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CLINICAL REPORT

Serum Creatinine Levels During and After Long-term Treatment with Cyclosporine A in Patients with Severe Atopic Dermatitis

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Safety data with respect to kidney function during long-term treatment with cyclosporine A (CsA) in patients with atopic dermatitis is limited. Data on serum creatinine levels before, during and after CsA treatment were collected in a retrospective cohort of adult patients with atopic dermatitis. The median duration of treatment of 150 patients was 280 days (interquartile range 203–528 days). There was a significant, but not clinically relevant, increase in serum creatinine compared with the baseline level after 3 weeks of treatment with CsA and stabilization during the maintenance phase at the group level. Twenty-two (14.7%) patients had a greater than 30% increase in serum creatinine (cut-off point for clinically relevant change) compared with baseline. These patients were significantly older than the patients without a 30% increase (mean ± standard deviation age 41.4 ± 15.6 vs. 33.8 ± 11.7 years ($p = 0.01$)). During follow-up, all patients had a less than 30% increase in serum creatinine levels compared with baseline levels. At the group level serum creatinine levels during follow-up were not significantly different from baseline. ***Key words: atopic dermatitis; cyclosporine A; kidney function.***

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Atopic dermatitis (AD) is a chronic inflammatory skin disease with exacerbations and (partial) remission. Although most patients with AD can be treated adequately with topical corticosteroids, topical immunomodulators or ultraviolet (UV) light therapy, a subgroup of patients with moderate-to-severe AD requires oral immunosuppressive treatment.

Cyclosporine A (CsA) is a potent inhibitor of T lymphocyte-dependoderate immune responses and used in the treatment of moderate-to-severe AD. The clinical efficacy of CsA has been shown in several controlled and uncontrolled trials.

CsA increases vascular resistance, which may lead to decreased renal plasma flow and decreased clearance of endogenous creatinine (2). Therefore, kidney function must be carefully monitored during treatment with CsA. While the population variation in serum creatinine is large, the within-individual variation in serial measurements is much smaller (10%) and can detect a change in renal function (3). In acute kidney injury a serum creatinine increase of 50% is considered relevant according to the Rifle criteria. For chronic use of CsA an increase of 30% can be considered as a cut-off to predict kidney dysfunction. In patients with persistent serum creatinine increase after discontinuation of CsA therapy, structural kidney damage may occur (4).

In patients with severe AD, several years of maintenance therapy with CsA is sometimes necessary to achieve adequate disease control and improvement in quality of life. Therefore there is a need for information on the long-term effect of CsA on kidney function in patients with AD.

Long-term CsA treatment is used in patients with organ transplantation as an immunosuppressive treatment to prevent rejection. However, this patient group is not comparable to patients with AD because of differences in baseline renal function, co-morbidity, concomitant medication, CsA dosing and the confounding effect of rejection in case of renal transplantation. Fear of irreversible kidney damage after long-term use of CsA by dermatologists is mostly based on publications about patients with psoriasis (5). The European Dermatology Forum guideline on psoriasis recommends a maximum duration of CsA maintenance treatment of 2 years based on expert opinion (6). However, a recent population-based cohort study demonstrates that moderate-to-severe psoriasis itself is associated with an increased risk of chronic kidney disease (based on diagnostic code in general practitioner medical records, glomerular filtration rate (GFR) or both), independent of traditional risk factors and medication such as CsA (7). As there is no evidence for intrinsic kidney disease in patients with AD, data concerning kidney function during CsA treatment in patients with psoriasis cannot be extrapolated to patients with AD. At present, there is limited data on safety with respect to kidney function during long-term (>1 year) CsA treatment in patients with moderate-to-severe AD.

The aim of the present study was to investigate serum creatinine levels during and after long-term maintenance treatment with CsA in a non-selected group of patients with moderate-to-severe AD in daily practice.

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METHODS

Patients, study design and outcomes

The medical records of all patients with moderate-to-severe AD (diagnosed according to the criteria of Hanifin & Rajka) (8) treated with CsA from November 1994 until data lock in December 2013 at the Department of Dermatology of the University Medical Center Utrecht were analysed with respect to serum creatinine levels during and after CsA treatment. Patients eligible for inclusion were treated with CsA according to the standard treatment and monitoring protocol used in the outpatient clinic (Table SI[1]). Missing data for serum creatinine level at baseline, due to starting CsA in another hospital, was an exclusion criterion. Treatment periods with CsA < 6 weeks were also excluded from the analyses, as in clinical trials significant serum creatinine increase was not a reason for discontinuation of treatment during administration of high-dose CsA early in treatment (9).

