerlen; Maasland Hospital, Sittard; and St. Joseph Hospital, Veldhoven) and 1 university hospital (Leiden University Hospital) in The Netherlands.

All patients included in each of the 4 studies had active disease at the time of inclusion, and fulfilled the inclusion criteria of their respective studies (17–20). Renal function impairment was an exclusion criterion in the second, third, and fourth study, but not in the first study (17–20). A history of malignancies was an exclusion criterion in all 4 studies.

Control patients. All but 1 of the index patients were each matched with 2 control patients. The control patients had to meet the same inclusion criteria as their corresponding index patient at the time of their enrollment in the respective studies. All control patients in the 3 RCTs, except those who had received CSA subsequently, were still designated as control patients in this study (n = 75). The additional control patients were obtained from a registry of RA patients managed by a large hospital in the east of Holland (Medisch Spectrum Twente, Enschedé).

With the help of a computerized database, a stratified sample of control patients was obtained. Patients were matched for age (strata of 5 years), sex, and disease duration (strata of 1 year). According to the inclusion criteria, all control patients had been started on a new DMARD in the same time period as their respective index patient.

Data collection and followup. All data were derived from the patient's rheumatologic charts. The investigators who extracted the data from the medical records (IH, FS, PvdH) were blinded with regard to the underlying hypothesis. The quality of the extracted data was verified by another investigator (BvdB). All index and control patients fulfilled the 1958 diagnostic criteria for RA of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) (21) in the first and second studies or the 1987 ACR criteria for RA (22) in the third and fourth studies.

The following baseline characteristics were obtained: date of birth, sex, year and date of diagnosis, presence of rheumatoid factor, erosions at the time of diagnosis, the number, kind, and treatment duration of previously used DMARDs, and concomitant diseases. The following data were collected on followup: duration of exposure to CSA in the index group or to respective DMARDs in both groups, duration of followup (defined as the time between the start of CSA in the index group or control DMARD in the control group and December 1, 1995), and number and kinds of DMARDs used after CSA in the index group. Duration of exposure to CSA in the index group or to DMARDs in both groups was expressed in exposure years.

Outcome. The end points of followup were 1) diagnosis of malignancy or premalignant disease, and 2) death. A diagnosis of malignancy or premalignant disease was established by 1) verifying the data in the rheumatologic medical chart of each patient, or 2) verifying the information in the database of the Pathological Anatomical National Automated Archives (PALGA) in Amsterdam, The Netherlands. PALGA consists of all results of histopathologic examinations that have been performed in The Netherlands since 1974. The pathology departments of most hospitals in The Netherlands (including all hospitals that had assigned index patients or control patients in this study) contributed their data to PALGA during the entire period of followup. The number and kind of malignancies found in the medical charts were compared with

the PALGA data. Only malignancies or premalignant diseases that had occurred between the start of treatment exposure and December 1, 1995 were taken into consideration.

In order to evaluate whether patients were alive as of December 1, 1995, visits to any department in a given hospital after December 1, 1995 were checked in that hospital's registry system or in the patient's rheumatologic charts. Further information was obtained from general practitioners or from first-degree relatives. Following this strategy, adequate data on all included patients could be obtained. In the case of death, the date of death, cause of death (obtained from an autopsy report, medical correspondence, or the general practitioner), and, if available, autopsy findings were recorded. In the patients who had developed a malignancy or who had died, the correctness of the extracted data was verified by one of us (BvdB).

Statistical analysis. The risk of malignancies or death in RA patients who had ever been exposed to CSA in comparison with RA patients who had never been exposed to CSA was calculated as the relative risk (RR) with 95% confidence intervals (95% CI). The difference in incidence of malignancies or mortality between both groups was tested by chi-square test or Fisher's exact test where appropriate, assuming that a finding of no differences was the null hypothesis. A P value of less than 0.05 was considered to be statistically significant.