Data about patient characteristics, duration of CsA treatment and follow-up were extracted from medical records. The following data with respect to kidney function were recorded: (*i*) serum creatinine level at baseline; (*ii*) serum creatinine after 3 weeks of CsA treatment (high dose 3.5–5 mg/kg/day); and (*iii*) mean serum creatinine level during the maintenance phase (intermediate dose ≤ 3.5 mg/kg/day).

Patients with serum creatinine increase >30% compared with baseline were further examined with respect to the presence of clinical symptoms (e.g. oedema), age and serum creatinine levels after dose adjustment. Also intercurrent causes of the increase (age-related increase in serum creatinine (more than 5 years compared with baseline (10), co-morbidity, medication use influencing kidney function) were investigated.

In patients who stopped CsA treatment, the most recent serum creatinine value from the medical record was registered. In patients who restarted CsA or another oral calcineurin inhibitor, the serum creatinine value before the restart was registered.

Data analysis

Statistical analyses were performed in SPSS (for Windows, version 20, SPSS Inc., Chicago, IL, USA). Skewed distribution in treatment duration and duration of follow-up were observed; therefore median and interquartile ranges (IQR) were described. Differences in serum creatinine at the different time-points during treatment were compared using a paired *t*-test. Differences between patient groups were compared using one-way analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Probability levels of 0.05 and below were considered statistically significant.

RESULTS

A total of 150 patients who met the inclusion criteria were identified. At the time of data analysis, 10 (6.7%) patients were still using CsA and 140 (93.3%) patients had discontinued treatment. Follow-up data was available for 92/140 (65.7%) patients. Starting treatment in another hospital was an exclusion criterion for 52 patients and 24 patients were excluded because the duration of CsA treatment was less than 6 weeks.

*Serum creatinine during CsA treatment (*n = *150)*

The median duration of CsA treatment in the 150 patients was 280 days (IQR 203–528 days). Fifty-three (35.3%) episodes had a duration of one year or longer, of which 24 (16.0%) episodes had a duration longer

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Table I. *Serum creatinine level during and after cyclosporine A (CsA) treatment and a subdivision in the duration of treatment and follow-up*

				Serum creatinine (μmol/l)						
	n (%)	Duration of treatment, days, median (IQR)	Duration of follow-up, median (IQR)	Baseline Mean ± SD	3 weeks (3.5–5 mg/kg) Mean ± SD	*p*-value[a]	Mean during maintenance (≤3.5 mg/kg) Mean ± SD	*p*-value[b]	Latest after discontinuation	*p*-value[c]
During CsA										
Total patient group	150	280 (203–528)		79.0 ± 12.8	83.8 ± 14.3	0.000	82.9 ± 13.1	0.000		
Duration of treatment										
<6, months	32 (21.3)	110 (70–167)		76.7 ± 11.9	82.6 ± 16.8	0.001	82.3 ± 15.2	0.003		
6–12, months	65 (43.3)	269 (244–293)		79.5 ± 12.4	83.6 ± 14.0	0.000	82.3 ± 12.9	0.013		
12–24, months	29 (19.3)	520 (443–652)		78.9 ± 13.5	85.1 ± 14.6	0.007	83.6 ± 13.9	0.031		
>24, months	24 (16.0)	1,309 (832–1,865)		80.8 ± 14.6)	84.3 ± 12.0	0.159	84.7 ± 10.3	0.051		
One-way ANOVA				*p* = 0.661	*p* = 0.992		*p* = 0.867			
After CsA										
Total patient group	92	269 (188–423)	357 (87–1,005)	80.8 ± 12.9	85.0 ± 14.5	0.000	84.8 ± 13.0	0.000	80.5 ± 12.9	0.832
Follow-up <2 years	61	274 (177–432)	112 (50–357)	80.7 ± 12.2	85.3 ± 14.6	0.001	84.3 ± 12.9	0.006	79.5 ± 12.1	0.391
Duration of treatment										
0–12 months	42	253 (152–276)	94 (48–369)	81.0 ± 13.1	86.2 ± 15.4	0.003	84.3 ± 13.6	0.039	79.7 ± 12.3	0.433
>12 months	19	575 (437–742)	229 (57–353)	80.1 ± 10.2	83.3 ± 12.9	0.214	84.3 ± 11.4	0.074	79.2 ± 11.7	0.726
Follow-up >2 years	31	260 (203–407)	1,730 (899–2,528)	80.9 ± 14.4	84.6 ± 14.5	0.059	85.9 ± 13.3	0.017	82.5 ± 14.3	0.368
Duration of treatment, months										
0–12	22	244 (164–267)	1,628 (879–2,109)	79.3 ± 12.1	84.7 ± 14.4	0.005	86.4 ± 13.8	0.001	83.8 ± 14.5	0.013
>12	9	702 (464–1,051)	2,493 (1,971–3,111)	84.9 ± 19.3	84.4 ± 15.5	0.929	84.6 ± 12.9	0.948	79.3 ± 14.2	0.166
One-way ANOVA				*p* = 0.940	*p* = 0.840		*p* = 0.582		*p* = 0.294	

[a]Baseline – 3 weeks. [b]Baseline – mean during maintenance. [c]Baseline – latest after discontinuation.
IQR: interquartile range; SD: standard deviation; ANOVA: analysis of variance.

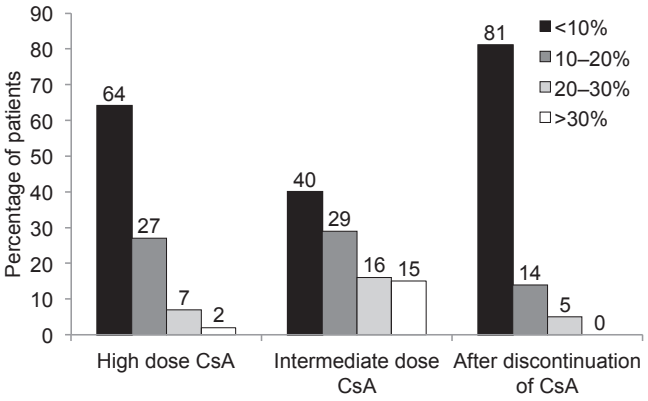

Fig. 1. Percentage increase in serum creatinine in individual patients during and after cyclosporine A (CsA) treatment, determined at 3 weeks (high dose 3.5–5 mg/kg/day), during maintenance phase (intermediate dose ≤ 3.5 mg/kg/day), and after discontinuation compared with baseline level. Serum creatinine levels were available for 150 patients during high-dose CsA and intermediate-dose CsA; serum creatinine levels after discontinuation of CsA were available for 92/150 patients.

than 2 years (Table I). The age and sex distribution of the patients was similar in the 4 groups with a total mean ± SD of 34.9 ± 12.5 and M:F of 79:71.

The mean ± SD serum creatinine level at baseline was 79.0 ± 12.8 µmol/l, this level increased to 83.8 ± 14.3 µmol/l after 3 weeks of CsA treatment (high dose 3.5–5 mg/kg/day) and to a mean ± SD level of 82.9 ± 13.1 µmol/l during the maintenance phase (intermediate dose ≤ 3.5 mg/kg/day). Although increases in serum creatinine levels were small in individual patients (Fig. 1), in the total group of patients CsA treatment during high dose and intermediate dose resulted in a significant increase in serum creatinine compared with baseline levels ($p = 0.000$). Serum creatinine levels were not significantly different with respect to duration of treatment.

Follow-up: serum creatinine after discontinuation of CsA treatment (n = 92/140)

Follow-up data was available for 92 (65.7%) of the 140 patients who had discontinued CsA treatment (Table I). The median duration of follow-up was 357 days (IQR 87–1,005 days). The mean ± SD serum creatinine at baseline (80.8 ± 12.9 µmol/l) was not significantly different from the latest mean level after CsA discontinuation (80.5 ± 12.9 µmol/l). Serum creatinine levels were not significantly different during follow-up with respect to treatment duration and duration of follow-up (except for patients with a follo w-up > 2 years and a treatment duration of < 1 year).

The percentage serum creatinine increase compared with baseline after discontinuation of CsA treatment per patient is shown in Fig. 1. Overall, the serum creatinine level was within the normal variation of 10% compared with baseline in 74 (80.5%) patients, increased by 10–20% compared with baseline in 13 (14.1%) patients, and by 20–30% in 5 (5.4%) patients. Possible intercurrent causes of more than 10% variation in serum creatinine level (the within-individual variation of serial measurements) during follow-up were: recent discontinuation of CsA (< 1.5 months) (4 patients, 10–20% increase), more than 5 years increase of age compared to baseline (2 patients 10–20% increase; 1 patient 20–30% increase) and medication influencing kidney function (angiotensin-converting-enzyme (ACE) inhibitor and diuretic) (2 patients 20–30% increase). In 9 patients no intercurrent cause was found (7 patients 10–20% increase; 2 patients 20–30% increase).