Log-rank actuarial life-table analysis was used to compare the time to the occurrence of malignancy or to mortality between both groups. Cox proportional hazards model was used to assess the importance of the following potential confounders in the assessment of risk of malignancy or death: age, sex, disease duration, the presence of rheumatoid factor, erosions, or extraarticular manifestations, the kind and number of DMARDs taken before and after the index period, and comorbidity. The risk of death was assessed using Cox regression, with the occurrence of malignancy as a time-dependent covariate.

RESULTS

Characteristics of patients and controls. The characteristics of the 208 index patients and 415 control patients are summarized in Table 1. Age, sex, disease duration, the proportion of patients with rheumatoid factor and extraarticular symptoms, and the duration of followup were similar in both groups. Significantly more patients in the index group than in the control group had erosions at the time of inclusion.

Before the beginning of followup, the median number of DMARDs to which patients had been exposed was 2 (range 0–7) in both groups. Significantly more patients in the index group compared with the control group had used more than 2 different DMARDs (data not shown). Methotrexate (18% versus 6%, respectively) and azathioprine (17% versus 4%, respectively) had been taken more frequently by patients in the index group than the control group. Cyclophosphamide had only been taken by 1 patient in each group.

Table 1. Characteristics of the cyclosporin A–treated patients and the matched control patients with rheumatoid arthritis

Characteristic	Index group (n = 208)	Control group (n = 415)	Between-group difference (P)
Median age (range), years	55 (21–75)	57 (22–75)	0.37
Female, %	73	70	0.46
Median disease duration (range), years	5.7 (0.3–36)	4.0 (0.2–42)	0.48
Presence of rheumatoid factor, %	83	82	0.83
Presence of erosions in hand or feet, %	81	69	<0.01
Presence of extraarticular symptoms, %	19	21	0.75
Median duration of followup (range), years	4.7 (1.4–12.0)	5.5 (1.7–11.9)	0.10

A summary of all of the DMARDs administered to patients through the followup period is shown in Table 2. Each DMARD, except cyclophosphamide, had been taken more frequently by the index patients than the control patients. Corticosteroids had been given or were being given to 46% of the index patients and 33% of the control patients ($P < 0.01$).

CSA therapy. The index group was treated with CSA for 1.6 ± 1.6 years (mean ± SD; range 0.1–11.4 years), with a mean maintenance dosage of 2.9 ± 1.4 mg/kg/day (range 1.3–10.0 mg/kg/day). Of the 208 index

Table 2. Frequency distribution of the disease-modifying antirheumatic drugs (DMARDs) administered to the cyclosporin A–treated patients and the matched control patients with rheumatoid arthritis*

DMARDs	Index group (n = 208)	Control group (n = 415)	Between-group difference (P)
Cyclosporin A	100	0	–
Antimalarials	79	74	0.17
Intramuscular gold	76	57	<0.01
Methotrexate	56	38	<0.01
Sulfasalazine	53	40	<0.01
Corticosteroids	46	33	<0.01
D-penicillamine	45	30	<0.01
Azathioprine	32	15	<0.01
Oral gold	18	10	<0.01
Cyclophosphamide	2	2	0.77

* Values are the percentage of patients.

Table 3. Number and kind of malignancies found in the cyclosporin A–treated patients and the matched control patients with rheumatoid arthritis

Malignancy	Index group, no. (n = 208)	Control group, no. (n = 415)	Crude relative risk (95% confidence interval)	Adjusted relative risk (95% confidence interval)*
Malignant lymphoproliferative diseases†	2	6	0.67 (0.14–3.27)	0.51 (0.21–2.43)
Malignant myeloproliferative diseases‡	0	2		
Solid tumors	6	32	0.37 (0.16–0.88)	0.39 (0.16–0.96)
Skin cancer	2	12	0.33 (0.08–1.47)	0.59 (0.22–1.64)
Squamous cell carcinoma	0	2		
Basal cell carcinoma	1	8	0.25 (0.03–1.98)	
Other skin cancers§	1	2	1.00 (0.09–0.94)	
Breast cancer	3	4	1.50 (0.34–6.62)	
Lung cancer	1	4	0.50 (0.06–4.43)	
Carcinoma of the bladder	0	4		
Carcinoma of the endometrium	0	2		
Carcinoma of the kidney	0	2		
Other solid cancers¶	0	4		
Total malignancies	8	40	0.40 (0.19–0.84)	0.47 (0.24–0.94)

* Adjusted for age and sex.
† Including Hodgkin's disease (1 control patient), lymphoma (2 index patients, 5 control patients), and chronic lymphocytic leukemia (1 control patient).
‡ Including acute myeloid leukemia (1 control patient) and granulocytic sarcoma (1 control patient).
§ Including Bowen's disease (1 index patient, 2 control patients).
¶ Including carcinoma of the prostate (1 control patient), thyroid (1 control patient), salivary gland (1 control patient), and colon (1 control patient).

patients, 181 were treated for at least 3 months, 147 for at least 6 months, 103 for at least 1 year, 65 for at least 2 years, and 38 for at least 3 years.

Outcome of CSA therapy. *Malignancies.* Forty-eight cases of proven malignancy were identified in 47 patients (7.5% of all patients, or 12.2 cases per 1,000 patient-years of observation). One control patient had 2 malignancies: a carcinoma of the kidney and a basal cell carcinoma of the skin. Of the 48 identified cases, 31 cases were primarily found in the medical charts and subsequently confirmed in PALGA, 15 cases (7 skin cancers and 8 solid tumors) were found only in PALGA, and 1 case of malignant LPD (stage IV Hodgkin's lymphoma) and 1 case of malignant myeloproliferative disease (acute myeloid leukemia) was found in the medical charts but not in PALGA. In these latter 2 control patients, the diagnosis was established by a hematologist in a bone marrow aspirate.

The number and kind of malignancies in the index and control groups are summarized in Table 3. All kinds of malignancies occurred less frequently in the index group. The RR of any malignancy was 0.40 (95% CI 0.19–0.84), the RR of malignant LPD was 0.67 (95% CI 0.14–3.27), and the RR of skin cancer was 0.33 (95% CI 0.08–1.47). The malignancy-free survival curve for each group is shown in Figure 1 ($P = 0.026$ by log-rank test). During the entire followup period, the risk of malignancies was lower in the index group. A separate analysis of only those index and control patients who were derived from the 3 randomized studies (n = 167) showed an RR for the development of any malignancy of 0.51 (95% CI 0.17–1.49) for the index group. There were no differences in the particular kinds of malignancies that occurred between the index group and the control

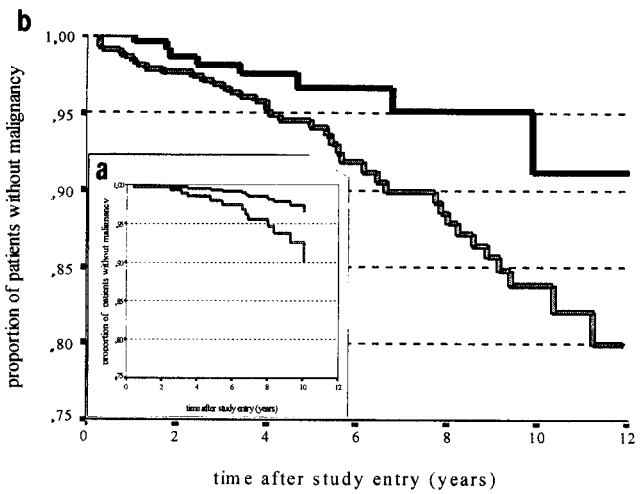


Figure 1. Proportion of patients without malignancy among patients with rheumatoid arthritis (RA) treated with cyclosporin A (solid bar) and matched control RA patients (shaded bar). The malignancy-free survival among only those patients derived from the randomized controlled trials (n = 167) (**a**) was compared with that among the whole group of 208 RA patients and 415 matched control RA patients (**b**).