Patients with > 30% serum creatinine increase compared with baseline level during CsA treatment (n = 22/150)

Twenty-two (14.7%) patients had a > 30% increase in serum creatinine compared with baseline level during CsA treatment. In 3/22 patients this increase developed during high-dose CsA and continued during the maintenance phase, and in 19/22 patients the increase developed during the maintenance phase of treatment. Clinical symptoms were not reported. Patients with a > 30% increase in serum creatinine level were significantly older than patients without a 30% increase in serum creatinine (mean ± SD age 41.4 ± 15.6 vs. 33.8 ± 11.7 years) ($p = 0.01$)). Sex and duration of CsA use had no influence on the occurrence of clinically relevant increases in serum creatinine. No intercurrent causes of serum creatinine increase were found in these patients (co-morbidity, other medication use influencing kidney function or interactions with co-medication).

A flow chart with adjustments for the management of the 22 patients with a clinically relevant increase in serum creatinine is shown in Fig. S1[1]. One patient discontinued CsA immediately and 14 patients had a dose adjustment. Successful dose reduction, defined as normalization of serum creatinine with controlled AD, was reported in 7 patients. In 7 patients dose reduction was not successful (due to uncontrolled AD in 4 patients and insufficient decrease in serum creatinine level in 3 patients); CsA treatment was subsequently discontinued in these patients. In the remaining 7 patients CsA dose was not adjusted and serum creatinine levels were further monitored.

At the time of data analysis 3/22 patients were still being treated with CsA. Serum creatinine values for these patients were ± 0%, +3% and +36% compared with baseline level, respectively, at the time of data lock. The patient with a 36% increase in serum creatinine had a very low starting value (47 µmol/l), probably due to hyperfiltration. During follow-up serum creatinine values stabilized, so no dose adjustments were made.

Follow-up of patients with > 30% serum creatinine increase compared with baseline level during CsA treatment (n = 22)

Follow-up of serum creatinine levels of 19/22 patients who had discontinued CsA showed 7 patients with

serum creatinine levels within 10% compared with baseline, 4 patients with an increase of 10–20% compared with baseline, and another 4 patients with an increase of 20–30% compared with baseline. Follow-up of serum creatinine levels was missing in 4 patients. However, in these patients serum creatinine levels had already decreased to 103%, 107%, 109% and 117% compared with baseline during CsA treatment.

DISCUSSION

This study retrospectively analysed serum creatinine levels during long-term CsA treatment in a large group of unselected AD patients who were treated in daily practice.

There was a significant, but not clinically relevant, increase in serum creatinine compared with the baseline level after 3 weeks' treatment with CsA (high dose 3.5–5 mg/kg/day) and stabilization during the maintenance phase (intermediate dose $\leq$3.5 mg/kg/day) at the group level.

The significant increase in serum creatinine during CsA treatment compared with baseline could be explained by increased vascular resistance due to CsA, which may cause decreased renal plasma flow and decreased clearance of endogenous creatinine (2). However, in most cases, the rate of increase was within the normal variation of 10% in individual patients and, therefore, not clinically relevant.

There are few data available on kidney function during CsA treatment in patients with AD. Schmitt et al. (1) reported the effect of CsA on serum creatinine levels in patients with AD in a meta-analysis of clinical trials. An increase in serum creatinine of more than 30% compared with baseline was an adverse event in up to 10.9% of patient months of active treatment with CsA. The duration of CsA treatment ranged from 6 weeks to 1 year, and the initial dose of CsA ranged from 2.5 to 5 mg/kg/day. An increased serum creatinine level was one of the main side-effects resulting in discontinuation of CsA treatment. In a retrospective study of Hijnen et al. (11) 73 patients with severe AD were treated with CsA doses varying between 2.5 and 5 mg/kg/day in daily practice. A mean peak increase in serum creatinine level of 15.8% compared with baseline was reported after a mean $\pm$ SD treatment duration of 192.9 $\pm$ 252.7 days. An increase in serum creatinine of more than 30% compared with baseline was reported in 9.6% of patients. In 5.5% of patients dose reduction was successful, and in 4.1% of patients the increase in serum creatinine was followed by discontinuation of treatment. No information on the reversibility of serum creatinine levels during follow-up was reported.

In our median observation period of 280 days (IQR 203–528 days), 22 (14.7%) patients had an increase in serum creatinine > 30% compared with baseline level. This relatively high percentage compared with earlier studies can be explained by differences in the patient population. Our study included non-selected patients treated in daily practice, and most patients were treated for longer periods compared with most clinical trials.