Table 4. Number and causes of deaths in the index patients and matched control patients with rheumatoid arthritis

Cause of death	Index group, no. (%) (n = 208)	Control group, no. (%) (n = 415)	Relative risk (95% confidence interval)
Total	16 (7.7)	57 (13.7)	0.56 (0.33–0.95)
Cardiovascular diseases	4 (1.9)	22 (5.3)	0.36 (0.13–1.04)
Myocardial infarction	1	5	
Congestive heart failure	1	6	
Cerebrovascular incidents	0	5	
Acute heart failure	2	2	
Cardiac arrhythmias	0	1	
Malignancies	3 (1.4)	8 (1.9)	0.67 (0.18–2.43)
Breast cancer	2	1	
Lung cancer	0	3	
Malignant lymphoproliferative disease	1	1	
Carcinoma of the colon	0	1	
Carcinoma of the kidney	0	1	
Carcinoma of the thyroid	0	1	
Infectious diseases	5 (2.4)	9 (2.2)	1.11 (0.38–3.27)
Sepsis	3	6	
Pneumonia	1	3	
Pulmonary fungal infection	1	0	
Pulmonary diseases	1 (0.5)	9 (2.2)	0.22 (0.03–1.74)
Obstructive pulmonary disease	1	3	
Pneumonitis	0	2	
Adult respiratory distress syndrome	0	2	
Pulmonary fibrosis	0	1	
During pulmonary surgery	0	1	
Other causes	3 (1.4)	8 (1.9)	0.75 (0.20–2.79)
End-stage renal failure	1	3	
Accident	1	0	
Bleeding stomach ulcer	0	1	
Electrolyte disturbances	0	1	
Not known	1	2	

group, either in the whole group or in the group composed only of the randomized patients.

In the proportional hazards regression analysis, CSA therapy (ever or never used) had a negative contribution to the occurrence of malignancies (RR 0.41, 95% CI 0.19–0.89). Of all other included variables, only age contributed significantly to the occurrence of malignancies (RR 1.06, 95% CI 1.03–1.10). When concomitant diseases were left out of the analysis, similar results were obtained (data not shown).

A separate proportional hazards regression analysis was performed in only the index patients, in order to investigate whether the maximum CSA dose, the cumulative dose of CSA, and the duration of therapy had influenced the risk of malignancies. Such a relationship between intensity of therapy and the risk of malignancies could not be demonstrated (data not shown).

Mortality. Seventy-three patients had died during followup (12% of all patients, or 18.5 patients per 1,000 patient-years of observation), of whom 16 were in the index group and 57 in the control group. The number and causes of deaths are summarized in Table 4. There was a significantly higher mortality in the control group than in the index group (RR 0.56, 95% CI 0.33–0.95). Regarding all patients, the major cause of death was cardiovascular disease (n = 26; 36% of all deaths). Furthermore, a relatively high number of patients had died of infectious disease (n = 14; 19% of all deaths) and, more particularly, of sepsis (n = 9, 12% of all deaths). The survival curves for index and control patients are shown in Figure 2 ($P = 0.222$ by log-rank test). A separate analysis of only those index and control patients who were derived from the 3 randomized studies (n = 167) showed an RR of mortality of 0.62 (95% CI 0.32–1.20) for the index group compared with the control group.

Of the 8 index patients and 40 control patients with a malignancy, 4 (50%) and 17 (43%), respectively, had died. In 3 index patients and 8 control patients, malignancy was the primary cause of death, and in 1

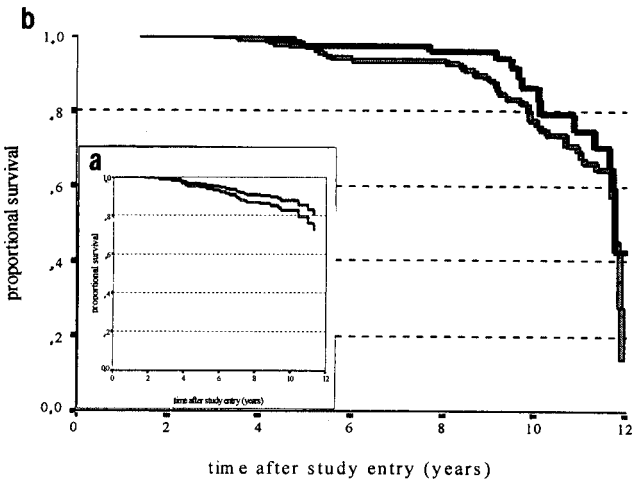


Figure 2. Proportional survival in patients with rheumatoid arthritis (RA) treated with cyclosporin A (solid bar) and matched control RA patients (shaded bar). The proportional survival of only those patients derived from the randomized controlled trials (n = 167) (**a**) was compared with that in the whole group of 208 RA patients and 415 matched control RA patients (**b**).

index patient and 9 control patients, a primary cause of death other than malignancy was reported. Of all the patients who died, the risk of dying of a particular malignancy in index patients was not statistically different from that in control patients with the same malignancy (75% versus 47%; RR 2.73, 95% CI 0.34–22.16). Fatal infections, pulmonary disease, and other reasons as the primary cause of death were equally distributed in both groups. End-stage renal failure was the primary cause of death in only 1 index patient. The maximum dosage of CSA in this patient was 10 mg/kg/day and treatment duration was 2 years.

In the proportional hazards regression analysis, CSA therapy (ever or never used) did not significantly contribute to the risk of death (RR 0.87, 95% CI 0.45–1.67). Of all other included variables, the occurrence of malignancies (RR 2.24, 95% CI 1.29–3.89), age (RR 1.11, 95% CI 1.08–1.16), the presence of cardiovascular disease before study entry (RR 2.10, 95% CI 1.20–3.66), and treatment with intramuscular gold (RR 0.46, 95% CI 0.26–0.80), D-penicillamine (RR 0.37, 95% CI 0.21–0.64), and oral corticosteroids (RR 1.99, 95% CI 1.19–3.32) contributed significantly to death.

DISCUSSION

The results of this retrospective, controlled cohort study showed that RA patients who had ever been treated with CSA did not have an increased risk of cancers of any kind, including malignant LPDs and skin cancers. In addition, CSA-treated RA patients did not die earlier than comparable non-CSA–treated RA patients. Since mortality due to end-stage renal failure and cardiovascular complications, as well as to malignancies, was not increased in the CSA group, it can be concluded that CSA-related renal function disturbances and hypertension do not lead to life-threatening cardiovascular complications, and that cancers developing during or after CSA therapy do not have a more aggressive course. On the contrary, the results of this study suggest that the risk of developing a malignancy is somewhat lower in patients who have ever taken CSA compared with those who have not.

Two forms of assembly bias might have been present in this study. First, most control patients in this study were not randomly allocated, but obtained retrospectively. Serious attempts were made to match the control patients as closely as possible to the index patients with respect to demographic and disease-specific characteristics. In every case, the question was posed regarding whether a particular control patient would have met the inclusion and exclusion criteria of the clinical trial in which the index patients had been included. A history of malignancy, hypertension, and renal failure were of special interest, and control patients with 1 or more of these conditions were excluded. Both groups were comparable with respect to baseline characteristics, suggesting that we were successful in matching and in minimizing this kind of assembly bias. Successful matching was supported by the similar results obtained when only the patients from the randomized studies were analyzed.

Second, significantly more DMARDs had been given to index patients than to control patients, including methotrexate and azathioprine. These latter drugs have been suggested to increase the risk of malignancies (6,9,23). Higher exposure to these DMARDs in the CSA group therefore strengthened the observed differences in the number of malignancies in favor of the index patients. After correction for the numbers and kinds of DMARDs used, the risk reduction in terms of development of malignancy was still present, but the risk reduction with regard to mortality had disappeared. Other confounding factors, such as smoking habits or socioeconomic status, may have influenced the results on malignancy and mortality, but it is unlikely that their contribution would be so substantial that the primary conclusion of this study should be disputed.

Two forms of selection bias may have been

present. First, index patients and control patients lived in different geographic areas of The Netherlands. The majority of the control patients lived in a rural area in the eastern part of The Netherlands. The domestic areas of the index patients were geographically spread throughout the country. Using the national cancer registry, we checked whether important regional differences in the incidence of particular malignancies and in mortality existed between the eastern part of the country and the remainder. Such differences could not be found.