There was no significant difference in duration of CsA treatment between patients with and without an increase in serum creatinine of > 30% compared with baseline. This result suggests that the occurrence of a clinically relevant increase in serum creatinine is independent of the duration of CsA treatment. This is in contrast to patients with psoriasis, in whom longer duration of treatment appears to be a risk factor for kidney dysfunction (5). The mean age of the 22 patients with a clinically relevant serum creatinine increase in our study was significantly higher than the mean age of patients without this increase in serum creatinine. In patients with psoriasis treated with CsA higher age was also reported as a risk factor (5). In the retrospective study by Hijnen et al. (11), no correlation between age and serum creatinine levels was observed.

Although the treatment protocol prescribes dose reduction or discontinuation of CsA treatment in case of serum creatinine increase of > 30% compared with baseline, the dermatologist did not always comply with this protocol. This might be attributed to the fact that there is a large inter-individual variation in the range of normal serum creatinine levels. A clinically relevant increase in serum creatinine may still fall within the normal range and, for this reason, go unnoticed. This may apply, in particular, when the serum creatinine level before the start of CsA treatment is very low, as was observed in one patient in this study (47 μmol/l). Although our treatment and monitoring protocol advises dose reduction in case of 2 consecutive measurements of >30% serum creatinine increase, dose adjustments in many patients were based on a single measurement (11 out of 22 patients had an adjustment based on a single measurement). This may have led to an overestimation of the number of patients with clinically relevant serum creatinine increase.

The second part of our study analysed serum creatinine levels after stopping CsA. These follow-up data are important because a persistently elevated serum creatinine level after cessation compared with baseline is an indication of structural kidney damage (5). Like Maza et al. (5) we decided to consider an increase of > 30% as clinically relevant.

Follow-up data were not always available, as the treatment and monitoring protocol does not advise measurement of serum creatinine level after discontinuation of CsA. The most frequent reasons for measuring serum creatinine levels during follow-up were the start of a new oral immunosuppressive drug or monitoring recovery in patients with increased serum creatinine levels during CsA treatment. Therefore, the follow-up data consist of a selection of patients with difficult to treat AD (multiple

oral immunosuppressive drugs necessary) and patients with elevated serum creatinine during CsA treatment. In 48/140 patients follow-up was not available. However, these patients had no clinically relevant increase in serum creatinine level during CsA treatment.

The 92 patients showed serum creatinine levels within a 30% increase over baseline in all patients, indicating no clinically relevant serum creatinine increase after discontinuation of CsA. Treatment duration and duration of follow-up had no effect on serum creatinine levels.

Eighteen patients, however, maintained a moderately elevated serum creatinine level between 10% and 30% compared with baseline, of which the clinical relevance is unclear. We recommend additional monitoring of kidney function and blood pressure at set intervals (e.g. annually via a general practitioner) to evaluate the course of this elevation over time.

A limitation of this study is the retrospective design. Although laboratory results are reliable other information in the medical records may be of lower quality. For this reason no estimates of the cumulative dose of CsA or other possible influencing factors (co-morbidity, obesity and co-medication) could be made.

In this study kidney function is reflected by serum creatinine levels and not by GFR or proteinuria, which are currently more often used to assess renal function. Although estimated GFR (eGFR) is considered more reliable than serum creatinine for assessment of kidney function, there were several reasons for reporting creatinine values. First, changes in creatinine can be interpreted just as easily by the use of creatinine values as with eGFR (a 30% increase in creatinine will inadvertently result in a 30% reduction in eGFR) since race and sex are fixed and a increase in age of only 1 or 2 years influences the results of these formulas only very modestly. Moreover, most frequently used formulas tend to underestimate kidney function, particularly when eGFR is > 60 ml/min/1.73 m^2, which is approximately the norm for patients with AD. Thirdly, to apply these formulas accurately data on race is required, but this is not regularly available in the hospital records (12, 13).

Proteinuria and microalbuminuria are known signs of calcineurin inhibitor nephrotoxicity and are associated with a worse renal prognosis (4, 14). However, measurement of proteinuria and microalbuminuria are not in the current monitoring protocol of CsA treatment for patients with AD; therefore we could not use these parameters.

In conclusion, in contrast to previous studies in other patient groups, long-term treatment with CsA was not associated with clinically relevant serum creatinine increase during treatment and follow-up. The consequent monitoring of serum creatinine levels and CsA dose adjustment if creatinine levels increase in our study population may explain the lack of irreversible serum creatinine increase. Therefore, close monitoring of serum creatinine levels during CsA treatment remains strictly recommended. Patients with increased age are at higher risk of developing clinically relevant increases in serum creatinine. In patients with a greater than 10% increase in serum creatinine compared with baseline after discontinuation of CsA, additional monitoring of kidney function and blood pressure at set intervals is recommended.

The authors declare no conflict of interest.

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