Second, the index patients were prospectively selected and the majority of the control patients were retrospectively selected. The prospective selection with regard to the absence of hypertension, renal function impairment, and malignancies in the index patients may have been more thorough than the retrospective selection in the corresponding control patients. The influence of this kind of selection bias is only modestly important, since the relative risks of malignancies and mortality did not essentially change after the removal of the retrospectively assembled control patients from the analysis.

One may question whether all malignancies had been detected. The combination of checking for malignancies by both chart review and the use of PALGA optimized the search for malignancies. Since the pathology departments in all of the hospitals from which patients had been recruited had taken part in PALGA during the entire followup period, and a complete printout of all PALGA data on each patient was checked for a record of malignancies, it is unlikely that cases of cancer were missed. Nevertheless, the possibility cannot be excluded that a few cases of skin cancers that were not offered for pathologic examination had been missed. However, there is no reason to assume that this preferentially took place in 1 of the 2 groups.

The significant risk reduction in the CSA group concerning the development of malignancies is a second issue for discussion. The robustness of this observation was supported by demonstrating a similar risk reduction in the analysis of only the randomized patients. Lack of statistical power because of insufficient patient numbers explains the loss of statistical significance in this analysis, but the trend is still obvious. The advantage of randomization is that selection for inclusion has taken place prior to the allocation of treatment, thus ruling out all forms of selection bias. Another argument for the robustness of the results is the finding that the relative risks were only modestly influenced by the multivariate analysis, which was corrected for a large number of potentially confounding factors. The magnitude of risk reduction, however, declined somewhat in the multivariate analysis, suggesting that the overall effect was not large.

The significant risk reduction in the index group concerning malignancies can, in our opinion, partly be ascribed to assembly bias. All index patients, but only a proportion of the control patients, had been thoroughly checked for the presence of malignancy before inclusion in their former clinical trial. The remainder of the control patients had been retrospectively assembled. It is possible that a small number of malignancies, which might have been discovered earlier after a thorough check, had now been diagnosed during followup. An important argument in favor of this hypothesis is the preferential occurrence of some slow-growing solid tumors in the control group.

A second possibility to explain the risk reduction with regard to malignancies in the index group is a protective effect of CSA on the development of malignancies. It is, however, difficult to find a biologic rationale for such a protective effect. Therefore, we believe that a protective effect of CSA, although not to be excluded entirely, is a highly unlikely possibility.

The results observed in this study contradict those obtained in CSA-treated transplant patients. In CSA-treated transplant patients, the increased risk of malignant LPDs and squamous cell skin cancer has been attributed to loss of immunosurveillance, to which the hematopoietic system would be especially sensitive (3,24). Loss of immunosurveillance might also explain a more aggressive course of LPDs and skin cancers in CSA-treated transplant patients, as well as the observed increased risk of LPDs in RA patients treated with methotrexate (25), azathioprine (6), and cyclophosphamide (7). We did not find an increased incidence of LPDs or squamous skin cancers nor a higher malignancy-related mortality in CSA-treated patients, which would have suggested a more aggressive course of these malignancies. Three factors may be important to explain this discrepancy. First, in contrast to the "lifelong" CSA exposure in transplant patients, the RA patients in our study were exposed to CSA during a relatively short period. Second, the level of immunosuppression in transplant patients may be more profound due to higher doses of CSA in combination with other immunosuppressive drugs. Our study included only a small number of patients who were receiving a high dosage of CSA ($\geq$5 mg/kg/day) and these patients all had relatively short treatment durations. Third, disease-specific factors, such as HLA–B mismatch in kidney transplant patients and the reported association with squamous cell skin cancer (5), might be more important

than the immunosuppressive treatment itself in determining the risk of cancer.

In summary, this study has shown that relatively short-term and low-dose CSA therapy is not associated with an increased risk of malignancies in general and malignant LPDs or skin cancers in particular in patients with RA. There is also no evidence that malignancies in CSA-treated RA patients have a more aggressive course. Furthermore, CSA treatment in RA does not increase mortality due to cardiovascular disease nor to any other cause.

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